



Hyperacute Excitotoxic Mechanisms and Synaptic Dysfunction Involved in Traumatic Brain Injury

Brendan Hoffe* and Matthew R. Holahan*

Department of Neuroscience, Carleton University, Ottawa, ON, Canada

OPEN ACCESS

Edited by:

James P. Clement,
Jawaharlal Nehru Centre
for Advanced Scientific Research,
India

Reviewed by:

Vijayalakshmi Santhakumar,
University of California, Riverside,
United States
Poonam Thakur,
Indian Institute of Science Education
and Research, Thiruvananthapuram,
India

*Correspondence:

Brendan Hoffe
brendanhoffe@carleton.ca
Matthew R. Holahan
MatthewHolahan@Cunet.Carleton.ca

Specialty section:

This article was submitted to
Molecular Signaling and Pathways,
a section of the journal
Frontiers in Molecular Neuroscience

Received: 08 December 2021

Accepted: 07 February 2022

Published: 24 February 2022

Citation:

Hoffe B and Holahan MR (2022)
Hyperacute Excitotoxic Mechanisms
and Synaptic Dysfunction Involved
in Traumatic Brain Injury.
Front. Mol. Neurosci. 15:831825.
doi: 10.3389/fnmol.2022.831825

The biological response of brain tissue to biomechanical strain are of fundamental importance in understanding sequela of a brain injury. The time after impact can be broken into four main phases: hyperacute, acute, subacute and chronic. It is crucial to understand the hyperacute neural outcomes from the biomechanical responses that produce traumatic brain injury (TBI) as these often result in the brain becoming sensitized and vulnerable to subsequent TBIs. While the precise physical mechanisms responsible for TBI are still a matter of debate, strain-induced shearing and stretching of neural elements are considered a primary factor in pathology; however, the injury-strain thresholds as well as the earliest onset of identifiable pathologies remain unclear. Dendritic spines are sites along the dendrite where the communication between neurons occurs. These spines are dynamic in their morphology, constantly changing between stubby, thin, filopodia and mushroom depending on the environment and signaling that takes place. Dendritic spines have been shown to react to the excitotoxic conditions that take place after an impact has occurred, with a shift to the excitatory, mushroom phenotype. Glutamate released into the synaptic cleft binds to NMDA and AMPA receptors leading to increased Ca^{2+} entry resulting in an excitotoxic cascade. If not properly cleared, elevated levels of glutamate within the synaptic cleft will have detrimental consequences on cellular signaling and survival of the pre- and post-synaptic elements. This review will focus on the synaptic changes during the hyperacute phase that occur after a TBI. With repetitive head trauma being linked to devastating medium – and long-term maladaptive neurobehavioral outcomes, including chronic traumatic encephalopathy (CTE), understanding the hyperacute cellular mechanisms can help understand the course of the pathology and the development of effective therapeutics.

Keywords: traumatic brain injury, synaptic dysfunction, excitotoxicity, dendritic spine, neurodegeneration

INTRODUCTION

The synapse is regarded as the fundamental site of communication between cells of the nervous system and synaptic dysfunction may represent a choke point for the multitude of upstream factors and downstream responses that lead to neuron atrophy or death. Synaptic malleability is a key component to behavior and cognition, with the formation, reshaping and strengthening of synapses being a key feature underlying learning and memory (Bourne and Harris, 2007;

González-Tapia et al., 2016; Noye Tuplin and Holahan, 2019). Prolonged pathological changes at the synaptic level have been shown to play a role in several psychiatric and neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, Fragile X syndrome and schizophrenia (Calabrese et al., 2006; Herms and Dorostkar, 2016).

Over the past 15 years there has been an increase in attention to the relationship between traumatic brain injury (TBI), Alzheimer's disease and chronic traumatic encephalopathy (Omalu et al., 2005; McKee et al., 2013; Goldstein et al., 2014; Albayram et al., 2020). Given that TBI can be regarded as a singular event (Wojnarowicz et al., 2017), the cellular processes that take place at the synapse dictate how the cell responds to the change in environment. These cellular processes can be categorized into four main time phases: hyperacute, acute, subacute, and chronic (Guerriero et al., 2015; MacFarlane and Glenn, 2015). While much research exists on the changes occurring days to months after TBI, there is comparatively little research investigating the hyperacute synaptic changes occurring within minutes to hours. These short-term changes could reveal the pathological mechanisms that are responsible for the later stages of neurodegeneration which may help shed light on potential therapeutic routes for neurodegenerative diseases associated with head trauma. This review will focus on and highlight the synaptic dysfunction during the hyperacute phase post-TBI, combining crucial findings from both *in vitro* and *in vivo* data to better understand what occurs at the synapse within minutes to hours after an impact has occurred.

TIME PHASE FOLLOWING IMPACT

The timeline of cellular responses that occur after brain impact spans four phases: hyperacute (minutes to hours), acute (hours to several days), subacute (several days to weeks) and chronic (months and beyond; Guerriero et al., 2015; MacFarlane and Glenn, 2015). During the hyperacute phase, affected neurons undergo substantial and abnormal electrical and cellular activity leading to maladaptive remodeling, potentially as an attempt to regain homeostasis following impact. While the affected cells work to re-establish internal homeostasis during each phase, if damage were to remain unresolved (ex. further damage, or severity of initial damage) the pathology continues and moves into the next phase. As each phase progresses to the next, the damage severity increases. This can ultimately lead to the major neurodegeneration observed in pathologies associated with head trauma (Figure 1).

Hyperacute Changes to the Pre-synaptic Terminal

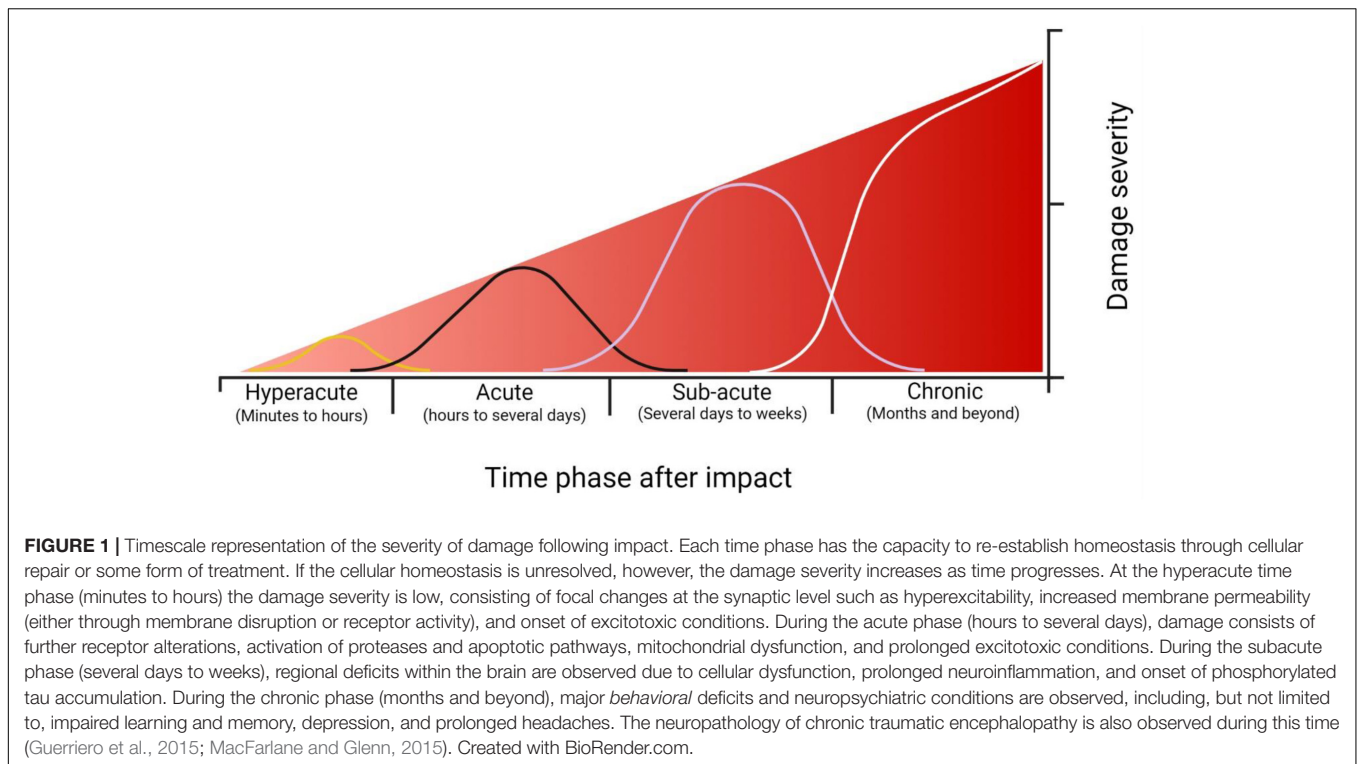
The promotion of excitotoxic conditions requires prolonged release and presence of glutamate within the synaptic cleft, leading to overactivation of *N*-Methyl-d-aspartate receptors (NMDAR) and of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) on the post-synaptic membrane. *In vitro* neuronal stretch models have demonstrated an increase in membrane permeability within minutes after

stretch through dysregulated ionic channels or the membrane physically rupturing (Smith et al., 1999; Weber, 2012; Siedler et al., 2014). Wolf et al. (2001) found that within minutes following stretch strain, an increase in intracellular Ca^{2+} was observed with levels that continued to rise during the time course of the experiment (1-20 min). This increase was dependent on the influx of Na^+ as blockade of the voltage gated Na^+ channels with tetrodotoxin inhibited this rise in intracellular Ca^{2+} (Wolf et al., 2001).

Increased intracellular Ca^{2+} in the pre-synaptic neuron prime the readily releasable pool of synaptic vesicles and the SNARE complex that mediates the fusion of vesicles to the membrane wall via various docking proteins (Hackett and Ueda, 2015; Kaeser and Regehr, 2017; Chen et al., 2021). Carlson et al. (2016) found that 6 h after cortical impact to rodents, there was a noticeable increase in SNAP-25 complex, as well as syntaxin, that steadily decreased over a 2-week period. This is of importance as SNAP-25 and syntaxin are two of the three main SNARE proteins responsible for vesicle-membrane fusion at the pre-synaptic terminal (Kaeser and Regehr, 2017; Chen et al., 2021). Ahmed et al. (2012) found that within 30 min following stretch damage to *Drosophila* motor neurons, there were elevated levels of Synaptotagmin, a Ca^{2+} sensitive vesicle trafficking protein that interacts with SNAP-25, within the pre-synaptic terminal. These synaptic changes, along with changes to the post-synaptic neuron, are summarized in Figure 2.

Hyperacute Inflammatory Response

Neuroinflammation plays a significant role in modulating the damage after brain injuries, with the activation of numerous proinflammatory cytokines such as interleukin-1, 6, tumor necrosis factor- α (TNF- α), and interferon- γ reported within the hyperacute phase following injury (Patterson and Holahan, 2012; Smith et al., 2012; Xiong et al., 2018). Recently, attention toward molecular recognition of damage has been gaining interest as possible mechanisms for signaling the immune response after injury. Toll-like receptors (TLR) are a class of pattern recognition receptors that activate and mediate the production of cytokines involved in proinflammatory response (Vaure and Liu, 2014). TLR-4, specifically, has been shown to influence neuronal excitability through cytokine-enhanced NMDAR currents in hippocampal cultures (Balosso et al., 2014). In the context of TBI, however, TLR-4 enhances neuronal excitability through upregulation of Ca^{2+} -permeable GluR1, and not NMDAR, hours after impact (Li et al., 2015; Korgaonkar et al., 2020). Using the fluid percussion injury (FPI) model in juvenile rats, Li et al. (2015) demonstrated elevated neuronal expression of TLR-4 within the hippocampus 4 h after impact, with a peak at 24 h, then returning to similar levels as 4 h at 3 days post-impact. This early increase in TLR-4 expression was accompanied with enhanced non-NMDA excitatory postsynaptic currents in granule cell and mossy cells at 3 days. The contribution of TLR-4 to increased neuronal excitability is through the downstream effector of nuclear factor kappa B (NF- κ B; Vaure and Liu, 2014). In neurons, increased synaptic expression of NF- κ B has been shown to promote excitatory synapses and spinogenesis through NMDAR regulated Ca^{2+} influx (Boersma et al., 2011). In glial



cells, TLR-4-activated NF- κ B has downstream effects on the upregulation on proinflammatory factors such as interferon-beta (IFN- β) and TNF- α (Vaure and Liu, 2014). Overproduction of these factors in microglia have been shown to promote excitotoxic conditions by downregulating excitatory amino acid transporter-2, thus reducing glutamate reuptake from astrocytes (Sitcheran et al., 2005). Another mechanism includes the TNF- α induced increase in AMPAR lacking GluR2, increasing the Ca²⁺ permeability (Stellwagen et al., 2005; for review see Olmos and Lladó, 2014).

Maladaptive Role of Inhibition During Hyperacute Phase

While not directly in the scope of this review paper, the role of γ -aminobutyric acid (GABA) in the promotion of excitotoxic conditions is important. Immediately following FPI (i.e., within minutes of impact to tissue fixation), Toth et al. (1997) demonstrated that large basket-like cells within the granular layer of the rat hippocampus were damaged, as evident from positive Gallyas silver staining. The neighboring granule cells, however, showed no signs of damage indicating that, due to their size, these GABAergic interneurons were at more risk of damage compared to the tightly packed granule cells. Further, the authors note that the damage to GABAergic interneurons immediately after impact can further promote the state of hyperexcitability as there is limited inhibitory signals within this region of the hippocampus (Toth et al., 1997). More recently, studies have shown further downregulation of GABAergic subunits within the rat hippocampus, particularly α 1, α 2, γ 2, and δ , 6 h following FPI (Raible et al., 2012; Drexel et al., 2015). Interestingly, both groups

found upregulation of α 4 subunits, with Raible et al. (2012) showing increase in the ipsilateral side, but not contralateral, and Drexel et al. (2015) showing increase in both ipsilateral and contralateral to region of impact. Considering how the α 1, α 2 and γ 2 GABA subunits regulated phasic inhibition, and the α 4 subunit regulates tonic inhibition, the increase in α 4 subunit expression could be an indication of a compensatory mechanism to counteract the hyperexcited state occurring after impact (Drexel et al., 2015).

Electrophysiological Changes Following Impact

Excitotoxic conditions arise from the prolonged release of glutamate into the synaptic cleft with subsequent binding to and activation of post-synaptic receptors. Having established an increase in membrane permeability, which leads to influx of Na⁺ and Ca²⁺, as well as the efflux of K⁺ (MacFarlane and Glenn, 2015), one would assume that the dysregulation of ions across the membrane could be enough to trigger aberrant depolarizations and produce a hyperactive state shortly after trauma. However, much like the dynamics of the pre-synaptic terminal, there remains limited research into the hyperacute phase of TBI (Cohen et al., 2007). This could be in part due to the complexity of techniques from one study to another, or experimental limitations associated with electrophysiological recordings from slice preparations in such a protracted timeframe. Nonetheless, there have been a handful of studies looking at the electrophysiological properties that occur within the hyperacute phase following TBI.

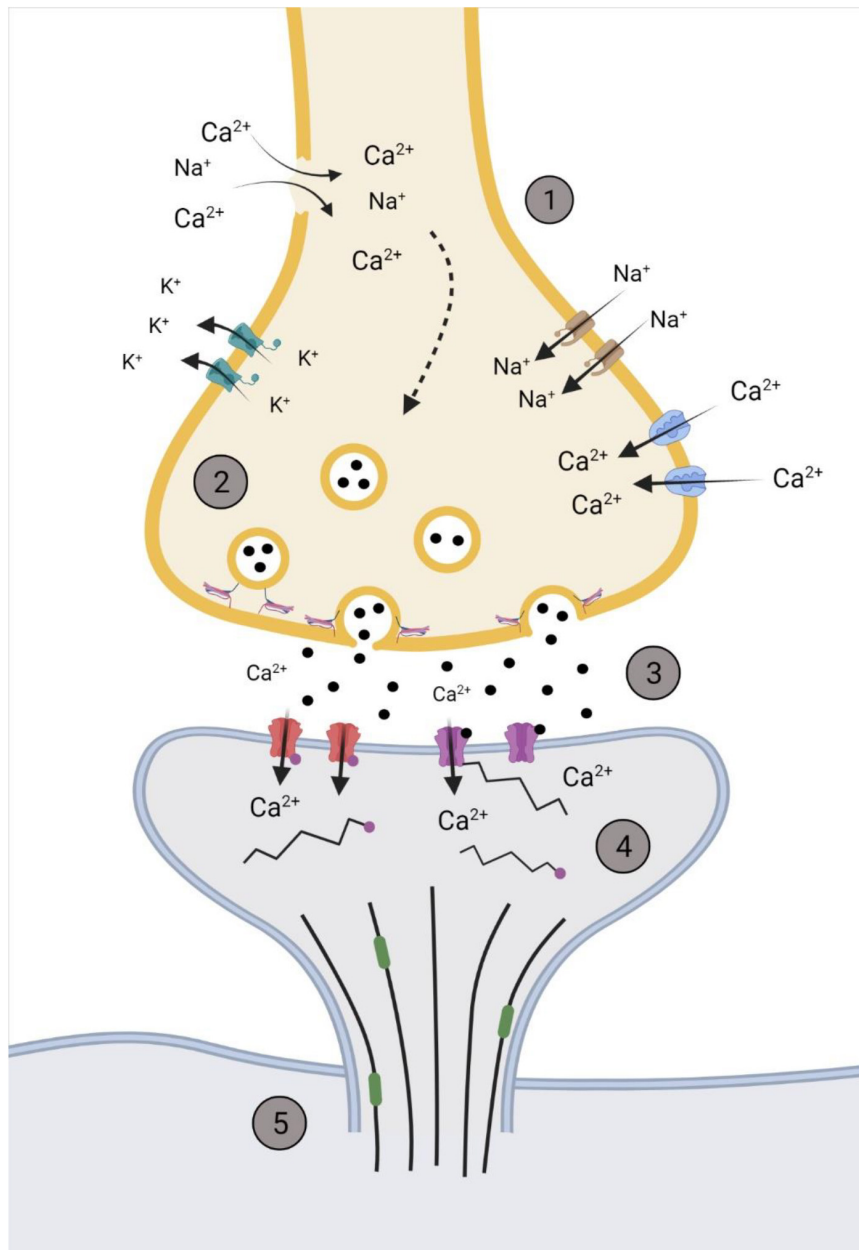


FIGURE 2 | Representation of the synapse within the hyperacute phase after impact. (1) Membrane permeability increases soon after impact through the influx/efflux of ions via voltage gated channels or rupturing of the pre-synaptic membrane. (2) The increase in Ca^{2+} primes glutamate filled vesicles and increases the rate of fusion and release of glutamate. (3) Increased and sustained release of glutamate (black dots) into the synaptic cleft activates NMDA receptor NR2B subunits (purple) and increases post-synaptic concentrations of Ca^{2+} . This activates various kinases that phosphorylates AMPA GluR1 subunits (red), further promoting the influx of Ca^{2+} . (4) Post-synaptic cytoskeleton alterations occur through phosphorylation (pink dots), with disinhibition of remodeling proteins, such as end-binding protein 3 (green), occurring to allow for the restructuring of the dendritic spine cytoskeleton. (5) Downstream cascades from the influx of Ca^{2+} alter microtubule dynamics within the cytoskeleton of the neuron. Created with BioRender.com.

Using microelectrode arrays to measure neural population activity following cortical compression, Ding et al. (2011) found a time-dependent shift in electrical activity after compression. Within minutes of injury, there was a depression in cortical activity, with a gradual rise in excitability within an hour post injury, eventually resulting in cortical hyperexcitability by the

2-h mark. Similarly, using an *in vitro* stretch model, it was shown that within 30 min there was a reduced occurrence of spontaneous action potentials in neurons that were damaged (Magou et al., 2015). Interestingly, the authors found that in the adjacent neurons that did not experience stretch damage, there was an increase in action potentials generated within that

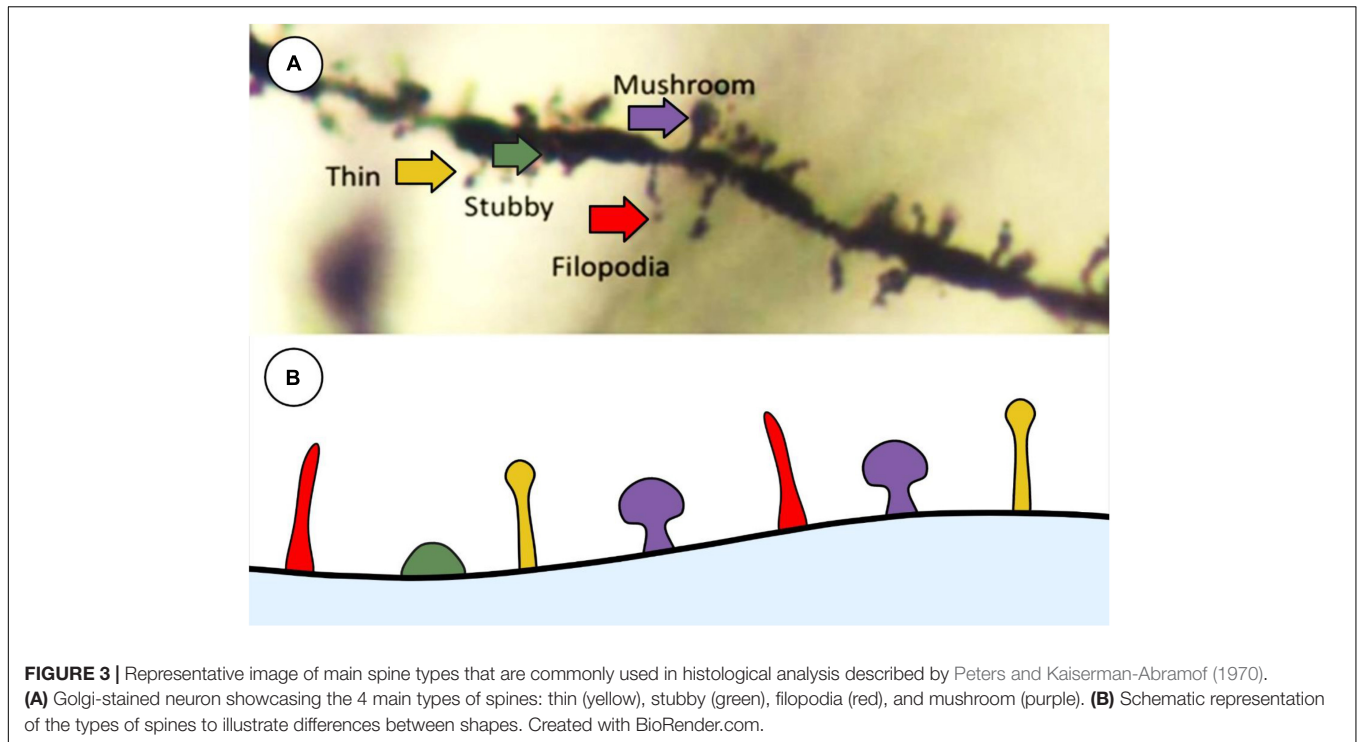


FIGURE 3 | Representative image of main spine types that are commonly used in histological analysis described by Peters and Kaiserman-Abramof (1970). **(A)** Golgi-stained neuron showcasing the 4 main types of spines: thin (yellow), stubby (green), filopodia (red), and mushroom (purple). **(B)** Schematic representation of the types of spines to illustrate differences between shapes. Created with BioRender.com.

timeframe. This could potentially indicate that due to imbalance of ionic homeostasis immediately after trauma, the depression of electrical activity could act as a primer for the hyperexcitability experienced shortly after (Berger et al., 2008; Ding et al., 2011). This enhanced activity in adjacent neurons could propagate hyperexcitatory conditions, potentially initiating the secondary, maladaptive intracellular pathways associated with TBI.

The release of ions following injury has also been shown to be enhanced within 24 h after injury and alter electrophysiological properties. In a rather paradoxical way, D'Ambrosio et al. (1998) demonstrated a loss of long term potentiation (LTP), but not long term depression (LTD), in hippocampal slice recordings, 24 h after FPI in rats. They found that rats who received FPI had higher thresholds required to evoke population spikes within the CA1. However, previous work from Katayama et al. (1990) demonstrated, *in vivo*, a massive increase in extracellular K^+ following FPI resulting in neuronal hyperexcitability. D'Ambrosio et al. (1998) attribute their opposite finding to differences in the microenvironments between *in vivo* and *in vitro* settings. They note that the elevated efflux of K^+ abolishes LTP as the sudden overactivation of NMDAR and firing of the post-synaptic neuron leaves the neuron unable to undergo further potentiation after injury; something not reproducible in an *in vitro* setting (D'Ambrosio et al., 1998). Interestingly, a year later D'Ambrosio et al. (1999) demonstrated altered neuronal activity due to excessive accumulation of extracellular K^+ 24 h after FPI in hippocampal slices. This accumulation led to a hyperexcited state in CA3 neurons, as evident by the higher percentage of burst discharges in the post-FPI slices. The authors also note a significant loss of inward rectifying K^+ currents from recruited glia cells. These findings

indicate a disruption to mechanisms responsible for maintaining extracellular homeostasis, such as the decreased K^+ clearance from glia cells plus the prolonged release of K^+ from hyperactive neurons (D'Ambrosio et al., 1999).

A report by Ross and Soltesz (2000) examined the electrophysiological properties of interneurons in the dentate gyrus after lateral FPI. Within the dentate gyrus, there was an observed increase of spontaneous interneuron firing rates due to Na^+/K^+ -ATPase-related depolarizations. This increase in interneuron firing rates after impact led to increased frequency and amplitude of spontaneous inhibitory postsynaptic potentials in dentate gyrus granule cells. It is important to note that this increase in spontaneous inhibitory postsynaptic potentials occurs simultaneously to a decrease in miniature inhibitory postsynaptic current frequency. The authors describe this post-FPI increase in interneuron depolarization and increased GABAergic transmission could increase the efficacy of incoming excitatory signals to further promote interneuron firing after impact. This rather paradoxical mechanism has been reported in previous models of hyperexcitability, such as kindling seizures, chronic stress-induced seizures, and febrile seizures (Nusser et al., 1998; Chen et al., 1999; MacKenzie and Maguire, 2015).

Hyperacute Changes to the Post-synaptic Terminal

Using animal models of TBI, it has been shown that extracellular glutamate levels rise drastically within minutes after impact and remained elevated for hours (Faden et al., 1989; Folkersma et al., 2011; Xiong et al., 2019). Along the post-synaptic membrane, AMPAR and NMDAR become over-activated from the increased

presence of glutamate within the synaptic cleft. The GluR1 subunit of AMPAR plays a crucial role in LTP and membrane conductance under normal conditions; however, they have been implicated in progressing neurodegenerative diseases under pathological conditions (Spaethling et al., 2012). Unlike the GluR2 subunit, which limits membrane permeability of Ca^{2+} , phosphorylated GluR1, via Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) and PKC, increases membrane permeability to Ca^{2+} and promotes the upregulation of GluR1 insertion into the membrane and the influx of Ca^{2+} (Isaac et al., 2007). In the context of TBI, *in vitro* stretch models reveal an increase in GluR1 phosphorylation within hours of injury and increased levels of intracellular Ca^{2+} (Spaethling et al., 2008, 2012). Phosphorylation of GluR1 is mediated through NMDAR activity, specifically the NR2B subunit activity, as blocking the NR2B subunit blocked the rise in Ca^{2+} levels and reduced levels of phosphorylated GluR1 in stretched neurons (Spaethling et al., 2012). This has been observed in animal models of TBI, with increased CaMKII autophosphorylation and GluR1 observed within the hippocampus as early as 15 min after using weighted drop controlled cortical impact (CCI; Schumann et al., 2008) and 1 h post FPI (Atkins et al., 2006).

Calcium influx via the activation of NMDAR is crucial for synaptic plasticity and activating various biochemical pathways responsible for neuronal physiology. However, sustained activation of NMDAR promotes pathological secondary cascades which underlie the onset of neurodegenerative diseases (Kalia et al., 2008; Shohami and Biegon, 2014). Within the hyperacute phase of TBI, phosphorylated NR2B levels begin to rise and promote the upregulation of other NMDAR subunits, such as NR1 and NR2A (Schumann et al., 2008). The NR2B subunit is responsible for high influxes on Ca^{2+} into the neuron, with dysregulation of this subunit leading to excitotoxic conditions (Arnsten et al., 2021). In cultured neurons, the loss of functional connectivity is primarily mediated through activation of NR2B subunit (Patel et al., 2014). The NR2B subunit appears to be the focal subunit of potential neurotoxic effects, as administration of inhibiting kinases involved in regulating the receptor reduced the elevated levels of phosphorylated NR2B and improved long term neurological function after trauma (Schumann et al., 2008; Zhou and Sheng, 2013; Patel et al., 2014).

DENDRITIC SPINE CLASSIFICATION

Dendritic spines are the primary site for excitatory synaptic communication between two neurons and their morphology can greatly dictate neural function. Dendritic spines are dynamic in their morphology, constantly shifting between phenotypes depending on the surrounding environment or internal cellular conditions (Hering and Sheng, 2001). The constant remodeling and development of spines is termed spinogenesis with these changes taking place in the time frame of seconds to minutes to days to weeks (Calabrese et al., 2006). The remodeling and retracting of spines is a highly conserved trait across species, with evidence to show spinogenesis rates changing during

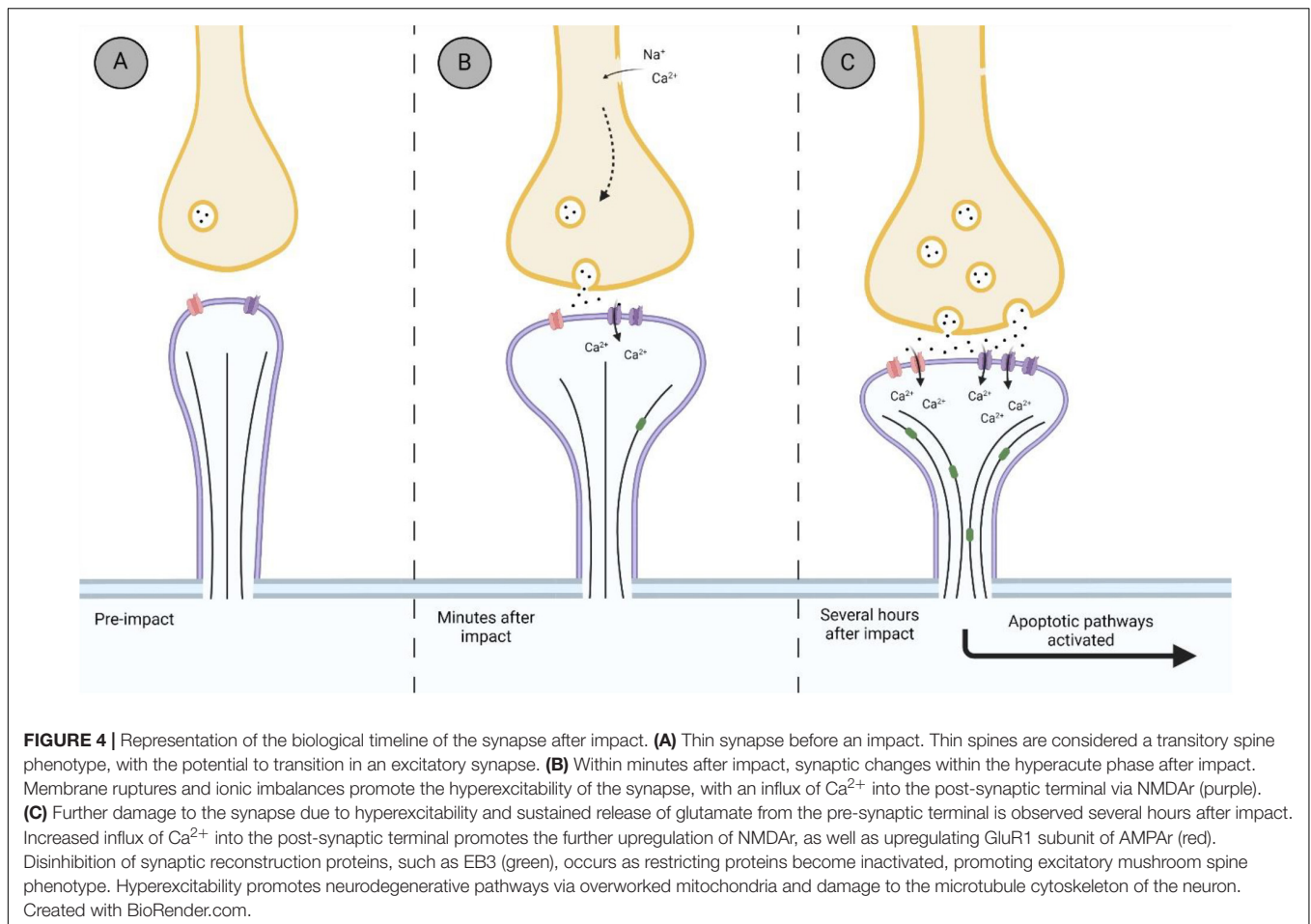
learning and memory (Tønnesen and Nägerl, 2016; Luengo-Sanchez et al., 2018), disease progression (Calabrese et al., 2006; Aguayo et al., 2018; Jamjoom et al., 2021) and naturally with age (Benavides-Piccione et al., 2013).

In their 1970 paper, Peters and Kaiserman-Abramof (1970) described the three main categories of spine type: thin, stubby and mushroom. Thin spines represent a transitory phenotype that are primed to develop into mushroom-type spines through repeated synaptic activity (Pchitskaya and Bezprozvanny, 2020). Stubby spines represent immature spines and are less likely to be a place of synaptic communication between neurons (Helm et al., 2021). Mushroom spines are considered to represent an excitatory synapse and are associated with synaptic plasticity achieved through LTP (Jaworski et al., 2009; Helm et al., 2021). Using modern neuronal reconstruction, Luengo-Sanchez et al. (2018) characterized the spine morphology in human cortical pyramidal neurons using three dimensional meshes on individual spines and quantitative features such as, but not limited to, height, growth direction of the spine, and volume. This group was able to categorize dendritic spines into six distinct clusters based on the Bayesian information criterion, which contained sub-sets of spine shapes based on the authors described criterion. Bokota et al. (2016) produced 10 distinct spine clusters using automatic three-dimensional dendritic spine reconstruction, with each cluster containing a range of spine morphology subsets. While modern imaging techniques show that spine classification exists on a continuum at any one time (Rodriguez et al., 2008; Bokota et al., 2016; Luengo-Sanchez et al., 2018), the categories set forth by Peters and Kaiserman-Abramof (1970) are still widely used to classify spines when performing histological analyses (Figure 3).

Dendritic Spine Physiology

The cytoskeletal filaments within the spine head are made up of an intricate network of actin filaments that form the basis for morphological spine remodeling. These filaments, along with the molecular machinery involved in the dynamics of the spine cytoskeleton, act independently from the machinery in neighboring spines (Newpher and Ehlers, 2009). The ultrastructural changes within a single dendritic spine involve the recruitment of several protein kinase families that regulate actin filament dynamics within the spine head (Meng et al., 2003; Jaworski et al., 2009; Aguayo et al., 2018; Reza-Zaldivar et al., 2020). Lim-kinase (LIMK), for example, is a major family of protein kinases that regulate the shape of dendritic spines and their function and plays a major role in LTP (Meng et al., 2003). Through the influx of Ca^{2+} via NMDAR, CaMKI, and CaMKII stimulate the activity of Rac1. The stimulation of Rac1 has downstream effects of promoting LIMK-1 activity which ultimately leads to actin polymerization and the maintenance of spine morphology [for full review see Saneyoshi et al. (2010)]. The rate in which LIMK-1 is activated and suppressed is achieved by brain derived neurotrophic factor (BDNF) and microRNA-134 (miRNA-134), respectfully, however the exact mechanisms in which this operates is not well understood (Schratt et al., 2006; Saneyoshi et al., 2010; Reza-Zaldivar et al., 2020).

In addition to the regulation of dendritic spine actin, the activity along the synaptic membrane and the scaffolding



proteins that make up the post-synaptic density (PSD) regulate cytoskeletal dynamics of the spine. The PSD is roughly 50 nm wide and is enriched in a wide variety of proteins responsible for synaptic integrity and regulating what enters the neuron (Harris and Kater, 1994). One of the most important synaptic proteins responsible for synaptic stability is PSD-95. PSD-95 is a scaffolding protein responsible for the regulation of AMPAR and NMDAR, as well as neuroligins and neuexins responsible for anchoring the pre-synaptic and post-synaptic terminals together (Keith and El-Husseini, 2008; Jeong et al., 2019). Knockdown models of PSD-95 have shown decreased spine numbers, altered formation of functional synapses and decreased rates of spinogenesis (Jeong et al., 2019). The overexpression of PSD-95 promotes development of excitatory synapses along the dendrite (Levinsoni et al., 2005).

Dendritic Spine Receptors

The basis for synaptic plasticity and LTP involves the movement of ions across the membrane through AMPAR channels and NMDAR channels. NMDAR have been largely implicated in the consequences of excitotoxicity, however there is mounting evidence to suggest the upregulation of the AMPA GluR1 subunit contributes to excitotoxic conditions (for review see Guerriero et al., 2015). AMPAR are the primary fast excitatory

receptor within the nervous system, consisting of 4 subunits, GluR1 to GluR4, which form tetrameric complexes that have distinct receptor binding subtypes. Most AMPAR contain the Ca^{2+} -impermeable GluR2 subunit, however a subset of AMPAR contain the Ca^{2+} -permeable GluR1 subunit (Song and Huganir, 2002). Once glutamate is bound, the pore of the receptor opens allowing for cations (Na^+ and Ca^{2+}) to move across the membrane resulting in depolarization (Chater and Goda, 2014). NMDAR consist of three main subfamilies, GluN1, N2, N3, with multiple subunits within each family. A combination of subfamilies makes up the NMDAR channel, with GluN1 and N2 subunits pairing together, or GluN2 and N3 together. Acting as a coincidence detector, the opening of NMDAR channels requires the depolarization of the neuron as well as the binding of glutamate followed by the removal of the Mg^{2+} ion within the membrane-spanning domain of the channel (Paoletti et al., 2013). Once Mg^{2+} is removed, the NMDAR becomes permeable to Na^+ and Ca^{2+} . NMDAR activation and Ca^{2+} play a crucial role in the LIMK pathway through activating CaMKII and remodeling the actin cytoskeleton of the dendritic spine (Newpher and Ehlers, 2009; Saneyoshi et al., 2010). The influx of Ca^{2+} into the neuron is required for normal cellular functioning through the activation of various enzymes, protein complexes, and immediate early genes (Paoletti et al., 2013). Too large of an influx of Ca^{2+} ,

however, has been established as a main factor in the onset of excitotoxic conditions that put the neuron at risk of cell death, and ultimately the onset of various neurodegenerative diseases.

Cytoskeleton Changes Within the Dendritic Spine After Impact

Within the post-synaptic membrane, the synaptic architecture is stabilized primarily through PSD-95 which is regulated through the activity of NR2B subunits (Szydłowska and Tymianski, 2010; Frank et al., 2016; Jeong et al., 2019). PSD-95 has also been shown to restrict the remodeling of dendrites by mediating the activity of end-binding protein 3 (EB3); a protein responsible for growth and microtubule dynamics (Patel et al., 2019). EB3 is a well conserved member of the EB family responsible for restructuring dendritic spine cytoskeleton, maintenance of excitatory synapses, shuttling organelles into dendritic spines, and has shown to be involved in LTP (Jaworski et al., 2009; Penzes et al., 2009). The activity of PSD-95 is regulated by phosphorylation on cyclin-dependent kinase 5 (cdk5; Keith and El-Husseini, 2008). Park et al. (2013) demonstrated an increase in phosphorylated PSD-93, a similar scaffolding protein to PSD-95, several hours following FPI in the rodent cortex. These proteins are considered deactivated once phosphorylated (Nowacka et al., 2020). This could suggest that following TBI, the disruption of PSD-95/93 allows for the remodeling of the dendrite and spine through proteins such as EB3 (Figure 4), as their activity is no longer inhibited (Patel et al., 2019). Very few studies have investigated the remodeling of dendritic spine morphology post-TBI within the hyperacute phase. Pijet et al. (2019) found that 24 h after CCI, dendritic spines in the ipsilateral cortex became shorter and wider, a characteristic of excitatory mushroom-type spines (Jontes and Smith, 2000). The expression of shorter-wider spines was accompanied by an increase in the matrix metalloproteinase-9 (MMP-9). This extracellular protease has a role in synaptic plasticity as it is present in excitatory synapses within the hippocampus, cerebellum and cerebral cortex (for review see Michaluk and Kaczmarek, 2007). Moreover, inhibition of MMP-9 activity has been shown to make spines resistant to excitotoxic damage from TBI as well as post-impact-induced seizures (Michaluk and Kaczmarek, 2007; Hayashi et al., 2009; Pijet et al., 2019). Expression of MMP-9 has been seen to increase 30 min after TBI, and remaining elevated for hours and days (Wang et al., 2000; Truettner et al., 2005; Hayashi et al., 2009; Pijet et al., 2018). While not reported in Pijet et al. (2018), it would be interesting to see if the increase in MMP-9 expression 30 min after CCI would be accompanied by a change in dendritic spine phenotype, similar to what they found a year later at 24 h after impact.

DAMAGE TO THE DENDRITE OUTSIDE OF THE SPINE HEAD FOLLOWING IMPACT

The large influx of Ca^{2+} that follows TBI activates various downstream pathophysiological cascades that put the neuron at

risk of degeneration. One of these pathways includes alterations to the neuronal microtubule network. Microtubules provide both cytoskeletal structuring to the neuron, as well as act as a “molecular highway” for proteins and organelles to travel throughout the neuron. Calpain is a family of calcium-activated proteases involved in numerous physiological functions ranging from modifications to receptors and channels, activation of apoptotic proteins and regulation of structural proteins (Saatman et al., 2010). The activation of calpain can occur within minutes of injury and be sustained for several days (Saatman et al., 2010). In particular, calpain-2 has been shown to have neurodegenerative consequences several hours post-TBI, as evidence by increased calpain-2 levels correlating with the activation of apoptotic pathways in mice (Wang et al., 2018). Calpain-2 also disrupts microtubule dynamics by phosphorylating tau, the accumulation and aggregation of which has been well documented in the onset of tauopathy's such as chronic traumatic encephalopathy and Alzheimer's disease (Goldstein et al., 2012; Baudry and Bi, 2016; for review see McKee et al., 2013).

Along with activation of neurodegenerative pathways such as calpain-2, the influx of Ca^{2+} that follows a TBI places stress upon the mitochondria of the neuron (Watts et al., 2015). In data not shown, Griesemer and Mautes (2007) noted an increase in adenosine triphosphate levels 1 h post closed head impact, with a decrease occurring by hour 4. Overworked mitochondria fail to buffer the rise in intracellular Ca^{2+} levels and as a result damaging reactive oxygen species, such as H_2O_2 , are created (Vercesi et al., 2018). While these secondary pathophysiological pathways take time to develop, the initial onset of the sequelae begins with a moment of disruption shortly after impact. Further investigations into the hyperacute neuronal responses to TBI will be beneficial in the development of possible therapeutic targets and better understanding of how these chronic diseases initiate.

CONCLUSION

The hyperacute phase that follows TBI has been relatively understudied when it comes to understanding the dynamics of head trauma. The changes at the level of the synapse showcase the disrupted communication between neurons and how it reacts to the change in the environment. These subtle changes at the synapse amplify as further damage occurs, progressing the pathological pathway that is seen in the sub-acute and chronic phases of diseases associated with TBI. Understanding where the biochemical changes begin following head trauma could direct the field of research to the development of effective treatments and therapeutics soon after an impact has occurred.

AUTHOR CONTRIBUTIONS

BH contributed to the research and drafting of manuscript. MRH contributed to the revisions and final approval of manuscript. Both authors contributed to the article and approved the submitted version.

REFERENCES

- Aguayo, F. I., Tejos-Bravo, M., Díaz-Véliz, G., Pacheco, A., García-Rojo, G., Corrales, W., et al. (2018). Hippocampal Memory Recovery After Acute Stress: A Behavioral, Morphological and Molecular Study. *Front. Mol. Neurosci.* 11:283. doi: 10.3389/fnmol.2018.00283
- Ahmed, W. W., Li, T. C., Rubakhin, S. S., Chiba, A., Sweedler, J. V., and Saif, T. A. (2012). Mechanical tension modulates local and global vesicle dynamics in neurons. *Cell. Mol. Bioengine.* 2012, 155–164. doi: 10.1007/s12195-012-0223-1
- Albayram, O., Albayram, S., and Mannix, R. (2020). Chronic traumatic encephalopathy—a blueprint for the bridge between neurological and psychiatric disorders. *Transl. Psychiatry* 10:424. doi: 10.1038/s41398-020-01111-x
- Arnsten, A. F. T., Datta, D., and Preuss, T. M. (2021). Studies of aging nonhuman primates illuminate the etiology of early-stage Alzheimer's-like neuropathology: An evolutionary perspective. *Am. J. Primatol.* 83:23254. doi: 10.1002/ajp.23254
- Atkins, C. M., Chen, S., Alonso, O. F., Dietrich, D., and Hu, B.-R. (2006). Activation of calcium/calmodulin-dependent protein kinases after traumatic brain injury. *J. Cereb. Blood Flow Metab.* 26, 1507–1518. doi: 10.1038/sj.jcbfm.9600301
- Balosso, S., Liu, J., Bianchi, M. E., and Vezzani, A. (2014). Disulfide-containing high mobility group box-1 promotes N-methyl-d-aspartate receptor function and excitotoxicity by activating toll-like receptor 4-dependent signaling in hippocampal neurons. *Antioxid. Redox Signal.* 21, 1726–1740. doi: 10.1089/ars.2013.5349
- Baudry, M., and Bi, X. (2016). Calpain-1 and Calpain-2: The Yin and Yang of Synaptic Plasticity and Neurodegeneration. *Trends Neurosci.* 39, 235–245. doi: 10.1016/j.tins.2016.01.007
- Benavides-Piccione, R., Feraud-Espinosa, I., Robles, V., Yuste, R., and DeFelipe, J. (2013). Age-Based Comparison of Human Dendritic Spine Structure Using Complete Three-Dimensional Reconstructions. *Cereb. Cortex* 23:1798. doi: 10.1093/CERCOR/BHS154
- Berger, M., Speckmann, E. J., Pape, H. C., and Gorji, A. (2008). Spreading depression enhances human neocortical excitability in vitro. *Cephalalgia* 28, 558–562. doi: 10.1111/j.1468-2982.2008.01556.x
- Boersma, M. C. H., Dresselhaus, E. C., de Biase, L. M., Mihalas, A. B., Bergles, D. E., and Meffert, M. K. (2011). A requirement for nuclear factor- κ B in developmental and plasticity-associated synaptogenesis. *J. Neurosci.* 31, 5414–5425. doi: 10.1523/JNEUROSCI.2456-10.2011
- Bokota, G., Magnowska, M., Kuśmierczyk, T., Łukasik, M., Roszkowska, M., and Piewczynski, D. (2016). Computational approach to dendritic spine taxonomy and shape transition analysis. *Front. Comput. Neurosci.* 10:140. doi: 10.3389/fncom.2016.00140
- Bourne, J., and Harris, K. M. (2007). Do thin spines learn to be mushroom spines that remember? *Curr. Opin. Neurobiol.* 17, 381–386. doi: 10.1016/j.conb.2007.04.009
- Calabrese, B., Wilson, M. S., and Halpain, S. (2006). Development and regulation of dendritic spine synapses. *Physiology* 21, 38–47. doi: 10.1152/physiol.00042.2005
- Carlson, S. W., Yan, H., Ma, M., Li, Y., Henchir, J., and Dixon, C. E. (2016). Traumatic brain injury impairs soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex formation and alters synaptic vesicle distribution in the hippocampus. *J. Neurotrauma* 33, 113–121. doi: 10.1089/neu.2014.3839
- Chater, T. E., and Goda, Y. (2014). The role of AMPA receptors in postsynaptic mechanisms of synaptic plasticity. *Front. Cell. Neurosci.* 8:401. doi: 10.3389/fncel.2014.00401
- Chen, F., Chen, H., Chen, Y., Wei, W., Sun, Y., Zhang, L., et al. (2021). Dysfunction of the SNARE complex in neurological and psychiatric disorders. *Pharmacol. Res.* 165, 1043–6618. doi: 10.1016/j.phrs.2021.105469
- Chen, K., Baram, T. Z., and Soltesz, I. (1999). Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits. *Nat. Med.* 5, 888–894. doi: 10.1038/11330
- Cohen, A. S., Pfister, B. J., Schwarzbach, E., Sean Grady, M., Goforth, P. B., and Satin, L. S. (2007). Injury-induced alterations in CNS electrophysiology. *Prog. Brain Res.* 161, 143–169. doi: 10.1016/S0079-6123(06)61010-8
- D'Ambrosio, R., Maris, D. O., Grady, M. S., Winn, H. R., and Janigro, D. (1998). Selective loss of hippocampal long-term potentiation, but not depression, following fluid percussion injury. *Brain Res.* 786, 64–79. doi: 10.1016/S0006-8993(97)01412-1
- D'Ambrosio, R., Maris, D. O., Grady, M. S., Winn, H. R., and Janigro, D. (1999). Impaired K⁺ homeostasis and altered electrophysiological properties of post-traumatic hippocampal gila. *J. Neurosci.* 19, 8152–8162. doi: 10.1523/jneurosci.19-18-08152.1999
- Ding, M. C., Wang, Q., Lo, E. H., and Stanley, G. B. (2011). Cortical excitation and inhibition following focal traumatic brain injury. *J. Neurosci.* 31, 14085–14094. doi: 10.1523/JNEUROSCI.3572-11.2011
- Drexel, M., Puhakka, N., Kirchmair, E., Hörtnagl, H., Pitkänen, A., and Sperk, G. (2015). Expression of GABA receptor subunits in the hippocampus and thalamus after experimental traumatic brain injury. *Neuropharmacology* 88, 122–133. doi: 10.1016/j.neuropharm.2014.08.023
- Faden, A. I., Demediuk, P., Panter, S. S., and Vink, R. (1989). The role of excitatory amino acids and NMDA receptors in traumatic brain injury. *Science* 244, 798–800. doi: 10.1126/science.2567056
- Folkersma, H., Foster Dingley, J. C., van Berckel, B. N. M., Rozemuller, A., Boellaard, R., Huisman, M. C., et al. (2011). Increased cerebral (R)-[11C]PK11195 uptake and glutamate release in a rat model of traumatic brain injury: A longitudinal pilot study. *J. Neuroinflamm.* 8:67. doi: 10.1186/1742-2094-8-67
- Frank, R. A. W., Komiyama, N. H., Ryan, T. J., Zhu, F., O'Dell, T. J., and Grant, S. G. N. (2016). NMDA receptors are selectively partitioned into complexes and supercomplexes during synapse maturation. *Nat. Commun.* 7:ncmms11264. doi: 10.1038/ncomms11264
- Goldstein, L. E., Fisher, A. M., Tagge, C. A., Zhang, X. L., Velisek, L., Sullivan, J. A., et al. (2012). Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci. Transl. Med.* 4:134ra60. doi: 10.1126/scitranslmed.3003716
- Goldstein, L. E., McKee, A. C., and Stanton, P. K. (2014). Considerations for animal models of blast-related traumatic brain injury and chronic traumatic encephalopathy. *Alzheimers. Res. Ther.* 6:64. doi: 10.1186/s13195-014-0064-3
- González-Tapia, D., Martínez-Torres, N. I., Hernández-González, M., Guevara, M. A., and González-Burgos, I. (2016). Plastic changes to dendritic spines on layer V pyramidal neurons are involved in the rectifying role of the prefrontal cortex during the fast period of motor learning. *Behav. Brain Res.* 298, 261–267. doi: 10.1016/j.bbr.2015.11.013
- Griesemer, D., and Mauter, A. M. (2007). Closed head injury causes hyperexcitability in rat hippocampal CA1 but not in CA3 pyramidal cells. *J. Neurotrauma* 24, 1823–1832. doi: 10.1089/neu.2006.0237
- Guerriero, R. M., Giza, C. C., and Rotenberg, A. (2015). Glutamate and GABA Imbalance Following Traumatic Brain Injury. *Curr. Neurol. Neurosci. Rep.* 15:1. doi: 10.1007/s11910-015-0545-1
- Hackett, J. T., and Ueda, T. (2015). Glutamate Release. *Neurochem. Res.* 40, 2443–2460. doi: 10.1007/s11064-015-1622-1
- Harris, K. M., and Kater, S. B. (1994). Dendritic spines: Cellular specializations imparting both stability and flexibility to synaptic function. *Annu. Rev. Neurosci.* 17, 341–371. doi: 10.1146/annurev.ne.17.030194.002013
- Hayashi, T., Kaneko, Y., Yu, S. J., Bae, E. K., Stahl, C. E., Kawase, T., et al. (2009). Quantitative analysis of matrix metalloproteinase activity after traumatic brain injury in adult rats. *Brain Res.* 1280, 172–177. doi: 10.1016/j.brainres.2009.05.040
- Helm, M. S., Dankovich, T. M., Mandad, S., Rammner, B., Jähne, S., Salimi, V., et al. (2021). A large-scale nanoscopy and biochemistry analysis of postsynaptic dendritic spines. *Nat. Neurosci.* 24, 1151–1162. doi: 10.1038/s41593-021-00874-w
- Hering, H., and Sheng, M. (2001). Dendritic spines: structure, dynamics and regulation. *Nat. Rev. Neurosci.* 2, 880–888. doi: 10.1038/35104061
- Hermes, J., and Dorostkar, M. M. (2016). Dendritic Spine Pathology in Neurodegenerative Diseases. *Annu. Rev. Pathol. Mech. Dis.* 11, 221–250. doi: 10.1146/annurev-pathol-012615-044216
- Isaac, J. T. R., Ashby, M., and McBain, C. J. (2007). The Role of the GluR2 Subunit in AMPA Receptor Function and Synaptic Plasticity. *Neuron* 54, 859–871. doi: 10.1016/j.neuron.2007.06.001
- Jamjoom, A. A. B., Rhodes, J., Andrews, P. J. D., and Grant, S. G. N. (2021). The synapse in traumatic brain injury. *Brain* 144, 18–31. doi: 10.1093/brain/awaa321
- Jaworski, J., Kapitein, L. C., Gouveia, S. M., Dortland, B. R., Wulf, P. S., Grigoriev, I., et al. (2009). Dynamic Microtubules Regulate Dendritic Spine Morphology and Synaptic Plasticity. *Neuron* 61, 85–100. doi: 10.1016/j.neuron.2008.11.013

- Jeong, J., Pandey, S., Li, Y., Badger, J. D., Lu, W., and Roche, K. W. (2019). PSD-95 binding dynamically regulates NLGN1 trafficking and function. *Proc. Natl. Acad. Sci. U S A* 116, 12035–12044. doi: 10.1073/pnas.1821775116
- Jontes, J. D., and Smith, S. J. (2000). Filopodia, Spines, and the Generation of Synaptic Diversity. *Neuron* 27, 11–14. doi: 10.1016/s0896-6273(00)00003-9
- Kaesler, P. S., and Regehr, W. G. (2017). The readily releasable pool of synaptic vesicles. *Curr. Opin. Neurobiol.* 43, 63–70. doi: 10.1016/j.conb.2016.12.012
- Kalia, L. V., Kalia, S. K., and Salter, M. W. (2008). NMDA receptors in clinical neurology: excitatory times ahead. *Lancet Neurol.* 7, 742–755. doi: 10.1016/S1474-4422(08)70165-0
- Katayama, Y., Becker, D. P., Tamura, T., and Hovda, D. A. (1990). Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J. Neurosurg.* 73, 889–900. doi: 10.3171/jns.1990.73.6.0889
- Keith, D., and El-Husseini, A. (2008). Excitation control: Balancing PSD-95 function at the synapse. *Front. Mol. Neurosci.* 1:4. doi: 10.3389/fnmo.2008.02.004
- Korgaonkar, A. A., Li, Y., Sekhar, D., Subramanian, D., Guevarra, J., Swietek, B., et al. (2020). Toll-like Receptor 4 Signaling in Neurons Enhances Calcium-Permeable α -Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor Currents and Drives Post-Traumatic Epileptogenesis. *Ann. Neurol.* 87, 497–515. doi: 10.1002/ana.25698
- Levinsoni, J. N., Chéry, N., Huang, K., Wong, T. P., Gerrow, K., Kang, R., et al. (2005). Neuroligins mediate excitatory and inhibitory synapse formation: Involvement of PSD-95 and neuexin-1 β in neuroigin-induced synaptic specificity. *J. Biol. Chem.* 280, 17312–17319. doi: 10.1074/jbc.M413812200
- Li, Y., Korgaonkar, A. A., Swietek, B., Wang, J., Elgammal, F. S., Elkabes, S., et al. (2015). Toll-like receptor 4 enhancement of non-NMDA synaptic currents increases dentate excitability after brain injury. *Neurobiol. Dis.* 74, 240–253. doi: 10.1016/j.nbd.2014.11.021
- Luengo-Sanchez, S., Fernaud-Espinosa, I., Bielza, C., Benavides-Piccione, R., Larrañaga, P., and DeFelipe, J. (2018). 3D morphology-based clustering and simulation of human pyramidal cell dendritic spines. *PLoS Comput. Biol.* 14:1006221. doi: 10.1371/journal.pcbi.1006221
- MacFarlane, M. P., and Glenn, T. C. (2015). Neurochemical cascade of concussion. *Brain Inj.* 29, 139–153. doi: 10.3109/02699052.2014.965208
- MacKenzie, G., and Maguire, J. (2015). Chronic stress shifts the GABA reversal potential in the hippocampus and increases seizure susceptibility. *Epilepsy Res.* 109, 13–27. doi: 10.1016/j.eplepsyres.2014.10.003
- Magou, G. C., Pfister, B. J., and Berlin, J. R. (2015). Effect of acute stretch injury on action potential and network activity of rat neocortical neurons in culture. *Brain Res.* 1624, 525–535. doi: 10.1016/j.brainres.2015.07.056
- McKee, A. C., Stein, T. D., Nowinski, C. J., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., et al. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136, 43–64. doi: 10.1093/brain/aww307
- Meng, Y., Zhang, Y., Tregubov, V., Falls, D. L., and Jia, Z. (2003). Regulation of spine morphology and synaptic function by LIMK and the actin cytoskeleton. *Rev. Neurosci.* 14, 233–240. doi: 10.1515/REVNEURO.2003.14.3.233
- Michaluk, P., and Kaczmarek, L. (2007). Matrix metalloproteinase-9 in glutamate-dependent adult brain function and dysfunction. *Cell Death Differ.* 14, 1255–1258. doi: 10.1038/sj.cdd.4402141
- Newpher, T. M., and Ehlers, M. D. (2009). Spine microdomains for postsynaptic signaling and plasticity. *Trends Cell Biol.* 19, 218–227. doi: 10.1016/j.tcb.2009.02.004
- Nowacka, A., Borczyk, M., Salamian, A., Wójtowicz, T., Włodarczyk, J., and Radwanska, K. (2020). PSD-95 Serine 73 phosphorylation is not required for induction of NMDA-LTD. *Sci. Rep.* 10, 1–11. doi: 10.1038/s41598-020-58989-2
- Noye Tuplin, E. W., and Holahan, M. R. (2019). Exploring time-dependent changes in conditioned place preference for food reward and associated changes in the nucleus accumbens. *Behav. Brain Res.* 361, 14–25. doi: 10.1016/j.bbr.2018.12.031
- Nusser, Z., Hájos, N., Somogyi, P., and Mody, I. (1998). Increased number of synaptic GABA(A) receptors underlies potentiation at hippocampal inhibitory synapses. *Nature* 395, 172–177. doi: 10.1038/25999
- Olmos, G., and Lladó, J. (2014). Tumor necrosis factor alpha: A link between neuroinflammation and excitotoxicity. *Mediators Inflamm.* 2014:861231. doi: 10.1155/2014/861231
- Omalu, B. I., DeKosky, S. T., Minster, R. L., Kamboh, M. I., Hamilton, R. L., and Wecht, C. H. (2005). Chronic traumatic encephalopathy in a National Football League player. *Neurosurgery* 57, 128–133. doi: 10.1227/01.NEU.0000163407.92769.ED
- Paoletti, P., Bellone, C., and Zhou, Q. (2013). NMDA receptor subunit diversity: Impact on receptor properties, synaptic plasticity and disease. *Nat. Rev. Neurosci.* 14, 383–400. doi: 10.1038/nrn3504
- Park, Y., Luo, T., Zhang, F., Liu, C., Bramlett, H. M., Dalton Dietrich, W., et al. (2013). Downregulation of Src-kinase and glutamate-receptor phosphorylation after traumatic brain injury. *J. Cereb. Blood Flow Metab.* 33, 1642–1649. doi: 10.1038/jcbfm.2013.121
- Patel, M. V., Sewell, E., Dickson, S., Kim, H., Meaney, D. F., and Firestein, B. L. (2019). A Role for Postsynaptic Density 95 and Its Binding Partners in Models of Traumatic Brain Injury. *J. Neurotrauma* 36, 2129–2138. doi: 10.1089/neu.2018.6291
- Patel, T. P., Ventre, S. C., Geddes-Klein, D., Singh, P. K., and Meaney, D. F. (2014). Single-neuron NMDA receptor phenotype influences neuronal rewiring and reintegration following traumatic injury. *J. Neurosci.* 34, 4200–4213. doi: 10.1523/JNEUROSCI.4172-13.2014
- Patterson, Z. R., and Holahan, M. R. (2012). Understanding the neuroinflammatory response following concussion to develop treatment strategies. *Front. Cell. Neurosci.* 6:58. doi: 10.3389/fncl.2012.00058
- Pchitskaya, E., and Bezprozvanny, I. (2020). Dendritic Spines Shape Analysis—Classification or Clusterization? Perspective. *Front. Synaptic Neurosci.* 12:31. doi: 10.3389/fnsyn.2020.00031
- Penzes, P., Srivastava, D. P., and Woolfrey, K. M. (2009). Not Just Actin? A Role for Dynamic Microtubules in Dendritic Spines. *Neuron* 61, 3–5. doi: 10.1016/j.neuron.2008.12.018
- Peters, A., and Kaiserman-Abramof, I. R. (1970). The small pyramidal neuron of the rat cerebral cortex. The perikaryon, dendrites and spines. *Am. J. Anat.* 127, 321–355. doi: 10.1002/aja.1001270402
- Pijet, B., Stefaniuk, M., and Kaczmarek, L. (2019). MMP-9 contributes to dendritic spine remodeling following traumatic brain injury. *Neural Plast.* 2019, 42–45. doi: 10.1155/2019/3259295
- Pijet, B., Stefaniuk, M., Kostrzewska-Ksiezyk, A., Tsilibary, P. E., Tzinia, A., and Kaczmarek, L. (2018). Elevation of MMP-9 Levels Promotes Epileptogenesis After Traumatic Brain Injury. *Mol. Neurobiol.* 55, 9294–9306. doi: 10.1007/s12035-018-1061-5
- Raible, D. J., Frey, L. C., Cruz Del Angel, Y., Russek, S. J., and Brooks-Kayal, A. R. (2012). GABAA receptor regulation after experimental traumatic brain injury. *J. Neurotrauma* 29, 2548–2554. doi: 10.1089/neu.2012.2483
- Reza-Zaldivar, E. E., Hernández-Sápiens, M. A., Minjarez, B., Gómez-Pinedo, U., Sánchez-González, V. J., Márquez-Aguirre, A. L., et al. (2020). Dendritic Spine and Synaptic Plasticity in Alzheimer's Disease: A Focus on MicroRNA. *Front. Cell Dev. Biol.* 8:255. doi: 10.3389/fcell.2020.00255
- Rodriguez, A., Ehlenberger, D. B., Dickstein, D. L., Hof, P. R., and Wearne, S. L. (2008). Automated three-dimensional detection and shape classification of dendritic spines from fluorescence microscopy images. *PLoS One* 3:1997. doi: 10.1371/journal.pone.0001997
- Ross, S. T., and Soltesz, I. (2000). Selective depolarization of interneurons in the early posttraumatic dentate gyrus: Involvement of the Na⁺/K⁺-ATPase. *J. Neurophysiol.* 83, 2916–2930. doi: 10.1152/jn.2000.83.5.2916
- Saatman, K. E., Creed, J., and Raghupathi, R. (2010). Calpain as a Therapeutic Target in Traumatic Brain Injury. *Neurotherapeutics* 7, 31–42. doi: 10.1016/j.nurt.2009.11.002
- Saneyoshi, T., Fortin, D. A., and Soderling, T. R. (2010). Regulation of spine and synapse formation by activity-dependent intracellular signaling pathways. *Curr. Opin. Neurobiol.* 20, 108–115. doi: 10.1016/j.conb.2009.09.013
- Schratt, G. M., Tuebing, F., Nigh, E. A., Kane, C. G., Sabatini, M. E., Kiebler, M., et al. (2006). A brain-specific microRNA regulates dendritic spine development. *Nature* 439, 283–289. doi: 10.1038/nature04367
- Schumann, J., Alexandrovich, G. A., Biegon, A., and Yaka, R. (2008). Inhibition of NR2B phosphorylation restores alterations in NMDA receptor expression and improves functional recovery following traumatic brain injury in mice. *J. Neurotrauma* 25, 945–957. doi: 10.1089/neu.2008.0521
- Shohami, E., and Biegon, A. (2014). Novel Approach to the Role of NMDA Receptors in Traumatic Brain Injury. *CNS Neurol. Disord. Drug Targets* 13, 567–573. doi: 10.2174/18715273113126660196

- Siedler, D. G., Chuah, M. I., Kirkcaldie, M. T. K., Vickers, J. C., and King, A. E. (2014). Diffuse axonal injury in brain trauma: Insights from alterations in neurofilaments. *Front. Cell. Neurosci.* 8:429. doi: 10.3389/fncel.2014.00429
- Sitcheran, R., Gupta, P., Fisher, P. B., and Baldwin, A. S. (2005). Positive and negative regulation of EAAT2 by NF- κ B: A role for N-myc in TNF α -controlled repression. *EMBO J.* 24, 510–520. doi: 10.1038/sj.emboj.7600555
- Smith, D. H., Wolf, J. A., Lusardi, T. A., Lee, V. M. Y., and Meaney, D. F. (1999). High tolerance and delayed elastic response of cultured axons to dynamic stretch injury. *J. Neurosci.* 19, 4263–4269. doi: 10.1523/jneurosci.19-11-04263.1999
- Smith, J. A., Das, A., Ray, S. K., and Banik, N. L. (2012). Role of pro-inflammatory cytokines released from microglia in neurodegenerative diseases. *Brain Res. Bull.* 87, 10–20. doi: 10.1016/j.brainresbull.2011.10.004
- Song, I., and Haganir, R. L. (2002). Regulation of AMPA receptors during synaptic plasticity. *Trends Neurosci.* 25, 578–588. doi: 10.1016/S0166-2236(02)02270-1
- Spaethling, J. M., Klein, D. M., Singh, P., and Meaney, D. F. (2008). Calcium-permeable AMPA receptors appear in cortical neurons after traumatic mechanical injury and contribute to neuronal fate. *J. Neurotrauma* 2008, 1207–1216. doi: 10.1089/neu.2008.0532
- Spaethling, J., Le, L., and Meaney, D. F. (2012). NMDA receptor mediated phosphorylation of GluR1 subunits contributes to the appearance of calcium-permeable AMPA receptors after mechanical stretch injury. *Neurobiol. Dis.* 46, 646–654. doi: 10.1016/j.nbd.2012.03.003
- Stellwagen, D., Beattie, E. C., Seo, J. Y., and Malenka, R. C. (2005). Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor- α . *J. Neurosci.* 25, 3219–3228. doi: 10.1523/JNEUROSCI.4486-04.2005
- Szydłowska, K., and Tymianski, M. (2010). Calcium, ischemia and excitotoxicity. *Cell Calcium* 47, 122–129. doi: 10.1016/j.ceca.2010.01.003
- Tønnesen, J., and Nägerl, U. V. (2016). Dendritic spines as tunable regulators of synaptic signals. *Front. Psychiatry* 7:101. doi: 10.3389/fpsy.2016.00101
- Toth, Z., Hollrigel, G. S., Gorcs, T., and Soltesz, I. (1997). Instantaneous perturbation of dentate interneuronal networks by a pressure wave-transient delivered to the neocortex. *J. Neurosci.* 17, 8106–8117. doi: 10.1523/jneurosci.17-21-08106.1997
- Truettner, J. S., Alonso, O. F., and Dietrich, W. D. (2005). Influence of therapeutic hypothermia on matrix metalloproteinase activity after traumatic brain injury in rats. *J. Cereb. Blood Flow Metab.* 25, 1505–1516. doi: 10.1038/sj.jcbfm.9600150
- Vaure, C., and Liu, Y. (2014). A comparative review of toll-like receptor 4 expression and functionality in different animal species. *Front. Immunol.* 5:316. doi: 10.3389/fimmu.2014.00316
- Vercesi, A. E., Castilho, R. F., Kowaltowski, A. J., de Oliveira, H. C. F., de Souza-Pinto, N. C., Figueira, T. R., et al. (2018). Mitochondrial calcium transport and the redox nature of the calcium-induced membrane permeability transition. *Free Radic. Biol. Med.* 129, 1–24. doi: 10.1016/j.freeradbiomed.2018.08.034
- Wang, X., Jung, J., Asahi, M., Chwang, W., Russo, L., Moskowitz, M. A., et al. (2000). Effects of matrix metalloproteinase-9 gene knock-out on morphological and motor outcomes after traumatic brain injury. *J. Neurosci.* 20, 7037–7042. doi: 10.1523/jneurosci.20-18-07037.2000
- Wang, Y., Liu, Y., Lopez, D., Lee, M., Dayal, S., Hurtado, A., et al. (2018). Protection against TBI-Induced Neuronal Death with Post-Treatment with a Selective Calpain-2 Inhibitor in Mice. *J. Neurotrauma* 35, 105–117. doi: 10.1089/neu.2017.5024
- Watts, L. T., Shen, Q., Deng, S., Chemello, J., and Duong, T. Q. (2015). Manganese-Enhanced Magnetic Resonance Imaging of Traumatic Brain Injury. *J. Neurotrauma* 32, 1001–1010. doi: 10.1089/neu.2014.3737
- Weber, J. T. (2012). Altered calcium signaling following traumatic brain injury. *Front. Pharmacol.* 3:60. doi: 10.3389/fphar.2012.0060
- Wojnarowicz, M. W., Fisher, A. M., Minaeva, O., and Goldstein, L. E. (2017). Considerations for experimental animal models of concussion, traumatic brain injury, and chronic traumatic encephalopathy—these matters matter. *Front. Neurol.* 8:240. doi: 10.3389/fneur.2017.00240
- Wolf, J. A., Stys, P. K., Lusardi, T., Meaney, D., and Smith, D. H. (2001). Traumatic axonal injury induces calcium influx modulated by tetrodotoxin-sensitive sodium channels. *J. Neurosci.* 21, 1923–1930. doi: 10.1523/jneurosci.21-06-01923.2001
- Xiong, Y., Mahmood, A., and Chopp, M. (2018). Current understanding of neuroinflammation after traumatic brain injury and cell-based therapeutic opportunities. *Chinese J. Traumatol. English Ed.* 21, 137–151. doi: 10.1016/j.cjtee.2018.02.003
- Xiong, Y., Mahmood, A., and Chopp, M. (2019). Remodeling dendritic spines for treatment of traumatic brain injury. *Neural Regen. Res.* 14, 1477–1480. doi: 10.4103/1673-5374.255957
- Zhou, Q., and Sheng, M. (2013). NMDA receptors in nervous system diseases. *Neuropharmacology* 74, 69–75. doi: 10.1016/j.neuropharm.2013.03.030

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Hoffe and Holahan. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.