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Animal models of post-traumatic epilepsy and their neurobehavioral comorbidities

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ABSTRACT

Traumatic brain injury (TBI) is defined as a disturbance in brain functioning caused by an external force. The development of post traumatic epilepsy (PTE) is a serious risk associated with TBI. Indeed, other neurological impairments are also common following TBI. In this review, we analyze and discuss the most widely used and best validated rodent models of TBI, with a particular focus on their contribution to the understanding of the PTE development. Furthermore, we explore the importance of these models for the study of other neurobehavioral comorbidities associated with brain injury. The efficient and accurate diagnosis of epilepsy and other neurological comorbidities as a consequence of brain trauma should improve the survival and quality of life of patients after TBI.

1. Traumatic brain injury and post-traumatic epilepsy

Traumatic brain injury (TBI) is defined as a disruption of brain functioning, or other brain pathology, caused by an external force [1]. The TBI is typically accompanied by one or more clinical signs immediately following the injury; including lost or altered consciousness, amnesia, neurologic deficit, intracranial lesion, and seizures [2]. Seizures produced by TBI can be classified as: (1) acute seizures, which occur less than 24 h after injury; (2) early seizures, which occur less than 1 week after injury; and (3) late seizures, which occur more than a week after injury and are constituents of a post-traumatic epilepsy (PTE) diagnosis [3–7].

1.1. Epidemiology

The incidence of PTE is highest among young adults as they are more prone to head injury [8,9]. However, the rate of unprovoked seizures and PTE development decreases in children but increases in the elderly populations (>65 years old) [8,10]. PTE represents 20% of symptomatic epilepsy in the general population and 5% of all epilepsy patients referred to specialized epilepsy centers [8,11,12]. It has been well-established that the incidence of PTE increases with the severity of TBI [9]. For example, in head injury-military veterans with penetrating injuries, the incidence of PTE is higher (up to 50%) compared with the general population [13]. After the injury, the incidence of acute seizures ranges from 1% to 4%, early seizures 4% to 25%, and depending on the sample series, late seizures 1.9% to >30% [9,13–15]. Approximately, 80% of individuals with PTE experience their first seizure within the first 12 months post-injury and more than 90% by the end of the second year [16].

1.2. Common comorbidities

Mortality risk associated with PTE has been widely studied, as it was reported that patients experiencing TBI have up to 10 times higher risks of death by respiratory, digestive, or neurologic disorders [17,18]. Further, it was shown that individuals that suffered a TBI have up to 50 times higher probability of mortality due to seizures compared to the general population [19]. Although presently, the number of studies that evaluate the effects of PTE beyond mortality is limited. It has been shown that patients that survived after TBI frequently have higher risks of developing disabilities and comorbidities in the long term. These associated secondary effects could negatively affect the quality of life of the patients [20]. Consequently, subjects with PTE would be less likely

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to return to ordinary lives compared to those without PTE.

Depending on the neuronal networks affected by the injury, the PTE can co-occur with one or more comorbidities, such as anxiety, mood disorders, post-traumatic stress disorder (PTSD), personality alteration, cognitive changes, chronic pain, sleep difficulties, moto-sensory impairments, endocrine alteration, gastrointestinal disturbances, increase risk of infections, pulmonary dysfunction, and Parkinson's disease [21]. Evidence shows that cerebrovascular diseases are common in patients with PTE; in contrast, dementia and violent behavior are more associated with patients without PTE, specifically in young patients [17,22]. Cognitive and psychosocial performance can be significantly impaired in the patients after developing PTE. Liu et al. [23] published a retrospective study in humans with PTE and found a significant decrease in the Self-Rating Depression Scale and the Self-Rating Anxiety Scale in people with PTE compared with a control group. Importantly, factors such as anxiety, therapeutic compliance, depression, poor control of epileptic seizure, and the site of trauma influenced Liu et al.'s conclusion [23]. Additionally, there is evidence that PTE can predict anxiety and depression for up to 2 years after TBI [23]. The existence of these neurological comorbidities after TBI could be the result of shared biomolecular pathways, psychological adjustment, or psychological trauma of the patients after experiencing seizures and their associated events [24]. Another possible mechanism involved in the bidirectional connection between epilepsy and other neurological disorders include the effects of stress on seizure thresholds. Multiple studies suggest that stress precipitates the seizures in patients with epilepsy [25–29]. The elevation of corticotropin releasing hormone and corticosterone has been shown to increase seizure susceptibility by altering GABAergic neurotransmission [30], as well as presenting as a risk factor of PTSD [31].

A particularly valuable group in which to study PTE and its sequelae are the survivors of military injury, since the highest incidences of PTE are in this population (32% to 53%). In general, the military population consists of healthy young people who are epilepsy-free before their injury and are without a history of neurological disorders [32]. In a long-term follow up study in Vietnam War veterans who suffered penetrating brain injuries, the patients with PTE performed more poorly on cognitive tasks, were more depressed, and were more poorly adjusted than the head-injured patients without PTE; both did more poorly than uninjured controls [32,33]. In a different study using the same population, the relationship between seizure subtype and interictal changes in personality was evaluated. Results showed that patients with focal impaired awareness or generalized seizures as a group showed significant increases in psychopathology compared to uninjured controls. However, there were no significant differences between seizure subtypes [34].

2. Animal models of post-traumatic epilepsy

2.1. Fluid percussion injury (FPI)

The fluid percussion injury (FPI) is the most extensively utilized and highly studied animal model of TBI [35]. The FPI induces a mixed focal-diffuse brain injury pattern that models human closed-head TBI [35–37] and triggers many neurobiological alterations, including neuronal death, gliosis, axonal sprouting, and neurogenesis. All of these contribute to the circuitry reorganization strongly associated with the development of PTE [35,38,39]. Many studies in rodents have shown that lateral FPI (LFPI) increases the seizure susceptibility and production of spontaneous epileptiform discharges when a proconvulsive chemical is administered [40,41]. In rats, a single severe LFPI is sufficient to induce spontaneous chronic seizures evidenced by intracortical EEG recordings and behavioral manifestations [40,42].

2.1.1. LFPI protocol

The LFPI was originally described by McIntosh et al. in 1989 [43]. Under anesthesia, a 3 or 5 mm craniectomy is performed in the lateral cortex of the rat (centered from bregma: AP −4.5 mm and 2.5 lateral to midline). Then, a modified Luer-Lock syringe cap is anchored over the craniectomy and set with dental acrylate. The injury hub is filled with saline solution (0.9%) and the injury is induced with a fluid-percussion device (pendulum device). A range of pressure pulses may be delivered with low magnitude injury at 1.5 atmospheres (atm) pressure pulse lasting 20 ms in duration and high magnitude injury at 3–3.4 atm pressure pulse lasting 20 ms in duration [44]. Then, the injury cap is removed, the scalp sutured, and the animals are returned to their home cages for recovery.

2.1.2. Post-traumatic epilepsy expression

Acute EEG seizures associated with freezing behavior or episodes of non-convulsive status epilepticus have been recorded during the first 7 days after severe LFPI in rats [45,46]. Studies have shown that severe LFPI triggers epileptogenesis in adult rats that culminates in the occurrence of spontaneous seizures [38,39]. These studies showed that 43% to 50% of injured animals developed epilepsy, with a latency period between 7 weeks to 1 year after the insult. The mean seizure frequency was 0.3 ± 0.2 seizures per day and mean seizure duration was 113 ± 46 s. Behavioral seizure severity increased over time in the majority of animals. Focal to bilateral seizures comprised an average of $66\% \pm 37\%$ of all seizures [39].

The process by which FPI induces epileptogenesis is not well understood. Studies in rats after mild to severe LFPI (2.5 - 3.1 atm) show acute and progressive tissue loss in vulnerable brain regions including cortex, hippocampus, thalamus, and medial septum for up to one year [35,47,48]. The neuronal damage occurs more prominently in the region ipsilateral to the injury. However, some studies have shown that the pathology could extend into the brainstem or contralateral hemisphere [48–51], where hippocampal atrophy and hilar neuronal loss have been demonstrated [51].

2.1.3. Other associated neurobehavioral disorders

Immediately after LFPI, injured animals present a suppression of neurological reflexes which have been demonstrated using tests of neuromotor function such as the beam balance, beam walk, rotarod, and inclined plane tests [52,53]. Using the Morris water maze, impairment in memory is observed [48,54,55], and spatial learning deficits are detectable up to one year after LFPI [35,48,56–59]. Additionally, tests of working memory have demonstrated injury-induced cognitive deficits [56,60]. Deficient conditioning in the Perspex box test, which evaluates conditioned freezing, is observed after mild traumatic lesion [61,62]. Furthermore, LFPI induces acute increases in the stress response as measured by serum hormone levels [53,63,64].

2.2. Controlled cortical impact (CCI)

The controlled cortical impact is a widely accepted and reproducible method of TBI modeling, which replicates many pathological manifestations of penetrating TBI seen in the clinic. This model is used in rats and mice to induce focal cortical contusions with a range of severities at different developmental ages [65].

2.2.1. Protocol of the model

For the CCI induction, using the stereotaxic frame a 3 mm diameter craniectomy is performed over the parietal cortex in juvenile rats (from bregma: 1 mm posterior and 2 mm lateral to midline) [65,66]; or directed to the frontoparietal cortex in adult rats (0.2 mm anterior to bregma and 0.2 mm lateral to midline) [67]. After ensuring that the dura is intact, a pneumatic or an electromagnetic piston impacts the exposed cortex with defined speed and depth. The impact produces a cortical contusion related to hemorrhage, disturbances of the blood–brain barrier (BBB), and edema [65]. Lastly, the craniectomy is sealed permitting the development of intracranial hypertension [68]. The peripheral tissue

shows a prominent decrease in cerebral blood flow which generates secondary injuries [69,70]. These injuries progress from the lesion site to surrounding tissues and are a combination of processes such as apoptosis, inflammation, and excitotoxicity [66]. The CCI animal model reproduces behavioral, anatomical, and functional features of human PTE and temporal lobe epilepsy (TLE) in rodents [71,72]. The extent, variability, and progression of cortical and hippocampal damage after CCI have been well described [71].

2.2.2. Post-traumatic epilepsy expression

In mice, 20% to 36% of the animals develop spontaneous seizures weeks after injury. This is similar to clinical studies indicating up to 39% of patients with severe TBI suffer PTE [9,72]. Previous studies show that the dentate gyrus of injured mice with mossy fiber sprouting, mostly ipsilateral to the injury, became epileptogenic [72]. Mossy fiber reorganization is a phenomenon frequently observed in TLE patients and animal models 2–4 weeks after an epileptogenic insult and continues for years [73]. Aside from mossy fiber sprouting, other anatomical factors are associated with epileptogenesis, including neuron loss, neurogenesis, gliosis, and morphological changes [74]. Another possible origin of PTE after TBI by CCI could be the decreased inhibitory input onto granule cells, which may be driven by the loss of GABAergic interneurons in epileptic animals [75]. In this context, it was observed that following CCI in mice, the levels of the α1 and γ2 $GABA_AR$ subunits decrease based on the severity of the impact apparently due to transcriptional regulation. Additionally, it has been shown that the JAK/-STAT pathway is activated after the CCI injury, and the pharmacological inhibition of this pathway improves the vestibular motor function but not memory function, nor reduces the development of PTE [76].

Another study described that TBI by CCI facilitated epileptogenesis in mice as result of the increase of neuronal expression of nitric oxide synthase 1 N and the cortical expression of genes encoding proteins related to β-amyloid clearance in a model of Alzheimer's disease (AD) [77].

2.2.3. Other associated neurobehavioral disorders

Using the CCI model in adult mice, there is an impairment of neurogenesis within the dentate gyrus of the hippocampus resulting in the presence of depressive-like behavior after TBI [78]. Bumetanide, a sodium-potassium-chloride importer antagonist, has a strong suppressive effect on the presence of depressive-like behavior. The mechanism facilitating this effect implicates changes in the expression of chloride regulatory proteins and qualitative changes in the $GABA_A$ transmission after TBI [78].

The PTSD and TBI show similar behavioral changes including cognitive dysfunction, anxiety, and exaggerated startle response [79]. Literature shows that veterans with TBI are at a higher risk for developing PTSD [80]. A recent study using a mouse model highlighted the comorbidity between TBI and PTSD using the single prolonged stress (SPS) protocol in combination with a CCI protocol [79]. SPS paired with CCI in mice produced unique behavioral impairments in gait and fear recall that are not present in either condition alone. Similarly, studies in rats have revealed that the presence of stressful events increases the vulnerability to epilepsy, and this association can predict the development of other comorbidities such as depression and cognitive deficits [81,82]. In contrast, a study demonstrated that moderate TBI induced by CCI in rats produces a stable suppression of the acoustic startle reflex (ASR) intensity up to 98 days after injury. The authors suggest that chronic TBI may exert a masking effect on the typically hypersensitive ASR of subjects that are experiencing PTSD [67].

It is important to mention the existence of other external risk factors that worsen the negative effects of TBI, such as obesity. After CCI, obese individuals experienced worse outcomes compared to non-obese people with similar diagnoses [83]. There is evidence showing that adult obese mice that suffered a mild brain injury exhibit higher levels of anxiety, significantly reduced corticosterone levels, and a reduced rate of weight gain after trauma compared to non-obese mice [83]. The exact mechanisms of these effects are unknown. However, it has been determined that obese individuals produce higher levels of pro-inflammatory cytokines [84]. In the brain, associations between obesity, neuroinflammation, neurodegeneration, and mood disorders have been previously described [83,85–88]. Particularly, neuroinflammation has been detected in the rat brain using the CCI model of TBI [89].

2.3. Neocortical isolation (cortical undercut)

The neocortical isolation has been developed to replicate a penetrating brain injury in humans [90,91], and it's a well-established animal model of PTE. The epileptiform activity occurs spontaneously or could be evoked in chronically injured slices [91].

2.3.1. Protocol of the model

The frontoparietal cortex of anesthetized rats (1 to 5 weeks of age) is unilaterally exposed, leaving the dura and blood vessels intact. Then, parasagittal transcortical incisions in the sensorimotor cortex are performed inserting a 27–30 gage needle that is bent 90° 2–3 mm from the tip. A mark is placed along the vertical needle shaft ~2 mm from the bend in line with the direction of the needle point; this is done so that the surgeon can gage the depth of the transcortical cut and the location of the needle tip within the brain. The needle is carefully inserted through the dura and under the pia, typically in the parasagittal plane, and straightened so that the bent end is visualized just beneath and parallel to the pial surface. The needle is then pushed down through the cortex for 2 mm (full cortical thickness; 1 to 1.25 mm in mice or young rats) to make a transcortical cut; rotated 180° (away from midline) to undercut the cortex; raised through cortex until it is visualized just beneath the pial surface to make an extension of the transcortical cut; and carefully removed through the point of insertion. To make a more severe cortical isolation, a second transcortical cut could be made without needle rotation 0.5 mm posterior to bregma [92]. After the recovery period (2–4 weeks), electrodes can be implanted for *in-vivo* electrophysiological recordings [92,93]. Depending on the study design, *in-vitro* neocortical slices also can be prepared and studied electrophysiologically at any time after the injury. However, the slice procedure is more difficult during the first few days after the lesion because the isolated area tends to separate from the rest of the slice, and some edema may be present [92,93].

2.3.2. Post-traumatic epilepsy expression

After the recovery period, some *in-vitro* electrophysiological experiments have shown that animals with neocortical isolation evoked epileptiform field potentials in neocortical slices, and approximately one-third of these animals exhibited spontaneous epileptiform events [91–93]. Importantly, the hyperexcitable region of cortex did not extend beyond 2 mm from the transcortical lesion, and was rarely observed in slices having only an apparent white matter injury [91]. Some observations suggest that rats subjected to cortical undercuts might develop electrographic seizures several months after the injury. These seizures could be associated with behavioral symptomatology typical of focal seizures [38,92,93]. Studies in adult C57BL mice found that half of the animals developed spontaneous seizures between 16 and 50 days after the cortical undercut surgery [94]. However, generalized motor seizures have not been seen in cortically undercut rats on casual observation. Nevertheless, it is possible that these cortically undercut rats might have developed electrographic seizures several months after injury.

2.3.3. Other associated neurobehavioral disorders

Only a few behavioral studies on the cortical undercut animal model have been completed to date [91,92]. In these studies, rats were observed briefly (15–30 min per day) for motor deficits and responses to manual vibrissae stimulation. These authors do not indicate any motor deficits or abnormalities induced by neocortical isolation [91,92].

2.4. Intracortical injection of iron

The intracortical injection of iron is a model of TBI which has been used to explore the pathophysiology of PTE. This injection produces histological damage in the inoculated area (likely due to oxidative damage) as well as other changes such as hyperexcitability-associated alterations of ionic channels and ionotropic receptors [95,96].

2.4.1. Protocol of the model

The procedure begins by placing the rat on a stereotaxic apparatus under anesthesia. A small craniectomy (1 mm in diameter) is made directly over the sensorimotor cortex at 5 mm lateral of the midline and 2 mm posterior to bregma. Then, using a microinjection syringe (outer diameter, 0.25 mm; 30-gage needle) and an infusion micropump, 5 microliters of 100 mM ferrous chloride solution are injected at 1 ml/min at a depth of 1.5–2 mm. At the end of the surgery, the craniectomy is covered using bone wax and the skin is sutured [95].

2.4.2. Post-traumatic epilepsy expression

All the neurological consequences of iron accumulation in the brain after TBI are unknown at the present time, but they share some features with PTE development. The injection of ferrous or ferric-chloride solution into the cortex has been shown to produce acute and chronic epileptic activity. The duration of the epileptic activity induced by this model has been detected up to three months after the iron injection [97,98]. Iron injection injury is followed by intracerebral hemorrhage. Meanwhile, phagocytosis of red blood cells can lead to the focal deposition of the heme iron in the form of hemosiderin [96,99]. Hemosiderin is an insoluble iron storage complex that is believed to result from the degradation of ferritin, and the presence of these complexes indicates hemorrhage [100]. The hemosiderin accumulation is an important histopathological feature of human PTE [101]. Histopathological analyses of the brain after trauma indicate hemosiderin deposition, formation of axonal retraction balls, reactive gliosis, and microglial star formation. Furthermore, macrophages, neurons, and astroglial cells surrounding the epileptic focus have been detected with depositions of iron [96,101].

2.4.3. Other associated neurobehavioral disorders

Not all of the consequences of iron deposition in brain tissue have been identified to date. Although some studies have indicated a possible association between iron deposition and the presence of PTE [97,98,102,103], the information regarding association of this model with the development of other neurological comorbidities is scarce. It has been shown that abnormal accumulation of iron in the brain can produce reactive oxygen species and oxidative stress that exacerbate the deleterious effects of TBI [104]. Moreover, it is possible that a link between this model of TBI and the development of a diverse number of neurological disorders may be the excess of iron in the brain. For example, the excess of iron produces cell damage that contributes to the development of other neurological conditions including AD [105] and Parkinson's disease [106,107]. Experiments using a model of AD in mice demonstrated that the ferrous chloride solution injected into the stomach crosses the BBB and then accumulates on the disease sites of the AD's brain. This accumulation leads to *in-vivo* biosynthesis of magnetic iron oxide nanoclusters that can be detected by magnetic resonance imaging and is a new strategy for the diagnosis of AD [108]. Future studies will confirm or refute the role of this model in the development of neurological diseases.

2.5. Impact acceleration "weight-drop"

The impact acceleration model, also known as weight-drop model, reproduces diffuse TBI [109]. This model was developed by Feeney and collaborators in 1981 [110,111]. The impact acceleration model produces functional and structural changes in the dentate gyrus of the hippocampus including selective cellular loss, hyper-excitability, and mossy fiber synaptic reorganization, which are implicated in TLE and may be also involved in PTE [112]. Even though this model leads to many of the known features of human TBI, it only produces PTE at very high intensities and survivability of the experimental animal is low. This is probably due to the diffuse injury produced by the weight-drop model instead of a focal cortical damage [113].

2.5.1. Protocol of the model

Rodents are deeply anesthetized, placed into a stereotaxic frame, and the skull is exposed with or without a craniectomy (closed-head injury). A craniectomy is performed (3 mm of diameter) and is 2.3 mm posterior and 2.3 mm lateral to bregma to expose the dura. A weight-drop device is positioned on the stereotactic arm over the dura. Then, a weight is dropped from a determined height above the skull. After the impact, the wound is sutured and the animal is returned to the home cage for recovery [111,114]. Alterations in the heights and weights of the drop result in differences in the severity of the trauma [115].

2.5.2. Post-traumatic epilepsy expression

The acute phase of the TBI with this model is characterized by the presence of mild seizures, apnea, and hypertension followed by some severe seizures up to 15 weeks after impact. Furthermore, there is an enhanced susceptibility to pentylenetetrazole-induced seizures 15 weeks after TBI with craniectomy [112].

2.5.3. Other associated neurobehavioral disorders

Studies have shown long-term impairments in anxiety, cognition, vestibular functioning and motor functioning up to 18 weeks after a mild closed-head TBI by the impact acceleration model in mice [116]. In another study, the passive avoidance test was used to evaluate short- and long-term memory in mice. The results showed that severe closed-head TBI causes cognitive impairments detected at 7 days post TBI [117]. A different study that used the same TBI model indicated that the injured mice showed a significant reduction in the ability to learn during the passive avoidance test at one-month post-trauma [118]. Additionally, repetitive mild TBI by the impact acceleration model without craniectomy in mice produced an injury in the optic nerve, cerebellum, and retina. [119]. There is evidence showing that 10 days after the induction of mild TBI, the animals exhibited increased anxiety and depressive-like behaviors, while intermediate and severe TBI induced memory impairments. Intermediate and severe closed-head TBI produced extensive histological brain abnormalities [120]. Similarly, investigations using the weight-drop model without craniectomy in rats showed that the animals that received TBI demonstrated depression-like behavior in both modified open-field and elevated plus-maze paradigms. Anxiety-like behavior was found in the same animals during the social interaction and marble-burying tests [121].

2.6. Penetrating brain injury

Considering all the TBI animal models, penetrating brain injuries have been shown to have a significantly elevated risk of developing PTE. Penetrating ballistic injuries are the most common sources of this type of lesion and receivers frequently have retained fragments, including bone and whole or fragmented bullets composed predominantly of copper-coated lead [109]. The penetrating brain injury animal model mimics the acute hemispheric swelling, increased intracranial pressure, and significant intracerebral hemorrhage observed in patients [122]. Currently, there are several animal models of penetrating ballistic brain injury that include an inflatable small balloon probe into the brain [123–125] and some other models that use pistons that are driven into the brain by a pellet [126].

2.6.1. Protocol of the model

Under anesthesia, the rats are placed in a stereotaxic frame. After the skull is exposed, a high-speed drill is mounted vertically on the

Table 1
Rodent models of post-traumatic epilepsy.

Model	Seizure activity development	TBI Comorbidities	Advantages	Disadvantages
FPI	Acute/Chronic	Motor, Memory and learning deficits	Simulate the histopathological aspects of TBI including in human such as diffuse white matter injury, focal contusion, cerebral edema, progressive gray matter damage	Long time course to increased seizure susceptibility
CCI	Acute	Depressive-like behavior, PTSD	Mimics most features of human TBI such as cortical tissue loss, hematoma, axonal injury, BBB damage	Device necessary for trauma
Neocortical Isolation (Cortical Undercut)	Acute	Motor deficits	Ideal for *in-vitro* neocortical studies	No clear evidence about long term seizure activity
Intracortical Injection of Iron	Acute/Chronic	Unidentified	Simple procedure, reproducible model, reflects the pathogenetic mechanisms responsible PTE in humans	Consequences are unknown
Impact acceleration model (Weight Drop Model)	Acute/Chronic	Anxiety, depressive-like behaviors, cognitive disorders	Simple procedure, low-cost, diverse degrees of trauma severity	Low reproducibility, high mortality rate, inconsistent generation of spontaneous seizures, less focal injury patterns
Penetrating Brain Injury	Acute/Chronic	Anxiety, memory deficits	Copper-embedded model increase seizure susceptibility and mortality rate	Low rate of spontaneous seizures

stereotactic arm. Then, a steel burr (1.5 mm diameter) is pushed through the skull and dura into the hippocampus at 1000 rpm. A fragment of either copper wire or stainless-steel wire is introduced into the lesion. Finally, the scalp is closed, and the rats are allowed to recover [127].

2.6.2. Post-traumatic epilepsy expression

Video-EEG recordings in rats implanted with electrodes five to nine months after the injury show that 96% of the animals with copper wire developed epilepsy with higher seizure severity and frequency compared with both control animals and stainless-steel embedded animals. In addition, rats with embedded copper-wire demonstrated an enlargement of the lesion and necrosis at seven months post-injury. The authors conclude that the copper may be an independent risk factor for the development of epilepsy and possible secondary injury [127]. On the other hand, the development of acute seizures has also been shown with the presence of electroencephalographic seizures in rats from 2 h [125] to 7 days [127] following the penetrating brain injury.

2.6.3. Other associated neurobehavioral disorders

During the beam-walking task, most rats with a penetrating brain injury (11/15 rats) were unable to balance or move on the beam during the acute period [123,126]. This impairment was gradually recovered in the following 15 days. In the same study, the authors used the elevated plus maze and observed that the injured rats spent less time in closed arms compared to control rats, revealing mild symptoms of anxiety. Furthermore, the rats used in this study showed deficits in reference memory, but not in working memory after injury. A possible explanation could be the extensive damage to the thalamus seen in this model. Notably, normal motor functioning returned after 7 days. Future exploration of the neurobehavioral effects will focus on long-term effects preferably in epileptic rats [126].

The forelimb asymmetry task at either 7- or 21-days post-injury (n = 7/group) has also been assessed [124]. These authors report that injured rats demonstrated a significant preference for using the ipsilateral (to the injury) limb, indicative of sustained sensorimotor dysfunction in the contralateral forelimb [124]. In the same work, the animals showed transient motor deficits on the accelerating-speed rotarod test at 3 days post-injury, but they recovered to sham levels by 7 days post-insult. Additionally, cognitive behavior was evaluated by the Morris water maze task. This set of experiments showed that penetrating brain injury caused significant impairment on the latency and distance to find the hidden platform. These results may be partly due to an inability of the injured rats to initiate new search strategies, a deficit known to exist after prefrontal cortical lesions [124]. Furthermore, although injured rats that were initially tested at 2 weeks post-injury, they displayed significant (39%) improvement in Morris water maze performance when re-tested at 4 weeks post-injury. These results suggest that the penetrating brain injury induced disruption of spatial learning [124].

3. Conclusions

The modeling of clinical TBI and their consequences is the main challenge for basic science. At the present there are no conclusive studies that examine the neurological comorbidities in epileptic and non-epileptic animals in the existing models of TBI. The present review provides a compendium of evidence that supports the use of these animal models as a reliable alternative for the study of PTE as well as other neurological disorders associated with the injury. Currently, there is no ideal animal model that replicates all the clinical comorbidities of the TBI and/or PTE, as we show in Table 1. Acknowledgement of the strengths and weaknesses of each animal model is key in determining which model provides the necessary conditions for specific research questions, especially when neurological comorbidities are considered. Thus, the use of the appropriate animal model will allow insight into shared mechanisms that might lead, on one hand, to the discovery of reliable biomarkers that would predict an increased susceptibility to epilepsy and its comorbidities. On the other hand, knowledge of the shared mechanisms will lead to the discovery of novel, broad-spectrum treatments that could allow a better approach to the management of PTE and its consequences.

CRediT authorship contribution statement

Cesar E. Santana-Gomez: Conceptualization, Methodology, Writing – review & editing. **Jesús Servando Medel-Matus:** Conceptualization, Methodology, Writing – review & editing. **Brian K. Rundle:** Writing – review & editing.

Declaration of Competing Interest

The authors Cesar Santana-Gomez and Jesus Servando Medel-Matus, declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Dr. Brian Rundle, discloses that no part of his contribution to this article was done using the time or resources of Baylor Scott and White Research institute.

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