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Pathophysiology and Treatment of Memory Dysfunction after Traumatic Brain Injury

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Abstract

Memory is fundamental to everyday life, and cognitive impairments resulting from traumatic brain injury (TBI) have devastating effects on TBI survivors. A contributing component to memory impairments caused by TBI are alterations in the neural circuits associated with memory function. In this review, we aim to bring together experimental findings that characterize behavioral memory deficits and the underlying pathophysiology of memory-involved circuits after TBI. While there is little doubt that TBI causes memory and cognitive dysfunction, it is difficult to conclude which memory phase i.e., encoding, maintenance or retrieval is specifically altered by TBI. This is most likely due to variation in behavioral protocols and experimental models. Additionally we review a selection of experimental treatments that hold translational potential to mitigate memory dysfunction following injury.

Keywords

Traumatic brain injury; Memory; Hippocampus; Prefrontal cortex; Fluid percussion injury; Controlled cortical impact injury

Introduction

Traumatic brain injury (TBI) is defined as any force to the head that causes alteration in neurological function. TBI presents a significant health issue in the United States, with more

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than 2.5 million cases resulting in emergency department visits, hospitalizations or fatality [1]. Furthermore, memory impairment is one of the most common neurological manifestations of TBI [2–4]. Indeed, memory and TBI appear to be intrinsically linked, as the hippocampus and cortex, significant brain regions involved in the physiological circuits of memory, are often damaged after TBI [5,6]. In order to manage and mitigate memory dysfunction ascribed by TBI patients [7] it is imperative to determine the physiological mechanisms linking TBI and these neural substrates of memory.

In this review, we aim to present the current state of research linking memory and TBI by systematically describing the type of memory tested and the different animal models implemented. Additionally, we review studies addressing the underlying neural physiology of memory-associated circuits, predominately within the hippocampus and cortex, and how experimental models of TBI contribute to understanding amnesic pathophysiology. Lastly, we provide a brief overview of promising therapeutic strategies that have potential to target these physiological vulnerabilities within neuronal circuits of memory.

Experimental animal models of TBI

In order to study TBI pre-clinically, scientists have developed several animal models to mimic human pathophysiology. TBI animal models can be divided into closed and open head injury models. The closed head injury (CHI) models, such as Marmarou's and Feeney's weight-drop models, are characterized by the fact that the skull remains intact before the injury [8–10]. CHI causes blood brain barrier disruptions, edema permeability and transient alterations in neurological status [11]. Apart from the weight-drop models, another CHI model type is blast injury, which consists of projecting blast pressure waves from a compressed-gas driven shock tube onto the head of an anesthetized animal [12]. The blast model of TBI was developed to mimic the pressure waves from improvised explosive devices (IEDs) during combat warfare, and has also been shown to replicate human TBI cognitive symptoms and pathology [13].

In contrast to CHI models, open head injury models administer the injury through a craniectomy, directly onto the surface of the dura. The most common forms of these types of models are lateral fluid percussion injury (LFPI) and controlled cortical impact (CCI) [14,15]. LFPI induces injury by delivering a fluid pressure wave onto the exposed dura, and as a result, inducing a focal cortical contusion at the desired level of severity, as well as diffuse subcortical neuronal injury in the side ipsilateral to the injury [16,17]. CCI on the other hand, utilizes a pneumatically-driven impactor on the exposed dura to produce a precise injury, characterized by a focal cortical contusion. Both models replicate aspects of human TBI pathology as well as injury-induced cognitive deficits.

A hallmark of all the aforementioned injury models is that they can be adjusted to produce various levels of injury severity. While each of these models has certain strengths in replicating aspects of TBI, they each have limitations in that they cannot recapitulate all features of human TBI. Therefore, attention must be paid to the model selected in experimental studies in order to understand which aspect of injury the authors are best trying to replicate. Even with the individual limitations of animal models, they remain essential for

studying the functional, biomechanical, cellular and molecular aspects of human TBI that are difficult to address in the clinical realm. Though we have highlighted a few common models here, please refer to additional reviews that further detail the diversity of animal models [18–20•].

Types of memory and TBI

Memory is a dynamic neural and cognitive progression characterized by three separate processes: encoding, maintenance and retrieval [21]. Encoding is the transformation of an experience into a discrete neural representation, known as the memory engram. Maintenance refers to the endurance of the engram across time, and retrieval is the ability to voluntarily reinstate the engram into the forefront of consciousness. It is widely accepted that the hippocampus plays a major role in all three of these memory processes [22,23]. However, it is unknown how, and whether, TBI disproportionately alters one of these processes as compared to the others.

Previously, memory was categorized into short-term or long-term durations. However, this distinction is presently laden with misunderstanding and controversy [24]. Current research conceptualizes the time dependence of memory traces as working, episodic, and semantic memory. Working memory is defined as the cognitive ability to transiently hold, process, and manipulate information [25]. In regards to episodic and semantic memory, these types are actually less dependent on time, but rooted more in the amount of personal experience associated with the memory [26]. Episodic memory receives and stores information about temporally-dated episodes or events, and temporal-spatial relations among these events (e.g., “I remember that last Tuesday at 3pm I was sitting at my desk, talking to my co-worker, who was standing by the door”) [27]. Semantic memory, on the other hand, refers more to the retrieval of memorized facts or events, and their meanings, that one might not necessarily have had a personal experience with (e.g. reciting state capitals) [28]. Importantly, the transition from episodic to semantic memory is governed by a hypothetical cognitive process called consolidation. Studies in cognitive neuroscience have suggested that consolidation mediates the transition of the engram from the medial temporal lobe to the cerebral cortex [29]. Memory engrams that have presumably passed the consolidation phase and remain constant over time are often referred to as “reference memory” in rodent behavioral tasks.

In TBI animal models, it is common to use different type of behavioral tasks to study memory. The lack of standardized memory tasks in these studies makes it difficult to map any one result to specific types (working, episodic, and semantic) or processes (encoding, maintenance, and retrieval) of memory. To help clarify this, we have organized all of the animal studies linking TBI and memory based on the type of memory tested (Table 1). These studies are discussed in further detail below.

Working memory

In the TBI animal literature, working memory is tested primarily using three different tasks: T-maze, radial arm maze, and a specific working memory protocol with the Morris water maze (MWM) [30–32][32,31,30]. Each task consists of 3 trial phases: sample, delay, and choice phase. In the sample phase, animals must learn the path to the maze endpoint,

whether that endpoint be a food reward at the end of a T-maze arm, or escape to the hidden platform. In the choice phase, depending on the learned rule, animals must choose the appropriate arm for T-maze and radial maze, or reach the hidden platform location in the MWM. A short delay with a duration lasting from seconds to minutes, separates the sample and choice phases to probe memory recall.

Following (moderate, severe or mild) CCI, working memory dysfunction persists for at least 16 weeks post-injury as assessed with all three of the previously described working memory tasks. [33–35]. After LFPI, working memory dysfunction follows a temporal evolution that is dependent on injury severity. Acutely, after mild/moderate LFPI, animals demonstrated a deficit in the first 7 post-injury days (PID) with zero time delay between sample and choice phases, indicating a working memory deficit [36•]. When animals were allowed to recover for 15 to 60 PID, no deficits were seen when the delay time was less than 30 seconds, however working memory performance was impaired with a delay time above or equal to 30 seconds [37–40]. Taken together, these data support the hypothesis that TBI diminishes the ability to encode new information in the acute post-injury phase and to maintain information chronically up to 60 days in rodents.

Spatial navigation memory

Spatial memory, a type of memory that records information about a subject's environment and navigation within that environment, has representations in both working and episodic memory. In animal models, spatial memory is tested using different behavioral tasks. One of the most common spatial learning and memory tasks in rodents is the MWM [32,41,42]. In this task, animals are placed in a circular, cloudy water pool with a submerged platform. The goal of the task is for the animal to learn the fixed location of the submerged platform using visual cues located on the walls surrounding the pool, thereby developing a spatial map of the maze. Other widely used spatial tasks include the Barnes and radial arm mazes, in which animals have to find the escape hole after been placed either on an illuminated, circular platform or in an 8-arm radial maze [43,44]. In addition, in each of these tasks, reference memory can also be tested with the use of a probe trial. This trial is added after the testing period to determine if the animal can remember the spatial path. The reference trial is often referred to has an assessment of "long-term" memory, however as discussed above, the probe trial actually is examining the consolidation process.

With respect to spatial episodic memory, which includes information regarding a specific spatial episode/location, numerous experiments have been undertaken in order to test spatial memory after TBI. Specifically, two types of memory have been tested: retrograde and anterograde. In retrograde memory, animals are trained before injury and tested hours/days after injury. This procedure tests the ability of TBI animals to recall previously learned information. In the anterograde memory protocol, animals are robustly trained after injury for many days and then tested.

Anterograde spatial memory

When tested in Barnes and Morris water mazes after moderate CCI, animals demonstrated a significant impairment of spatial learning performance when examined at 10 PID and up to 1

month after injury [45–48]. Specifically, TBI animals exhibited an increased escape latency in the ability to reach the platform or the dark hole, and a more peripheral search pattern compared to sham. Over time, TBI animal performance improved, reaching a performance plateau that could be maintained up to 15 days from the last training day [47,49]. The CHI experimental animal model, in a similar fashion, demonstrated an impaired spatial performance up to 3 months post-injury [50].

Using the LFPI animal model, the severity of the injury causes different behavioral changes. Specifically, a MWM study using two different levels of mild LFPI severity (1.0–1.5 atm) demonstrated an increased latency to escape during the learning trials. However, in testing trials, only the higher injury severity resulted in longer latency to reach the platform [51]. Moderate LFPI on the other hand was associated with significant impairments in spatial learning performance up to 15 PID. These animals recover with no deficit observed at 3 months post-injury [52–54]. Of note, behavioral tasks examining spatial learning performance with TBI animals has demonstrated that enhanced training leads to better testing performance. Rigorous training results in TBI animals successfully completing the task when compared to cohorts with nominal training [55]. Further experiments are needed to specifically determine whether this effect is due to establishment of a neural spatial representation of the maze or, a non-spatial strategy.

Retrograde spatial memory

Animals trained before undergoing LFPI (i.e., retrograde) demonstrated an impairment in recalling the already learned information up to 14 PID [56]. A study with a radial arm maze showed impairment in memory retention after mild and moderate TBI up to 25 PID [35,37,56–59]. Interesting, no deficits were observed when given a brief reminding procedural prompt [35,55]. These data suggest that information learned before TBI can be recalled with longer recovery time and robust reminder training.

Episodic memory

After TBI, there are few experiments focused on examining episodic memory. In order to test the time (or “when”) component of episodic memory, Gurkoff and colleagues used a temporal order task [60•]. Specifically, these animals were exposed to an odor sequence and after an hour delay or longer, were tested for their ability to discriminate the initial odor sequence versus a new sequence. Sham animals preferentially explored the initial odor, whereas injured animals demonstrated no preference. In similar fashion when using a different task, animals with mild CHI were unable to discriminate between odors up to 90 PID [61]. The propensity for control animals to prefer the initial sequence is analogous to the primacy effect in humans, which describes the tendency to more easily remember the first items presented in a sequence during a memory task [62,63].

To test the spatial (or “where”) component of episodic memory, topological tasks, such as object place recognition tasks, are typically used [64]. Here, animals are tested for their ability to distinguish when two objects have their locations transposed in space. Mild and moderate LFPI demonstrated no significant impairments when a short delay time window is used between familiarization and test phase [60•]. However, at a longer time window (1

hour), TBI animals were unable to discriminate that the object's new location from the old location (unpublished data).

Pathophysiology of memory impairment after TBI

Underlying the deficits seen in experimental models of TBI, are alterations in the physiological circuitry of brain regions that confer the different types of memory we have detailed in this review. Disruption to the hippocampus and cortex—regions critical to memory function—are pathological features of both human and animal models of TBI [5,6,65]. The hippocampus is a key part of a large network of brain areas that interact to store and retrieve recent events, and guide memory-driven actions. It receives inputs from different cortical regions which are essential for episodic memory. Specifically, the hippocampus receives spatial and non-spatial information about the environment via projections from the medial entorhinal cortex and lateral entorhinal cortex, respectively. Interactions between the hippocampus and the prefrontal cortex are also involved in encoding, processing, and performance of working memory.

In order to review the current knowledge of TBI-induced pathophysiology within the hippocampus and cortex, we have chosen to view these structures and their sub-regions, with a "circuit-level" perspective. Therefore, we have narrowed our definition of pathophysiology to include functional changes in neuronal output (i.e., how likely it is to fire an action potential), examined by electrophysiological techniques. Additionally, we recognize that even though the hippocampus and prefrontal cortex have been physiologically well studied in the TBI literature, other brain regions that are important for memory, such as upstream cortical regions (e.g., entorhinal cortex) have not been as well characterized.

Hippocampus

As described earlier, experimental models of TBI show deficits in episodic memory. Physiological disruption of hippocampal circuitry, comprised of the dentate gyrus, areas CA3 and CA1, are thought to be largely responsible for disruption of episodic memory after TBI, including spatial memory [66–71].

Dentate gyrus

The dentate gyrus (DG) is considered an important region in hippocampal memory processing. Specifically, it is involved in pattern separation of cortical inputs [72–77]. Consequently, the DG is a crucial regulator of incoming excitability to the hippocampus, and acts as a filter or gatekeeper of cortical input to the hippocampus [78]. The filtering function of the DG is conferred by the low excitability of its principal cell type, the granule cell. Normally, granule cells have an extremely low propensity to fire action potentials due to a combination of their intrinsic properties and strong $GABA_A$ergic inhibition by diverse interneuron populations located around the granule cell layer and in the hilus [79–83]. However, after TBI, the DG becomes hyperexcitable, thus disrupting its filtering capabilities [84–86].

TBI has been shown to alter inhibitory transmission onto granule cells, comprised of phasic and tonic components. Phasic, synaptic $GABA_A$ergic transmission onto the granule cells is

diminished by TBI [84,85,87]. One month after LFPI phasic inhibition recovers; however after CCI, inhibition remains diminished for several months post-injury [88,89]. Compromised phasic inhibition is associated with reduced expression of the potassium-chloride membrane transporter KCC2, thus decreasing the driving force of chloride through $GABA_A$ receptors [90]. Therefore, a reduction in phasic $GABA_A$ergic inhibition appears to be present across TBI models, but the duration of these changes varies with injury severity.

In contrast, tonic inhibition is altered in opposite directions depending on the cell type. For example, tonic inhibition is enhanced onto granule cells, while it is diminished onto a subpopulation of granule cells, known as semilunar granule cells [91–95]. Therefore, alteration in inhibition leads to a complicated dysfunction of the DG.

In order to understand alterations in granule cell firing, it is imperative to examine alterations in DG interneurons. Of the diverse $GABA_A$ergic interneuron subtypes, only somatostatin-positive (SOM) interneurons, have been examined physiologically after TBI. A study by Hunt and colleagues demonstrated that SOM interneurons receive more glutamatergic synaptic input after injury, and fire more action potentials [89]. In addition, glutamatergic mossy cells have been shown to fire more action potentials, resulting in delayed excitatory postsynaptic currents in granule cells [87]. Increased mossy cell firing is due to a shift in enhanced afferent excitatory input as well as homeostatic compensation of intrinsic properties after TBI [96].

In summary, the current literature suggests that posttraumatic DG hyperexcitability is primarily due to changes in $GABA_A$ergic and glutamatergic synaptic transmission within this sub-region. Future studies are needed to explore the functionality of the other DG interneuron types.

Area CA3

Area CA3 also plays an important role in episodic memory encoding and retrieval [72–74,97,98]. Despite the importance of this circuit in memory processing, few electrophysiological studies have examined area CA3 after TBI. It is known however, that area CA3 neurons are vulnerable to death after moderate TBI [86,99–102]. One study using a CHI model showed no acute change in the intrinsic membrane properties of CA3 pyramidal neurons acutely after injury, but was not able to examine later time points because cell survival did not exceed 3 days after injury [103].

In addition to injury-induced cell loss, CA3 pyramidal cells may also be vulnerable to oxidative damage from *in vitro* slice preparation, if taken from mature, adult tissue [104]. Therefore, the high susceptibility to both intended and unintended tissue injury, may explain why so few studies have focused on area CA3 after experimental TBI.

Area CA1

Area CA1 has a distinct role in the encoding and retrieval of episodic memories [105–108]. In contrast to the DG's hyperexcitable response to injury, area CA1 circuit activity becomes hypoexcitable. One week after FPI, CA1 has demonstrated a decreased net response to afferent fiber stimulation, accompanied by a higher threshold to initiate population spikes

[84,109]. Therefore, the output of the CA1 circuit, mediated by the firing of CA1 pyramidal neurons, is diminished after injury.

The hypoexcitable state of the CA1 circuit can partly be explained by changes in synaptic inputs onto pyramidal cells. A study utilizing a model of lateral cortical contusion injury showed a reduction in fiber volley amplitude of afferent Schaeffer collaterals two days after injury [110]. This same study also found that at 7 PID, fiber volley amplitudes were restored, yet synaptic strength remained depressed. One week following FPI, postsynaptic responses to evoked glutamatergic events from both AMPA- and NMDA-receptors have also been shown to be diminished [111]. This indicates that while glutamatergic afferent fibers can re-innervate their targets, the postsynaptic machinery may still be disrupted.

In addition to decreased glutamatergic excitation, pyramidal cells also receive increased $GABA_A$-receptor mediated inhibition from local interneurons. A study from our laboratory using voltage-sensitive dye imaging revealed hyperpolarization in stratum oriens of area CA1 after LFPI, due to enhanced GABAergic inhibition from cannabinoid-sensitive cholecystokinin (CCK) interneurons [112]. Therefore, imbalances in excitatory and inhibitory synaptic inputs appear to underlie diminished CA1 circuit efficacy.

There are other studies from the TBI literature that instead report hyperexcitability in area CA1 after TBI. Two days after moderate LFPI, pyramidal cells showed hyperexcitability accompanied by transiently enhanced afferent input [113,114]. One study using a CHI model of injury, observed more frequent spontaneous action potentials in CA1 pyramidal cells [103]. Additionally, one week following CCI, CA1 pyramidal cells were shown to receive less inhibitory currents, as well as a selective loss of $GABA_A$ergic interneurons in stratum pyramidale [115]. Taken altogether, these differential results in CA1 may reflect experimental variations such as time points examined after injury, injury model, or injury severity, as well as slice preparation. Much is left to future studies to examine the effects of these factors on CA1 circuit function.

After TBI, only a few studies have attempted to correlate *in vivo* hippocampal activity with memory-associated behavior. Fedor and colleagues measured the correlation between hippocampal theta rhythm—a narrow neuronal oscillation associated with memory processing—and spatial memory performance in a Barnes Maze after moderate FPI [54]. Rats that had poor spatial strategies in the maze demonstrated a decrease in theta activity. Another study measuring single-neuron spiking activity found that FPI animals had decreased bursting activity in place cells, which was also associated with poor memory performance in the T-maze [116]. In contrast, in a mild FPI model, a study showed only a decrease in broadband activity (a measure of the overall multi-unit activity) and not theta oscillations [117] supporting the hypothesis that TBI severity leads to different pathologies.

Prefrontal cortex

The prefrontal cortex (PFC), a cortical region heavily connected to the hippocampus, is critically involved in working memory. Recently, we demonstrated that an impairment of working memory in a T-maze task is accompanied by reduced excitability in the medial PFC [36•]. One week after LFPI, layer II/III neurons received an imbalance of more frequent

spontaneous and miniature EPSCs and smaller amplitude IPSCs. Changes in synaptic inputs were additionally accompanied by an increase in action potential threshold, as well as a decrease in principal neuron firing rate. Downstream in layer V of medial PFC, pyramidal neurons did not experience a change in afferent synaptic inputs, but rather had shifted intrinsic membrane properties, such as a decrease in input resistance. In contrast another study, using an acute slice injury model, reported increased excitatory, and decreased inhibitory, synaptic currents onto layer V pyramidal cells [118]. These results demonstrate that a combination of layer-specific synaptic and intrinsic alterations occur in the medial prefrontal cortex after injury.

In cortical slices, it has been demonstrated that there can be differential effects on the intrinsic properties of pyramidal neurons and their firing properties. Both axotomized (i.e., severed) and intact cortical pyramidal neurons maintain normal membrane properties, yet the axotomized cells have a lower propensity to fire action potentials compared with intact neurons [119]. An *in vitro* model of TBI mechanical with cultured cortical neurons, resulted in the membrane composition of glutamatergic receptors. That is, after stretch injury, calcium-permeable AMPA receptors were upregulated in plasma membranes [120,121].

In relation to brain macrocircuitry, the prefrontal cortex is involved in rhythmic neuronal oscillations, such as the thalamocortical relay. While no *in vivo* study has been conducted, *in vitro* brain slices reveal a significant decline in the presence of these oscillations after FPI [122]. In summary, there are significant functional shifts in the PFC circuit that diminish large-scale brain activity patterns and correlate with working memory impairments.

Potential therapeutic strategies to improve memory dysfunction after TBI

To date, the promising results from animal studies of potential TBI therapies (calcium-channel antagonist, steroids, glutamate agonists, NMDA-receptor antagonists, oxygen free-radical scavengers, immune system modulation, statins, progesterone, hypothermia, etc.) have not been translated into successful phase 3 clinical trials. The reasons for the failure to translate bench research to bedside clinical practice are multi-fold and a recent review authored by Chakraborty et al 2016 analyzes in detail potential different causes of this failure [123][123]. However, even with unsuccessful clinical trial results, we believe that some of those therapies can be useful in TBI treatment if they would be designed to guide the pathophysiology. Below, we will focus on new potential therapies that have demonstrated memory improvement, but have not been tested yet in the clinical setting with a clinical trial. All studies are described in the text and summarized in Table 2.

Deep brain stimulation

Electrical stimulus therapy has been used successfully to treat motor dysfunction in Parkinson disease, however only few studies tested this treatment in TBI. Only in the last few years, has deep brain stimulation been tested in TBI animal models with promising results. The basis of deep brain stimulation therapy is to improve abnormal synchrony between different brain regions [124]. Specifically, it was found that stimulation given within the theta frequency band to the medial septal nucleus transiently increased theta activity in the hippocampus and led to improved spatial search pattern and decreased escape

latency during Barnes Maze performance 5–7 PID after moderate LFPI [125]. Another deep brain stimulation study showed an increased exploration time when animals were exposed to new objects [126]. Furthermore, theta stimulation of the midbrain medial raphe and dorsal raphe showed a decreased learning peak during reference memory acquisition, and theta-burst stimulation of the fornix demonstrated improved working memory performance [40,127]. Clinically, there have been a few studies where stimulation electrodes have been successfully implanted in severe TBI patients chronically [128–132].

Neural Stem Cell Transplantation

In the last decade, the ability to repair and regenerate the injured brain has been used as potential therapeutic target for TBI. Different types of cells have been used for neural transplantation in TBI animal models. Interestingly, embryonic stem cell transplantation successfully improved cognitive dysfunction [133–135]. However, some limitations on this technique have been raised due to a limited neural long-term survival and increased tumor risk [136]. Few studies investigated adult neural stem cell implantation showing interesting results but none of them tested memory performance [137,138]. Instead, as alternative strategy with less side effects, bone marrow stromal cells have shown therapeutic promise. This technique resulted in improved cognitive dysfunction, a decreased brain lesion volume and enhanced focal brain angiogenesis [139,140]. Despite the encouraging results of the neuronal transplantation from the animal setting, the clinical translation is still far off. Some issues such as generating sufficient neurons able to integrate in the existing neural network, controlling the hostile environment due to the injury, need to be solved before treating human brain to obtain a successful outcome.

Dietary therapy

Due to altered excitatory/inhibitory (E/I) balance caused by TBI, our laboratory sought to develop a dietary therapy based on precursors of the excitatory neurotransmitter glutamate. The inhibitory neurotransmitter GABA is synthesized from glutamate [141]. Branched chain amino acids (BCAAs) are key amino acids involved in *de novo* glutamate synthesis [142]. We have found that dietary BCAA therapy restores limbic E/I balance and ameliorates hippocampal-dependent contextual fear memory impairment in a mild/moderate FPI mouse model [143]. Furthermore, we have demonstrated that BCAA therapy mitigates injury-induced inability to maintain wakefulness [144••]. Specifically, BCAA therapy was shown to restore brain EEG activity during wake and sleep cycles and increases hypothalamic orexin neuronal firing, which are important in mediating wakefulness. We are currently investigating the efficacy of our dietary therapy on altered episodic-like and working memory tasks and the electrical brainwave activity that sub-serves these functions.

Environmental enrichment

As a non-invasive therapeutic approach, environmental enrichment has been demonstrated to robustly attenuate TBI-induced memory impairments [145–149]. Environmental enrichment is a rodent housing condition which combines complex motor, sensory, and social stimuli within a large living space [150]. The most beneficial effects of this treatment have been seen when rodents are introduced to an enriched environment immediately after TBI and housed continuously for the duration of testing [151,152]. As a continuous-exposure model

may not translate effectively in a clinical setting, other studies have demonstrated that environmental enrichment can still have cognitive benefits when delayed after injury, and also in abbreviated daily time periods [153,154]. Future studies optimizing the temporal effects of environmental enrichment will readily facilitate its therapeutic efficacy in human patients.

Conclusion

In consideration of the information summarized in this review, it is our opinion that the success of future TBI clinical trials will depend on a preclinical approach that incorporates both memory behavior and its underlying neural circuitry. While the current state of the literature reflects overall deficits in certain types of memory, future behavioral studies should expand on how the *components* of memory—encoding, maintenance, and retrieval—are affected after TBI. Specifically, behavioral assessment of these memory components will identify *where* TBI disrupts memory function.

To better understand alterations to memory components observed behaviorally, a circuit-level physiological approach can be of major benefit. By examining cellular and synaptic changes in the hippocampus and cortex, we can understand how behavioral memory deficits occur. New technologies such as optogentics or chemogenetics, could be utilized to substantiate the involvement of physiological mechanisms in behavioral outcome. In conclusion, a combination of behavior and circuit physiology in preclinical studies will aide in the discovery of specific therapeutic targets for clinical translation, and lead to meaningful recovery of memory function in TBI patients.

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Table 1

Summary of behavioral changes in experimental models of TBI

Table 1. Overview of the current literature organized by type of memory disrupted after experimental TBI. Abbreviations: d, day; CCI, controlled cortical impact; FPI, fluid percussion injury; ITI, inter-trial time; mod, moderate; LFPI, lateral fluid percussion injury; MWM, Morris water maze; PID, post injury days; rec, recent; ref, reference; rem, remote; sec, seconds; TOR, temporal order recognition memory.

Ref	Injury Model	Animal age and gender	Animal group	Memory Task Protocol	Test performance PID	Behavioral effects (TBI vs Sham)	p value
Working memory							
Kobori et al (2006)	Moderate-severe CCI	Adult male rats	Sham: 8 TBI: 8	MWM working mem Training: 5 trials with 5 sec delay between sample and choice phase and 4 min ITI Test: the following day	13–14 and 27–28	⇑ latency to reach the platform at 14 and 28 PID	p<0.001
Hoskinson et al (2009)	Moderate-severe CCI	Adult male rats	Sham: 6 TB:I 10	MWM working mem Training 5 trials with 5 sec delay between sample and choice phase and 4 min ITI for 1 day followed by test Swim T maze: 10 training trials/d for 7 d (10 s ITI) followed by 5 d testing	120 (3 months)	⇑ latency to reach the platform in MWM task	p<0.05
						⇓ correct choice percentage with the same amount of training in swim T maze	p<0.001
Sebastian et al (2013)	CCI	Adult male rats	Sham: 3–4 TBI: 3–4	Radial 8-arm maze Training: 10 trials/d for 6 d starting at 21 PID Test: 3–5 trials followed by test at 42 PID	42 (5 weeks)	⇑ number of working memory errs	p<0.05
						Both groups (Sham & TBI) improved performance over days	p<0.001
Sebastian et al (2013)	CCI	Adult male rats	Sham: 3–6 TBI: 3–6	Radial 8-arm maze Training: 10 trials/d for 6 d starting at 42 PID Test: 3–5 trials followed by test at 63 PID	63 (9 weeks)	⇑ number of working memory errs during training	p<0.001
						No difference during test	NS
Lyeth et al (1990)	Mild – Moderate LFPI	Adult male rats	Sham: 8 TBI mild: 7 TBI mod: 10	Radial 8-arm maze Training: 1 session per day (10 sec ITI) until < 1 err/d for 3 consecutives days before TBI	5 – 25	Impaired working memory performance up to 5 PID in mild TBI	p<0.05
						⇑number of working memory err up to 15 PID in moderate TBI	p<0.05
						Intact ref memory	NS
Whiting et al (2006)	Moderate LFPI	Adult male rats	Sham: 9 TBI: 10	Swim T maze Training: 15 trials/d with 7 sec delay between sample and choice phase (11–15 PID). Test: 15, 30, 120 sec between sample and choice phase	16–18	No difference with 15 sec delay	NS
						Impaired working memory performance with delay 30 and 120 sec	p<0.05

Ref	Injury Model	Animal age and gender	Animal group	Memory Task Protocol	Test performance PID	Behavioral effects (TBI vs Sham)	p value
Eakin et al (2012)	Mild LFPI	Adult male rats	Sham: 3 TBI: 3	Swim T maze Training: 0 delay between sample and choice phase. Test: 15, 30, 60, 120 delay between sample and choice phase	30–60	Impaired working memory performance with delays	p<0.01
Sweet et al (2014)	Moderate midline FPI	Adult male rats	Sham: 6 TBI: 6	Swim T maze Training: 0 delay between sample and choice phase for 5 d. Test: 15 trials/d with 60 sec delay between sample and choice phase for 12 d	3 weeks after electrodes implantation	Impaired working memory performance during test	p<0.01
Smith et al (2015)	Mild/moderate LFPI	Young adult mice	Sham: 9 TBI: 7	T maze Training: 10 trials/d with 0 delay per 7 d before TBI Test: immediately after TBI for 7 continuous days	7	Impaired working memory performance	p<0.01
Spatial anterograde memory							
Hamm et al (1992)	Moderate CCI	Adult male rats	Sham: 8 TBI: 8	MWM ref 4 trials/d for 5 d (4 min ITI)	11–15 & 30–34	⇑ latency to reach the platform at both time points	p<0.05
						⇑ time spent in the peripheral part	p<0.05
Dash et al (1995)	CCI	Adult male rats	Sham: 10 TBI: 10	MWM ref 4 trials/d for 5 d (4 min ITI)	14	⇑ latency to reach the platform	p<0.01
Fox et al (1998)	CCI	Adult male mice	Sham: 11 TBI: 15	Barnes maze 1 session/d for 4 d	7–10	⇑ escape latency	p<0.05
						⇓ spatial pattern strategy	p<0.05
Pierce et al (1993)	Moderate LFPI	Adult male rats	Sham: 15 TBI: 12	MWM ref 1992	7–8	⇑ latency to reach the platform	p<0.01
Whiting et al (2008)	Moderate LFPI	Adult male rats	Sham: 8 TBI: 8	MWM ref Training: blocks of 3 trials (30 min between blocks) until criteria reached Test: after 4, 8, 24 h	11–12	⇑ trials to reach the criteria	p<0.01
						No difference to reach the platform after 4, 8, 24h delay	NS
Fedor et al (2010)	Moderate LFPI	Adult male rats	Sham: 8 TBI: 12	Barnes maze Training: 2 trials (2 min ITI) for 3 d	90	No difference in the escape latency	NS
						⇑ peripheral search strategy	p<0.01
Hylin et al (2013)	Mild LFPI (1 atm) & Mild LFPI (1.5atm)	Adult male rats	Sham: 17 TBI (1atm): 20 TBI(1.5 atm): 11	MWM ref Training: 10 trials/d (4min ITI) for 1 d followed by a probe trial after 30 min	5	No difference in the mild (1 atm) group	NS
						⇑escape latency during training and probe trial in the mild (1.5 atm) group	p<0.01
						⇑ peripheral search strategy	p=0.05

Ref	Injury Model	Animal age and gender	Animal group	Memory Task Protocol	Test performance PID	Behavioral effects (TBI vs Sham)	p value
Lee at al (2013)	Moderate LFPI	Adult male rats	Sham: 14 TBI: 13	Barnes maze Training: 2 trials (2 min ITI) for 3 d	5–7	⇑escape latency	p<0.05
						⇑ peripheral search strategy	p<0.05
Zohar et al (2011)	CHI	Adult male mice	Sham: 10 TBI: 10	MWM ref Training: 6 trials/d for 4 d and test the following day	7, 30, 60, 90	⇑escape latency	p<0.05
Spatial retrograde memory							
Smith et al (1991)	Moderate and severe LFPI	Adult male rats	Sham: 12 TBI mod: 12 TBI sev: 13	MWM ref Training: 10 trials/d for 2 days until 2.5 h before TBI Test: 42 h post-injury	42 h	Impaired task performance	p<0.01
Okiama et al (1992)	Moderate LFPI	Adult male rats	Sham: 11 TBI: 20	MWM ref Training: 10 trials/d for 2 days before TBI Test: 42 h post-injury	42 h	⇑escape latency	p<0.01
Hicks et al (1993)	Mild LFPI	Adult male rats	Sham: 10 TBI mild: 7	MWM ref Training: 10 trials/d for 2 days until 2.5 h before TBI Test: 42 h post-injury	42 h	Impaired task performance	p<0.05
Smith et al (1994)	Moderate LFPI	Adult male rats	Sham: 11 TBI: 12	MWM ref Training: 10 trials/d for 2 days until 2.5 h before TBI Test: 7 PID	7	Impaired task performance	p<0.05
Smith et al (1994)	Moderate LFPI	Adult male rats	Sham: 15 TBI: 11	MWM ref Training: 10 trials/d for 2 days until 2.5 h before TBI Test: 14 PID	14	Impaired task performance	p<0.05
Whiting et al (2008)	Moderate LFPI	Adult male rats	Sham: 8 TBI rec: 8 TBI rem: 8	MWM ref Training: 5 trials/d for 5 d (10 min ITI) before (1 or 13 days) TBI Test: at 14 PID a reminder trial and a second probe trial	14	No difference with any delays	NS
Sebastian et al (2013)	CCI	Adult male rats	Sham: 4 TBI: 4	Radial 8-arm maze Training: 10 trials/d for 6 d before TBI Test: 3–5 trials followed by test at 14 PID	14	No impairment in ref memory	NS
						Impaired working memory performance	p<0.05
Episodic memory							
Gurkoff et al (2013)	Moderate LFPI	Adult male rats	Sham: 12 TBI: 11	TOR three times 5 min acquisition separated by 15 min interval followed by test	14	Impaired temporal order discrimination	p<0.05
Gurkoff et al (2013)	Moderate LFPI	Adult male rats	Sham: 11 TBI: 12	Topological task Habituation for 15 min Test after 5 min delay	14	No difference in the ability to discriminate a spatial change in the object	NS

Ref	Injury Model	Animal age and gender	Animal group	Memory Task Protocol	Test performance PID	Behavioral effects (TBI vs Sham)	p value
Gurkoff et al (2013)	Moderate LFPI	Adult male rats	Sham: 9 TBI: 10	Metric tsk Habituation for 15 min Test after 5 min delay	14	Impaired ability to discriminate a distance change between objects	p<0.05
Zhang et al (2015)	Mild CHI	Adult male rats	Sham: 8 TBI: 11	TOR	45 and 90	Impaired temporal order discrimination	p<0.05

Table 2

Summary of neurobehavioral changes induced by therapy in experimental models of TBI

Overview of promising TBI therapeutic strategies. Abbreviations: BCAA, branched chain amino acids; CCI, controlled cortical impact; d, day; DBS, deep brain stimulation; DR, dorsal raphe; EE, environmental enrichment; E/I, Excitatory/Inhibitory; FPI, fluid percussion injury; HFS, high frequency stimulation; hNSCs, fetal human neural stem cell; LFPI, lateral fluid percussion injury; LFS, low frequency stimulation; MR, Midbrain medial raphe; MSN, medial septal nucleus; MWM ref, Morris water maze reference protocol; NOR, novel object recognition task; PID, post injury days; sol, solution; STD, standard; TBS, theta burst stimulation; TOR, temporal order recognition task;

Ref	Injury Model	Animal age and gender	Memory Task	Brain target	Therapy	Behavioral effects (TBI + therapy vs TBI)	p value
Deep brain stimulation (DBS)							
Lee et al (2013)	Moderate LFPI	Adult male rats	Barnes maze (5–7 PID)	Medial septal nucleus (MSN)	DBS: 7.7 Hz, 1 msec pulse width, 80 uA for 1′ before task performance	⇓ escape latency	p=0.05
						⇑ spatial strategy search	--
Carballosa et al (2013)	Moderate LFPI	Adult male rats	MWM ref (35–37 PID) MWM working (38–39 PID)	Midbrain medial raphe (MR), dorsal raphe (DR)	DBS MR: 8 or 24 Hz, 5′ trains alternate with 5′ break during daylight, starting 4–6 h post-injury for 7d DBS DR: 8 Hz, starting 4–6 h post-injury for 7 d DBS MR delay: starting 7 PID for 7 d	⇑ spatial learning in the group DBS MR or DR 8 Hz.	p<0.05
						Improved working memory in the group DBS MR 8 Hz	p<0.05
Sweet et al (2014)	Moderate midline FPI	Adult male rats	Swim T maze MWM ref	Fornix	LFS: 5 Hz HFS: 130 Hz TBS: 200 Hz in 50 ms trains (5 trains/sec)	Improved performance in both tasks with TBS stimulation	p<0.05
Lee et al (2015)	Moderate LFPI	Adult male rats	Object exploration task (5 PID) Barnes maze (5–7 PID)	Medial septal nucleus (MSN)	DBS LFS: 7.7 H z (20, 80, 200 uA) DBS HFS: 100 Hz (80uA) (DBS started 1 min before task performance and terminated before to return to the home cage)	⇑ objects exploration and improved latency and search strategy in the group DBS 7.7 Hz, 80 uA	p<0.05
Neural stem cell transplantation							
Gao et al (2006)	Moderate LFPI	Adult male rats	MWM ref (11–15 PID)	Ipsilateral hippocampus	Fetal human neural stem cell (hNSCs) transplantation (1PID)	Improved escape latency	p<0.05
						⇑GNDF secretion	p<0.05
Shear et al (2004)	CCI	Young adult male mice	MWM ref (30, 90, 360 PID)	Ipsilateral striatum	Neural progenitor cell (NPC) transplantation (7 PID)	Improved escape latency	p<0.05
Bakshi et al (2006)	Severe LFPI (3.1atm)	Adult male rats	MWM ref (42–45 PID)	Perilesional region	GDNF-expressing C17.2 cells transplantation (1PID)	⇑ spatial learning	p<0.05

Ref	Injury Model	Animal age and gender	Memory Task	Brain target	Therapy	Behavioral effects (TBI + therapy vs TBI)	p value
Lu et al (2007)	CCI	Adult male rats	MWM ref (31–35PID)	Cavity lesion	Human marrow stromal cells transplantation (4 PID)	⇑ spatial learning	p<0.05
Xiong et al (2009)	CCI	Young adult male rats	MWM ref (31–35 PID)	Cavity lesion	Human marrow stromal cells transplantation (7 PID)	⇑ spatial learning	p<0.05
Dietary therapy							
Cole et al (2010)	Mild-moderate LFPI	Adult male mice	Fear conditioning (6–7PID)	Restore hippocampal E/I balance	ad libitum BCAA (100 mM sol): starting 2 PID for 7 d	⇑ freezing percentage	p<0.05
Lim et al (2013)	Mild-moderate LFPI	Adult male mice	Sleep/wakefulness cycle	Re-activation of orexin neurons	ad libitum BCAA (100 mM sol): starting 2 PID for the entire experiment	Mitigation of injury-induced inability to maintain wakefulness	p<0.05
Environmental enrichment (EE)							
Hamm et al (1996)	Moderate midline FPI	Adult male rats	MWM ref (11–15 PID)	⇑ neural plasticity	EE: immediately after TBI for 15 days	⇑ spatial learning	p<0.01
Passineau et al (2001)	Severe LFPI	Adult male rats	MWM ref (11–15 PID)	⇑ neural plasticity	EE: immediately after TBI for 15 days	Improved escape latency	NS
						⇓learning acquisition than Sham	NS
Hicks et al (2002)	Moderate LFPI	Adult male rats	MWM ref (15 PID)	⇑ neural plasticity	EE + handling: immediately after TBI for 15 days	Improved escape latency	NS
						⇓learning acquisition in TBI +EE vs Sham	NS
						No changes in neurotrophin/ receptor mRNA	--
Kline et al (2007)	CCI	Adult male rats	MWM ref (14–18 PID)	⇑ neural plasticity	EE: immediately after TBI for 21 days	⇑ spatial learning	p<0.01
Hoffman et al (2008)	CCI	Adult male rats	MWM ref (14–18 PID)	⇑ neural plasticity	Early EE: immediately after TBI for 7 d followed by 2 weeks STD Delay EE: 1 week STD followed by 2 weeks EE Continuous EE: immediately after TBI for 3 weeks	⇑ spatial learning in continuous and delay group	p<0.01
Matter et al (2011)	CCI	Adult male rats	MWM ref (14–18 PID)	⇑ neural plasticity	Continuous EE: immediately after TBI for 3 weeks Early EE: immediately after TBI for 1–2 weeks Early and late EE: 1 week EE+1 week STD+1 week EE	⇑ spatial learning in continuous and delayed (starting after 7 PID)	p<0.01

Ref	Injury Model	Animal age and gender	Memory Task	Brain target	Therapy	Behavioral effects (TBI + therapy vs TBI)	p value
					Early and late STD: 1 week STD +1 week EE+1 week STD		
de Witt et al (2011)	CCI	Adult male rats	MWM ref (14–18 PID)	⇑ neural plasticity	Early and continuous EE: immediately after TBI for 3 weeks Abbreviated EE: 2, 4, 6 h per day	⇑ spatial learning in continuous and abbreviated 6h group	p<0.01
Cheng et al (2012)	CCI	Adult male rats	MWM	⇑ neural plasticity	EE: immediately after TBI for 3 weeks followed by STD EE continuous: immediately after TBI for 6 months	⇑ spatial learning up to 6 months post-rehabilitation in both groups (EE+STD and EE continuous)	p<0.01
Darwish et al (2014)	CCI	Adult male rats	NOR (7 and 14d) [test 1′ and 15′ delay]	⇑ neural plasticity	EE: 2 h per d, beginning 1 PID and continuing for 14 d	Improved recognition memory at 7 PID but not at 14 PID with 1′ delay No improvement at 7 and 14 PID with 15′ delay	NS
Darwish et al (2014)	CCI	Adult male rats	TOR (60′ delay)	⇑ neural plasticity	EE: 2 h per d, beginning 1 PID and continuing for 14 d	No improvement at 7 and 14 PID	NS

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