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Chapter 24

Memory Deficits and Transcription Factor Activity Following Traumatic Brain Injury

Chris Cadonic and Benedict C. Albensi

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/57447

1. Introduction

Traumatic brain injury (TBI) is a serious condition and a leading cause of death and disability [1]. No two head injuries are alike and multiple complications are common in TBI. The most serious aspect of TBI is that of cognitive impairment as evidenced by animal and clinical studies focusing on synaptic plasticity and memory [2-5]. However, post trauma effects also include communication problems, sensory deficits, emotional and behavioral problems, physical complications and pain, increased suicide risk, and an increased risk for chronic CNS diseases, such as Alzheimer's disease [6, 7].

In this chapter we provide an introduction to the study of TBI and how it affects memory functioning. In addition, we survey some of the existing evidence that describes how TBI leads to memory impairment as measured in animal models and also the evidence for how TBI results in memory impairment as seen in human studies. Given that specialized proteins called transcription factors are required for the formation of long term memories, we also explore the major transcription factors that are involved in long term synaptic plasticity and long term memory. Finally, we discuss the experimental studies that investigate the effect of TBI on transcription factor regulation and the associated consequences on memory.

2. Traumatic brain injury (TBI)

TBI is a type of acquired brain injury. Acquired brain injuries can be subcategorized into either non TBI or TBI types. Examples of non TBI include anoxia, strokes, and brain infections, to name a few. TBI can be further divided into open brain injury or closed brain injury. In general, open and closed types of TBI can occur as a result of assaults, falls, motor vehicle accidents,

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blast injuries, and sports injuries etc. However, open brain injury is specifically caused by penetrating injuries, whereas closed brain injury is a result of internal pressure and shearing associated with blunt trauma to the head. Young men in their twenties and the elderly are most at risk for TBI.

The process of TBI is further characterized by the physical and neurochemical changes that are subjected upon the brain, which occur in a time dependent manner. In other words, we call the primary injury the causative event that occurs at the moment of injury, such as a baseball hitting the skull or a bullet penetrating the brain. These sorts of events are on the order of seconds; whereas so-called secondary injury is characterized by biochemical and neurological changes that drive pathophysiological processes in the weeks to months following the primary injury. These changes include vascular alterations, astrocyte swelling and astrogliosis, glutamate excitotoxicity, calcium overload, mitochondrial dysfunction, protease activation, cytoskeletal breakdown, cytokine release and inflammatory responses, the initiation of cell death programs, and cognitive impairment, to name a few.

3. Classifying TBI and memory functioning

Numerous studies report that TBI frequently results in impaired functioning in a wide range of cognitive tests [8, 9]; most commonly affecting processes such as attention [10-12], memory [10, 13] and information processing [14-16]. Despite the widespread cognitive sequelae following TBI [17], there exists a prominent body of work devoted to detailing its consequences for memory functioning [18-20]. However, given the heterogeneous nature of characterizing TBI, such as separating diagnoses by injury severity or duration of loss of consciousness [21-23], variability in memory impairments following TBI are quite common in the literature [9, 19, 24]. Thus, it is important to consider the manner in which TBI is classified and the paradigms used to gauge cognitive impairments [9, 19]. Furthermore, the extent to which memory functioning becomes impaired independent of attention processes or executive functioning becomes problematic to determine, and thus the integrative nature of memory must be taken into account during interpretation [19]. Given these considerations in interpreting the impairments that accompany TBI, it is nonetheless necessary to conceptualize the deficits within a simplistic framework for non-injured memory functioning.

4. Characterization of memory function

Memory has long been known to represent much more than a single, localized functional system [25, 26], but rather a diffuse system of cognitive processes that collectively amount to the internal processing, storage and retrieval of information for ongoing and/or future use [27]. Categorizing the constituents of this diffuse system involves identifying two dimensions: the time frame at which storage of information moves to retrieval, i.e., short-term or long-term memory; and the nature of this information, e.g., explicit or implicit memory [27]. Short-term

memory systems regard information that is maintained transiently, and thus only retain information in an accessible state for a short period of time [28]. A related system known as working memory, that may be distinguished from short-term memory only functionally, represents the active system of information that is operated upon and processed during behavior [28, 29]. The working memory system involves three primary components: an active verbal (or speech-based) information subsystem, referred to as the phonological loop; an active visuospatial information subsystem, referred to as the visuospatial sketch pad; and a processing center that coordinates, controls and schedules mental operations as well as cognitive resource allocation for these operations, referred to as the central executive [30]. Beyond the timeframe of seconds on which short-term memory systems operate, memory becomes selectively transferred into a system known as long-term memory, which not only operates on the order of hours to days to months, but also with a capacity far beyond that of short-term memory [27, 28].

Long-term memory may be categorized with regard to the nature of the information stored; explicit memory (or declarative memory), which regards information that is consciously learned and accessible; and implicit (or nondeclarative memory), which regards information that does not require conscious awareness to learn or access [27]. Explicit memory may be further divided into episodic and semantic memory; episodic memory represents knowledge regarding personal events or information in one's life, such as what one had to eat for dinner last Friday; while semantic memory represents learned facts, meanings, understandings or general knowledge about the world, such as what the definition of an island is [31]. In addition to specialized categorization, the processing of explicit memory has been identified to involve four different operations: encoding, consolidation, storage, and retrieval [27]. Encoding involves incorporation of incoming information with existing information in memory, and thus more efficient encoding processes result in more effective memory functioning, referred to as deep encoding [32]. Consolidation refers to the stabilization of transiently encoded information to facilitate transition to permanent storage; this process is incurred by the activity of transcription factors and protein synthesis that mediate long-term potentiation (LTP), a molecular correlate of memory, and synaptic connectivity [33]. Storage of explicit memory refers to the mechanisms by which information has been processed and stabilized, and thus has been allocated to long-term memory [27]. Finally, the process of retrieval involves accessing stored memories from long-term memory and making the information usable in working memory at the time of retrieval [27]. Implicit memory may also be further subcategorized into priming and procedural skills [27, 34, 35]; priming represents the facilitation of memory processing for an item following previous exposure to either that item or another item similar on some dimension; while procedural skills involve the learning of a skill or sequence of action. It's important to note that although long-term memory may be divided into explicit and implicit systems, these systems don't always necessarily operate independent of each other [20]. This is apparent when considering a system that may be evaluated through either explicit or implicit memory tests, such as source memory or context [19], which refers to knowledge regarding any background information that accompanied the presentation of an item or event [19].

Though memory involves a much more intricate and integrative cognitive network than discussed above, memory impairments following TBI often fall within the scope of the proposed framework, and any supplementary knowledge may follow from the results and/or experimental designs to be discussed. Major avenues of investigation for these impairments typically separate into experimental designs involving induced or simulated TBI in animal models [36] and experimental or clinical evaluation of human brain injury at various time points post-injury [19, 20].

5. Evidence for memory impairment from animal models

5.1. Animal models for assessing TBI

To accommodate the variability often seen in human brain injury, numerous animal models have been developed to elucidate the typical patterns of cognitive and neurobehavioural dysfunction, as well as both the biochemical aspects of primary and secondary injury and more recently, the neurobiological consequences of head trauma [36-38]. Commonly used models for simulating human brain injury in animals include the controlled cortical impact model (CCI) [39, 40], the central or lateral fluid percussion injury model (CFP or FPI) [41], the weight-drop model [42] and the blast injury model [43, 44]. Commonly used to supplement these models as a paradigm for approximating memory impairments are memory tests that measure either: spatial memory, as measured by the Morris water maze (MWM) [45], the Barnes maze [46] or the Olton radial arm maze [47]; or associative learning, as measured by passive-avoidance [48] or operant conditioning paradigms [49].

The CCI model of TBI involves the use of an impact device to deliver a controlled strike to an exposed area of the dural surface [38]. The physical parameters of the strike, such as velocity and depth of impact, are easily controlled in the CCI model [38] and is thus a useful model for detecting the biomechanical consequences of TBI [36, 37]. In the FPI model of TBI, injury is incurred by a pendulum striking a fluid reservoir resulting in a calculated increase of intracranial pressure, which varies as the height and force of strike are altered, leading to deformation of neural tissue [50]. The weight-drop model involves dropping a weight onto an immobilized animal [42], with injury severity adjusting proportionately with alterations in the mass of the weight [38]. In blast models of TBI, the effects of blast waves from an explosion are emanated at varying locations and carried through shock tubes (or open exposure, as in [44]) to an immobilized animal [51, 52]. The blast model provides an accurate representation of TBI incurred by explosives devices such as improvised explosive devices (IEDs) [44].

The Morris water maze (MWM) task is a paradigm that is commonly used to assess spatial memory functioning [53-55]. The MWM task involves placing an animal into a large water tank that contains a platform submerged in an opaque liquid, so as to conceal the location of the platform. The animal is free to swim in the liquid until it either discovers the platform, or reaches a pre-determined maximum time allotment for a single trial, at which point the animal is placed on the platform for a short amount of time. During the acquisition phase, the animal progresses to learn the location of the platform relative to environmental cues (e.g., visual cues)

and will show a decrease in path length and time spent locating the platform using these cues in retained spatial memory systems [45, 56]. The Barnes maze similarly examines spatial memory [46], but rather than implementing a water tank filled with opaque liquid, the Barnes maze utilizes a large *table based* open field platform with numerous holes dispersed across it. One of the holes on the platform allows the animal to escape, and thus the animal will learn to find which hole allows escape from the open area only after utilizing environmental cues to find its relative position [38]. The Olton radial arm maze assesses spatial memory as well, but instead involves the use of a maze with eight arms extend outward from a center platform. Each of the arms are experimentally determined to either contain food or not to contain food, and after placing an animal on the center platform, measuring the number of visits to arms without food provides an indicator for errors in reference memory [38]. Additionally, animals with intact working memory will visit the arms with food and avoid those without food. Finally, measuring associative memory in animals following TBI may be carried out by implementing operant conditioning procedures by having reinforcement be contingent on pressing a bar only in a specific location [13]. Associative memory may also be measured through avoidance conditioning. This is done by placing an animal in one of two connected chambers, where one is entirely black and the other is entirely white; animals placed in the white side have the propensity to cross over to the black side, which is accompanied by a mild foot shock. A measure of acquired avoidance thus becomes a correlate of the latency the animal shows before crossing to the black side, and poor memory performance will show little to no increase in latency [38].

5.2. Memory impairment in animal models

Cognitive impairment in the CCI model shows a high degree of variability and inconsistency, since not only do the methodological and analytical protocols for many studies disagree, but the number of studies that report simulated injury severity amongst CCI studies is variable [38]. Upon taking this variability into consideration, however, many studies were shown to have demonstrated that TBI in rodents show a deficit in spatial memory following TBI induction using the CCI model [53-55, 57]. Interestingly, mild injury produced by the CCI model show no physical damage to the cortex or hippocampus, but still show deficits in both acquisition and retention in the MWM task [55]. Using a variation of the Morris water maze designed to measure working memory, Kobori and Dash [58] showed that significant and long-lasting working memory impairment followed CCI-induced TBI. Soblosky et al. [59] showed no significant working memory impairments following CCI-induced TBI, although deficits in reference memory were significant.

The FPI model of TBI provides a consistent measure of memory impairment following variations of injury severity and experimental paradigm alteration [38]. MRI studies of TBI in rats have shown a temporal evolution of brain injury incorporating both cytotoxic and vasogenic forms of edema where injury extends to the hippocampal formation, a region associated with new memory formation [60]. Bramlett et al. [61] demonstrated not only that impairment in retention occurs on a standard MWM paradigm occurring before TBI induction, but also impairment in acquisition when being retrained on the MWM task following TBI

induction. Furthermore, by altering the MWM paradigm to include a cue on the platform throughout the acquisition stage, deficits remained, indicating effects outside of hippocampal functioning occurred [61]. Whiting and Hamm [62] utilized the FPI model to induce TBI and measure memory impairment using the MWM task. Whiting and Hamm found that there was no significant change in spatial memory impairment for 4, 8 and 24 hour post-training conditions, but when conducting the MWM prior to introducing FPI-induced TBI either 1 or 14 days post-training, cognitive impairment was significantly increased in the injured animals, only recovering when being trained on the MWM once again. The work of Whiting and Hamm indicates that the primary deficit following FPI-induced TBI may be centralized in task acquisition, but not long-term memory retention. In using the Barnes maze as a measure of spatial memory impairment, Lima et al. [63] showed that cognitive testing 1 month and 3 months prior to Barnes maze training resulted in escape latencies that were significantly increased for FPI-induced TBI animals in contrast to healthy controls. In adopting a similar testing paradigm as Whiting and Hamm, Lyeth et al. [64] trained animals in the Olton radial arm maze and subsequently introduced mild and moderate FPI-induced TBI. Contrary to evidence from CCI model data [59], FPI-induced TBI resulted in no significant impairment for reference memory, but resulted in working memory deficits in both mild and moderate TBI groups, though the severity correlated with recovery time with regard to working memory. To reconcile this discrepancy, Chown et al. [38] discuss the cortical damage present in only the CCI-induced TBI, which may account for the reported errors in reference memory that were found in only CCI-induced TBI in addition to several studies using FPI-induced TBI where cortical damage was found, reconsolidating the results of Soblosky et al. [65, 66]. Gorman et al. [13] measured associative learning functionality in FPI-induced TBI rats by training the subjects to depress an operant lever by location, and to neglect another bar that was not previously rewarding. Gorman et al. found that FPI-induced TBI performed significantly worse than controls, showing more prominent dysfunction when inter-trial times increased. Interestingly, Gorman et al. also reported that shortly after the FPI procedure, long-term memory deficit was significant in a visual discrimination task, only to return to baseline after repeated test sessions. In avoidance conditioning, Hamm et al. (1993) were unable to show acquisition deficits in animals given avoidance condition 9 days after FPI-induced TBI, even though Yamaguchi et al. (1996) were able to produce a significant deficit. What may reconcile this difference is that the timing at which animals were trained relative to post-injury time-frames, aren't as necessarily representative of the relative condition of TBI between groups they are designed to characterize [67]. Similar to the cognitive consequences found in FPI-induced TBI studies, blast models show a range of general impairments and frequently demonstrate a deficit in spatial memory functioning [44]. Interestingly, however, Rubovitch et al. [44] additionally reported recovery following TBI-induction was common for low pressure blast waves, but memory impairment was persistent at higher pressure blast waves.

Weight-drop models of TBI have been shown to induce severe retrograde amnesia impairments, showing a reduced deficit for increasing time delays between avoidance conditioning and subsequent TBI induction [68]. Zhou and Riccio also demonstrated that this induced amnesia was alleviated when rats were presented with a pre-test reminder cue, which was

argued to signify that memory impairment following TBI induction reflected a deficit for memory retrieval, rather than a deficit in encoding or consolidation.

Although animal models have provided evidence for a general framework for the cognitive sequelae following TBI, particularly regarding spatial learning, and acquisition and retention deficits in memory, rarely have animal models investigated memory functioning beyond spatial memory assessments [38]. Thus a supplemental discussion beyond that of spatial memory deficits evident from animal models of TBI may be readily apparent in clinical and experimental models for TBI in the human populace.

6. Evidence for memory impairment from clinical and experimental models

Memory impairments are not only one of the most consistently reported cognitive deficits following TBI [67], but also one of the most persistent deficits, showing slower recovery than other cognitive functions [69] and in some cases continuing several years later [70]. In considering the pervasiveness of these memory impairments, however, it is necessary to consider the injury severity with which these deficits may be correlated, since variations of severity often correlate well with degree of recovery [20] and variations of clarity with regard to defining the nature of memory impairments [19]. Thus, discussing memory impairments that occur in mild TBI separately from those found in moderate or severe TBI may help to not only identify the overarching memory impairments found in general TBI, but to also detail the persistence of memory impairments.

6.1. Mild TBI memory impairments

TBI severity is characterized by one of, or more commonly, a combination of three measures [19]: the Glasgow Coma Scale (GCS), which measures a collection of motor, verbal and attentive responses to assess conscious activity [71]; the period over which consciousness has been lost (LOC); and Post Traumatic Amnesia (PTA), which represents the timeframe over which current events are not properly processed and stored [72]. Mild TBI (mTBI) typically falls within the range of a GCS score of 12 – 15, length of coma shorter than 20 minutes, and PTA length shorter than 1 day; while moderate TBI corresponds to a GCS score of 9 – 12, length of coma between 20 minutes and 36 hours, and PTA length between 1 – 7 days; and finally severe TBI corresponds to a GCS of 3 – 8, length of coma longer than 36 hours, and a PTA length of longer than 7 days [19].

Though memory deficits appear to be one of the most prevalent concerns for patients recovering from mTBI, up to 90% of these patients show recovery within 3 months post-injury and typically only show chronic memory dysfunction alongside cognitive function impairment [20]. Upon recovery to ostensibly normal cognitive functioning, re-emergence of general impairment may become apparent under appropriate variations to test conditions, such as stress induction [73] or modality of presentation [14]. Imaging studies have shown that this recovery may only be a symptomatic alleviation, however, as specific areas of frontal cortex activity rise in mTBI despite exhibiting recovered cognitive functioning [74], thus showing that

although cognitive performance appears normal, the compensatory mechanisms responsible for this recovery commonly results in fatigue and similar neurobehavioural concerns [20]. For mTBI patients that have shown no such recovery, many studies have agreed in addressing the resulting memory deficits are rarely direct disruptions of explicit memory storage processing (i.e., consolidation and storage), but are frequently a result of dysfunction in executive processing; such as strategies for effective memory retrieval; information grouping strategies, known as semantic clustering; selective attention; and processing efficiency [20].

Nolin [75] showed that patients with mTBI were impaired on not only a standard free recall memory test, but also showed a high incidence of incorrect word reports and false-positives on a subsequent recognition test, and were much more susceptible to interference by a distractor word list. This test performance coincides with that of patients with amnesia since both groups show difficulty with memory retrieval, but while patients with amnesia show no improvement when given appropriate cues during the recognition test, patients with mTBI do, indicating that retrieval may be recovered in mTBI patients when central executive process reliance is reduced by avoiding retrieval strategy selection [20]. To further test the consequences for working memory following mTBI, McDowell et al. [76] assessed performance on a visual reaction time test when singly presented, and while concurrently being presented with a digit span test, which examines short-term memory span ability for a sequence of digits recalled both forward (digits forward) and backward (digits backward). Patients with mTBI showed much slower reaction times on the visual reaction time test, and a larger decrement for reaction time performance when presented with both tasks simultaneously, further illustrating the role for mTBI in central executive processing. Following evidence indicating a greater importance for working memory functioning for the visuospatial sketch pad than the phonological loop, patients with mild executive dysfunction exhibited more pronounced and persistent impairment for visual memory than that for verbal memory [20, 77].

It appears that changes in the modulation of working memory or executive cognitive processes due to mTBI may be largely responsible for the memory deficits seen [78], as argued above. And with this, there becomes a wide-reaching set of memory processes that may be affected by the observed impairment of the central executive. This may be readily apparent in memory functions that: are reliant on attention processes [76, 79], involve planning and selection of cognitive strategies for memory functioning, involve creating and maintaining scheduled plans, regard goal-directed behavior such as multitasking or involve primarily visuospatial memory [20, 77, 78].

6.2. Moderate to severe TBI memory impairments

As in the case of mTBI, much research has been devoted to addressing a basis for memory dysfunction following moderate to severe TBI [19]. Similar consequences for working memory as a result of mTBI are prevalent in moderate to severe TBI as well. Using digit span tests, Brooks [80] identified a deficient central executive but intact phonological loop following TBI, a result corroborated by Levin et al. [81] specifically in visual short-term memory. Haut et al. [82] found a deficiency in the processing speed for short-term memory by employing Sternberg's paradigm, which involves presenting the participant with a set of digits of length two,

four or six. Participants are subsequently presented with a digit that is either consistent or inconsistent with the set shown, and reaction times are recorded and corrected to signify a measure of short-term memory scanning time. TBI patients exhibited longer reaction times than for healthy controls, indicating a requirement for longer short-term memory scanning to complete the task. Research regarding verbal and visual modalities in working memory following moderate to severe TBI show a similar result as in mTBI, but have yet to be directly contrasted. Zec et al. [70] employed a battery of verbal memory tests, and found consistent impairment across all tests in severe TBI patients in contrast to performance of a spinal cord injury group. Logical memory and association processing were found to be significantly impaired in TBI patients [80, 83]. Haut et al. [84] found no difference in the sensitivity of meaning of information units in TBI patients and controls in a logical memory test derived from the WMS-R (see [85]). Kersel et al. [86] employed an auditory verbal learning test in severe TBI patients six months and one-year post injury, which showed a significant impairment on all test trials for both post-injury time points. Similar to the result from the mTBI section, noticeable improvement was observed for verbal memory in both time points. Turning to visual memory, Brooks [80] utilized a variety of visual memory tests that all indicated impairment following TBI. Under only alterations of the testing paradigm used, many studies reliably corroborated this deficit in visual memory [70, 87, 88]. Shum et al. [89] used a visual learning test composed of Chinese characters, a standard Rey AVLT verbal memory test (see [90] for a review) and a spatial memory test; the results showed a significant impairment on learning rate and visual pattern recognition score, but did not show a difference in susceptibility to interference (dissimilar to the results found in mTBI; see [75]) or a substantial difference in spatial memory performance (dissimilar to the results from animal studies; see [55]. Skelton et al. [91], however, found a significant spatial memory deficit on a computer generated arena maze. This discrepancy may reside in methodology employed in each maze setup, which would inherently be different and thus may contribute to any alterations in performance. And with this is mind, it appears that both visual and verbal memory systems are impaired in TBI, although there remains more work in directly contrasting the modalities under similar conditions.

The rate at which learning occurs (i.e., the learning rate) following TBI has been posited to be affected in a similar manner as memory, and thus a slower learning rate post-injury is expected. Many studies have found slower rates in TBI patients contrasted with controls [70, 92, 93], TBI patients contrasted with controls on verbal, visual or both verbal and visual presentation modalities [94]. To explain the source of this slowed learning effect often observed in TBI patients, Paniak et al. [95] and Blackstein et al. [96] interpreted the rate deficiency as inefficient organization and learning strategies (consistent with mTBI; see [75]). Interestingly, Vakil and Oded [97] compared learning rates in TBI patients on both free recall and cued recall, which indicated that the deficit in learning was apparent only in free recall. This can be accounted for by recalling that memory retrieval organization appears to be impaired in both mTBI and TBI, and thus facilitating memory retrieval through cuing relieves the executive processes of carrying out any retrieval plan operations. On the opposite end of the spectrum, studies show that the rate at which information is lost (i.e., forgotten) is faster in TBI patients [82, 84, 98], and this effect is more pronounced in free recall paradigms [99]. To explain this effect, DeLuca

[100] argued that this rapid forgetting rate found in TBI patients may be an issue of encoding, but not consolidation nor retention. Organization of meaning in memory, otherwise known as semantic organization, has so far produced largely inconsistent results in TBI patients. Attempts to reconcile these discrepancies have resulted in detailing these varied results by noting that TBI patients will have difficulty in tasks that require applying and/or learning a strategy, but will not have such difficulty when no active strategy or an automatic/passive strategy is necessary [98, 101, 102].

Implicit memory consists of priming and procedural skill learning, which have sub-categorization. Priming studies have shown that impairment typically follows only deep encoding, while explicit memory tasks showed impairment regardless of level of encoding [103]. In many subsequent studies, priming effects have shown to occur similarly in TBI patients and controls [104-106], but a deficit would then become apparent under a variation of divided attention [106, 107]. Priming alterations between conceptual priming (i.e., priming on conceptual relations) and perceptual (i.e., priming on superficial characteristic relations) showed that conceptual priming consistently produced deficits in TBI patients [105]. Procedural skill learning has been previously accepted to have no alteration for well-practiced skills acquired prior to the injury [104, 108], but evidence demonstrating deficits post-injury remain inconsistent. Vakil [19] argues that inconsistencies in the literature regarding whether skill learning remains intact [109] or is impaired [110] following TBI is dependent on whether the testing methodology involves frontal lobe activity (as the frontal lobes are particularly vulnerable to TBI) or tasks that do not involve the frontal lobes.

To further elucidate effects on explicit and implicit memory following TBI, source memory can be surveyed explicitly, as through direct inquiry to recall background information for a specific event or situation, or indirectly, as through priming effects due to context [19]. Measuring different aspects of context and source memory, however, yields some varying results. When measured directly, source memory for spatial location was significantly impaired [111], as was frequency of occurrence for words from a study list [112]. Thus explicit measures of source memory were consistently impaired relative to controls [19]. Temporal order judgments for study lists did not yield consistent results, either showing no effect [113] or a significant impairment [111]. Further investigation into the effects of TBI on integrative memory concepts such as source memory and context may help provide a more definitive connection between explicit and implicit memory systems consequences.

7. Transcription factors and memory

Literally, hundreds of molecules have been shown to play a role in various forms of memory. In addition, specialized proteins known as transcription factors have also been implicated in memory. However, there are only a few families of transcription factors that are actively studied and that appear to be critically involved in long term synaptic plasticity and long term memory [114]. These include activating protein 1 (AP-1), CCAAT enhancer binding (C/EBP) protein, early growth response (Egr) factor protein, nuclear factor kappa B (NF-κB) protein, and cAMP response element-binding (CREB) protein.

The factor AP-1 is composed of proteins coded by several genes such as *c-fos*, *c-jun* and *ATF*. The C/EBP family of transcription factors is coded by six distinct genes: *C/EBPα*, *C/EBPβ*, *C/EBPγ*, *C/EBPδ*, *C/EBPε*, and *C/EBPζ*. Among the Egr family of transcription factor genes, the *zif 268* gene (a.k.a. *Egr-1*, *Krox24*, *NGF-I-A*, *TZs8* or *Zenk*) is probably the most well studied. There are several genes that contribute to the NF-κB transcription factor complex that include *NF-κB1*, *NF-κB2*, *c-Rel*, *RelA*, *RelB*, *IkBα*, *IκBβ*, *IκBε*, and *IκBζ*. The CREB (or CREB/ATF) family of transcription factor proteins is produced with three homologous genes, which are *creb*, *crem*, and *atf-1*.

Transcription factors are important for biological processes where they regulate the basal process of transcription, the selective activation of genes, and/or the repression of genes. More specifically, transcription factors control transcriptional regulation where information encoded in the DNA of each cell is copied into a molecule of RNA. Ultimately, transcription factors regulate multiple functions on different time scales and in different spatial regions. In some cases, transcription factors even initiate the expression of additional transcription factors, which hints at the multiphasic layering and the overall complexity of transcriptional regulation.

8. Transcription factor activity following TBI

The use of DNA gene microarrays has greatly increased our understanding of how genes are differentially regulated following TBI. In particular, these techniques enable the simultaneous evaluation of thousands of genes, which assist in protein expression profiling and the identification of molecular mechanisms that are involved in the pathophysiology of secondary injury in TBI. For example, alterations in the transcription of genes following TBI lend insight into a neuron's response to trauma. These responses involve both the initiation of programmed cell death and the restoration of compromised cell function. Understanding these complex responses no doubt is central to the discovery and development of therapeutic strategies for treating TBI.

Early studies using these methods [115] demonstrated alterations in several classes of genes following TBI, including neurotrophic factor genes, heat shock protein genes, cytokine genes, and immediate early genes (IEGs). IEGs (e.g.s., *c-fos* and *Egr-1*) received considerable attention in initial studies given these genes are responsible for the encoding of proteins that regulate growth factors, growth factor receptors, cytoskeletal proteins and transcription factors, etc. For example, in one gene array study *c-fos* and *Egr-1* mRNA expression levels were significantly increased in both ipsilateral and contralateral regions at 120 mins following TBI [116]. These findings are interesting in light of the fact that both genes code for transcription factors, thus controlling the expression of other genes. In another gene array study by Kobori et al. [117], which was broader in scope, CCI was induced in C57BL/6 mice and approximately 10,000 genes were evaluated. In this study, 7 functional classes of genes were found to be increased following CCI; this included transcription factors, signal transduction genes and genes coding for inflammatory proteins. Of these, the transcription factor, *c-jun* and the neurotrophic factor,

bdnf mRNA levels increased as a result of TBI. Gene arrays have also been used following TBI in human subjects. For example, in a study by Michael et al. [118], global changes in gene expression were evaluated in 4 patients during surgery following TBI. These results showed that 4 genes previously shown to be associated with TBI (i.e., *c-Fos, Egr-1, Jun B,* and *HSP70,*) were all up-regulated in at least one TBI subject. Collectively, these studies show that IEGs are upregulated in both animal models and in human subjects following TBI suggesting IEGs play essential roles in secondary injury associated with TBI.

Other transcription factors have also been investigated following TBI. In a mouse study by Beni et al. [119], a closed head injury (CHI) model was utilized and the transcription factors NF-κB and AP-1 were evaluated in the presence of the pineal hormone melatonin. Besides being involved in pineal function, melatonin also acts as an antioxidant, which was being evaluated for its potential to attenuate the effects of TBI. Here it was found that CHI-induced TBI activated NF-κB and AP-1 at 24 hours following CHI. In particular, the study showed a transient activation of AP-1 and a longer activation of NF-κB after CHI. Interestingly, melatonin inhibited the late-phase activation of NF-κB and decreased AP-1 to below basal levels when measured at 8 days following CHI. These results suggested inhibition of NF-κB by melatonin was associated with improved outcome, whereas the prolonged activation of NF-κB after CHI was harmful. NF-κB activity has also been studied in other TBI models. In a study by Chen et al. [120], NF-κB and also TLR4, IL-β, TNF-α, IL-6 and ICAM-1 were upregulated in a weight drop model of TBI. However, when the cholesterol-lowering agent simvastatin was used, the induction of TLR4/NF-κB pathway was suppressed after TBI.

CREB activity has also been looked at following TBI. In an earlier study by Dash et al. [121] using rats, the phosphorylation of CREB was found increased just 5 minutes after lateral cortical impact, but decreased to control levels after 30 minutes. In addition, c-Fos and the AP-1 complex expression was found increased following CREB phosphorylation. Hu et al. [122] also looked at changes in CREB pathway signaling following TBI in a context of hippocampal mossy fiber reorganization, which occurs after various CNS pathological events or insults. In this study the FPI model was used in rats and it was found that signaling pathways of TrkB–ERK1/2–CREB/Elk-1 were robustly activated in association with mossy fiber organization. These results suggest that activation of the CREB signaling pathway may contribute to mossy fiber reorganization after the onset of TBI. However, some studies also demonstrate that CREB is downregulated following TBI. For example, Atkins et al. [123] used a parasagittal FPI model in rats to study CREB signaling. Here it was found that the activation of ERK and CREB after 30 seconds of glutamate stimulation or KCl depolarization was decreased in hippocampal slices from animals at 2, 8, or 12 weeks after TBI as compared to control rats. One reason for the apparent inconsistency among these CREB studies may have to do with the time course of the measurements. For example, deficits in CREB activation in the study by Atkins et al. may be due to synaptic loss *in the weeks* following TBI, as opposed to CREB measurements shortly after TBI. In addition, CREB family members can function as either transcriptional activators or repressors, and family members may have distinct functions under different conditions, which could also explain some of the differences seen in CREB activity following TBI. Another observed function of CREB following TBI may have to do with the regulation of apoptotic

activity. Wu et al. conducted a study [124] to see if CREM-1 was involved in CNS injury or repair, and performed TBI in rats. Here they looked at the association of CREM-1 with p-CREB on PC12 cells. Their results suggested that the association of CREM-1 with p-CREB was enhanced in apoptotic cells and therefore, CREM-1 might regulate neuronal death after TBI by interacting with CREB.

Some studies evaluating the C/EBP family of transcription factors in TBI have also been conducted. For example, in a study by Sandhir and Berman [125], C/EBP isoforms were evaluated since they are known to regulate the expression of proinflammatory genes. In this study, CCI was subjected on either younger adult (5-6 mos old) or older (21-24 mos old) C57BL/6 control mice and C/EBP mRNA and protein expression levels were evaluated during the first week following CCI. In this study it was found that protein and mRNA expression levels of C/EBP isoforms overall were similar in younger brains and in older brains before CCI. Following CCI, C/EBPα mRNA expression appeared to go down on day 1 in young adult and in older brains, but these results were not statistically significant. However, a significant increase in C/EBPα mRNA expression was seen on days 3 and 7 in the young adult brains and on day 7 in the older brain as compared to levels before CCI. Also, C/EBPα protein levels were significantly elevated on days 3 and 7 in young and older brains as compared to pre CCI levels. It was also found that a significant upregulation of C/EBPβ mRNA expression occurred on days 1 and 3 in both young and older adults, which was associated with significant increases in C/EBPβ protein levels on the same days in the same groups as compared to pre CCI levels. With regard to C/EBPδ mRNA levels, only on day 1 in older brains was there a significant increase in expression, whereas protein levels of C/EBPδ were significantly increased in both young and old brains on days 1, 3, and 7. Collectively, these results show clear differences in the temporal expression among the C/EBP isoforms. These results overall suggest that C/EBP transcription factors contribute to inflammatory responses following TBI in aged brains, where, the expression of C/EBPβ and δ appear to play roles in the early phase of the inflammatory response.

9. Conclusions

TBI is a serious condition resulting in disability or death. Currently, there is no standardized treatment. However, research has been attempted in animal models and human trials have been conducted showing the effects of TBI on various outcomes. In addition, a large amount of evidence has been collected that demonstrates that TBI is associated with cognitive impairment and memory dysfunction. A considerable amount of data also show that long term memory is associated with the activation of transcription factors, which regulate and initiate new gene expression. The protein products from this expression contribute to biological functions associated with the formation, retention, and reconsolidation of long term memories. However, following TBI numerous mechanisms associated with transcriptional regulation become affected. In fact, we now know that transcription factor regulation following TBI is complex where some transcription factors contribute not only to processes of memory formation, but also contribute to neurodegenerative processes. In other words, multiple

signaling pathways exist and play various roles in inflammatory signaling, programmed cell death, mossy fiber reorganization, endogenous neuroprotection, and the initiation of neurodegenerative processes. It is hoped that by understanding the complexity of transcriptional regulation after TBI, that new targets can be identified which could be exploited for pharmacological intervention. In this regard, our understanding is still quite infantile and further research is necessary.

Acknowledgements

Dr. Benedict C. Albensi, Principal Investigator, is also the Everett Endowment Fund Chair and is supported in part by the Everett Endowment, which funds his Alzheimer's research at the St. Boniface Hospital Research Centre - Division of Neurodegenerative Disorders. Other funding supporting basic memory research in his lab is from NSERC. Dr. Albensi is also an Associate Professor in the Dept. of Pharmacology and Therapeutics, Faculty of Medicine and an Adjunct Professor in the Dept. of Electrical and Computer Engineering in the Faculty of Engineering both at the University of Manitoba. He is also a Research Affiliate at the Centre on Aging and a Scientist at the Manitoba Inst. of Child Health (MICH) at the Univ. of Manitoba.

Author details

Chris Cadonic[1,3] and Benedict C. Albensi[1,2,3*]

*Address all correspondence to: balbensi@sbrc.ca

1 Biomedical Engineering Program, Faculty of Engineering, University of Manitoba, Canada

2 Dept. of Pharmacology & Therapeutics, Faculty of Medicine, University of Manitoba, Canada

3 Division of Neurodegenerative Disorders, St. Boniface Hospital Research, Winnipeg, Manitoba, Canada

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