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# Elucidating opportunities and pitfalls in the treatment of experimental traumatic brain injury to optimize and facilitate clinical translation

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## Abstract

The aim of this review is to discuss the research presented in a symposium entitled "*Current progress in characterizing therapeutic strategies and challenges in experimental CNS injury*" which was presented at the 2016 International Behavioral Neuroscience Society annual meeting. Herein we discuss diffuse and focal traumatic brain injury (TBI) and ensuing chronic behavioral deficits as well as potential rehabilitative approaches. We also discuss the effects of stress on executive function after TBI as well as the response of the endocrine system and regulatory feedback mechanisms. The role of the endocannabinoids after CNS injury is also discussed. Finally, we conclude with a discussion of antipsychotic and antiepileptic drugs, which are

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provided to control TBI-induced agitation and seizures, respectively. The review consists predominantly of published data.

**Keywords**

antiepileptic drugs (AEDs); antipsychotic drugs (APDs); controlled cortical impact (CCI); endocannabinoids; executive function; fluid percussion (FP) injury; Morris water maze (MWM); rehabilitation; stress; traumatic brain injury

## 1. Introduction

With an estimated ten million traumatic brain injuries (TBI) reported annually worldwide, the World Health Organization predicts that TBI will surpass many diseases as the major cause of death and disability by the year 2020 (Langlois et al., 2006; Hyder et al., 2007; Faul and Coronado, 2015; Coronado et al., 2015). Further, the economic impact of acute and long-term care was estimated at $61 billion in the U.S. in 2000 by the Centers for Disease Control and Prevention (CDC) (Faul et al., 2007), and approximately $40 billion in Europe in 2010 (Olesen et al., 2012).

Approximately 75% of reported TBIs are mild and are typically referred to as diffuse TBI or concussion, as determined by a Glasgow Coma Scale (GCS) score of 13–15 (Thurman et al., 1999; Grossman et al., 2010). Mild TBIs are generally caused by sporting accidents, falls, motor vehicle crashes, and domestic violence (Faul and Coronado, 2015). By definition, TBI results in mechanical damage occurring due to the torsion and deformation of the brain as it rapidly moves within the skull. The signature pathology of diffuse TBI is diffuse axonal injury (DAI), which refers to the physical shearing of axons and the sequelae of events that lead to axon disconnection from the cell body; a pathology that is disseminated throughout the brain while being located adjacent to healthy tissue (McGinn and Povlishock, 2016).

The remaining 25% of TBIs consist of focal, penetrating, and combined (diffuse + focal) injuries. Focal injuries can occur from epidural and subdural hematomas and gross tissue damage resulting in focal lesions that are characterized by cell death and contusion. According to the CDC, deaths from TBI are down 7%, but there are currently 5.3 million Americans living with disabilities directly related to the TBI. Improved safety equipment and improved acute medical treatment have contributed to the worldwide trend for an increased population of TBI survivors. Unfortunately, with limited treatments available, many patients live out the rest of their lives with disabilities associated with the TBI. With such a large population affected by TBI, symptom management and optimization of rehabilitation are paramount for medical professionals.

### 1.1. Types of rehabilitation for post-concussive symptoms and TBI-related disabilities

Acute and persisting post-concussive symptoms (PCS) after various forms of TBI are composed of somatic (e.g., headache, dizziness, light and sound sensitivity, balance and vision problems), cognitive (e.g., memory, executive function, confusion), and affective (e.g., anxiety, sleep disorders, emotionality) deficits. Most patients recover from PCS within 1–3 weeks. However, for 15–20% of the TBI population, PCS persist for months and even

longer (McAllister 1992; Alves et al., 1993; McAllister et al., 2001; Ragnarsson, 2002; Radhakrishnan et al., 2016). After a TBI that requires hospitalization, the prevalence for persisting (at least 1 year) somatic, cognitive, affective, and motor deficits increases to over 43% of survivors (Selassie et al., 2008). Moreover, several studies indicate that females are more likely to have persistent symptoms after mild TBI (Farace and Alves, 2000; Bazarian et al., 2010; Mott et al., 2012; Iverson and Pogoda, 2015; Silverberg et al., 2015). In particular, headaches and dizziness (Farace and Alves 2000), loss of confidence (Colantonio et al., 2010), depression (Bay et al., 2009), and anxiety (Liossi and Wood, 2009) are quite common. This finding is troubling given that females make up approximately 41% of the TBI population in the United States. The true incidence of persisting PCS is unknown as many TBI patients do not seek medical care likely because they do not identify the injury as the etiology of their symptoms (Langlois et al., 2006).

Despite the growing awareness of persisting PCS and TBI related disabilities, especially in the athletic community, treatments are limited and mainly consist of symptom-specific pharmacological and rehabilitation approaches (Radhakrishnan et al., 2016). Rehabilitation for this population includes cognitive-behavioral therapy, attention and strategy training, emotional therapy, re-socialization, cervicovestibular and oculomotor rehabilitation, and tactile stimulation (Mittenberg et al., 1996; Cicerone et al., 2005; Rohling et al., 2009; Silverberg et al., 2013; Schneider et al., 2014; Broglio et al., 2015; Gertler et al., 2015; Parianen Lesemann et al., 2015). It is recommended that therapists approach each patient individually as success of rehabilitation is impacted by the type of injury, gender, age, nutrition, pre- and post-morbid conditions, polytrauma, and overall attitude and level of determination of each patient. Also, the timing, duration, intensity, and type of rehabilitation can largely influence success (Kay et al., 1992; Ponsford et al., 2000; Yen and Wong, 2007; Cook et al., 2008; Bazarian et al., 2010; Purohit et al., 2013; Thomas et al., 2015).

In general, cognitive deficits and impairments refer to any deficiency in cognitive processes that impact intellectual performance and abilities in comparison to pre-injury status. Most affected after TBI are memory, information processing, attention, and executive function (Carr and Shepard, 1998; Bondi et al., 2014a, 2015). Cognitive-behavioral therapy provides educational materials, therapist-guided symptom management strategies, and guidance toward resuming pre-injury activities. Patients adhering to the recommended guidelines reported decreased duration, frequency, and severity of symptoms (Mittenberg et al., 1996; Miller and Mittenberg, 1998). Attention and strategy training improves mild memory impairment, attention deficits, and communication deficits by teaching and practicing strategies to compensate for residual effects rather than depending on restoration of original function (Cicerone et al., 2005).

Therapies dedicated to affective disorders after TBI are often focused on mitigating apathy, anxiety, anger, aggression, frustration, and depression that can impede overall rehabilitation efforts and social interactions brought about by adapting to injury-induced deficits (McDonald and Flanagan, 2004). Thus, in a subsequent section of this review, a discussion of drugs that are aimed at managing agitation and aggression will be discussed. Rehabilitation includes mechanisms for managing stress, setting realistic goals, and emotional support. For the latter, therapists recommend that the family also be educated on

injury-induced emotional instability and strategies to demonstrate support of the patient. Often, temporary use of pharmacological treatments are recommended to facilitate learning of new strategies (Vaishnavi et al., 2009).

In addition to persisting cognitive and affective PCS, somatic symptoms include sensory hypersensitivity to light and sound, vestibular (i.e., dizziness and imbalance) and ocular-motor impairments, such as gaze instability, visual fatigue, and visual motion sensitivity (Ventura et al., 2016). Cervicovestibular rehabilitation is a newer approach that uses a combination of vestibular rehabilitation and cervical spine physiotherapy in patients with symptoms of dizziness, neck pain, and headaches (Schneider et al., 2014). Other approaches to vestibular rehabilitation after mild TBI for balance and sensory integration are non-aerobic exercise interventions and computerized dynamic posturography, a test of balance that evaluates the sensory input from the feet and legs involving vision and vestibular function. Posturography is used for diagnosis, tracking of patient progress, and aiding the therapist in designing an individual rehabilitation program (Lin et al., 2015). Oculomotor training includes the use of eye patches, penlights, mirrors, lenses, and prisms to improve the performance of ocular muscles (Broglio et al., 2015). Regardless of the type of rehabilitation, education, support, and regular monitoring are key to long-term success (Dittmar, 1997).

For severe TBIs that involve focal lesions, motor rehabilitation may also be necessary. The severity of deficits can range from a coma state to loss of fine articulation of peripheral appendages. To avoid atrophy and muscle shortening brought about by immobility in coma patients, passive stretching is recommended for at-risk muscles. For the greater range of severity, a degree of physical, occupational, and speech therapy may be necessary for the return of daily activities and work. Rehabilitation may take the form of task-oriented motor training, gait correction, resistance training, or constrained-induced movement therapy (Cimolin et al., 2012).

### 1.2. Animal models of TBI

There are several models of experimental TBI that replicate many aspects of the human condition (Kline and Dixon, 2001; Cernak, 2005; Morganti-Kossmann et al., 2010; Marklund and Hillered, 2011; Osier and Dixon, 2016). Specifically, the fluid percussion (FP) and controlled cortical impact (CCI) are the most widely used, but weight-drop and blast are rapidly gaining momentum. Each has been modified over time to increase validity toward specific aspects of the clinical situation, with concussion, contusion, diffuse axonal injury (DAI), and hemorrhage being the primary pathological features of interest (Xiong et al., 2013). The pathological outcomes from FP injury can be produced by varying the placement of the craniectomy and the fluid pulse. For example, if the craniectomy is placed along the midline suture, the result is a diffuse brain injury in both hemispheres (Dixon et al., 1987; McIntosh et al., 1987), whereas a lateral craniectomy results in a ‘mixed pathology,’ containing a focal brain injury with a diffuse component (McIntosh et al., 1989; Thompson et al., 2005). To better replicate the susceptibility of athletes to repetitive concussion, repetitive mild TBI models are becoming more available. An extensive table of repetitive TBI models can be found in an excellent review by Brody and colleagues (2015).

The CCI injury model consists of a direct impact delivered to the exposed dura using a pneumatic piston or electromagnetic actuator attached to a rod. TBI induced from CCI can range from mild to severe, and injury type can vary depending on the velocity, depth of deformation, duration, size/shape of rod, and site of impact (Bondi et al., 2015; Osier and Dixon 2016).

In addition to brain trauma models, a variety of animal models (e.g., mice, rats, cats, dogs, sheep, swine and non-human primates) have also been utilized in preclinical research. However, the overwhelming majority of studies have been conducted in rodents. The small size, accelerated lifespan, modest cost, and extensive normative data for rats provides the ability to evaluate structural, functional, cellular and molecular sequelae, and rehabilitative approaches over time that cannot otherwise be addressed in a clinical setting (Morganti-Kossmann et al., 2010; Xiong et al., 2013). Hence, the preclinical information provided in this review will be limited to rodent studies.

### 1.3. Behavioral impairment after experimental TBI

Behavioral impairment is evident after TBI, regardless of the model utilized. Structural, functional, and behavioral tests can be used to evaluate the efficacy of rehabilitation, depending on the model chosen and the parameters identified for the injury. Cognitive assessment is most often accomplished using the Morris water maze (MWM) (Morris, 1984), but deficits have also been revealed using the radial arm and Barnes mazes, as well as the attentional set-shifting task (Smith et al., 1991; Hicks et al., 1993; Pierce et al., 1998; Sanders et al., 1999; Sanderson et al., 1999; Lyeth et al., 2001; Piot-Grosjean et al., 2001; Griesbach et al., 2004; Hoover et al., 2004; Kline et al., 2002, 2007a,b, 2008, 2010, 2012, 2016; Bondi et al., 2014a, 2015). Learning capability has also been documented in the freezing response test and object recognition tests (Fujimoto et al., 2004). Sensory processing deficits have been identified using sticky paper removal, limb placement, the whisker nuisance task, and a stationary shock zone on a rotating arena (O'Dell et al., 2000b; Riess et al., 2001; Baki et al., 2009; McNamara et al., 2010). Affective dysfunction can be tested with anxiety-like tests such as the elevated-plus maze, exploratory activity, and open field tests; sometimes with the presence of a predator or predator urine (Xiong et al., 2013). Forced-swim tests, acoustic startle response, tail suspension, and social dominance paradigms are other tests that can be indicative of depression-like symptoms or other affective changes.

In order to test the efficacy of preclinical TBI models for translational rehabilitation, the model must demonstrate persisting behavioral deficits. Despite the number of behavioral tests available, only a small subset of experimental TBI models are evaluated at time points greater than a month post-injury, and thus are not indicative of persisting behavioral morbidity. However, there have been some attempts at identifying late-onset or persisting cognitive deficits at one month or greater post-injury. Muccigrosso and colleagues (2016) measured cognitive deficits at one month following midline FP injury in adult male BALB/C mice using the Barnes maze. Cognitive deficits as measured by novel object recognition and Y-maze at 30 days post-injury in male mice subjected to weight drop TBI have been reported from several labs (Rachmany et al., 2013; Baratz-Goldstein et al., 2016; Ji et al.,

2016). Cheng and colleagues (2012) showed that rats housed in standard (STD) living conditions exhibited spatial learning deficits even up to 6 months after a CCI injury of moderate severity. Also utilizing CCI injury models, Lindner and colleagues (1998) and Dixon and co-workers (1999) showed cognitive deficits for up to a year after the insult. A similar long-term finding was observed after FP injury (Pierce et al., 1998) and a repetitive TBI using a modified version of the weight drop model that also induces rotational forces (Meehan et al., 2012; Kalish and Whalen, 2016).

To establish a connection between post-traumatic stress disorders after blast-induced mild TBI for returning veterans, a number of investigators rely on outcome measures that test affective deficits. Heldt and colleagues (2014) reported on a novel closed-head model of mild TBI caused by primary overpressure blast to the cranium that produced sustained deficits in mice as demonstrated by increased acoustic startle response, tail suspension, and evidence of elevated fear response. Sajja et al., (2015) reported elevated avoidance and decreased short-term memory at 1 and 3 months post-injury after blast-TBI. In a repetitive blast injury model, adult male rats were subjected to 1 blast overpressure per day for 3 consecutive days and tested out to 25 weeks post-injury (Elder et al., 2012). At 24 weeks or more post-injury, blast exposed rats demonstrated anxiety-like behaviors, increased acoustic startle response, and altered response to a predator scent challenge (Elder et al., 2012). After lateral FP injury, Palmer and colleagues (2016) reported diminished amygdala activation and increased behavioral threat response in adult c57b mice. Despite multiple reports of persisting anxiety-like or altered fear response behaviors in blast TBI models, no changes were measured after lateral FP injury (Lifshitz et al., 2007) or weight drop injury (Vallez Garcia et al., 2016).

Persisting somatic deficits have been studied extensively using midline and lateral FP injury models. At 3–4 weeks after a mild-moderate midline FP injury, rodents develop a late-onset gain-of-function hypersensitivity to whisker stimulation that persists to at least 56 days post-injury (McNamara et al., 2010; Learoyd and Lifshitz, 2011). This hypersensitivity to whisker stimulation is mediated through a glutamatergic circuit in rodents that connects the somatosensory ventral posteromedial (VPM) thalamic nucleus to the barrel fields of the primary somatosensory cortex (S1BF) and corresponds with the onset of hypersensitive presynaptic glutamate release, increased regional activation in response to whisker stimulation, and increased microglial activation at 7 and 28 days post-FP injury in the VPM and S1BF (Woolsey and Van der Loos, 1970; Land et al., 1995; Robertson et al., 2001; Lifshitz et al., 2016; Hall and Lifshitz, 2010; McNamara et al., 2010; Lifshitz and Lisembee, 2011; Thomas et al., 2012, 2016; Cao et al., 2012). Rats undergoing lateral FP injury experienced anxiety-like behaviors (elevated plus maze and open field), cognitive deficits (MWM), sensorimotor deficits, and somatosensory deficits twelve-weeks following injury (Curia et al., 2008; Jin et al., 2011; Johnstone et al., 2015; Allitt et al., 2016).

### 1.4. Rehabilitation in animal models

There are strengths and weaknesses associated with the incorporation of rehabilitation paradigms in translational research. Experimental models simplify the complex issues involved with human TBI in exchange for a reproducible model that allows for the study of

the etiology underlying persisting behavioral morbidity. TBI models reproduce DAI or focal injury while controlling for injury severity, age, sex, nutrition, pre- and post-morbid conditions, polytrauma, along with timing, duration, intensity, and type of rehabilitation (Thomas et al., 2015). However, when controlling for so many variables, the translational relevance of each experiment is only specific for a small subset of clinical patients. Also, with the limited amount of rehabilitation literature, there are few studies that have similar variables, which can complicate interpretation and translation to the clinical setting.

After TBI, in addition to DAI, ensuing vascular permeability and inflammation contribute to neural circuit disconnection and dysfunction (Jin et al., 2006, 2011; Farkas and Povlishock, 2007; Curia et al., 2008). In response to the ensuing damage, both degenerative and regenerative neuronal processes occur that repair or compensate for lost connections, potentially by uncoordinated regenerative responses that likely lead to maladaptive circuit reorganization underlying morbidity (Radulovic et al., 1995; Farkas and Povlishock, 2007; Thomas et al., 2016; Hoffman et al., 2017). Rehabilitation serves to overcome circuit disruption by strengthening the remaining circuits and guiding new connections.

**1.4.1. Environmental enrichment (EE)—**To provide cognitive, motor, and cellular rehabilitation after TBI, varying types of environmental enrichment (EE) paradigms have been implemented. The EE parameters used in the studies reviewed here include, but are not limited to, larger cages, various bedding types, cage mates, platforms, and visual and tactile stimuli such as balls and tubes that are placed in the cages. EE is typically administered immediately following injury for a set period of time. The implementation of these environments confers numerous benefits by increasing neuroplasticity, motor activity, and sensory stimulation throughout the rehabilitation process (Bondi et al., 2014b). A substantial amount of EE research has been conducted using controlled cortical impact (CCI) models with EE showing beneficial effects with regard to cognitive deficits (Bondi et al., 2014b; Kline et al., 2007a; Leary et al., 2007; Matter et al., 2011; Sozda et al., 2010; Folweiler et al., 2017; de Witt et al., 2011; Cheng et al., 2012; de la Tremblaye et al., 2016), and has been reviewed in detail (Bondi et al., 2014b).

Using only enriched housing, multiple studies have found beneficial, rehabilitative results up to 6 months post-injury (Cheng et al., 2012). In an attempt to rehabilitate the somatosensory deficits observed in whisker sensitivity (discussed previously), Alwis and colleagues (2014) demonstrated that EE decreased the development of late-onset sensory sensitivity by decreasing the hyperexcitability of neurons within the barrel cortex. It is of note that McNamara and co-workers (2010) found conflicting results in that EE did not significantly improve whisker sensitivity after injury. It is possible that because EE was only administered for 45 minutes, 3 days a week for 4 weeks, that the amount of time per a day was not sufficient to confer beneficial effects. Indeed, studies after CCI injury have shown that abbreviating EE for only 2 hours per day was insufficient to promote cognitive benefits in both male (deWitt et al., 2011) and female (Radabaugh et al., 2016) rats. Studies have shown that two weeks following FP injury, rats that had undergone EE exhibited marked cognitive improvements in a MWM task without changes in motor function (Passineau et al., 2001; Hicks et al., 2002). Additionally, cognitive effects have been observed in reference to behavioral testing in the Barnes maze, showing spatial memory improvements as early as

two weeks after injury and retained until at least two months (Kovesdi et al., 2011; Lippert-Gruner et al., 2011). The long-term benefits of EE reported after mild TBI corroborate with EE studies after moderate CCI injury that show motor and cognitive benefits for up to 6 months (Cheng et al., 2012; Bondi et al., 2014b).

In order to elucidate possible mechanisms of EE-induced benefits, multiple studies have evaluated pathological and chemical changes following TBI. These studies have provided evidence to support that implementation of EE lead to significantly smaller cortical lesions in rats undergoing EE rehabilitation versus those housed in STD conditions (Passineau et al., 2001; Maegele et al., 2005; Bondi et al., 2015). A decrease in neuronal cell loss has also been reported after FP and CCI injury (Lippert-Gruner et al., 2007; Kline et al., 2007a,b, 2010, 2012; Bondi et al., 2015). Other groups have looked at cell signaling pathways following injury and found that benefits observed by EE are not mediated by changes in BDNF, TrkB, or neurotrophin-3 gene expression (Hicks et al., 2002). However, other possible mechanisms may include changes to neurotrophic factor expression, neurotransmission, neurotransmitter receptor expression, synaptic protein expression, morphological changes including dendritic branching, synaptic density, neurogenesis, or cell survival (Kline et al., 2010; Briones et al., 2013; Alwis and Rajan, 2014; Bondi et al., 2014b, 2015).

In this brief summary of EE administered after TBI, it remains important to note that many factors may influence the beneficial effects observed with EE. Primarily the time of introduction of the enrichment following injury and amount of time spent in the environment have been shown in studies utilizing CCI injury to directly influence overall effects with too little exposure having no observable influence (de Witt et al., 2011; Matter et al., 2011; Bondi et al., 2014b, 2015). Furthermore, in a review of articles using polytherapy, it was found that the majority of studies found positive effects when combining individual therapies that each had been shown to be beneficial, thus indicating that future studies should evaluate multiple types of EE rather than targeted monotherapies (Kline et al., 2016).

**1.4.2. Exercise—**There is a paucity of models that are solely diffuse TBI being evaluated in rehabilitation paradigms, but several exist for lateral FP injury, which as indicated previously is a model typically considered to be of a diffuse nature. Daily physical exercise has been implicated in benefitting brain injury patients on many levels. Appropriate daily exercise improves sleep, controls weight, increases cerebral integrity and neurocognition, mediates the HPA axis in response to stress, and elevates mood (Mead et al., 2008; Fatouros et al., 2010; Hoffman et al., 2010; Archer, 2012). Several studies report that physical exercise also promotes neurogenesis, neuronal survival, and neuroplasticity. Hence, exercise is an inexpensive, non-invasive rehabilitation tool for patients with TBI (Griesbach, 2011; Wogensen et al., 2015). Despite the large amount of support for exercise therapy, it is important to consider the therapeutic window for exercise. It has been proposed that prematurely initiating exercise after TBI could exacerbate PCS, especially if the exercise increases chances of a second TBI, like premature return-to-play in American football (Guskiewicz et al., 2007).

In rodents, there is evidence that upregulation of BDNF during exercise contributes to synaptic plasticity, learning and memory, and improves behavioral outcomes (Gomez-Pinilla, 2008). However, if the exercise regime is too rigorous or forced, it could activate a stress response, elevating circulating levels of corticosterone and downregulating BDNF, thereby neutralizing some of the positive benefits of exercise (Schaaf et al., 2000). Evidence of stress-induced corticosterone release interfering with recovery was demonstrated when TBI rats treated with chronic corticosterone for 3 months lead to worse behavioral outcomes (White-Gbadebo and Hamm, 1993). Supporting these studies, Greisbach and colleagues (2014) reported that forced exercise resulted in a stress response (circulating corticosterone) with no change in BDNF levels. Therefore, when evaluating the effectiveness of exercise as a rehabilitation paradigm, it is important to consider timing, duration, intensity, and frequency in regard to levels of stress in TBI models. Translationally, stress management should be taken into account when constructing clinical rehabilitation plans that include exercise therapy.

In addition to timing, willingness to participate in exercise and the severity of injury have also been assessed in regard to improving outcome. Voluntary exercise (running wheel) initiated immediately after injury has been reported to be detrimental to cognitive recovery and has failed to upregulate BDNF in comparison to controls. However, delaying voluntary exercise improved cognitive function and upregulated BDNF expression similar to sham controls (Griesbach et al., 2004; 2009). In another study, BDNF upregulation after exercise was dependent on injury severity and onset of exercise, where mild FP injury upregulated BDNF when exercise began 14–20 days post-injury, while moderate FP injury required a later onset of exercise, 30–36 days post-injury, to increase in BDNF (Griesbach et al., 2007). After a closed-head injury in mice resulting in an ipsilateral focal lesion (mixed pathology), forced moderate intensity exercise using a treadmill demonstrated improved cognitive recovery and upregulated BDNF if initiated at 2 days post-injury, but not at 9 days post-injury (Chen et al., 2013a). After lateral FP injury, forced exercise (treadmill) for 18 days did not improve behavior, but did increase BDNF (Hicks et al., 1998). Wu and colleagues (2013) reported that voluntary running exercise in rats starting immediately after mild lateral FP injury and lasting for 12 days improved cognitive recovery. These data emphasize the importance of timing (early vs. delayed), intensity, and type (forced vs. voluntary) of exercise and the severity of injury in regard to recovery and neuroplasticity after exercise rehabilitation (Kreber and Griesbach, 2016). Translationally, these data reinforce the necessity for individualized care programs catered to the severity of injury and symptoms.

**1.4.3. Alternative approaches—**Several other therapeutic approaches have been identified to improve rehabilitation after TBI. When fed a docosahexaenoic acid (DHA)-enriched diet, cognitive scores after brain trauma were enhanced in both exercised and non-exercised groups (Bailes and Mills, 2010; Wu et al., 2004, 2011, 2013, 2014; Schober et al, 2016 PMID 26247583). Other therapeutic approaches include sensory stimulation (de Diego et al., 2013; Wan Yunus et al., 2015), exposure to music (Hegde, 2014), and transcranial magnetic stimulation (Beom et al., 2016). Testing these approaches alone or in combination with exercise and EE paradigms could provide evidence for alternative therapies that would further specialize rehabilitation (Kline et al., 2016).

**1.4.4. Beyond behavioral outcomes for assessing recovery after TBI—**Aside from behavioral improvement, alternative quantitative outcome measures to support preserved or repaired circuit integrity and circuit function would be beneficial. One such approach would be the use of immediate early genes (IEG). IEGs are a useful marker for neuronal activity because they are rapidly upregulated in neurons associated with specific tasks. For example, cFos staining after whisker stimulation 4–6 weeks after TBI showed an increased area of activation within the cortical and thalamic relays of the whisker circuit, indicative of a loss of circuit integrity that paralleled the hypersensitivity to whisker stimulation at late-time points (Hall and Lifshitz, 2010; McNamara et al., 2010). A more expedited approach could be to use rtPCR to quantify IEG expression in small biopsies of brain areas relevant to the circuit being tested. For instance, gene expression of the IEG, Arc, in the somatosensory cortex after whisker stimulation has been shown to be a quantifiable and input-dependent marker of circuit activation that may be able to quantify the impact of TBI and subsequent rehabilitation paradigms (Khodadad et al., 2015). These types of studies would provide novel approaches to quantify circuit activation by assessing cellular activation.

## 2. Behavioral assays of executive function

### 2.1. Clinical tests for executive function and behavioral flexibility

The frontal lobe is one of the four major lobes in the mammalian cerebral cortex that governs a wide range of functions, from executive function to motor control. Executive function represents a collection of higher-order cognitive processes that dictate thought, feelings, and action, categorized as the ability to display inhibition, control, flexibility, planning, goal-oriented behavior, and emotional regulation. TBIs involving the frontal lobe have been shown to negatively impact executive function, with cognitive dysfunction being a major problem within the first weeks to months post-injury, and impaired mental switching and behavioral inhibition deficits also being common outcomes of severe TBI (Batty et al., 2015). Even mild to moderate TBIs, such as ones that do not cause detectable lesions, can disrupt cognition and produce functional deficits (Heffernan et al., 2013). Moreover, the cognitive recovery post-TBI may last years following the injury, with great variability among individuals (Millis et al., 2001, Ord et al., 2010).

The Wisconsin Card Sorting Task (WCST) is a popular multi-factorial test used to measure executive function and attentional set shifting (Tait et al., 2014), having been successfully employed numerous times in clinical populations with frontal lobe damage or dysfunction, psychopathological conditions thought to affect higher-order cognitive function, as well as neurodegenerative diseases. The WCST requires patients to sort cards based on three categories (color, shape or number of shapes), with rule acquisition occurring based on trial-by-trial experimenter feedback indicating whether the previous response is correct or incorrect. Rules and dimensions alternate without the subject's knowledge, who must identify errors and switch attention to the new salient dimension, which previously represented an irrelevant dimension (Lapiz-Bluhm et al., 2008). Ord et al. (2010) reported a dose-response relationship between the severity of the TBI and the consequent deficits in performance on the WCST, such that mild TBIs did not have a measurable impact on

executive functions related to the WCST 12-months post injury, while moderate-to-severe TBI patients saw an increased likelihood of functional impairment. While the WCST has particular shortcomings with regard to performance depending on multiple cognitive mechanisms (e.g., trying to recall previously salient contingencies), as well as intrinsic difficulty when switching between multiple perceptual card features (e.g., color to shape), the intradimensional/extradimensional (ID/ED) task of the Cambridge Neuropsychological Automated Testing Battery (CANTAB) has also been employed to examine behavioral flexibility capabilities in both humans and non-human primates (Sahakian and Owen, 1992). During this task, line segments are superimposed on a touchscreen onto abstract shapes, thus requiring visual discriminative capabilities between stimulus features, and allowing for identifying executive function deficits in a variety of psychopathological conditions (Tait et al., 2014), as well as in TBI patients (Moore et al., 2010). Considering that performance on both WCST and ID/ED tasks recruit a widespread neural network directly or indirectly involving the frontal lobe, as well as other brain regions such as basal ganglia, hippocampus or parietal cortex, it is of paramount importance to further expand animal models that similarly detect alterations in cognitive flexibility, behavioral inhibition, and memory formation in order to translate putative rehabilitation approaches back to the clinic for the patients affected by neurobehavioral sequelae post-injury (Bondi et al., 2015).

### 2.2. Digging-based attentional set shifting test

Preclinical testing methods are used to create an understanding of different behavioral tests as well as pharmaceutical therapies before they become available for human patients. The preclinical studies included in this section specifically pertain to rodent models assessing attentional set-shifting and stimulus reversal, operant-based contingency learning, and the ability to discriminate between rules after experimental brain trauma. Discrimination tasks are used to test a person or animal's ability to recognize different stimuli and respond to them appropriately, with one version being employed in the laboratory as a "dig task". This odor-discrimination task used by Martens and colleagues (2012) assessed deficits in decision-making behaviors for rats with cortical contusions in the frontal and parietal lobes by requiring rats to retrieve cereal rewards in various scented sands. Frontal cortex-injured rats demonstrated severe memory deficits for the initial discrimination of the dig task, as well as reinforcement reversals, and novel scent discriminations. Conversely, rats with parietal cortex injury performed at sham (i.e., uninjured control) levels on all task measures, thus rendering a pivotal role played by the frontal lobe in non-hippocampal cognition tasks, which warrants further experimentation in laboratory models (Martens et al., 2012). To further begin to address frontal lobe-mediated executive dysfunction in rodent models of TBI, Bondi and colleagues (2014a) began to implement an attentional set-shifting task (AST) previously demonstrated to represent the rodent analogue for the ID/ED and WCST tasks (Birrell and Brown, 2000; Bondi et al., 2008; Tait et al., 2014). The AST comprises a series of increasingly difficult perceptual dimensions to obtain a reinforcer (i.e., small piece of Honey-nut Cheerio®) and uses odor and tactile cues paired within small terracotta bowls for successive two-choice discrimination learning and stimulus reversals. Subjects must recognize the salient stimulus discrimination (i.e., odor or digging medium) based on a predetermined randomized stimulus order and must learn to ignore overlapping secondary dimension distractors, similar to the ID/ED task in the clinic (Bondi et al., 2008, 2014a).

Bondi et al. (2014a) produced parietal CCI injuries of varying cortical deformation depths (2.6, 2.8, or 3.0 mm) and reported impact depth-dependent alterations of behavioral flexibility and executive function in the AST, seen as an increased number of trials to reach criterion of 6 consecutive correct responses and increased total errors in the more severe injury groups, namely 2.8 and 3.0 mm cortical deformation depth. This study paved the way towards further investigating measures of executive function sensitively and reliably disrupted in TBI models. Ongoing studies focus on assessing gender differences on executive performance parameters following TBI, as well as pharmacological and rehabilitative therapies relevant to the clinic, such as antidepressants and EE. Moreover, we are performing multiple injury site comparisons (e.g., frontal versus parietal CCI) on executive function outcome, as well as the interaction between TBI and chronic stress exposure on long-term recovery. New directions also include multimodal approaches aiming to dissect behavioral flexibility domains via operant-based behavior versus the innate foraging-based AST.

### 2.3. Operant-based discrimination and sustained-attention tests

To more closely mimic injuries observed in human patients and investigate TBI-related region-specific behavioral deficits, Chou and colleagues (2016) applied the CCI method in a recent report to induce a unilateral frontal cortex TBI (1.25 mm cortical deformation depth, at speed of 4 m/s) in mice, and measured prefrontal cortex (PFC) function at various chronic time points post-injury. The study assessed injury effects of social behavior, cognitive flexibility, and anxiety, by employing the thee-chamber sociability task, the rule shift paradigm, and the elevated plus-maze test, respectively. Results suggested that frontal lobe contusion impaired social recognition and orbitofrontal cortex (OFC)-dependent rule reversal behavior, however not rule shifting, at one month post-TBI. The deficits persisted for 5.5 months after experimental TBI. Conversely, there was only a trend for increased anxiety and no impairment on hippocampal-dependent memory. The specificity of this approach outlines the OFC as a target region aiding in behavioral outcome differentiation following parietal and frontal contusion models, and further studies involving OFC-related behavioral flexibility capabilities could support the fine-tuning to TBI pharmaco- or cognitive-rehabilitative therapies (Chou et al., 2016). The concept of brain region-specificity with regards to executive function and cognitive flexibility domains has increasingly been a focus in rodent behavioral models. A recent report further investigated the role of the PFC and the hippocampus at performing cognitive shifts – either reversal learning or set-shifting (Mala et al., 2015) by employing anteromedial frontal cortex ablation and fimbria-fornix transection models, alone or in combination, to individually target important structures for mediating flexible behaviors and complex rule learning, namely the PFC and hippocampus, respectively. Neither single lesion nor combined lesions affected the rats' ability to acquire a spatial discrimination task. During the reversal of spatial learning, the performance of the individual lesion groups was not significantly different from sham controls. In contrast, rats with dual lesions were impaired on both error rate and acquisition speed relative to all other groups. Regarding the set-shifting in a visual discrimination task, all lesioned groups were comparably impaired relative to the sham group, suggesting that the two brain structures are mutually dependent regarding reversal learning, albeit not set-shifting (Mala et al., 2015).

An important research direction aiming to fulfill a void of information comprising frontal lobe-mediated goal-directed behavior alterations post-injury, as well as the impact of pharmacotherapies relevant to psychopathological and neurotransmitter changes following TBI, has been steadily emerging in recent years by the use of more complex and cognitively demanding behavioral approaches considered standard in the field of behavioral pharmacology, namely operant chamber-based tasks such as the three- or five-choice serial reaction time task (Vonder Haar et al., 2016). Firstly, given that higher-order cognitive processes can be affected chronically post-injury, it becomes relevant to consider the long-term cognitive effects of TBI given during development. Following the administration of mild TBI (concussion-like) or sham injury at post-natal day 30 (P30) using a closed-head weight-drop injury model, Mychasiuk and colleagues (2015) used the five-choice serial reaction task (Go/No-Go paradigm) and open field test to measure hyperactivity, sustained attention, impulsivity, and response inhibition in both male and female rats. It was reported that mild TBI was associated with deficits of sustained attention, impulsivity, and response inhibition in both sexes, albeit male rats were more impaired when tested for inaccuracy and impulsivity on the Go/No-Go task. In addition, while only a trend, injured male rats were more likely to be hyperactive when tested at P58, whereas females with an early injury displayed a hypoactive phenotype (Mychasiuk et al., 2015), thus offering insight into the relationship between mild TBI and executive function outcome, as it relates to targeted delivery of preventative or rehabilitative strategies to normalize neurobehavioral function. In a quest to further differentiate roles on attentional performance among the medial PFC (mPFC) and other structures intimately connected to the PFC, Kosaki and Watanabe (2012) investigated the effects of ibotenic acid lesions of the mPFC, the anterior cingulated cortex and the hippocampus on the repeated acquisition of three-choice positional discrimination tasks, which included a reversal component and employs a simplified three-lever version of the five-choice serial reaction time task. Lesioning each of these areas had different outcomes on behavior flexibility, with the mPFC being responsible for the inhibition of existing responses, the hippocampus being involved in previously reinforced stimulus-responses, and the anterior cingulate accounting for error correction, therefore shedding light on functional interactions between brain structures in the mediation of flexible behavior (Kosaki and Watanabe, 2012).

An initial study using standard automated operant behavior in adult rats was published by Vonder Haar et al. (2014b) and provided a characterization of deficits in a two-choice, high vs. low tone discrimination, with subjects being trained and tested at baseline, and following a bilateral frontal CCI injury, for both the discrimination contingency and reversal learning. Frontal TBI decreased accuracy on the operant tone discrimination task in a manner that was consistent throughout subjects, along with transient decreases in responses, impaired discrimination accuracy, and increased bias towards one side, thus highlighting the potential for other operant attentional measures to ensue in subsequent studies (Vonder Haar et al., 2014b). The same group followed up with another report (Vonder Haar et al., 2014a) assessing motivational and motor factors that could putatively contribute to deficits in discrimination. Specifically, Long Evans adult male rats were trained on a two-choice discrimination task (i.e., performance accuracy) and progressive ratio task (i.e., motivation), given a bilateral frontal CCI, and then reassessed on the behavioral paradigms. Frontal CCI

rendered significant deficits in both the discrimination and motivation tasks, with no effects being detected for gross motor measures. When rats were retrained on the discrimination task, it was reported that motivation might play an important factor for mediating the observed discrimination deficits. Nevertheless, the use of operant chambers to assess cognitive measures following TBI is gaining a definite interest in the field. The most recent study by Vonder Haar and colleagues (2016) involves the assessment of frontal CCI of varying degrees of injury severity on the five-choice serial reaction time task for measures of attention and impulse control, as well as the putative efficacy of multiple clinically relevant therapies, namely amphetamine, atomoxetine, and amantadine, on post-injury cognitive recovery rate. The authors reported that all TBI groups rendered significant, persistent, and often injury severity-dependent impairments on a variety of domains measured by the five-choice serial reaction time task, such as attention, impulse control, ability to complete trials, choice, and reinforcer collection latencies. Moreover, amphetamine treatment reduced impulsivity and improved attention in chronically impaired rats, whereas atomoxetine and amantadine reduced premature responding while increasing omission rates, suggesting depression of psychomotor skills (Vonder Haar et al., 2016). These studies are prime examples of steady progress in the multimodal assessment of various facets or domains of higher order cognitive performance in relation with long-term effects of TBI, and the emergence of applicable and effective treatments. TBI is a complex public health issue, therefore future implementation of clinically-relevant experimental models and approaches may further highlight the altered brain neurochemistry patterns and delineate pathways for therapeutic agents.

## 3. Endocannabinoids, stress, and TBI

### 3.1. Clinical assessments of neuroendocrine stress after TBI

TBI-related persisting symptoms (i.e., affective, somatic, and cognitive) share a great overlap with neuroendocrine abnormalities. Clinical studies in patients with mild to severe TBI report neuroendocrine abnormalities affecting corticotropin, growth hormone, gonadotropin, thyrotropin, prolactin, and vasopressin (Behan et al., 2008; Javed et al., 2015). Hypothalamohypophyseal dysfunction has been reported in 17% of patients with a severe trauma, rated 3 to 12 on the GCS, as a late consequence of craniocerebral trauma, and is more frequent in adults and less in children and adolescents (Krahulik et al., 2016). Current recommendations involve screening all moderate to severe TBI patients beginning with testing for hypocortisolism with a morning cortisol level within seven days post injury as hypopituitarism treatment may improve emotional and cognitive function in these patients (Renner, 2015). Yet, glucocorticoids are not recommended for routine use in brain-injured patients to reduce brain swelling and inflammatory responses, as a metaanalysis of randomised controlled trials showed that corticosteroid steroid treatment increases the risk of death or severe disability in around 80% of acute traumatic brain injury patients (Alderson and Roberts, 2005). Serum BDNF levels are reduced while cerebrospinal fluid and serum interleukin (IL)-1β, IL-4, IL-6, IL-7, IL-8, IL-10, and tumor necrosis factor alpha (TNFα) cytokines levels are higher after TBI, which is correlated with impaired memory scores, injury severity, depressive symptoms, and disinhibition to suicidal ideation (Failla et al., 2016; Juengst et al., 2014, 2015). Interestingly, plasma cortisol levels tend to increase

after mild to moderate TBI in the early post-injury period, whereas after a severe injury, cortisol levels are reduced (Tanriverdi et al., 2010). Animal studies show similar severity-dependent alterations in HPA reactivity to stress, characterized by an attenuation of the stress response after moderate TBI, and a facilitated stress response in a milder TBI.

### 3.2. Animal models of neuroendocrine stress after TBI

TBI-induced affective symptoms often include anxiety, anger, agitation, and depression, as well as altered neuroendocrine responses that directly impact affective symptoms. Decreased baseline CORT levels and altered stress responses are also observed months post-FP injury (Rowe et al., 2016). CCI injuries lead to a severity-dependent dysregulation of the neuroendocrine stress response to 30 min of restraint stress observed from 1–10 weeks and to a 15-min forced swim stress paradigm at 21 and 54 days after injury (Taylor et al., 2006, 2008). Similarly, adult male rats show a hyper-HPA responsiveness to an acute restraint stress at 7 and 14 days post FP injury, despite basal levels being the same between groups (Griesbach et al., 2011). Plasma ACTH and CORT levels are increased 6 hr following CCI, which is associated with reduced glucocorticoid receptor (GR) mRNA expression in the injured hippocampus (McCullers et al., 2002). Indeed, hippocampal GR and BDNF protein expression increased at 24 hr, but gradually decreased by 7 and 14 days post injury as compared to controls (Griesbach et al., 2012b). In addition, while, early forced, but not voluntary exercise potentiates CORT and ACTH levels up to 11 days after FP injury is associated with decreased hippocampal GR, but not BDNF protein levels (Griesbach et al., 2012a), delayed exposure to forced or voluntary exercise post FP injury increases hippocampal BDNF expression and recovers ACTH and CORT to sham levels (Griesbach et al., 2014). Administration of the GR antagonist, mifepristone, or $GABA_A$-receptor antagonist, bicuculline after CCI suppresses the stress-induced HPA response, suggesting that this neuroendocrine dysregulation post TBI may be mediated by the inhibitory actions of both GR and GABA (Taylor et al., 2013). CORT administration during the first 14 days post FP injury reduces HPA axis dysfunctions (Chen et al., 2013b), while the synthetic glucocorticoid analog, dexamethasone over-suppresses ACTH and CORT responses to a 30 min-restraint stress paradigm at 7 and 35 days after moderate CCI, indicating increased glucocorticoid negative feedback sensitivity, which may be related to greater hippocampal cell loss in the moderate TBI group compared the mild TBI or sham-injured groups (Taylor et al., 2010).

Corticotropin releasing hormone (CRH), a key peptide hormone regulating the neuroendocrine stress response, is upregulated at 2 and 4 hr post FP injury (Grundy et al., 2001; Roe et al., 1998), and post-treatment with CRH reduces cerebral edema observed 24hr after CCI (Beaumont and Marmarou, 1998). However, at both 7 and 35 days post CCI, peripheral injection of CRH stimulates CORT and ACTH secretion similarly in all rats, regardless of injury condition (Taylor et al., 2010), indicating that the effect of CRH may be more apparent at the central rather than peripheral level. Indeed, the CRH expression is noticeably increased in several brain regions in response to acute or chronic stress (Chen et al., 2012; Wang et al., 2013), and elevated CRH has been shown to effect hippocampal glutamatergic strength and synaptic plasticity, and to modulate cognitive function in a time-and-dose-dependent manner (Maras and Baram, 2012). CRHR1 is highly expressed on

dendritic spines of hippocampal pyramidal cells (Van Pett et al., 2000), and CRHR1 signaling is primarily responsible for the stress-impaired hippocampal glutamatergic transmission and memory function (Refojo et al., 2011).

Interestingly, EE has been shown to suppress the upregulation of hippocampal CRH mRNA and protein expression while also decreasing histone H3 acetylation, and increasing 5′-cytosine methylation in the CRH in the hippocampal CA1 in rats subjected to postnatal maternal separation (Wang et al., 2014). Early-life EE reduces anxiety behavior in the novelty induced suppression feeding task and increases the mRNA expression of endogenous cannabinoid CB1 receptors in the amygdala and the hypothalamus (El Rawas et al., 2011). These data provide evidence that TBI results in persisting HPA dysfunction and that EE may have beneficial effects regarding rehabilitation of the HPA axis after TBI.

### 3.3. CB1 receptors in TBI

The cannabinoid family of receptors has shown promise as a treatment for TBI in regard to neuroprotection of cellular, molecular, and behavioral impairments (Mechoulam et al., 2002; Schurman and Lichtman, 2017). However, its use in rehabilitation and treatment of affective symptoms, like stress, is less understood. Many reports indicate the deleterious effects of stress and impact on the HPA access after TBI, where treatment with either an agonist or antagonist of the cannabinoid CB1 and CB2 receptor may prove beneficial. The CB1 receptor is widely distributed on cell bodies, dendrites, and axons in the forebrain and has a more restricted distribution in the hindbrain and the spinal cord (Tsou et al., 1998). CB1 receptors are expressed within cortico-limbic and hypothalamic circuitry, including the paraventricular nucleus, the basolateral nucleus of the amygdala, the hippocampus, the bed nucleus of the stria terminalis, and the prefrontal cortex where they regulate HPA axis activity and glucocorticoid-mediated negative feedback (Melis et al., 2006). It is clear that the endocannabinoid system plays a major role in regulating the HPA axis (Hill et al., 2010) and indeed appears to reduce the consequences of chronic stress (Gorzalka et al., 2008). Also, cannabinoids administered shortly after exposure to a traumatic event can potentially prevent PTSD symptoms in humans (Berardi et al., 2016). Knowledge of HPA dysregulation after TBI in patients and animal models, as well as the increased incidence of comorbid TBI and PTSD highlights potential value.

### 3.4. Emotional behaviors in animal models of TBI

Anxiety and depression are common TBI-induced symptoms with behavioral changes indicative of anhedonia, despair, cognitive deficits, and changes in level of activity or novel exploration with evidence of mediation by the CB1 receptor. Anhedonia as measured with the saccharin preference test and despair in the forced swim test is associated with spatial learning and memory impairments in the MWM and hippocampal cell death after CCI injury (Cope et al., 2011, 2016; Watanabe et al., 2013). Increased immobility in the forced swim test is also accompanied by persistent spatial and passive avoidance memory impairments after more mild FP injury in rats (Milman et al., 2005) and closed-head injury (CHI) in mice (Milman et al., 2008; Zohar et al., 2011). Anxiety-like behavior in the elevated plus maze is increased one week after FP injury and is associated to increased neuropeptide-Y1 receptor (NPY1R), a maker of posttraumatic stress, and reduced protein levels of BDNF and its

receptor TrkB and other signaling pathway proteins (CaMKII, Akt and CREB) in the frontal cortex, which can be worsened by maladaptive dietary habits (Tyagi et al., 2013). CB1 knockout mice exhibit depression-like behavior in the tail suspension test, associated with reduced BDNF protein expression in the hippocampus as well as altered serotonin (5-HT) receptor density in the dorsal raphe nucleus (Khare et al., 2006). Similarly, chronic treatment with the CB1 antagonist, SR141716A leads to depressive-like behaviors and downregulation of hippocampal cell proliferation and survival, which is associated with decreased 5-HT release and BDNF mRNA in the PFC (Beyer et al., 2010). CB1 and BDNF have a bidirectional relationship, where CB1 signaling promotes BDNF expression in the hippocampus, enhancing neuronal plasticity and reducing emotional behavior (Aso et al., 2008; Butovsky et al., 2005; Khaspekov et al., 2004; Steiner et al., 2008), while increased BDNF is shown to inhibit CB1 activity in GABAergic striatal synapses, which is associated with stress-induced emotional behavior (De Chiara et al., 2010; Rossi et al., 2008).

Foot shock stress worsens the effects of repetitive concussive TBI in increasing anhedonia in the sucrose preference test, despair in the tail suspension test and social recognition impairments in mice, which could be reduced by treatment with the SSRI antidepressant sertraline (Brody et al., 2015; Klemenhagen et al., 2013). Similarly, chronic SSRI escitalopram treatment reduces emotional and social avoidant behavior following impact accelerated TBI in rats (Mahesh et al., 2010; Pandey et al., 2009). Rats exposed to three days of low-level blast once daily, under general anesthesia, show increased anxiety, contextual conditioned fear, and aversive response to predator scent exposure that remained evident months following the last blast exposure (Elder et al., 2012). Blast-exposed rats still exhibit evidence of anxiety and exaggerated fear responses, as well as subtle object recognition memory impairments, measured between 28 and 35 weeks following the last blast exposure (Perez-Garcia et al., 2016a). A single predator scent challenge delivered 8 months after the last blast exposure induces chronic anxiety in the open field, still present 45 days later, indicating that blast exposure sensitizes the brain to subsequent psychological stressors (Perez-Garcia et al., 2016b). Repeated unpredictable stress and a single mild blast leads to long lasting increases in anxiety and spatial memory impairment, compared to sham stressed animals, which is associated with elevated serum levels of CORT and elevated protein markers of neuroinflammation, vascular changes, and neuronal and glial cell loss in the hippocampus and the prefrontal cortex (Kwon et al., 2011). Yet, rats exposed to an adult cat for 1 hr, one day before CCI induction, and then again exposed to the same predator stress 10 days later, fail to show exacerbated neuroinflammation and neuronal cell loss post TBI (Acosta et al., 2013), indicating that the consequences of stress exposure on TBI recovery are time and context specific. TBI is a potent physiological stressor, leading to altered circulating corticosterone levels, but it is still not clear how a threatening environment prior or after injury may render some individuals more impaired and others resilient to the deleterious effects of stress on cognitive and emotional impairments arising from the insult.

### 3.5. CB1 and neuropathology following TBI

A role for CB1 receptors in the treatment of neuroinflammation and oxidative stress may be a therapeutic strategy for depressive-like behavior after TBI (Fenn et al., 2015; Higashi et al., 2014; Kabadi et al., 2014). Increased lipid peroxidation and over activation of the

antioxidant glutathione are observed in the ipsilateral cortex and hippocampus of mice exhibiting increased anxiety and depressive-like behaviors after CHI (Schwarzbold et al., 2010). Increased immune response to a lipopolysaccharide (LPS) challenge, as evidenced by increased microglia (IBA-1), and cytokine IL-1β and TNFα expression, is associated with prolonged social withdrawal, despair, and anhedonia in mice at 30 days post FP injury (Fenn et al., 2014). Simvastatin, an anti-inflammatory agent reduced neuronal apoptosis, microglia and astrocyte activation, and TNF-α expression in the CA3 region of the hippocampus, which was associated with increased immobility in the forced swim tests following FP injury in rats (Lim et al., 2017). Activation of cannabinoids CB1 and mostly CB2 receptors in activated microglia drives microglia to a M2 pro-resolution state, decreasing the production of pro-inflammatory mediators and protecting neurons from damage, which influence the development of psychiatric disorders, such as anxiety, depression, schizophrenia, and stress-related disorders (Lisboa et al., 2016). CB1 and CB2 receptor antagonists are shown to block the protective actions of the anti-inflammatory agent, minocycline, on reducing edema and improving the neurological score following CHI (Lopez-Rodriguez et al., 2013). CB1/CB2 receptor agonists (Firsching et al., 2012) as well as exogamic endocannabinoids have been shown to be protective when administered after TBI (Cohen-Yeshurun et al., 2013). 2-AG levels are elevated 1 hr after CHI in the injured hemisphere, peak at 4 hr and are sustained at 24 hr. 2-AG reduces brain edema, lesion volume, and hippocampal CA3 neuronal death (Panikashvili et al., 2001). 2-AG also reduces blood–brain barrier (BBB) permeability, pro-inflammatory cytokines-IL-6, TNF-α, IL-1β, NF-κB mRNA levels, while also increasing antioxidant levels following CHI (Panikashvili et al., 2006), which can be dose-dependently attenuated by the CB1antagonist, rimonabant, or by the CB1 receptor knockout mice (Panikashvili et al., 2005; Panikashvili et al., 2001).

Moreover, chronic treatment with PF3845, a selective FAAH inhibitor, enhances AEA levels and reverses CCI-induced impairments in fine motor movement, working memory, and anxiety-like behavior by activation of CB1 and CB2 receptors (Tchantchou et al., 2014). Similarly, Pre-treatment with the FAAH inhibitor, URB597, decreases anandamide metabolism and reduces the production of superoxide anions in the PFC of adolescent rats after ethanol consumption (Pelicao et al., 2016). Selective inhibitors of degradation enzymes for AEA and 2-AG injected 30 min post FP injury improve BBB integrity and reduce astrocyte and microglia activation (Katz et al., 2015). These studies indicate a protective role of endocannabinoid signaling against inflammation and oxidative damage post TBI. However, CB1 receptor and endogenous cannabinoid 2-AG are more highly expressed in rats exhibiting post-traumatic epilepsy than rats showing no epileptogenesis 12 months after FP injury, indicating that CB1 receptor signaling may mediate long-term neuron hyperexcitability after TBI (Zumbrun et al., 2015).

In conclusion, the endocannabinoid system plays a key role in mediating the neuroendocrine stress system, which is dysregulated after TBI. We have shown that the CB1 receptor, in a time and context-dependent manner, confers neuroprotective effects by attenuating neuroinflammation and oxidative stress, as well as improving neurobehavioral and cognitive outcome. Hence, the CB1 receptor may be an effective therapeutic target for alleviating depression, anxiety, PTSD, as well as other psychiatric disorders impairing functional recovery after TBI.

## 4. When therapeutic strategies go awry

In addition to the motor and cognitive deficits induced by TBI, other debilitating behavioral manifestations include agitation and aggression. These behavioral symptoms present frequently according to recent studies indicating that 24% to 96% of patients surviving TBI exhibit agitated behavior in the acute recovery phase (Levin and Grossman, 1978; Wolf et al., 1996; Nott et al., 2006; Ciurli et al., 2011) and 11% demonstrate aggressive behavior (Brooke et al., 1992). Clearly these maladaptive behaviors require rapid management as disruptive patients pose a physical risk to themselves and/or hospital staff, which ultimately complicates treatment and hinders rehabilitation efforts (Chew and Zafonte, 2009). The administration of antipsychotic drugs (APDs) is routine for managing TBI-induced agitation (Stanislav, 1997; Lombard and Zafonte, 2005; Elovic et al., 2008; McNett et al., 2012; Rao et al., 2015) albeit the risks of this approach on behavioral recovery are becoming increasingly clearer due to preclinical studies evaluating this class of drugs (Kline et al., 2007b, 2008; Hoffman et al., 2008; Phelps et al., 2015, 2017; Folweiler et al., 2017). The onset of seizures is also more pronounced in TBI patients. A recent study reported an incidence rate of 8.9% acutely (i.e., < 24 hours) after TBI and a sharp rise to 20.5% at year 5 (Ritter et al., 2016). Therefore, antiepileptic drugs (AEDs) are also provided to patients. However, like the APDs, AEDs have also been shown to impede behavioral recovery. Hence, the goal of this section is to present data and discuss the ramifications of providing APDs and AEDs after TBI. The data show that the two heavily-prescribed classes of medications, APDs and AEDs, may provide immediate relief, but at the expense of sacrificing potential recovery after TBI.

### 4.1. Antipsychotic drugs

Despite their widespread utilization in the clinic, a stunning collection of research has revealed APDs typically impair, or even exacerbate, functional outcome after experimental TBI. Feeney and colleagues initially revealed that haloperidol (HAL) delayed motor recovery after unilateral ablation of the sensorimotor cortex (Feeney et al., 1982). HAL appears to similarly impair cognitive recovery as rats exposed to HAL display definitive deficits in the MWM, a behavioral task that assesses spatial learning and memory (Morris, 1984). The deleterious impact of HAL on functional recovery has been replicated and corroborated utilizing a variety of experimental TBI models. Specifically, cortical-ablation models (Goldstein and Bullman, 2002), FP injury models (Wilson et al., 2003), and open-skull CCI models (Hoffman et al., 2008; Kline et al., 2007b, 2008) have all revealed similar impairments in functional recovery. Moreover, the cognitive deficits induced by chronic HAL administration appear to persist for at least 3 months following drug discontinuation (Phelps et al., 2015). Further, it has been conclusively shown that the cognitive impairments induced by HAL cannot be attributed to mere sedation as shown by two studies with similar drug doses and number of doses, but with different timing of administration (Hoffman et al., 2008; Kline et al., 2008). Furthermore, it has been revealed that the detrimental impact of chronic HAL administration is powerful enough to reinstate beam-walking deficits even after recovery (Feeney et al., 1982), to block the beneficial effect of amphetamine on binocular depth perception after visual cortex injury in the cat (Hovda and Feeney, 1985),

and to mitigate the beneficial effects of EE on motor and cognitive function after CCI injury in the rat (Folweiler et al., 2017).

**4.1.1. Antipsychotic drugs (potential mechanisms)—**The mechanistic underpinning of HAL-induced impairment is likely related to inappropriate dopamine (DA) manipulation. Given that D2-receptor agonists, such as bromocriptine, improve functional recovery, it is reasonable to conclude that the D2-receptor antagonism of HAL and other APDs may underlie their pernicious effects (Phelps et al., 2015). APDs that possess a significantly lower affinity for the D2-receptor do not appear to compromise recovery. At low-doses, clozapine does not impact functional recovery (Goldstein and Bullman, 2002). Meanwhile, risperidone, an APD with a stronger affinity for the D2-receptor, impairs functional recovery similar to HAL (Kline et al., 2007b, 2008; Hoffman et al., 2008). Further, olanzapine and quetiapine have not been observed to impact functional recovery in rats (Weeks et al., 2016; Wilson et al., 2003). Although olanzapine has a high affinity for the D2-receptor, it has a dissociation rate constant that is significantly different than HAL and risperidone (Kapur and Seeman, 2000). Though the exact degree to which these dissociation rate constants differ is not certain, but it is at least several fold (Sahlholm et al., 2016). It may be the case that the superior “fast-off” dissociation rates of olanzapine, quetiapine, and clozapine allow for better endogenous dopaminergic responses (Kapur and Seeman, 2001). Given the importance of the dopaminergic system, this responsiveness could determine whether an APD produces impairments in cognition or other parameters of functional recovery. Ultimately, it is clear that DA plays some pivotal role in APD-induced impairments in functional recovery.

Nevertheless, sedation is still necessary to create an optimal rehabilitative environment. As noted, APDs with low affinities for the D2-receptor represent one possible avenue for clinicians to achieve sedation. However, the previously mentioned clozapine may not be the most appropriate choice, given it has a significantly higher rate of ictogenesis than its counterparts (Kumlien and Lundberg, 2010). Another option may be the atypical APD aripiprazole, a partial D2-receptor agonist and 5-$HT_{1A}$ receptor agonist. Our laboratory has revealed that aripiprazole not only eludes functional impairment, but may offer rehabilitative benefits at some doses (Phelps et al., 2017). Recent research has also revealed that intermittent HAL does not induce the deficits seen with chronic administration (Weeks et al., 2016). It is possible that intermittent administration avoids inducing a state of depolarization block, where DA neurons remain chronically depolarized and spontaneous discharge is significantly attenuated (Grace et al., 1997). While traditionally considered a delayed-process, recent schizophrenia research has suggested that depolarization block may be achieved rapidly in diseased brains (Valenti et al., 2011). Thus, it is possible that depolarization block occurs rapidly in the post-TBI environment. Studies exist on every end of the spectrum, with some claiming long lasting deficits, some neuroprotection, and others no effect (Feeney et al., 1982; Kline et al., 2007b; Tang et al., 1997). These differences may be explained by the severity of the injury model utilized. Moderate-to-severe injuries may differentially impact the integrity of the blood-brain barrier and manipulate drug exposure. Therefore, it may be the case that sporadic sedation does not significantly impact functional recovery. Indeed, it has been shown that neither a single dose of HAL nor risperidone

impairs motor and cognitive outcome after TBI (Kline et al., 2007b). Altogether, it is clear that clinicians ought to express particular care in the selection and utilization of sedatives after TBI.

### 4.2. Anti-epileptic drugs

Much like APDs, AEDs are commonly prescribed after TBI and can have a deleterious impact on functional recovery. Phenytoin (PHE) has historically been the most-utilized and heavily prescribed AED, likely achieving its therapeutic effect through frequency and voltage-dependent inhibition of Na+ channels (Mantegazza et al., 2010; Ragsdale and Avoli, 1998; Ragsdale et al., 1991). This voltage-dependent inhibition appears to reduce Ca++ influx and subsequent glutamate release, both particularly relevant players in the pathophysiology of TBI (Sitges et al., 2016). While research has revealed some neuroprotective qualities sans anti-ictogenesis, there are serious concerns about its impact on functional recovery (Farber et al., 2002). Chronic administration of PHE after TBI impaired cognitive recovery in the MWM and exacerbated hippocampal cell loss in the CA1 region (Darrah et al., 2011). PHE has also shown deleterious effects in some clinical studies (Bhullar et al., 2014). A randomized clinical trial with placebo controls found cognitive impairment only in severe TBI cases (Dikmen et al., 1991). Notably, this impairment was not present at one year, and patients appeared to improve following the withdrawal of PHE when compared to placebo controls. Limited, acute usage of PHE may have a moderate beneficial effect as indicated by increased exploratory behavior, reduced hippocampal cell loss, and increased GAP-43 expression with a 2-day administration paradigm after TBI (Darrah et al., 2011). More research is needed to elucidate the characteristics of PHE-induced impairment.

Levetiracetam (LEV) has been proposed as a suitable alternative to phenytoin. LEV is believed to achieve its therapeutic effect through inhibition of synaptic vesicle 2A, mitigating the effects of negative allosteric modulators on inhibitory GABAA and glycine receptor-mediated responses, and the selective inhibition of voltage-gated N-type Ca++ channels (Loscher and Brandt, 2010). Chronic administration of LEV has been shown to positively influence GAP-43 and synaptophysin in the hippocampus and frontal cortex, while simultaneously attenuating IL-β (Zou et al., 2013). LEV has also conferred neuroprotective benefits as demonstrated by greater exploratory behavior, higher cell survival, and attenuated TBI-induced decreases in glial glutamate transportation. In contrast, abbreviated administration does not show pronounced effects (Zou et al., 2015). LEV appears to be well-tolerated and as effective as phenytoin, though one clinical study has revealed abnormal EEG readings (Jones et al., 2008; Khan et al., 2016). Presently, LEV serves as a highly suitable alternative to PHE.

Valproate (VPA) has recently seen relatively extensive investigation of its neuroprotective and neurotrophic benefits. VPA likely achieves its anticonvulsant properties through a variety of mechanisms, including inhibition of histone deacetylase and glycogen synthase kinase (GSK)-3β and blocking voltage-gated sodium and low-voltage T-type calcium channels (Chen et al., 2014). Further, it suppresses GABA transamination and NMDA-mediated neuronal excitability. VPA has been shown to reduce inflammation, apoptotic cell

death, lesion volume, and aggression. It has also been reported to upregulate brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF), and can help preserve blood-brain barrier integrity when used in combination with lithium (Chen et al., 2014; Wroblewski et al., 1997; Yu et al., 2013). Starting 30 minutes post-insult, five days of VPA administration improved motor and cognitive function in the MWM (Dash et al., 2010). When administered after a three hour delay, VPA improved motor performance but not cognition. VPA may be particularly desirable in cases of polytrauma. VPA has shown pronounced benefits when combined with fresh frozen plasma, preserving mitochondrial function and attenuating glutamate-mediated excitotoxicity (Hwabejire et al., 2013). Clinical trials of valproate have revealed neither deleterious nor advantageous effects on cognitive outcome (Dikmen et al., 2000). However, one randomized trial did show a trend towards increased mortality compared to PHE (Temkin et al., 1999). While displaying promise preclinically, VPA needs more clinical support to justify preferential use.

Other AEDs have been investigated, with varying impacts on functional recovery. The neuroprotective benefits of topiramate have also been investigated (Hoover et al., 2004; Kouzounias et al., 2011). Influencing both inhibitory GABAA and excitatory AMPA-receptors, topiramate appears to offer neuroprotection against glutamatergic storms *in vitro* and *in vivo* (Alves et al., 2003; Angehagen et al., 2003). Nevertheless, the impact of topiramate on patients at the clinical level is presently understudied. Carisbamate, remacemide, and talampanel have been shown to be mildly neuroprotective, though similarly understudied in TBI patient populations (Belayev et al., 2001; Keck et al., 2007; Smith et al., 1997). Vigabatrin and lacosamide do not appear to impact functional recovery after experimental TBI (Montanez et al., 2001; Pitkanen et al., 2014; Wallace et al., 1999). Phenobarbital has been used for its anticonvulsant like properties, though its utilization could be detrimental to recovery (Montanez et al., 2000). Nevertheless, clinical studies have not yet found phenobarbital to conclusively drive poor outcomes (Majdan et al., 2013). Recent research utilizing bumetanide, a $Na^+$-$K^+$-$2Cl^-$ (NKCCl) cotransporter blocker, in combination with phenobarbital displayed promising anti-ictal results in the acute phase. However, long-term plastic responses appeared to exacerbate ictogenesis (Dzhala and Staley, 2015). Utilization of benzodiazepines, such as diazepam, also appear to disrupt recovery after injury (Jones and Schallert, 1992; Schallert et al., 1986). This effect may be mitigated by utilization of GABAergic agonists in combination with benzodiazepines (O'Dell et al., 2000a). GABAergic agonist use alone appears to, instead, deleteriously impact recovery (Hernandez and Schallert, 1990). Thus, the use of barbiturates, benzodiazepines, and GABAergic agonists should ideally be used as a last-resort. Gabapentin and ethosuximide have not yet been appropriately investigated for their impacts on functional recovery. Ultimately, it is important for clinicians to remain cognizant when prescribing AEDs. While the risks of posttraumatic seizure are genuine, care should be taken to preferentially utilize medications with beneficial, or minimal negative, impacts on long-term outcome.

## 5. Conclusions

The overall discussion highlighted both experimental diffuse and focal traumatic brain injury (TBI) as well as clinical brain trauma and their ensuing chronic behavioral deficits, which ranged from simple motor performance to spatial learning and memory impairment.

Executive function, which is higher cognition was also discussed. Rehabilitative approaches for the TBI-induced dysfunctions were discussed as well as the therapies that are provided to TBI patients to control affective symptoms and seizures, respectively.

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## Highlights

- Neurorehabilitation is effective after experimental TBI
- Digging- and operant-based attentional tasks are sensitive measures of executive function after TBI
- CB1 receptors implicated in neuroendocrine stress and plasticity
- Antipsychotic and antiepileptic drugs impair functional recovery