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Found in translation: understanding the biology and behavior of experimental traumatic brain injury

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Abstract

BONDI, C.O., B.D. Semple, L.J. Noble-Haeusslein, N.D. Osier, S.W. Carlson, C.E. Dixon, C.C. Giza and A.E. Kline. Found in translation: understanding the biology and behavior of experimental traumatic brain injury. NEUROSCI BIOBEHAV REV. The aim of this review is to discuss in greater detail the topics covered in the recent symposium entitled “Traumatic brain

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injury: laboratory and clinical perspectives," presented at the 2014 International Behavioral Neuroscience Society annual meeting. Herein we review contemporary laboratory models of traumatic brain injury (TBI) including common assays for sensorimotor and cognitive behavior. New modalities to evaluate social behavior after injury to the developing brain, as well as the attentional set-shifting test (AST) as a measure of executive function in TBI, will be highlighted. Environmental enrichment (EE) will be discussed as a preclinical model of neurorehabilitation, and finally, an evidence-based approach to sports-related concussion will be considered. The review consists predominantly of published data, but some discussion of ongoing or future directions is provided.

Keywords

Attentional set-shifting test (AST); closed head injury; concussion; controlled cortical impact (CCI); environmental enrichment (EE); fluid percussion (FP); neurorehabilitation; pediatrics; social behavior

1. Introduction

Traumatic brain injury (TBI) affects approximately 10 million individuals worldwide each year. Two million of those occur in the United States (U.S.), making it one of the most prevalent of all neurological disorders (Goldstein 1990; Selassie et al., 2008; Faul et al., 2010). In the U.S. approximately 300,000 of the TBI cases are severe enough to warrant hospitalization, where roughly 50,000 patients die (Sosin et al., 1995; Faul et al., 2010). Of the 250,000 survivors, 70,000 to 90,000 endure long-term disabilities leading to costly medical and rehabilitative care (Max et al., 1991; Thurman et al., 1999; Selassie et al., 2008; Summers et al., 2009). In addition to physical impairments that limit routine daily function, other pervasive and persistent challenges faced by TBI survivors are significant disturbances in cognitive function, such as memory loss, poor response inhibition, distractibility and the inability to acquire or store new information, particularly as it relates to prior experience or environmental feedback (Busch et al., 2005; Horneman and Emanuelson, 2009; Walker and Tesco, 2013). These disturbances occur not only in moderate to severe TBI cases, but also in patients with mild TBI who are reported to develop post-concussion symptoms characterized by cognitive impairments comorbid with other neurobehavioral symptoms such as emotional alterations (Levin and Robertson, 2012).

Unfortunately, treatment options for brain injury are limited and therefore continued research is critical. In this vein, several experimental models have been developed with the intent to better comprehend the pathophysiology and neurological sequelae of TBI. These models are utilized extensively to induce brain injury replicating features and outcomes that are seen clinically. The expectation is that understanding pathological mechanisms through empirical research may lead to therapeutic interventions capable of attenuating motor and/or cognitive dysfunction. The objective of this review is to provide a broad perspective of the contemporary models of TBI that are in use today, as well as to present data on neurobehavioral and social deficits resulting from their use in pediatric and adult rodents. The review will also discuss the value of pharmacological and environmental interventions

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in promoting recovery, and will conclude with a bench to bedside perspective on concussion.

2. Contemporary laboratory models of traumatic brain injury

Experimental models of TBI have been developed to study injury biomechanics, discover pathological mechanisms, and develop therapies with the goal of reducing TBI-induced human suffering. This section will describe contemporary animal models of TBI and will focus on the neuropathology and relevant neurobehavioral outcomes. Regarding the latter, commonly used behavioral tasks presented at the symposium will also be highlighted as we consider them to be integral components of TBI models. While other less common behavioral tasks are available to assess function after TBI, they were not discussed at the symposium and hence are not considered germane to this review.

2.1. Fluid percussion

First described by Lindgren and Rinder in a rabbit model of TBI (Lindgren and Rinder, 1966), the fluid percussion (FP) device has been used in several other animal species, including cats (Sullivan et al., 1976), rats (Dixon et al. 1987; McIntosh et al., 1989), pigs (Armstead and Kurth, 1994), and mice (Carbonell et al., 1998). The FP device (Figure 1A) consists of a Plexiglas cylinder filled with physiologic saline and enclosed at one end by a male Luer-Lock fitting that is subsequently paired with a female fitting. Injury is produced when a metal pendulum strikes the piston of the device from a predetermined height and causes the rapid injection of saline into the closed cranium. The resulting pulse induces a brief increase in intracranial pressure with associated displacement and deformation of neural tissue. The severity of injury is regulated by varying the height of the pendulum, which corresponds to variations in extracranial pressure pulses expressed in atmospheres.

2.1.1. Rat midline fluid percussion—Midline FP in rats is produced by placing the injury screw along the central sagittal suture midway between bregma and lambda. Midline FP has been used to induce concussive injuries (Dixon et al., 1987) and can produce cognitive deficits in the absence of overt hippocampal cell death (Lyeth et al., 1990). Although the lateral FP model has been more popular for studying neuronal cell death mechanisms, there is a recent resurgence of interest in midline FP because of the increased interest in diffuse brain injury associated with sports concussions and blast-induced TBI.

2.1.2. Rat lateral fluid percussion—Lateral FP in rats is produced by placing the injury screw over the parietal cortex midway between bregma and lambda. Lateral FP is advantageous for producing hippocampal cell death and cortical contusions (McIntosh et al., 1989). Furthermore, lateral FP injury in the rat has been shown to disrupt the blood-brain barrier (Cortez et al., 1989) and reduce cerebral blood flow (Yamakami and McIntosh, 1991). Other established consequences of lateral FP injury in rats include increased cerebral edema, tissue shearing, and intraparenchymal hemorrhage (Graham et al., 2000). Taken together, these consequences contribute to the formation of a focal lesion in the injured cortex (Tanno et al., 1992; Dietrich et al., 1998).

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2.2. Controlled cortical impact

Experimental TBI induced with a pneumatic impactor was first introduced for use in laboratory ferrets by Lighthall and colleagues (Lighthall, 1988; Lighthall et al., 1990) and subsequently adapted for rats by Dixon and associates in an attempt to better control the biomechanical parameters of brain injury (Dixon et al., 1991). Unlike the FP injury device that disperses a stream of solution intracranially that cannot be readily quantified, the controlled cortical impact (CCI) model of experimental TBI takes advantage of biomechanical events contributing to injury (Figure 1B). These events can be analyzed by establishing a quantifiable relationship between measurable engineering parameters, such as force, velocity, and tissue deformation, and the magnitude of tissue damage or functional impairment. These controlled mechanical variables enable accurate, reliable, and independent control of the deformation parameters over a wide range of contact velocities.

The CCI injury device typically consists of a rod that is actuated either 1) pneumatically using a small-bore (1.975 cm), double-acting stroke-constrained pneumatic cylinder with a 5.0-cm stroke (Dixon et al., 1991), or 2) electromagnetically (Brody et al., 2007). The actuators are rigidly mounted on either a crossbar or stereotaxic manipulator arm in either an angled (perpendicular to the dura surface) or vertical position. The lower rod end has an impact tip attached that varies in geometry (rounded or flat edge), material (rigid metal or soft tip), and diameter (commonly 5 to 6 mm for rat CCI). CCI devices typically contain a velocity-measuring sensor system. The velocity of the impacting shaft is controlled by varying the gas pressure, in the case of pneumatic pistons (Dixon et al., 1991) or by varying electrical power in electromagnetic actuators (Brody et al., 2007). The impactor tip is driven at a predetermined velocity, to a target depth, and for a set duration of tissue deformation.

For mild or concussive TBI, the tip can strike the intact skull. For more severe TBI, the brain is impacted directly at a greater velocity through a craniectomy. Some research teams produce increasingly severe injury by driving the impactor tip deeper into the tissue. In rats, a depth of penetration of 2.6 to 2.8 mm with a velocity of 4.0 m/sec and a dwell time of 50 to 150 msec consistently produces an injury of moderate severity. However, it is important to note that the abovementioned guidelines regarding how to produce moderate injury are based on those used by the authors; the exact injury parameters depend on the particular laboratory. For example, Washington et al. (2012) used a Leica Impact One electromechanical CCI to produce mild, moderate, and severe TBI in mice, by keeping the velocity (5.25 m/sec), tip size (3.5 mm diameter) and dwell time (0.1 sec) constant, while scaling the depth as follows: 1.5 mm depth for mild-, 2.0 mm for moderate-, and 2.5 mm for severe-injury. Budinich et al. (2012) used the same CCI device (Leica Impact One) to produce moderate and severe injury in mice; notably, in this study while severe injury was produced with a 2.5 mm depth, moderate injury was induced with a depth of merely 1.0 mm. In the Budinich et al. (2012) study, the size of the impact tip and velocity were also different from the Washington et al. (2012) study; a 3.0 mm impact tip was driven at a velocity of 5m/s, with a dwell time of 0.1 seconds. The differences in injury parameters used in the Washington et al. (2012) and Budinich et al. (2012) studies highlight the variability across labs and the importance of making thoughtful choices in study design as they relate to injury severity. It is also important to note that injury severity can be selected or validated using

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physiologic criteria such as blood pressure and breathing outcomes. For example, Igarashi et al. (2007) consider severe injury to be characterized by apnea as well as transient post-injury hypertension followed by hypotension, whereas lower-grade injuries do not result in apnea and are characterized by immediate and prolonged hypotension. Other research teams use other physiological outcomes to set and refine their injury parameters to achieve the desired extent of injury. Researchers can also base injury severity on the nature or extent of functional deficit observed. Notably, there is no consensus regarding how to equate histopathological or behavioral outcomes or injury severity. Injury parameter settings should be informed by the research goals, a thorough review the literature, and, when possible, evidence from pilot studies.

2.2.1. Rat controlled cortical impact—The rat CCI model also produces morphologic and cerebrovascular injury responses that resemble certain aspects of human TBI. Commonly observed are graded histologic and axonal derangements (Lighthall 1988; Dixon et al., 1991; Goodman et al., 1994; Meaney et al., 1994), as well as disruption of the blood-brain barrier (Dhillon et al., 1994; Kochanek et al., 1995), subdural and intraparenchymal hematoma, edema, inflammation, and alterations in cerebral blood flow (Hall et al., 2005). Similarly, the CCI model also produces neurobehavioral and cognitive impairments similar to those observed in human patients. For example, Briones and colleagues (2013) found the CCI significantly impaired spatial memory, as evidenced by increased latency to find the escape platform in a Morris water maze (MWM) task. Working memory deficits are common after human brain injury and also been reported following rat CCI injury (Kline et al. 2002a). As will be discussed in greater detail in section 4.1, frontal lobe function has also been observed to be impaired in rats following CCI when evaluated using the attentional set-shifting test (AST) 4 weeks post-injury (Bondi et al. 2014). In contrast to other TBI models, the CCI device produces a pronounced cortical contusion, which is calculated by measuring tissue loss in serial coronal sections stained with hematoxylin and eosin or cresyl violet (Kline et al., 2004; Olsen et al., 2012; Monaco et al., 2013; Bondi et al., 2014). Hippocampal neuronal loss/survival is measured semi-quantitatively by counting healthy-appearing neurons or by using unbiased stereologic methods (Baldwin et al., 1997; Kline et al., 2004; Olsen et al., 2012; Monaco et al., 2013). Studies of CCI with the de Olmos amino-cupric-silver staining method have indicated that CCI can induce neurodegeneration in regions distant from the site of impact in rats (Hall et al., 2005).

2.2.2. Mouse controlled cortical impact—With the development of mutant strains of mice, including both gene knockout and transgenic lines, a version of the CCI model in mice has logically followed. Smith and colleagues characterized this model in the C57BL6 mouse - the background commonly used to produce relevant mutant strains (Smith et al., 1995). While the depth of deformation is scaled down to 1.0 to 1.2 mm based on the cortical thickness of the mouse versus rat, and for a given impact velocity, an insult of similar severity to that commonly seen in rats is produced. Because mice are steadily becoming more widely used, the mouse CCI model is taking on greater importance in the field of TBI. Neurobehavioral deficits in the mouse are similar to those seen in rat and many of the behavioral testing strategies are identical or similar, but on a smaller scale. For example, spatial memory deficits have been observed following CCI when evaluated using both the

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MWM and the Barnes maze (Fox et al., 1998, 1999). More recently, dysfunctions in social interaction, such as impaired social investigation, loss of preference for sociability, loss of presence for social novelty, and increased aggression were reported for adult mice who received a pediatric CCI injury (Thau-Zuchman et al., 2012).

2.2.3. Pig controlled cortical impact—In general, large-animal models of TBI are justified for complex physiologic and biomechanical studies that require large brain mass, more white matter content, or greater cortical complexity. By increasing the size of the impact tip and depth of impact, the CCI model has easily been scaled up to larger animals such as the pig. Using a direct focal impact method, Duhaime and associates demonstrated in piglets of different ages a vulnerability to mechanical trauma that increased progressively during maturation (Duhaime et al., 2000). CCI produced in swine with a pneumatic impactor has been shown to result in clinically relevant pathophysiology such as edema, cell death, white matter damage, and cerebrovascular dysregulation (Alessandre et al., 2003; Manley et al., 2006). Pig CCI models may be the most useful TBI model to mimic the neurological intensive care unit environment due to the ease of monitoring clinically-relevant physiological parameters in these larger animals (Zhou et al., 2009).

2.3. Closed head injury

Closed head injury models are thought to produce injury by transmitting mechanical forces through the skull to the brain. There are three main variations of closed head injury models. The first is a focal impact applied to the intact skull. Hall and coworkers produced concussive injury in mice by dropping a 50-g weight 18 cm onto the intact skull (Hall et al., 1988). Other investigators have characterized and applied a closed head impact model in both rats (Shapira et al., 1988) and mice (Chen et al., 1996) that produces edema, functional deficits, and significant hippocampal neuronal cell death. For weight drop models, the height and mass of the falling weight are adjusted according to the desired severity of injury, with farther distances and increased weight producing more injury than less distant and lighter weights.

The second type of closed head model is the Marmarou impact acceleration model (Marmarou et al., 1994) (Figure 1C). In this model, a weight is attached to a string, and when the predetermined height above the cranium is obtained, the weight is released through a guide tube that subsequently strikes a cemented disk (“helmet”) on the rat skull to prevent fractures (Marmarou et al., 1994). During impact the head is rapidly accelerated downward onto a foam pad, which facilitates relatively slower head deceleration. Impact acceleration produces a diffuse injury without noticeable contusions or hippocampal cell loss. However, brainstem and/or diffuse axonal injury (Okonkwo and Povlishock, 1999) and elevations in intracranial pressure have been observed after closed head impact acceleration injury (Engleborghs et al., 1998).

The third type of closed head TBI models is the head rotation model. Initially characterized in non-human primates (Gennarelli et al., 1982), it was later successfully adapted to swine (Ross et al., 1994). Diffuse axonal injury and transient posttraumatic unconsciousness are produced in miniature swine by rapid acceleration and deceleration of the head in the

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coronal plane, without impact (Ross et al., 1994). When applied to immature piglets this model produces a range of clinically relevant functional deficits that correlate with neuropathologic axonal damage (Friess et al., 2007). For example, piglets exposed to moderate injury had impaired visual-based problem solving and were less interested in exploring their environments (Friess et al., 2007). Sullivan and colleagues (2013) developed a highly sensitive and specific battery of neurobehavioral assessments to facilitate quantification of cognitive, motor, and other behavioral changes after experimental TBI in piglets.

2.4. Blast relevant TBI

Animal models have been developed to simulate elements of blast-relevant TBI (bTBI) including explosive or pressurized gas-driven shock tubes to generate pressure waves similar to those produced by explosives (Svetlov et al., 2010). bTBI models have focused on mimicking the primary overpressure shock wave as it is a key aspect of explosive blast that differentiates itself from civilian and penetrating models of TBI. The classic method of evaluating blast on living tissue is to produce a controlled detonation with animals placed at standardized standoff distances. While such models are clinically and biomechanically relevant to military bTBI (Bauman et al., 2009) their accessibility is limited to only a few facilities and thus they are not yet available for widespread investigation. Laboratory models of bTBI typically expose anesthetized animals to a controlled generated Friedlander waveform that is characterized by an initial peak pressure followed by a negative pressure.

Non-explosive shock tubes are the most common methods to generate shockwaves in laboratory environments. These tubes are typically comprised of a driver section that is separated by a longer driven section by a diaphragm. The driver section is pressurized until the diaphragm bursts allowing rapid expansion of the gas into the driven section producing a pressure waveform that mimics elements of an explosive shockwave. Varying the thickness of the diaphragm material can control the pressure of the burst. The test animal can be placed at varying distances from the end of the tube, or inside the tube. Furthermore, the torso can be shielded to mimic body armor and minimize non-cerebral damage. Another way to produce bTBI to the head only is to use smaller shock tubes where the expelled gas is limited to the head (Svetlov et al., 2010). In general, these models not only mimic the primary blast shock waves, but also produce clinically relevant cognitive and neuropathological responses (Long et al., 2009; Elder et al., 2012).

2.5. Motor assessment tests

2.5.1. Beam-balance and beam-walk tests—Motor function is a common deficit in TBI patients. These deficits include difficulty with balance and fine motor performance, increased dizziness, and reductions in muscle strength. Clinically relevant rodent models of TBI have utilized complex vestibulomotor and strength tasks to evaluate similar deficits in experimental TBI. The beam-balance task is used to assess motor and vestibular functioning by observing the rodents' ability to balance on a stationary beam. Briefly, it consists of placing the rat on an elevated beam (1.5 cm wide) and recording the time it remains on for a maximum of 60 sec. The beam-walk task, originally described by Feeney and colleagues (1982), consists of training/assessing rats using a negative-reinforcement paradigm to escape

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ambient light and white noise by traversing an elevated narrow beam (2.5 × 100 cm) and entering a darkened goal box situated at the opposite end. When the rat enters the goal box the adverse stimuli (light and noise) are terminated thus serving as reinforcement (reward) for completing the task. Performance is assessed by recording the elapsed time to traverse the beam. Both beam tasks (beam-walking and beam-balance) were used to characterize the FP (Dixon et al., 1987) and CCI (Dixon et al., 1991) models of TBI and are used extensively after TBI to evaluate therapeutic manipulations (Fujimoto et al., 2004; Kline et al., 2004a,b, 2007, 2008, 2010; Cheng et al., 2007, 2008; Sozda et al., 2010).

2.5.2. Rotarod test—The rotarod test has been used to assess fine motor function in both rats (Hamm et al., 1994; Hamm, 2001; Monaco et al., 2013) and mice (Mouzon et al., 2012). As is the case for the beam-walk and beam-balance, the rats are trained prior to TBI or sham injury to perform the task. Typically, training begins two to three days prior to surgery and consists of both fixed rate and accelerating protocols until the rats are able to perform proficiently (Monaco et al., 2013). On the day of surgery the rats are provided three trials according to the accelerating protocol, which may vary from laboratory to laboratory, to establish baseline performance. Motor assessment is then conducted at prescribed time points after TBI. The testing procedure evaluates the time and/or speed of revolutions before the rat loses its balance and falls off the accelerating rotating rod.

2.6. Cognitive assessment tests

2.6.1. Acquisition of spatial learning and memory—The Morris water maze (MWM), developed by Morris et al., (1982) was first applied to *in vivo* TBI research in a study of CCI conducted by Hamm and colleagues (1992). Several studies have found long-term deficits in the acquisition of spatial learning that persist from 6 months after CCI injury (Cheng et al., 2012) to one year after either CCI injury (Lindner et al., 1998; Dixon et al., 1999) or lateral FP brain injury (Pierce et al., 1998). It has since become one of the most widely used tools for assessing the potential benefits of various therapeutic manipulations on spatial learning in preclinical TBI research (Bramlett et al., 1995; Scheff et al., 1997; Kline et al., 2002a,b; Cheng et al., 2007, 2008; Olsen et al., 2012; Yelleswarapu et al., 2012). Briefly, the maze consists of a pool (typically 180 cm diameter; 60 cm high) filled with tap water (26 ± 1°C) to a depth of 28 cm and is situated in a room with salient visual cues that remain constant throughout the study. The platform is a clear Plexiglas stand (10 cm diameter, 26 cm high) that is positioned 26 cm from the maze wall in the southwest quadrant and is held constant for each rat. Spatial learning typically begins on post-operative day 14 and consists of providing a block of four daily trials (4-min inter-trial interval) for five consecutive days (14–18) to locate the platform when it is submerged 2 cm below the water surface (i.e., invisible to the rat). For each daily block of trials the rats are placed in the pool facing the wall at each of the four possible start locations (north, east, south, and west) in a randomized manner. Each trial lasts until the rat climbs onto the platform or until 120 sec have elapsed, whichever occurs first. Rats that fail to locate the goal within the allotted time are manually guided to it. All rats remain on the platform for 30 sec before being placed in a heated incubator between trials. The times of the 4 daily trials for each rat are averaged and used in the statistical analyses.

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Another common use of the MWM is to assess memory retention via a probe trial. In this subtest, the platform is removed from the water maze and the percent time the rodent swims in the quadrant of the pool that contained the platform during acquisition is measured. The rationale is that a rat that has learned and remembers the location of the hidden platform should spend more time in the target zone searching for it. Numerous studies have shown benefits with various therapies in memory retention during a relative acute time period of 3 weeks (Kline et al., 2004a,b, 2007, 2010, 2012; Monaco et al., 2013). However, the task is also sensitive to long-term effects (i.e., 1 year) as demonstrated by Dixon and colleagues (Dixon et al., 1999). A more recent study by Byrnes et al. (2012) found that performance on the MWM probe trial was poorer among TBI-exposed mice than their control (sham or naïve) counterparts.

The MWM can also be used to assess working memory after experimental TBI. Hamm and colleagues (1996) have shown working memory deficits following FP injury and Fox et al. (1998) have reported similar working memory deficits in mice following CCI injury. Kline and colleagues (2002a) demonstrated working memory deficits in male rats after TBI. In the latter study, spatial working memory was assessed on postoperative days 11–15. Briefly, each rat received eight pairs of trials per day with a maximum of 120 sec to find the escape platform on each trial and a 10-sec delay between trial 1 (information trial) and trial 2 (retention trial). The start points (North, East, South, and West) and goal locations (1, 2, 3, and 4) were quasi-randomly assigned each day with the requirement that during the 8 pairs of trials each rat was tested twice from each start position and goal location.

2.6.2. Novel object recognition memory—Recognition memory is defined as the ability to successfully match an encounter (e.g., person, object, location) to a representation stored as memory upon re-experience (Norman and O'Reilly, 2003). Recognition memory represents an important component of human long-term memory and is of interest to researchers using data from both humans (Kelly et al., 1996; Wright et al., 2014) and animals (Bevins and Besheer, 2006). TBI patients have impaired recognition memory (Hannay et al., 1979; Millis and Dijkers, 1993), a finding that has been replicated in animal models using a variety of assessments. For example, the novel-object recognition (NOR) test has been used in a number of in vivo TBI studies (Ji et al., 2012; Yang et al., 2013; Scafidi et al., 2010; Zhao et al., 2012). However, in our experience, subtle changes in the NOR paradigm with respect to the nature of the objects used (e.g., size, shape, color) and proximity of the objects to one another may affect NOR performance. A review of the methodological modifications of the NOR test and its application to behavioral pharmacology research was recently published (Antunes and Biala, 2012).

2.6.3. Contextual fear conditioning—Assessment of post-injury fear responses can be evaluated using contextual fear conditioning (CFC). Originally developed by Michael Faneslow (Faneslow and Tighe, 1988), CFC is rooted in Pavlovian fear conditioning in that through repeated pairing with a threatening exposure (e.g., loud noise), a non-threatening stimulus begins to elicit fear responses (Kim et al., 1992; Phillips and LeDoux, 1992; Rudy and O'Reilly, 1999). Brain regions responsible for CFC include the hippocampus and amygdala. CFC has been widely used in diverse in vivo studies (Young et al., 1994). CFC

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was only recently applied to a few TBI specific studies as an outcome measure (Klemenhagen et al, 2013; Titus et al., 2013; Luo et al., 2014).

2.7. Limitations of TBI models

Overall, the TBI devices discussed mimic many of the important histopathological changes (e.g., axonal injury, cell death, inflammation) and functional deficits (e.g. spatial memory problems, social dysfunction) seen following human TBI. However, an important caveat is that experimental TBI models do not fully capture the breadth and complexity of human brain injury outcomes with respect to the neurobehavioral correlates, particularly those functions involving communication and language. Moreover, some neurobehavioral outcomes are less well studied in experimental TBI. For example, frontal lobe dysfunction is understudied in this context because of challenges associated with designing analogs of complex frontal lobe functions such as impulse control and language, although as described later in section 4 of this review executive function can be assessed quite sensitively. Similarly, while adolescent TBI survivors have been found to display impaired empathy and moral reasoning compared to their non-injured peers (Beauchamp et al., 2013), there are no clear analogous outcomes for empathy and moral reasoning in animal models.

3. Social behavior after injury to the developing brain

TBI at a young age may have adverse consequences on the development of normal social behavior(s); however, few preclinical studies have addressed this important outcome measure. In this section we describe the application of behavioral assays for social investigation, socio-sexual behaviors, and social communication in experimental TBI models, and present recently identified social changes in a mouse model of pediatric TBI. Factors that potentially impact social outcomes will also be considered, including age-at-injury, severity of injury, and time post-injury.

3.1. Social deficits in young brain-injured patients

TBI is the primary cause of morbidity and mortality among young children and older adolescents (Schneier et al., 2006). Within these populations, brain injury results in a wide range of physical, neurological, cognitive, and psychosocial difficulties, which may persist long-term (Beauchamp et al., 2013; Karver et al., 2012; Levin et al., 1992). Compared to the adult, the pediatric brain shows some unique responses to TBI. For example, a greater head-to-torso ratio and higher brain water content in the child compared to adult brain contribute to an injury that may be more diffuse in nature (Kochanek, 2006). Indeed, both clinical (Adelson et al., 1997; Koskiniemi et al., 1995) and experimental studies (Bittigau et al., 2004; Fan et al., 2003; Tsuru-Aoyagi et al., 2009) have demonstrated that the developing brain is inherently more vulnerable to injury compared to the adult (Anderson et al., 2005; Bauer and Fritz, 2004; Potts et al., 2006). Further, functional deficits may emerge over time post-injury as survivors fail to reach age-appropriate milestones (Anderson et al., 2005; Anderson and Moore, 1995; Koskiniemi et al., 1995).

The normally developing brain, characterized by complex changes in both structure and composition, is likewise associated with the emergence of temporally specific behaviors.

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Developmentally-regulated processes of myelination, synaptic pruning, and structural reorganization continue throughout early childhood and adolescence in a region-specific manner, while physiological measures such as intracranial, arterial, and cerebral perfusion pressures also vary with age (Adelson et al., 2003; Donders and Warschausky, 2007; Kochanek et al., 2012). It has become clear that the developing brain exhibits age-dependent vulnerability to TBI, with children under four years of age typically exhibiting poorer outcomes compared to older children (Anderson and Moore, 1995; Karver et al., 2012). To better understand the pathobiological mechanisms underlying this vulnerability, several of the abovementioned experimental models of TBI have been adapted for use in rodents at an early post-natal age (Adelson et al., 1996; Adelson et al., 1998; Prins et al., 1996; Tong et al., 2002). One such model utilizes a unilateral CCI in mice at postnatal day (PND)-21, approximating a toddler-aged child (Semple et al., 2013; Yager and Thornhill, 1997). This model generates a distinct, reproducible pattern of neuronal loss in the injured frontoparietal cortex and underlying subcortical structures, associated with widespread white matter damage (Tong et al., 2002). Progressive neuronal loss results in an increase in tissue atrophy over time (Claus et al., 2010; Pullela et al., 2006), consistent with ongoing neurodegeneration seen after TBI in young patients (Keightley et al., 2014). Functionally, brain-injured mice display a phenotype of transient anxiolysis and persistent hyperactivity, as well as spatial memory deficits that are delayed in onset (Pullela et al., 2006). These features are consistent with neurobehavioral sequelae seen in brain-injured children (Konrad et al., 2000; Levin, 1998; Max et al., 2011).

Problems with social functioning are common after TBI in both adults and children, and have widespread quality of life consequences including academic achievement, relationships and re-integration into society (Yeates et al., 2007; Rosema et al., 2012; Bigler et al., 2013; Rosema et al., 2014). While motor and physical symptoms tend to stabilize or diminish over time after injury, functional impairments including cognitive and emotional disturbances cause the greatest long-term distress (Yeates et al., 2004; Catroppa et al., 2008; Chapman et al., 2010; Catroppa et al., 2012). In children, severe TBI is associated with low peer acceptance and high levels of rejection and victimization in the classroom (Bigler et al., 2013; Rosema et al., 2014). The maturation of social behaviors is protracted through childhood and adolescence in a normally-developing child, suggesting that TBI at a young age is likely to adversely affect the acquisition and establishment of social skills (Wells et al., 2009). In addition, brain injury at a young age is predictive of poorer language and non-verbal communication (Ewing-Cobbs et al., 1997; Wells et al., 2009; Sullivan and Riccio, 2010), which may complicate the ongoing development of social skills (Didus et al., 1999) and persist up to 20 years after severe TBI during childhood (Cattelani et al., 1998; Hoofien et al., 2001; Ryan et al., 2013).

To address the increasing clinical data indicating the prevalence of post-traumatic social dysfunction and its importance in long-term prognosis, behavioral tests to assay social function are beginning to be incorporated into preclinical TBI studies. Much can be learned from paradigms developed and validated by colleagues in autism research, where assessment of social behaviors forms the basis of disease diagnosis (Crawley, 2012).

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3.2. Behavioral assays of social behavior in rodents

Social behavior is a complex collection of actions including approach, affiliation and agonistic encounters. Many of these interactions are readily observable in rodents, and mouse models have been developed to study the core symptoms seen in autism spectrum disorders as well as other neurodevelopmental conditions such as fragile × syndrome (Kooy et al., 1996; McFarlane et al., 2008; Young et al., 2010). Laboratory *Mus musculus* display a broad repertoire of quantifiable social behaviors including approach to olfactory pheromones and other mice, ultrasonic vocalizations, communal nesting, scent marking, aggression, sexual and play behaviors (Terranova and Laviola, 2005; Silverman et al., 2010; Crawley, 2012). The most common paradigms to assess social behavior are described here briefly. Behaviors are typically scored from videotapes by investigators blinded to genotype, treatment or injury group, or by software linked to video-tracking or photocell detection systems (Spencer et al., 2005; Ohayon et al., 2013).

3.2.1. Reciprocal social interactions—Observation of *reciprocal social interactions* is currently the most common experimental paradigm for social behavior. Two unfamiliar rodents are permitted free exploration within a specified arena, and social investigation is quantified (Wöhr and Scattoni, 2013). Different interactive actions including sniffing, body contact, aggressive behaviors, climbing, mounting, huddling, close following and play behaviors may be assessed, and parameters such as the session length, arena size, time of day and prior social experiences can be modified according to the experimental aims (Terranova and Laviola, 2005; An et al., 2011). Repeated testing of the same mice is usually possible, allowing for the evaluation of developmental trajectories across age (Silverman et al., 2010). The *resident-intruder test* is an adaption of this test, typically conducted in the home cage of the experimental animal, to which an unfamiliar stimulus is introduced (Duvoisin et al., 2011; Koolhaas et al., 2013). The stimulus rodent may be male or female, to examine male-to-male interactions or sociosexual behaviors, respectively. Further, the stimulus is typically either naïve or an experimental animal matched to the condition of the animal being tested, and may be of a younger age to minimize antagonistic behaviors. Another adaption of this paradigm is the *partition test*, where the test and stimulus mice are physically separated by a perforated partition. Investigation close to the partition is quantified as a measure of social interest towards the stimulus mouse (Kudryavtseva, 2003; Silverman et al., 2010).

3.2.2. Three-chamber social approach task—The *three-chamber social approach* test, established by Crawley and colleagues, is now considered the ‘gold-standard’ for evaluating social deficits in autism mouse models (Nadler et al., 2004; Silverman et al., 2010; Yang et al., 2011). In this paradigm, the test mouse has a choice of spending time in the central (neutral) chamber or two adjacent chambers, one containing a wire cup-enclosed stimulus mouse and the other containing an empty cup. A mouse exhibiting normal sociability typically favors proximity of the stimulus mouse in preference over the empty cup (Moy et al., 2004, 2008). In contrast to tests of free social exploration, the physical confinement of the stimulus mouse in a wire cup permits olfactory, visual and auditory cues while preventing aggressive and sexual behaviors, and limits the initiation of social contact to the test mouse only. A subsequent test stage involves the introduction of a second novel

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mouse into the previously empty chamber, thereby presenting the test mouse with a choice of social partners. Typically, mice will spend more time in proximity of the novel stimulus, indicating social recognition and social memory of the now-familiar mouse (Silverman et al., 2010). An alternative test for social recognition is the *habituation-dishabituation* paradigm. This design consists of short, sequential encounters between pairs of mice, whereby habituation usually occurs and the time spent engaged in social investigation declines over time. During the final encounter, a novel stimulus mouse is instead introduced, and social recognition of this individual stimulates an increase in social interest (Guan and Dluzen, 1994).

3.2.3. Social aggression—Social aggression, typically exhibited by paired males, can be evaluated during resident-intruder scenarios as described above, by quantifying the frequency, duration, temporal and sequential patterns of antagonistic behaviors (Miczek, 1979; Miczek et al., 2001). An alternative measure is the *tube-dominance task* that evaluates the dominant-submissive relationship established between male mice during a brief encounter enclosed within a narrow tube in which they cannot turn around (Molina et al., 2008; Wang et al., 2011). The establishment of dominance in this test is thought to reflect a tendency for aggression, although it may also be dependent upon social anxiety (Spencer et al., 2005).

3.2.4. Social communication—The *social transmission of food preference* is another useful test of olfactory-based social memory in both rats and mice (Galef et al., 1983; Wrenn, 2004). In this paradigm, the test mouse interacts with a "demonstrator" mouse that has recently eaten a novel food. As a result, the test mouse will eat more of the now-familiar food compared to a completely new food when presented with the choice. This phenomenon depends on the test mouse detecting meaningful olfactory cues from the demonstrator during their interaction, and the subsequent food preference serves as a measure of social memory (Wrenn et al, 2003; Wrenn 2004). This task has not yet been evaluated in experimental TBI.

In addition to the evaluation of social investigation and contact, novel methods to assess social communication between rodents have also emerged from the autism field. *Urinary scent marking* is performed by male mice in a context-specific manner to mark territories, attract mates, and communicate health status information (Hurst and Beynon, 2004; Wöhr and Scattoni, 2013). A reduction in scent marking has been observed in several mouse strains characterized by low sociability (Wöhr et al., 2011a,b). Male mice will deposit scent marks onto absorbent paper in response to a female mouse or female urine, and these can be readily quantified (Arakawa et al., 2007, 2008).

Another means of communication between rodents is by *ultrasonic vocalizations (USV)*, which are produced by male mice in response to the presence of a female or female scent (Whitney and Nyby, 1979; Bean, 1982). Male-emitted USV's have been described as an index of social and sexual interest, recognition and motivation (Hammerschmidt et al., 2012; Wöhr and Scattoni, 2013), and changes have been reported in the context of autism-like social deficits (Scattoni et al., 2011; Wöhr et al., 2011a,b; Yang et al., 2012).

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3.2.5. Considerations for study design—Experimental design and conditions can profoundly influence behavioral results from these tests; potentially more so for subtle changes in social behaviors compared to when assaying for motor or cognitive functions. Social behaviors in rodents are predominantly mediated by olfactory cues and are therefore dependent upon intact olfactory function (Ryan et al., 2008). Thus evaluating the ability of experimental mice to detect volatile odors, for example, in a buried food olfactory discrimination task, is advisable (Yang and Crawley, 2009). In addition, social behaviors are particular sensitive to handling and housing conditions, as well as previous life experiences, particularly social isolation (Pietropaoloa et al., 2004; Terranova and Laviola, 2005; Crawley, 2007). Test variables including lighting, background noise, cage/arena size, the length of the habituation period and test duration, vary widely across studies and make comparisons somewhat difficult between different laboratories. As such, the evaluation of social parameters in experimental TBI requires meticulous control and evaluation of many subtle factors that may influence mouse behaviors and interfere with assessments.

3.3. Social deficits in experimental models of brain injury

Despite the above mentioned readily available assays of social behavior, there is a paucity of research examining social changes in the context of neurotrauma, a field that traditionally has focused on measures of cognitive and sensorimotor outcomes. Studies that have incorporated social tests into the study design to date (Table 1) provide some insight into the mechanisms and comorbidities associated with social dysfunction. Here, we will consider social tests and findings from different models of TBI that have been described in detail in the preceding section.

Pandey and colleagues (2009) examined depression-like and anxiety-like behaviors in rats at 14 days after diffuse impact-acceleration injury. Social interactions were assessed in an open field arena during a 5 minute session, and unfamiliar pairs of TBI rats were found to engage in a shorter duration of social investigation compared to paired sham-operated rats. In concert with abnormal behavior in the marble-burying test (Njung'e and Handley, 1991), the authors interpreted this finding as the manifestation of anxiety-like behavior (Pandey et al., 2009). In addition, sociosexual interactions were assessed in response to a sexually-receptive naïve female rat during a 20 min session in a neutral arena. Here, TBI rats showed a significant reduction in the number of genital probing, thrusting and pursuit episodes, and an increased latency to perform such behaviors (Pandey et al., 2009). The authors interpret this to reflect depressive-like behavior, based upon the understanding that sexual anhedonia is one of the key features of clinical depression (Kennedy, 2008).

Another recent study, using the midline FP injury model of diffuse TBI, examined ‘social withdrawal’ as the degree of social engagement with a novel juvenile mouse introduced into the home cage of the experimental animal (Wohleb et al., 2012; Fenn et al., 2013). After a peripheral inflammatory challenge at 30 days post-injury, brain-injured mice showed a reduction in total social exploration, which coincided with the presence of primed microglia and an exacerbated cytokine response (Fenn et al., 2013). This finding was again interpreted as a depressive-like phenotype, a concept first postulated by File and Hyde (1978), who

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observed that social interactions between rats often correlated with measures of emotionality (File and Hyde, 1978).

Several studies in models of mild or concussive brain injuries have recently considered social behavior as a phenotype independent of anxiety. Shultz and colleagues found that neither single nor repeated mild injuries at adulthood affected rat social behavior when tested at either 24 h or 4 weeks post-injury, despite evidence of a persistent cerebral inflammatory response (Shultz et al., 2011, 2012). Here, they employed a lateral FP injury to deliver 1, 3, or 5 insults, spaced 5 days apart, and an automated video-analysis system determined the distance between paired experimental rats in a neutral arena. In another study, two closed-skull impacts timed 24 hr apart were paired with a stressor (foot shock fear-conditioning paradigm) to examine the potential consequences of post-traumatic stress on TBI outcomes, including social behavior in a habituation-dishabituation paradigm at 10 days post-injury (Klemenhagen et al., 2013). They found that TBI (non-stressed) mice showed normal habituation towards an unfamiliar stimulus mouse across 9 consecutive trials; however, when a novel mouse was subsequently introduced, TBI mice interacted significantly less than sham animals. In comparison, TBI mice that were also stressed by foot shock additionally exhibited decreased interactions with an unfamiliar mouse during the habituation phase, suggesting that post-traumatic stress worsens the severity of social deficits (Klemenhagen et al., 2013). Together, these studies also suggest that social deficits may be less prevalent or less apparent after mild concussive TBI compared to more severe injuries, although further research is clearly needed to confirm this assertion.

Only one study to date has examined social dysfunction specifically after bTBI. Koliatsos and colleagues (2011) used a shock tube to generate shock waves in mice that are comparable to open-field blast waves. In addition to motor abnormalities and spatial memory deficits, mice underwent a habituation-dishabituation paradigm in a neutral arena across a series of 3 × 2 min exposures with the same mouse, followed by a final 2 min session with a novel stimulus mouse. The initial level of social exploration was similar between sham and bTBI mice, indicating no effect of bTBI on baseline sociability. However, blast-injured mice failed to show habituation to a familiar mouse across repeated exposures, suggesting that they failed to recognize or remember the stimulus mouse. These deficits were transient, detected at 1 week post-injury, but normalized by 2 weeks, and are in contrast to spatial memory deficits that still persisted at this latter time point (Koliatsos et al., 2011). Further research is needed to delineate potential correlations between comorbid functional deficits after TBI, such as the relationship between cognitive, emotional and social functioning (Milders et al., 2008; Pepin et al., 2000; Spikeman et al., 2012).

3.4. Social deficits after pediatric TBI in mice

To date, only two published studies have examined social behaviors after TBI to the developing brain, using the CCI model in male mice at PND-21 (Tong et al., 2002). In the first study, brain-injured and sham-operated control mice underwent the partition test, resident-intruder paradigm, Crawley three-chamber social approach, and tube-dominance tasks during adolescence (PND 35-42) and again at early adulthood (PND 60-70), in encounters with naïve age-matched stimulus mice (Semple et al., 2012). Despite normal

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social behaviors at adolescence, by adulthood, brain-injured mice showed reduced social investigation towards stimulus mice during the resident-intruder task, as well as a loss of preference for sociability in the three-chamber task. TBI mice also lacked a preference for social novelty, indicative of deficit in social recognition or memory. Also at adulthood, early-life TBI was associated with more frequent exertion of dominance in the tube task compared to sham-operated controls, a finding suggestive of increased aggressive tendencies. Of note, these deficits were evident despite normal olfactory function, as determined during the buried food test (Semple et al., 2012). Together, these findings reveal an emergence of aberrant social behavior over time after injury, a trajectory that parallels the development of cognitive deficits in this model, as well as behaviors seen in brain-injured children.

To address the extent to which the age at injury influences social behaviors, a subsequent study from the same investigators recently compared mice injured at PND 21 or PND 35 (Semple et al., 2014). Mice injured at a young postnatal age (PND 21), when tested at adulthood, exhibited reduced scent marking behavior and an alteration in context-dependent USVs in response to female stimuli. In contrast, mice injured at adolescence (PND 35) showed remarkable resilience to develop social deficits at adulthood. Together, these findings are in line with accumulating clinical evidence suggesting that the younger brain may show greater vulnerability to social deficits compared to older children or adults (Didus et al., 1999; Wells et al., 2009; Anderson et al., 2010).

3.5. The challenge: understanding mechanisms of social dysfunction

While social dysfunction is evident after TBI in patients and experimental models, the question inevitably arises - what is the pathobiology contributing to the manifestation of such deficits? Evidence from clinical neuroimaging, combined with animal models involving region-specific experimental lesions, is being utilized to address this issue. A better understanding of the mechanisms underlying social deficits may aid in the development of symptom-specific interventions for brain-injured patients.

Social behaviors in humans are mediated by the ‘social brain,’ comprised of the superior temporal sulcus, fusiform gyrus, temporal pole, medial prefrontal cortex, orbitofrontal cortex, amygdala, temporoparietal junction, and inferior parietal cortex (Beauchamp and Anderson, 2010; Blakemore, 2008; Yeates et al., 2007). Neuroimaging has revealed ongoing reorganization and connectivity of these structures during childhood and adolescence, indicating considerable development during brain maturation (Heyes et al., 2012). After TBI, psychosocial dysfunction has been adversely associated with frontal lobe pathology in patients (Levin et al., 2004; Wilde et al., 2005), particularly to regions implicated in social cognition and information processing (Eslinger et al., 1992; Spikeman et al., 2012; Wilde et al., 2005).

However, the relationship between regional neuroanatomy and social deficits is likely to be more complex, particularly in the context of a brain that is still undergoing maturational processes. Although adult models of frontal injury exist (Hoane et al., 2004; Kilbourne et al., 2009; Lindner et al., 1998), few have considered a juvenile age of injury or examined social functions. By adapting the standard CCI model to the parietal lobe of juvenile mice (Semple

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et al., 2012; Tong et al., 2002), to instead impact the unilateral left frontal lobe, Chen and colleagues hypothesized that injury to this location would also result in notable social dysfunction (Chen et al., 2013). Contrary to expectations, however, frontally-injured mice were indistinguishable from sham-operated controls in a battery of social tests at adolescence and adulthood after PND-21 injury; instead, the predominant phenotype was a persistent motor deficit, likely attributed to volumetric loss of the motor cortex (Chen et al., 2013). This surprising lack of social dysfunction may result from lesion laterality or age-dependent vulnerability to social deficits, based upon the region-specific maturational state at the time of injury. These findings support a more global mechanism underlying abnormal social function after TBI. It has also been proposed that the developing brain is less functionally-specific compared to the mature brain, such that regional localization of social functions may not yet be complete at an early postnatal age, rendering the young brain primed for more rapid establishment of compensatory connections (Spencer-Smith and Anderson, 2009).

In line with these findings, there is increasing evidence that diffuse axonal injury, which disrupts white matter connectivity between regions of the social brain network, may underlie many TBI-induced social deficits (Bigler et al., 2013; Ryan et al., 2013). Changes in the corpus callosum in terms of volumetric atrophy, microstructural integrity or connectivity (Ewing-Cobbs et al., 2008; Wu et al., 2010; Ewing-Cobbs et al., 2012; Semple et al., 2014) have been associated with poorer social outcomes in both adults and children after TBI (Beauchamp et al., 2009; Ryan et al., 2013). In children, volumetric changes of both grey and white matter structures after injury are likely to reflect not only ongoing neurodegeneration, but also result from the retardation of normal growth trajectories. Further, there is the potential for compensatory mechanisms that may result in aberrant regrowth. Techniques such as susceptibility-weighted, diffusion, and functional magnetic resonance imaging may be required to elucidate the complex relationship between neural circuitry, connectivity of specific pathways, and social behaviors.

4. The attentional set-shifting test as a novel behavioral paradigm for TBI

Brain-injury models in the laboratory, whose aims are to target relevant injury-related symptomatology and mimic neurochemical, motor and cognitive recovery after TBI, have been associated for decades with decline in long-term learning and memory. Nevertheless, the types of behavioral tests performed to date, albeit important for providing validity to experimental models of injury, such as the MWM for reference memory, the Barnes maze test for working memory, a combination of both in the radial arm maze test, as well as the novel object recognition test for declarative memory, have failed to focus on the complex attention impairments related to the frontal lobe, which are common in many if not most TBIs throughout all injury severities.

4.1. Neuropsychological tests of executive function

Executive function and cognitive flexibility represent sophisticated brain capabilities to use environmental feedback to “unlearn” a previously valid set of rules, switch gears and filter unwanted distractions, in order to acquire a new rule by shifting attention from a salient stimulus dimension to a previously irrelevant one (Bondi et al., 2008). In 1948, the

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Wisconsin Card Sorting Test (WCST) was developed as a multi-factorial test to assess strategy-switching deficits as an index of behavioral flexibility in healthy young subjects (Berg, 1948; Grant and Berg, 1948), and subsequently demonstrated to detect deficits in patients with frontal lobe damage or dysfunction, age- or neurodegenerative illness-related cognitive impairments or dementia, as well as schizophrenia or attention deficit hyperactivity disorder (Tait et al., 2014). This neuropsychological test requires subjects to orient themselves based on a "correct" rule in order to match a deck of cards displaying a number of colored objects to a set of exemplars based on three dimensions: color, number, and shape. Subjects must acquire the sorting rule (color, number, or shape) based on trial-by-trial feedback indicating whether the previous response is correct or incorrect. Once a given contingency is learned, the rules are changed without the knowledge of the subject, who must then identify and interpret an error, suppress a previously successful but now incorrect approach, and adapt to the new sorting rule by switching attention from the previously salient dimension to a previously irrelevant dimension (Lapiz-Bluhm et al., 2008). An assessment of executive function and behavioral flexibility can be derived from the number of trials to reach criterion as well as number of errors required to learn the new rule after a shift (Tait et al., 2014).

Attentional sets represent information "stores" mediated by top-down control mechanisms that prioritize stimuli based on perceptual, reward-predicting features within a salient dimension identified via environmental and trial-by-trial feedback (Leber and Egeth, 2006; Tait et al., 2014). As new dimensions become relevant, the salience of stimulus features needs to be updated accordingly in order to receive positive feedback and receive a reward. Upon formation of an attentional set, discriminations that are congruent with the relevant dimension will be achieved faster, even with presentation of novel stimuli, whereas tasks requiring an attentional set-shift will take more trials to appropriately solve (Tait et al., 2014). In order to overcome certain drawbacks of the WCST regarding its dependence on multiple cognitive mechanisms, such as subjects' performance being affected by trying to recall previously salient rules or an inherent difficulty shifting attention from one perceptual feature of the cards (e.g., shape) to another (e.g., color), another neuropsychological test, the intradimensional (ID)/extradimensional (ED) task in the Cambridge Neuropsychological Automated Testing Battery (Sahakian and Owen., 1992), has also been successfully used in both human and non-human primates to assess attentional set-shifting capabilities. This task employs visual discriminations between pictorial features of the stimuli presented on a touchscreen (i.e., line segments superimposed onto abstract shapes) and has provided valuable information about executive function impairments in a plethora of mental and neurological disorders (Tait et al., 2014), as well as in TBI (Moore et al., 2010). Studies have shown that the WCST and ID/ED tasks recruit a widespread neural network of brain regions (Stuss et al., 2000) such as the prefrontal (PFC) and parietal cortices, basal ganglia, and hippocampus (Nyhus and Barcelo, 2009), all of which are vulnerable to injury and play a direct role in measured neurobehavioral sequelae (McAllister 2008; Schwarzbold et al., 2008; McAllister 2011). Therefore, neuropsychological difficulties associated with damage of PFC regions or afferent innervations comprise specific deficits in planning, cognitive flexibility, behavioral inhibition, poor organization of learning, memory and language formation. Considering the intricate direct or indirect connectivity of the PFC with a variety

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of brain regions, such as hippocampus, hypothalamus, amygdala, striatum or thalamus, there is a growing interest to investigate pathological mechanisms through which TBI results in abnormalities in the coordinated activation among these brain regions. Integrating an animal model of cognitive flexibility in the standard neurotrauma measures of behavior after brain injury is paramount to investigating complex cognitive problems and in finding therapies more relevant to the clinic.

4.2. The attentional set-shifting test: a measure of executive function in rodents

To specifically explore similar behavioral flexibility capabilities assessed in such neuropsychological tasks administered to humans and primates, an analogous ID/ED behavioral test was developed to measure attentional set-shifting and stimulus reversal learning performance in rats and demonstrated a pivotal role played by the rodent PFC in mediating such complex cognitive processes (Birrell and Brown, 2000; McAlonan and Brown, 2003). Moreover, this rodent task employs the natural foraging behavioral tendencies of rats by asking them to dig in small terracotta bowls to obtain a food reward, rather than learning visual discriminations. Using odor and tactile cues provides for fast acquisition of successive two-choice discriminations within a few hours, which is considerably faster than hundreds of trials of training and testing across multiple days for visual discrimination tasks (Tait et al., 2014). The attentional set-shifting test (AST) is characterized by a series of increasingly difficult perceptual discriminations to obtain a food reward that requires rodents (rats and mice) to form and maintain an attentional set or subsequently shift from one stimulus dimension to another that previously served as an overlapping distractor. Subjects are trained to retrieve a food reward from small terracotta pots containing distinctive digging media and marked with different odors on the upper rim. After they acquire the contingency on each stage to a criterion of six consecutive correct responses, the rules are changed and they progress to the next stage (Lapiz-Bluhm et al., 2008; Bondi et al., 2014). Subjects must learn to recognize the salient stimulus dimension (odor or digging medium) associated with the reward, based on a predetermined randomized order of stimulus presentation and overlying secondary dimension distractors, while facing rule changes as in the WCST or ID/ED task upon learning a given contingency (Bondi et al., 2008, 2014). In the first stage, the rats must learn to locate the reward based only on a single salient cue, either the odors applied to the rims of the two pots, or the texture of the digging material in each pot (simple discrimination). Then, the second dimension is introduced in a stage called the compound discrimination, serving as a distractor, but the salient cue remains the same. For example, if odor was the commencing relevant dimension for discriminating towards a reward, then two different digging media are introduced into the pots with odor remaining the salient cue. The third stage is a reversal, in which the negative cue from the relevant dimension (e.g. odor) in the previous stage becomes positive, and the positive cue from the previous stage is negative. The fourth stage is the ID shift, with all new stimuli (odors and media) being used, but in this case odor would still be relevant and media would still be irrelevant. After the subjects complete this new discrimination, a second reversal ensues. In all stages up to this point, the rats will have learned repeatedly that one stimulus dimension is informative when the rules are changed and an error is encountered (i.e. forming a cognitive set). The sixth stage (ED set shift) introduces an additional degree of difficulty, in that all new stimuli are again introduced, but the previously irrelevant

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dimension (e.g., medium) becomes relevant, and the previously informative dimension (e.g., odor) becomes irrelevant. The last stage is a final reversal (Table 2). The dependent measure in this test is the number of trials required to reach criterion on each stage (Lapiz-Bluhm et al., 2008).

4.3. The neurobiological basis of attentional set-shifting

Validity of the AST as a model of prefrontal cortical cognitive function in rats has been demonstrated initially using electrolytic or neurotoxic lesions to specific sub-regions of the prefrontal cortex. For example, lesions of medial PFC selectively disrupted ED set-shifting (Birrell and Brown, 2000), whereas orbitofrontal cortex (OFC) lesions impaired reversal learning (McAlonan and Brown, 2003). These results are in line with the brain region-related effect specificity using similar tests of ED set-shifting and reversal learning in primates (Dias et al., 1996, 1997). Cognitive inflexibility and perseveration in the AST have been previously described in rodent models of various neuropsychiatric and emotional disorders, such as in the spontaneously hypertensive rat, a genetic model of attention-deficit hyperactivity disorder (Cao et al., 2012), the neonatal ventral hippocampal lesion model (Brooks et al., 2012), the 6-hydroxydopamine model of Parkinson's disease (Tait et al., 2007), in glutamate N-methyl-D-aspartate receptor antagonist-induced schizophrenia-like symptomatology (Broberg et al., 2009; Goetghebeur et al., 2010; Kos et al., 2011), aging-induced cognitive decline (Young et al., 2010) or chronic unpredictable (Bondi et al., 2008, 2010) or restraint stress (Liston et al., 2006) exposure. The neurobiological circuitry that facilitates attentional set-shifting in rats is primarily mediated in the PFC by ascending projections from various neurotransmitter systems, such as norepinephrine, but also dopamine (DA), serotonin, and acetylcholine (Aston-Jones and Cohen, 2005; Chudasama and Robbins, 2006; Robbins and Arnsten, 2009). Therefore, TBI-induced secondary and long-term sequelae involving disruption of endogenous neurotransmitter influences in the mPFC and OFC could be responsible for the impaired cognitive performance revealed by Bondi and colleagues (Bondi et al., 2014). This is consistent with a growing body of experimental TBI literature suggesting alterations in multiple neural pathways, such as neurotransmitter synthesis, release, or signaling, as well as effects on neurobehavioral outcome post-injury (Dixon et al., 1999; Cheng et al., 2008; Wagner et al., 2009; Shin et al., 2011; Olsen et al., 2012; Bondi et al., 2014; Wang et al., 2014).

4.4. Novel assessment of executive function in experimental TBI

Therefore, in order to begin to address alterations in frontal cortex-mediated executive function in a rodent model of TBI, Bondi and colleagues (2014) set out to investigate whether a CCI injury of various cortical deformation depths (2.6, 2.8, or 3.0 mm) would induce cortical impact depth-dependent cognitive deficits in the attentional performance of adult male rats on the AST (Bondi et al., 2014). TBI produced impact depth-dependent impairments in ED set-shifting and stimulus reversals, seen as a significant increase in the number of trials to reach criterion, as well as increased total response errors and set loss errors (i.e., failure to maintain acquisition of correct stimulus contingency), when assessed at 4 weeks post injury. Specifically, rats subjected to the milder TBI condition (2.6 mm impact depth) did not display cognitive deficits in the AST; however, rats in the TBI (2.8 mm) group showed impaired cognitive performance throughout all the measures evaluated in this

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task, such as trials to reach criterion, total errors, and set-loss errors, whereas rats in the TBI (3.0 mm) group also exhibited selective ED set-shifting deficits in trials to criterion and set-loss errors. Moreover, as a validation of surgery methodology and cortical impact depth-dependent injury severity, the TBI (3.0 mm) group displayed a significant increase in return to righting ability post-anesthesia, as well as significantly larger cortical lesion volumes, in comparison to the TBI (2.6 mm) group (Bondi et al., 2014). Also, there were no differences between sham (i.e., rats that received craniectomies) and naive (i.e., no manipulation) animals, suggesting that this task is not differentially impacted by anesthesia and/or craniectomy.

Taken together, these results provide a novel assessment of complex, frontal cortex-mediated cognitive processes, specifically executive function and behavioral flexibility, which were sensitively and reliably disrupted in this model of TBI (Bondi et al., 2014). Future studies could further evaluate pharmacological and cognitive rehabilitation therapies alone and in combination as a relevant preclinical paradigm, as well as elucidating mechanisms underlying the neuropsychological deficits. This is relevant considering that, similar to the study by Bondi et al. (2014) a growing body of clinical research also suggests that executive dysfunction is associated with the level of brain injury severity in TBI patients (Ord et al., 2010; Finnanger et al., 2013; Sorg et al., 2014). Moreover, cognitive recovery after TBI occurs in a variable time-dependent manner across individuals and may continue for years after injury (Millis et al., 2001).

5. Environmental enrichment: a preclinical model of neurorehabilitation after TBI

Environmental enrichment (EE) is an experimental strategy where housing is substantially different from that of usual experimental laboratory rats. Specifically, in the EE condition the rats are group-housed in an expansive living space and exposed to multiple objects of various shapes and sizes (Figure 2). The environment affords enrichment and integration of exploratory, physical, and social elements (Kline et al., 2007, Sozda et al., 2010; for comprehensive review see Bondi et al., 2014). This distinctive milieu is in marked contrast to standard (STD) housing where single or paired subjects live in traditional laboratory-sized cages and receive only basic amenities (i.e., food and water).

As previously indicated, TBI produces a loss of cortical and hippocampal neurons, changes in neurotransmitter expression and function, and a downregulation of neurotrophin expression, all of which have been reported to correlate with behavioral dysfunction (McIntosh et al., 1994; Thompson et al., 2005; Bales et al., 2009). Because EE has been shown to affect neuroanatomical and neurochemical changes (Bennett et al., 1964; Diamond et al., 1966, 1976; La Torre 1968; Walsh et al., 1969) it seemed reasonable to theorize that these neuroplastic changes could affect the brain’s response to injury and perhaps serve as a potential rehabilitative therapy. Indeed, EE has consistently been shown to enhance motor and cognitive performance, as well as reduce histological damage after TBI (Passineau et al., 2001; Kline et al., 2007; 2010, 2012; Hoffman et al., 2008; Sozda et al., 2010; de Witt et al., 2011; Matter et al., 2011; Cheng et al., 2012) and thus has been likened to physiotherapy (Will et al., 2004; Kline et al., 2010).

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5.1. Early and continuous enrichment: typical paradigm

5.1.1. Effects of EE in males after TBI—The typical EE protocol consists of placing rats (or mice), usually male, in the environment immediately after TBI with continuous exposure. Several studies have shown that this paradigm is beneficial after either FP or CCI injury. The first study to assess the potential benefits of EE after TBI was carried out by Hamm and colleagues (1996). Following a moderate FP injury or sham injury, the rats were placed in either EE or STD cages. Cognitive performance (i.e., acquisition of spatial learning) was measured using a MWM task on post-operative days 11-15. Rats housed in EE performed significantly better than STD controls, and did not differ from uninjured sham controls (Hamm et al., 1996). Passineau and colleagues (2001) and Hicks and coworkers (2002) observed similar behavioral benefits after FP injury. Moreover, EE lead to a reduction in cortical cavitation, suggesting a neuroprotective effect (Passineau et al., 2001). Adding multimodal early onset stimulation (i.e., auditory, motor, olfactory, and visual stimuli) to the EE paradigm was found to enhance motor, cognitive, and histological outcome after FP injury beyond that of EE alone (Maegele et al., 2005a,b; Lippert-Gruner et al., 2007). Regarding the effects of EE in pediatric rats, the behavioral outcomes after FP or CCI injury have been mixed. Specifically, no cognitive benefit was observed after a FP injury in PND 19 rats, despite evidence of plasticity (Fineman et al., 2000; Ip et al., 2002), while after CCI injury in PND 17 rats a robust cognitive benefit was observed (Monaco et al., 2014).

Following CCI injury Smith and colleagues (2007) reported faster recovery of skilled forelimb function in rats chronically exposed to EE post injury. Recently, Briones et al. (2013) showed that 4 weeks of EE significantly improved performance in a non-matching-to-sample task. EE has also been shown to provide benefit after bTBI. Kovesdi et al. (2011) used a rodent model of bTBI via a compression-driven shock tube (as described in a previous section) and assessed the rats on the elevated plus-maze and Barnes maze tests on days 15, 44 and 66 days post injury. While EE did not affect anxiety relative to STD, it did significantly improve spatial memory in the Barnes maze (Kovesdi et al., 2011).

EE-induced benefits have also been reported in adult male C57BL/J6 mice subjected to a FP injury. The mice exhibited enhanced locomotive activity (i.e., number of visits and nose pokes) at 24 hr post injury and complete restoration at 72 hr. Moreover, striatal cell loss at 72 hr post injury was significantly reduced compared to STD housing (Muthuraju et al., 2012).

5.1.2. Effects of EE in females after TBI—The first study assessing the potential efficacy of EE in females reported no significant benefit in the acquisition of spatial learning (Wagner et al., 2002). However, in a recent study designed to address this disparity, Monaco et al (2013) used experimental procedures that were similar to those of Wagner et al. (2002), which included adult female rats receiving a CCI injury at various phases of the estrous stage to mimic clinically relevant scenarios. Behaviorally, EE improved beam-balance, beam-walk, and rotarod performance as well as spatial learning vs. STD-housed females. Histologically, EE increased hippocampal $CA_{1/3}$ cell survival and decreased cortical lesion volume (Monaco et al., 2013). The marked difference between the two CCI studies may be

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due to the inclusion of the rotarod task in the Monaco et al (2013) study, which may have augmented rehabilitation.

5.1.3. Endurance of EE benefits—While the aforementioned studies have shown for several years that EE confers benefits after TBI induced by various models, it was unknown until recently whether the benefits could be maintained after EE (i.e., rehabilitation) is discontinued. Demonstrating effect persistence is crucial for any therapeutic approach if it is to be successful in clinical translation. Hence, to evaluate the endurance of EE, Cheng et al. (2012) subjected rats to a CCI or sham injury and then during phase 1 of the experiment randomly assigned them to 3 weeks of EE or STD housing. Motor and cognitive assessments were performed using the standard beam and MWM tests described previously (in the models section). The findings showed that EE significantly improved both motor and cognition relative to STD controls, which replicated previous studies (Kline et al., 2007, 2010, 2012; Hoffman 2008). During phase 2 of the experiment, which was designed to mimic a real-world rehabilitative strategy, half of the improved rats in the EE condition were transferred back to STD housing conditions, thus mimicking patients completing rehabilitation. The rats were subsequently retested for motor and cognition at 1-month intervals for 6 months. The EE-continuous and EE-withdrawal groups performed better than the continuous STD-housed group, but did not differ from one another, which indicates that EE-induced motor and cognitive benefits are maintained for up to 6 months following the cessation of EE (Cheng et al., 2012). The long-term efficacy of EE further supports this paradigm as a potential preclinical model of neurorehabilitation.

5.2. Delayed and abbreviated EE

5.2.1. Delayed EE—While EE exposure immediately after TBI has shown marked benefits, realistically this paradigm is not clinically relevant because TBI patients will not engage in rehabilitation until after acute critical care. Hence, two studies in adult male rats were conducted to determine whether the EE-mediated benefits after TBI are dependent on early and constant exposure or whether delayed initiation could still provide benefits (Hoffman et al., 2008; Matter et al., 2011). Briefly, the findings from two separate studies showed that delaying EE by a week after TBI enhanced cognition to the same extent as the early and continuous paradigm. However, providing EE immediately after TBI for only one week was not beneficial. These findings suggest that there is a threshold of EE that is necessary to confer benefits (Hoffman et al., 2008; Matter et al., 2011). The timing of EE initiation is also important as shown by Giza and colleagues (2005) who subjected PND-19 rats to a FP injury and then assigned them to two different EE conditions. Specifically, one group received EE for 17 days from PND 20-37 and the other received the same amount of EE, but not until PND 34-50. The group exposed to EE sooner after FP injury performed significantly better in the MWM than those who received it later (Giza et al., 2005).

5.2.2. Abbreviated EE—In addition to the requisite delay in rehabilitation, another important timing issue to consider in modeling EE as a rehabilitative paradigm is that once rehabilitation is initiated the duration of the therapy will be limited. Typical time frames of rehabilitation in the clinical setting vary widely, but usually 3-8 hr is the norm (Blackerby 1990; Shiel et al., 2001; Zhu et al., 2007; Vanderploeg et al., 2008). Thus, to more

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accurately mimic the clinical scenario, de Witt et al. (2011) evaluated the efficacy of an abbreviated enrichment paradigm that consisted of 2, 4, or 6 hr of EE per day and compared those times to either continuous EE or STD housing. The findings revealed two important outcomes. First, providing only 2 or 4 hr of EE was ineffective as evidenced by the two groups not differing from the STD-housed group. Second, providing EE for 6 hr per day conferred significant improvements in motor and cognitive performance, and importantly for the validity of the model did not differ from the continuous EE group (de Witt et al., 2011) These findings suggest that abbreviated EE is sufficient for promoting optimal functional benefits after moderate TBI in rats, but also indicate that a minimum threshold of daily enrichment exposure may be required to elicit neurobehavioral recovery following TBI, as previously reported (Matter et al., 2011).

5.3. Combining EE with pharmacotherapies

5.3.1. EE plus 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT)—Successful translation of preclinical findings to the bench side may be, at least partially, attributed to the use of mono-therapies, as opposed to a more realistic approach of combining therapies with rehabilitation. Hence, the following section describes the effects of combining EE with acute or chronic administration of 8-OH-DPAT. In an initial study evaluating the effect of 8-OH-DPAT, it was shown that *acute* treatment (single administration at 15 min after TBI) promoted behavioral recovery and restored neuropathological alterations post TBI (Kline et al., 2002b, 2004a). Subsequently, Kline et al. (2007) sought to investigate whether combining 8-OH-DPAT with EE would confer additional benefit relative to either treatment alone. As per the acute pharmacotherapy regimen, the rats received a single administration of 8-OH-DPAT after TBI or sham injury and then were provided early and continuous EE. Both 8-OH-DPAT and EE exposure enhanced behavioral recovery and rescued hippocampal CA_3 cell loss following TBI, which replicated previous studies (Kline et al., 2002b, 2004a). Cognitive differences were also observed following the combination of EE and 8-OH-DPAT vs. the STD plus 8-OH-DPAT group, with the former being significantly better, suggesting that EE enhanced the effect of 8-OH-DPAT. However, an additive effect of combined treatments could not be claimed because there were no significant differences between the combination treatment group and the EE alone group (Kline et al., 2007).

Chronic administration of 8-OH-DPAT has also been shown to reduce histopathology and improve neurobehavioral recovery after CCI injury (Cheng et al., 2008). Hence, to mimic the clinic where TBI patients may be provided pharmacotherapies chronically in concert with rehabilitation a subsequent study combined chronic 8-OH-DPAT with EE (Kline et al., 2010). Motor and cognitive recovery as well as an attenuation of hippocampal CA_3 and choline acetyltransferase (ChAT) medial septal cell loss were reported when each therapy was provided singly. In combination, the therapies reduced TBI-induced ChAT cell loss, but did not enhance hippocampal cell survival or neurobehavioral performance beyond that of either treatment alone. The authors suggested that a possible explanation for the lack of an additive behavioral effect might be that the EE paradigm is a robust treatment and thus there may have been a ceiling effect that precluded 8-OH-DPAT from conferring additional statistically significant improvement.

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5.3.2. EE plus buspirone—The 5-HT_{1A} receptor agonist buspirone has also been shown to enhance spatial learning and reduce histopathology after TBI (Olsen et al., 2012). Moreover, this therapy is already used in the clinical setting to treat anxiety and depression, hence safety and tolerability parameters are well characterized (Chew and Zafonte, 2009). To determine whether the benefits of buspirone can be augmented further, Kline and colleagues (2012) administered buspirone to TBI or sham rats and then provided them rehabilitation in the form of EE (Kline et al., 2012). Buspirone alone also provided significant neurobehavioral recovery in injured rats. Furthermore, the TBI animals in EE, regardless of whether buspirone or vehicle-treated, had less CA_3 hippocampal cell loss, improved motor function, and enhanced spatial learning and memory retention compared to STD-housed controls. Overall, these results demonstrated significant benefits by buspirone and EE. However, the prediction that greater benefits would ensue with the combination paradigm was not supported. The lack of an additive effect in adult rats may once again be attributable to a ceiling effect produced by an early-and-continuous EE paradigm.

In contrast, the combination of buspirone and EE after a TBI in PND-17 male rats produced an additive effect as revealed by the combined treatment group performing significantly better in the acquisition of spatial learning and memory relative to the buspirone rats housed in STD conditions and the EE rats receiving no other treatment (Monaco et al., 2014). A potential explanation for the differences in additive effects between the adult and immature rats is that in the latter there is a robust surge in synaptogenesis and subsequent changes in synaptic efficacy that is associated with cognitive processing (Teyler et al., 1989), which may make the developing brain more sensitive to the combination of EE and buspirone. These novel findings in pediatric rats may have potential rehabilitative implications for clinical pediatric TBI.

5.4. Potential mechanisms for EE-induced benefits after TBI

In addition to the reduction in ChAT-positive cell loss after TBI (Kline et al., 2010), EE induces additional neuroplastic changes after trauma that may mediate the behavioral benefits observed. For instance, several studies have reported significant changes in neurotrophin expression after TBI (Yang et al., 1996; Hicks et al., 1997, 1998, 1999, 2002; Chen et al., 2005). Using the fluid percussion model of TBI that was described earlier in this review, Hicks and colleagues (1997) reported increased expression of brain-derived neurotrophic factor (BDNF) mRNA in the CA_3 and dentate gyrus at various time points after injury. Neurotrophin-3 (NT-3) mRNA was also significantly reduced in the dentate at 6 and 24 hr post injury, supporting the hypothesis that secondary events following TBI are multifaceted. Based on findings that long-term exposure to EE in a non-TBI setting modulates mRNA brain expression for these neurotrophins (Falkenberg et al., 1992; Torasdotter et al., 1998; Ickes et al., 2000), Hicks and colleagues (2002) sought to evaluate the relationship between EE and neurotrophin gene expression after TBI. It was found that 2 weeks of EE exposure facilitated the acquisition of spatial learning in the MWM task, but did not change BDNF, tyrosine receptor kinase-B, and NT-3 mRNA levels in hippocampal sub-regions.

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EE has also been reported to alter DA after CCI injury (Yan et al., 2001, 2002; Wilson et al., 2005; Bales et al., 2009). Hence, Wagner and colleagues sought to further investigate gender-dependent responsiveness to EE and DA regulation post injury. It was found that dopamine transporter (DAT) protein expression in males undergoes larger decreases after CCI injury compared to females, but EE exposure has larger effects on post injury DAT expression in females vs. males (Wagner et al., 2005). Subsequent studies evaluating the effects of EE on the dopaminergic system found a downregulation of tyrosine hydroxylase (Shin et al., 2012).

In addition to changes in neurotrophins and dopaminergic markers that may mediate some of the benefits of EE, other potential mechanisms were recently elucidated by Briones and colleagues who showed that continuous EE reverses CCI-induced increases of the pro-inflammatory cytokines interleukin-1 beta and tumor necrosis factor alpha. EE also decreases interleukin-10 in the prefrontal cortex and hippocampus. Lastly, markers of brain energy homeostasis, such as the ratio of phosphorylated adenosine monophosphate-activated protein kinase and the ubiquitous mitochondrial creatine kinase were decreased post injury in the same brain regions, an effect significantly normalized by EE exposure (Briones et al., 2013).

Together, these studies reveal complex, region-specific, and potential gender differences in potential molecular mechanisms mediating EE-induced recovery; this elucidation may provide new avenues for pharmaceutical targets and rehabilitative approaches after TBI.

6. Evidence-based approach to sports concussion management

6.1. Sports concussions

Concussions are a form of mild TBI resulting in pathophysiological disturbances and neurological dysfunction imparted by biomechanical forces to the brain (McCrory et al., 2013). Common acute signs and symptoms include headache, dizziness, disorientation, memory impairment, nausea, light and noise sensitivity, dizziness, incoordination, vomiting, behavioral changes and rarely, loss of consciousness. It is estimated that over 3 million sports-related concussions occur annually in the U.S. (Langlois et al., 2006). Important considerations when investigating concussions in sport include the widespread occurrence of these injuries in youth, whose brains are still undergoing development, and the fact that after injury, there is an expectation of eventual return to play and potential risk of recurrent or repetitive injury. Understanding the science of sports concussions requires both a strong understanding of basic animal TBI models as well as a robust translational perspective to link neurobiological mechanisms to real-world clinical problems.

6.2. Post-concussive dysfunction

6.2.1. Clinical concussion and acute management—Following human concussion there is ongoing evidence of neural dysfunction. This can take the form of subjectively reported symptoms such as headache and dizziness, or observable clinical signs like amnesia, incoordination, or unconsciousness. In general these signs and symptoms peak within the first hours after injury and then gradually resolve over 7-10 days (McCrea et al., 2003). There is ample evidence that different domains of impairment may not resolve

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simultaneously, and most recent clinical guidelines advocate detecting and monitoring post-concussion dysfunction using multiple metrics, such as symptoms, cognition, balance, and reaction time. Multiple tools have been devised in an attempt to quantify these deficits, with each having its own advantages and challenges (Giza et al., 2013).

It is also increasingly recognized that there are a number of individual risk factors for more severe symptoms or more prolonged recovery after concussion. These include a prior history of concussions (Guskiewicz et al., 2003; Eisenberg et al., 2013), younger age (Field et al., 2003; Covassin et al., 2012), headache/migraine symptoms (Mihalik et al., 2005), acute mental status symptoms (amnesia, confusion or loss of consciousness) and premorbid behavioral or cognitive challenges. Other risk factors with varying degrees of supporting evidence include specific symptoms (e.g., fogginess or dizziness), family history of neurobehavioral disorders, family history of migraine and probably genetic factors.

The knowledge of the natural course of post-concussion recovery and the relationship of recovery to clinically measurable parameters has led to individualized concussion management, and abandonment of prior concussion severity scales (Giza et al., 2013). Multiple tools have been developed to standardize evaluation of symptoms, attention, memory, balance/coordination and reaction time. Some of these are part of the clinical history and examination, some are paper and pencil or computerized tests, and some require other devices. Furthermore, the determination of a given patient's risk factors is a clinically useful way of anticipating who may require more time to recover.

6.2.2. Animal models and outcome measures—Animal models have significant challenges to accurately model all of the biomechanical parameters of human concussion. The mass and orientation of the human brain is different from all quadrupedal animals. Most animal investigations are done in rodents, which are lissencephalic and have relatively small proportions of white matter, while human brains are gyrencephalic and have proportionately large amounts of white matter.

Most animal TBI models attempt to quantitate injury by histological evidence that is not typically seen in human concussion and mild TBI. However, animal models may also quantitate post-TBI dysfunction using physiological parameters, such as glucose metabolism, cerebral blood flow, or electrophysiology. While older methods of measuring metabolism or blood flow may have required cross-sectional terminal studies, newer modalities of imaging are allowing longitudinal examination of brain water content, white matter integrity and even neural activation. Outcome assessments in animal models that are translatable to humans include behavioral tests of working and spatial memory, among others as previously described.

6.3. Vulnerability to second injury

6.3.1. Clinical vulnerability and repeat concussion—As mentioned above, having had a concussion is both a risk factor for sustaining another concussion and a risk factor for more severe symptoms or longer recovery after a second or recurrent concussion. It is known from multiple studies that a history of prior concussion increases the risk for subsequent concussion by a factor of about 3-fold (Guskiewicz et al., 2000). Several

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prospective studies have found that 75-90% of in-season repeat concussions happen within 7-10 days of the initial one (Guskiewicz et al., 2003; McCrea et al., 2009).

Other clinical studies have examined the severity or duration of symptoms. Again, evidence here suggests that recurrent concussions manifest either more severe acute symptoms or a more prolonged recovery (Guskiewicz et al., 2003; Eisenberg et al., 2013). These facts led to the recommendation that any player suspected of having a concussion be removed from contact-risk activity until evaluated by a health care professional with expertise and training in concussion.

While previous human correlates with the neurometabolic cascade of concussion involved intracranial sensors utilized in comatose patients with severe TBI, advanced neuroimaging now allows clinical researchers to noninvasively evaluate neurobiological changes after concussion/mild TBI. Diffusion tensor imaging (DTI) examines directional water diffusion which is used as a surrogate for integrity of white matter tracts. DTI measures change after TBI of all severities, although the exact time course, tract location and correlation with measurable symptoms or neurocognitive impairments varies between studies (Wilde et al., 2008; Mayer et al., 2012). Magnetic resonance spectroscopy provides a window into cerebral metabolism. Reductions of N-acetylaspartate/creatine (NAA/Cr) ratio have been reported after human sports concussion and may take 30 days to resolve. During this time, however, correlation with clinical symptoms is loose. Interestingly, for a small subset of subjects who sustained a second concussion before recovery from the first one, the reductions of NAA/Cr were larger and took 45 days until resolution (Vagnozzi et al., 2008, 2010). These data suggest there may be a biological window of vulnerability, but again, correlation with signs and symptoms is still needed to determine whether these imaging changes are indicative of clinically important dysfunction.

6.3.2. Animal models of repeat injury and impairment—There are an increasing number of experimental models producing repeated TBI. Most involve rodents, although a few studies of repeat injury in piglets have also been reported. More traditional experimental TBI models suffer from the limitation of requiring a craniectomy (i.e., FP and CCI) or having a significant risk for skull fracture (i.e., weight drop). Newer variations have used less severe weight drops or closed skull pneumatic impactors to induce less severe TBI that, in some cases, demonstrates minimal impairment after a single injury but significant cognitive dysfunction after repeated injury (Longhi et al., 2005; Prins et al., 2010).

Some of these models also show more severe histopathology after repeat concussive injury, including evidence of greater traumatic axonal injury. Experimental studies examining levels of energy metabolites have suggested a metabolic window of vulnerability during which repeated concussions have worse pathophysiology, but outside of which a second concussion behaves similarly to an isolated one (Vagnozzi et al., 2007). More recently, using 2-deoxyglucose autoradiography and carefully controlled timing of repeated injury in a rat closed head injury model, two injuries within 24 hours resulted in both worse metabolic activity and memory impairment, while if separated by 5 days metabolism and memory deficits were similar to a single injury (Prins et al., 2013). These animal studies strongly support the concept of a biological window of vulnerability and help support the clinical

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management strategy of keeping concussed athletes from returning to contact play early after injury.

6.4. Activating the injured brain

6.4.1. Recovery and return to activity in humans—Beyond the increased risk for repeat or more severe concussion attributable to premature return to play, there is a growing body of research investigating whether early neural stimulation itself may exacerbate or alleviate impairments. Initially based upon clinical observations that acute symptoms and signs of concussion may be exacerbated with increased cognitive effort, busy environments, sustained attention or stress, clinical management of post-concussive activity has run the gamut from the old school approach of back to normal activity right away to severe restriction of activities (e.g., including texting, studying, watching TV, or computer time) for a few days or as long as weeks-months in symptomatic individuals.

Beyond anecdotes, clinical studies suggest that extremes of activity were associated with greater subacute symptom burden, lower computerized cognitive test scores or prolonged recovery (Majerske et al., 2008; Brown et al., 2014). These data have led to most concussion management strategies to include a brief period of cognitive rest, followed by a gradual return to school/work, which is limited if symptoms increase. There is no controlled evidence that complete cognitive rest for more than a couple of days enhances recovery. Moreover, clinical studies of return to activity for other conditions (e.g., low back pain, chronic headache) suggest that bed rest or inactivity may actually prolong recovery (Malmivaara et al., 1995; Milde-Busch et al., 2010).

6.4.2. Neural activation following experimental injury—Early studies utilized a cortical lesion that resulted in contralateral motor impairment. If the unimpaired limb was restrained then the animal was forced to rely upon the impaired limb, a paradigm termed ‘forced overuse’. If the restraint was applied within the first week after the lesion, the increased activation was associated with a significantly larger cortical lesion. If the restraint were applied >1 week after the lesion, then lesion size was unaffected (Humm et al., 1998).

Animal models using non-lesion FP injury have also examined the timing of motor activation induced by voluntary wheel running. In these experiments, early running resulted in lower levels of hippocampal neurotrophic factors and worse cognition. However, if access to the running wheel were delayed until 1 week post-concussion, then exercise enhanced neurotrophin production and facilitated cognitive recovery (Griesbach et al., 2004; 2007). These data support an initial rest period, followed by a gradual increase in neural activation. Determining the window for optimal return to activity remains a challenge, but appears to loosely parallel the time course of neurometabolic recovery.

Lastly, in pediatric models of mild TBI, an impairment of experience dependent neuroplasticity in response to rearing in an enriched environment has been demonstrated (Fineman et al., 2000). Injured animals appear to interact normally with the novel environment, but fail to demonstrate the microanatomical changes (e.g., increased dendritic branching; Ip et al., 2002) or behavioral enhancements, such as improved spatial learning and memory (Giza et al., 2005) typically induced by such experience (as described in the

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preceding section). Interestingly, this period of altered responsiveness largely resolves after a couple weeks, but subtle deficits are still detectable. These data also support a window of deficient cerebral activation after concussion, and have the same potential significance and challenges as mentioned above.

6.5. Long-term consequences

6.5.1. Chronic cognitive impairment or chronic traumatic encephalopathy?—

There is conflicting clinical evidence regarding the long-term consequences of repeated concussion, although in general the data support a dose-dependent cognitive impairment. Multiple studies of professional athletes, taking neurocognitive tests as well as some determination of the dose of their exposure to contact, show measurable neurocognitive impairments. Six of eight studies measured the 'dose' of concussion exposure in some way and in all six there was a dose-dependent relationship with chronic neurocognitive impairment, suggesting causality (Jordan et al., 1997; Kutner et al., 2000; Matser et al., 1998; Wall et al., 2006; Guskiewicz et al., 2005, 2007). However, in a much larger group of studies in amateur athletes, only half were found to exhibit chronic impairment. In any case, these data as a whole would indicate that repeated high level exposure to concussions may have a long-term cognitive cost (Giza et al., 2013). None of these studies specifically looked at neurodegeneration or progressive impairments.

There is also a high profile series of autopsy cases, mostly from professional athletes, but including amateurs as well and even high school athletes, where post-mortem pathological findings of neurodegeneration have been reported. The largest series proposes a condition termed chronic traumatic encephalopathy (CTE), which is characterized by aggregated tau deposits perivascularly and in the depths of cortical sulci in milder cases, and more pervasive and involving hippocampus/amygdala with evidence of atrophy in more severe cases (McKee et al., 2012). Not all reported cases had tauopathy, but the vast majority did, and in a pattern that was distinct from other known neurodegenerative conditions. A smaller case series of pathological specimens found that only half (3 of 6) had evidence of CTE-like tauopathy, but all also had evidence of another neurodegenerative disease at the same time (Hazrati et al., 2013).

Overall, there is credible evidence of some cognitive cost to high levels of exposure to collision/contact sports, with a dose-dependent relationship in multiple professional sports. This indicates there is a risk for chronic neurocognitive impairment associated with repeated concussions, but there are currently no longitudinal data to definitively prove that these impairments are degenerative/progressive. The case series suggest there is a subset of individuals who will develop pathological evidence of neurodegeneration, such as CTE, and these individuals are often symptomatic; however, the incidence and relative risk of developing CTE are unable to be determined from existing published reports.

6.5.2. Biological linkage of early pathophysiology with neurodegeneration—

While extensive animal models exist for both TBI and for neurodegeneration, the biological linkage between the two remains to be clearly elucidated. Several hypotheses exist and studies are ongoing to better delineate these relationships.

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Acute energy crisis is a fundamental component of TBI pathophysiology. While it is rarely lethal to the cell in mild forms of TBI, repeated injury, genetic susceptibilities or other factors may tip the balance where metabolically compromised cells pass a 'point-of-no-return'. This could be mediated through excessive calcium flux, mitochondrial dysfunction, and activation of proteases. Protease activation can then lead to cytoskeletal disruption and triggering of delayed cell death pathways. There are multiple longitudinal studies after moderate-severe experimental TBI that demonstrate ongoing cell death and atrophy (Kochanek et al., 2002; Pullela et al., 2006; Immonen et al., 2009); long-term studies using models of repeated mild TBI/concussive injury are underway.

It is also known that there can be abnormal accumulation of proteins after TBI. Tau deposition has been described after FP and bTBI in rodents, but not chronically after repetitive mild TBI. Amyloid precursor protein accumulation is a commonly used measure for impaired axonal transport/axonal injury acutely/subacutely after experimental TBI, but chronic deposition of amyloid is distinct from this phenomenon. There is some evidence for chronic accumulation of amyloid in transgenic animals vulnerable to neurodegeneration (e.g., 3xTG-apoE4; Tran et al., 2011; Bennett et al., 2013).

Normal cellular protein homeostasis requires energy and a complex called the proteasome (Tanaka et al., 2012). Dysfunction of the proteasome can be triggered by acute or chronic oxidative stress. Proteasome dysfunction has been linked to abnormal/toxic accumulation of proteins, which in turn, have been implicated in various forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Martinez et al., 2010). A few laboratory studies have demonstrated post-TBI proteasomal dysfunction; in one study it was also associated with increased apoptosis (Wan et al., 2014).

7. Conclusions

In this review, we discussed contemporary models of TBI and how their application alters behavioral responses, be it social, motor, or cognitive. We also described potential therapies that have been shown to attenuate TBI-induced behavioral deficits. Lastly, we provided a clinical perspective tying in the experimental models with the clinic, especially concussion. As a caveat, it should be noted that although the terms "model" and "device" were used interchangeably, it is not the intention of the authors to imply that a model of TBI is only a means of producing an injury. Rather, we believe that a model of TBI consists of a combination of device, species of animals used, location and severity of injury, choice of anesthesia, and the behavioral assessment tests employed.

While there are several differences and similarities between the *in vivo* models that have been presented, we contend that the observed differences between them are associated mainly with differences in the primary injury. This is most apparent in the morphologic response to experimental TBI where some models produce extensive cortical cavitation (e.g., CCI) while others do not (e.g., FP). We further state that the similarities between the models are associated with a relatively universal cascade of secondary injury processes that occur regardless of the physical/mechanical initiator of TBI. Despite not mimicking all the characteristics of human TBI, each of the *in vivo* models discussed have been instrumental

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in enhancing our knowledge about potential mechanisms of TBI. They have also afforded the opportunity to screen potential pharmacotherapies and rehabilitative approaches.

The identification of social deficits in animal models of TBI paves the way for the elucidation of underlying cellular and genetic mechanisms that may be targeted to improve long-term psychosocial outcomes and quality of life. Future studies to examine social behaviors relative to advanced neuroimaging correlates are warranted, to better understand the neuroanatomical basis underlying social dysfunction following childhood TBI. Consideration of potential sex-related differences in social behavior is also needed, with all experimental TBI studies to date focusing exclusively on males. As we move towards the goal of optimizing recovery after TBI, the inclusion of sociability measures when assessing candidate therapeutics will likely result in more rigorous standards for defining efficacy.

Current and ongoing findings employing the AST as a task of executive function and behavioral flexibility after brain injury are of significant relevance for expanding the validity of experimental models of TBI, by mimicking higher function cognitive impairments in humans, with the ultimate goal of improving rehabilitation and pharmacological treatment paradigms in the clinic. AST is a novel task to the neurotrauma field and warrants integration in the standard neurotrauma behavioral battery after TBI in order to evaluate sensitive cognitive dysfunction and subsequent relevant therapies.

From a rehabilitation perspective, the conclusions regarding EE as a therapy is that it benefits behavioral and histological outcome in male and female as well as adult and pediatric rats after brain injury produced by various models. Taken together, these findings provide the impetus for considering EE as a generalized and robust preclinical model of neurorehabilitation. The section has highlighted possible pharmacotherapies that impact dopaminergic and inflammatory pathways that can be coupled with EE. Development and refinement of these applicable variables will advance a clinically relevant experimental model of rehabilitation that can be applied to the TBI setting to facilitate rehabilitation research that can lead to increased translatability. The success of the transition from bed to bedside will be strengthened further by continuing to expand the model in males and females, as well as developing it further in pediatric and aged populations.

Current clinical management of sports-related concussions is still evolving, but good consensus and evidence-based guidelines are available. The focus is on removal of athletes with suspected concussion from play, to reduce the risk for repeat concussion, which is increased early after an initial concussive injury. Neural dysfunction after concussion manifests as symptoms such as headache and neurological impairments in cognition, reaction time, and balance. Multimodal clinical tests are available to assess these functions and may provide clinical guidance in the diagnosis of, and recovery from, concussion, but there is no *single* test to diagnose concussion accurately. Clinically identifiable risk factors for prolonged recovery have been identified (repeated concussion, younger age, migraine, etc), and have support from our understanding of basic neurobiology. Neural activation is impaired in the acute/subacute period of concussion recovery, suggesting that the highest level of activity may be associated with worse outcomes. However, translational studies also suggest that properly timed moderate activity may ultimately prove to facilitate recovery.

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Chronic neurocognitive impairment appears to be a consequence of higher levels of repetitive exposure to biomechanical force, and chronic neurodegeneration (i.e., CTE) has been described in case series of autopsy specimens, but the relative risk for CTE is unknown. Ongoing translational studies are underway to help better determine the biological linkage between acute TBI and chronic neurodegeneration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AST	attentional set-shifting test
bTBI	blast traumatic brain injury
BDNF	brain-derived neurotrophic factor
CCI	controlled cortical impact
CD	compound discrimination
CFC	contextual fear conditioning
ChAT	choline acetyltransferase
Cr	creatine
CTE	chronic traumatic encephalopathy
DA	dopamine
DAT	dopamine transporter
DTI	diffusion tensor imaging
ED	extradimensional
EE	environmental enrichment
FP	fluid percussion
ID	intradimensional
MWM	Morris water maze
NAA	N-acetylaspartate
NOR	novel-object recognition

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NT-3	neurotrophin-3
OFC	orbitofrontal cortex
PFC	prefrontal cortex
PND	postnatal day
R1	first reversal
R2	second reversal
R3	third reversal
SD	simple discrimination
STD	standard
TBI	traumatic brain injury
USV	ultrasonic vocalizations
WCST	Wisconsin Card Sorting Test
5-HT$_{1A}$	serotonin$_{1A}$
8-OH-DPAT	8-hydroxy-2-(di-*n*-propylamino) tetralin

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Highlights

- *in vivo* TBI models provide essential understanding of mechanisms and recovery
- Multiple deficits in social behavior can be detected after TBI in young rodents
- The AST is a sensitive measure of executive function after experimental TBI
- Environmental enrichment is a preclinical model of neurorehabilitation
- No *single* test exists to diagnose concussion accurately

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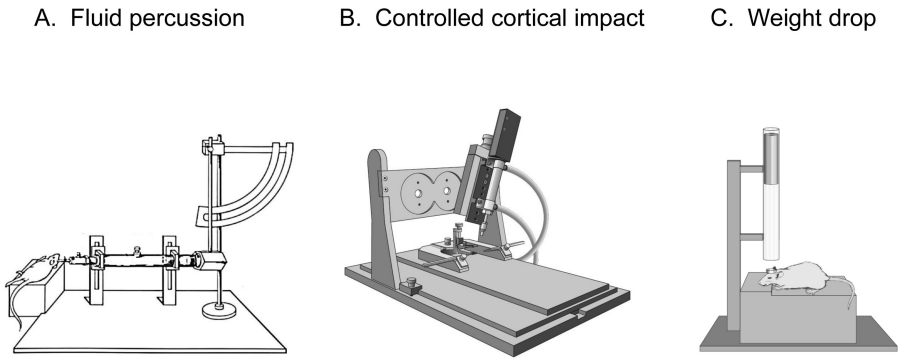

Figure 1.

Modified illustrations of the three most commonly used rodent models of traumatic brain injury (TBI). Fluid percussion (A), controlled cortical impact (B), and closed head impact-acceleration/weight drop (C).

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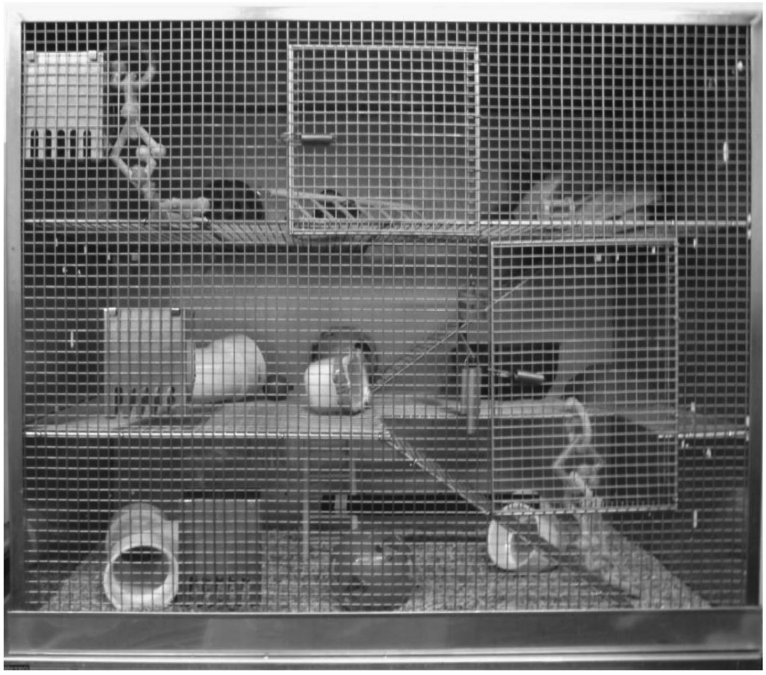

Figure 2.

Photograph of the environmental enrichment (EE) cage with multiple levels and wide array of sensory stimuli (e.g., balls, ramps, tubes, and nesting materials). Typically 10-12 rats, which include a subset of all experimental groups (i.e., both TBI and sham controls) are housed together to ensure equal conditions. The continuously housed rats are removed only briefly for behavioral assessments, weighing, and if applicable, drug administrations, while those in abbreviated rehabilitation paradigms are removed after their prescribed time and returned to STD laboratory cages.