Clinical Relevance of Behavior Testing in Animal Models of Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is a leading cause of morbidity worldwide, with patients often suffering from consequences such as cognitive deficits, social abnormalities, anxiety, depression, pain, and motor dysfunction. Given that these impairments often have a significant impact on the patient's quality of life, a key aim of therapeutic intervention in TBI is to mitigate these effects. Translational strategies to develop such interventions have heavily featured animal models of TBI. To assess the efficacy of interventions in these models, a range of behavioral outcomes are utilized. However, in light of the past translational failures that have plagued the TBI field, the clinical relevance of these preclinical behavioral tests is now being scrutinized. This article will summarize the behavioral consequences of TBI in humans; describe common methods available for testing cognition, social function, motor ability, pain, as well as depression- and anxiety-like behaviors in animal models of TBI; provide an overview of the results from TBI animal model studies that have utilized these methods; and discuss these pre-clinical behavior methods and findings in terms of their relevance to the clinical TBI setting. We conclude that there is translational value in these methods and their related findings, but also suggest strategies and future research to improve the clinical relevance of behavior testing in animal models of TBI.

Keywords: anxiety; cognition; depression; emotion; large animal; motor; pain; rodent; social

Introduction

TRAUMATIC BRAIN INJURY (TBI) commonly results in functional consequences that significantly reduce the quality of life (QoL) in survivors.^{1,2} Impairments in TBI patients include cognitive deficits, social abnormalities, pain, motor dysfunction, anxiety, depression, and other emotional disorders.^{1,2} Although some of these effects have been relatively well characterized in TBI patients, a great deal of research is still required to fully understand the extent and nature of these impairments, as well as identify the physiological mechanisms that underlie them. The need for such research is evidenced by the lack of current treatment known to improve long-term outcomes in TBI survivors.^{1,2} Given that it is challenging to comprehensively study the effects, pathophysiological mechanisms, and treatments of TBI purely in human patients, a translational research approach involving animal models has been a common strategy in an attempt to provide insight into TBI.^{3–6}

In principle, animal models of TBI complement human studies because they allow for rigorous investigation into the causal rela-

tionship between TBI and functional deficits, examination of the underlying pathophysiological mechanisms, and assessment of experimental treatments to improve outcomes, in a tightly controlled, time- and cost-efficient manner.^{3–6} A range of tasks that include measures of cognition, social function, motor ability, pain, as well as depression- and anxiety-like behaviors have been implemented in past studies to assess the consequences of TBI and efficacy of interventions in animal models.^{3–6} Indeed, some therapies have been found to improve outcomes on these measures in animal models of TBI. Unfortunately, because none of these therapies have been found to improve functional outcomes in TBI patients, the clinical relevance of the behavioral tests used in pre-clinical research is under scrutiny given that a lack of relevance may be one of the factors that can account for these past translational failures.^{6–10}

The aim of this article is to therefore examine whether behavior testing in animal TBI models has clinical relevance to the different behavioral abnormalities experienced by human TBI patients. We will begin by briefly summarizing some of the common consequences of TBI in humans, as well as highlight some of the

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challenges in human TBI studies that provide the rationale for the use of complementary animal model research. Next, we provide an overview of behavioral methods commonly used to assess cognitive, social, motor, pain, depression, and anxiety in animal TBI models. We will also give examples of results from TBI animal model studies that have utilized these methods and discuss these findings in terms of their relevance to clinical TBI. While we ultimately conclude that there is translational value in these methods and their related findings, in the final section we also suggest strategies and avenues for future research to improve the clinical relevance of behavior testing in animal models of TBI.

The Behavioral Consequences of Traumatic Brain Injury in Human Patients

Cognitive impairments

Cognition is a broad term that includes a number of subdomains such as attention, executive function, learning, as well as many different forms of memory. Cognitive deficits are common and devastating effects of TBI, and many previous studies have investigated cognition in TBI patients. As such, a comprehensive review of this literature is beyond the scope of this article, and the reader is directed to other reviews that are focused on different cognitive impairments in TBI patients.^{11–16} Rather, here we provide a brief summary of the spectrum of cognitive deficits in TBI patients to assist in evaluating the clinical relevance of the animal model behavior methods and findings discussed below.

Briefly, studies in TBI patients report deficits in mental fatigue,^{17,18} information processing,^{19,20} attention,^{21,22} learning,^{23,24} executive function,^{16,19,25} problem solving,²⁶ short-term and working memory,^{11,27–29} and long-term memory.^{19,30–32} It is important to note that onset of these abnormalities can be immediate or delayed and can be transient, evolving, delayed, or permanent.^{15,19,33–35} Further, the nature of the cognitive deficits may be affected by the patient's age, biological sex, pre-existing cognitive capacity/cognitive reserve, genetics, injury severity, injury mechanism, and brain structures affected.^{12–15,19,24,34,36} Needless to say, the range of cognitive deficits in TBI patients is highly heterogeneous, and further studies are needed to better characterize and comprehensively understand the topic. Unfortunately, because of the large degree of interpatient variability and possible modifying factors, this is a highly challenging task to complete purely in the patient population.

Emotional disorders

Many TBI patients experience a psychiatric illness after a TBI, with depression and anxiety the most common presentations.^{37,38} Rates of presentation can vary, possibly the result of the heterogeneity of the brain injury—both severity/type and region of impact can influence outcomes—as well as the study type. For example, a prospective, cohort study found that prevalence of any psychiatric illness in the first year after moderate-to-severe TBI was 49%, whereas prevalence of those experiencing mild TBI was 34%—significantly higher than the comparison group at 18%.³⁹

Prevalence of depression after TBI—the most common psychiatric presentation—varies wildly and can range between 15% and 70% after injury.^{40,41} Population-based studies also report the rates of depression after TBI in adults as much higher than the general population.⁴² These psychiatric consequences of TBI are long-lasting, causing vulnerability for years to decades after the incident,⁴¹ and many reports suggest that past history of psychiatric

illness is a significant predictor of subsequent illness after injury. In addition, occurrence of depression and anxiety after TBI are often linked to greater functional disability,⁴³ which is a great concern for long-term QoL and rehabilitation. Rates of post-traumatic stress disorder (PTSD) are also high for TBI sufferers, particularly in military settings.⁴⁴

The underpinnings of emotional abnormalities after TBI are difficult to determine. Mechanical or microstructural trauma to emotion-regulating networks, including pre-frontal cortex or mesial temporal lobe, may result in such symptoms.⁴⁵ However, emotional disorders in humans with TBI may also be related to psychosocial changes related to other consequences of TBI such as physical and cognitive disabilities, disfigurement, unemployment, dependence on others, changed family roles, social isolation, changes in personality, and bereavement of others involved in the incident. This difficult process can give rise to depression and anxiety in some people and may not be a direct pathophysiological effect of the TBI itself.^{2,46} Consequently, it can be challenging to identify whether the emotional consequences of TBI are caused directly by the injury, are a result of other consequences of the injury, or some combination. Conversely, emotional disorders can affect cognitive functions and can confound interpretation of such impairments. In this regard, valid animal models, coupled with translational assessments, can be of great value to disentangle psychosocial from neurobiological mechanisms of depression and anxiety after TBI.

Social deficits

Impairments in social functioning have historically been understudied in the context of TBI, although such deficits are now recognized as being among the most debilitating issues for TBI survivors in the long term.⁴⁷ Social function is a key contributor to long-term QoL, and changes in social function as a consequence of TBI have a largely negative impact on QoL by reducing life satisfaction and community integration.^{48,49}

Increasing evidence demonstrates that TBI survivors are at an elevated risk of reduced social interactions, impairments in verbal and non-verbal communication, and adaptive behaviors, compared to age-matched peers or orthopedic-injured controls.^{48,50,51} The clinical literature on this topic is hampered by small sample sizes and the heterogeneous nature of TBI pathology, as well as limited tools for assessment of social functioning, and the frequent reliance on parent or self-reporting of symptoms.^{48,52} Nonetheless, impairments in social cognition—the ability to recognize, attend to, and interpret the social cues that guide behavior—are commonly reported after TBI across the life span, persisting for up to 20 years after severe childhood TBI.^{50,52,53} Deficits in Theory of Mind, or the ability to infer the beliefs, feelings, and intentions of others, have also been identified, with suggestions that such higher-order cognitive processes are particularly vulnerable to even mild brain injuries.^{52,54,55} Problems with social interactions and social communication have been documented across an extensive time course, from months to years post-injury.^{47,56,57}

Social behavior deficits may emerge and evolve over time. This observation appears to be particularly the case after TBI during early childhood, prompting the hypothesis that a TBI interferes with the acquisition and consolidation of new social skills for affected individuals.⁵⁸ Whereas further studies are needed to better understand the injury and environmental factors that contribute to social dysfunction after TBI, to date, a younger age-at-insult, white matter pathology, and pre-existing socioeconomic disadvantage

have been associated with an increased likelihood of social difficulties for TBI survivors.^{48,59} Neuropathology in many brain regions has been associated with extent of social dysfunction in patients, including the hippocampus, amygdala, temporal lobe, and thalamus.^{55,60} In particular, progressive atrophy of white matter tracts, such as the corpus callosum, after TBI correlate with poor social and cognitive impairments.⁶¹

Motor deficits

The motor deficits associated with TBI are often less obvious, understudied, and sometimes considered less pervasive than the cognitive and social impairments individuals experience.^{62,63} Post-TBI motor deficits may result from shearing injuries, axonal damage, and overt cell loss in motor regions of the brain.^{64–67} Clinical studies have demonstrated fractional anisotropy abnormalities in the corpus callosum,⁶⁴ robust cerebellar damage characterized by injury or loss of Purkinje cells,^{65,66} and injury to corticospinal tract and anterior corona radiata.⁶⁷ TBI may affect the mechanical aspects of motor behavior, such as range of movement and muscle strength, and interfere with postural and phasic motor movements.^{68,69} Balance disturbances are one of the most commonly reported deficits after TBI.^{63,70,71} Although simply defined as the ability to maintain one's center of mass over its support, it requires complex interactions and integration of many neural and musculoskeletal systems.⁷¹ Damage to the cerebellum may interfere with balance, but also result in disruptions to movement timing and execution.⁶⁸ Speeded performance and response speed deficits, as detected with finger-tapping measures, are also frequently reported, even after mild TBI.⁷² Overall, the motor deficits associated with TBI (from mild to severe) result in coordination, balance, walking, agility, strength, hand function, and speech impairments,^{62,73–75} which can result in unemployment and financial hardship, poor school performance, and a loss of independence.

Despite the growing evidence that early neuromotor impairments offer prognostic abilities for TBI pathology,⁷⁶ the existing literature does not adequately describe the temporal evolution of motor symptomology. Identification of the specificity of motor deficits, their magnitude, and improvement trajectories should be one of the first steps in designing rehabilitation and therapeutic strategies.⁶³ Commonly used human measures of motor impairment after TBI include gait analysis, the Gross Motor Function Measure, the Developmental Hand Function Test, and the Purdue Pegboard test.⁶² However, more recent patient-based studies have incorporated robotic assessment of motor skills using technologies such as KIN-ARM exoskeleton robots.⁷⁷

Pain

Nociception is the sensory system's protective response to harmful or potentially harmful stimuli. In a nociceptive response, intense mechanical, chemical, or thermal activation of sensory nerve cells, called nociceptors, produce signals that traverse nerves through the spinal cord to the brain.⁷⁸ Conversely, pain is a highly subjective and dynamic experience that is determined by the interplay between sensory and contextual (i.e., emotions, beliefs, cognitions, and motivations) features.⁷⁹ Pain processing involves the integration of neural activity across multiple brain regions, whereby activation and flexibility of these functional connections determines the pain experience.⁷⁹

Pain syndromes, such as headaches and musculoskeletal pain, are common and debilitating consequences of TBI and may contribute to other deficits.^{80–82} For example, chronic headache is

common across the TBI spectrum (i.e., mild, moderate, and severe), with reported prevalence rates ranging from ~20% to 95% in TBI patients.⁸⁰ The source of pain in TBI patients is generally unknown and may occur as a direct result of the injury (e.g., peripheral nerve or plexus damage) or be a secondary consequence of the trauma. Although the etiology is often unknown, post-traumatic pain has been associated with impairment in the inhibitory aspects of the descending pain pathways from the sensorimotor cortices to the spinothalamic tracts and increased neuroinflammation.^{81,82}

Challenges in traumatic brain injury patient studies and the rationale for animal models

As alluded to above, the large degree of variability in patient outcomes and the many possible modifying factors in the clinical TBI setting, along with other challenges related to clinical TBI research (e.g., selection bias, genetics, socioeconomic and lifestyle factors, participant dropout, high time and cost requirements, and ethical considerations), makes it difficult to fully elucidate the behavioral impairments after TBI, determine the pathophysiological mechanisms that underlie these behaviors, and develop appropriate interventions to facilitate recovery purely in patient studies. Alternatively, studies that use animal models of TBI, both in rodents and larger mammals, provide a means to investigate behavioral impairments in a highly controlled, rigorous, ethical, and efficient manner.^{4–6}

Behavior Testing in Rodent Models of Traumatic Brain Injury

As described below, there are many behavioral methods that can be applied in rodent TBI models that allow for assessment of clinically relevant behavioral outcomes. Note that this section does not represent a systematic review of the enormous number of behavioral studies that have been conducted in the many different preclinical brain injury models. Rather, we will provide an overview of the utility and clinical relevance of some of the most commonly used tasks in the pre-clinical TBI field and present examples of findings from studies that have used these tests. It is also important to acknowledge that TBI is a highly heterogeneous condition and, depending on the injury mechanism, severity of injury, and time post-injury, can result in a broad range of pathological changes that may manifest in different behavioral deficits.

There are different animal models of TBI that have been demonstrated to model different aspects of clinical TBI pathology (e.g., diffuse, focal, mixed, blast; mild, moderate, severe; see previous works^{4,5} for reviews on this topic), and the behavioral outcomes in these models can consequently differ. Comparing and contrasting results from the various behavioral tasks, both within (e.g., mild vs. moderate vs. severe; acute vs. subacute vs. chronic) and between (e.g., diffuse, focal, diffuse, focal, mixed, and blast), the models/pathologies are beyond the scope of this review, but is an important consideration in study design.

To provide the reader a more comprehensive overview of previous behavioral findings, and help guide in identifying behavioral tasks appropriate for different TBI severities at different recovery times, we have provided a table (i.e., Table 1) at the end of this section. It should also be noted that there is still a limited understanding of the causal pathological mechanisms that underlie the various behavioral changes that occur in TBI patients or animal TBI models. This makes it difficult to determine whether the behavioral changes after TBI in patients and rodents are attributed to the same pathological mechanisms, and future research is needed to clarify

TABLE 1. SUMMARY OF THE UTILITY OF BEHAVIORAL TASKS FOR RODENT-BASED TBI RESEARCH

		Mild TBI			Repeated mild TBI			Moderate TBI			Severe TBI			References
		Acute		Chronic	Acute		Subacute	Chronic	Acute		Subacute	Chronic		
		+	-	?	+	-	?	+	-	?	+	-	?	
Cognitive	Morris water maze	+	-	?	+	+	+	?	+	+	+	+	+	85, 86, 88–97, 112, 118, 123, 152, 161–163, 169, 194, 203, 207, 231–243
	Barnes maze	-	+	?	+	+	+	+	-	+	-	+	-	100, 101, 103, 120, 160, 192, 244–247
	Radial arm maze	-	+	-	-	+	+	-	-	+	-	+	-	106–108, 248
	Y-maze	-	?	x	-	-	?	+	x	?	-	+	+	117, 118, 161, 183, 232, 244, 247, 249–256
Anxiety/ Depression	T-maze	-	-	-	-	-	-	-	-	-	+	+	-	120, 257
	NOR	+	+	x	+	+	+	-	+	+	+	+	-	120, 123, 125, 126, 130, 131, 206, 212, 213, 232, 236, 238, 243, 249–251, 255, 256, 258–261
	5-CSRTT	-	+	-	-	+	+	-	+	+	-	+	+	134, 135
	Touchscreen	x	x	-	-	-	-	-	+	+	-	-	-	262, 263
	Elevated plus maze	?	?	x	?	+	+	+	x	+	-	x	-	85, 89, 112, 123, 130, 131, 149, 153, 162, 163, 169, 181, 183, 192, 213, 225, 235, 236, 245, 252, 254, 255, 261
	Elevated zero maze	x	x	?	-	x	?	-	+	x	-	x	-	90, 154, 212, 251, 261, 264
	Open field	?	x	x	x	x	?	+	+	+	+	+	-	89, 90, 94, 125, 149, 154, 160, 166, 234, 236, 242, 244, 252, 258
	Light-dark box	x	?	-	-	-	-	-	-	-	+	x	-	149, 154, 265
	Sucrose preference	-	?	-	-	-	+	-	-	-	-	?	-	149–152, 154, 183
	Forced swim	?	?	-	x	+	+	?	+	+	+	-	-	112, 130, 149, 153, 154, 157, 158, 160–163, 212, 213, 225, 247, 251, 260
Social	Tail suspension	-	x	+	-	+	+	+	-	+	-	-	+	151, 162, 166, 183, 194, 243, 276
	Social interactions	x	?	+	x	x	+	+	+	+	-	+	+	151, 163, 164, 169, 180, 181, 183, 194
	Three chamber	-	x	-	-	+	+	-	-	+	-	+	-	180, 181, 183, 192, 193, 244
Motor	Rotarod	?	x	x	?	?	?	?	+	+	+	+	-	89, 117, 124, 194, 202–204, 206, 208, 231, 234, 235, 237, 241, 242, 244, 253, 254, 264, 266–272
	Beam	+	x	-	+	+	?	+	+	+	+	+	-	85, 89, 90, 94, 100, 130, 131, 134, 163, 169, 207, 225, 236, 239, 240, 243, 247, 249, 252, 273–275
Pain	General locomotor	?	?	x	x	?	?	+	?	?	x	+	x	130, 134, 163, 183, 194, 212, 213, 242, 244, 252, 257, 264, 276, 277
	Gait analysis	+	-	+	+	?	?	+	+	-	-	+	-	214, 216, 264
	von Frey	+	+	-	-	?	?	-	+	-	-	-	-	224–226, 230, 265, 278–282
	Thermal plate	x	?	-	-	-	-	-	-	-	-	-	-	227, 228, 282
	Grimace scale	-	-	-	-	-	-	-	+	+	-	-	-	221, 230

Please note that this table is intended as an indication of the utility of each of the behavioral tasks for mild, moderate, and severe TBI severities at acute, subacute, and chronic recovery times post-injury. Findings were collated from >120 recent, rodent-based TBI studies; however, this is not a systematic review of the literature. This table does not account for variations in age, sex, injury-model– and behavioral-task variants. Some behavioral tasks have rarely been utilized in certain injury severities and stages post-injury. Acute stage was defined as ≤3 days post-injury; subacute >3 days and <3 months; chronic ≥3 months. “+” denotes injury effects detected in ≥75% of studies assessed. “x” denotes injury effects detected in ≤25% of studies. “?” denotes injury effects detected in <25% and <75% of studies. “-” denotes technique not used at this injury phase/severity.

TBI, traumatic brain injury; NOR, Novel Object Recognition; 5-CSRTT, 5-Choice Serial Reaction Time Task.

this and further validate the relevance of behavioral outcomes in animal models. With that said, there is evidence that animal models can induce pathologies (as alluded to above) and behavioral abnormalities (as described below) that are similar to those that occur in human TBI.

Cognitive tasks and impairments in rodent traumatic brain injury models

As summarized above, a range of cognitive deficits have been documented in human TBI patients. As such, tests to assess cognitive function are commonly applied in experimental models of TBI. Spatial learning and memory is perhaps the most commonly studied aspect of cognition in rodent TBI studies, with the Morris water maze (MWM), Barnes maze, and the radial 8-arm maze (RAM) among the tasks most frequently used.

The MWM consists of a circular pool of water that contains an escape platform and is surrounded by visual spatial cues that the rodent can use to assist it in locating the escape platform.⁸³ The escape platform size, location, and visibility often vary depending on the laboratory or MWM protocol.^{83,84} There are a number of measures that can be used to assess a rodent's ability to locate the platform, including search latency, swim path, distance traveled, time spent in the platform quadrant, and search strategy/efficiency (e.g., direct and circle swims). Previous MWM studies in rodents given TBI have found deficits in learning, cognitive flexibility, working memory, as well as retrograde and anterograde amnesia.⁸³⁻⁹⁷

The Barnes maze evaluates spatial learning and memory in rodents and has the advantage of eliminating the stress associated with water/swimming.⁹⁸⁻¹⁰⁰ The apparatus consists of a large circular disk (~100–150 cm in diameter) that typically has 12–40 escape holes. One of the holes leads to an escape cage, whereas the others are open holes with no method of escape. The maze is surrounded by spatial cues that assist in locating the correct escape hole. A mildly aversive stimulus, such as a light or a fan, above the apparatus provides ample motivation for the rodents to find the escape hole. The escape latency, distance, and velocity are commonly used estimates for learning and memory. Consistent with MWM findings, deficits in the Barnes maze are also present in rodents subjected to TBI.¹⁰⁰⁻¹⁰³

The RAM also tests spatial cognition in rodents, and the apparatus consists of baited (i.e., containing a food reward) and unbaited arms (eight arms in total).^{104,105} The rodent searches for the baited arms over repeated trials, and success relies on memory of the baited arms (reference memory) as well as visited/unbaited arms (working memory). Experimental TBI has been found to affect both short- and long-term memory in this task.¹⁰⁶⁻¹⁰⁸

In support of the translational value of the above tests in rodents, virtual spatial learning and memory tasks have been adapted for use in humans, and TBI patients display deficits on such tasks.¹⁰⁹ Further, the brain regions (i.e., hippocampus, entorhinal cortex, pre-frontal cortex, frontal cortex, parietal cortex, and corpus callosum) implicated in the spatial learning and memory deficits in the rodent tasks^{85,89,94,97,110-113} are also commonly affected in human TBI.¹¹⁴ Though it should be noted that one disadvantage of the RAM, Barnes maze, and some MWM paradigms, is that extensive and time consuming training is required before testing.

The Y-maze and T-maze are other tests that can be used to evaluate reference and working memory, as well as spatial learning, in rodents. The Y-maze apparatus is composed of three arms, two open and one closed, as well as constant spatial cues.¹¹⁵ Through a

habituation phase the rodents are familiarized to the open arms, and in the exploratory phase they are exposed to the novel arm (i.e., previously closed arm). The amount of time spent in the novel arm is the primary outcome and is a measure of working memory, as well as exploration tendency.¹¹⁶ TBI has been found to reduce time spent and/or entries into the novel arm, which has been interpreted as a deficit in spatial working memory.^{117,118} The T-maze apparatus consists of two arms that intersect to form the shape of a "T." The rodent starts in one arm and chooses to go left or right at the intersection. Depending on the T-maze protocol, testing can involve assessing either spontaneous left-right discrimination/alteration, or either the left or right can be baited with a reward.¹¹⁹ Memory deficits after TBI in the T-maze and Y-maze have been linked to a number of neuroanatomical structures (e.g., hippocampus, pre-frontal cortex, and hippocampus) that are also implicated in human TBI.^{114,117,120}

The Novel Object Recognition (NOR) test evaluates recognition memory¹²¹ and involves placing a rodent in an open field that contains familiar and/or novel objects. The animal is first familiarized with two objects, and following an intertrial time interval, one of these original/familiar objects is replaced with a novel object. This novel object is typically recognized and preferred by healthy rodents,¹²² whereas rodents given TBI have short- and long-term cognitive deficits.¹²³⁻¹²⁶ These findings are consistent with those from human TBI studies that have reported impairments in recognition memory.¹²⁷ The Novel Context Mismatch (NCM) test is an adaptation of the NOR test and, in addition to novel object recognition, also assesses context and spatial memory. During a habituation phase of the NCM, the animal is placed in two different environments (i.e., contexts), each with two different objects. A testing session follows where the exploratory preference is measured when objects are presented in one of the two contexts. The object not previously placed in the testing context acts as the novel object and is typically preferred.^{128,129} Previous studies have found that rodents given mild TBIs have cognitive deficits in the NCM task.^{130,131}

The 5-Choice Serial Reaction Time Task (5-CSRTT) is a common behavioral test that assesses attention (i.e., an important aspect of cognition that is commonly affected in TBI patients) versus impulse behavior.^{132,133} The 5-CSRTT apparatus consists of a testing chamber that has five holes. The task involves one of the holes lighting up for a brief time and the rodent responding to the stimuli with a nose poke. Correct responses are rewarded with food/drink. An incorrect response, defined as failure to indicate the illuminated hole or responding before illumination (i.e., impulsive behavior), is followed by brief darkness and no reward. Deficits in this task have been detected in mild, moderate, and severe TBI models.^{134,135} Importantly, the 5-CSRTT is based on the principles of the human continuous performance task,¹³² which TBI patients consistently display deficits on,¹³⁶ illustrating the translational value of the 5-CSRTT.

Although the tasks detailed above allow researchers to examine a range of cognitive processes in rodents and are commonly used in TBI models, it is important to note that other cognitive tests and platforms are now available that may provide additional translational value to TBI studies. For example, advanced touchscreen assays for rodents have also been developed for rodent testing to probe similar cognitive domains as those in humans.¹³⁷⁻¹⁴² These touchscreens are built on an operant response whereby rats are trained to make nose-poke responses to visual stimuli displayed on an infrared touchscreen in order to obtain a food/liquid reward.¹³⁷⁻¹⁴⁰ The testing battery includes several tasks that examine

distinct cognitive functions including tests of executive processes such as cognitive flexibility, response inhibition, working memory, and attentional processing.^{137–140} As such, this platform allows for animals to be tested on a range of higher cognitive functions.^{137–140} Further, performance can be compared across tasks as they are completed in the same test apparatus; outcomes are quantified using automated methods; there is minimal experimenter handling; and there is relatively low dependence on motor function.^{137–140}

With respect to translational relevance, studies using touchscreen testing to assess similar cognitive functions can also be done in human TBI patients.^{141,142} Though it should also be noted that there are several limitations with the touchscreen testing platform in rodents that include a significant amount of training and time to complete, the reliance on visual stimuli, and being reward based.¹³⁷

Anxiety- and depression-like behaviors in rodent traumatic brain injury models

Translational assessments of any psychiatric disorder are, by their nature, challenging. The diagnostic criteria of these are complex, heterogeneous, non-exclusive, and multi-factorial. In addition, several of the symptoms associated with psychiatric disorders are uniquely human and cannot be accurately translated—for example, auditory hallucinations or suicidal tendencies are challenging to assess in non-human subjects. When considering animal models of depression/anxiety disorders, two primary attributes must be considered. The first is how to generate a “depressive-like” or “anxiety-like” state. There are many methods to achieve this—probably the most common involves some form of chronic stress,¹⁴³ but there are also surgical and genetic methods.¹⁴⁴ In the current review, the precipitating model is a TBI, although those used for studying depression and anxiety outcomes are quite diverse with varying levels of translational potential.²

Given the evidence suggesting that personal history of psychiatric disorders are risk factors for problems after TBI, it would be very interesting to observe the effects of chronic stress preceding TBI on behavioral outcomes. The second aspect involves assessment of behavioral traits indicative of depressive/anxiety symptoms. Those published in this regard have varying degrees of face validity—observable similarities akin to the symptoms exhibited by human subjects. We consider these aspects as most relevant (as opposed to those showing construct or predictive validity) in the context of the current review focusing on translational models of depression and anxiety.

Similar to the clinical evidence described earlier, there are many reports which describe increases in depressive-like behavior in models of TBI.² The most striking feature of these reports is the consistency of the depressive phenotype, which is commonly observed despite these studies being conducted in many different laboratories and incorporating a wide variety of injury models, ages, and species of animal, time of measurement after injury, injury frequency, and severity and the reported outcome measures. This suggests that this is indeed a robust consequence of TBI. The two most common assessments of depression-like behavior in TBI models examine anhedonia and behavioral despair. Although other tests behaviors and physiological markers of depression, such as sexual drive and weight gain/loss, can be readily assessed and have strong face validity,¹⁴⁵ these are rarely used as outcomes in models of TBI.

Perhaps the outcome measure with the most direct face validity used in these studies assesses anhedonia, or reduced motivation or ability to experience pleasure—a symptom frequently observed in

patients experiencing depression.^{146,147} In rodents, hedonic behavior can be measured using the sucrose preference test. This test involves two water bottles that are presented continuously for several days, one with normal tap water and the other with 1% sucrose added.¹⁴⁸ Most rodents will strongly favor the sucrose drink, presumably deriving pleasure from consuming the sweetened drink. A comparator animal who does not prefer the sucrose is thought to exhibit anhedonia. Some researchers choose to use saccharin, instead of sucrose, to avoid the caloric impact of the sucrose. A variety of different experimental models of TBI, including the weight-drop model and the controlled cortical impact (CCI) model have been found to exhibit anhedonia after injury, both in rats and mice.^{149–152}

Of note, one study utilizing a mild weight-drop injury, induced anhedonic behavior in injured mice and demonstrated reversal of this phenotype with the antidepressant, fluoxetine,¹⁴⁹ suggesting predictive validity of this phenotype also. However, in several studies, sucrose preference is not disturbed in models of TBI,^{153,154} calling into question the clinical relevance of this test. In addition to face validity, the sucrose preference test also exhibits construct (chronic stress is linked to psychiatric disorders, and in rodents reduces sucrose preference) as well as predictive (chronic, but not acute, antidepressant treatment improves loss of preference) validity, so an alternative explanation is that the particular models of TBI utilized in these negative studies do not replicate the pathophysiological alterations occurring in some humans after TBI which lead to anhedonia.

Another common method used to identify a depression-like phenotype in rodents involves measurement of behaviors thought to be related to despair or lack of motivation. The tasks used in this pursuit are the forced swim test¹⁵⁵ and the tail suspension test.¹⁵⁶ In these tasks, animals are placed into an inescapable situation, such as a tall beaker of water, or hanging upside down. Animals will initially struggle to escape these unpleasant situations, but after time, they stop struggling and give up, adopting a floating or hanging posture. The time spent immobile is the primary outcome measure, and greater levels of immobility represent greater despair. These tests were initially developed as predictive tools by the pharmaceutical industry, and antidepressants are recognized to reduce these behaviors.

Several studies have used these assessments to demonstrate increased behavioral despair, or depressive-like behavior, after TBI. These include both severe and mild injury severities, and incorporate a variety of TBI models, including weight drop, the CCI model, fluid percussion injury, and blast injury.^{96,157–166} Though, as shown in Table 1, the forced swim and tail suspension tests do not always provide positive data, the depressive phenotype observed in some models of TBI allows investigation of new therapeutics. Indeed, several diverse pharmacological approaches have demonstrated improvements in TBI-associated depression-like behaviors, including inhibition of glycogen synthase kinase 3,¹⁵⁷ anti-inflammatory agents,¹⁶¹ as well as CB2 cannabinoid receptor inverse agonism.¹⁶⁵ In addition, the presence of these behaviors facilitates the study of biological mechanisms responsible for generating depression-like symptoms after TBI without the added complexity of psychosocial attributes that complicate investigations in humans.

Although less commonly reported, several pre-clinical studies also document the presence of anxiety-like behaviors after TBI. Measures of state anxiety benefit from being simpler to model in animals—fear is an innate and readily observable behavior of rodents. In particular, fear/anxiety of open spaces is an evolutionary

behavior developed to avoid predators. Many tasks have been designed to measure anxiety in rodents, several pitting the animal's natural conflicts of fear of open spaces against the desire to explore its environment to search for food. The Elevated Plus Maze (EPM), the Elevated Zero Maze, the Open Field, or the Light-Dark Box are behavioral tasks which use this strategy and have been used to explore anxiety-like behaviors after TBI. Previous studies have observed increases in anxiety using these tasks in both rats and mice after TBI when the injury is induced using weight-drop injury, CCI, fluid percussion injury, and blast injury.² These phenotypes can last for several months after the precipitating insult.^{112,153}

Other studies utilize the novelty-suppressed feeding test,¹⁶⁷ a test whereby animals are food-deprived for 1 day, and then placed in a novel, brightly lit arena with a sample of food in the center of the arena. Latency to eat the food is considered a measure of anxiety, and this outcome has demonstrated anxiety-like behavior after CCI in mice.¹⁶¹ Contrasting reports describe reduced levels of anxiety in injured rodents,^{96,168,169} but some researchers interpret this as increased risk-taking, or increased exploration, as opposed to an anxiolytic effect of TBI.^{162,169}

Another relevant outcome when investigating anxiety disorders after TBI involves models of PTSD, the most common of which involves fear conditioning. PTSD is a psychiatric condition in its own right, and TBI is an established risk factor for development of PTSD.¹⁷⁰ In rodents, the fear conditioning task examines associative learning ability by exposing the animal to a noxious stimulus (usually a foot shock) which is paired with a neutral stimulus (cued conditioning, such as a tone) or environment (contextual conditioning). Several cue-shock or context-shock pairings are presented to allow association to develop, and then the animal is only exposed to the neutral stimulus (either the cue or the environment). If the animal has learnt the association, it will freeze in anticipation of the expected foot shock. Given that PTSD is relatively common after TBI (particularly with military personnel)—one might anticipate exaggerated freezing responses in models of TBI attributed to heightened responsivity of fear/anxiety circuitry.

Although relatively few studies have investigated this, several indicate enhancement of fear-associated learning in these assessments. For example, after mild fluid percussion injury, rats exhibited increased fear conditioning using both cued and contextual fear conditioning paradigms.¹⁷¹ Similar phenotypes were observed after blast exposure and mild weight-drop injury in rats,^{172,173} suggesting that several TBI models in rodents can be used to study pathophysiology associated with PTSD.

Although psychiatric disorders, such as anxiety and depression, are defined by behavioral features, other physiological measures can also be incorporated as translational tools. For example, increases in blood pressure, heart rate, and body temperature occur during the physiological expression of anxiety, and these can be readily measured in rodents during such conflict tests. These have not yet been comprehensively studied in the context of TBI, but should be strongly considered in future studies. In addition, these are directly translational tools, being easily studied in humans and rodents. Further consideration in this regard should also be given to whether brain pathologies observed in humans after TBI, and the methods we use to model this condition, impact brain regions that are implicated in affective disorders. The most prominent brain structures implicated in affective disorders, including those discussed above, include, but are not limited to, temporal lobe regions, such as amygdala and hippocampus, as well as pre-frontal cortex and basal ganglia.¹⁷⁴

With the heterogeneity of injury associated with TBI, as discussed above, brain pathology can sometimes be observed in some or all of these regions, and this would be expected to compromise normal function and lead to such disorders. Several of the animal models described above can result in injury to these same limbic regions, suggesting that these could be used as translational tools to study pathology associated with affective disorders. For example, fluid percussion injury results in focal as well as diffuse axonal pathology permeating to the temporal lobes,¹⁷⁵ whereas other injuries, such as weight-drop and blast injuries,^{176,177} can similarly result in neuronal damage and impact normal function of these deep brain structures.

Social testing and abnormalities in rodents with traumatic brain injury

Several forms of social functioning, including changes in social interactions, social communication, and aspects of social cognition, have been explored in a range of experimental models of TBI. The most common paradigm involves the introduction of an unfamiliar animal to the test animal as a "social stimulus" and quantifying the degree of social interest. The stimulus may be age-, sex-, and strain-matched to the test animal; alternatively, some investigators chose to use a different strain (e.g., a different color, for ease of identification) or juvenile stimulus, to minimize antagonistic or aggressive behaviors.^{178,179} Known as the resident-intruder or reciprocal social interactions test, this paradigm may be used as a single exposure, or in a series of repeated experiments, the latter being used to evaluate changes over time and/or assess social habituation as an indicator of social memory formation.¹⁸⁰

Changes in social interactions have been reported after a moderate weight-drop model of TBI¹⁸¹ and after CCI in both juvenile and adult mice.^{182–184} In contrast, several studies in mild TBI models have failed to detect an effect of injury on social interactions.^{169,185} Use of an opposite-sex stimulus animal in this paradigm allows for the investigation of sociosexual interactions, leading to several reports of reduced sociosexual interest by male TBI animals.^{184,186,187} Social play behaviors between two juvenile animals can also be assessed in this format,¹⁷⁹ with mixed findings to date regarding whether a single mild TBI can influence play behaviors in young animals.^{164,188,189}

The three-chamber social approach test is increasingly being used to evaluate social interactions in brain-injured rodents. This paradigm involves physical separation of the test and stimulus animals, with the stimulus restrained in a small cage within one of two outer chambers of the apparatus. This restricts the initiation and motivation of the interaction to the test subject, which is thought to reduce dependence of task performance on the behavior of the stimulus subject, as well as making the task easier to objectively quantify.^{180,190,191} The test is usually performed in three consecutive stages, whereby stage 1 involves habituation to the apparatus, stage 2 involves introduction of a stimulus animal to one side chamber, and stage 3 (optional) involves introduction of a second stimulus animal to the other side chamber. Stages 2 and 3 therefore allow for evaluation of a preference for sociability (spending time with the stimulus animal compared to the empty chamber) and social novelty (spending time with the second, novel stimulus animal compared to the now-familiar first stimulus), respectively.¹⁹¹

Mice and rats have an innate curiosity and will typically spend increased time in proximity to the novel animal, indicating social memory for previous exposure to the first stimulus animal.¹⁸⁰ Using the three-chamber test, in general, a reduction in sociability and

social recognition memory has been reported after experimental TBI in juvenile and adult rats and mice.^{182,192–194} However, other studies using milder TBI models have failed to identify deficits on this task.¹⁹⁵ Although no causal evidence exists to date, deficits in social functioning after experimental TBI have been associated with the extent of hippocampal volumetric loss as well as neuroplasticity in the hippocampus and pre-frontal cortex.^{184,186}

Although several tests to quantify social communication between rodents have been developed,¹⁹⁶ few studies have incorporated these to date into experimental TBI models. Of note, Semple and colleagues detected changes in ultrasonic vocalizations and scent marking by adult mice exposed to a single severe CCI injury during early life.¹⁸⁶ Adult mice exposed to CCI, but not mild repeated concussions, also show reduced scent marking toward a novel stimulus mouse,¹⁹⁴ whereas another group found that a single mild closed-skull impact was sufficient to reduce social odor recognition in adult rats.¹⁹⁷ The clinical validity of such measures for social communication is yet to be verified.

Several advances in the quantification of social interactions in rodent models have yet to be applied to experimental TBI models. For example, several software packages now allow for the simultaneous evaluation of up to six freely interacting rodents in a home-cage environment.¹⁹⁸ Others have developed adaptations of the three-chamber social approach paradigm, noting that this test may be confounded by deficits in spatial navigation ability, and that use of “time in chamber” as the main outcome measure may result in disregard for subtle behavioral dynamics.¹⁹⁹ For example, one modification involves tethering of the stimulus rat within a large chamber, with a smaller “escape” chamber alongside it, such that the test animal can freely choose between social approach versus withdrawal.²⁰⁰ We and others have modified the three-chamber apparatus design,¹⁹⁹ for example, to locate the stimulus animals at the end of the outer chambers, rather than in their centers, which limits the interaction to a more easily defined zone for more precise quantification of social interest.¹⁸⁴

Moving forward, the focus on increasing use of automated tracking for high-throughput quantification of social interactions must be balanced with high sensitivity for subtle social behaviors.

Motor function in rodents with traumatic brain injury

To study neuromotor impairments and evaluate therapeutic strategies, pre-clinical models of TBI consistently incorporate three motor assessments: the rotarod, Beam Balance/Beam Walking, and general locomotor activity. First, the rotarod test is a behavioral measure generally used to assess neuromuscular and motor impairment.²⁰¹ The test measures the animal's ability to maintain itself on the rotating rod that turns at an accelerating speed. In order for the rat/mouse to maintain a walking gait on the device, the animal is required to grip the moving rods. TBI has been shown to decrease grip strength, allowing for increased sensitivity of the apparatus.^{202,203} Gradually increasing the speed of the rotation during the trials increases the sensitivity of the test and allows for discrimination between the injured and non-injured animals.²⁰⁴ However, some have noted limitations to the rotarod task given that it is often difficult for moderately and severely injured animals to actually complete the procedure.²⁰⁵

Beam walking tasks are specifically advantageous for testing motor impairments in animals given that they are not subject to practice effects and do not have any memory or learning components, which increases test validity. Unlike the highly automated rotarod, there are numerous variations of beam walking tasks that

have been used. For example, many studies examine beam-balance latency, a gross vestibulomotor function that can be evaluated by placing the animal on a narrow beam and measuring the duration of time it can remain on the beam.^{206–208} This task has significant translational relevance given that it measures balance deficits, one of the most common impairments identified in TBI patients. Other research groups have investigated beam-walking foot slips, a measure of fine motor coordination which utilizes a tapered beam and forces a rat to walk from a wide end to a narrower end.²⁰⁹ The experimenter can measure latency to cross the beam and the number of foot slips. Animals with TBI generally display deficits on this task and will exhibit more foot slips and take longer to cross the beam than their sham counterparts.^{131,208}

Given that locomotion is a primary behavior of rodents, the assessment of locomotor function is essential to comprehensive test batteries after TBI.²¹⁰ Open fields or activity boxes are used as general measures of exploratory locomotor behaviour.²¹¹ The open field does not require grip strength or overt motor coordination, as in the rotarod and beam walking tasks respectively. The open field and activity boxes rely on the animal's innate curiosity to explore a novel environment. While the animal travels throughout the arena, automated programs scrutinize distance traveled, speed of travel, rearing, and freezing behaviors. Depending on the severity and form of TBI, as well as the recovery time tested, animals with TBI can exhibit diminished activity, normal activity, or hyperactivity in the open field, which is also consistent with what can occur in the clinical setting.^{90,94,125,134,212,213} Whereas activity boxes and open fields highlight intrinsic aspects of exploratory behavior, it is important to note that this behavior is highly influenced by not only motor impairments, but also changes to motivational and cognitive function.²¹⁰

There are additional behavioral measures of motor dysfunction that are used, albeit less commonly, in experimental TBI such as gait analysis, the Montoya stair case test, and skilled reaching. Gait analysis tools such as CatWalk[®] are automated software systems used to assess locomotor and gait in small animals by analyzing intensity, print width, print length, interlimb coordination, cadence, swing, and walk speed.²¹⁴ Similar to TBI patients, animals with TBI exhibit slower walk speeds, disruptions in cadence, and reductions in step length.^{69,214} The Montoya stair case task was developed to assess the independent use of forelimbs in skilled reaching and grasping tasks.²¹⁵

Interestingly, in one particular TBI study by Shonfeld and colleagues, manual motor tests, such as the cylinder test and Montoya stair case test, are better at detecting fine motor deficits than automated gait analysis systems like CatWalk.^{215,216} Finally, skilled reaching has been used more routinely in stroke research, given that it is ideal for examining unilateral damage such as hemiparesis.²¹⁷ Given that extensive training required for skilled reaching is often considered a form of therapy in and of itself, it is often excluded as a measure of motor disturbances after experimental TBI.²¹⁸

Investigating pain in rodents with traumatic brain injury

As described earlier, pain and nociception differ, and given the subjective nature of pain, it is understudied within the realm of preclinical TBI. When referring to animal models of pain, including headache, testing is highly dependent upon measurements of nociception. The most common behavioral tests for nociception are the von Frey,²¹⁹ hot/cold plate,²²⁰ and direct observation of behavior (e.g., the grimace scale).²²¹ For headache specifically, the von Frey and behavioral observation are used regularly.^{222,223} The

von Frey task is a measure of mechanical activation and is believed to be a reliable indicator of pain tolerance. The test involves gradual increases in the size of filaments that poke the center of the rat's hind paw, with larger filament size being indicative of higher mechanical nociceptive (or pain) thresholds. The von Frey is not routinely used in the context of TBI, though findings to date suggest largely positive findings in mild and moderate TBI (see Table 1). For example, reductions in mechanical nociceptive sensitivity (i.e., reduced pain thresholds) have been identified in mice after moderate TBI,²²⁴ although there are mixed findings in terms of von Frey abnormalities after repeated mild TBI.^{225,226}

The thermal, or hot/cold, plate is a measure of thermal nociceptive sensitivity that relies on reaction latencies to a given thermal stimuli²²⁰ and may be a valuable tool for examining allodynia in pre-clinical TBI models. Testing usually requires that animals be placed on a small circular, temperature-controlled plate that is enclosed within a transparent cylindrical container. The amount of time required until the animal reacts (licks hind paw/jumps) is recorded and used as a measure of thermal sensitivity, with longer latencies being indicative of lower the pain sensitivities.²²⁰ Only a few studies have used the thermal plate in the context of mild TBI and have found mixed results (see Table 1). No differences were found acutely after a mild fluid percussion injury in rats,²²⁷ though, on an orofacial version of the test, rats given a mild TBI had aversive responses to the challenge temperatures.²²⁸

The grimace scale has been adapted to numerous animals, including horses, rabbits, and dogs, but is most commonly used with rodents.²²¹ The rodent grimace scale relies on observer judgements of specific facial action units, often referred to as the pain face. For example, when examining pain in rats, the observer looks for changes in orbital tightening, nose/cheek flattening, ear flexions, and whisker movements. Although mice and rats differ in their specific action units that signal the experience of pain, the grimace scales are reliable, accurate, and display high inter-rater reliability measures of pain.^{221,229} Similar to the thermal plates, there is a dearth of literature regarding pre-clinical TBI and the grimace scale. To our knowledge, only a single TBI study has utilized the grimace and found that there were deficits at 5 weeks after a moderate blast TBI.²³⁰ Though considering these promising initial results, the grimace scale may provide a useful method for examining the occurrence and severity of pain experienced by many different species.

Behavioral Testing in Gyrencephalic Traumatic Brain Injury Models

Alongside rodent models of TBI, there has been renewed interest in large animal models of TBI, particularly utilizing animals with a gyrencephalic brain. Research indicates that the gyrencephalic brain reacts differently to a mechanical insult. There is significantly more brain deformation in a gyrencephalic brain,²⁸³ and the forces are concentrated differently (i.e., at the base of the sulci in a gyrencephalic brain compared to close to the surface of the brain in a lissencephalic brain).^{284,285} Further, tissue deformation is influenced by the size of the brain as inertial effect is dependent on brain mass.²⁸⁶ Thus, larger brains undergo greater tissue deformation and shear strains, whereas the same forces applied to a smaller brain, like the rodent, produce lower strains and less injury.^{287,288} Sheep and pigs have much more developed white matter tracts, similar to those observed within the human brain, with widespread acknowledgement of the relative paucity of white matter tracts within the rodent.²⁸⁷ As such, gyrencephalic animal models provide a

useful step between rodent models and clinical translation and, as such, require well-characterized behavioral outcome measures with clinical utility.

Ferret behavioral tests

One of the smallest of the gyrencephalic animals utilized in TBI research is the ferret. Although the CCI model was originally developed for use in ferrets, their use in animal research fell out of favor, only returning to utilization in this field in the last few years.^{289,290} A mild CCI injury was associated with a chronic neuroinflammatory response (examined up to 16 weeks post-injury) that originated at the site of impact and progressed to deeper white matter.^{289,290} Behavioral outcomes were assessed through gait analysis for motor, T-maze, and NOR for cognition and time spent in the middle of the open field for anxiety, with minor memory impairment noted at 4 weeks post-injury.²⁸⁹ These represent adaptations of tasks commonly utilized in rodent studies, although it is important when modifying these tasks to consider the normal behavioral response of the animal of interest. For example, although rodents are fear averse of the center of the open field,²⁹¹ this does not seem to be similarly applicable to ferrets, decreasing the utility of this test as an anxiety measure. Indeed, no differences were noted between sham and injured animals.²⁸⁹ Although differences were noted on both the T-maze and NOR post-injury, because no control data were shown it is difficult to determine whether these alterations may relate to a repeated training effect rather than impaired cognition.²⁸⁹

Other behavioral tasks that have been validated in ferrets, but not yet used in TBI research, include spatial discrimination by a T-maze task,²⁹² spatial memory in the Lashley III maze,²⁹² and shock avoidance learning,²⁹³ which could be incorporated into future TBI studies. Nonetheless, these preliminary studies demonstrate that a clinically relevant model of TBI can be induced in ferrets, with persistent inflammation a key feature of clinical TBI.^{294,295} Indeed, chronic microglial activation, as observed in this ferret model, has been found to correlate with the degree of cognitive impairment observed post-injury clinically.²⁹⁴

Sheep and pig behavioral tests

Other large animal models that are currently utilized for TBI research include the pig and sheep. The pig TBI model most commonly utilized induces injury through inertial acceleration. This well-characterized model subjects the head to rapid angular acceleration, creating rotation at controlled rotational acceleration levels to produce graded neuropathological changes.^{296–298} The ovine TBI model uses a humane stunner targeted at the temporal region to cause unrestrained head movement that is similarly graded depending on the force used.²⁹⁹

Importantly, both the sheep and pig TBI models are able to produce widespread axonal injury in subcortical and deep white matter, as well as the thalamus,^{296–298} consistent with previous clinical reports.^{287,295,300} Given that the thalamus is a key relay center for cortical fiber projections, damage in this region has been associated with executive dysfunction post-TBI.³⁰¹

Moderate-severe TBI in sheep and pig models also leads to a rapid rise in intracranial pressure and significant falls in cerebral perfusion pressure and brain oxygenation.^{296–298} This closely mimics the clinical situation, where low brain oxygenation is a key predictor of morbidity.³⁰² However, no survival studies have yet been performed in adult animals, with to date behavioral assessment only conducted after TBI in 3- to 5-day-old piglets. Injury was

associated with difficulties in a number of simple cognitive tasks, including a glass barrier task and food cover task, where piglets were required to navigate an obstacle to obtain food, as well as in a balance beam motor task.³⁰³ This motor deficit may be explained by the presence of widespread axonal injury, particularly in the internal capsule, with damage to this region previously correlated with motor impairment in other neurological conditions.³⁰⁴

Despite lack of utilization to date, there are a large variety of behavioral tests that have been developed in pigs and sheep, with some validated in other neurological conditions, including stroke and spinal cord injury. For assessment of motor function, the most basic test is a neurological score. For example, a 27-point scale has been utilized after stroke in sheep that incorporates measures of facial and neck muscle weakness, gait disturbance, and limb strength.³⁰⁵ This was sufficient to differentiate injury severity after occlusion of the middle cerebral artery for varying lengths of time.³⁰⁵ A similar scale has been utilized in minipigs, but also incorporated measures of appetite and utterance as well as assessing strength of the limbs and face, with this showing impairment up to 3 days after a small lacunar infarct.³⁰⁶ Beams of varying sizes have also been adapted for use in piglet models of TBI as an assessment of balance,³⁰³ but given the size of adult sheep and pigs, this would be a less-practical option.

Gait analysis provides a more-detailed examination of motor outcome and can incorporate walking on a treadmill or through specially designed runs.^{307–309} The treadmill allows control over velocity and can reduce variability that can affect assessment. Analysis of gait can be done by direct visual analysis, the quality of which is investigator dependent, captured by high-speed video or through semiautomated methods.³¹⁰ Some of these semiautomated methods, like Qualisys, are available for both quadruped and clinical analysis, providing a potential direct translational link. However, the systems are costly and quadrupeds compensate differently to motor impairment compared to bipeds, making direct comparison difficult.³⁰⁷ Nonetheless, gait analysis can provide information in regard to stride length, step velocity, and step height, with the addition of force platforms and/or reflective markers around joints providing information about kinematics. For example, spinal cord injury in sheep and stroke in pigs both resulted in gait abnormalities.^{307,309} This evidence suggests that gait analysis could similarly detect difference post-TBI in a large animal model to provide direct clinical relevance.

A wide range of cognitive tasks have been developed in the pig and minipig, although few have been directly assessed in relation to sensitivity to neurological impairment. These cognitive tests range from sequential choice mazes, like the T-maze and Hebb-Williams maze,^{311,312} where animals have a fixed starting point and a fixed goal to free choice mazes, like the RAM,³¹³ where rewards are present at various locations and the animal is free to explore.³¹⁴ The spatial holeboard is another maze-like task, where food is hidden in a certain number of holes. The NOR has also been adapted for use in pigs, with adult boars exploring a novel object significantly more than the familiar object.³¹⁵ Pigs have also been successfully trained on a go-no-go task.^{316,317}

Fewer cognitive tests are available in sheep, with those currently available predominantly developed to allow assessment of cognitive decline in Huntington's disease.^{318–320} Specifically, the Morton laboratory has evaluated executive function in sheep using a set-shifting paradigm either within a simple maze or as a touchscreen task. Sheep were successfully able to learn simple discrimination and reversal, as well as attention-set shifting where the rule that defines the correct choice undergoes an extradimensional shift (e.g.,

from color to shape).^{318,319} A stop-signal task has also been validated, where sheep learn to respond to a “go” signal and then stop this previously initiated movement if a “stop” signal is presented.³²⁰ Although no studies have been published utilizing these tests in cognitively impaired sheep, the availability of these paradigms is highly desirable for promoting translational research.

Common rodent tests for anxiety have also been adapted for use in the pig, including exploration of the open field and the EPM. The EPM has only been used in young animals (<3 months of age),^{321–324} and given the size of even fully grown minipigs, it would be difficult to use this test in adults. Further, it is unclear whether these tasks are relevant behavioral measures given the difference in behavior between rodents and pigs, with pigs not typically averse to open spaces.³²⁵ Indeed, studies have found that pigs do not show unconditioned avoidance of the open arms, one of the main assumptions of the EPM.^{322,326}

Similar difficulties in regard to their natural behavior are encountered with the use of the open field as a measure of anxiety in pigs. As such, it is often combined with a novel object test,^{327–329} to measure the response to an unfamiliar stimulus, rather than time spent in the center of the open field. However, reports vary in the literature, with no effect on test parameters reported after depletion of serotonin or administration of an anxiolytic in diazepam,^{321,329} whereas administration of a tranquilizer, azaperone, increased time spent engaging with a novel object.³²²

Thus, to develop a measure of emotionality that can be utilized in these large animal models, cognitive bias tasks have been developed for both sheep and pigs.^{330–332} This involves training animals to distinguish between a positively associated stimulus and a negatively associated stimulus and then evaluating their response to an ambiguous cue. Clinically anxious individuals tend to interpret ambiguous or neutral information in a more negative manner than non-anxious individuals.³³³ In pigs trained to distinguish between two auditory cues, one of which was associated with a food reward and the other no reward, environmental enrichment led to an increased response rate to an ambiguous cue.³³²

A different approach is to evaluate attentional bias, where anxious individuals show an increased tendency to direct attention toward threatening stimuli. In sheep, such a test has been designed where they are brought into a pen where a threatening stimulus (e.g., a dog) is briefly shown behind a barrier in one corner.³³⁴ Despite the fact that these cognitive bias tests appear amenable to detecting emotion state, application post-TBI may prove difficult given that underlying cognitive deficiencies may impair learning of the original task. Further investigation may be required to determine the best approach to behavioral measures of emotion in large animal models post-TBI.

Conclusions and Future Directions

The aim of this article was to review the behavioral tasks available for use in animal models of TBI and evaluate the clinical relevance of these methods and related findings. As described above, there are a growing number of behavioral tasks that can be applied to evaluate different aspects of cognitive, social, motor, and emotional function in animal models of TBI. Indeed, initial studies have already applied many of these tests in this context. With that said, there are strategies that pre-clinical TBI researchers can apply to improve the translational relevance of their behavioral studies. For example, it is often the case that only a single behavioral test at a single recovery time point is used in experimental TBI research.

Given the heterogeneous nature of TBI outcomes, scientists should include multiple tests that evaluate a range (e.g., cognitive, motor, social, and emotional) of behavioral abnormalities. It is also important to recognize that even within a single classification of behavior, numerous subdomains exist and broad conclusions based on a single test should be avoided. For example, cognition incorporates many different mental processes that are affected in TBI, and a single test (e.g., the MWM) is not able to assess each of these adequately. As such, the use of multiple complementary tests will provide a more comprehensive analysis. Related to the above point, despite the progressive and chronic nature of TBI, many studies only assess behavior at a single recovery time and often focus on acute and subacute outcomes.

Future studies should incorporate behavior testing at serial/multiple recovery times, and include chronic assessments, when possible and relevant. Though it is important to note that not all behavioral tests are appropriate for serial testing, given that they are dependent on the novelty of the task. In this scenario, the scientist must decide on either the single most relevant recovery time to test or to include multiple cohorts to test at different recovery times.

Although there is translational value in many of the behavioral tests used in past and present TBI studies (e.g., the MWM in rodents and the virtual version in humans),¹⁰⁹ and the clinical relevance of these methods may be improved by applying the strategies suggested above, researchers must continue to develop and integrate behavior methods that better translate to the human condition. For example, touchscreen testing of cognition is now relatively widely available in rodents and should be applied in the context of TBI, particularly given the ability to apply similar testing in human TBI patients.^{141,142} Ideally, new tests, or adaptations of current tasks, that are developed should allow for rapid data collection, automated data analysis, result in robust differences, and allow for serial testing in the same animal.

Although this article focused on tests of cognition, emotion, anxiety, depression, pain, motor function, and social behavior, there are other aspects of behavior/function that are known to be affected in human TBI that can also be examined in animal models. For example, sleep-wake disturbances are common in TBI patients,^{335–338} can be studied and are affected in animal TBI models,³³⁹ and may underlie or contribute to other behavioral and cognitive deficits.^{335–338} Similarly, measures of sensory sensitivity also offer translational value given that abnormalities occur in both clinical and pre-clinical TBI.^{340,341} Ocular motor measures are also affected in human TBI patients,^{25,260,342} and provide other clinically relevant outcomes that can be assessed in pre-clinical models. In particular, ocular motor function (e.g., saccades) can be tested in larger animals, such as ferrets,³⁴³ and is one of the many potential abovementioned benefits of using larger animal species with gyrene to help bridge the translational gap between rodent and human studies.

Taken together, this article advocates for the translational value of behavioral testing in pre-clinical TBI models. If this is the case, it once again raises the question, “If pre-clinical behavioral measures are clinically relevant, why do treatments that are known to improve behavioral outcomes in experimental TBI models fail to improve outcomes in TBI patients?”. This is a complex and highly debated topic, and a comprehensive review of the many possible factors that may have contributed to the translational failures in TBI is beyond the scope of this article. Rather, the reader is directed to excellent review articles that have elegantly encompassed many of the key issues, both from the

clinical and preclinical perspective.^{344,345} However, on the topics of behavioral outcomes and pre-clinical modeling which are central to this article, there are several important points made in these reviews that should be reiterated here. First, clinical TBI is a highly heterogeneous condition in terms of injury mechanisms, pathology, pre-morbid conditions, genetics, age, etc. On the other hand, a particular pre-clinical TBI model features a specific form of a reproducible brain insult.

Although this specific form of TBI may be appropriate to model a specific subtype of clinical TBI, it does not model all forms, and thus results should not be broadly generalized to all cases of clinical TBI. There are strategies that pre-clinical studies can adapt to help counter this, including multi-center pre-clinical trials, the use of complementary models, and the development of new models that incorporate the modifying factors and pre-morbid conditions that occur in TBI patients. It is encouraging that in more recent years these strategies are becoming more common,^{4,241,346,347} indicating that pre-clinical scientists are learning from previous translational failures. It is also strongly suggested that the experimenters conducting behavioral studies be blinded to the experimental groups to avoid any bias.

Another important point is that there is a massive discrepancy between the outcome measures utilized in pre-clinical versus clinical trials in terms of sensitivity. As detailed above, pre-clinical studies will often incorporate a range of behavioral tests that are sensitive and specific to different subdomains of behavior. Meanwhile, clinical trials continue to rely on the same short, subjective, and standardized measures of QoL, such as the Glasgow Outcome Scale questionnaire, as their primary outcomes despite having access to more-precise measures that would better align with the testing done in pre-clinical models.

It is also important to recognize that there are human-specific complexities in some behaviors that will ultimately require human studies to examine. For example, higher-order self-reflection and abstraction in human TBI patients are factors that may contribute to other neuropsychological deficits, but are unlikely to do so in rodent models.² The psychosocial consequences (e.g., disfigurement, unemployment, dependence on others, changed family roles, social isolation, changes in personality, bereavement of others involved in the incident, etc.) of TBI in humans is another aspect that is difficult to model/assess in other animals.²

In conclusion, there are behavioral tests available for use in pre-clinical TBI research that are clinically relevant and can complement TBI patient studies and drug trials. However, the application of these methods, study designs, and modeling can be refined, in order to optimize the translatability of these outcomes. Further, it is also critical that clinical studies continue to evolve and improve in their designs and outcome measures so that they are better aligned with the pre-clinical studies that have guided the development of a particular intervention. In doing so, pre-clinical and clinical TBI research will unite to address the other limitations and reduce the likelihood of further translational failures.

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