Behavioral Study of Rodents After Traumatic Brain Injury

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Abstract: Traumatic brain injury (TBI) is the primary cause of injury-related morbidity and mortality globally, with an estimated annual cost of USD 400 billion. Consistently, traumatic brain injury (TBI) has been linked to communicative disorders comparable to anxiety and depression. A traumatic brain injury is the result of an external force that can cause damage to the brain's vasculature and neuronal cells. Vascular disruption is a primary effect that can result in a variety of secondary injury mishaps. In this review, we will discuss the role of behavioral tasks in assessing TBI-related issues. Depending on the type of injury and associated cognitive deficits in both the acute and chronic stages of injury progression, animal models and behavioral assessments provide varying strengths and weaknesses. Consequently, the purpose of this review is to provide guidelines for evaluating rectifiers by investigating the role of animal models and behavioral tasks for assessing TBI.

Key words: Neurotrauma; neurobehavioral; Traumatic brain injury; Animal models are terms of importance.

1. Introduction

Currently, traumatic brain injury (TBI) is the primary cause of injury-related morbidity and mortality worldwide, with an estimated annual global cost of USD 400 billion [1]. Behavioral outcomes associated with TBI commence with the initial brain injury caused by an external force [2]. These external forces can originate from direct contact between the brain and an object or from non-impact situations, such as rotational acceleration and blast-produced energy waves [3, 4]. TBI survivors have an increased risk of developing severe, long-lasting psychiatric disorders. In the first year after injury, 49% of those with moderate to severe TBI and 34% of those with mild TBI were diagnosed with a psychiatric disorder, compared to 18% of those without TBI [5]. TBI patients are prone to severe depression [6, 7], common anxiety disorders [8, 9], post-traumatic stress disorders [9, 10], societal withdrawal [11], indifference [12, 13], and aggression

[14, 15]. After a brain injury, these conditions can persist for decades [16, 17] and anticipated long rehabilitation and resumption of employment [18, 19].

Behavioural alterations following TBI are reported at rates ranging from 25% to 88% in individuals with moderate or severe TBI, with a higher prevalence associated with more severe TBI [20, 21]. These abrupt changes in emotional and social behavior may include indifference, egocentric behavior, emotional vulnerability, poor societal judgment and communication, aggression, apathy, impulsive, disinherited or irritable behavior [22, 23]. Apathy is a common neurobehavioral consequence of TBI, with dominant estimates ranging from 20% to 71% [24], which can disorient cognitive function, psychosocial outcome, and rehabilitation efforts. Apathy manifest asa symptom as well as sign, and may be regarded as separate diagnosis in addition to a secondary condition resulting from another underlying disorder [25]. According to this research, deferential behavior can inhibit aggression and aid in resolving conflicts before they reach up into violent stage. In addition to avoiding inferiority and submission, subordination and submission are associated with anxiety and melancholy. Self-reporting, observational, and behavioral techniques, as well as natural and experimental approaches [26, 27] have been used to validate models of dominant and submissive behavior in both human and animal research. Using multivariate statistical methods to examine the relationship among anxieties after TBI, depression after TBI, and changes in social behavior post TBI is the best way to determine the relationship between these variables. It is extremely difficult to prove a causal relationship in the human population due to ethical considerations. Consequently, preclinical investigations involving laboratory animals offer a viable solution. In line with the high prevalence of depression and anxiety in TBI patients, rodent models of TBI have also demonstrated an increase in depressive- and anxiety-like behavior [28]. Rats and rodents exhibit a wide range of objectively measurable social behaviors. The implications of research on this topic for the treatment of anxiety, depression, social alterations, and functional limitations following TBI would be significant.

2. Classification of the Severity of TBI Injuries

The mechanism by which the initial applied force is delivered to the cranium is predominantly related to the severity of a patient's traumatic brain injury.

2.1. Glasgow Coma Scale

Initial categorization of behavioural deficits following TBI in a clinical setting is based on the Glasgow Coma Scale (GCS), which was created in 1974 [29, 30]. Although the classification criteria for this system were devised nearly 50 years ago, it is still commonly used by medical professionals to assess the severity of head injury promptly following a head injury.

2.2. Classification of TBI by Mayo

Mayo Classification of TBI In order to expand upon the GCS method and provide a more comprehensive classification system for the evaluation of TBI injuries, the Mayo Clinic created a model in 2007 that incorporated a number of variables, such as death, loss of consciousness (LOC), post-traumatic anterograde amnesia (PTA), and computed tomography (CT) imaging [31].

3. Various types of TBI

The term traumatic brain injury (TBI) is often used to designate a generalized condition with varying degrees of damage, but the injuries associated with TBI are classified as focal, diffuse, and non-impact. In humans, focal injuries are caused by direct impact forces operating on the cranium, which leads to compression of the underlying tissue. Focal injuries include fractures of the cranium, contusions, lacerations, hemorrhages, subdural, epidural, and intraparenchymal hematomas [32].

4. TBI Animal Models

Animal models are valuable instruments for comparing human conditions to a variety of animal conditions. Understanding the mechanism underlying the progression of different diseases enables researchers to develop treatment protocols that can be optimized prior to human testing. These models have been developed for a variety of brain disorders, including TBI [33]. Animal models of TBI have contributed to the development of potential treatments for the reduction of oxidative stress, improvement of permeability, and other biochemical impairments following

TBI [34]. Multiple models have been devised, divided into three distinct categories based on clinical presentations of TBI: focal, diffuse, and non-impact injury [35].

5. Behavioral Analysis

Animal behavior is a common method for identifying post-TBI deficits. It has been demonstrated that severity, phase of secondary injury, number of injuries, area of impact, and type of injury influence post-traumatic brain injury (TBI) behavior [36,37–39]. Therefore, anyone wishing to utilize behavioral analyses must be aware of any potentially confounding issues that may arise during testing, such as motor deficits, visual impairment, animal duress, sex differences, and others. There are numerous types of behavioral analyses, which are categorized into four task groups: spatial learning and memory, nonspatial learning and memory, emotional intelligence, and motor coordination.

1. Spatial Memory and Learning Duties

Memory and spatial learning are governed by the ability to navigate using both allocentric and egocentric methods. Egocentric navigation relies more heavily on internal cues such as remembered sequence, pace, the direction of movement, and using closer indicators known as "signposts" than allocentric navigation does. The distinction between "signposts" and "landmarks" is crucial to the discussion of egocentric versus allocentric navigation. While signposts provide information for egocentric and allocentric navigation, respectively, they do not provide information regarding relationships. Signposts merely indicate where to change course and do not aid in determining one's location relative to other signposts. In contrast, landmarks do not inherently indicate where to change direction, but they can provide crucial information about one's position in relation to other landmarks [40]. Consider signposts to be a specific intersection where you know to turn right to reach your destination. Inversely, one could use the street sign as a landmark and their knowledge of the direction they are approaching from to know to turn right.

2. Nonspatial Memory and Learning

Unlike allocentric navigation, which was described previously, egocentric navigation is a method of determining how to travel in a manner analogous to how one would traverse a traditional

labyrinth, using memory of motions made in conjunction with interior focal points to mentally map the area. This type of navigation can be observed in patterns such as serial and non-spatial navigation. Although this type of navigation can occur in many spatial learning tasks, such as RAM, specific variations of spatial learning tasks can be modified to examine non-spatial learning and memory. While the overall administration of these tasks differs for preclinical models, clinical delayed non-match to sample and VR tasks can be modified to test nonspatial learning and memory using comparable parameters.

3. Emotional alterations

Emotional alterations following traumatic brain injury in humans are well documented. In spite of this, many of the emotional tests used to determine emotional deficits, such as anxiety-like behaviors, produce explicitly contradictory results depending on the paradigm, even when using the same procedures. These differences have led to the identification of both high and low levels of anxiety in the same open field test, as well as an equal level of anxiety compared to uninjured counterparts [41]. In TBI research, many of these experiments elicit similar conflicts. In addition, human patients have reported that their anxiety, depression, and other emotional indicators vary from day to day [42]. This may impact efforts to discover correlations between preclinical and clinical TBI studies. However, many of these models have been utilized for drug discovery in other fields, such as antidepressants, antianxiety medications, and other psychopharmacological medicines. This may mitigate some of the criticisms leveled against these tasks in TBI research, though the inherent variability of affective deficits in TBI may also account for this difference.

3.1. Forced Swimming Exam

The forced swim test was originally designed for antidepressant drug testing and is acknowledged as a preclinical model of depression [43] due to its use in antidepressant drug testing.

3.2. Test of Dark/Light Avoidance

The light/dark avoidance test is used to quantify behaviors associated with anxiety. As mentioned when discussing the BM, rodents have an inherent aversion to well-lit areas. The

light/dark test uses this to determine anxiety-like behaviors by defining the light area as an anxiolytic zone and measuring the time spent in the light and dark zones as well as the path length in each zone over the course of 15 minutes [44].

3.3. Open Field Test

The open field test is beneficial for measuring both locomotion and anxiety-like behaviors in rodents and is one of the most frequently employed methods of behavioral testing, particularly in rodents. The test is limited to 10 minutes and consists of a confined area with a light focused directly above it. For anxiety testing, measurements of the amount of time spent in the exterior area of the maze, known as thigmotaxis, are regarded as an indicator of anxiety-like behavior. The longer an animal spends in the center of the arena, the less anxious its behavior becomes. In addition, movement can be measured, with greater distances traveled representing an anxiety-like response [45].

3.4. Resident Intruder Test

The resident intruder test is a frequently administered test for aggression. The majority of the data collected from this test are behaviorally specific, with an emphasis on observing differences, frequency, and duration of offensive aggression, defensive aggression, and violence. During the test, the female is replaced with a new male and observed to determine a battery of scoring measuring two contrasting behaviors, aggression and sociability/anxiety, as measured by the Total Offense Score and Social Exploration Score, respectively [46].

Conclusions

In conclusion, we demonstrate that the effects on anxiety outcomes following traumatic brain injury may be the consequence of the variability in injury models used, behavioral assays of anxiety selected, and assessment time points. Categorizing the animal models according to previously established classification systems would provide researchers with an additional framework for comparing the various models. In addition, classifying animal models generates an additional comparison to TBI in humans, which ultimately benefits diagnostic and treatment methods. Efforts should be made in the future to establish a standardized behavioral assessment

for comparing animal models, with the aim of achieving effective translation between cognitive deficits observed in animals and humans. Incorporating behavioral analysis would further strengthen the comparison between animal models and human TBI, resulting in greater clinical trial success.

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