Behavioural Brain Research 275 (2014) 201–211

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Pre and post-injury environmental enrichment effects functional recovery following medial frontal cortical contusion injury in rats

Justin Jacqmain, Evan T. Nudi, Sarah Fluharty, Jeffrey S. Smith*

The Brain Research Laboratory, Saginaw Valley State University, 7400 Bay Road, University Center, Michigan, 48710, USA

HIGHLIGHTS

- Enrichment improves performance compared to animals reared in standard housing.
- Housing conditions of rats prior to, and following, brain injury affects performance.
- Increased number of neurons and cortical area were observed in enriched injured rats.
- Data suggest that improving housing environments may improve translation of research.

ARTICLE INFO

Article history:
Received 24 July 2014
Received in revised form 23 August 2014
Accepted 27 August 2014
Available online 6 September 2014

Keywords:
TBI
Behavior
Neuroplasticity
Rat

ABSTRACT

The rodent has been the preferred research model for evaluating the mechanisms related to, and potential treatments for, traumatic brain injury (TBI). Many therapies previously determined to be effective in pre-clinical investigations have failed to show the same effectiveness in clinical trials. The environment a rodent is housed in plays an important role in brain and behavioral development. Housing rodents in non-enriched environments significantly alters the development of the rodent brain and its behavioral profile, negatively impacting the ecological validity of the rodent model. This investigation employed 113 male Long-Evans rats assigned to either an enriched environment (EE) or standard environment (SE) from post-natal day 25. At four months of age, rats received either a controlled cortical impact (CCI) to the medial frontal cortex (mFC) or sham injury. Rats assigned to EE or SE pre-injury were re-assigned to remain in, or switch to, EE or SE post-injury. The open-field test (OFT), vermicelli handling test (VHT) Morris water maze (MWM), and rotor-rod (RR), were used to evaluate the animals response to TBI. The data from the current investigation indicates that the performance of TBI rats assigned to pre-injury EE was improved on the MWM compared to the TBI rats assigned to pre-injury SE. However, those that were reared in the EE performed better on the MWM if placed into a SE post-injury as compared to those placed into the EE after insult. The TBI and sham groups that were raised, and remained, in the SE performed worse than any of the EE groups on the RR. TBI rats that were placed in the EE had larger cortices and more cells in the hippocampus than the TBI rats housed in the SE. These data strongly suggest that the pre-injury housing environment should be considered as investigators refine pre-clinical models of TBI.

1. Introduction

According to the Center for Disease Control and Prevention, 1.7 million people sustain a traumatic brain injury (TBI) in the United States annually [1]. A medial frontal cortex (mFC) contusion is the most commonly incurred TBI by adults involved in motor vehicle accidents [2]. Furthermore, motor vehicle accidents resulted in the highest percentages of TBI related deaths [1]. TBI is caused by a penetrating head wound or a blow to the head that disrupts brain function. The leading causes of TBI are car accidents, falls, falling objects, and assaults [1]. In addition, the consequences of conflict related blast injuries are becoming an increasing concern in active duty military personnel [3]. TBI often results in long-lasting deficits in cognitive, sensory, and motor function [4–7]. Additionally, TBI plays a major role in the emergence of anxiety-related neurological disorders [5]. To better understand the effects of TBI,

* Corresponding author. The Malcolm and Lois Field Endowed Chair in Health Sciences, Saginaw Valley State University, Department of Health Sciences, Crystal M. Lange College of Health & Human Services, 7400 Bay Road, University Center, Michigan 48710.
E-mail addresses: jmjacqma@svsu.edu (J. Jacqmain), etnudi@svsu.edu (E.T. Nudi), snfluhar@svsu.edu (S. Fluharty), jsmith12@svsu.edu (J.S. Smith).

http://dx.doi.org/10.1016/j.bbr.2014.08.056
0166-4328/

researchers often turn to animal models to replicate human injury in pre-clinical experiments [8].

Animal models play an important role in the process of evaluating and understanding the complex physiologic, behavioral, and histopathologic changes associated with TBI. The use of animal models allows for a better understanding of the neurobiological mechanisms underlying injury and therapeutic evaluation, which includes the testing of novel and improved treatments for brain injury [9,10]. Although rodents make useful models for TBI, many treatments that have been found to be effective in the rat are not consistent and fail to show the same effectiveness in human clinical trials [11]. One rationale for this could be that the standard environment (SE) that rats are raised in at laboratories and research breeding facilities is unlike the rats' natural environment; it does not offer stimulation, exercise, or socialization to the extent an enriched environment (EE) does [12,13]. Furthermore, the SE is different from the complex environment that humans live in, making the research model vastly different from the human condition.

An EE is a complex and variable housing condition. Tunnels, nesting materials, and toys are changed frequently [14]. EE animals are kept as a group in large cages where they have the opportunity for complex social interaction as well as enough space to exercise. Sozda and colleagues (2010) compared the typical EE (large cage + social interaction + toys), EE without social contact (large cage + toys/novel stimuli–social interaction), EE without stimuli (large cage + socialization–stimuli), SE typical (- toys/novel stimuli–social interaction), and SE with stimuli (- social interaction + toys/novel stimuli) [15]. The typical EE was found to significantly enhance cognitive and motor function; nonetheless, the individual components of the EE were more beneficial than no enrichment at all [15]. This suggests that the EE's components seem to have a synergistic effect and work better in combination [14]. Adequate room in the EE allows for naturalistic exploratory movements that facilitate gross and fine motor skills, stimulating areas of the motor cortex and the cerebellum [16]. The EE has been shown to promote neuronal activation, signaling, and plasticity throughout various brain regions; it activates and enhances somatosensory and visual cortices. The complex environment also allows for increased cognitive stimulation which helps rats with encoding information related to object recognition and spatial maps [16]. In addition, the EE has shown to increase dendritic arborization [17], cortical depth, weight, gliogenesis [18–20], learning [21], medial hippocampus size [22], cell proliferation and neurogenesis [23], changes in brain chemistry [13], improvements in motor function [24], increased visual system development [25], and neuroprotective effects [26]. Wright and Conrad (2008) found that raising rats in the EE resulted in fewer stress induced spatial learning and memory deficits when compared to the SE rats [26].

Rearing animals in the SE can be just as detrimental as the EE can be beneficial. It has been found that rodents can develop stereotypies in environments that are stressful and lack complexity. Stereotypies have been found in zoo, farm and laboratory animals, as well as in humans [27]. Altered function in the dorsal striatum resulting in reduced behavioral inhibition is thought to be a major influence of stereotypy development [27]. For example, one experiment discovered that gerbils would develop stereotypic digging behaviors when denied appropriate shelters [28]. For these reasons, it has been suggested that the SE might not be the ideal environment to study complex brain functions, and that present standards for laboratory environments are based on practicality and economy, rather than biological considerations [29]. It could be that species specific environments are necessary and result in optimal development of that species. Landers and colleagues (2011) found that raising mice in a protective enclosure within a forest composed of natural items altered the somatosensory cortex of the mice significantly more than the laboratory mice housed in traditional caging [30], suggesting that the closer the housing of the animal is to the animal's natural habitat leads to greater potential for neuroplasticity [30].

The controlled cortical impact (CCI) model is an often employed model used to induce a TBI in rodents. The impact damages the cortex [31,32], and leads to gross and fine motor deficits [33] as well as cognitive deficits [34]. While some diffuse damage occurs, the CCI is suggested to induce focal injuries with properties similar to what is seen in clinical cases [31]. The CCI model is advantageous because of its reproducibility and precise control over dwell time, velocity, and depth of the impact [8,35]. Moreover, the CCI model has an advantage when compared to models with gravity driven devices because of the lack of risk of rebound injury [8]. The trauma produced by the CCI model has been associated with cortical contusion [36], subdural hematoma, diffuse axonal injury, concussion, blood brain barrier dysfunction, and comas [35] and it has been suggested that the CCI model replicates the physical forces of motor vehicle accidents and falls [32].

Additionally, damage to the medial frontal cortex (mFC) injury is common in individuals who are involved in motor vehicle accidents due to rapid accelerating-decelerating forces [37]. The mFC is associated with higher executive brain function. It has been found to be crucial for reversal learning and strategy selection [38]. This function is important and allows for behavioral flexibility, especially during changing environmental conditions because it allows the mammal to learn a new strategy while inhibiting the execution of a previous strategy [39]. Damage to the mFC has also been shown to induce cognitive deficits on a variation of the stop-signal reaction time task (SSRT) [40]. Further, an mFC injury also creates deficits in response-inhibition, executive function, as well as sensorimotor deficits [41,42]. Enriching the environment has frequently been viewed as a beneficial post-operative treatment for TBI due to its ability to improve functional, behavioral, and anatomical recovery in a variety of post-operative models [43]. Research has also shown that rats that have been raised in impoverished conditions pre-operatively benefit from post-operative EE [24]. Although it has been suggested that they have greater initial deficits with regard to forelimb use, rats that are exposed to the EE post-injury recover quicker than rats that are not exposed [44].

Although rodents have been considered useful models for the study of TBI, many treatments that have been found to be effective in the rat are not consistent across strains and fail to show the same effectiveness in human clinical trials. There have been many therapies that have been found to ameliorate the deficits observed in animals, however, many do not translate into a clinically viable treatment for humans suffering from the consequences of TBI [35]. One rationale for this could be that the SE that rats are raised within, in laboratories and research breeding facilities, are unlike the rats' natural environment; it does not offer stimulation, exercise, or socialization to the extent that an EE or their natural habitat would [13,24]. Furthermore, the SE that rodents are currently housed in is very different from an analogous, complex environment that humans would be exposed to, potentially making the biology of the rodent model vastly different from the biology of a human. All of which would potentially decrease the usefulness of the data garnered from rodent based investigations.

Therefore, this study was designed to investigate the impact of environmental conditions on neuroplasticity and recovery from an mFC contusion and to gain further insight into what might be an optimal pre-and post-operative housing condition for pre-clinical evaluation. Based on previous evidence, it was hypothesized that the rats remaining in the EE throughout the study would perform better on the MWW and RR than the rats that were not reared in an EE throughout the course of the entire study. It was also hypothesized that the rats that remained in the EE would have