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Research report

A behavioral and histological comparison of fluid percussion injury and controlled cortical impact injury to the rat sensorimotor cortex

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HIGHLIGHTS

- We characterized two animal models of traumatic brain injury (TBI): Cortical Contusion Injury (CCI) and Fluid Percussion Injury (FPI).
- We evaluated behavioral and histological deficits in these models over the sensorimotor cortex (SMC).
- Gross behavioral sensory and motor deficits were found in the absence of cognitive deficits.
- Histological data verifying a more focal CCI injury and more diffuse FPI injury were found.
- Both of these injury models over the SMC produce severe and enduring behavioral deficits, ideal for evaluating treatment options.

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ABSTRACT

Our primary goal was to evaluate the behavioral and histological outcome of fluid percussion injury (FPI) and cortical contusion injury (CCI) to the sensorimotor cortex (SMC). The SMC has been used to evaluate neuroplasticity following CCI, but has not been extensively examined with FPI. In both the CCI and FPI models, a mechanical force of 4 mm in diameter was applied over the SMC, allowing for a direct comparison to measure the relative rates of histology and recovery of function in these models. Gross behavioral deficits were found on the sensory task (tactile adhesive removal task) and multiple motor assessments (forelimb asymmetry task, forelimb placing task, and rotorod). These sensorimotor deficits occurred in the absence of cognitive deficits in the water maze. The CCI model creates focal damage with a localized injury wheras the FPI model creates a more diffuse injury causing widespread damage. Both behavioral and histological deficits ensued following both models of injury to the SMC. The neuroplastic changes and ease at which damage to this area can be measured behaviorally make this an excellent location to assess traumatic brain injury (TBI) treatments. No injury model can completely mimic the full spectrum of human TBI and any potential treatments should be validated across both focal and diffuse injury models. Both of these injury models to the SMC produce severe and enduring behavioral deficits, which are ideal for evaluating treatment options.

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1. Introduction

TBI is among the leading causes of acute and chronic disability in the United States according to the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention [1]. Out of the 1.7 million Americans that endure a TBI each year, over 50,000 die [1]. Approximately 1.2 million Americans endure some sort of injury to their central nervous system, making recovery of function a major public health issue.

1.1. Primary vs. secondary injury

TBI occurs due to a blunt, rotational, accelerational, diffuse, focal, or concussive force to the head. Damage to the central nervous system is separated into two different classifications of injury, a primary and a secondary. Primary injuries result from the initial impact of mechanical forces. This initial disruption in tissue results in axonal shearing and cellular death of all types. This primary injury can be produced by collision forces to the skull, leading to a more focal compression of cortical tissue or by acceleration forces, inducing a more widespread injury causing brain swelling and diffuse axonal injury. Dependent upon the type of injury, a range of central nervous system (CNS) responses occur resulting in secondary damage. Secondary injury is comprised of multiple neurobiological, chemical, cytological, and physical changes that will occur for the remainder of the organism's life [2].

Human TBI is a disorder that can cause a variety of disabilities, dependent upon several factors, including the heterogeneous nature of the type and location of the injury. Different physical forces as well as CNS locations have different pathophysiological consequences. Therefore animal models should mimic this variability so that these findings translate to clinical TBI. To approach this problem, the TBI field has developed many different ways to model human TBI in animal models.

There are many different experimental animal models of brain injury; blast injury, acceleration/deceleration models, weight drop models, cryogenic brain lesions, fluid percussion injury (FPI), and controlled cortical impact (CCI), the most common models being FPI and CCI. To date there are few direct comparisons of FPI and CCI in the rodent. Direct comparisons have examined intracranial pressure, blood brain barrier breakdown, and markers of plasticity [3–5], but have failed to examine behavioral deficits and other common pathophysiological markers.

FPI is a diffuse model, first reported by Lindgren (1965), which induces axonal, somal, and microvascular swelling, leading to tissue distortion and axonal shearing both proximal and distal to the injury location [6–9]. Axonal injury following this diffuse damage includes a loss of plasticity and cytoskeletal damage to axons, as well as an impairment of axonal transport. This leads to axonal swelling, rapid deformations and a loss of connectivity [10].

The FPI device delivers a fluid pulse to the intact dural surface, creating a diffuse load to the brain [11,12]. This model is beneficial in that different graded levels of injury can be administered, it can be used in several species of animals, and it leads to cavitation as well as axonal injury. However, there are disadvantages to this model as well. The pressure characteristics are not directly related to the mechanical impact to the brain. The direction, displacement, and velocity of the pulse are dependent upon the geometry of the brain [11]. Additionally, it has been shown that any small shift in craniotomy location alters the neurological outcome, as well as the lesion size and location of the injury [13].

CCI's, first reported by Lighthall (1988) are focal, with localized tissue damage [14,15]. This model displays blood brain barrier disruption and both vasogenic and cytotoxic edema similar to that seen in clinical TBI [14,16]. The impactor device used for CCI is a pneumatic/electromagnetic cylinder, which houses a piston and impactor tip. The impactor tip is driven downwards at a specified velocity and depth, contacting the intact dural surface and creating a focal injury. The main benefit of this model is that the deformation parameters (velocity, depth, and time of dural contact) can be precisely controlled [17], making it highly reproducible. CCI mimics the whole spectrum of focal injury, it is highly reproducible, and it translates well to human TBI.

TBI in humans can create damage to any structure causing many behavioral deficits. When creating an animal model of TBI, creating damage to a well characterized structure allows us to measure deficits in behaviors related to this structure. Recovery of function in animal models is measured through a variety of behavioral tasks, so knowledge about deficits associated with the structure being damaged is important in creating a good post-injury behavioral assessment. A large difference between the sham and injured control groups creates an injury window that is optimal to assess neuroprotective agents following injury. This makes using a model with a large injury window crucial for success. The majority of research in animal models of TBI uses either a bilateral-frontal lobe model of injury or a unilateral–parietal lobe model of injury [18–21].

Cognitive, attentional, and spatial learning deficits associated with damage to this area are well cited in the literature [22] using the Morris water maze (MWM), which is a spatial learning task. However, the motor deficits [23] may be due to damage to motor planning areas [24] and the sensory deficits are suggested to be due to damage in areas associated with attention [25], although this direct claim remains to be demonstrated empirically.

The unilateral–parietal lobe injury is typically centered between Lambda and Bregma and approximately 2–3 mm lateral to the midline (in rat models). This injury model creates damage to the parietal lobe as indicated by the name and creates primarily cognitive deficits. The cognitive deficits usually seen at this injury coordinate are typically measured in the MWM [26,27]. Frequently sensorimotor deficits are seen, usually in the form of a hindlimb motor deficit, but are only detectable in our behavioral assays for the first two weeks following injury.

We have utilized both the bilateral-frontal and unilateral–parietal lobe injury models, demonstrating substantial spatial learning deficits in the MWM.[21,23,27] However, the deficits seen in sensory and motor related behaviors are often present initially, but partial spontaneous recovery is seen within the first two weeks following injury[21,28]. This spontaneous recovery makes it difficult to detect significant differences in a comparison group that received treatment. Creating an injury model with abundant and long lasting behavioral deficits is the best way to assess whether a neuroprotective drug is having beneficial effects.

Our laboratory has used the sensorimotor cortex (SMC), one of the most well characterized structures in the rodent CNS, to assess neuroprotective agents after TBI [19,28,29]. The forelimb SMC is well known for the plastic responses that follow both lesions and ischemic insult [for review, see: [30,31,32]. To summarize briefly, behavioral deficits ensue in the injured forelimb (contralateral to injury) following lesions of the forelimb SMC. However, post-injury behavioral experience (or direct cortical stimulation) alters the response to the injury. Rehabilitative training, including motor training, stimulates neural plasticity and helps compensate for loss of function. However, these post-injury experiences are time dependent [30]. More recently, it has been found that this behaviorally driven plasticity may be compromised following rodent TBI [20]. This along with the wealth of knowledge about the SMC map and the behavioral deficits associated with this area make this an exceptional target for an animal model of TBI.

No single animal model will ever be able to replicate the complete spectrum of changes that occurs in the CNS with this disorder