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Research article

Investigation of left and right lateral fluid percussion injury in C57BL6/J mice: In vivo functional consequences

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HIGHLIGHTS

- Left or right lateral TBI impaired MWM memory performance.
- Right lateral TBI produced modest MWM acquisition deficits compared to left.
- Both Left and right TBI produced similar neurological motor task deficits.
- Both left and right TBI produced impaired righting times and lesion volumes.
- Both left and right lateral TBI produced robust ipsilateral glial cell reactivity.

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ABSTRACT

Although rodent models of traumatic brain injury (TBI) reliably produce cognitive and motor disturbances, behavioral characterization resulting from left and right hemisphere injuries remains unexplored. Here we examined the functional consequences of targeting the left versus right parietal cortex in lateral fluid percussion injury, on Morris water maze (MWM) spatial memory tasks (fixed platform and reversal) and neurological motor deficits (neurological severity score and rotarod). In the MWM fixed platform task, right lateral injury produced a small delay in acquisition rate compared to left. However, injury to either hemisphere resulted in probe trial deficits. In the MWM reversal task, left-right performance deficits were not evident, though left lateral injury produced mild acquisition and probe trial deficits compared to sham controls. Additionally, left and right injury produced similar neurological motor task deficits, impaired righting times, and lesion volumes. Injury to either hemisphere also produced robust ipsilateral, and modest contralateral, morphological changes in reactive microglia and astrocytes. In conclusion, left and right lateral TBI impaired MWM performance, with mild fixed platform acquisition rate differences, despite similar motor deficits, histological damage, and glial cell reactivity. Thus, while both left and right lateral TBI produce cognitive deficits, laterality in mouse MWM learning and memory merits consideration in the investigation of TBI-induced cognitive consequences.

1. Introduction

The fluid percussion injury model of traumatic brain injury (TBI) in laboratory animals elicits functional and pathophysiological hallmarks of human TBI, including cognitive dysfunction, intracranial hemorrhage, edema, and progressive gray matter damage [1]. Originally developed as a midline injury in cats [2] and rabbits [3], a lateral fluid percussion injury was used in rats [4], and further adapted for mice [5], now widely used given the utility of transgenic lines. Lateral fluid percussion injury produces a combined focal cortical contusion and diffuse subcortical neuronal injury in rats [6], the extent and location of which is subject to small changes in craniotomy position [7]. It is noteworthy that small alterations in craniotomy position in rats lead to differences in cognitive

Abbreviations: FPI, fluid percussion injury; IHC, immunohistochemistry; LTP, long term potentiation; MWM, Morris water maze; NSS, neurological severity score; TBI, traumatic brain injury.

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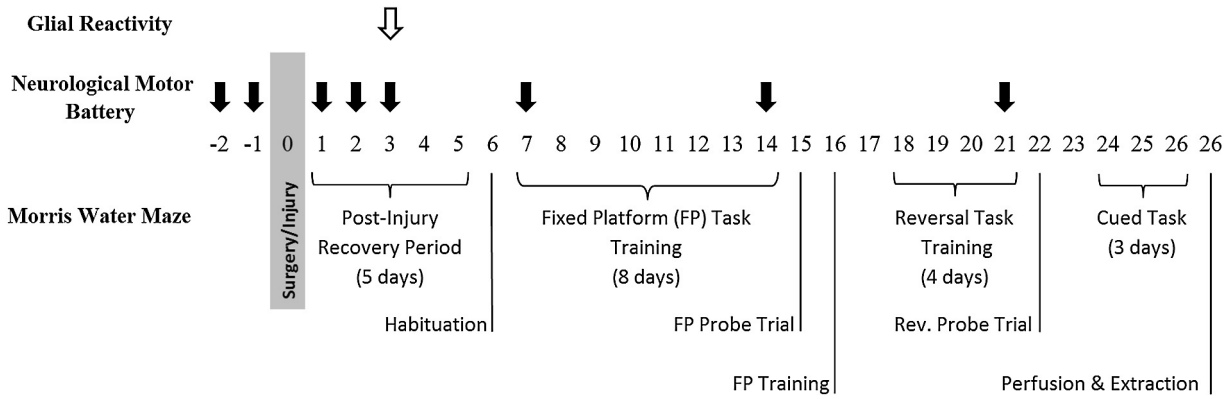

Fig. 1. Experimental timeline.
Experimental timeline (relative to injury) of neurological motor battery (indicated by down arrows) and spatial learning and memory tasks of the MWM, for left lateral and right lateral fluid percussion injuries.

performance [8]. In mice, left [9,10] and right [5,11] craniotomy placement generally differs across research groups; however, there are no systematic studies investigating craniotomy position on measures of learning and memory or motor effects in mice.

Several lines of evidence suggest existence of left-right hemisphere molecular [12,13], morphological [12,14], and functional differences [15,16] at hippocampal synapses in mice. Left-right morphological differences exist in the mouse hippocampus where left originating CA3 inputs innervate small spines, whereas inputs originating from the right CA3 innervate larger, mushroom-shaped spines [12,14]. The molecular composition of these smaller spines also differ, exhibiting a higher density of GluN2B subunits in post-synaptic spines receiving left CA3 input [12,17]. Morphological differences; size of left infrapyramidal mossy fiber projections, also positively correlate with precision in swimming navigation [18]. Furthermore, long-term potentiation (LTP) reveals hemispheric specialization in which LTP induction of CA3 synaptic inputs to CA1 when input originates from the left, but not the right CA3, using spike timing-dependent LTP [15], or conventional high-frequency stimulation-induced LTP [16]. Similarly, in behaving mice, silencing of left, but not right, CA3 pyramidal neurons resulted in Y-maze task deficits [16], and *inversus viscerum* mice (bred to express only a right phenotype at CA3-CA1 synapses) exhibited dry maze task deficits [19]. This evidence of structural and behavioral hemispheric differences raises the question of whether left versus right hemisphere TBI will reveal differing patterns of cognitive deficits.

The Morris water maze (MWM) is frequently used to assess TBI-induced spatial learning and memory impairments. Although hippocampal lesions [20] or TBI [10] severely impairs MWM performance, mice with bilateral hippocampal lesions demonstrate improved performance with multiple training trials [20]. Accordingly, MWM performance may employ brain areas in addition to the hippocampus, such as the striatum [21], basal forebrain [22], insular cortex [23], etc.; making this task a useful model to study the functional consequences of a lateralized brain injury in mice. MWM task variations are also used to infer the underlying processes affecting performance. Here, the Fixed Platform task assesses reference memory acquisition, and the reversal task; cognitive flexibility. Moreover, the Cued task, where the location of the hidden platform is made visible, infers sensorimotor and motivational influences. Based on the established left-right molecular and morphological asymmetry in the mouse hippocampus, we examine whether unilateral TBI of the left versus right hemisphere will elicit differential patterns of spatial memory and motor deficits in mice.

2. Materials and methods

2.1. Mice

All experiments used adult male C57BL/6J mice (Jackson Laboratories, Bar Harbor, Maine), left injury ($n = 10$), left sham ($n = 10$), right injury ($n = 8$), right sham ($n = 7$), (further described in the supplement), and complied with EC Directive 86/609/EEC, conducted in accordance with the National Institute of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978), and were approved by the Virginia Commonwealth University Institutional Animal Care and Use Committee.

2.2. Craniotomy and induction of lateral fluid percussion injury (FPI)

Under isoflurane anesthesia (2.5%, 250 mL/min) a sagittal scalp incision was made and a 2.7 mm trephine craniectomy performed over the left or right parietotemporal cortex, further description of which is included in the supplement. After a 2 h recovery period, mice were anesthetized with isoflurane (4%, 400 mL/min) and immediately subjected to a moderate lateral fluid percussion injury (1.94 ± 0.1 atm left lateral, 1.92 ± 0.1 atm right lateral injury), described in the supplement.

2.3. Behavioral and cognitive assessment paradigms

2.3.1. Neurological motor impairment evaluation

Mice were evaluated in Rotarod and Neurological Severity Score, 2 days prior to injury, and 1, 2, 3, 7, 14 and 21 days post-injury (see Fig. 1). Single Rotarod (IITC Life Science Rota-Rod, Woodland Hills, CA, with 3 cm diameter rotating drums) trials per day used an accelerating protocol, a description of which appears in supplementary information. A 10-point Neurological Severity Score (NSS) assessed the functional neurological status of mice based on the presence of reflexes and the ability to perform motor and behavioral tasks (see Supplementary Table 1). Further description appears in supplementary information.

2.3.2. Learning and memory assessment

The MWM consisted of a circular, galvanized steel tank (1.8 m in diameter, 0.6 m height) filled with opaque water (maintained at $20\,^{\circ}C \pm 2\,^{\circ}C$) with a submerged platform (10 cm diameter) and distal and proximal visual cues, further described in the supplement.