BRAIN RESEARCH 1582 (2014) 91–98

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Brain Research

Research Report

Controlled-cortical impact reduces volitional forelimb strength in rats

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ARTICLE INFO

Article history:
Accepted 24 July 2014
Available online 1 August 2014

Keywords:
Traumatic brain injury
Controlled cortical impact
Recovery
Behavior
Rat

ABSTRACT

Traumatic brain injury (TBI) is one of the largest health problems in the United States and affects both cognitive and motor function. Although weakness is common in TBI patients, few studies have demonstrated a reduction in strength in models of brain injury. We have developed a behavioral method to measure volitional forelimb strength and quantify forelimb weakness following traumatic brain injury. In this paper, we report the ability of the isometric pull task to measure both acute and chronic impairments in forelimb motor function following a controlled cortical impact (CCI) in rodents. Following CCI, volitional forelimb strength is reduced by 36% and remains significantly reduced after 6 weeks of post-lesion training. We also show that CCI results in impairment of multiple additional measures of forelimb function for several weeks post-injury.

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1. Introduction

Traumatic brain injury is a serious public health problem in the United States. Annually two million people suffer a TBI, and at least 275,000 of these cases lead to prolonged stays in the hospital (Faul et al., 2010). TBI commonly results in cognitive deficiencies such as memory loss and changes in emotion or sensation. However, moderate to severe cases often result in motor dysfunction such as weakness, lack of balance, or a loss of coordination (Greiffenstein et al., 1996; Kuhtz-Buschbeck et al., 2003).

Animal models have been developed to study the effects of TBI. One common model of TBI is the controlled cortical impact (CCI) model (Edward Dixon et al., 1991). The CCI model reproduces many facets of the clinical presentation of TBI, including increased intracranial pressure (Cherian et al., 2000), brain edema (Başkaya et al., 1997), and compression of the brain. In addition, the CCI model allows for control of

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http://dx.doi.org/10.1016/j.brainres.2014.07.039
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mechanical parameters such as impact velocity and the amount of brain deformation. Behavioral impairments observed in animal models of CCI resemble cognitive and motor characteristics observed in TBI patients. Both mice and rats have impaired spatial memory using the Morris water maze task extending up to 30 days post-injury (Hamm et al., 1992; Fox et al., 1998; Yu et al., 2009). Similarly, long-term impairments in motor skill-learning have been observed in rats (Ding et al., 2001).

Studies have documented motor impairments following CCI using tests such as skilled reaching, beam traversal, grid walk, and rotorod (Hamm et al., 1994; Hamm 2001; Whishaw et al., 2004). While these tests have provided much valuable data, many of them do not report chronic impairments (Edward Dixon et al., 1991; Soblosky et al., 1996), and no studies that we are aware of have reported deficits in volitional strength following CCI. Volitional forelimb strength is the voluntary application of force using the musculature of the upper limb. As weakness is believed to be the major factor contributing to disability after brain damage (Canning et al., 2004), the ability to quantitatively measure volitional forelimb strength in an animal model of TBI could provide a framework to test potential therapies to improve recovery of forelimb strength in TBI patients.

We have developed the isometric pull task, a novel method to quantitatively measure forelimb impairment after an acute brain lesion (Hays et al., 2012). In this study, we used the isometric pull task to measure multiple parameters of forelimb function following a CCI.

2. Results

2.1. *Acquisition of the isometric pull task*

Animals were trained on the isometric pull task as previously described (Hays et al., 2012). Animals were trained in a standard operant cage that was equipped with an aluminum handle sitting 0.75 in. beyond the inner cage wall. Animals were required to reach through a slot and pull on the handle with 120 g of force to receive a food reward. The rats took an average of 3.4±0.2 days to acquire the task, as indicated by independent engagement of the pull handle. All animals became highly proficient at the task, reaching a pre-lesion performance criterion of five consecutive days averaging at least an 85% success rate in 26±0.4 days. The average hit rate during the pre-lesion stage was 91.8±0.7%. Average maximal pull force per trial was 165.4±4.9 g, well-exceeding the 120 g threshold.

2.2. *Performance after controlled cortical impact to primary motor cortex*

Once animals reached the 85% pre-lesion criterion, they were given a unilateral CCI lesion to the primary motor cortex. After one week of post-surgical recovery in the home cage, animals returned to post-lesion behavioral testing for six weeks.

CCI worsens performance of the task and alters the average force profile during trials (Fig. 1). To quantify changes in the force profile of lesioned animals, we integrated the force as a function of time for the pre-lesion stage and during the first week of post-lesion assessment. The average force profile contained two peaks, demonstrating that rats often initiated multiple pull attempts per trial. Following CCI, force peaks were dramatically reduced, consistent with a reduction in strength. A significant decrease was seen in the early post-lesion force profile resulting from weaker pull forces compared to pre-lesion. During the first second of the trial the post-lesion FTI was significantly reduced compared to pre-lesion (pre-lesion: 46.4±3.6 g s s. post-lesion: 29.1±2.5 g s, $p=0.001$). In addition, a significant increase in the force profile was seen later into the trial window for post-lesion animals compared to pre-lesion, indicating later application of force. Post-lesion FTIs calculated for the second and third seconds of the trial window were significantly greater than pre-lesion ($p=0.005$ and $p=0.001$ respectively). This indicates that during the first week of post-lesion assessment, lesioned animals were both pulling with weaker force at the beginning of the trial window and still attempting late into the trial window.

Volitional forelimb strength was substantially reduced following CCI (Fig. 2A). A repeated measures ANOVA on maximal force revealed a significant effect of the TBI ($F[144,1]=10.6$, $p=0.003$), time post-lesion ($F[144,6]=11.1$, $p<0.001$), and a significant interaction ($F[144,6]=9.39$, $p<0.001$). Maximal force exerted by lesioned animals during a trial was significantly reduced when compared to pre-lesion (week 1: 105.6±8.2 g; paired t-test, $p<0.001$ vs. pre-lesion). This significant reduction of maximal force in TBI animals was observed during the following weeks, despite extensive training, compared to both pre-lesion (pre-lesion vs. weeks 2–6: paired t-test, all $p<0.001$) and unlesioned controls (weeks 2–6: unpaired t-test, all $p<0.05$ except week 5 $p=0.067$), suggesting a chronic deficit in strength. Although animals failed to recover to pre-lesion levels, maximal pull force did significantly improve compared to week 1 of post-lesion for some weeks. By the third week maximal pull force was significantly increased compared to the first week of post-lesion training (week 3: 130.6±7.9 g; paired t-test, $p=0.001$ compared to week 1), and remained so for the duration of training (week 1 vs. weeks 4–6: all $p<0.05$). Further analysis revealed that maximal force in unlesioned controls was significantly lower than pre-lesion at only one time point (week 5: 149.38±5.4 g; paired t-test vs. pre-lesion, $p=0.02$).

Hit rate was markedly impaired following CCI (Fig. 2B). A repeated measures ANOVA revealed significant effects of both time ($F[144,6]=9.5$, $p<0.001$) and TBI ($F[144,1]=17.9$, $p<0.001$), and an interaction effect ($F[144,6]=7.32$, $p<0.001$). The percentage of successful trials in lesioned animals was significantly reduced compared to pre-lesion performance (week 1: 48.7±5.7%; paired t-test, $p<0.001$ vs. pre-lesion). Hit rate in lesioned animals demonstrates a trend toward improvement over the remainder of training, but significant improvement is only seen during weeks 3–5 (post-lesion week 1 vs. weeks 3–5; paired t-test, all $p<0.05$). Hit rate of lesioned animals was significantly lower than unlesioned controls during all post-lesion epochs (post-lesion weeks 1–6; unpaired t-test, all $p<0.05$). At the sixth week of training, hit rate was still significantly impaired compared to pre-lesion, indicating a chronic deficit in forelimb function (week 6: 64.1±7.5%; paired

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