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Research report

Temporally-patterned deep brain stimulation in a mouse model of multiple traumatic brain injury

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HIGHLIGHTS

- Mice with traumatic brain injury have decreased motor activity.
- Deep brain stimulation was used to increase motor activity in brain injured mice.
- Stimulation was delivered to the central thalamus.
- The temporal parameters of the stimulation influenced the activity increase.

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ABSTRACT

We report that mice with closed-head multiple traumatic brain injury (TBI) show a decrease in the motoric aspects of generalized arousal, as measured by automated, quantitative behavioral assays. Further, we found that temporally-patterned deep brain stimulation (DBS) can increase generalized arousal and spontaneous motor activity in this mouse model of TBI. This arousal increase is input-pattern-dependent, as changing the temporal pattern of DBS can modulate its effect on motor activity. Finally, an extensive examination of mouse behavioral capacities, looking for deficits in this model of TBI, suggest that the strongest effects of TBI in this model are found in the initiation of any kind of movement.

1. Introduction

1.1. Traumatic brain injury

TBI (traumatic brain injury) is a common form of survivable brain injury. It can result, depending on severity, in a quickly healing concussion, sustained loss of consciousness, or death [1]. TBI is a contributing factor of 30.5% of all injury-related deaths in the United States [2,3]. An estimated 1.7 million TBIs occur in the US every year [2], resulting in 52,000 death, 275,000 hospitalization, and 1.4 million visits to emergency departments [2,3]. Due to the high prevalence and impact of such injuries, it is crucial to understand the consequences of TBI for the brain, and to learn how to prevent or reverse long-term functional impairment.

A host of animal models for TBI exist [4]. As most forms of TBI result from a blow to the head, we opted to use a multiple weight-drop model, which simulates a moderate closed head injury.

While large numbers of studies have imposed TBI on rats and mice, the great majority of those studies focused on consequent morphological, neurochemical and molecular damage in the brain, the latter studies including altered mRNA levels. Attempts at amelioration have usually focused on environmental manipulations. Examples of these would include the traditional 'enriched environment' [5] and the opportunity for exercise on running wheels [6]. With rare exceptions (see Discussion), deep brain stimulation (DBS) has not been tried with the intention of improving behavioral arousal in the manner that is currently being attempted with human patients [7]. The current study uses central thalamic DBS

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(successful with a human patient, see below) in conjunction with behavioral measures of motoric arousal, supplemented by other behavioral assays.

1.2. Previous research on DBS to alter arousal in humans

Deep brain stimulation (DBS) involves implantation of stimulating electrodes placed into specifically targeted brain regions, and has been used to ameliorate symptoms of epilepsy and psychiatric disorders. A recent study has indicated that DBS can be effective for patients in a minimally conscious state (MCS) [8]. The target of stimulation in that study was the nonspecific nuclei of the central thalamus (CT). This region is uniquely poised for neuromodulation of the injured brain due to its widespread neuroanatomical projections to the basal ganglia and cerebral cortical regions [9]. While patients in MCS may retain the thalamo-cortical connections needed to support cerebral activation, they lack sufficient innervation from the arousal systems to sustain awareness [10]. Therefore, DBS of the CT in a severely injured brain could approximate this missing arousal input, allowing the CT to support cerebral activity and cognition [10].

1.3. Significance of DBS temporal patterns and neural coding

It has been proposed that information can be encoded in the temporal patterns of neural spike trains [11–13], a hypothesis well supported in literature describing temporally-patterned neural responses [14–24], information theoretic analyses of temporally-patterned responses [15,23,25,26], physiological explanations for the presence of temporal patterns [27–29], and neural network models that utilize temporal patterns [30,31]. In addition, a small number of direct experiments examined the response of a neural system to temporally-patterned inputs [16,32].

Arousal systems are likely to depend on nonlinear dynamics [33] to ensure adequate lability, enabling them to amplify small perturbations in order to produce fast responses to salient stimuli, as is the case for several biological phenomena [34]. Despite the potential utility of non-linear stimulation, conventional DBS commonly utilizes fixed frequencies. We hypothesized that temporally-patterned DBS might be more effective for increasing arousal, as compared to fixed frequency stimulation. We therefore chose a simple deterministic chaotic source, the logistic equation, to produce temporal patterns for use in DBS. A true random number generator that is internally independent was chosen as a control [35].

2. Methods

2.1. Animals and materials

Experiments used C57BL/6J mice bred in house, at 6–9 weeks of age. Mice were singly-housed on a 12:12 hour light/dark cycle with lights on at 6 pm, with food and water available *ad libitum*. Mice were implanted bilaterally with monopolar electrodes (PlasticsOne) in the central thalamus (anterior/posterior: −1.70 mm, lateral: ±1.00 mm, depth: −3.00 mm, coordinates relative to Bregma) with ground wires placed on the surface of the skull [36]. Surgical and injury procedures were done under ketamine/xylazine anesthesia (80/12 mg/kg). Analgesia (flunazine 5 mg/kg) was given twice daily for 2 days after all survival surgeries as well as after injury. All animal procedures were approved by the Rockefeller Institutional Animal Care and Use Committee.

2.2. Traumatic brain injury model

To ensure that motor activity deficits lasted the length of the experiment, we used a multiple TBI model. On the day of injury, mice were anesthetized and placed under the weight drop apparatus. As small pointed 20 g weight was dropped from a height of 25 cm onto the right side of the mouse's skull up to 5 times. Less than 5 drops were used when the animal's behavior indicated that the injury was severe (for example, through altered posture or temporary seizure). Mice were visually inspected for signs of hemorrhage and skull fracture as both of these indicated injuries of higher morbidity that were likely fatal. Analgesia was administered as described above.

2.3. Neurological severity screen

A Neurological Severity Screen (NSS) [37] was used as a general indicator of neurological deficits after injury. Two hours after TBI, mice were placed in a circular open maze with a single small exit, and four tests were scored: (1) ability to exit circle within three minutes, (2) spontaneous investigation of environment (seeking behavior), (3) ability to walk straight, and (4) presence of acoustic startle (freezing or flinching in response to a sudden loud clap). The mouse was then picked up by the tail and the reflexive hind limb flex was scored. The more difficult function tasks followed. Mice were placed on flat and round beams (0.5 cm width or diameter) and scored on their ability to perch on the beams (all four feet touching the beam) for at least 10 s. Finally, mice were placed on a simple platform with 3 cm, 2 cm, and 1 cm wide beams, each 30 cm long, and tested on whether they were able to walk across to get to another platform. Each test is scored pass-fail: failing receives a score of 1, succeeding a score of 0. For each mouse, scores on all 10 tests were summed to produce an overall score; normal mice receive an overall score of 0 and mice with the most severe deficits receive an overall score of 10.

2.4. Motor activity observation

In addition to NSS, motor activity for each mouse was observed. In the 3D home cage monitoring system (Accuscan Instruments), two data measures were recorded: horizontal activity, which consists of beam breaks in the horizontal plane, thought to represent fidgeting; and total distance, which includes non-repeating beam breaks in the horizontal plane, thought to represent ambulation. Mice were placed into the home cage monitors 5 days prior to injury, and motor activity data were collected from this point until the end of the experiment. To determine the rate of recovery, one set of mice ($n = 12$) were left alone and observed for 14 days post-injury. A second set of mice ($n = 13$) was implanted with electrodes bilaterally in the central thalamus two days post-injury and allowed to recover from surgery for an additional 4–6 days. After recovery, these mice were stimulated for several epochs (as described below) for one day.

To calculate gross indications of deficit, daily activity was recorded as a sum of motor activity within 24 h, normalized to pre-injury baseline activity, grouped by baseline, post-injury, or post-surgery (only stimulated mice), and averaged across mice. To check for characteristic day-night activity patterns, daily activity was subdivided into two 12 h sums, normalized to average total daily baseline activity, grouped by baseline, post-injury, or post-surgery (only in stimulated mice), and averaged across mice. For analyses on the effects of stimulation, activity data directly surrounding the stimulation (10 min before, 10 min during, and 10 minutes after stimulation) were analyzed.