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Research Report

Decreased bursting and novel object-specific cell firing in the hippocampus after mild traumatic brain injury

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ABSTRACT

Objective: mild traumatic brain injury (mTBI) can produce lasting memory deficits even in the absence of cell loss. We investigated changes in hippocampal firing patterns during exploration and during a novel object recognition (NOR) task. *Methods:* six male Sprague-Dawley rats were subjected to mTBI via fluid percussion injury and were compared with sham-operated rats. Microelectrodes were implanted into CA1 and CA3 and multiple units were recorded from the pyramidal cell layer. Spontaneous "burst" characteristics were analyzed and temporal firing patterns were correlated with object encounters to establish object-specific firing patterns. *Results:* mTBI was associated with significantly less hippocampal bursting ($p<0.05$) with a trend toward longer bursts and lower interburst spike frequency. mTBI was also associated with no preference for a novel object at 12 h ($p<0.05$). During the NOR task, a subset of pyramidal cells were identified which consistently demonstrated a transiently increased firing rate upon encounter of a specific object ("object-specific" cell). Across both groups, there was a significant ($p<0.05$) correlation between preference for object novelty and the difference between the total number of novel object-specific cells and familiar object-specific cells. The proportion of object-specific cells that responded to the unexpected (novel) object compared to those responding to the familiar object was significantly smaller in rats that had been exposed to mTBI ($p<0.05$). *Conclusion:* memory deficits after mTBI are associated with decreased intrinsic burst activity and impaired context-specific firing patterns in the hippocampus during object exploration.

1. Introduction

Traumatic brain injury (TBI), termed a "silent epidemic" by the Centers for Disease Control and Prevention (CDC), is experienced by over 1.7 million U.S. residents each year (Faul et al., 2010). Mild (m)TBI, defined as TBI without prolonged loss of consciousness, accounts for more than 75% of all reported cases (CDC 2003). Unlike moderate and

Abbreviations: CDC, Centers for Disease Control; ISI, interspike intervals; mTBI, mild traumatic brain injury; NOR, novel object recognition; TBI, traumatic brain injury

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severe TBI, which can produce extensive destruction to neural tissue with widespread neuronal death and axonal disruption, mTBI frequently does not cause overt morphological changes, and the degree of dysfunction after mTBI does not appear to correlate with the extent of neural cell loss (Zohar et al., 2003). mTBI is nonetheless associated with significant functional deficits, and memory problems are particularly common (Levin et al., 1987). Alterations in hippocampal firing rates, synaptic function, and field potentials persist after TBI and correlate with behavioral abnormalities (Witgen et al., 2005; Fedor et al., 2010; Eakin and Miller, 2012). Pyramidal cell bursting patterns have not been studied after mTBI, although they are known to be associated with learning deficits in other contexts (Goonawardena et al., 2011).

We have previously demonstrated reduced density and complexity of context-specific action potentials in the CA1 and CA3 pyramidal cell layers after mTBI during a delayed-nonmatch-to-sample swim T maze (Eakin and Miller, 2012). While swim maze paradigms allow sophisticated identification and characterization of subtle deficits, determination of the full neurological impact of mTBI will require measurement of neural activity and its changes under more natural physiological conditions. The novel object recognition task is ideally suited to this, since environmental exploration and object examination represent typical behavior for rodents. In this study, we recorded hippocampal cellular activity during exploration and novel object recognition to determine the effect of mTBI on electrophysiological correlates of memory.

2. Results

2.1. Injury

The average intensity of the pressure pulse was 1.5 atm (1.4–1.6 atm). Average return of the righting reflex was 286 s for the injured animals (standard deviation 106 s, range 198–492 s) and less than 60 s for all sham animals.

2.2. Bursting analysis

A Student's *t*-test compared mean frequency, bursts per minute, mean burst duration, mean spikes in burst, mean ISI in burst, mean frequency in burst, and mean inter-burst interval among animals in sham and TBI groups. Forty-seven individual units were identified among animals in the sham group and forty-five in the TBI group. Spike frequency did not significantly differ between sham and TBI groups. However, the number of bursts per minute recorded during the 5-minute session was significantly different, with sham animals exhibiting more bursts per minute compared with TBI animals ($p<0.05$, Student's *t*-test) (Fig. 2a). There was a nonsignificant trend toward longer bursts and lower inter-burst spike frequency as well (Fig. 2b–f).

2.3. Novel object recognition task

Novel object recognition performance showed a significant difference in preference index between sham and mTBI groups ($p<0.05$, Student's *t*-test) (Fig. 3). There was no consistent correlation between animal location and firing rates, so no "place cells" were identified. A subset of pyramidal cells consistently demonstrated increased firing upon encounter of an object (Fig. 4a). There was no difference in the number of these cells observed for each object during the exposure period for either sham or mTBI animals. During the recall phase, there was a significant correlation between preference for object novelty and the difference between the total number of novel object-specific cells and familiar object-specific cells across both groups ($r^2=0.396$, slope—0.089, intercept—−0.022, $p<0.05$) (Fig. 4b), although this was not significant for either group individually. The proportion of cells demonstrating object-specificity during the recall phase was significantly different between sham and mTBI rats ($F[3,15]=4.758$, $p<0.05$) (Fig. 4c). The total number of object-specific cells that responded to the unexpected (novel) object compared to those responding to the familiar object was significantly greater in sham-injured rats compared with rats exposed to mTBI ($p<0.05$, Fisher's exact test).

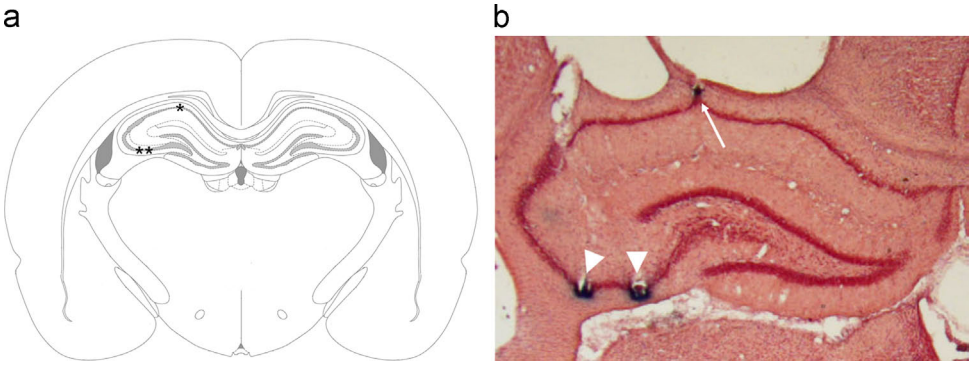

Fig. 1 – (A) Location of electrodes according to the atlas of Paxinos and Watson. The microelectrode recording array is implanted in the CA1 (*) and CA3 (**) subregions of the hippocampus ipsilateral to injury. Each array consists of eight contacts in each subfield located along the rostrocaudal axis (relative to Bregma: M/L—2.9 mm, A/P—3.00 mm, D/V—3.2–−3.5 mm, rotated laterally 30° from the midline, placing the longer (lateral) row of electrodes into CA3 and the shorter row into CA1). (B) Example of Prussian blue staining demonstrating location of electrodes within CA1 and CA3.