Behavioural Changes Associated with Repeated Subconcussive Head Impact Exposures in Rats: Preliminary Evidence of a Second Mechanism for Concussion

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I. INTRODUCTION

Sport-related concussion accounts for over 200,000 visits to the Emergency Department per annum in the United States. The traditional biomechanical mechanism for concussion involves a single head impact resulting in high rate head rotational acceleration. In recent times, repetitive subconcussive head impact exposure (HIE) has begun to be recognised as a possible second mechanism for concussion in contact sports due to the high number of head impacts that athletes experience in sports such as American football, rugby and combat sports. Our preliminary studies have identified significantly elevated HIE in American college football athletes, relative to matched controls, who sustained concussion following unremarkable head impacts [1]. However, this mechanism will require validation using an animal model that removes variability in human studies associated with concussion/head impact history and individual thresholds for reporting concussion. Accordingly, this study was conducted using a rodent concussion model to identify whether repeated low-level head accelerations can produce a cumulative effect with behavioural changes consistent with concussion.

II. METHODS

Research methods were approved by the Institutional Animal Care and Use Committee (IACUC) at the Medical College of Wisconsin. Adult male Sprague-Dawley rats were exposed to anaesthesia, head rotational acceleration (for all groups except shams) and behavioural assessment. Rats were assigned to one of four experimental groups that included Single Impact, Moderate HIE, High HIE, and Sham. The Single Impact group received anaesthesia five days per week (Monday–Friday) without head acceleration for three weeks and four days, followed by a single head rotational acceleration (~550 krad/s^2) on the last day. Acceleration magnitude was consistent with development of concussion-type behavioural changes [2]. Moderate and High HIE groups were exposed to repeated low-level head rotational accelerations five days per week for four weeks. Frequency and severity of head accelerations were based on head impact data collected in non-concussed NCAA Division I American football athletes [3]. The Moderate HIE group received eight head accelerations per day (total 160) and the High HIE group received 30 per day (total 600). Peak head rotational accelerations were scaled from human exposures based on brain mass scaling [4] and had peak magnitude of approximately 75 krad/s^2. The Sham group was subjected to the entire four-week injury protocol, including anaesthesia, without head rotational acceleration.

All rats received behavioural assessment following the four-week injury protocol. The Morris water maze (MWM) identified cognitive changes and the elevated plus maze (EPM) identified changes in emotionality. The MWM assessment consisted of four MWM trials per day for four consecutive days. Each four-trial set consisted of rats placed at each of the cardinal locations within the 183 cm diameter maze (N, S, E, W), facing the outer wall. Rats were allowed to swim in the 25 cm deep water until finding and mounting a hidden platform. The platform was maintained in an identical location (SE), 1 cm below the surface of the water. Movements of the rats inside the MWM were tracked and latency to find the platform was computed for each trial. Average latency over Trials 2, 3 and 4 was compared between sets. Increased MWM latency was associated with cognitive deficits. The EPM was used to assess anxiety-related behaviours and consisted of four perpendicular

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10x90 cm arms suspended 50 cm above the floor. A 10x10 cm central platform connected the arms. One pair of opposing arms was enclosed by 40 cm high walls. Rats were placed on the central platform, facing an open arm, and allowed to explore the maze for five minutes. EPM assessments consisted of time spent in open/closed arms and centre platform, total distance travelled and number of arm changes. Behaviours associated with increased anxiety included decreased percentage of time spent in open arms, fewer arm changes and a decrease in the total distance travelled.

III. INITIAL FINDINGS

A total of 35 rats were exposed to the injury protocol, with nine rats each in the Sham group, the Single Impact group and the High HIE group. The Moderate HIE group had eight rats. Average peak head rotational accelerations for the Single Impact group were 513±43 krad/s^2 (mean ± standard deviation). Average peak head rotational accelerations for the High HIE and Moderate HIE groups, across all exposures, were 74.8±2.5 and 78.2±2.1 krad/s^2, respectively. Post-injury behavioural assessments demonstrated some non-significant trends. For example, rats in the High HIE group demonstrated 113% increased latency compared to all other rats (p=0.057) during Trial 2 of the MWM assessment (Fig. 1, left). High HIE rats also had the highest latency in Trial 3 of the MWM, although the difference (+33%) was less remarkable. Groupwise differences were also evident in the EPM (Fig. 1, centre and right), wherein High HIE rats had decreased activity (i.e. arm changes and total distance travelled), as well as decreased time in the open arms. In contrast, the Single Impact group demonstrated increased activity and increased time in the open arms of the EPM.

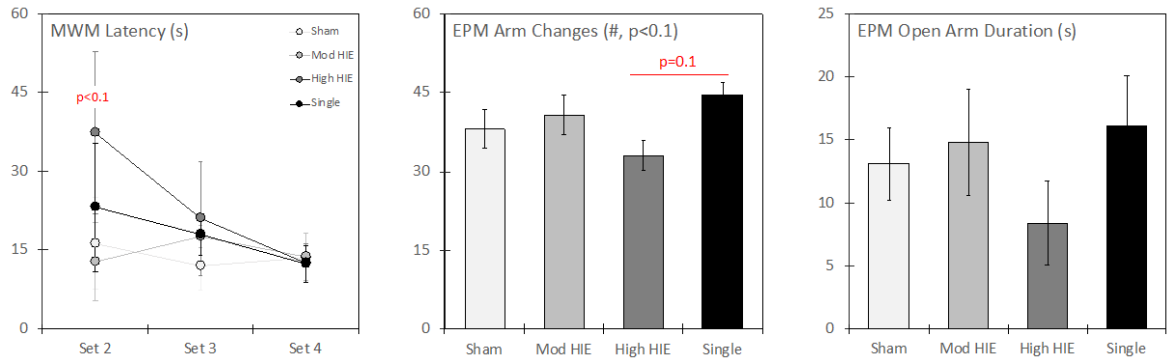

Fig. 1. Groupwise differences in Morris water maze (left) and elevated plus maze (centre, right) assessments.

IV. DISCUSSION

These findings have demonstrated: (1) evidence of cognitive (MWM) and emotionality (EPM) changes in rats following repeated exposure to low-level head rotational accelerations, (2) differing behavioural outcomes between the High HIE group and the Single Impact group, and (3) evidence of a possible threshold for cumulative HIE, as the Moderate HIE group had no remarkable behavioural changes compared to Sham group. Exposure groups were designed to match HIE in American football athletes, with a consistent frequency of exposures and average peak acceleration scaled from the human (~1,000 krad/s^2) to the rat (~75,000 krad/s^2). Accordingly, repeated accelerations were well below the threshold for even mild concussion [5] and would not be expected to result in any behavioural changes in the rat following a single exposure. However, repeated exposures over the course of days to weeks may contribute to cumulative damage that manifests as cognitive deficits (i.e. increased MWM latency) and changes in emotionality (i.e. anxiety-type behaviours in EPM). These preliminary findings in a limited number of rats have, for the first time, identified that repeated exposures to low-level head rotational accelerations over the course of time may lead to cumulative deficits under a different mechanism from the traditionally accepted mechanism of a single high-magnitude head impact. Further validation will be obtained using advanced MRI, blood biomarkers and histology in these ongoing studies.

V. REFERENCES

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