Notice of the Final Oral Examination
for the Degree of Doctor of Philosophy

of

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BSc Hons. (Wilfrid Laurier University, 2013)

“A novel preclinical pediatric concussion model causes neurobehavioural impairment and diffuse neurodegeneration”

Division of Medical Sciences

Friday, April 16, 2021
1:00 P.M.
Conducted Virtually

Supervisory Committee:
Dr. Brian Christie, Division of Medical Sciences, University of Victoria (Supervisor)
Dr. Leigh Anne Swayne, Division of Medical Sciences, UVic (Member)
Dr. Sandy Shultz, Department of Neuroscience, Monash University (Outside Member)

External Examiner:
Dr. Liisa Galea, Department of Psychology, University of British Columbia

Chair of Oral Examination:
Dr. Mohsen Akbari, Department of Mechanical Engineering, UVic

Dr. Stephen Evans, Acting Dean, Faculty of Graduate Studies
Abstract

Concussions are the injury and symptoms that can result from transmission of a biomechanical force to the brain. They represent a significant global health burden, and are the subject of a growing body of medical research. A concussion can only be definitively diagnosed by a medical professional based on symptoms, although advanced neuroimaging and biomarker-based approaches are promising future diagnostic tools. There is no treatment for concussion beyond following return-to-work or -play guidelines, which recommend avoiding strenuous physical and cognitive activities until they no longer exacerbate symptoms. Preclinical models of concussion have been used to examine pathophysiological processes underlying symptoms, which is an important step in developing tools for diagnosis and treatment. Historically the clinical translation of preclinical concussion research has been limited, and the use of anaesthesia, and preference for adult male rats may contribute to this. These means of reducing variability are justified, but preclinical research moving forward should address these limitations to translatability by including more clinically relevant subjects and avoiding anaesthesia. To this end, we developed a new preclinical model for pediatric concussion. Our awake closed head injury (ACHI) model is well-suited to this purpose because it produces a helmeted closed-head injury involving vertical and rotational displacement of the head, and does not require anaesthesia. Before the ACHI model can be used to investigate concussion mechanism, diagnosis, and treatment, it needs to be characterized to demonstrate that it produces clinically relevant neurobehavioral and pathological changes. We developed a modified neurologic assessment protocol to test neurologic function immediately after each injury. The Barnes maze, elevated plus maze, open field, and Rotarod were used to measure injury-related changes in cognition, anxiety, and motor function. The Barnes maze reversal task was used to detect more subtle cognitive impairments of executive function. Structural MRI was used to search for visible lesion, hemorrhage, or atrophy; and silver-stain histology was used to detect neurodegeneration. We determined repeated ACHI produced acute neurologic impairment with the NAP, and a mild spatial learning deficit potentially mediated impaired cognitive flexibility in the Barnes maze and reversal training. These were accompanied by neurodegeneration in the optic tract, hippocampus, and ipsilateral cortex during the first week of recovery. Thus, following the internationally recognised definition developed by the concussion in sport group, we demonstrated 1) an “impulsive” force transmitted to the head
results in 2) the rapid onset of short-lived neurologic impairment that resolves spontaneously. This occurs 3) with normal structural neuroimaging, and 4) produces cognitive impairment, and LOC in a subset of cases. The ACHI model is the first in Canada to forego anaesthesia, and this is the first demonstration of neurocognitive impairment accompanied by diffuse neurodegeneration in the absence of structural MRI abnormalities after mild traumatic brain injury in juvenile male and female rats.