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Modulation of Adolescent TBI via the Orexin System, Sleep, and Glymphatic Function

Traumatic brain injury (TBI) is one of the most under-addressed and expensive pediatric health problems in Canada. Mild TBIs account for the majority of these brain injuries and incur national costs well above $3 billion/year. Adolescence is a particularly vulnerable time for mild TBI, and in particular repetitive mild TBI (RmTBI). Despite the fact that adolescents demonstrate heightened sensitivity to mild TBI, and are at increased risk for RmTBI, adolescence is a scarcely studied population within this context.

A recently discovered waste clearance system for the brain, the glymphatic system, has been linked to functional recovery from brain injury and neurodegenerative disorders such as Alzheimer's disease. This waste clearance system is much more effective during sleep, essentially disengaging while the individual is awake. Given that 70% of patients with mild TBI report sleep disturbances and adolescents are significantly more likely to be sleep deprived, we hypothesized that RmTBI in adolescence impairs sleep and glymphatic system function, resulting in increased risk for short and long-term neurological consequences.

Using a clinically relevant animal model of mild TBI, this project proposes to 1) explore the short- and long-term neurological outcomes associated with RmTBI in adolescents using behavioural, epigenetic, and MRI techniques; 2) determine how RmTBI in adolescence disrupts circadian rhythms, sleep and the glymphatic system; and 3) remediate pathology associated with adolescent RmTBI with a pharmacological agent that improves sleep and targets the glymphatic system.

We believe this project will capitalize on exciting and novel innovative mechanisms like the glymphatic system and sleep to vastly improve our understanding of RmTBI in the adolescent brain. Pharmacological treatment of the RmTBI with a sleep-promoting agent will provide mechanistic insight into mTBI pathology and provide new therapeutics for treatment of RmTBI in adolescents.