

## Progress Report

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Title of Project: Assessing the therapeutic effects of non-invasive brain stimulation in children with post-concussion syndrome: a brain connectivity approach

### *Summary:*

Mild traumatic brain injuries (mTBI) account for 90% of traumatic brain injuries in children. The lack of knowledge regarding the complex association between whole-brain connectivity and diverse behavioural profiles in mTBI is a major impediment to the development of efficient management strategies for persistent post-concussion symptoms (PCS) in paediatric populations. Furthermore, there are few evidence-based treatments for PCS and none for persistent PCS in children.

The primary purpose of this project was to investigate the neural principles underpinning the effect of local perturbations on whole-brain connectivity in children exhibiting persistent PCS symptoms. We developed advanced brain mapping approaches to characterise changes to whole-brain connectivity (i.e. the brain's communication pathways) when induced by non-invasive brain stimulation (NiBS) in paediatric populations with concussion. Using NiBS we expected that results from this study will provide new information on how NiBS induces changes to whole-brain connectivity and could help alleviate post-concussion symptoms in children.

For current data collection we are utilising repetitive transcranial stimulation (rTMS) delivered over 2 weeks of treatment. Our group has implemented a randomized double-blind, placebo controlled clinical trial (RCT) study design with imaging and EEG to be collected pre and post intervention, with a joint decision to unblind the participants and analyse all data materials once data collection is completed. Unfortunately, we have experienced recruitment delays in all rTMS activities. Mainly, the hospital ethics committee at Queensland Children's Hospital required additional safety certifications for the KidStim laboratory (pictured below) and an initial evidence base that provided support for the use of brain connectivity methods. In this regard, we are happy to report that we have obtained all necessary approvals. We have also extensively worked on generating important evidences that linked persistent concussion symptoms in a large population of PCS children with our brain connectivity methods. These evidences were recently published in American Neurology Association journals [1, 2]. We have also built significant momentum in our future recruitment pathways, with Brisbane Metropolitan catchments actively engaged

(Queensland Children's Hospital, Princess Alexandra, Royal Brisbane and Womens' Hospitals) and receiving state-wide support (Children's Health Queensland) for the trial. The support of our clinical partners has enabled us to advertise the trial on a broader platform and ensure that a wide recruitment database can be established.

### *Hypothesis vs Findings*

1. We expected that larger changes in brain connectivity induced by prefrontal stimulation would relate to better clinical outcomes.
2. In particular, expect that baseline connectivity strength (prior to stimulation) in brain networks showing a significant activity change following brain stimulation are expected to predict better response to the intervention.

As per the above, we have been unable to test our hypotheses until all participants have been collected and made available for analysis (due early 2022). We look forward to sharing these results with you.

### *Unanswered Questions*

As above

### *What these research outcomes mean*

Clinically, this study is significant in that it will generate results that provide the first evidence base for implementing a new therapeutic intervention that limits the chances of developing future neurodevelopmental and behavioural problems arising from a concussion during childhood.



### References

1. Iyer, K.K., et al., *Relating brain connectivity with persistent symptoms in pediatric concussion*. Ann Clin Transl Neurol, 2019. **6**(5): p. 954-961.
2. Iyer, K.K., et al., *Default mode network anatomy and function is linked to pediatric concussion recovery*. Ann Clin Transl Neurol, 2019. **6**(12): p. 2544-2554.