Are visual evoked potentials enhanced in subjects with persistent post-traumatic headache?

Preregistration 4/3/21

**HYPOTHESIS:** Individuals reporting headache lasting 1 month or longer will have increased pattern reversal visual evoked potentials (prVEP) compared to those who recover.

**STUDY DESIGN**

Subjects will be included who were recruited as part of the Minds Matter concussion research program. They will be age 11-21 of any biological sex. Subjects will have normal or corrected to normal visual acuity in both eyes. Subjects will have recorded VEP, signs and symptoms during VEP recording (headache, eye strain, frequent blinking, etc.), and Post-concussion symptom inventory (PCSI)1 scores recorded. Subjects will be compared in the following groups:

1. Post-traumatic headache subjects will meet the following criteria

* Diagnosed with concussion
* VEP recorded between 1 month and 6 months following concussion
* PCSI headache score of 1 or greater at the time of VEP recording

1. Recovered subjects will meet the following criteria

* Diagnosed with concussion
* VEP recorded between 1 month and 6 months following concussion
* PCSI headache score of 0 and total PCSI score of 3 or less at the time of VEP recording

1. Healthy control subjects will meet the following criteria

* No prior history of concussion
* PCSI headache score of 0 and total PCSI score of 3 or less at the time of VEP recording

At least 14 subjects will be collected per group based on prior reported differences in VEP amplitude in chronic migraine compared to healthy controls and episodic migraine2.

VEP recordings will meet ISCEV standards3 and are previously described4.

**ANALYSIS**

Subject demographics comparison: subject age, biological sex, race/ethnicity, and total PCSI scores will be compared. Further, PCSI headache and migrainous symptom scores (i.e. light sensitivity, sounds sensitivity, and nausea) will also be compared. For post-concussion subjects, the distribution of days post-concussion will be compared. Proportions will be compared with a proportional z-test, and distributions (eg. age, PCSI) will be compared with using KS test.

Primary outcome measure

The primary outcome measure will be comparison of PTH, recovered concussion, and healthy control subject’s prVEP as represented in 7-dimensional PCA space4 using a linear regression model. ANOVA of the 7-dimensional model, and for individual PCs accounting for multiple comparisons will be used for statistical analysis of the linear regression model. PC coefficents will be adjusted for age and biological sex to remove potentially confounding differences between the groups.

Secondary outcomes/additional analysis

1. Peak analysis on the N75-P100 peak amplitude and N75 and P100 peak latencies to compare to prior work.
2. For all concussion subjects, prVEPs represented in 7-dimensional PCA space will be included in a linear regression model with headache represented on a 7-point Likert scale with and without migrainous features (light sensitivity, sound sensitivity, and nausea).
3. Waveforms will be displayed by calculating the mean prVEP response and calculating the 95% confidence intervals by bootstrap analysis.
4. The presence/absence of signs and symptoms of visual discomfort will be put in a multiple correspondence analysis and used in a linear regression model to compare the PTH, recovered concussion, and healthy control groups

**REFERENCES**

1. Barlow, K. M. *et al.* Epidemiology of Postconcussion Syndrome in Pediatric Mild Traumatic Brain Injury. *Pediatrics* (2010). doi:10.1542/peds.2009-0925

2. Chen, W. T. *et al.* Persistent ictal-like visual cortical excitability in chronic migraine. *Pain* (2011). doi:10.1016/j.pain.2010.08.047

3. Odom, J. V. *et al.* ISCEV standard for clinical visual evoked potentials: (2016 update). *Doc. Ophthalmol.* **133**, 1–9 (2016).

4. Patterson Gentile, C. *et al.* Developmental Effects on Pattern Visual Evoked Potentials Characterized by Principal Component Analysis. *Transl. Vis. Sci. Technol.* **10**, (2021).