Addendum to:

Experiment Title: Quantifying light perception via perceptual and physiologic measures in response to melanopsin and cone stimulation in migraineurs with interictal photophobia and in headache-free control subjects

Research Project: Photoreceptor directed light modulation: perception, pupillometry, EMG

Additions to Research Team: Kelly Heath

Purpose: This addendum concerns primarily the addition of a study population to our on-going experiment. The original pre-registration describes measurements in people with migraine and in headache free controls. Here, we describe how we will enroll and study an additional population of people with a history of mild traumatic brain injury (mTBI) and photophobia. We also list refinements to the experimental protocol that we have adopted since the original pre-registration document was posted.

The addition of a mild traumatic brain injury cohort:

Participants will be recruited from the Philadelphia Veteran Affairs Medical Center within the Polytrauma Clinic. Participants must be between the ages of 25 and 40 (to minimize misclassification of subjects who might harbor migraine but not yet have become symptomatic; Stewart 1991, Stang 1992, and to correspond to the typical age range of blast-injury mTBI patients). Dr. Heath will conduct pre-screening to identify people who will then be invited to participate. Eligible subjects are those who have a clinical diagnosis of mTBI, which per VA/DOD current criteria includes sustaining an event that lead to at least one of the following: 1) loss of consciousness; 2) dazed and confused at the time of the injury; and/or 3) loss of memory for events immediately prior to or after injury. This clinical diagnosis will be made by Dr. Kelly Heath. All patients will complete a Neurobehavioral Symptom Inventory (NSI; Cicerone 1995). Candidate subjects must indicate “moderate” or greater sensitivity to light on the NSI. Exclusion criteria will include a pre-existing history of migraine headache (as determined using the Gervil 1998 criteria) prior to the TBI (history of post-traumatic headache will not be used for exclusion) and women who are pregnant or plan to become pregnant. Subjects who meet all inclusion and exclusion criteria will be considered *candidate subjects* and will be referred a study coordinator for further evaluation for enrollment.

Candidate subjects will then complete the Penn Online Evaluations of Migraine (POEM), which includes the Choi 2009 questions regarding visual sensitivity during and between headache, and the Visual Discomfort Score (VDS) survey. Subjects will be eligible for the study regardless of their POEM headache diagnostic label or responses to the Choi questionnaire or VDS survey. Candidate subjects will then continue through the enrollment process as described for Candidate subjects as described in the original pre-registration document. Exclusion criteria not related to headache and mTBI history as outlined in the original pre-registration document will hold for this population as well.

We will continue to recruit and test subjects until we have 40 completed subjects in this group (mTBI). The subjects will complete the primary experiment as outlined in the original pre-registration document. The primary planned comparison will be between controls (headache-free subjects with no history of TBI) and mild TBI subjects. The control group will not be sex matched to the mild TBI group. In a secondary analysis, we will examine the control group to

determine if there are sex differences in response. If so, we will perform additional analyses in which we compare the TBI group to a subset of the controls that are matched as closely as we can to the gender distribution of the TBI group. Otherwise,data will be analyzed as described in the original document.

Protocol clarifications and refinements:

- From the outset of the initially pre-registered protocol we have excluded subjects with a history of ophthalmologic disease. During subject screening, we ask "Do you have a history of ophthalmologic disease?" and subjects who answer affirmatively are excluded from further study.
- We have added an exclusion criterion to the enrollment of migraine subjects. Our screening surveys include a question that asks how long ago was the last migraine headache or aura event. Starting on September 6, 2018, all recruited migraine subjects will only be enrolled if their last event was within the last month or week. Prior to the adoption of this criterion, we enrolled a total of 7 migraine subjects who did not met this criterion (2 migraine with aura, and 5 migraine without aura. The data from these 7 subjects will not be excluded from the study.
- We have explicitly defined the operating range for background luminance of our light flux stimuli. We initially stated that we would “attempt to maintain the background luminance of the light flux stimulus within a ±0.1 log unit range of this value at the start of data collection.” We can now clarify that this range is 160 to 254 cd/m^2, 0.1 log units above and below our starting value of 202 cd/m^2. For all sessions completed to date, the stimuli have fallen within this range.
- We email our migraine (with and without aura) subjects one week after completion of a session to ask if they have had a migraine since the session, and if one occurred to let us know when that migraine was.
- We now measure spherical and cylindrical refractive error for all enrolled subjects. This information will be used to assist with pupil tracking. We are planning to obtain this measurement for all enrolled subjects, including bringing back subjects who had already completed the study prior to the addition of this measurement.
- We are asking all subjects to complete the ‘Morningness-Eveningness Questionnaire’ to gather more information about our subjects' sleep. These measurements will allow us to investigate if our light sensitive subjects have altered sleep or circadian rhythms.
- We have clarified the information given to our subjects about what the EMG is measuring. We now say, if asked, that the EMG measures “eye responses”. We had previously informed subjects, if asked, that the EMG measures “squinting activity”. This change in subject instruction was initiated on 6/28/2018.
- We have also refined our procedure for pupil gaze calibration. Prior to the beginning of a session, subjects are asked to fixate at various positions on the eyepiece while the contralateral eye is recorded. This video allows us to estimate the position of the subject’s eye relative to the camera (a process we refer to as constraining the scene geometry) and thereby improve pupil tracking. At the end of a session, we have the option to run an additional pupil gaze calibration if the operator judges the subject to have moved during the course of the experiment relative to the subject’s placement during the initial pupil gaze calibration video. If we have more than 1 calibration video, we will use the last one under the assumption it best reflects the subject’s position during the course of the acquisition.