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Research Project: Trigeminal sensitivity in Migraine

Purpose and Approach

In a prior study (BLNK_2021; Kaiser et al 2023 Clin Neurophysiology), we measured properties of the blink reflex in response to parametric variation in the intensity of an air-puff stimulus. We found that the amplitude of blink response (expressed as a proportion of lid closure) varies with stimulus intensity, following a two-parameter Weibull CDF.

In the current study, we will collect blink response data from a population of headache-free control subjects and a population of subjects with migraine. Following a procedure similar to Kaiser 2023, we will fit a Weibull CDF to the amplitude of blink evoked at different stimulus intensities. We will then test if there are differences between the headache and control population in the parameters of the psychometric function.

The study will end on April 1, 2024, even if we have not yet met our recruitment goal. In this instance, we will report our results given the subjects we have studied to that point.

Subjects

We will collect a complete dataset from 40 healthy participants, ages 18-40, with 20 participants studied from each of two categories:

- **Control** participants will meet all of these criteria:
    1) Classified by the POEM (Kaiser et al., 2019; and as updated in the POEM analysis code as of the date of this pre-registration) to be “headache-free”.
    2) Answered “no” to a question regarding a family history of migraine headaches.
    3) Answered “no” to a question regarding a history of childhood motion sickness.
    4) Answer “no” to the question “are your eyes sensitive to light” and score zero on the Choi photophobia questions (as modified for headache-free participants).
    5) Have an Allodynia Symptom Checklist (ASC) score (Lipton et al, 2007) of 0-2 (None).
- **Migraine** participants will meet all these criteria:
    1) Classified by the POEM as: a) migraine without aura; or b) migraine with visual aura; and/or migraine with other aura.
    2) Report a headache frequency between 5-20 days a month.
    3) Have a MIDAS score of 11 or greater (MIDAS Grade III moderate disability).
    4) Have an ictal ASC score of 4 or greater (Mild).
    5) Note: Of the candidates who qualify, we will preferentially enroll those who:
        a) Endorse inter-ictal allodynia (most preferred).
        b) Have an ictal ASC score of 6 or greater (Moderate).
        c) Endorse inter-ictal photophobia.

Exclusion criteria for all subjects include:

- A history of concussion in the last 2 years, or ongoing symptoms from a concussion.
- A history of current ophthalmologic disease requiring ongoing treatment, or any history of ophthalmologic disease involving the anterior segment of the eye, or risk factors for a

poor response to dilating eye drops (prior reaction to pharmacologic dilation; strong family history of glaucoma). The exception to the foregoing is a history of dry eye. We will enroll subjects with a history of dry eye, but who are not currently using medicated eye drops (e.g., cyclosporine). Past use of cyclosporine or past treatment with a tear duct plug will not necessarily lead to exclusion from the study.

- A history of Bell's palsy, facial weakness, ptosis, or other dysfunction of facial strength, sensation, or eye closure.
- Receiving onabotulinum toxin (i.e., "Botox" of any type) to the cranium for cosmetic purposes or the treatment of chronic migraine, facial spasm, etc. within the past 24 weeks.
- Having received treatment with a nerve block or neuromodulation device to the head in the 24 hours prior to a session.
- Ongoing use of muscle relaxant medication.
- Any history of using hard contact lenses.
- Inability to discontinue use of soft contact lenses in the 2 weeks prior to a session.
- A color vision impairment defined as scoring below 17 on the first 21 plates of the Ishihara test.
- A best corrected visual acuity (BCVA) below 20/25 for either eye.
- A dry eye score greater than $(2 \times sum\_of\_scores) + 10$ (for $sum\_of\_scores \leq 25$) or a $sum\_of\_scores > 25$ based on the Ocular Surface Disease Index.
- Receiving eyelash extensions within the past 8 weeks prior to a session or inability to discontinue the use of false eyelashes, mascara, and eyeliner on the day of testing.
- An alteration in the appearance of the eyelids as judged by an in-person screening. Specifically, if the palpebral fissures are not of approximately equal height, both eyes do not close completely and equally, or both eyes do not open completely and equally.

It is possible that we will identify other exclusion criteria as we screen subjects for the study. If subjects are excluded for reasons identified prior to their participation in blink data collection, we will simply add these reasons to the list of exclusion criteria and not consider this a deviation from the protocol.

Subject Preparation

At the start of a data collection session, subjects will be acclimated to the experimental room. The operator will then review the experimental procedure with the subject and adjust the apparatus and chair for subject comfort. Subjects may hold onto the tripod to stabilize themselves if air puffs are startling to them.

Room illumination will be with a single, torch-style lamp in the corner. We will measure and report the luminous intensity present in the room at the subject location.

Apparatus and Stimulus

Trigeminal responses are measured using a custom-modified EyeStat device, positioned over the eye of the seated subject. Data will be collected and analyzed as described in Kaiser 2023, with the following modifications/additions:

- We will use 5 stimulus levels (PSI): 0, 5, 10, 20, 40

- Acquisitions will be grouped into blocks of 5, with each block including all five stimulus levels in a different order.
- The data from a first acquisition at pressure level 20 (not belonging to any block) will be discarded. This is to familiarize the subject with the stimulus procedure.
- The subject will be provided with lubricating eye drops before each block of acquisitions. The experimenter will assist with instilling these eye drops if needed.
- The subject will wear noise-canceling headphones and, during each acquisition, we will play brown noise at a volume sufficient to mask the sound of the stimulus delivery.
- Subjects take at least a two-minute break between each block. Up to a 10-minute break may be taken if necessary to (e.g.) use the bathroom.

Data analysis and primary hypothesis testing

Data analysis will proceed as described in Kaiser 2023. The temporal profile of lid position will be fit with the 3-component model described in Kaiser 2023. The amplitude of response (expressed as a proportion of lid closure) will be obtained for each pressure level, and a Weibull CDF will be fit to the data across pressure levels. In planned tests, we will compare the 50% threshold and slope of the psychometric function between the two groups (headache and control) with each comparison evaluated using a t-test.

Each acquisition consists of 8 airpuff trials. The response to the first airpuff trial from each acquisition will be discarded in analyses that fit the Weibull CDF to the response across pressure levels. This is to allow initial habituation of the blink response. In other analyses that examine the habituation of the blink response across trials, this trial will be retained.

Data Exclusion Criteria and handling errors in data collection

Device
If the testing apparatus fails temporarily (due to e.g., software crash, exhaustion of a pressure cartridge) and it is possible to resume testing, then we will discard the single acquisition during which the failure occurred, repeat this acquisition, and then continue to complete the session. If the failure occurs between acquisitions, then the study can continue as originally planned after recovering from the failure.

There may be failures of the testing apparatus that cannot be resolved within a few minutes. If the failure occurs at some point during the 5^{th} experimental block, then we will keep the data collected up to that point and consider the measurement for the subject complete. If the failure occurs during or prior to the 4^{th} experimental block, then we will discard all the data collected for the subject until that point. We will invite the subject to return for testing on a different day.

Operator
It may be the case that the operator may make an error in providing the specified order or number of acquisitions of each pressure level:
- If the operator detects the mistake, then the omitted acquisitions can be collected at the end of the experiment in a "6^{th}" experimental block.
- We will tolerate errors in the ordering of the acquisitions and not omit data on this basis.
- If an operator error causes loss of data from more than 5 acquisitions total, or more than 1 acquisition at any one pressure level, then we will discard the entire dataset for the subject. In this event, we would invite the subject to return for a make-up session.

Subject

If a subject leaves the study prior to the completion of the entire data collection session, we will exclude their collected data from the study. Subjects can take breaks up to 10 minutes in length during data collection. Breaks longer than this will constitute “leaving” the study.

Subjects sometimes close their eyes for extended periods during data collection. If either eye is held fully closed for 4 or more of the 8 trials in a given acquisition, we will discard the data from that acquisition. If 3 or more acquisitions total are discarded on this basis for a subject for the acquisitions at 20 PSI or below, then we will exclude the data from this subject completely. There may be some subjects who are unable to tolerate the 40 PSI stimulus and thus hold their eyes closed during these acquisitions or are otherwise unable to participate in the 40 PSI acquisitions. If these subjects demonstrate full eye closure for the 20 PSI stimulus, then we will be able to retain their data and treat their response at 40 PSI as being a 100% eye closure on all trials. If a subject has 3 or more discarded acquisitions at 40 PSI, and does not have complete eye closure at 20 PSI, then we will discard the entire data set for the subject, as we are unable to measure their full response function.

The operator may observe subject behavior during the session that prompts concern that the collected data will be of low quality (e.g., excessive movement and fidgeting or sleepiness). The operator will discuss these observations with the study team, and data for a subject may be excluded from the study on this basis, as long as the decision is made prior to examination of the blink response data.

If subjects are excluded, we will recruit additional subjects in an effort to meet our pre-specified study numbers.