STUDY INFORMATION

Title: Intra- and inter- subject variability in pattern reversal visual evoked potentials in a pediatric population determined by principal component analysis.

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Description:
The primary goal of this study is to establish intra- and inter-subject variability of prVEP in a pediatric control population using Principal Component Analysis (PCA). PCA could offer an unbiased means of measuring variability of VEP data. A secondary goal of this project is to reduce the dimensionality on extensive demographic, medical history, symptom, and behavioral data collected in conjunction with prVEP. This work will set the foundation for future data analysis on prVEP in children and adolescents under baseline conditions and following concussion.

Objectives:

1) Determine intra-subject and inter-subject variability of prVEP in children and adolescents using principal component analysis (PCA)
2) Determine intra-subject and inter-subject variability of prVEP in children and adolescents using traditional methods (peak-to-peak amplitude and latency of pre-defined peaks)
3) Identify a lower dimensionality of subject demographic, medical history, symptom, and behavioral data

DESIGN AND DATA COLLECTION PLAN

Study type
Longitudinal observational study to collect normative VEP data for children and adolescents.

Existing Data
Data have been collected on 152 subjects between February 2018 and February 2020. Subject demographic data including age, sex, Data include VEP responses, Post-concussion Symptom Inventory (PCSI), and visual signs and symptoms reported during testing. Between 1 and 5 sessions was collected for each subject. For analysis of this work, only subjects who have at least 2 sessions collected in this time frame will be included (105 subjects total) and only sessions 1 and 2 will be considered for the main analysis.

Data collection procedures
Subjects: Subjects between the ages of 8 and 17 years were recruited from a local high school.

Visual stimuli and viewing conditions:
Subjects are prescreened to ensure normal or corrected normal visual acuity. Subjects are seated in a well-lit environment (unable to be in a dark room due to automated lights in one of the testing spaces) 39 cm from the visual stimulus monitor. Data are collected under binocular viewing conditions. Visual stimuli were presented on the Diopsys NOVA^{TM} vision testing system. The monitor is a 17" LCD screen with 1280 x 1024 resolution, and a 75 Hz refresh rate.

Visual stimulus and paradigm: Visual stimuli consist of a wide field 85% contrast checkerboard whose pattern reverses at a rate of 2 reversals per second (4 Hz) with checks 1.6 degree visual angle in size. Subjects were instructed to fixate on a central red fixation 'x' for the duration of the stimulus presentation. During viewing the checkerboard stimulus, visual signs and symptoms were recorded. Stimuli were presented for a continuous 20 seconds for a total of 40 reversals in a single block. The block was repeated 5 times in a single session.

VEP recordings: VEPs were recorded with a Diopsys NOVA^{TM} vision testing system. Two reference electrodes were placed in the center of the participant's forehead and on either the right or left temple with the active electrode placed at Oz by 10-20 international EEG placement criteria. Raw voltage by time data in the format of matlab files uploaded from the Diopsys NOVA^{TM} vision testing system will be used for data analysis. Data were recorded at a sampling rate of 1024 samples/second.

Sample size
105 control subjects with multiple data sessions already collected will be used for this study. Of those, 50 subjects will be used for exploratory analysis and the remaining subjects will be used for validation.

Manipulated variables
VEP data were collected from subjects at multiple sessions.

Measured variables
- Participant demographics: age, sex, race, and ethnicity
- Participant past medical and family history were collected. This included the following:
    - Personal history or family history: migraine, chronic headache, dyslexia, ADHD/ADD, learning disability, motion sickness, sleep problems, vision correction for reading, vision correction for distance, strabismus, amblyopia, anxiety, depression, bipolar, drug/alcohol abuse, other psychiatric disorder, autism, seizures/epilepsy, tic disorder, amplified pain syndrome, POTS, suicidal ideation, history of speech therapy, history of vestibular therapy, history of vision therapy
- Concussion history and concussion number
- Visual acuity

- PCSI (from each session)
- Visual symptoms reported by participants while viewing a checkerboard stimulus including the following:
    - Eye fatigue, dizziness, headache, nausea, eye pain, other
- Visual signs noted by the experimenter while the participant was viewing a checkerboard stimulus
    - Eye slowing, eyes watering, eyes reddening, eyes moving in a circular motion
- VEP response to pattern reversing checkerboards

ANALYSIS PLAN
Data analysis will be performed using Matlab® by MathWorks.

VEP preprocessing and basic analysis
Notch filters will be applied at 60 Hz and 120 Hz to remove powerline noise. Data will be parsed into 500ms intervals corresponding to each pattern reversal. All VEP trials will be normalized to a baseline of 0. Specifically, the mean VEP signal across the first 50ms following a pattern reversal will be subtracted from the trial to set the VEP voltage pre-stimulus response to 0.

All analyses will be conducted over the 500ms (the duration of one reversal). The mean will be used when averaging VEP responses across trials, sessions, or subjects. Representations of VEP averaged data across trials, sessions, or subjects will be presented with 95% confidence intervals by bootstrap analysis.

Principal component analysis
PCA will be calculated using singular value decomposition method across all subjects. PCA will be decentered (i.e. the mean will not be subtracted from the responses for the analysis). The first 6 principal components (PCs) will be looked at in subsequent analysis.

prVEP peak amplitude and latency analysis
The following peaks will be defined based on the following criteria:
- N75: local minimum between 50ms and 90ms following pattern reversal
- P100: local maximum between 90ms and 120ms following pattern reversal
- N145: local minimum between 120ms and 180ms following pattern reversal

These peaks are based on prior literature, and by the mean prVEP response across all subjects and sessions. I will calculate the mean and 95% confidence interval by bootstrap analysis for the latency of each peak, and peak-to-peak amplitude between N75 and P100, and between P100 and N145.

Evaluating intra-subject test-retest reliability
PCA analysis: The Pearson Correlation Coefficient will be calculated for the first 6 PC scores for each subject from session 1 and session 2 to compare similarity of PCs across sessions. We will compare these correlation coefficients to correlation coefficients between subjects. A separate

analysis will be completed including all sessions because in some cases up to 5 sessions were recorded.

Peak amplitude and latency analysis: The Pearson correlation coefficient of N75, P100, and N145 peak latencies and peak-to-peak amplitudes for session 1 and session 2 will be calculated. A separate analysis will be completed including all sessions because in some cases up to 5 sessions were recorded.

Data exclusion

Pattern reversal responses where there was a voltage change of >1 mV will be excluded because this is indicative of a large non-physiologic change in voltage.

Missing data

Of the 152 subjects, 47 only have a single session collected and therefore we will be unable to calculate intra-subject variability on these subjects and will exclude these subjects from the intra- and inter-subject variability analyses. They will be included in the exploratory analysis described in the next section.

Exploratory analysis

PCA will be implemented to decrease the dimensionality of the subject demographic variables, personal and family history variables, PCSI scores, and visual signs and symptoms elicited by the prVEP stimulus. This will help us identify a lower dimensionality of these variables that we can use to compare VEP responses in future studies.