Eye Movements, Visual Perception and Attention

Study Protocol and Statistical Analysis

NCT03884985

Date: 08-20-2018

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1. STUDY OVERVIEW – PURPOSE AND BACKGROUND

During visual fixation, small eye movements of which we are usually not aware, prevent the maintenance of a steady direction of gaze. These eye movements are finely controlled and shift retinal projection of objects within the fovea, the region of the retina where visual acuity is highest. This program of research examines the link between these eye movements and attention, and tests the hypothesis that attention, similarly to eye movements, can be controlled at the foveal level. Psychophysical experiments with human subjects, using state-of-the-art techniques, high resolution eyetracking and retinal stabilization are conducted to address these questions. Gaze-contingent calibration procedures are employed to achieve high accuracy in gaze localization. A custom developed gaze-contingent display is used to shift in real-time visual stimuli on the monitor to compensate for the observer eye movements during fixation periods and to maintain stimuli at a desired location on the retina. Some experiments will use a non-invasive electroencephalogram (EEG) machine (64 channel ActiveTwo made by BioSemi) to measure electrical activity on the scalp. The correlation of data from the eye-tracker and the EEG will help us better understand the neural mechanisms underlying the control of eye movements and attention. Experiments involve visual discrimination/detection tasks with stimuli presented at selected eccentricities within the fovea. Participants' performance and reaction times are examined under different conditions, in which various types of attention are manipulated. In addition to advancing our basic understanding of visual perception, this research leads to a better understanding of attentional control at the foveal scale and of the contribution of microscopic eye movements to the acquisition and processing of visual details. In addition to the experiment procedures, we will use an optical coherence tomography (OCT) scan (Cirrus HD-OCT made by Carl Zeiss Meditec) to characterize subjects' retinae. This procedure will allow inspection of separate retinal layers as seen in cross-section. These measurements will contribute to establish a link between eye movements, subjects' performance in high acuity tasks, and retinal anatomy.

2. CHARACTERISTICS OF THE RESEARCH POPULATION

2.1. Subject Characteristics

a) **Number of Subjects:**
A total of 550 subjects will be enrolled over the lifetime of the study.

To ensure accurate statistics for each investigated visual task (discrimination, detection, etc.) we need an average of 15 subjects. Based on our experience of the last 17 years we expect that approximately one fourth of the subject will not be able to complete the experiment because of changes in their schedules. Most of our subjects are students at the University, several of whom discover that they no longer have the time to participate in the experiments as the exam periods approach. Therefore, an enrollment of 20 subjects per task will ensure that sufficient statistics will be collected even if five of them do not complete the experiments.

b) **Gender and Age of Subjects:**
There are no gender-based enrollment restrictions; enrollment in the study is expected to cover multiple genders within the limitations imposed by the site population.

All subjects will be at least 18 years of age. Some experiments may be restricted to participants between 18-30 years of age, the period during which contrast sensitivity and a number of visual functions are optimal.

c) **Racial and Ethnic Origin:**
Every effort will be made to recruit a mix of subjects that is representative of the racial and ethnic mix of the populations being studied.

d) **Vulnerable Subjects:**
Individuals who are present at the university (such as students and employees) will likely hear about and sign up for this study, due to the university being the study site. Regardless of an individual's affiliation with the university, we will speak extensively about the procedures involved in the study, encourage any questions that a subject may have, and give everyone ample opportunity and assurance of their right to withdraw at any time if they no longer wish to participate.

2.2. Inclusion and Exclusion Criteria

a) **Inclusion Criteria:**
Subjects will be eligible for the study if they:

- Are at least 18 years old
- Speak English
- Have read, understood, and signed the informed consent form
- Have visual acuity in one of the following categories (as determined by a standard visual acuity screening by means of a Snellen chart or an online vision test):
    - Normal visual acuity (20/20 or better) without correction (i.e. without glasses or contact lenses) and no known visual deficits
    - Visual acuity ranging from -0.25 to -10 spherical diopters with correction, and no other visual deficits

b) **Exclusion Criteria:**
Subjects will be excluded if they:

- Are under 18 years old
- Cannot understand the experimental procedures
- Have visual deficits such as astigmatism or other vision defects

3. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

3.1. Method Of Subject Identification And Recruitment

Subjects will be recruited by means of flyers distributed around the University of Rochester River Campus and Medical Center and at libraries and supermarkets in the greater Rochester area with permission granted by each individual location, via digital advertisements posted on Craigslist, and via email through the subject pool maintained by the BCS department (RSRB#00021944). This study will also identify potential subjects for recruitment using the CTSI Research Participant Registry (RSRB#42818). Finally, we intend to use ResearchMatch to find potential matches and contact eligible individuals. When recruiting or scheduling subjects from the BCS Department List of Research Participants or the CTSI Research Participant Registry, we will follow the procedures outlined for access as approved by the RSRB for those protocols.

Subjects will be asked to self-report their eligibility, but as noted below, investigators will conduct a screening to ensure eligibility prior to conducting the consent process. Each subject may participate in any number of the experiments according to their schedules and availability. Each experiment may further consist of multiple experimental test runs. Contact and scheduling of sessions will occur via email or, if the subject prefers so, via phone. Additionally, subjects will also be allowed to participate in a follow up experiments where contact and scheduling will occur via the subject's previously preferred method.
Only those responding to an advertisement or recruitment tool will be recruited to the study; no individual will be approached and asked to take part in the study. This will minimize potential coercion, particularly in the student and employee population.

3.2. Process of Consent

a) Informed consent will be obtained by one of the investigators. The investigator will meet with potential subjects at least 24 hours before an experiment is due to start. The investigator will first explain the general goals of the research, the procedure, and the apparatus, as well as the experimental task and the number of sessions that the experiment will entail. If the subject is still interested in participating in the experiment, the investigator will obtain verbal consent to conduct a general vision screening test using either (1) the Snellen eye chart or an online vision test to ensure that the subject possesses normal uncorrected vision, or (2) an Autorefractor to determine glasses prescription. Failure to pass this test based on requirements will result in dismissal of the individual. If the subject passes the vision screening and is willing to continue, they will be asked to read the informed consent document and will confirm that the experimental rationale and protocol have been explained to them to their satisfaction. If subjects are interested in participating in the experiment and are completely satisfied with the explanations, they will come back to the laboratory on the day of the experiment, will read the informed consent document again, and will ask for further clarifications if there are aspects of the experiments which are still not completely clear. If they are willing to proceed, they will then sign the consent form and provide date of birth. Once the consent form is signed by the consenting subject, the investigator is required to finalize the document by providing their name. A date and timestamp of the consent will then be recorded.

   If physical consent is unfavorable, an eConsent option using REDCap will be provided. The eConsent process is developed under the Guideline for Using REDCap for Electronic Informed Consent:
   http://www.rochester.edu/ohsp/documents/ohsp/pdf/policiesAndGuidance/Guideline_REDCap_eConsent.pdf.
   The research team will obtain approval from Research and Academic IT for the REDCap-based electronic consent form. The IRB-approved consent form will be developed in REDCap, a secure, web-based, HIPAA-compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users. Potential subjects will participate in the consent process by eConsent Obtained Remotely with Required Remote Consent Process. It will be carried through video meeting with computers or smart phones, and the link to the eConsent will be emailed to the potential subject. The investigator must obtain verbal permission to send the eConsent via email. The permission request will state: "Because URMC can't control the security of email or text messages once we send them, we need your permission to text or email you. Do you want to receive the link to the eConsent via text or email?" The permission will be

documented. The investigator will ensure that the subjects have the opportunity to consider whether or not to participate and to ask questions during the video meeting. Subject signature and date of birth will be obtained using a typed signature and date. To authenticate that the individuals signing is that person, a known information security question is added on the signature page of the eConsent. The security question is "What is your favorite color", whose answer will be established during the video meeting with the subject. The person obtaining consent will be required to initiate the eConsent process from within REDCap for their name and a timestamp to appear on the study subjects signed consent form, which will be documented electronically on REDCap. Once the consent form is signed and submitted, subjects will be able to receive a print-out of the paper copy, download a pdf, and/or receive an email with a PDF attachment of the signed consent form.

If an experiment involves more than one testing session with a given technique (EEG or DPI tracking), no additional consent will be obtained for subsequent testing sessions (although subjects can always refuse to participate in these additional testing sessions). However, if the same subject returns for testing using a different technique than the one for which consent has been obtained, the subject will be re-consented for the new technique. The consent form will indicate that only some of the experiments will use EEG procedures; this will be highlighted during the consent process.

b) **Vulnerable Populations:**
During the consenting process, both verbally and in written statements, potential subjects who are students or employees at the University will be informed that there will be no penalties for non-involvement and no bonus for involvement relative to other study participants, and that they may discontinue involvement at any time without any effect on their student or employment status. Subjects who normally work for the Principal Investigator will be consented by a person (the study coordinator) to whom they do not report directly. As with all subjects recruited, we will let vulnerable subjects know at the beginning of the study that they are free to withdraw from the experiments at any time, and that there will be no repercussions for doing so.

4. METHODS AND STUDY PROCEDURES

4.1. Study Procedures and Assessments

All the experiments planned for this study will take place in the Active Perception Laboratory at the University of Rochester.

To ensure appropriate safety precautions when conducting in-person study procedures, the process for conducting in-person visits outlined in the Guidance for Human Subject Research will be followed. The study team will remain vigilant about any further changes that need to be made to study procedures if there are changes to the guidance. Guidance being referenced and followed by the study team will be accessed at the website below:
https://www.urmc.rochester.edu/coronavirus/coronavirus-research/guidance-for-researchers/human-subjects-research.aspx

Methods of data collection: In the experiments, participants will sit in front of a computer monitor located a less than a meter of distance and will analyze the content of images extracted from collections of natural and computer-generated scenes. Subjects will be asked to report verbally or by pressing keys on a keyboard on image characteristics such as the locations of the objects present in the scenes, their number and/or their identities. Some experiments will

involve a search paradigm in which subjects will have to report on the location and/or fine characteristics of a target element among a field of distracting similar elements, and/or visual discrimination tasks. The duration of the interval of time in which the image is maintained on the screen may be varied between few tens of milliseconds to several seconds. In a set of experiments, the eye movements performed by the subjects during the execution of the visual tasks will be recorded as explained below. In other experiments, the position of the displayed image will be suitably altered in real-time while subjects analyze it, to maintain stimuli at specific foveal eccentricities throughout the duration of a trial.

Details regarding experimental interventions: Although several non-invasive techniques have been developed to measure eye movements, only few of them are capable of detecting accurately the microscopic eye movements which occur during visual fixation. The most accurate and widely used non-invasive method to record microscopic fixation eye movements is based on the differences between light reflections from different layers of the cornea. Light rays striking the eye produce four reflections, called Purkinje images, from the front and rear surfaces of the cornea and lens. Either an analog or a digital Dual-Purkinje-Image (DPI) eye-tracker will be used to record the participants' eye movements. A DPI eye-tracker estimates the motion of the eye on the basis of differences between the first and fourth reflections of a low-energy infrared beam of light. By being in the infrared spectrum, such beam of light does not interfere with normal visual processing, and the subject can move his/her eyes freely. This device is a standard tool in oculomotor research (this is a commercial device; the intensity of the infrared beam is way below safety limits and does not pose any harm). The analog DPI has been used in the field for almost 40 years. In the PI's laboratory it has been used for longer than 10 years on a population of 100 subjects without ever causing any discomfort or complaint. The digital DPI eyetracker is a modern version of its analog counterpart, it uses the same principles to work but the motion of the eye is recorded by means of high-resolution cameras. To prevent head and body movements from corrupting the measurements, subjects' head will be restrained by means of a custom-made bitebar and a chin and forehead rest that are part of the eyetracker. Every experimental session will start with preliminary setup operations, which include: (a) positioning the subject optimally and comfortably in the apparatus; (b) tuning the eyetracker; and (c) calibrating the computer which controls the eye tracker. These procedures last a few minutes. Subjects are never constrained in the experimental setup for more than 20 minutes consecutively and can stop the experiment at any moment by simply moving their head away from the chin-rest.

Time required from each subject: The number of experimental sessions will vary based on the specific experiment. It will range from a minimum of three experimental sessions (two sessions in addition to the introductory one) to a maximum of 30 experimental sessions. On average we will run 5-10 sessions per subject. Subjects will be informed about the number of sessions that the experiment will entail at the time of their initial meeting with the investigator. Each experimental session will last approximately one hour and will consist of brief periods of data collection followed by frequent breaks in which the subject can relax. The length of breaks (i.e. the speed of data collection) will be determined by individual subjects. Different experimental sessions will be held on different days in order to ensure that subjects are not fatigued and continue to pay attention to the images displayed on the monitor. The approximate duration of the entire study for one subject is three years. If subjects participate in a follow up experiment, the time required from each subjects will follow the above, or it can be shorter.

Use of equipment: A computer connected with a custom developed system for gaze-contingent display (EyeRIS) is coupled with a Dual Purkinje Image (DPI) eyetracker. EyeRIS is a system to interface the DPI eyetracker with the PC enabling data collection. EyeRIS is not a separate

device. This system has been extensively tested and it has been proved to efficiently allow for gaze-contingent manipulations of visual stimuli (Santini et al, 2007; Rucci et al, 2007; Poletti et al, 2013)**.** As subjects perform the visual tasks an eyetracker will record where they look. The DPI eye-tracker used in this research is a non-invasive device which monitors changes in the positions of reflections of light from the cornea and the lens. It provides accurate estimate of the direction of gaze over a large, two-dimensional visual field without any attachment to the eye. There will be no physical attachment between the subject and the device. Visual stimuli are presented either on a CRT display or on a fast refresh-rate gaming monitor. Eye movements data are recorded digitally and saved in the experimental computer.

For experiments involving EEG measurements: The following procedures will be used:
First, we measure the subject's head circumference with cloth measuring tape to determine the size of the cap to use. We have two cap sizes which are each equipped with elastic bands inside; most subjects will fit into one of those two caps. A clean, absorbent towel is placed around the subject's neck and shoulders, after which the electrode cap is placed on the subject's head.

Once the cap is securely on the subject's head, each hole in the cap is filled with a small amount of gel using a blunt-tip plastic needle and a syringe. (The company's recommended gel is Parker Signa gel, but all other medically available gels for EEG can be used with the system.) The electrodes are then fit into each hole in the cap, similar to closing a snap button. There are several additional flat-type sensors that are applied to points on the subject's face to record signals from blinks and jaw movements, so that those may be more easily filtered out of the data.

We may take pictures of the cap after it has been placed on the subject's head and/or simple measurements of the size of the subject's head and the placement of the sensors for use as reference later on. These photos and measurements may be shared in a secure fashion with members of the study team to help data analysis and interpretation.

Bundles of wire from the electrodes are connected to the amplifier box. The computer will automatically check for any loose connections, which will be corrected by applying more gel or adjusting the seating of the electrodes on the scalp. There are 64 electrodes total in the array.

This preparation process is expected to take around 30 minutes. After the EEG preparation is complete, subjects proceed as normal with the DPI portion of the experiment, which takes up to an hour.

At the conclusion of the experiment, the cap is removed from the subject's head. Subjects are provided with shampoo and a clean towel that they can use to wash their hair in one of the lab sinks if they want to clean up. Some of the electrodes—particularly the ones applied to the face—may leave small temporary red marks; subjects will be made aware of these marks as well as their temporary nature.

After subjects are finished, the Sensor Net is cleaned and disinfected. It is rinsed in fresh tap water and placed in disinfectant solution, followed by an additional rinse cycle. Any batch of disinfectant solution will be reused for the length of time recommended by the solutions' manufacturer.

The subject's part in an EEG experiment is expected to take no more than 2 hours.

For the OCT measurement: During one of the later study visits, subjects will be asked to sit for the OCT test session. For this test, the subject will be asked to sit at the machine and place their chin on a chinrest. The OCT machine will then scan their eye non-invasively. The scan takes 10 to 15 minutes to complete. The session will be included in the study visit.

For the Autorefractor measurement: Subjects taking part in studies allowing for glasses prescriptions will be asked to sit for the Autorefractor test during their first session. In the Autorefractor test, the subject will be sitting in front of the machine, with their chin on a chinrest, and forehead against a bar. The Autorefractor will then scan their eye non-invasively. The procedure takes 5-10 minutes to complete.

4.2. Costs to the Subject

Subjects will bear no cost for participating in any of these studies. All costs of conducting the research will be borne by the investigators using monies from the funding agencies described on ClickIRB.

4.3. Payment for Participation

Subjects will be paid a $15.00 per hour for participation in eye-tracking-only experiments; they will be paid $20 for participating in the EEG experiments. They will be paid in cash after each individual experimental session, or they will be paid in cash or by check after completing all experimental sessions.

5. SUBJECT WITHDRAWALS

Subjects will be advised during the consent process that they have the right to withdraw from the study at any time without penalty. Subjects may be withdrawn from the study without their consent if they cannot keep appointments or if they cannot complete study activities. Subjects who withdraw or are withdrawn from the study will still receive payment for participation.

6. RISK/BENEFIT ASSESSMENT

6.1. Risk Category

These experiments involve minimal risk.

6.2. Risks to Subjects

The only minor discomfort from the procedure will be the necessity to sit still during the course of the experiments. A chin and forehead rest will be used to minimize the subject's discomfort and reduce the range of involuntary body movements. We will ensure that subjects sit in an ergonomically sensible way so that they will be physically comfortable during the course of the experiment and focus on the visual task. Sessions will also be kept short. A typical experimental session of one hour will be divided in batches of trials each lasting no longer than 15 minutes, with breaks in between batches in which the subjects can stretch and walk around if they to.

In the unlikely event that participants perceive the computer monitor to be too bright, they will be instructed to look somewhere else and inform the investigator to lower the brightness of the monitor. If at any moment, subjects do not feel comfortable, they will be instructed to lift their head from the chin rest and the experimental session will be suspended. An investigator will be at all times in the room with the subject to ensure that the experiment is correctly executed and answer any questions the subject may have. The subject's participation in the study will be suspended at any time if he/she so desires.

It has been anecdotally reported that an extremely small percentage of subjects have mild allergic reactions to the gel after having the electrode cap on for a number of hours. We do not anticipate this being a problem with the anticipated duration of these experiment sessions. However, if any subjects report discomfort, we will immediately stop the experiment, remove the cap, and advise subjects to wash or wipe their head. All subjects will be advised to wash the gel from their heads immediately after completing the experiment.

The OCT and Autorefractor scans presents no additional risk to subjects.

The other potential risk to subjects in this study is loss of privacy. This is discussed below, under "Confidentiality of Data and Information Storage".

If eConsent and eSreening are used, subject information will be transmitted by e-mail, which has a number of risks that subjects should consider. These include, but are not limited to, the following:

a) E-mail can be circulated, forwarded, stored electronically and on paper, and broadcast to unintended recipients.
b) E-mail senders can easily misaddress an e-mail.
c) Backup copies of e-mail may exist even after the sender or the recipient has deleted his or her copy.
d) Employers and on-line services have a right to inspect e-mail transmitted through their systems.
e) E-mail can be intercepted, altered, forwarded, or used without authorization or detection.
f) E-mail can be used to introduce viruses into computer systems.

6.3. Benefits to Subjects

Subjects will be given a free optometric screening both prior to and at the conclusion of testing. They will receive no other specific personal benefit.

6.4. Alternatives to Participation

Participation is entirely voluntary. The subject may choose to not participate at any time.

7. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

To protect subject identity, the names of all data files will not have any reference to the subject name. A number label randomly associated to the subject will be included in the structure name and will enable finding of the data from a particular subject in different experiments. Data originating from different subjects will be recognizable simply because they belong to different structures and have different reference numbers.

Subject identity will be kept strictly confidential. Subjects will be assigned a unique code (a random sequence of letters and numbers) for identification purposes. This code will be used in identifying subject data files and in all reports, publications, and references to the subjects. The correspondence between codes and subject's names will be stored in a single mastercode file maintained by the PI on a password protected flash drive. This flash drive will be kept by the PI. The code sequence will be shared by the PI only. As soon as subject has completed the experiment, their entry will be removed from the mastercode file, so that any relationship between the identification number and the subject identity will be permanently destroyed.

The subjects' contact information will be kept by the PI in the same key file where identification codes are stored, and will be shared with the relevant research assistant(s) during the period in which

the subjects participate in the experiments.

Demographics data collected for the purpose of reporting demographics distribution to the RSRB and to the funding agencies will be stored in the REDCap system at URMC (https://redcap.urmc.rochester.edu/redcap/). REDCap is a secure, web-based application for building and managing online surveys and databases. All information entered into the REDCap system is stored in a local data center at the University of Rochester and all web-based information transmission is encrypted. REDCap is recommended to University of Rochester researchers by the URMC Research Privacy Officer and the Office for Human Subject Protection.

Participants will have the option of filling out a paper demographic form in the lab which will later be entered into REDCap or filling the form out electronically via a link in an email which will be sent to them before coming to the lab for the experiment.

In order to facilitate calculating enrollment for RSRB Continuing Reviews and NIH Progress Reports, we will also maintain a list of experiments under this protocol in REDCap and each demographic form will be associated with the experiments the subject has participated in and the dates of participation.

Prior to data being downloaded for analysis for RSRB Continuing Review or NIH Progress Reports it will be automatically de-identified by the REDCap system. Principal investigators and study coordinators will be able to enter data into the system and have access to all demographic and study data after it has been entered. Research assistants will be able to enter demographic information and study information but will not have access to data.

The data will be destroyed after the retention dates specified by the RSRB and NIH, whichever is later. If a subject chooses, they have the right to ask for their demographic information to be modified or destroyed before the elapsed time.

Study data will be stored in files on computers in the PI's laboratory. Since we will use codes to map subjects' identity, all files will be anonymous. The computers where data will be stored are routinely backed-up by the University of Rochester. The investigators listed above will be responsible for data storage and protection. Data will be kept de-identified until the study is complete.

8. RESEARCH INFORMATION IN MEDICAL RECORDS

None of the research data will be included in the subject's medical record.

9. DATA ANALYSIS AND DATA MONITORING

9.1. Planned Statistical Analysis

In this project, all data will be analyzed in MATLAB, a standard widespread software in the field. Recorded signals will be stored in ASCII files, a format easily readable by MATLAB as well as by most other data-processing toolboxes. A MATLAB metastracture will hold the data from all trials for a given subject in a given experiment. For each trial, this structure will include the original recordings of eye movements (the actual samples given by the eye-tracker, which has a digital output) and the location of gaze on the display, which will be calculated based on a calibration procedure. Data will be analyzed using standard statistical methods, such as z-tests, t-tests, and ANOVA. Post-hoc adjusted analyses will be carried out. Data from the EEG will be stored in the form of electrical activity over time at each electrode site (64 sites per subject) and kept for later data analysis. The relative concentration changes of electrical activity collected from the EEG will be analyzed throughout the experiment. These changes

will be correlated with looking behavior as recorded by the DPI system.

9.2. Data and Safety Monitoring

N/A