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Assessment of saccadic eye movements in healthy subjects using consumer-grade mobile devices

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ASSESSMENT OF SACCADIC EYE MOVEMENTS IN HEALTHY SUBJECTS USING CONSUMER-GRADE MOBILE DEVICES

by

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ABSTRACT

Assessing eye movement features may provide insight into neurological health, inform diagnoses, and guide clinical intervention. The potential to utilize saccadic eye movement latency is especially promising as a clinical biomarker in identifying and treating neurodegenerative disease. Artificial intelligence and deep learning technology have improved the feasibility of eye-tracking methodology and scalability in research studies. Tablet and smartphone-based tracking equipment have been shown to provide quantitative data of comparable accuracy to more costly, special-built equipment while reducing cost and complexity in experimental procedures. Establishing an efficient and accurate measurement tool to aid the detection and tracking of diseases may benefit the development of comprehensive treatment and monitoring strategies. This study, therefore, seeks to examine oculomotor function through saccade latency and error rate in healthy adults with respect to age, demonstrating a mobile device's efficacy in assessing subtle eye movements and establishing a dataset upon which to guide further investigation.

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LIST OF ABBREVIATIONS

AD — Alzheimer’s Disease
ANOVA — Analysis of Variance
CN — Cranial Nerve
Ms — Millisecond
PD — Parkinson’s Disease
PSP — Progressive Supranuclear Palsy
SEM — Saccadic Eye Movement
VOR — Vestibulo-Ocular Reflex

INTRODUCTION

The mechanisms by which the brain controls sensorimotor functions are a prominent area of clinical research. Oculomotor function refers to both voluntary and involuntary movement of the eyes, particularly when presented with stimuli or visual tasks (Engbert 2006). Voluntary eye movements such as saccades, smooth pursuits, and vergence shifts are critical in examining oculomotor performance to study the varied and complex physiological roles involved in fixation and tracking visual cues (Lappi 2016). In conjunction with higher-level cognitive processing, the brain responds to visual stimuli via signals carried through three cranial nerves that control the extraocular muscles to respond to stimuli and execute somatic, voluntary tasks (Joyce 2021). Analysis of subsequent eye movement data can be analyzed to provide critical information regarding oculomotor function and neurological health.

OCULOMOTOR FUNCTION

NEURAL CONTROL

Of the six extraocular muscles, four are innervated by the oculomotor nerve, CNIII, with the two remaining innervated respectively by the trochlear nerve, CNIV, and abducens nerve, CNVI (Sanders 2009). Together, these cranial nerves support the movement of the eyes and allow for motion along the horizontal, vertical, and torsional (diagonal) axes. Whereas gaze shifting along the horizontal axis is manipulated by the lateral rectus and medial rectus muscles, movement along the vertical and torsional axes corresponds to the remaining superior rectus and superior oblique as well as the inferior rectus and inferior oblique muscles (Bae 2013). Furthermore, these six muscles operate in antagonistic pairs, functioning in tandem to contract or relax, thereby drawing the eyeball in opposite directions (Kruchinina 2018).

Central control of eye movements stems predominantly from the frontal and parietal lobes (Pierrot-Deseilligny 2004). However, perception of vision is transmitted independently by way of the optic nerve, CNII, and relayed to the primary visual cortex, located in the occipital lobe, which plays the predominant role in processing visual information (De Moraes 2013). The integration of this information with interpretation, conscious perception, and the detection and tracking of stimuli are accomplished through neural circuitry involving several regions throughout the cerebral cortex, cerebellum, and brainstem (Munoz 2002). These areas serve distinct roles concerning voluntary eye movement, with direct and indirect impacts on oculomotor function stemming from neurological disorders, diseases, or injury.

CLINICAL EYE ASSESSMENT

Normal eye movement is dependent mainly on the paired fixation of the eyes on objects of interest, stabilized gaze during head movement, and proper alignment (Schor 2011). These features are most typically measured in clinical settings with bedside assessments to test cardinal eye movements and the vestibulo-ocular reflex, or VOR, involved in stabilizing movement in terms of axis and distance (Ting 2014). In addition, muscle imbalances may be measured via shining light on the cornea, stimulating an involuntary corneal light reflex resulting in an observable, central reflection (Curnyn 2003). Similarly, each of the six extraocular eye muscles may be examined together by observing cardinal fields of gaze, as an individual is observed when presented with an H-pattern to track visually without head movement (Han 2022). Abnormalities in accomplishing these tests may indicate lesions, nerve damage, or eye trauma. As such, clinical eye examination tests prove especially useful in identifying such instances by observing strabismus, or misalignment issues, and nystagmus, or involuntary, rhythmic movements that result from vestibular disorders (Choi 2017 Traboulsi 2008). Disconjugate, unpaired eye movements may further indicate potential lesions, trauma, or neurodegenerative illness (Samaduni 2015).

VOLUNTARY EYE MOVEMENTS

Three eye movements are employed to test oculomotor ability in initiating rapid actions or sustaining gaze with focused target tracking. These include saccadic eye movements (SEM), smooth pursuits, and vergence (Alvarez 2010). Saccadic eye movements and smooth pursuits are methods by which humans can voluntarily shift their gaze with respect to an object in one's field of view (Santini 2016). Smooth pursuits refer to the eye's ability to remain fixated on a moving target, whereas saccades refer to the rapid movement of both eyes made between two independent states of fixation on a target of interest (Otero-Millan, 2018). On the other hand, Vergence shifts are involuntary adjustments made to accommodate the object's distance relative to the observer (Brune 2018).

Because smooth pursuits require ongoing modification via visual feedback while tracking a target, this process offers greater clinical insight into functional integration for multiple brain regions when presented with slower, sustained tasks (Buizza 2021). Within the brain, the frontal lobe and superior colliculus support smooth pursuits, particularly in identifying a target as well as initiating and providing direction to the eye movement. However, several regions of the brain and brainstem are involved in sustaining the action, controlling velocity via extraocular muscles, and maintaining accurate focus (White 2021). While saccadic movements are executed distinctly from slower, prolonged tracking movements, smooth pursuits function simultaneously with involuntary stabilization responses such as optokinetic nystagmus and ocular following response (Lencer 2019). As such, smooth pursuits are not as isolated a measure as saccades.

In contrast, vergence shifts refer to the movement of the eyes as they rotate toward or away from each other (Demer 2019). The eyes thus converge when observing a target closer to the viewer and diverge as a target moves further away from the viewer (Yaramothu 2018). Dysfunction in vergence often arises in visible symptoms such as seeing overlapping, duplicate, or blurred vision and may result from imbalances in the extraocular muscles, disorders in vestibulo-ocular signaling, and nerve lesions (Goering 2021).

The eyes are not truly at rest at any moment. Instead, frequent saccadic movements occur multiple times a second, adapting continuously to gaze fixation points (Binda 2018, Hutton 2008). Unlike smooth pursuits, these movements are considered independent of processes that contribute to gaze stabilization, such as VOR corrections (Colagiorgia 2017). The temporal delay between fixation points is referred to as saccade latency. Saccades are among the fastest motor movements and are noticeably impacted by pathological disorders (Morales 2021). Saccade latency may thus be measured and employed as a biomarker, or clinical indicator, to gain insight into oculomotor function and neurological health (Marandi 2019).

Intentional saccade execution relies largely on regions of the brain that support smooth pursuits, including frontal eye fields located in the frontal cortex and the superior colliculus (Hanes 2001). In addition, six additional eye fields are implicated in saccadic movements, two of which remain in the frontal lobe, with the three remaining located in the parietal lobe (Gaymard 2012). Together, these brain regions support the neural circuitry and pathways that accommodate proper saccadic movement and are thus of clinical interest in experimental studies.

Prominent regions affecting persons with neurodegenerative diseases such as Alzheimer's Disease (AD), Progressive Supranuclear Palsy (PSP), and Parkinson’s Disease (PD) often include simultaneous effects on motor function of the eyes (Garbutt 2008). Oculomotor performance may thus be tested via voluntary eye movements to provide insight into the status of implicated brain regions if neural lesions or atrophy may be expected. Damage to the frontal and parietal lobes and the brainstem are of particular interest. Within PD, for example, regions such as the subthalamic nucleus located within the thalamus lead to somatomotor symptoms producing physiological tremors, gait issues, and decreased oculomotor function. (Follett 2010).

Implementing eye-tracking assessments allows for greater clinical insight, as improvement or deterioration of oculomotor function may indicate broader treatment results and offer a method of longitudinally monitoring disease course within patients. Similarly, changes in oculomotor function may be utilized as a predictive tool in treating overlapping somatomotor symptoms (Bueno 2019). The information gained via eye tracking methods can guide additional interventions involving pharmaceutical or surgical treatment and encourage patient benefits such as reduced medication, long-term healthcare costs, and symptom severity (Dams 2013). The information gained via saccade latency and corresponding eye movement metrics thus offers significant value in guiding the treatment of neurological disorders while providing a safe method to examine patients long-term.

EYE-TRACKING METRICS

SACCADIC EYE MOVEMENTS

Saccades have been studied extensively in experimental and clinical environments, with latency offering a practical measure for investigating the neural circuits and oculomotor mechanisms accounting for reaction times (Leigh 2004). Direct activation of the extraocular muscles occurs via concerted activity between regions in the frontal, parietal, and occipital cortices to produce sufficient movement initiation, determine correct angular direction, and achieve adequate velocities to ensure focus on the targeted stimulus (Munoz 2002). Visually guided saccade tasks can effectively produce specific saccadic movements with which various metrics can be examined (Munoz 2004). As such, eye-tracking studies may be designed to amplify the observability of desired characteristics through specially tailored tasks.

Saccadic movements are categorized by the nature in which they are stimulated, along with the intended nature of the reaction (Kojima 2010). Eye-tracking studies often examine multiple variables via visually guided saccades in which the subject is presented with a target stimulus upon which to fixate. Pro-saccades are well documented, in which a visual stimulus is shown in the field of view and accompanied by a task of fixation by moving the eyes to focus on the stimulus (Bittencourt 2013). Anti-saccades, on the other hand, are characterized by movements away from a stimulus presented within the field of view (Walker 2000). Tasks that produce anti-saccades naturally encourage error rate, as successful actions entail intentionally inhibiting involuntary, reflexive saccadic movements (Koval 2004). The location of selected stimuli within fields of view is generally randomized to mitigate predictive techniques in subjects. Instead, predictive saccades can be studied using predetermined patterns with which stimuli are presented, along with slower, memory-guided saccades that may be studied via location recall of a previously provided stimulus (Bittencourt 2013). These patterns are especially useful in examining psychiatric disorders, in which latency may reflect decreased cognitive performance as opposed to oculomotor function alone (Smith 2022). Thus, eye tracking visual tasks can be selected to produce specific saccadic movements, target deficiencies and designed to fit research goals.

SACCADE VARIABLES

Saccade latency serves as a primary measure to study oculomotor function, representing the duration of delay between initiating a saccadic movement and fixation on a target (Kerber 2006). Additional metrics provide further functional insight and vary among individuals, particularly in the case of pathologies and physiological disorders. All forms of saccadic movements can be studied by latency duration along with distance, velocity, and error rate (Imaoka 2020). Distance is represented as amplitude, reflecting the change in angle that occurs as the eye travels from the fixation point at initiation of the saccade to the fixation point at the end of the movement (Paeye 2011). Saccades with larger amplitudes, therefore, correspond to more significant directional changes in focus and distance traveled.

Saccadic velocity, or angular speed of the movement between two fixation points, directly correlates with saccadic amplitude (Muhammed 2020). While the maximum saccadic amplitude within the ocular range of motion extends to 90°, natural saccadic movements typically fall well below this value (Gibaldi 2021). At peak velocity, angular speeds may reach 700° per second for larger saccades (Gibaldi 2021, Land 2006). However, rates begin to plateau at 500-600° per second at amplitudes of 15° (Dombrowe 2018). Thus, most saccades in regular movements fall within this range as tasks requiring higher amplitudes are accommodated with the directional change of the head (Albano 1996).

When studying pro- and anti-saccades, the error rate is an especially useful metric in assessing accuracy. For example, in anti-saccade tests, a stimulus is presented in peripheral vision, with the task being to look in the opposite direction. These tasks require resisting reflexive pro-saccadic movement towards the stimulus and can therefore produce incorrect directional movements in subjects (Mack 2020). Inhibiting this response stems from functions within the prefrontal cortex, and thus cognitive or neurological impairments within this region often lead to heightened error rates or decreased accuracy in subjects (Karpouzian-Rogers 2020). Similarly, impairments throughout the frontal or parietal lobes may reflect in other saccadic metrics such as delayed reaction time, extended latency, and diminished angular speeds (Douglass 2018).

TRADITIONAL EYE-TRACKING METHODS

MEASUREMENT TOOLS

Devices used to measure eye movement have seen significant development in recent decades, with several established methods being standardized for experimental or clinical applications. The most reliable form of experimental testing utilizes a search coil magnetometer, a contact lens implanted into the sclera that induces distinct, measurable electric currents in response to changes in horizontal and vertical eye position (Zhao 2018). These currents are encoded and interpreted in a manner that can be analyzed by researchers. However, this method requires invasive intervention and is therefore limited in its clinical applications.

The use of non-invasive infrared eye tracking devices has thus been implemented with success for human oculomotor studies (Schmitt 2007). Video-based and photo-based methods utilize infrared lighting to capture reflections upon physical eye features such as the cornea, pupil, iris, and sclera (Hutton, 2019). Electro-oculography eye movement measurement has also served to measure eye movements using highly sensitive electrodes measurements applied to the face surrounding the eyes (Jia 2019). Electrical potential recordings, combined with techniques that either track or stabilize head position, allow researchers to isolate eye rotation-derived electrical measurements (Bhatia 2020).

Video recordings are instrumental in that they can be played back with increased frame captures and a greater yield of data. Methods that utilize video and photo-oculography in more recently developed research applications sufficiently rely on corneal reflections (Li 2021). These techniques, in combination with headrests or head-tracking devices, yield data using high-speed camera equipment and screen-based setups to present eye movement tasks (Ehringer 2019). Subsequent image processing allows greater adaptability in research applications, such that video-based data may be collected in individual sessions and analyzed after testing procedures are completed. With further development extending to wearable sensors, headsets, and non-infrared light-based video capture, data quality must meet standards established by prior techniques (Valliappan 2020). As such, ensuring that novel eye-tracking technologies provide comparable data quality to that of traditional equipment remains necessary as advancements are made in the field.

HARDWARE LIMITATIONS

Given the involved processes and specialized equipment used in traditional eye-tracking experimental setups, several limitations arise that prevent overall scalability and accessibility for clinical use. The application of search coils, while highly accurate, are costly, introduce notable risk in the implantation, and can therefore not be reasonably expanded into routine patient assessments (Irving, 2003). Additionally, given the confounding factors stemming from head movement in infrared-based methods and traditional oculography setups, eye-tracking is performed with subjects seated while resting their chin on a headrest to restrict movement (Cognolato 2018). This can pose issues for certain patient groups and adds greater complexity to equipment requirements (Kok 2017).

Headrest-based setups are typically accompanied by the use of high-precision cameras, monitors, and computer systems to ensure accurate measurements. However, these systems are costly and can only be implemented within small cohorts. Similarly, the level of complexity decreases efficiency in terms of experimental session times, study location flexibility, and rely on patient travel to undergo testing (Lai 2019). The cost of commercial research eye-tracking cameras alone average $50,000, with high-fidelity units such as the Phantom v25-11 reaching prices of approximately $100,000 (Bott 2017, Lai 2018). The use of these systems may further require modified examination rooms that restrict use for other purposes when in clinical environments, require additional training to operate, and can reduce the potential for longitudinal studies given the limited adaptability in their applications.

Data processing introduces additional complexity in integrating compatible programming software and analytical tools. Thus, the practices used in eye-tracking studies vary, with drawbacks in the consistency of experimental designs being problematic for long-term clinical implementation (Carter 2020). Realizing the potential for eye tracking as a clinical tool with accessible biomarker metrics, therefore, requires innovative solutions that remedy the limitations regarding accessibility, scalability, and adaptability in traditional testing methodologies.

TECHNOLOGICAL ADVANCEMENTS

MOBILE DEVICE-BASED EYE-TRACKING

Research into alternative technologies has improved the feasibility of eye tracking studies, the potential for eye movement-based biomarkers, and scalability in longitudinal studies. Beyond screen-based infrared techniques, the use of cameras in webcam eye trackers, wearable sensors and headsets, and monitors have brought significant advancements for experimental design (Semmelmann 2018). Smartphones and tablets are especially promising in offering solutions to equipment limitations, given the integration of a screen, camera, adaptable software packages within a single consumer device (Lai 2018). This study aims to expand on these developments with proof of concept applications in mobile device-based data collection and video-oculography.

Prior research has demonstrated that smartphone-based tracking apparatuses provide quantitative data of equal accuracy to that of more costly, special-built equipment while removing the need for fixed headrests (Kok 2017). Mobile devices can also be more easily transported and adapted to clinical scenarios, thereby allowing patients with debilitating neurocognitive or somatomotor disorders to provide eye-tracking data without the need for uniquely trained personnel in specialized research settings (Lai 2020). Eye movement measurements may thus be integrated into clinical assessments with greater ease, aiding efficient setup and application to improve access to oculomotor function data.

Eliminating the requirement of a headrest via technological advancements in software further supports the implementation of newer tablet and screen-based eye-tracking methodologies. Additional solutions to eye feature infrared illumination have progressed with built-in software enhancements to video recordings, improving image quality upon which processing can be performed directly from mobile device front-facing camera data with sufficient quality (Kraftka 2016). Prior studies using eye tracking software packages have demonstrated the capacity to collect saccadic movement data in healthy subjects while using consumer-grade iPhone 6 devices (Lai 2018). Using a device that integrates a display, a camera, and the necessary software via a mobile app overcomes several barriers stemming from traditional equipment and may significantly strengthen research efforts in eye-tracking studies.

The application of automated image classification algorithms resolves several issues, typically complicating eye-tracking methods while retaining default consumer hardware settings. Applying a deep-learning computational model, the gaze of a subject can be approximated in video recordings while automatically addressing visual interference. This has been shown to yield data with negligible difference in quality to that captured with a high-speed camera and perform equally in the absence of a chin rest or physical head stabilization techniques (Lai 2019). This is beneficial for multiple reasons, chief among which is that head movement as a confounding factor may be removed via computer processing. Similarly, this eliminates potential causes of discomfort in patients or research participants resulting from prolonged contact with resting surfaces. By managing interference caused by eyeglass reflections via encoded processes, artificial intelligence-based methods also allow for a broader population to be studied without issues associated with power correction. With advancements in computational processing methods, this method suggests a possibility to expand the scope in which underlying disease progression symptoms can be identified and monitored through subtle changes in oculomotor performance. These advancements in testing methodology, therefore, suggest the useability of phones and tablets in eye-tracking applications may deliver improved flexibility and use-cases to researchers and clinicians in comparison to those previously available using traditional eye-tracking techniques.

CLINICAL APPLICATIONS FOR EYE-TRACKING

MONITORING NEURODEGENERATIVE DISEASE

Neurodegenerative diseases represent a broad category of illness characterized by progressive loss of function and death of nerve cells within the brain and nervous system (Amor 2010). Specific disorders arise via patterns of disease course and symptoms implicating motor and cognitive function. Relevant diseases include AD, PD, and PSP (Barnham 2004). Given the overlap in regions of the brain impacted by such diseases with those involved in oculomotor function, disease progression may yield detrimental effects on measures such as saccade latency.

With various mechanisms of genetic and subcellular degradation pathways, research into neurodegeneration has produced therapeutic treatments to reduce symptom manifestation and degenerative rates (Cuny 2012). However, such diseases remain incurable, therefore necessitating advanced methods to track progress both in terms of disease progression and therapeutic improvement. The monitoring of SEM among patients treated for PD, for example, has been utilized successfully to measure post-operative progress in oculomotor function and symptom reduction (Fawcett 2010).

Monitoring the improvement of somatomotor symptoms is often performed using various methods, including wearable sensors, neurophysiological signals, and tools and scales designed to assess disease severity (Heijmans 2019). Technological advancements represent a growing area of focus due to the increasing ability to measure cognitive function with natural disease courses and following treatment. Tools designed to assess human saccadic eye movements and neuromotor ability show considerable promise. Following a target stimulus depicted on a computer monitor, rapid, simultaneous movement of a subject's eyes towards or away from a stimulus can provide evidence for neurological performance via pro- or anti-directional movement, peak velocity, and timed oculomotor latency, or saccade, of eye movement post-stimuli (Hutton 2008). Performance in eye reaction times subsequently allows for clinical quantification of disease progression among individual patients and may additionally support biomarker prognosis and differential diagnosis.

SACCADE LATENCY AS A CLINICAL BIOMARKER

Oculomotor performance demonstrates significant promise as a means of the detection of underlying neurocognitive disease, monitoring progression, and guiding clinical treatment. Eye movement features have been shown to differ significantly between healthy individuals and those diagnosed with neurodegenerative disease (Anderson 2013). Greater accessibility via mobile device-based video oculography permits heightened scalability in eye-tracking-based testing while addressing the limitations of traditional techniques. Thus, with proper implementation, saccade metrics such as error rate may prove especially useful as a clinical biomarker with ongoing technological advancements and growing feasibility.

Building upon the foundation of traditional techniques, increasing the availability of eye trackers to researchers would significantly strengthen efforts to deepen the medical understanding of oculomotor function, performance metrics, and predictive biomarkers for neurodegenerative diseases, motor neuron disorders, and ophthalmological pathologies (Crutcher 2009). Growing the research base for this area of focus would serve to strengthen systems aiming to treat symptoms following their detection and prevent further cognitive decline with timely intervention. Comparing individual patient performance to baseline population measures and utilizing longitudinal data may provide greater insight as to subtle changes and underlying disease development (Bueno 2019). Additional factors influencing oculomotor performance metrics that occur throughout the day related to fatigue may additionally guide testing procedures and consistency of data collection (Hopstaken 2016).

Developing methods to detect abnormalities subtly impacting voluntary saccadic movements would serve to deepen the understanding of broader diagnostic clues, distinctive eye movement features associated with specific illnesses, and potential relationships between identifiable changes and cognitive status.

Introducing innovative solutions to incorporate eye tracking into practice extends beyond in-person clinical sessions, as patients may undergo self-directed testing sessions using consumer devices and onboarded software (Saavedra-Pena 2018). Incorporating these tests into presymptomatic or at-risk persons may potentially supplement clinical examinations and disease prevention efforts. This methodology may be applied to various forms of neurodegenerative illnesses with the potential to compare oculomotor patterns and performance changes following invasive or pharmaceutical treatment efficacy (Lohnes 2012). Establishing an accessible and accurate biomarker tool to assess disease state and track progression would benefit clinical care and associated research efforts for novel treatment strategies. This study thus aims to test a mobile-device-based eye tracking tool in assessing saccadic eye movements and yielding sufficiently high-quality data for analysis.

SPECIFIC AIMS

This study aims to demonstrate a mobile device-based tool's ability to measure subtle eye movement features across time for their application as clinically relevant biophysical markers. The eye movement feature of interest is saccade. Saccade refers to the time delay between the appearance of a visual stimulus and when the eye starts to move towards said stimulus presented on a display. Both pro-saccades, towards the stimulus, and anti-saccades, away from the stimulus, will be tested, and compared with respect to subject age to determine potential correlations. Evaluating eye tracking performance within a normative data set of healthy adults will provide insight into the nature and variability of oculomotor performance with respect to age. These findings will support improvements to mobile devices as a means of accurate and accessible eye-tracking data collection. Finally, the results of this work will guide future research of these biophysical markers in patients, serving as a baseline for future research.

METHODS

PARTICIPANTS

This study focused on adult eye movement physiology, and thus subjects under the age of 18 years old were excluded from eligibility. Participants were all volunteers without a medical history of neurological disease—any history of a cognitive condition that impaired eye movement patterns resulted in exclusion from the study. Similarly, disorders affecting ocular motion such as nystagmus or strabismus were reviewed upon screening to ensure appropriate exclusion. Healthy adults were recruited from within the general population as well as the student population of the Massachusetts Institute of Technology in Boston, Massachusetts. Recruitment was performed via distributed flyers and word of mouth. English and non-English speakers were both eligible to participate, and verbal informed consent was collected in either circumstance. In cases in which individuals did not speak English, informed consent was obtained via a witness capable of understanding the subject's language to sign forms confirming the provision of appropriate participant information. Verbal explanations were provided to subjects in the case the literacy posed issues in procedural understanding, with witnesses similarly present to sign forms confirming correct information and consent was provided. Participation was additionally limited to healthy adults as those with cognitive impairment were not eligible, given the potential confounding effects on eye movement function. Elderly participants were eligible, with an assessment of cognitive impairment was performed via the testimony of care providers or at the discretion of study personnel based on a participant's ability to follow through with the process of informed consent and eye-tracking task instructions.

Questions asked of participants during recruitment were limited with

No compensation or reimbursement was provided to subjects for participating in the study. Additionally, no risks were identified that might stem from participation, given that the eye-tracking equipment utilized was non-invasive and unobtrusive. However, given the non-zero risk in privacy in cases such that video recordings or health information was inappropriately released, all information was de-identified and encoded such that personal data cannot be linked to research data during analysis, storage, or archival purposes. In the case that participants experienced discomfort or became ill, they were withdrawn from the experiment. Additionally, if any changes arose in patient health during the study, consent was re-acquired if appropriate.

METRICS EXAMINED

Demographic data collection for all participants was limited to age and gender and gathered via a brief medical questionnaire prior to eye-tracking sessions. Additional information collected on subjects during intake included handedness, general health status, and neurological condition according to inclusion criteria requirements. Eye-tracking tasks gathered data via video recording on Apple iPad tablets, with the onboard software automatically tracking and measuring saccadic movement data figures. This data was compiled into four eye movement variables for analysis, including mean pro-saccade, mean anti-saccade latency, pro-saccade error rate, and anti-saccade error rate. Distributions for individual saccadic movements were not assessed for the purpose of this study, as comparisons can be thoroughly conducted via average latency measurements.

EYE-TRACKING PROCEDURE

Eye-tracking data was collected via video recordings performed on Apple iPad devices that tracked gaze direction and eye movement patterns in individual sessions using a mobile app designed for the study. Participants were briefed on the study's purpose, disqualification criteria, and experimental protocol before beginning. Eye tracking was conducted in one of three ways. First, the subject would directly interact with the study staff in person for recording. This was the predominant and preferred method, with minimal risk of data quality errors. Secondly, the study staff may instead provide the subject with an iPad by either mailing a device to the participant or hand-delivering the iPad to the subject and subsequently retrieving it in a pre-arranged manner. Finally, the alternative method included the subject downloading the study app on their own compatible iPad device to provide data remotely. In instances where data was provided remotely, participants were provided a unique download link, instructed on how to ensure secure data upload via the app and requested to delete the app following session completion.

Once seated in front of an iPad display, the device was adjusted for distance and enabled for video recording through the study app that utilized the front-facing camera. Chinrests were used only in cases that were completely necessary, and eyeglasses were left on if appropriate. The app provided these instructions as well as feedback for remote data collection circumstances. A series of tasks then followed to prompt necessary saccadic eye patterns. Subjects were instructed to fixate their gaze on a stimulus at the center of the display, which would disappear and reappear at a different new location on display in the subject's periphery. The subjects are to then fixate their gaze on the new stimulus location for pro-saccades or subvert their gaze in the opposite direction of the stimulus for anti-saccades. In both cases, the sequence was repeated 40 times or for approximately 5 minutes for a full protocol. This protocol was performed multiple times for each subject, interspersed with 20-second breaks, to provide 120 saccade latencies for pro-saccadic and anti-saccadic movements. Upon completion, data was uploaded via the study app to the database upon which analysis was performed. For each participant that completed an entire session, saccade latency distributions for pro-saccades and anti-saccades yielded mean latencies and error rates for comparison.

DATA PROCESSING AND ANALYSIS

With data drawn from complete experimental sessions, SEM latency distributions were compiled. Video records gathered via the study app were subsequently transmitted to a singular database with de-identified participant information for processing and analysis. Each type of movement required at least 100 different data points to establish a full distribution. Distribution data was used to identify a mean for each subject. Mean latency data for pro-saccades and anti-saccades, along with directional error rates, were then compiled using the publicly available MATLAB software package. For this study, additional statistical and graphical analysis was performed using MATLAB 2022a as well as RStudio v2022.02.0 and Microsoft Excel 2103. Simple linear regression was performed to observe the potential correlation between participant age with session performance. As age-related effects on saccade are not expected within the range of 20 to 40 years, further age stratification was performed on broader age groups of 18 to 44 years, 45 to 65 years, as well as 65 years and above (Filoppopulos 2021). Given that approximately half of the data consists of participants between ages 22-44 with little expectation of age-related effects on saccade performance, data was also analyzed with an ANOVA test for mean metrics with respective age groups with linear regression of age group-based mean values to produce representative plots.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

A total of 207 participants were recruited for eye-tracking assessment, of which 75 were eligible, recorded demographic information, and completed a full experimental session for inclusion in the final dataset. Within the dataset of 75 participants, ages ranged from 22 to 80 years. As highlighted in Table 1, this age range was consistent among female participants, whereas males ranged from 23 to 80 years. Gender distribution was relatively even as 40 were female (53.33%), and 35 were male. Gender distribution within each respective age group is also similar. Of 35 participants ages 22 to 44, 21 were female (47.72%), 12 of the 27 participants within ages 44 to 64 were female (44.44%), and 7 of the 13 participants ages 65 and above were female (53.84%). The mean age overall was 46.8 years, with the mean age among females at 45.35 years and males at 48.45 years.

Table 1: Participant Demographic Information

Participant Age	All	Female	Male
18-44 Years	35	21	14
44-64 Years	27	12	15
65+ Years	13	7	6
Total (N)	75	40	35
Mean Age	46.8	45.35	48.45
Age Range	22-80	22-80	23-80

Table 2: Mean Eye Tracking Data for Age Group and Gender

Participant Subgroup	Mean Pro-Saccade Latency	Mean Anti-Saccade Latency	Mean Pro-Saccade Error Rate	Mean Anti-Saccade Error Rate
18-44 Years	231.46	201.66	0.016	0.21
44-64 Years	364.56	342.48	0.041	0.22
65+ Years	491.62	410.23	0.051	0.28
Female	249.95	215.03	0.033	0.26
Male	410	372.49	0.028	0.19
Total	324.64	288.51	0.031	0.23

LINEAR REGRESSION

According to the data, both mean saccade latencies and error rates were examined for both pro-saccadic and anti-saccadic movement with respect to the dataset's age range of 22 to 80 years. Within pro-saccadic movements, a significant relationship was observed between age and mean latency with a p-value of 0.009 ($p<0.05$), however, the R^2 value was very low at 0.09. This relationship is demonstrated in Figure 1. As shown in Figure 2, a statistically significant relationship was also observed among anti-saccadic movements with a p-value of 0.02 ($p<0.05$) with an R^2 value of 0.074.

Figure 1: Pro-Saccade Mean Latencies Compared to Age

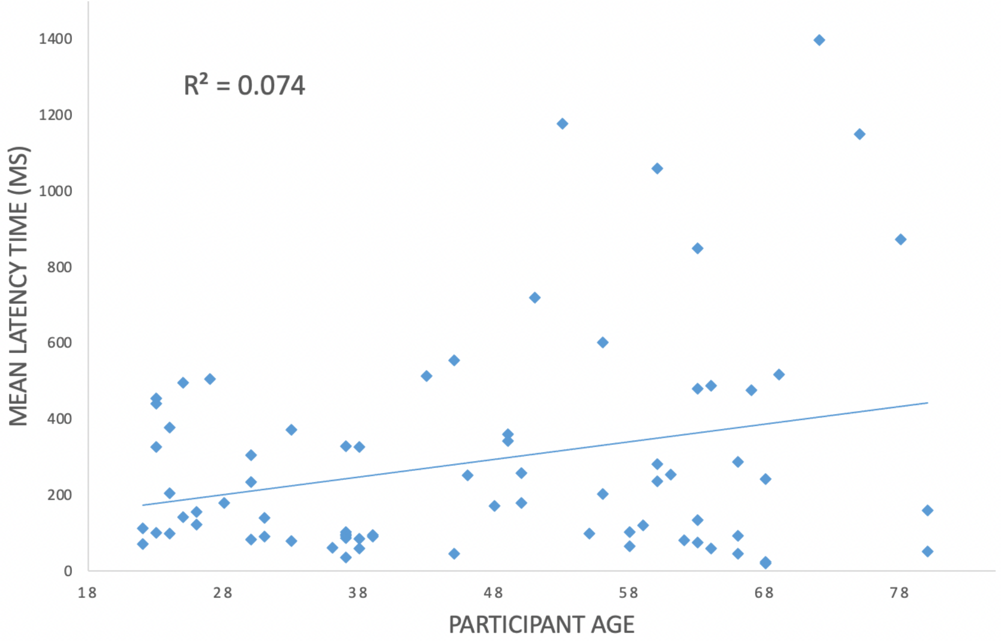
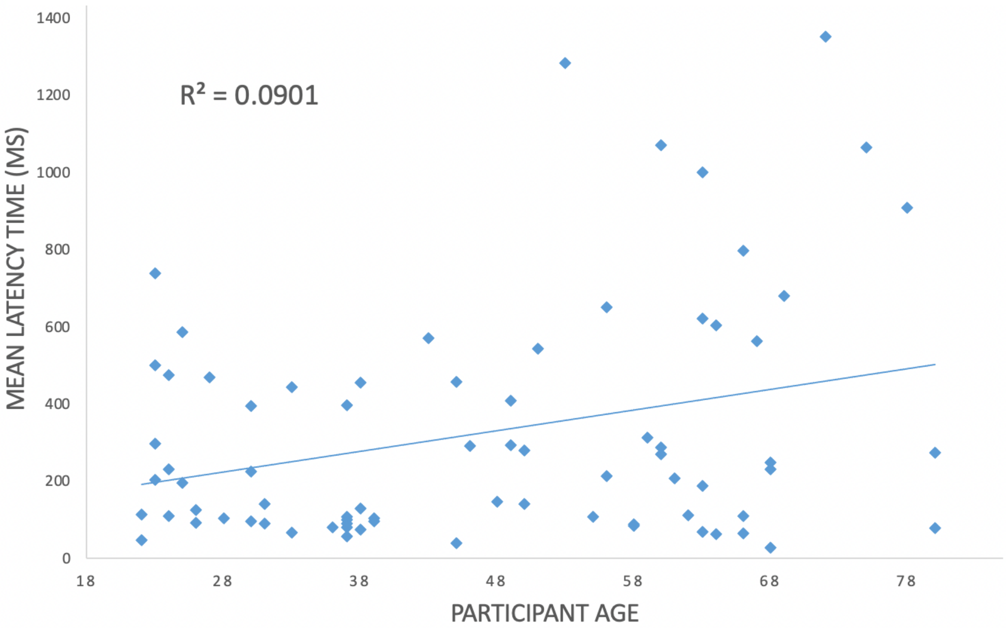


Figure 2: Anti-Saccade Mean Latencies Compared to Age



Among error rates, a statistically significant relationship was observed between age and mean error rate within pro-saccadic movements with a p-value of 0.0007 ($p<0.05$) with an R^2 value of 0.147, as noted in Figure 3. On the other hand, demonstrated in Figure 4, a statistically significant relationship between age and anti-saccade mean error rates was observed with a p-value of 0.03 ($p<0.05$) and a low R^2 value of 0.06.

Figure 3: Pro-Saccade Mean Error Rate Compared to Age

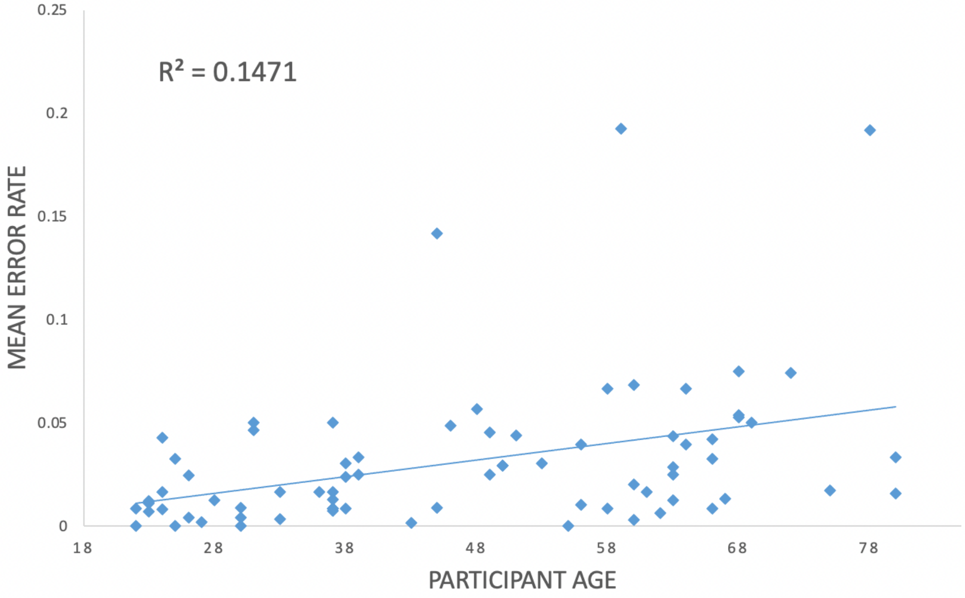
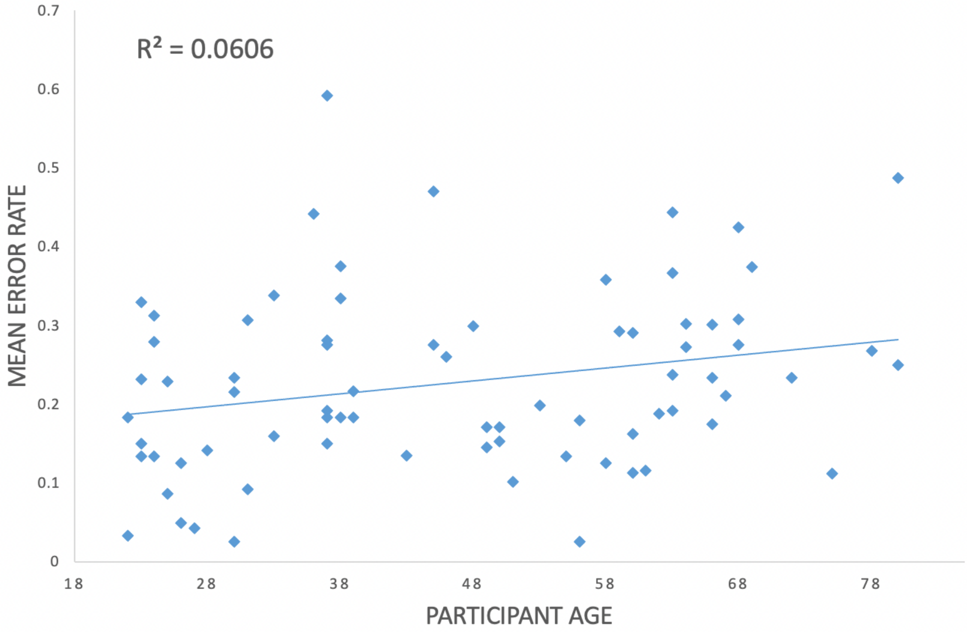


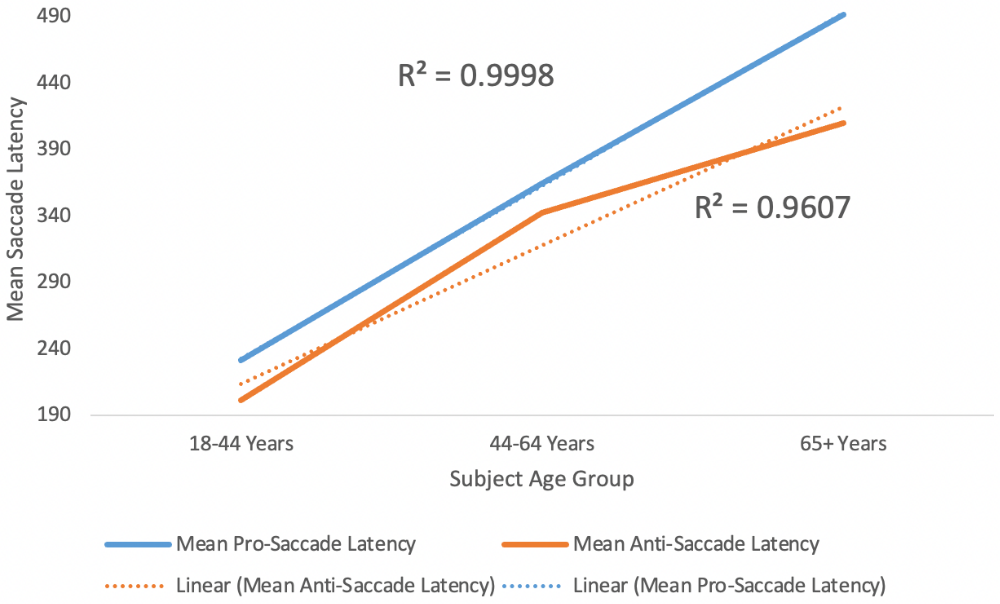
Figure 4: Anti-Saccade Mean Error Rate Compared to Age



ANALYSIS OF VARIANCE

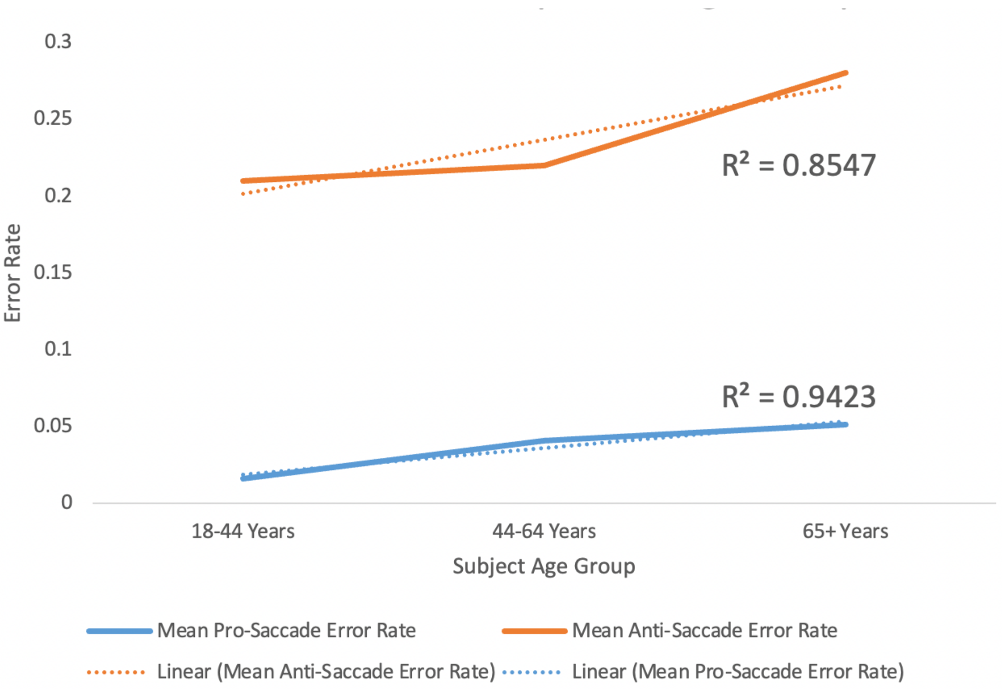
The means of saccade latencies were analyzed with respect to age in the age groups 22 to 44 years, 44 to 64 years, and 65 years and above using an ANOVA test. The age group of 18 to 44 years demonstrated the lowest mean pro-saccade latency at 231.46ms, as well as the lowest mean anti-saccade latency at 201.66ms. Participants aged 44 to 64 performed slightly slower, with a mean pro-saccade latency of 364.56ms and a mean anti-saccade latency of 342.48ms. Finally, participants aged 65 and above performed with the slowest latencies, with a mean pro-saccade latency of 491.62 and a mean anti-saccade latency of 410.23ms. A rising trend was noted in both pro-saccade, and anti-saccade latencies as participants' age groups were progressively higher. A statistically significant difference between the means of pro-saccade latencies was observed between the age groups with a p-value of 0.02 ($p<0.05$) with a positive F value to F-critical value ratio ($4.10>3.12$). Similarly, a statistically significant difference between the means of anti-saccade latencies was observed as well, with a p-value of 0.04 ($p<0.05$) with a positive F value to F-critical value ratio ($3.34>3.12$). Mean latencies for each age group are listed in Table 2, with the observable relationship linearly modeled in Figure 5.

Figure 3: Mean Saccade Latencies for Subject Age Group



Mean error rates, as listed in Table 2, were similarly analyzed with respect to age groups. Directional error rates were observable higher in anti-saccadic movements in comparison to pro-saccadic movements. Those within the group ages 22-44 demonstrated the lowest pro-saccade directional error rate of 0.016 as well as the lowest mean anti-saccade error rate of 0.21. Participants in the age group of 44-64 performed with slightly higher error rates with a mean pro-saccade error rate of 0.041 and a mean anti-saccade error rate of 0.22. Finally, those within the age group 65 years and above performed with the highest mean error rates with a pro-saccade error rate of 0.051 and a mean anti-saccade error rate of 0.28. A statistically significant difference was observed between the mean error rates between age groups for pro-saccadic movements with a p-value of 0.001 ($p<0.05$) and a positive F-value to F-critical value ratio ($6.92>3.12$). However, a statistically significant difference was not observed between the means of error rates for anti-saccadic movements between age groups with a p-value of 0.163 and a negative F-value to F-critical value ($1.85<3.12$). The relationship between mean error rates and age groups for both pro-saccadic and anti-saccadic movements is modeled linearly in Figure 6.

Figure 4: Mean Error Rates for Subject Age Group



DISCUSSION

This study sought to assess oculomotor function within health subjects through SEM, demonstrating a mobile-device's efficacy in assessing subtle eye movements as well as establishing a normative dataset upon further investigation can be performed. Both SEM latency and directional error rates were examined in a group of healthy adults using standard, consumer-grade iPad mobile devices such that a comprehensive collection of data could be established. With this, the expectations of SEM among healthy subjects may be considered in terms of the results that were gathered using the tools employed in this experiment. As oculomotor function is necessarily linked with neurological and neuromotor function, it was hypothesized that SEM performance would decline in older persons. With this, age was employed as the predictive variable upon which both mean saccade latencies and directional error rates may be compared.

Following from the results, both linear regression and ANOVA models demonstrated a statistically significant relationship between age and saccade latency. Though the ANOVA model predicting anti-saccade error rate among each age group did not reach significance, the remaining linear regression and ANOVA models for error rate did demonstrate a statistically significant relationship. This suggests that in most cases, particularly within pro-saccadic movements, that older age was positively and directly correlated with increased saccade latency and error rate. As such, the null hypothesis can be rejected in all but one case and instead accept the alternative hypothesis that age is a predictive variable in oculomotor performance when employing saccade latency as a measurable biophysical marker. Despite accepting the alternative hypothesis, the data did produce interesting results, likely due to variance within saccade latency and accuracy throughout the age range. While statistical analysis suggests a statistically significant relationship between age and saccade latency, the mathematical of this relationship remains unclear given the distribution of age in the sample population and the potentially non-linear relationship that may more accurately represent changes occurring throughout adulthood. When considering age as a continuous variable, the low R^2 value found in each linear regression reflected a notable lack of predictive strength when considering subject ages independently.

Though the significance of these tests indicates a relationship between age, mean saccade latency, and mean error rates, the models fail to predict the variance in eye movement metrics with, for example, the highest R^2 value only reaching 0.14, or 14% predictive accuracy, when comparing mean pro-saccade latencies to subject age (Figure 4). This is likely due to several reasons. First, approximately half of the subjects were in the lowest age group, in which age-related saccadic movement effects are not yet expected. Secondly, differences in individual subjects can result in varied eye movement performance, particularly when instructed to complete an unfamiliar task. Participants that are inclined towards responding to rapid stimulus changes employ techniques to ensure high directional accuracy to reduce error or focus on increased consistency in response time undoubtedly influence variance in results. Determining methods to study intra- and inter-subject variance more effectively in the future may provide technical solutions to differences and greater insight into such factors. Finally, the method with which the data was collected, in-person or remotely, may have influenced the data due to lighting or artifactual interference, varying levels of understanding regarding task instructions, or inconsistencies in the experimental setup. For these reasons, ANOVA must be implemented to provide an alternative method of analysis, utilizing a mean value in saccadic movement metrics with which age groups can be categorized and compared to account for notable variance.

Statistically significant findings suggest the expected decrease in eye movement performance as age increases. However, statistical significance was not observed in the ANOVA test assessing anti-saccade error rates (Table 2, Figure 6). As discussed, anti-saccadic movement tasks are unique in that they test a subject's ability to inhibit reflexive saccadic movements. Reflexive saccades that occur can result in rapid responses to stimuli, however, with dramatically decreased accuracy given a lack of intention on behalf of the subject. For this reason, anti-saccade error rates are expected to be increased in all individuals, especially those with decreased cognitive function. With respect to the data, a rising trend was observed in the mean error rates between each successive age group. However, the variance was noticeably pronounced throughout analysis, and considering that a greater proportion of the subjects were in the youngest age group, performance is reasonably inconsistent.

Despite the efficacy of this study's experimental tools to evaluate SEM, certain limitations impacted investigation. Firstly, individual saccade latency distributions were not explored. Instead, individual subject means were assessed to ensure efficient and thorough statistical analysis. Typically, broader population saccade latency means are examined; thus, comparing individual means did provide adequate detail for the purpose of this investigation. Additionally, smooth pursuits were not explored, given the ongoing development for the application to assess this category of movements effectively. In addition to saccadic movements, smooth pursuits may be studied in the future to further validate the mobile device platform in gathering comprehensive information regarding oculomotor function. Beyond this, limitations were present in the dataset itself, with which subjects were potentially unable to complete a full protocol or erroneous data occurred given functional errors. As such, a small portion of the dataset reflected incomplete or missing data points, decreasing the volume of data. Similarly, within the data, a limitation that arose was the distribution of age. In scenarios that emphasize age-related effects on saccade latency, a greater emphasis on older participants would be necessary for a more exhaustive analysis. Given that only 13 subjects were above the age of 65, for example, uneven age distribution likely influenced the results and may be improved for future studies, particularly in cases that examine linear regression and modeling in addition to ANOVA-based analysis.

In the general population, these results are to be expected based on the current understanding of aging, oculomotor performance, and neurological health.

Despite this, they remain important for several reasons. Primarily, findings that are consistent with expectations serve the main goal of this study, in gathering a sufficiently high-quality database that may highlight the efficacy of the hardware and software implemented. When considering the metrics collected in statistical analysis, the level of precision necessary to achieve these results is reflective of the challenges that impact traditional eye-tracking methods.

The Apple iPad tablet utilized in this study is unique among the commercially available eye-tracking equipment necessary for most research applications, given its relatively low cost, accessibility, and potential scalability in clinical scenarios. Using updated architecture based on previous iterations of tablets and smartphones, the app used in this study can be effectively applied to any consumer device that integrates a display and front-facing camera of comparable or superior quality. Of course, further comparisons of the accuracy and precision of the data obtained by these means are necessary. However, by foregoing many of the needs in traditional eye-tracking equipment such as headrests, infrared lighting, high-speed cameras, and specialized processing tools, mobile devices can integrate components of prior methods into a singular package. This alone was demonstrated in the study methodology, given the remote-testing procedure for subjects that chose to conduct full testing sessions with their personal device. The capacity to expand on this dataset with longitudinal eye movement tracking over different timelines is well within the scope of future research.

There is a significant capacity to expand and build upon this study's findings. First, comparisons can be drawn between mobile device-based eye tracking and established eye tracking methods. This is especially true in increasing the tasks that the software can measure via video recordings. In the case of smooth pursuits, for example, future iterations of software may be capable of accurately assessing both saccade latency and smooth pursuits. This will require further comparison with infrared-based tracking, electro-oculography methods, and, most crucially, implantable search coils that have demonstrated the most precise and accurate measurements. Short of meeting the standards set by invasive techniques, providing data of comparable quality to video-oculography methods will illustrate the potential of this technology moving forward in research settings. A next step in the development of eye-tracking via iPads, or consumer-grade mobile devices more generally, will naturally entail transitioning to adult subjects with diagnosed neurological disorders such as neurodegenerative diseases.

This collection of data for healthy subjects may be utilized in further research as a normative dataset with which the eye-tracking performance of diagnosed patients can be compared. Saccadic movements can be assessed in patients with various diseases such as AD, PD, PSP, as well as prion diseases, for example, to provide insight into the impacts these diseases have on oculomotor health. Potential differences in the nature of how various disease impact eye movement remains a field of study to be examined with greater detail in the future. Possible differences that arise in subtle eye movement patterns between diseases may be used for differential diagnosis, disease detection, and treatment monitoring. Implementing devices such as Apple iPads that can collect relevant data from patients in a manner that is efficient and useful for clinicians may greatly benefit prognosis and treatment methods.

Patients with diseases that impact regions of the brain associated with oculomotor function are of notable interest, given responses to long-term treatment. For example, deep brain stimulation implants and pharmaceutical interventions for patients with somatomotor disabilities may experience progressive functional improvements. Changes that are reflected in oculomotor function may be monitored via eye-tracking longitudinally prior to and after an intervention to gain a greater understanding of the resulting effects. By collecting data on an individual patient, clinicians may more effectively discern trends or changes that arise rather than those which may be observed in periodic examinations. In the context of future research, shifting eye-tracking activities from singular sessions to multiple, daily sessions over a more extended period may prove valuable in the treatment of neurological disease. Future adaptations to this study may therefore take on longitudinal designs, gather a greater volume of data, and contribute to a growing database of both healthy subjects and those with diagnosed illnesses. Developing methods to distinguish the signs of underlying disease in eye movement patterns, track patient improvement or decline, and guide clinical interventions remain foreseeable goals to pursue. Thus, improving the feasibility of eye-tracking in medical research and practice as a means of strengthening patient care should remain a focus moving forward.

The significance of findings demonstrated here does not alone bring to light particularly new insight into the association between eye movements and demographic characteristics such as age. They do, however, validate the use of an iPad application along with its related software algorithms in identifying different types of saccadic movements, measuring saccade latencies, and calculating error rates using video-based recordings. Comprehensive determinations of latencies following assigned visual tasks provided sufficiently high-quality data with which statistical analysis could be conducted on the mean eye movement performance for 75 individual subjects. There remain clear areas to build further upon this foundation, such as in evaluating additional types of eye movements, individualized data tracking, longitudinal assessment, and subjects impacted by neurological illness. However, by establishing a means to enable saccadic movement and error rate analysis, this technology fundamentally demonstrates potential in advancing our understanding of oculomotor function and eye tracking-based biomarkers in clinical practice.

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CURRICULUM VITAE

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