Spring 2017

Objective quantification of sensory function using a battery of smartphone applications

Kasra Zarei
University of Iowa

OBJECTIVE QUANTIFICATION OF SENSORY FUNCTION USING A BATTERY OF SMARTPHONE APPLICATIONS

by

Kasra Zarei

A thesis submitted in partial fulfillment
of the requirements for the Master of Science
degree in Biomedical Engineering in the
Graduate College of
The University of Iowa

May 2017

Thesis Supervisors: Associate Professor Mona K. Garvin
Professor Randy H. Kardon

Graduate College
The University of Iowa
Iowa City, Iowa

CERTIFICATE OF APPROVAL

_____

MASTER'S THESIS

_____

This is to certify that the Master's thesis of

Kasra Zarei

has been approved by the Examining Committee for
the thesis requirement for the Master of Science degree
in Biomedical Engineering at the May 2017 graduation.

Thesis Committee: _____
Mona K. Garvin, Thesis Supervisor

_____
Randy H. Kardon, Thesis Supervisor

_____
Chris A. Johnson

_____
Michael A. Mackey

_____
Terry L. Wahls

To my family, friends, and mentors who have helped me become the scholar I am today.

Technology is nothing. What's important is that you have a faith in people, that they're basically good and smart, and if you give them tools, they'll do wonderful things with them. It's not the tools that you have faith in – tools are just tools. They work, or they don't work. It's people you have faith in or not.

Steve Jobs, Co-founder, Chairman, and CEO of Apple Inc.
Steve Jobs in 1994: The Rolling Stone Interview

ACKNOWLEDGEMENTS

I would like to sincerely thank my mentors, Dr. Randy Kardon, Dr. Mona Garvin, and Dr. Pieter Poolman for their continued supervision and mentorship, without which I would be unable to mature as a physician scientist. I would like to sincerely thank Dr. Chris Johnson and Dr. Terry Wahls for their technical and clinical expertise and involvement. I would also like to thank them, and Dr. Michael Mackey for serving on my thesis committee. I would also like to thank Dr. Mackey and many professors in the department of biomedical engineering and the college of engineering for supporting me as a student for the last four years. I would like to give a sincere thank-you to Dean Heidi Arbisi-Kelm for being an incredible academic leader and an advocate of all students. I would also like to thank the Tau Beta Pi Association (Matthews No. 19 fellowship) and Fight for Sight for their financial support. Finally, I would like to thank my family (Zohreh, Keyan, and Sanam) and friends (specifically Jui-Kai Wang) for their continued support and encouragement.

ABSTRACT

Sensory deficits represent a major global public health problem. According to the World Health Organization, vision impairment affects an estimated 300 million people worldwide, and hearing impairment affects an estimated 360 million people worldwide. Consistent clinical evaluations for all individuals with sensory deficits cannot be practically realized due to the rising costs of healthcare, capital and labor limitations, and inaccessibility to healthcare due to a multitude of factors including proximity. The high prevalence of visual and hearing deficits can be lessened through consistent, comprehensive, at-home testing which can allow a larger amount of the affected and at-risk populations to be screened for abnormal function earlier and prior to permanent loss, and provide a wealth of patient-specific data that can be used to understand the time-scale of diseases and monitor the effectiveness of clinical interventions in unprecedented detail. While health-oriented smartphone applications exhibit a strong presence on the app stores, these applications are seldom vetted by expert scientists, engineers, and clinicians, and there are considerable opportunities for methodological improvements. The present work discusses the creation, calibration, and proof-of-concept, preliminary validation of a suite of psychophysical tests implemented as smartphone applications that can be utilized to rapidly and objectively quantify several functional sensory behaviors including flicker sensitivity, contrast sensitivity, visual acuity, and hearing-in-noise. Rigorous steps were undertaken to perform the necessary calibrations (a feat not routinely achieved by the creators of existing medical smartphone applications), and ensure the technical validity of the varying stimuli presented. Preliminary tests in the clinic have documented the potential of these tests to objectively provide numerous quantifications of, but not limited

to, individual visual and hearing function, and variation between normal and abnormal subjects and function. The foundation laid by this work allows novel psychophysical tests to rapidly be implemented, vetted, and added to this battery of publicly and universally accessible medical smartphone applications.

PUBLIC ABSTRACT

Vision and hearing impairments affect hundreds of millions of people worldwide. The current era of smartphones has the potential to provide universal, at-home self-testing of sensory function, namely vision and hearing, through well-engineered, vetted smartphone applications. While existing medical smartphone applications lack the necessary clinical and technical validation to be accepted and adopted by networks of clinicians and researchers, the presented suite of smartphone applications has been rigorously designed within the confines of smartphone technology and hardware, and tested through a series of preliminary, proof-of-concept experiments. Results obtained to-date demonstrate the potential of the implemented tests to quantify sensory behavior of individuals as well as functional differences between normative subjects and patients with impaired visual function.

TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF FIGURES

Figure

PREFACE

Presented before you is the thesis "Objective Quantification of Sensory Function Using a Battery of Smartphone Applications". It has been written to fulfill the graduation requirements of the Master's Degree program in Biomedical Engineering at the University of Iowa. This project was undertaken with the aim of developing a suite of smartphone applications that could ultimately be utilized to perform rapid, objective testing of sensory (visual and hearing) function. With the creation of a suite of well-engineered smartphone applications, I hope I have provided a foundation that can be built from to allow at-home and universal testing of visual and hearing function, and acquire large amounts of data that can be leveraged to ask and answer a plethora of questions in basic and clinical research.

CHAPTER 1

INTRODUCTION

The use of smartphone technology and mobile devices has become commonplace in health care settings, and has transformed multiple aspects of clinical practice and research [1, 2]. The presence of mobile hardware has caused the development of medical smartphone applications to proliferate. The term smartphone/mobile applications apps refers to software that is designed to accomplish a specific purpose and can be distributed through mobile devices. Numerous applications now exist to aid practicing health care workers with data collection for research, low-cost, efficient functional testing that requires minimal capital, and clinical decision-making.

Despite the many benefits of smartphone devices for health care workers, many are reluctant to adopt the technology for clinical and research purposes, particularly because the majority of medical mobile applications lack technical and clinical validation. This weakness must be addressed through medical applications that are well-engineered and created according technical and clinical standards. Credible medical applications must be subject to stringent, comprehensive technical evaluation and clinical validation. In designing bulletproof applications, a complete understanding of the device limitations, coupled with thorough device calibration, must be obtained so valid and sound testing can be performed.

A suite of mobile applications (the eyeApps and HearMe) have been developed as smartphone based tools to provide objective quantification of visual and hearing function. These tools serve as low-cost, efficient tools that have a wealth of clinical and research applications from collecting large-scale data of sensory behavior to at-home independent

testing to screen for sensory and neurological dysfunction and monitor responses to operations and therapeutic interventions. From a mechanistic perspective, very little is known about the time-scale of many diseases and their treatments. The following chapters in this thesis will outline pertinent background information related to important measures of visual and hearing function, the general design approach and implementation strategies of the developed applications, and necessary forms of technical evaluation and clinical validation that have been performed to date. The discussed work will ideally serve as a foundation for scientific, engineering, and clinical practices that must be rigorously followed for all purposes related to medical smartphone application development, from design to clinical adoption.

CHAPTER 2

BACKGROUND

2.1 Elements of Visual Function

Vision is composed of many simultaneous functions with measurements that can be obtained beyond the standard eye chart. A discussion of a subset of these functions (including flicker sensitivity, visual acuity, hyperacuity, and contrast sensitivity) is provided in the following sub-sections.

2.1.1 Flicker Perimetry

The ability to detect intermittent light and dark alterations of a visual stimulus, also referred to as flicker or temporal processing, is an important component of visual function. The rapid changes in the contrast or luminance of a stimulus can be crucially important for detecting environmental changes, motion, and awareness of objects in peripheral vision. Flicker perimetry is an informative clinical test that is relatively unaffected by confounding effects due to blur, refractive error, and media opacities [3]. Furthermore, it has long been established as a sensitive measure of a visual conduction time, which becomes abnormal in retinal and optic nerve disorders [4-7]. Multiple studies have reported high temporal frequency flicker sensitivity loss in conditions including glaucoma and ocular hypertension [4, 8, 9].

There are two primary methods of flicker perimetry testing: critical flicker fusion (CFF) and temporal modulation perimetry (TMP; also referred to as contrast modulation flicker) [3]. In CFF testing, flicker contrast is fixed at a predetermined level (usually maximum contrast) while the temporal frequency is varied and the highest temporal frequency to detect flicker is measured [3]. In TMP testing, the flicker rate is fixed at a

predetermined frequency or set of frequencies, with the contrast varied and the minimum amplitude or contrast needed to detect flicker is measured [3, 10]. While there are advantages to using different forms of flicker perimetry, both approaches have been proven useful in various clinical applications with strong test-retest reliability [3], but CFF is more prevalently used in clinical applications due to its robustness to a multitude of factors and the small influence of aging effects [3], the latter of which has been difficult for other forms of flicker perimetry to achieve [7, 11, 12]. The effect of age may reflect peripheral and central neuronal conduction time and may prove useful in other applications in which the conduction time may reflect other important aspects of neural network function, independent of retinal and optic nerve disorders.

CFF testing provides additional advantages compared to alternative methods of flicker perimetry. Particularly, CFF can provide information about the upper temporal frequency limits of flicker sensitivity, and can be easier to implement on existing instrumentation and technology. Multiple studies have been performed to evaluate the influences of varying testing stimuli and parameters on flicker sensitivity, in an effort to optimize methodologies for clinical testing and control for variations in factors, including pupil size and adaptation level, that can alter flicker sensitivity [8-10, 13, 14].

While a full discussion and history of the different methods of flicker perimetry is beyond the scope of this introduction, a discussion about the extension of flicker perimetry methodologies to smartphone devices is central to the work presented. There have been previous attempts to re-engineer CFF tests (such as a linear array of LEDs flickering at varying temporal frequencies), but these creations, while reduced in size, lack the ease of distribution and universal access that a smartphone-based approach could

provide. A previous study reported the use of a modified flicker fusion test as a more sensitive tool to denote neurological deficits in temporal vision in patients with MS [5]. This portable instrument consists of a frequency control knob, a frequency readout meter, and a monocular vehicle, and has been used in small-scale longitudinal studies in MS patients [5], but cannot feasibly be scaled to study larger cohorts nationally and internationally. A correctly implemented smartphone-based approach that can be accessed through a publicly available download, however, would present a useful method to collect data and conduct longitudinal studies.

However, while CFF possesses key strengths in the ease of implementation and the ability to determine upper temporal frequency limits, its use on display systems such as smartphone devices is severely limited. Smartphone devices currently are restricted to presenting a limited set of temporal frequencies (1, 2, 3, 5, 6, 7.5, 10, 15, and 30 Hz) for oscillating luminance values due to the 60 frames per second refresh rates of liquid-crystal displays (LCD). Furthermore, unless high-quality graphics or central processing units can be utilized, variations in frame refresh rates are common, as a result of multiple device settings (low battery, multiple apps or threads running, etc.), which further eliminates the higher temporal frequencies that cannot be reliably presented on a smartphone device with a reasonable degree of accuracy. With this technical understanding of smartphone devices in mind, a temporal modulation perimetry or contrast modulation flicker approach would be best suited within the confines on smartphone technologies. In fact, the implementation of this method was pursued in terms of the scope of the presented work and will be discussed in further detail later.

Regardless of the approach, flicker perimetry is useful for interrogating a wide range of physiological function. For instance, CFF has also been used as a sensitive measure of increasing intraocular pressure [15], and has been particularly useful in diagnosing optic nerve demyelination, specifically disorders including multiple sclerosis (MS) and optic neuritis (ON) where CFF is significantly decreased [5, 6, 16]. Deficits in CFF during MS are believed to be due to abnormal ephaptic transmission between demyelinated bundles of fibers, or more influentially, partial or complete conduction blocks caused by drops in axon membrane impedance [16].

As a sensitive measure of a visual conduction time, CFF and other forms of flicker perimetry have also been utilized in the detection of morphologic changes caused by aging [7, 10, 17], alcohol tolerance in alcoholics [18], and physiological fluctuations and deteriorations caused by elevations or alterations in core body temperature as the conduction velocity of peripheral nerve fibers is related to core body temperature [16].

The versatility of flicker perimetry also has great appeal in monitoring novel therapeutic interventions (in humans) related to the aforementioned disorders, from conventional forms of medicine that are drug-oriented to explored forms of complementary and alternative medicine that are more natural and less drug-oriented. For MS, for instance, Paleolithic diets have attracted great interest in the treatment and management of MS following pilot studies and randomized control trial evaluations [19].

2.1.2 Visual Acuity

Another characteristic of the human sense of vision is visual acuity, which in simple terms refers to the sharpness of an individual's vision related to spatial resolution and is commonly tested by determining the smallest optotype shape that an individual can

discern. One straightforward approach to measuring an individual's visual acuity makes use of standard, popular eye charts such as the LogMAR (Log of the Minimum Angle of Resolution) or Snellen charts (Figures 2.1 and 2.2) [20].

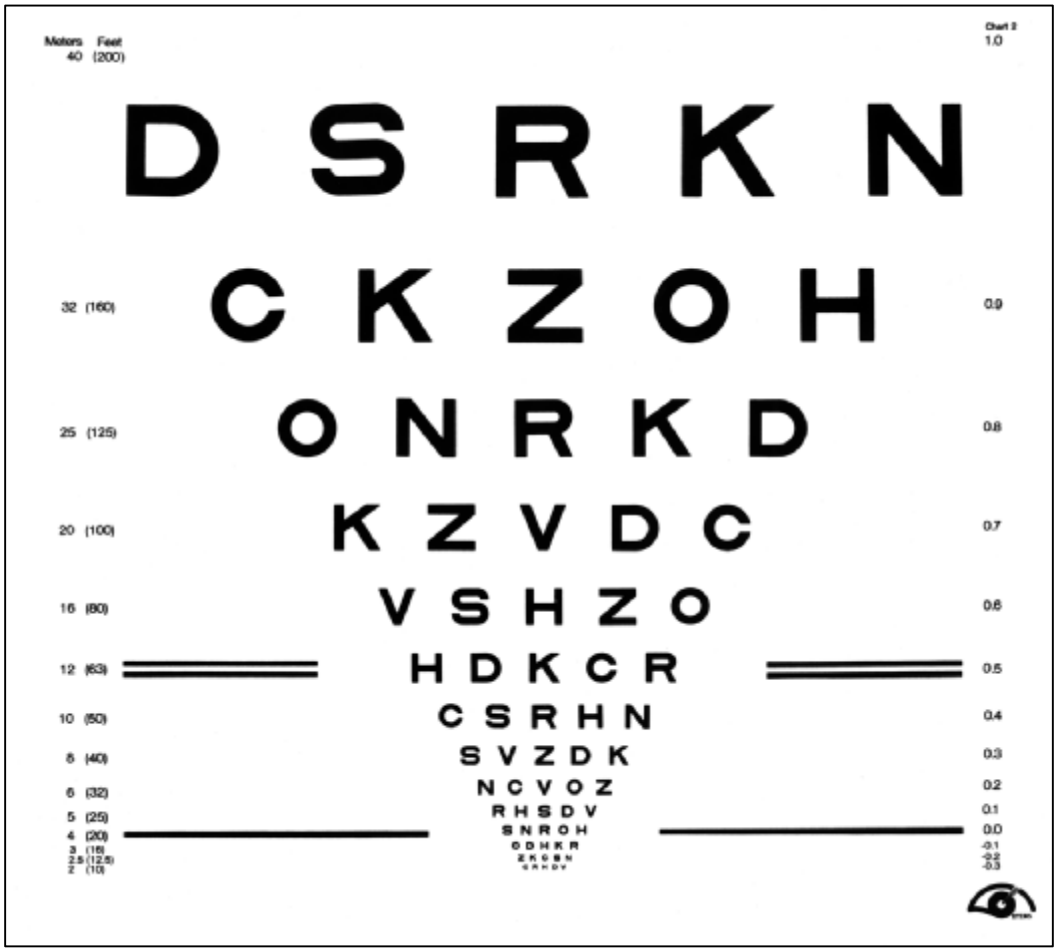

Figure 2.1: The LogMAR chart is an eye chart used to measure visual acuity [20]. This chart is designed to provide a more accurate estimate of visual acuity compared to other eye charts (specifically the Snellen chart). When using this chart, visual acuity is equated with reference to the logarithm of the minimum angle of resolution. The formula used for calculating the LogMAR visual acuity is expressed as follows: LogMAR VA = 0.1 + LogMAR value of the best line read – 0.02 X (number of letters read) [20]. Image courtesy of the National Eye Institute, National Institutes of Health.

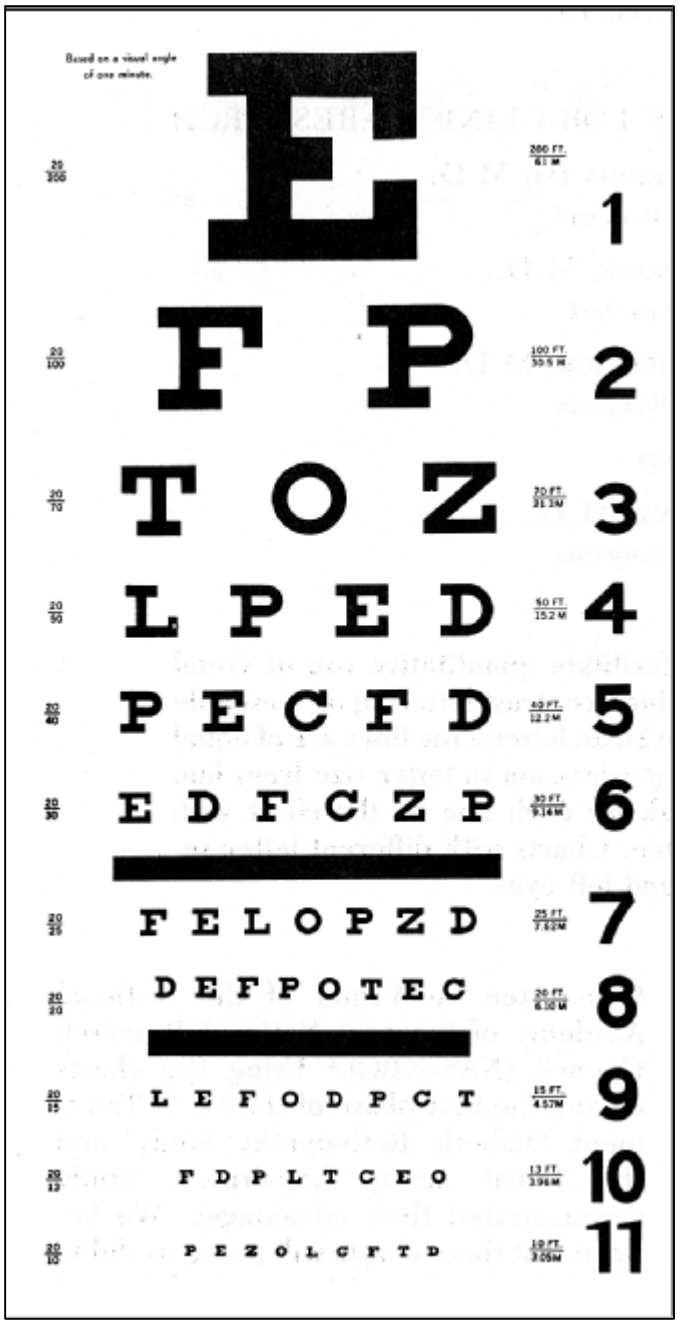

Figure 2.2: The Snellen chart is an eye chart used to measure visual acuity [21]. The standard Snellen chart is printed with eleven rows of block letters. An observer commonly takes the test standing six meters away from the chart and reads the letters on each row from top to bottom, covering one eye during each test. Subsequent rows a higher number of optotypes that decrease in size. Successful identification of all of the letters on one line translates to the visual acuity measure indicated in the rightmost column. The change in spatial frequency of letters on this chart is not logarithmic and in most clinical settings has been superseded by the LogMAR eye chart showing in Figure 2.1). Image courtesy of the National Eye Institute, National Institutes of Health.

These charts, although commonly used in a supervised clinical setting with an examiner recording the number of letters correctly read out loud by the subject, their utilization in a smartphone application are problematic for independent, at-home testing. While a user could simply read the lines of an eye chart on a smartphone, user responses to the various stimuli would require accurate speech recognition with this technology. Another approach is to have the subject select larger letters that match the ones they are trying to resolve. One solution that has overcome the problems inherent in the use of traditional eye charts to objectively quantify visual acuity on a smartphone, is the use of a Landolt C optotype, also termed a Landolt ring (a circle with a gap, Figure 2.3). In this test, the Landolt C is displayed and the user must indicate the direction of the gap in the ring in a forced-choice task [22]. The Landolt C or Landolt Ring consists of a ring that has a gap, with a stroke width and gap width of 1/5 of the target diameter [22]. This target is identical to the letter C of the Snellen chart (Figure 2.2) [21, 22]. The gap can be presented at various positions (left, right, bottom, top, and any of the 45-degree angle positions in between) and is successively reduced in size as the test progresses if the correct choice of the gap orientation is made by the subject.

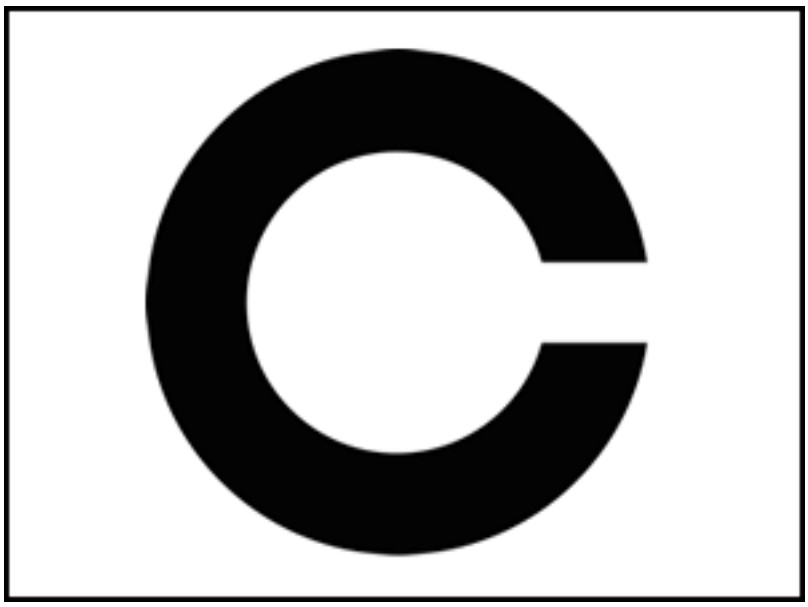

Figure 2.3: The Landolt C or Landolt Ring consists of a ring that has a gap, with a stroke width and gap width of 1/5 of the target diameter. This target is identical to the letter C of the Snellen chart (Figure 2.2) [21, 22].

The size of the Landolt C is successively reduced until the observer makes a specified error rate. Previous studies have reported a good measure of visual acuity (using the Landolt C approach) as being the smallest size where the direction of the gap is correctly recognized around half of the time (50% accuracy) [23, 24]. 1-up-1-down paradigm historically produce thresholds where the subject is able to detect the presence, or in this case correct orientation, of the stimuli 50% of the time [23].

2.1.3 Contrast Sensitivity, Contrast Sensitivity Functions, and Vanishing Optotypes

Another characteristic of visual function is contrast sensitivity. In simple terms, a contrast sensitivity test measures the ability to distinguish between finer and finer increments of light versus dark. Driving at night, for example, is a situation in which good contrast sensitivity is required as individuals who have low contrast sensitivity may have problems with driving during the nighttime. Contrast sensitivity has been found to

be a sensitive indicator of visual dysfunction and is often affected by retinal and optic nerve disorders out of proportion to visual acuity measures of spatial resolution.

The contrast sensitivity threshold determined can be equated using the Weber contrast or the Michelson contrast formulations [25]. Weber contrast is mathematically defined as:

$$Weber\ Contrast = \frac{I - I_b}{I_b}$$

where I and I_b represent the luminance of the features and background respectively [25].

The Michelson contrast is mathematically defined as:

$$Michelson\ Contrast = \frac{I_{max} - I_{min}}{I_{max} + I_{min}}$$

where I_{max} and I_{min} represent the highest and lowest luminance [25]. The Weber contrast is commonly used and preferred in situations where small features are present on a large uniform background, and the average luminance of the entire smartphone screen is approximately equivalent to the background luminance.

In addition to a simple measure of contrast sensitivity made at a specific spatial resolution, it may be useful to characterize contrast threshold over a range of spatial frequencies, termed a contrast sensitivity function, which may show specific patterns useful for identifying different causes of visual dysfunction (e.g. glaucoma vs. multiple sclerosis). Contrast sensitivity measurements that include both spatial frequency and contrast can be used to determine and plot an individual's contrast sensitivity function, a plotting of the curve (typically an inverted U-shape) that defines the lowest contrast level that an individual can detect for each spatial frequency tested [26, 27]. To be detected by the normal functioning human visual system, objects or optotypes with spatial

frequencies on both ends of the spectrum (high or low) must have significantly higher contrasts than objects with intermediate spatial frequencies. In other words, the optimal spatial frequency that yields the best contrast sensitivity is typically an intermediate spatial frequency value or medium-width grating or linewidth [26].

Valuable clinical information can be extracted through understanding how an individual's contrast sensitivity is a function of spatial frequency. For instance, some ocular and neurological disorders can alter aspects of contrast sensitivity but not spatial frequency, and vice-versa. Thus, there is a need to develop mobile modalities of determining individual contrast sensitivity functions, similar to the Vistech VCTS 6000 and 6500 Contrast Sensitivity Test charts (Figure 2.4) [28].

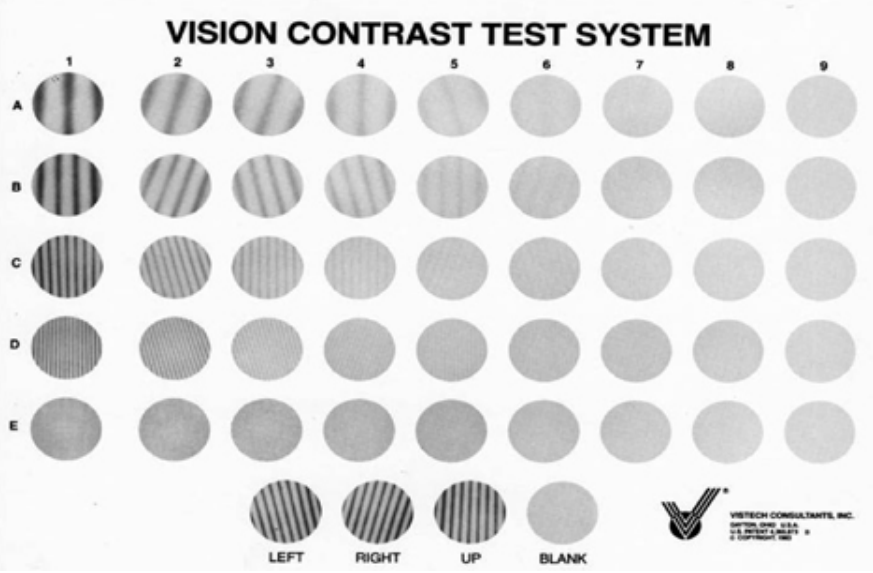

Figure 2.4: The Vistech VCTS Contrast Sensitivy Test that consists of patterned line targets (gratings) that increase in spatial frequency down a column, and decrease in contrast across a row [28]. The targets are presented at three different orientations (left, right, up, and blank), and the observer must discern the orientation of the target.

This work posits that the use of novel vanishing optotypes that can be used to quantify contrast sensitivity functions. To begin the discussion of vanishing optotype

targets, one must understand the concept of observation thresholds. For visual target objects, two observation thresholds are defined: detection and resolution. Detection refers to the threshold of observation of the presence of the object, and resolution refers to the threshold of recognition of the outline shape of the object [29, 30]. Under conditions exceeding the threshold of resolution but not detection, an observing subject can only identify the presence and position of an object but not its orientation or identifying features [29, 30]. Detection is controlled by the brightness of the object and its contrast. The level of detection thresholds can differ significantly from the resolution thresholds utilized by standard visual acuity charts. However, the unique properties of vanishing or disappearing optotypes, is that the detection and resolution thresholds occur at the same level, meaning that when one cannot resolve it, the optotype disappears or vanishes into the background. The subject's task becomes much simpler; resolution threshold can be easily determined by a binary process in which either the optotype is seen or not seen.

There are several benefits of using vanishing optotypes as visual targets. For instance, vanishing optotypes require increased levels of attention from observers, and are believed to produce more accurate measures of visual acuity in optometry [31-33]. Historically, vanishing optotypes have been widely used in preferential looking tests for applications such as measuring visual acuity development in toddlers [31-33]. Traditionally, a vanishing optotype is created from a line drawing of an object (an outline) and printed on a smooth, diffuse grayscale background. Then, by altering the thickness of the lines used to define the shape of the vanishing optotype, one can vary its acuity (spatial frequency resolution) without having to change the target size. An illustration of a set of circular vanishing optotypes is depicted (Figure 2.5).

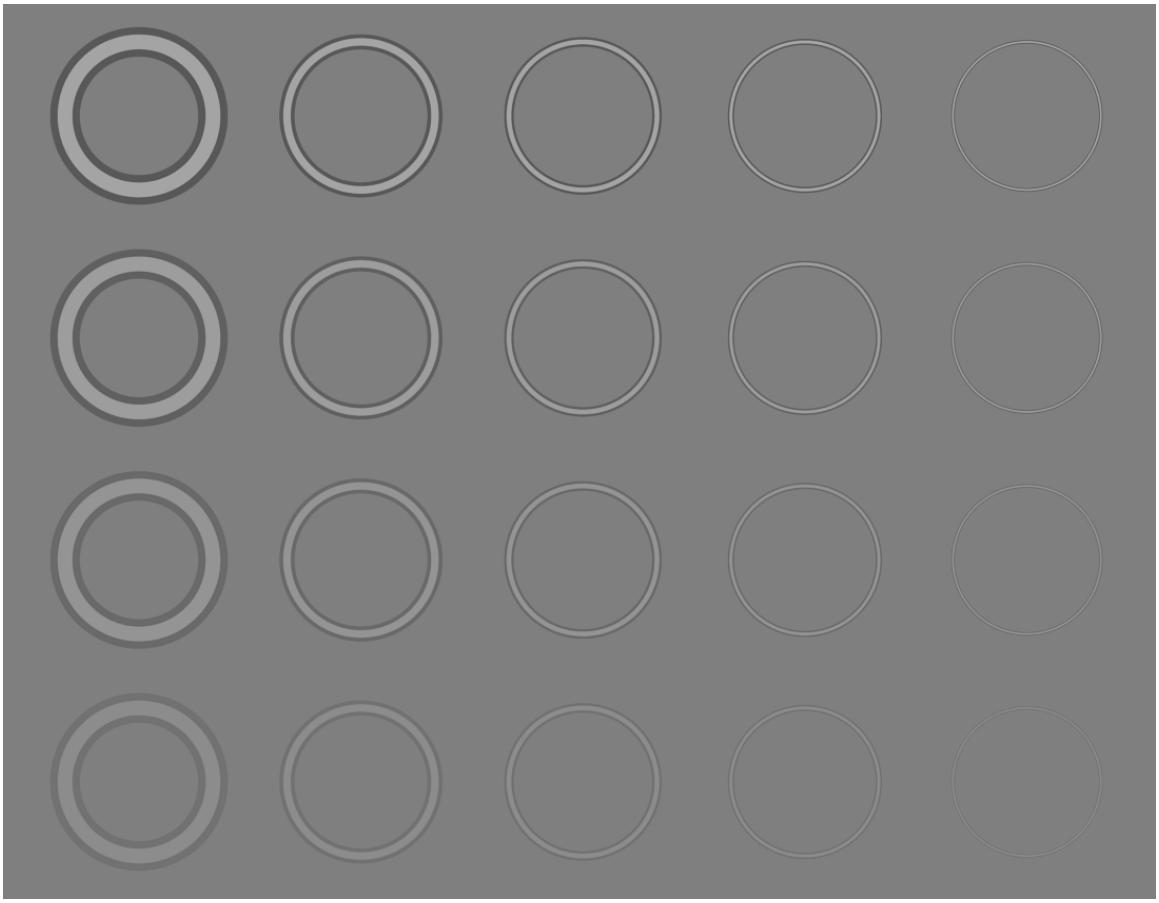

Figure 2.5: An example vanishing optotype grid consisting of circular visual targets that vary in contrast down a column, and increase in spatial frequency across a row.

When considering the implementation of circular vanishing optotypes, particularly on a smartphone, one has to be cautious of the pixel resolution of current displays that can lead to thicker effective line thicknesses than intended, as a result of anti-aliasing. Anti-aliasing effects implicitly reduce the high spatial frequency content of the displayed image, and become more pronounced with thinner lines.

2.1.4 Hyperacuity

Hyperacuity is another important measure of visual function closely related to visual acuity. Vernier acuity is commonly referred to as hyperacuity (for example, the precision of a sliding caliper), because of the higher dynamic range of resolution that can be tested, which is five to ten times higher than that of visual acuity. For example, a patient who may have 20/20 visual acuity on a traditional eye chart may still have early signs of visual dysfunction that can be more sensitively detected utilizing the greater dynamic range afforded by hyperacuity testing. The "Vernier Figure" consists of two lines atop each other with a varied horizontal offset (Figure 2.6) [34, 35]. The observer must judge which way, to the right or left, the top Vernier line is offset from the bottom one. The top Vernier line is randomly repositioned to the right or left of the bottom line with each modulation of the horizontal offset.

When considering the potential implementation of a hyperacuity test as a smartphone application, one must use anti-aliasing to achieve sub-pixel resolution. Threshold algorithms for hyperacuity tests are trivial and comparable to other forced choice tests already discussed [36].

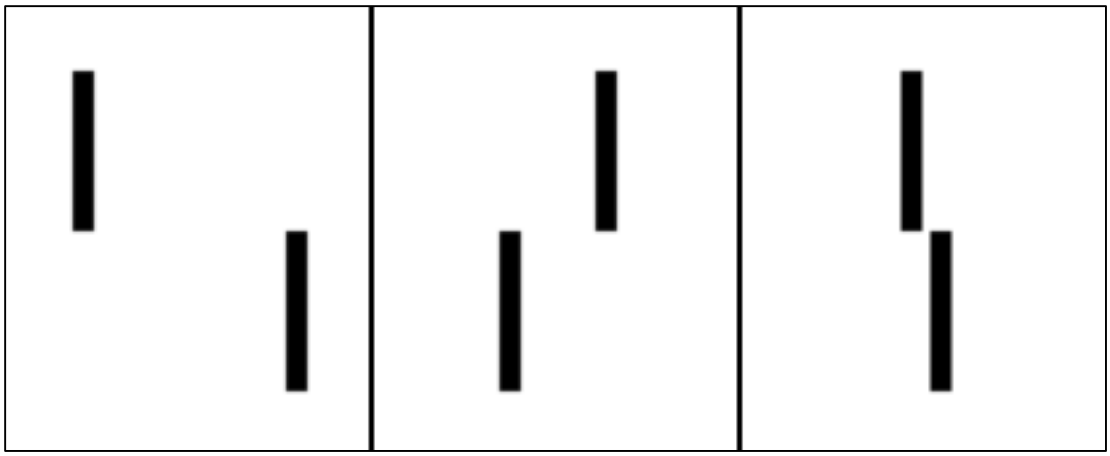

Figure 2.6: The Vernier Figure consists of two lines atop each other with a varied horizontal offset. In the panel of three Vernier Figures shown above, the horizontal offset decreases from left to right. In a hyperacuity test, the horizontal offset is modulated, with each stimulus presentation randomly orientating the top line to either the right or left of the bottom line.

2.1.5 The Mojon Chart

The Mojon chart is an optotype chart designed for the detection of nonorganic vision loss [37, 38]. Historically, subjects with organic visual loss are able to see all optotype sizes of this type (threshold for detection of spatial frequency does not become reduced as a function of target size), while patients with nonorganic visual loss claim only to see the larger optotypes. This particular optotype chart offers a different function (i.e. the ability to differentiate between cases of organic vs. nonorganic visual loss) not directly provided by the aforementioned implemented psychophysical tests, and is valuable to include in a comprehensive suite of smartphone applications.

The Mojon chart consists of a chart of chevron-like optotypes (Figure 2.7.1) [37, 38]. The contrast and spatial frequency remain fixed for each optotype in the chart, and smaller-sized optotypes are displayed on subsequent rows of each sub-chart (Figure 2.7.2

and Figure 2.7.3) [37, 38]. Much like the Landolt C, the Mojon optotype can be presented with the corresponding opening directed in different orientations (right, left, top, and bottom) [37, 38].

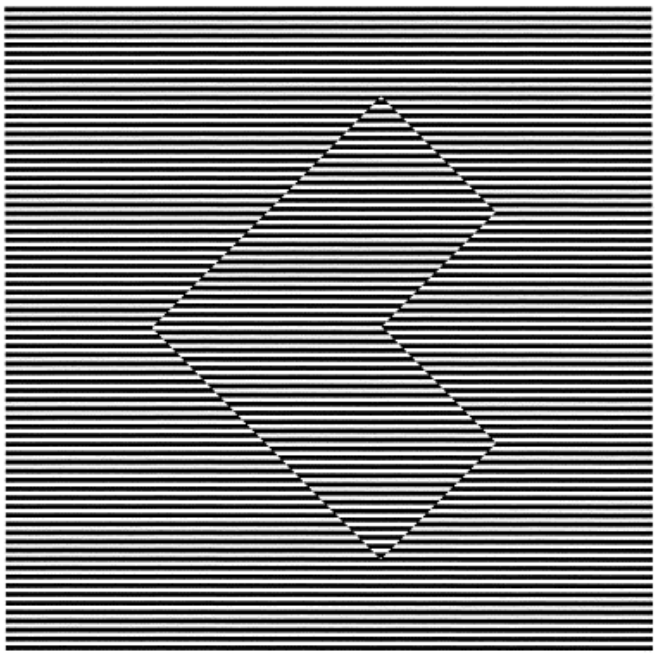

Figure 2.7.1: The optotype used in the Mojon chart. The contrast and spatial frequency of this optotype remain fixed in the chart, smaller-sized optotypes are displayed on subsequent rows (Figure 2.7.2 and Figure 2.7.3) [37, 38].

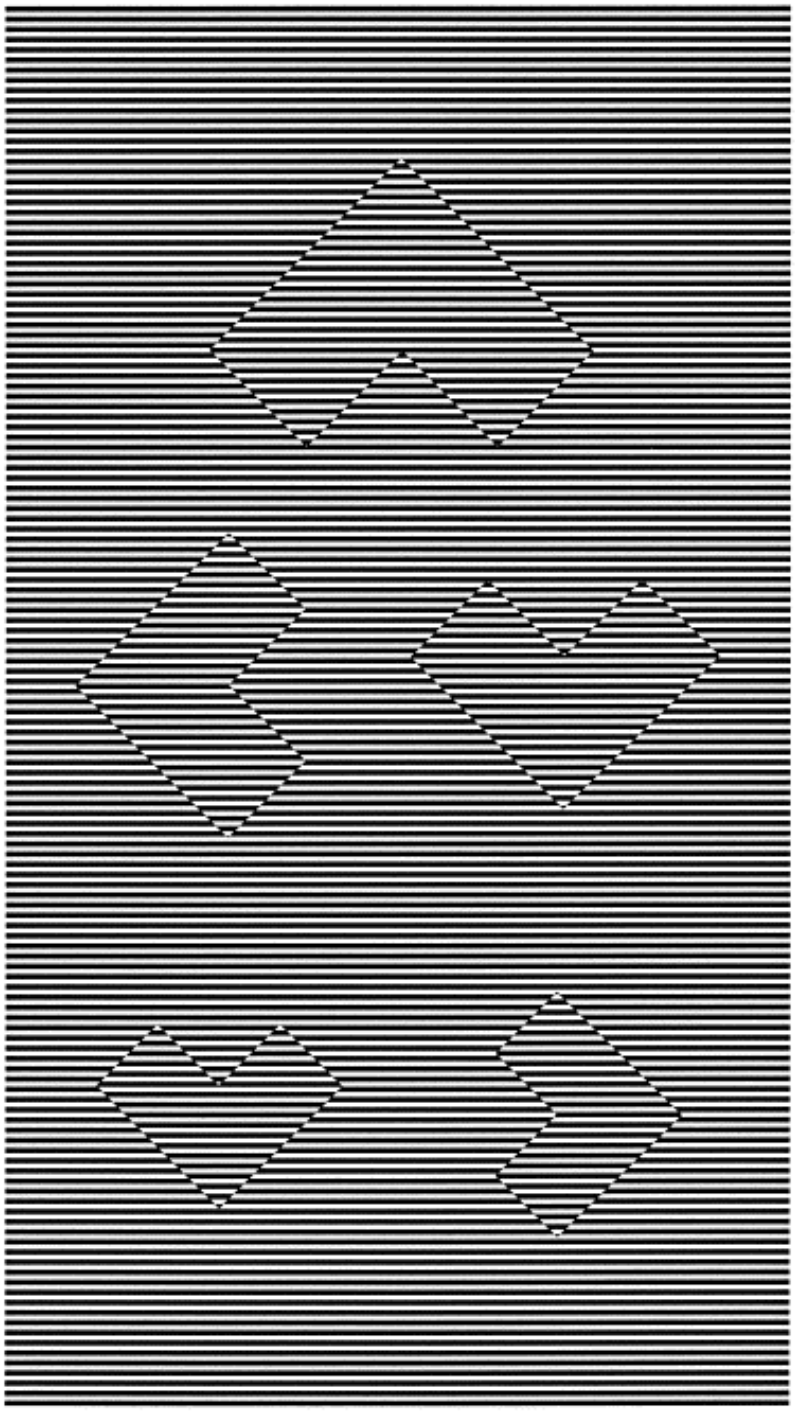

Figure 2.7.2: The first sub-chart of the Mojon chart consists of five optotypes for the observer to detect [37, 38].

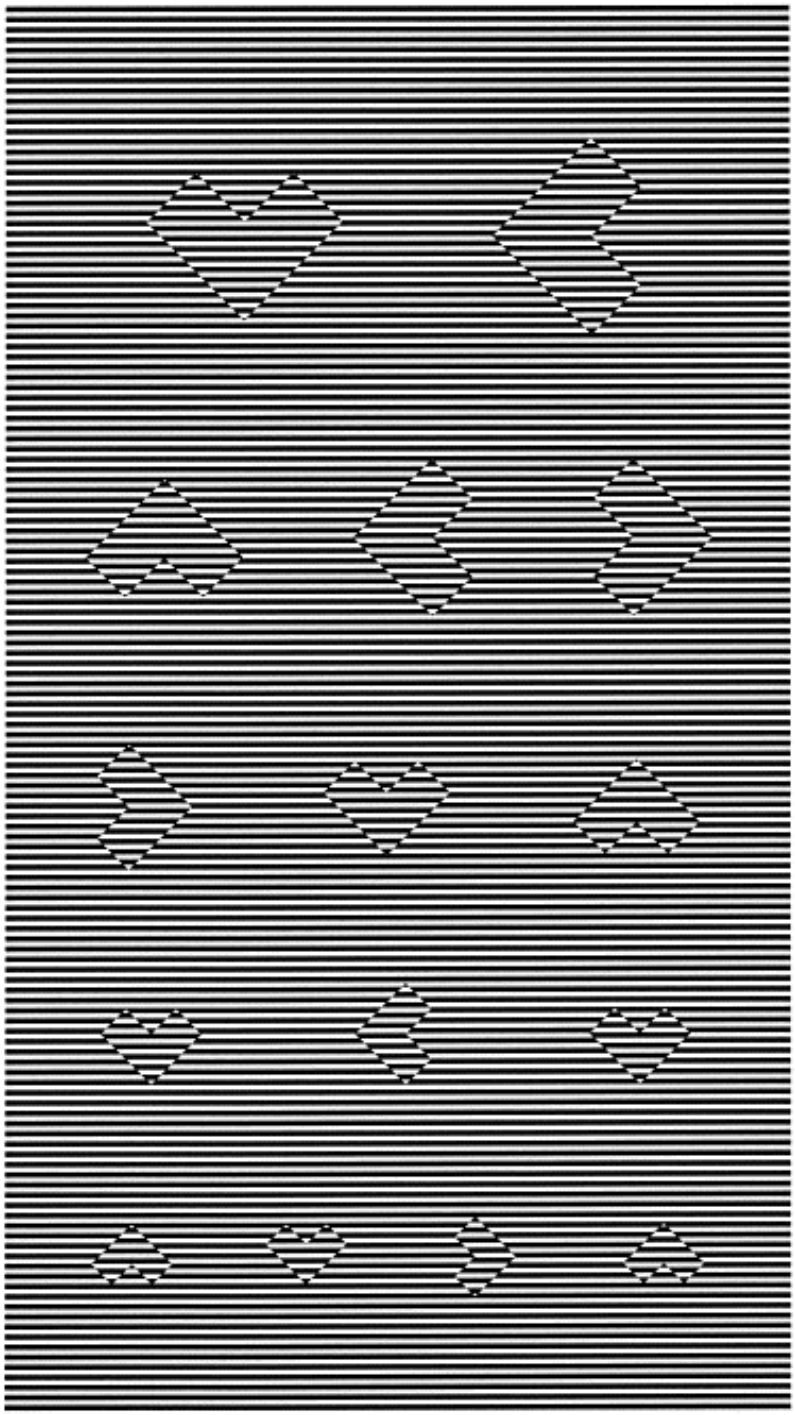

Figure 2.7.3: The second sub-chart of the Mojon chart consists of 15 optotypes for the observer to detect [37, 38].

2.2 Elements of Auditory Function

Previous work has also described the creation of a visual acuity in noise test that has been primarily used in subjects with amblyopia, where spatial resolution optotypes are presented on a background of visual "noise". Hearing test analogs can also be used to objectively quantify auditory system discrimination upon a background of noise using a smartphone. The Hearing-in-Noise Test (HINT) is the auditory equivalent of the vision in noise test and measures an individual's ability to hear speech in quiet and in noise.

2.2.1 Hearing-In-Noise Tests

HINTs are traditionally done testing both ears together as binaural hearing ability is key in noisy settings and everyday, functional hearing. Traditional HINTs take advantage of testing in four different situations: stimuli such as sentences presented with 1) no noise, 2) competing noise presented 0 degrees azimuth or front, 3) noise presented 90 degrees azimuth or right, and 4) noise presented 270 degrees azimuth or left [39-42].

Adaptive procedures are regularly used to determine speech recognition thresholds (SRT) in dB signal-to-noise ratio threshold (SNR). Specifically, SRT records the faintest speech that can be heard half of the time (or an intelligibility of 50%), and is more representative of a patient's hearing ability in real-life situations than pure-tone audiometry [39-42]. For this reason, SRT is considered a supra-threshold test with applications to quantify "hidden-hearing loss". For HINTs, the (white) noise is usually kept fixed (between 50-60 dB) at an audible level for the user, and the signal intensity is modulated [43].

Current HINTs use digit-triplets (digits in noise test), phonemes, or full-sentences presented with competing noise. Sentence tests are reported to be more efficient and

provide more reliable SRT measurements than single-word tests. During the tests, subjects must repeat or select digits/words/sentences, typically from a closed set. Each stimulus is scored as either correct or incorrect and the intensity of the stimulus is adjusted using a 1-up-1-down paradigm [43].

A 1-up-1-down paradigm is historically reliable and efficient. Stimulus levels chosen at a 1-up-1-down paradigm will oscillate about a mean level at which the stimulus is audible 50% of the time [40]. However, a 1-up-1-down paradigm is not the best procedure for estimating additional parameters of the psychometric response curve including slope, although mathematical/logistic functions can fit these curves and estimate slopes. Alternatively, 2-up-1-down paradigms provide an estimate of the SRT corresponding to a 70.7% positive response [39]. With 3-up-1-down paradigms, the user typically achieves a SNR where 80% accuracy is obtained. Commonly, a step-size of 1-2 dB is used for testing [43, 44].

CHAPTER 3

APPROACH

With the initial discussion of traditional measures of visual and hearing function, and the general use of medical smartphone applications, the subsequent sections will focus on how these tests have been extended to a smartphone platform.

3.1 Problem Statement and Functional Requirements

For the reasons and motivations discussed earlier, there is a documented need to develop a suite of validated smartphone-based tests that can be used to quantify individual visual function as well as other aspects of sensory behavior. Thus, one primary goal of the presented work is to design valuable and novel psychophysical tests and implement them for smartphone-based platforms. To accomplish this goal, a suite of applications called eyeApps and HearMe have been developed.

Before discussing the specifics regarding the design and implementation approaches of the developed psychophysical tests, a thorough list of functional requirements must be generated. The produced list of functional requirements, that the suite of smartphone applications (eyeApps and HearMe) are designed to meet, are articulated as follows:

1. The suite of applications should be developed for smartphone platforms. While any implementations for smartphone applications can easily be presented on tablet-based devices, all discussion in this work will be focused on smartphone devices as tablet devices are less commonly carried as handheld devices by clinical and household users.

2. All developed psychophysical tests should be intuitive for all potential users – that is, they should consist of easy to navigate interfaces and testing protocols. Individual, self-testing is one aim and application of the future trajectory of the discussed work. As will be discussed in greater detail later, all applications were designed to be used with minimal cognitive effort (i.e. requiring simple forms of input from the user) and in consideration with additional factors such as generational differences. Intuitive forms of testing are required to facilitate the data collection processes and preserved the authenticity of all collected data as purely objective measures of sensory function.
3. All developed testing protocols should be short in duration. The exact duration required to complete any of the smartphone applications can be determined as the optimal compromise between the level of precision of the quantification and the corresponding duration required to obtain it. For instance, a fine-grained measurement for any implemented app will likely correspond with increased user input responses and an increased testing duration (and vice-versa). The suite of smartphone applications developed thus aims to provide the maximally informative and clinically significant quantifications in the least amount of time. As will be discussed later, all implemented steps are subject to continued optimization of the testing duration.
4. All developed applications should allow the ease of transferring and extracting data between the smartphone applications and all backend databases, in accordance with all appropriate regulations including the Health Insurance

Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH).

5. The download size of all implemented mobile applications should be reduced as much as possible, as applications with large download sizes can reduce the number of prospective users as they may be forced to remove other forms of data and memory on their native devices.
6. All developed testing protocols should be devoid of potential biases in collecting data. The biggest concern in this regard, is the existence of learning effects, a phenomenon in which a specific test or protocol becomes easier with repeated use. To preserve the objective nature of measurements collected through psychophysical smartphone tests, a level of complexity must be introduced into all tests to avoid learning effects and additional biases in testing.
7. The output of the device (smartphone and tablet) in terms of multiple parameters including luminance, spatial resolution, and temporal resolution must match the intended input. These parameters are all under software control and must be rigorously inspected across a range of values to be properly characterized prior to their use in implementation and modulation in testing.
8. All developed testing protocols should be devoid of confounding effects. One primary example is the level of ambient light which can alter all measures of visual function collected. Similarly for hearing, ambient noise can be problematic. To address this, for certain developed applications (flicker sensitivity, contrast sensitivity, hearing-in-noise) use the notion of a relative difference for testing – a target intensity is modulated relative to a background

intensity. Thus, when the amount of ambient light increases, for instance, since both the luminance of the target and the background are increased, the same relative difference between the two is maintained.

The above section focuses on the functional requirements of all implemented smartphone applications (eyeApps and HearMe). The following sections discuss the system requirements, and the targeted users.

3.2 System Requirements

A set of system requirements has been specified (as follows) for all existing smartphone applications developed, as well as potential, future implementations of psychophysical tests that can be integrated into the already developed suite of applications.

1. All applications should be developed, at minimum, for Apple iOS devices (iPhones, iTouches, and iPads), preferably with the most recent software update. The developer tools, distribution platform, tight standards of calibration (to be discussed and confirmed later) and prevalence of iOS devices in the United States make it an ideal, existing choice for smartphone-based software and tests. Applications should also be developed for Android devices, but much extensive, further research is required to accomplish this feat as there is a much greater degree of variability in Android devices. Currently only the HearMe application is implemented for Android devices (this will be discussed in further detail later). The large degree of variation in the screen calibration of Android devices makes it more problematic for implementing and testing calibrated smartphone tests.

2. Low power modes (not to be confused with a device functioning on low battery) should be avoided as during this setting, the overall performance of all applications and device functionalities are sub-optimal for controlled testing.
3. As a backend database system, Firebase is a mobile and web application platform with the necessary tools and backend infrastructure to freely construct real-time databases, cloud messaging, and user authentication. As a mobile database solution, Firebase is integrated with google and requires a standard Gmail account to operate and monitor data collection. Thus, the use of Firebase has an inherent advantage in requiring authenticated users for testing. Furthermore, the Firebase platform also allows the storage of files and material that while required for an application to function, do not need to be included within the sub-directories of the software: such a feature allows the download size of an application to be minimized. Furthermore, to protect the personal information of application users, upon authentication, an individual's data is not stored under their actual email, but rather an encrypted key consisting of letters and numbers (standard encryption and decryption approaches are used by Firebase to map the storage of data to the appropriate user).
4. Regular or intermittent access to internet is preferred to ensure the secure transfer of data from the smartphone to the backend database. When access to internet is lost, any unsent data will be stored until connection to the internet has been re-established.

3.3 Data Management

All implemented applications provide end users and researchers with straightforward approaches to collect and transfer data in a manner consistent with ethical considerations. Once a particular smartphone test has been completed, the resulting metrics and performance features are stored in the backend cloud database and for convenience, can also be transmitted in a brief email report to a secure email for data collection and analysis.

3.4 Target Users

The suite of developed psychophysical tests target a wide spectrum of users including physicians and the network of providers and employees within the healthcare system, researchers and investigators interested in answering questions in basic and clinical sciences, and everyday smartphone users. For physicians and other occupations within a clinical setting, rapid smartphone applications serve as a tool to provide quick quantifications of sensory function that requires minimal resources, a characteristic that makes it practical and appealing for telemedicine, rural medicine, and global medicine applications.

For the researcher, the implemented smartphone applications allow comprehensive data to be collected on a large scale, a characteristic that is appealing when one is faced with the need to boost statistical power and significance for genotype-phenotype analyses, or when an investigator is tasked with monitoring outcomes on a regular basis following surgical or pharmacological interventions. As described earlier, very little is known about the time-course and variability of a plethora of diseases, specifically ocular and neurological disorders. Patient-centered, routine, at-home testing,

if done properly can help answer countless existing questions and provide quantitative representations of symptoms and expected clinical findings.

Most importantly, smartphone applications provide numerous benefits to individuals, regardless of background and occupation, who have new, mobile opportunities to quantify their vision and hearing through expert-constructed, accessible tools. Similar to monitoring heart rate, diet, and exercise, now, due to the tools developed and discussed in the present work, individuals have the ability to routinely monitor their sensory function over a specified interval of time, or before and after a general life event, operation, or procedure. With the several identified target user groups, there are far-reaching applications for objective psychophysical quantitative tests.

CHAPTER 4

METHODOLOGY AND IMPLEMENTATION

This section is devoted to describe, in full detail, the implementation of the aforementioned smartphone applications. Each sub-section focuses on the implementation of one psychophysical test, discussing the iterative design entailed (the level of which varies depending on the novelty of the test), the current interface and testing paradigms, future modifications to the current implementations that must be considered, and the objective measurements obtained through each psychophysical test.

Following the detailed descriptions of the suite of applications developed, the discussion will transition to the series of experiments conducted using the developed tools. These experiments span forms of what will be referred to as technical validation and clinical validation, and entail performing the necessary calibrations, testing the workflow of the system, and collecting data in normative and non-normative subjects.

4.1 Flicker Fusion Application (eyeFusion)

Critical flicker fusion and other methods of flicker perimetry have long been established as a sensitive measure of a visual conduction time, which becomes abnormal in retinal and optic nerve disorders. As motivated earlier, there is an appeal to having a smartphone flicker fusion test that could displace the use of other, traditional means of measuring critical flicker fusion. eyeFusion was developed for this purpose and measures flicker sensitivity.

4.1.1 Previous Test Iterations

Before the current implementation of eyeFusion is discussed, previous iterations of the testing protocol and stimulus must be described. Initially a bar pattern stimulus was used to generate the flicker, where adjacent bars of varying luminance would oscillate at a specified temporal frequency. Using this bar stimulus, three major design iterations were produced to ascertain the preferred presentation of the stimulus on the device of the screen. The first design iteration consisted of dividing the screen in half between the flickering half and the static half. In this iteration, a forced choice response task was implemented where the user must identify and tap the half that is flickering. This approach is important as it requires precise identification of the stimulus and allows the software to quantify response times (as opposed to waiting for the user to provide a yes/no response after the stimulus has been consistently presented for one second). However, problems associated with this stimulus presentation include the relatively large size of the stimulus and the absence of a smaller region for the user to fixate on (with a larger flickering target, users can use the peripheral vision to detect flicker).

In the next testing iteration with the bar stimulus, the stimulus presentation was moved to the central region, reducing its size and attempting to get potential users to focus on the center of the device's screen. Having the user fixate on the central region of the device screen is also important to reduce instances where they may miss a stimulus presentation because they were focusing on other regions of the screen. However, this iteration only included a flickering or a non-flickering stimulus (but does not present both concurrently), and an authentic forced choice selection task was not implemented. Thus, to combine the strengths of both flicker stimulus presentation approaches discussed thus

far, the two designs were merged together, creating a test presentation that includes a more traditional 2-alternative forced choice task for the test taker where the stimulus is presented in the central, stamp-sized region of the screen and the test taker must fixate on this central region. A schematic of the evolution of the testing interface discussed is illustrated in Figure 4.1

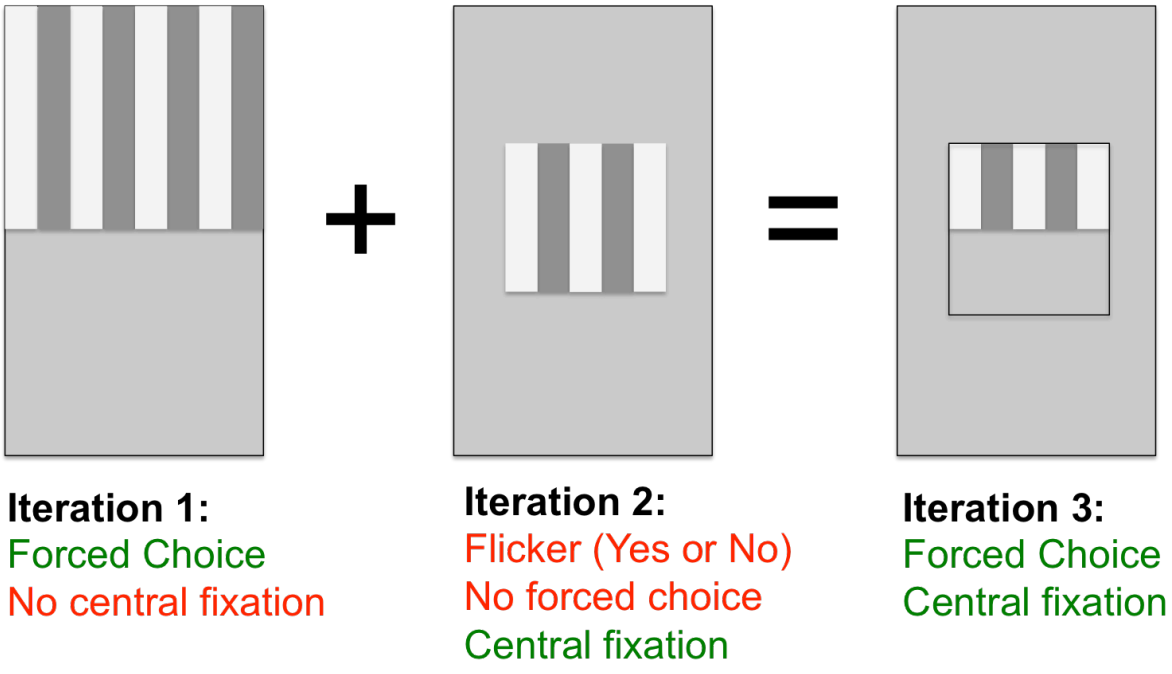

Figure 4.1: A schematic illustrating the interfaces of the previous flicker fusion test design iterations and stimuli presentations.

After determining the stimulus to be used and the manner with which to present it on the device screen, the next major component addressed was the method to modulate the stimulus. One approach that was considered was constructing a repository of videos that could be uploaded to the application. This approach was instantly disregarded as it is impractical and not dynamic. Hundreds of videos would need to be generated to cover the frequency and contrast combinations, whereas programmatically controlled parameters to be varied is a much more efficient process.

Current mobile device hardware limits the range of flicker frequencies that can be implemented. Existing mobile-phone and tablet devices have a maximum frame refresh rate of 60 frames per second. Considering the fact that one stimulus cycle requires two frames (for at least two different intensities), the maximum flicker frequency that could be achieved is 30 Hz. Furthermore, applying the same logic reveals that additional flicker frequencies that could be implemented include 2, 3, 5, 6, 7.5, 10, and 15 Hz. By altering only the flicker frequency, eyeFusion could only test around eight discrete points per user which would likely not be enough to measure significant differences across individuals considering that the range of frequencies from 2-6 Hz would be trivial for a majority of test takers. Additional ways must be considered to modulate the stimulus to sample from varying levels of difficulty, and measured fine-grained thresholds.

The limitations of only varying the flicker frequency resulted in the design decision to alter both the stimulus contrast (between the bars, still on a median grayscale background) and the flicker frequency. Thus, since the contrast is modulated, eyeFusion can be considered to be a flicker sensitivity test. By testing stimulus trials at a range of contrasts at multiple frequencies, eyeFusion can now compensate for mobile-phone and tablet device limitations and sample many data points, as opposed to a few distinguishable frequency points. Modulating the contrast parameters across a set of temporal frequencies is performed programmatically, removing the need for a large aggregate of pre-recorded videos.

Regarding the protocol specifications, minor additions to the application were made along such as including a menu screen, an instructions screen, and a screen at the end of the test to transmit all the collected data. Under the initial design iterations, the

need became apparent to introduce a fixation target (Figure 4.2) to direct the user's attention to the central region of the screen (where the stimulus would be presented). As a result, an additional consideration had to be made regarding how to present the stimuli with varied flicker frequencies and bar contrasts. Originally, the different trials were presented as random contrast and frequency combinations, with the fixation target immediately presented before each stimulus. However, as discussed shortly, this presented a great difficulty regarding how to quantify the threshold. The resulting test design of the first round of eyeFusion iterations includes multiple frequency levels, with contrast sweeps occurring at each frequency following a 2-up 1-down paradigm, with the fixation target presented before each frequency level. A basic form of user feedback was built into the eyeFusion test as a variably colored rectangular icon in the upper right-hand corner of the app (Figure 4.2).

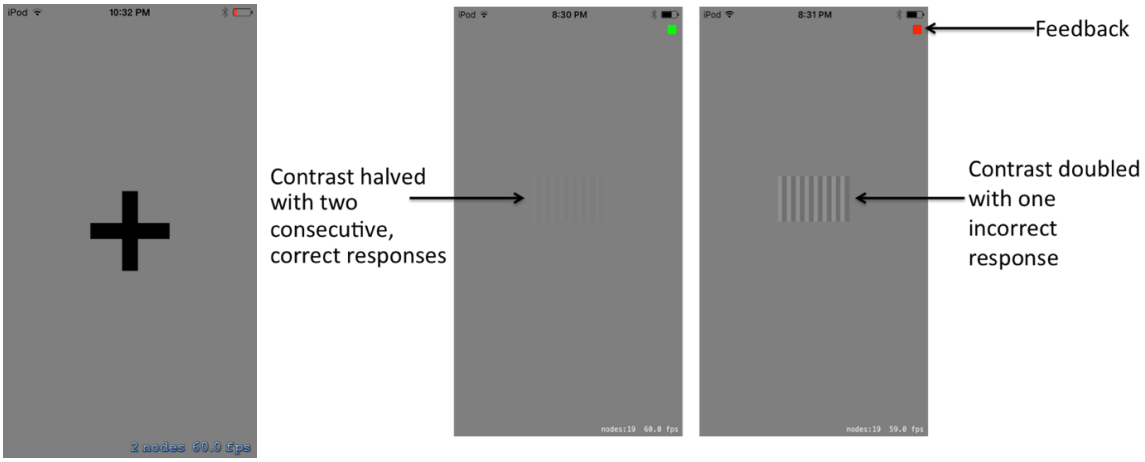

Figure 4.2: A schematic of the user interface illustrating the fixation target (left) and stimulus presentations (right) with an icon that provides feedback to the user, regarding whether their response was correct or incorrect.

In the initial stages of eyeFusion, the flicker sensitivity threshold could not be computed. This was due to the fact that random stimulus presentations were implemented and only a final score of the number of correct and incorrect responses could be determined. Once the testing protocol designed was altered to include a more systematic way of modulating the parameters through frequency levels and contrast sweeps, the threshold could be determined as the average of four response reversals. A response reversal is defined as one incorrect response followed by two, successive correct responses. A contrast sweep occurs until the user gets the minimum contrast level correct, or when four response reversals occur. The flicker fusion threshold is then computed as the average contrast of the reversals at the specific frequency. Another design decision was implemented that provided individuals with the ability to exit the test following a particular flicker frequency level (with the data still transmitted).

To summarize, the culmination of several iterations of an initial eyeFusion test was implemented as an iOS mobile-phone application to quantify flicker fusion threshold using contrast modulation. Throughout the testing protocol, the central region of the device's screen is divided between a static half and a flickering half, consisting of rectangular bars oscillating between two varying grayscale values, combined with a sinusoidal transform/cosine envelope. A fixation target is briefly displayed before each test presentation, and each presentation lasts one second, during which the user must provide a forced-choice response and select the flickering half.

Restricted by the 60 frames per second frame refresh rate of a standard mobile-phone, earliest iterations of eyeFusion tested four different temporal frequencies: 3, 10, 15, and 30 Hz. 3 Hz was selected as a suitable training phase for subjects as the low-

frequency stimulus flickers should be seen by most individuals (controls and diseased patients). 10 and 15 Hz were selected as “diagnostic” frequencies as various studies mentioned earlier have described temporal frequency flicker sensitivity loss at this range (or a lower range) of frequencies [4]. For each frequency, the bar-stimulus contrast was adjusted using a two-up one-down test paradigm. Figure 4.3 (below) depicts a schematic of the implemented test.

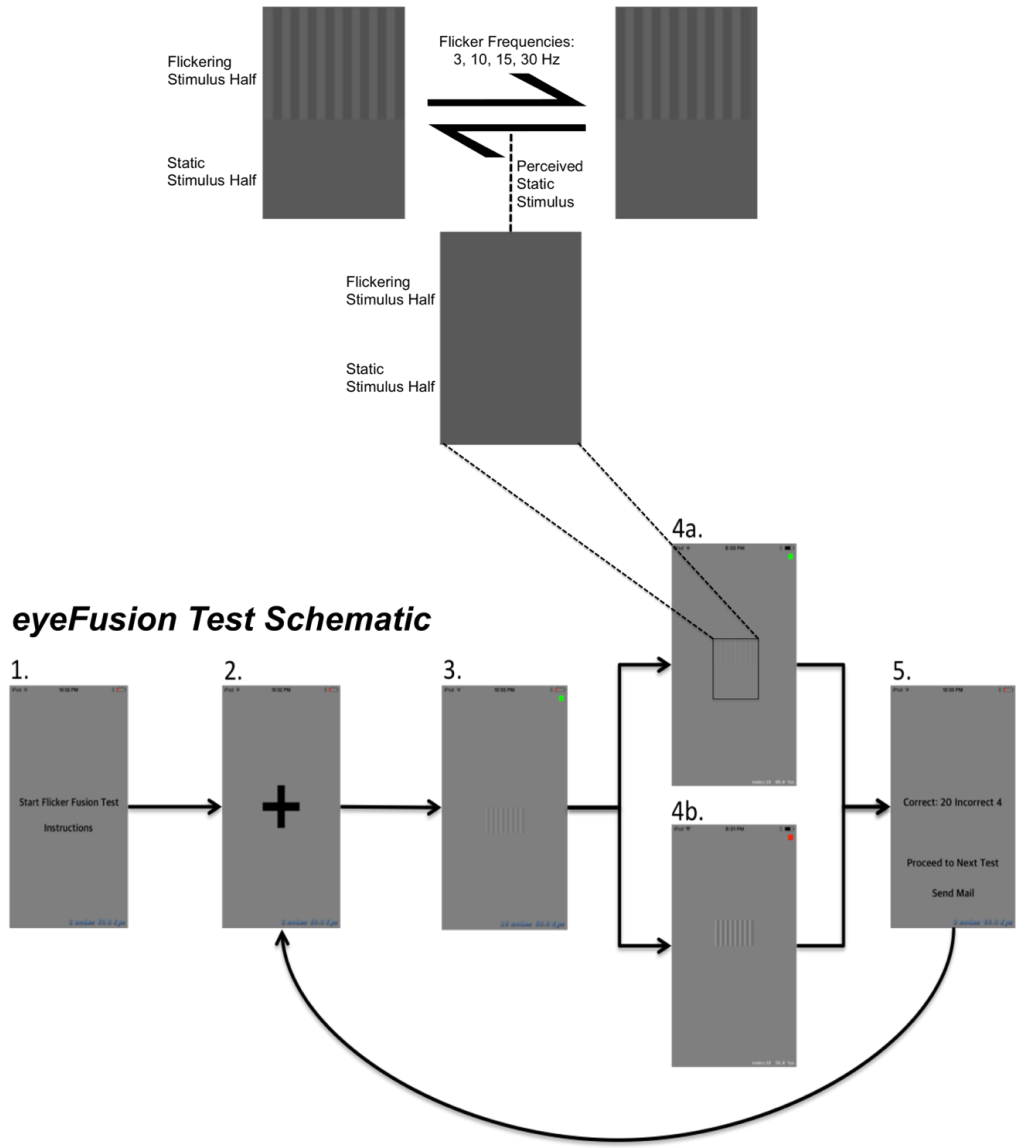

Figure 4.3: An early iteration of eyeFusion Testing Protocol and User Interface – this schematic depicts the test 1) menu screen, 2) fixation target to prime the user to continually fixate on the central region of the device to look for the flicker stimulus, 3) beginning of a contrast sweep with a one second presentation of flicker fusion bar stimulus at a specific temporal frequency, 4) user feedback in upper-right corner of device and presentation of the stimulus at the new contrast (a – decreased contrast; b – increased contrast) according to a 2-up 1-down test paradigm, and 5) repeat of fixation target and contrast sweep at an increased temporal frequency (in order - see Figure 2: 3, 10, 15, and 30 Hz).

A schematic of the initial testing protocol, depicting the exact ordering of the frequency levels and the contrast sweeps is shown below (Figure 4.4).

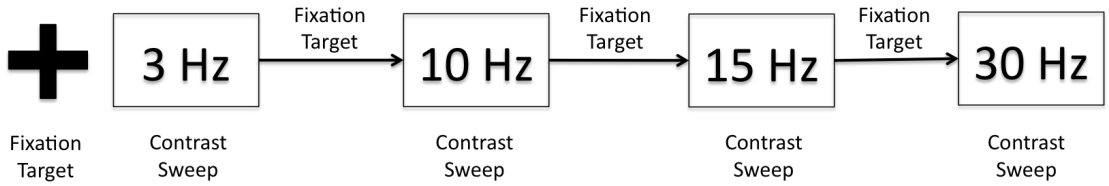

Figure 4.4: This diagram illustrates the eyeFusion Contrast and Frequency Parameter Modulation – this schematic illustrates the implemented algorithm for testing individual frequencies and performing the individual contrast sweeps. Prior to testing at a new temporal frequency, a fixation target is re-displayed to the user.

The flicker fusion threshold was measured as the average frequency/contrast combination for four response reversals. For the implemented 2-up 1-down test paradigm, a response reversal is defined as a three-consecutive response sequence when the user incorrectly selects the flickering half (which increases the bar contrast), and then correctly selects the flickering half for two consecutive trials.

4.1.2 The Improved eyeFusion Test

One major drawback of the initial flicker fusion (sensitivity) testing paradigm discussed so far is the testing duration. With a 2-up-1-down paradigm and multiple contrast sweeps, each test instance can last around one minute, which is significant when considering the need to measure critical flicker fusions thresholds for each eye and binocularly with both eyes together. Furthermore, patterned stimuli, such as oscillating bars, are subject to blur which can potentially compromise the nature of the objective flicker fusion measurement – that is, blurred vision from optical causes might be

mistaken for a deficient flicker fusion measurement, which is intended to measure retinal and optic nerve disorders affecting visual conduction. Flicker fusion tests are historically renowned for their resistance to blur, and this characteristic must be preserved in a smartphone-based implementation [3].

The resulting implementation of the flicker sensitivity test discussed is an adaptive, forced-choice procedure. Forced-choice techniques historically have high test-retest reliability and small training effects. However, one criticism of forced-choice techniques is they commonly require computer assistance in the form of a second individual to help the subject [6], which can be difficult to provide in independent, self-test settings. Adaptive paradigms, on the other hand, suffer from longer test durations and usability difficulties, and fatigue can become an issue in cases, for instance, that consist of testing of each eye and binocular testing. However, these two issues can be addressed through an engineered design that makes the maximum use of the smartphone screen real-estate and an intuitive, simplistic procedure.

It was decided that the formerly discussed implementation of eyeFusion would be discarded in favor of a quicker, more intuitive forced-choice protocol that contains stimuli that would be designed to be resistant to blur, with minimal learning effects. The new testing paradigm implemented consists of a ring of twelve circular stimuli (0.3 inches in diameter, which subtends 1.56 degrees visual angle for the diameter of each circular stimulus) at different grayscale contrasts (with a Gaussian onset and offset to rule out edge effects [7]), randomized in location to minimize learning and training effects, each centered on a median grayscale intensity background as illustrated in Figure 4.5. Nine stimuli oscillate at a specified temporal frequency of either 7.5 Hz or 15 Hz, while

the remaining three "control" targets do not flicker and are presented at zero percent contrast. The objective of the user is to tap each of the stimuli that appear to flicker, which then eliminates them from the screen. A temporal frequency of 7.5 Hz was introduced as this frequency occurs at the peak of the temporal contrast sensitivity function (thus, minimizing test retest variability while maximizing the dynamic range of the procedure) [45, 46], while 15 Hz was selected as a more challenging test to add another layer of measurement and potentially provide a more fine-grained measure of flicker sensitivity to differentiate normal and abnormal function.

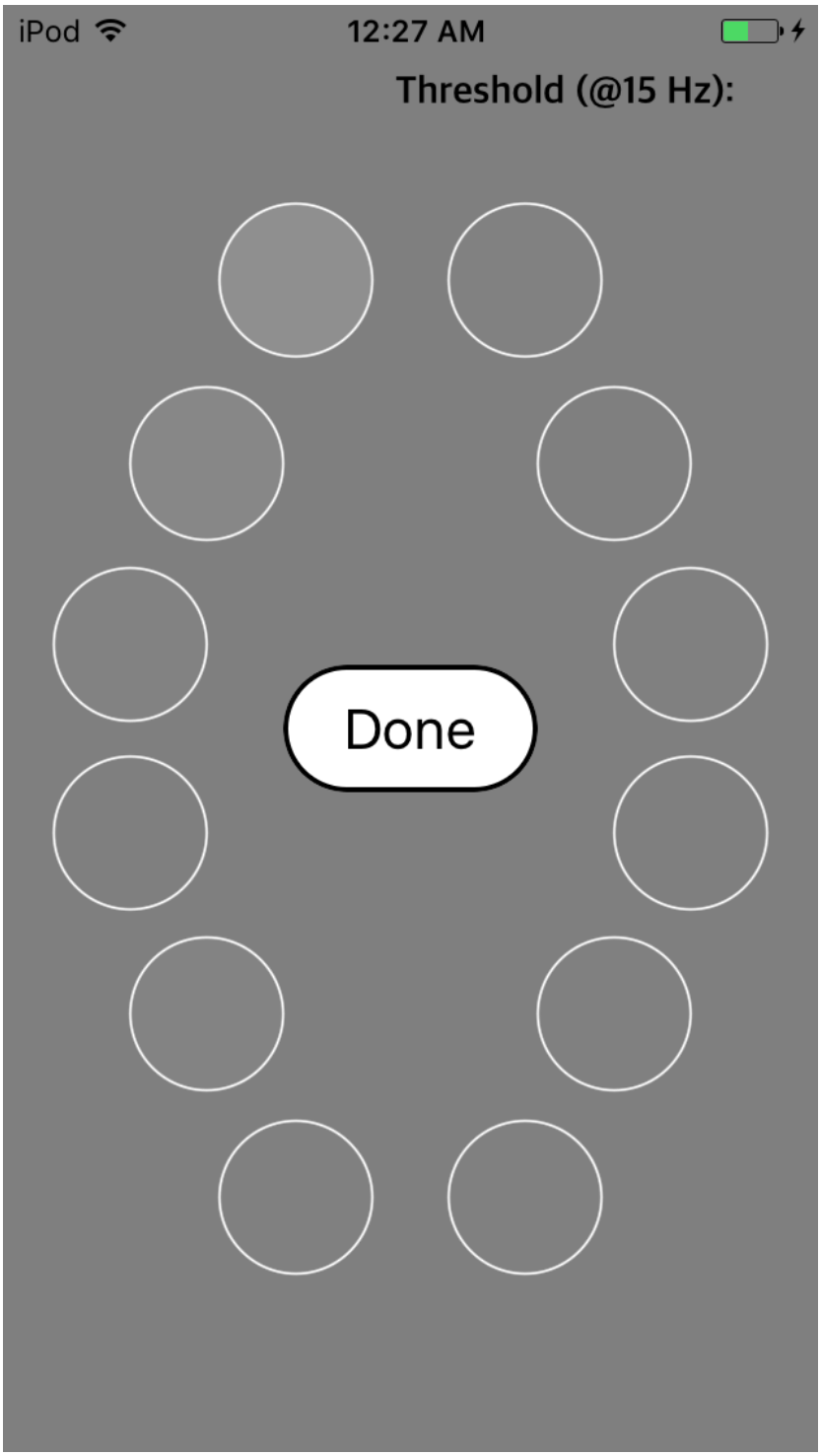

Figure 4.5: The new eyeFusion testing paradigm that consists of a ring of twelve circular stimuli flickering at the same rate (e.g; 15 Hz) and which vary in contrast.

4.2 Landolt "C" Visual Acuity Application (eyeAcuity)

A characteristic of the human sense of vision is its visual acuity, which in simple terms refers to the sharpness of an individual's vision or the smallest visible feature that an individual can discern. One straightforward approach to measuring an individual's visual acuity makes use of standard, popular eye charts such as the LogMAR or Snellen charts (Figure 2.1 and 2.2). These charts, although historically used in clinically supervised settings, can be easily converted to a smartphone application but are problematic for being used as an intuitive application for independent, at-home testing. While a user could simply read the lines of an eye chart on a smartphone, user responses to the various stimuli can be difficult to record using this approach.

To address this chief concern of using traditional eye charts to objectively quantify visual acuity on a smartphone, a Landolt C or Landolt ring (a circle with a gap) can be displayed where the user must indicate the direction of the gap in the ring in a forced-choice task. eyeAcuity implements this interface as a Landolt C surrounded by eight arrows aligned with the eight different orientations and openings at angle multiples of 45 degrees (Figure 4.6).

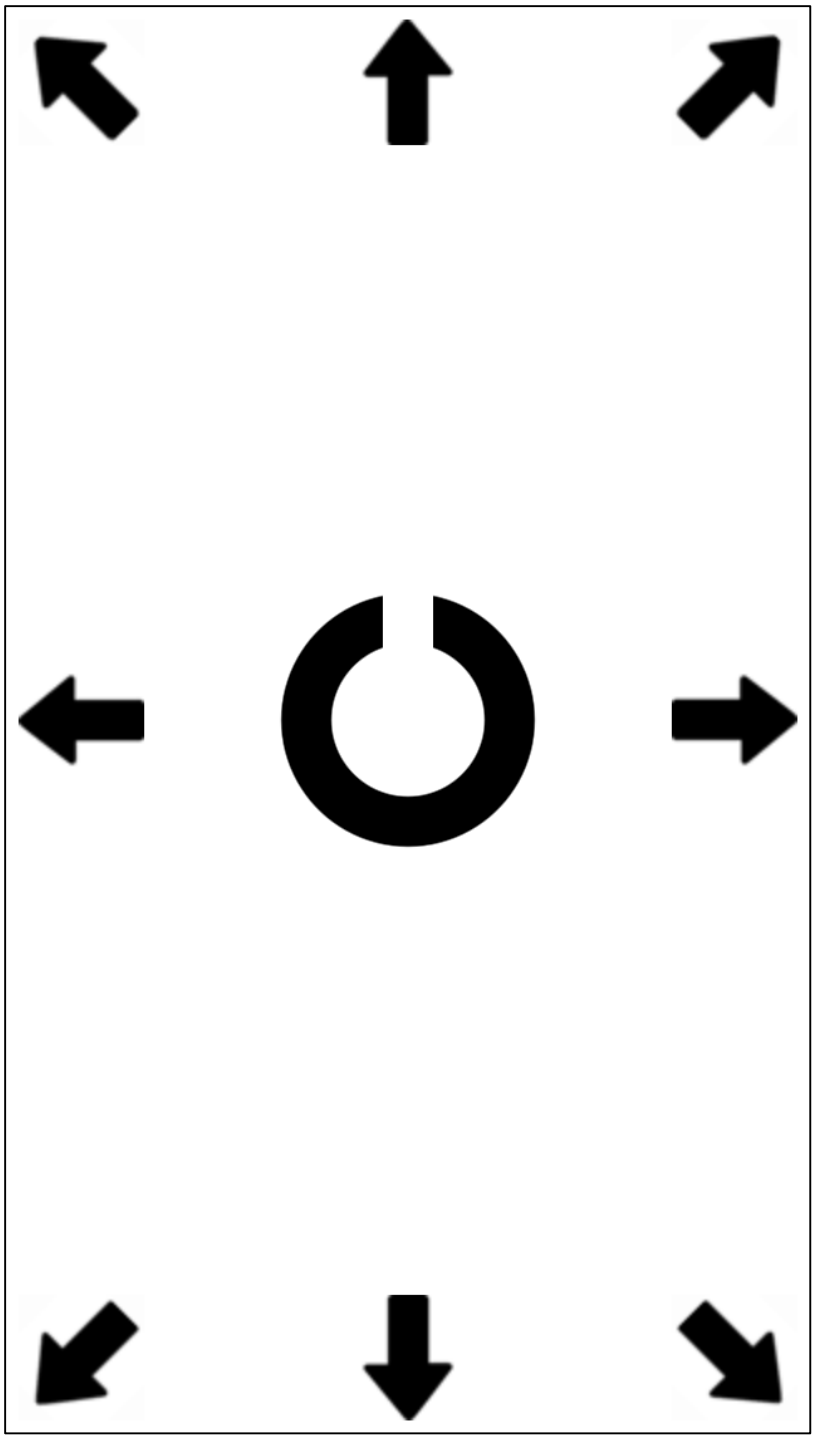

Figure 4.6: The user interface of the eyeAcuity Landolt C visual acuity test. The user taps the arrow located at the gap in the C and if correct, the size of the C successively becomes smaller, testing the threshold for detection at higher spatial frequencies which equates to detection of spatial resolution of a subject's vision.

Previous studies have reported a good measure of visual acuity using the Landolt C approach as being the smallest size where the direction of the gap is correctly recognized around half of the time (50% accuracy). Thus, the testing paradigm implemented utilizes a 1-up-1-down paradigm where each correct response results in a 1.5-fold decrease in the radius of the ring, and each incorrect response results in a 1.5-fold increase in the radius of the ring (subject to the spatial limits of the device screen). 1-up-1-down paradigm historically produce thresholds where the subject is able to detect the presence, or in this case correct orientation, of the stimuli 50% of the time.

To save testing time, the average of four response reversals is used to quantify an individual's visual acuity. Response reversals refer to instances where an incorrect response is immediately preceded by a correct response (with a response referring to the correct determination of the gap of the Landolt C). Returned by the smartphone is the dimension of the radius of the Landolt C at the averaged threshold. This measurement, in the units of the device screen, must be equated to the physical distance of gap opening (which is equivalent to 0.4 times the radius of the ring as the gap opening is one-fifth of the diameter of the ring radius), and then converted to a visual angle according to the approximate distance that the device was held at (the tangent inverse of the average reversal gap opening divided by the observing distance of 0.4 meters).

4.3 Contrast Sensitivity Application (eyeContrast)

Another characteristic of visual function is contrast sensitivity. In simple terms, a contrast sensitivity test measures the ability to distinguish between finer and finer increments of light versus dark. Driving at night, for example, is a situation in which

good contrast sensitivity is required as individuals who have low contrast sensitivity may have problems with driving during the nighttime.

Similar to the visual acuity application described earlier, the application developed to measure contrast sensitivity also makes use of the Landolt C (Figure 4.7). The testing paradigm, and nature of the forced-choice test remain the same. However, the stimuli are presented at a fixed radius throughout the entire testing duration. Rather than changes in visual angle, the contrast between the Landolt C and the background is modulated with each stimulus presentation.

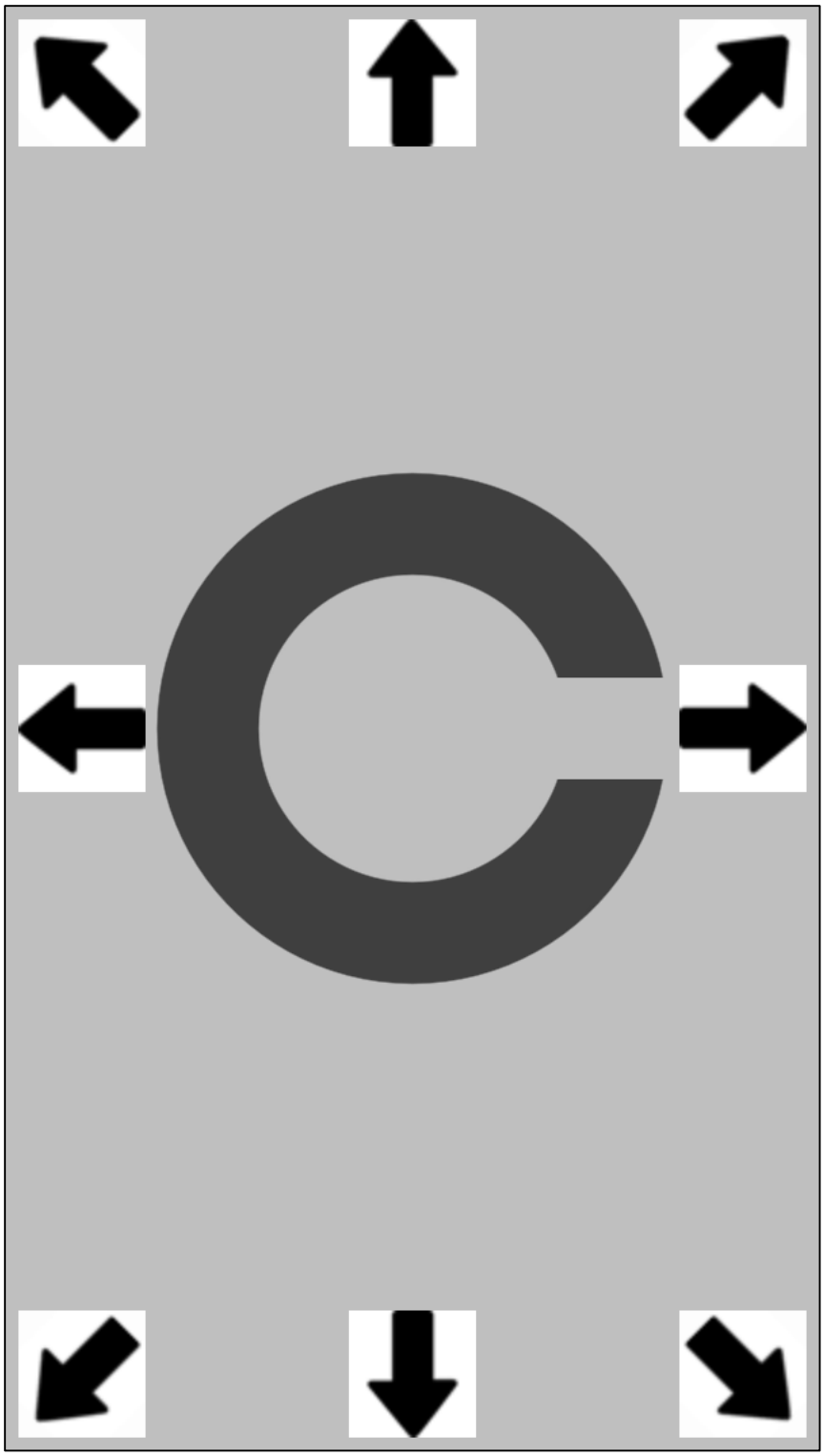

Figure 4.7: The user interface of the eyeContrast contrast sensitivity test. The size of the Landolt C is fixed at a large, low resolution size and the contrast between the C and the background is varied to determine the threshold for detecting the minimal contrast needed to identify the location of the gap in the C.

Similar to visual acuity, the threshold measure of contrast sensitivity (using the Landolt C approach) is defined as being the minimum contrast sensitivity where the direction of the gap is correctly recognized around half of the time (50% accuracy). The testing paradigm implemented again utilizes a 1-up-1-down paradigm where each correct response results in a 1.5-fold decrease in the contrast of the Landolt C, and each incorrect response results in a 1.5-fold increase in the contrast of the Landolt C (subject to the contrast and luminance limits of the device screen). The average of four response reversals is used to quantify an individual's contrast sensitivity.

The contrast sensitivity threshold determined can be equated using the Weber contrast or the Michelson contrast formulations. Weber contrast is mathematically defined as:

$$Weber\ Contrast = \frac{I - I_b}{I_b}$$

where I and I_b represent the luminance of the features and background respectively.

The Michelson contrast is mathematically defined as:

$$Michelson\ Contrast = \frac{I_{max} - I_{min}}{I_{max} + I_{min}}$$

where I_{max} and I_{min} represent the highest and lowest luminance.

The Weber contrast is commonly used and preferred in situations where small features are present on a large uniform background, and the average luminance of the entire smartphone screen (for the scenario of the presented work) is approximately equivalent to the background luminance. The criteria for using the Weber contrast over the Michelson contrast are met for the circumstances of the suite of applications

discussed in the present work, particularly the contrast sensitivity, flicker fusion, and vanishing optotype tests.

4.4 Vanishing Optotype Application (eyeVanish)

Central to quantifying and characterizing the visual function of any individual is determining his or her contrast sensitivity function. Contrast sensitivity measurements that include both spatial frequency and contrast can be used to determine and plot an individual's contrast sensitivity function, a plotting of the curve (typically an inverted U-shape) that defines the lowest contrast level that an individual can detect for each spatial frequency tested. To be detected by the human visual system, in most cases, objects or optotypes with spatial frequencies on both ends of the spectrum (high or low) must have significantly higher contrasts than objects with intermediate spatial frequencies. In other words, the optimal spatial frequency that yields the best contrast sensitivity is typically an intermediate value or medium-width grating or linewidth.

Valuable clinical information can be extracted through understanding how an individual's contrast sensitivity varies as a function of spatial frequency. For instance, some ocular and neurological disorders can alter aspects of contrast sensitivity but not spatial frequency, and vice-versa to produce specific patterns of the contrast sensitivity function which may help to differentiate one cause of visual dysfunction from another (e.g. multiple sclerosis, compressive optic neuropathy, glaucoma, ischemic optic neuropathy).

Thus, there is a need to develop mobile modalities of determining the contrast sensitivity function of each eye of an individual, similar to the Vistech VCTS 6000 and 6500 Contrast Sensitivity Tests (Figure 2.4). This work posits that the concept of a

vanishing optotype test can be used to quantify contrast sensitivity functions in an efficient manner that is relatively easy for a subject to self administer.

The current implementation of the vanishing optotype test, eyeVanish, is an attempt to construct a quick smartphone-based test to measure an individual's contrast sensitivity function. This application presents the user with a grid of square targets comprising 15 combinations of five different spatial frequencies and three different contrasts, presented in random locations of the device screen as illustrated in Figure 4.8.1. Contrasts are defined as the difference between the grayscale values of the interior of the square optotypes and the space averaged value of the inner and outer square borders of the optotypes. Spatial frequencies are altered through varying the line widths of the three different portions (outer, middle, and inner) of the square optotypes. For instance, the highest spatial frequency corresponds to a 1-2-1 linewidth pattern (all in pixel units or 1/72 of an inch for standard-resolution screens) corresponding to the outer, middle, and inner linewidths respectively.

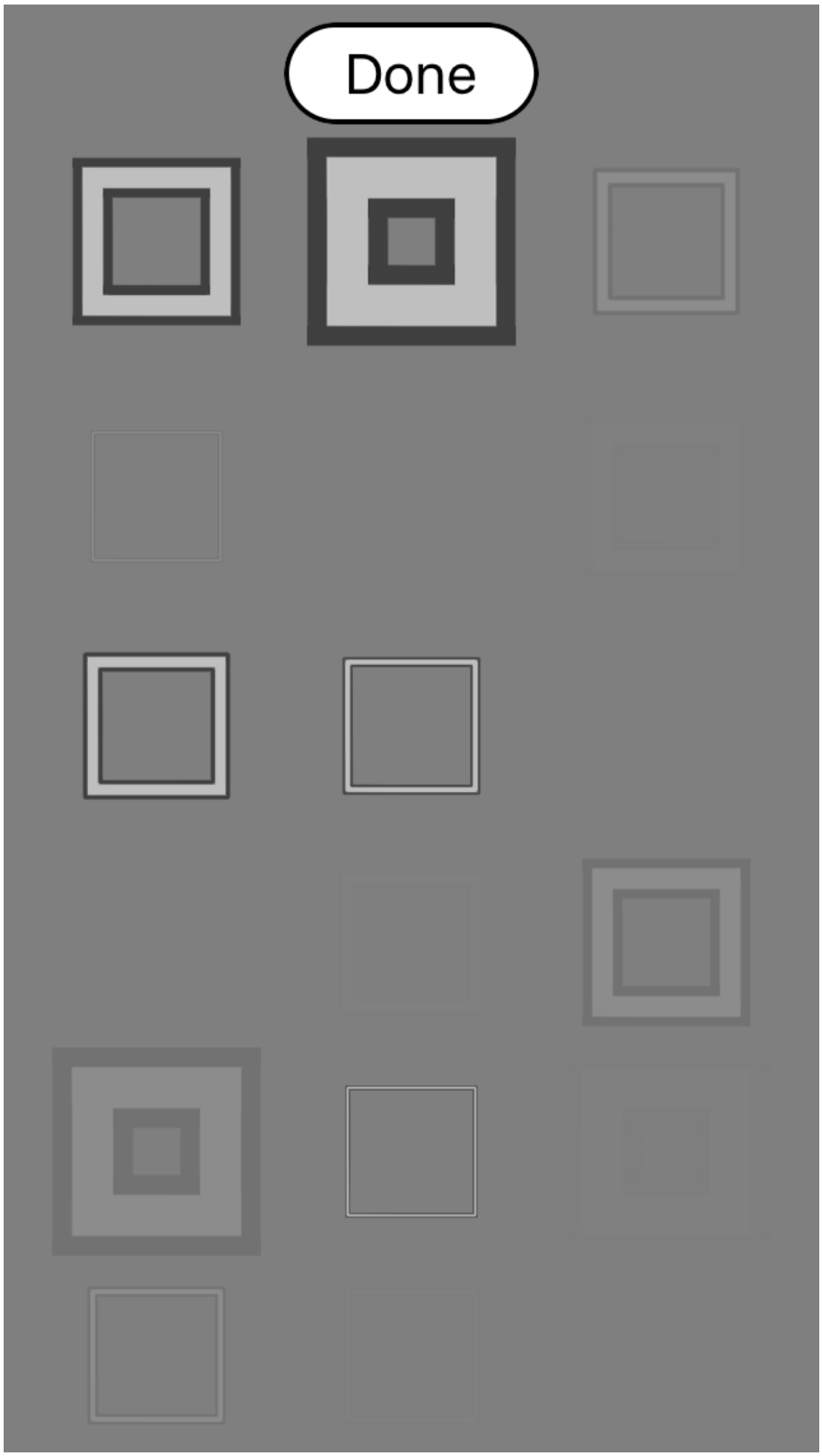

Figure 4.8.1: The user interface of the first step of the eyeVanish vanishing optotype test showing objects that vary in both spatial frequency and contrast.

Similar to the objective of the flicker fusion application discussed earlier (eyeFusion), the objective of the user is to tap all the targets they can see. Once the first step is completed, a second display consisting of 15 targets is presented at the (fixed) highest spatial frequency that can be detected with a much finer gradation of contrast values (Figures 4.8.2 and 4.8.3). In the end, the combination of the highest spatial frequency and the lowest contrast detected by the user is quantified to derive the contrast sensitivity function of each eye tested.

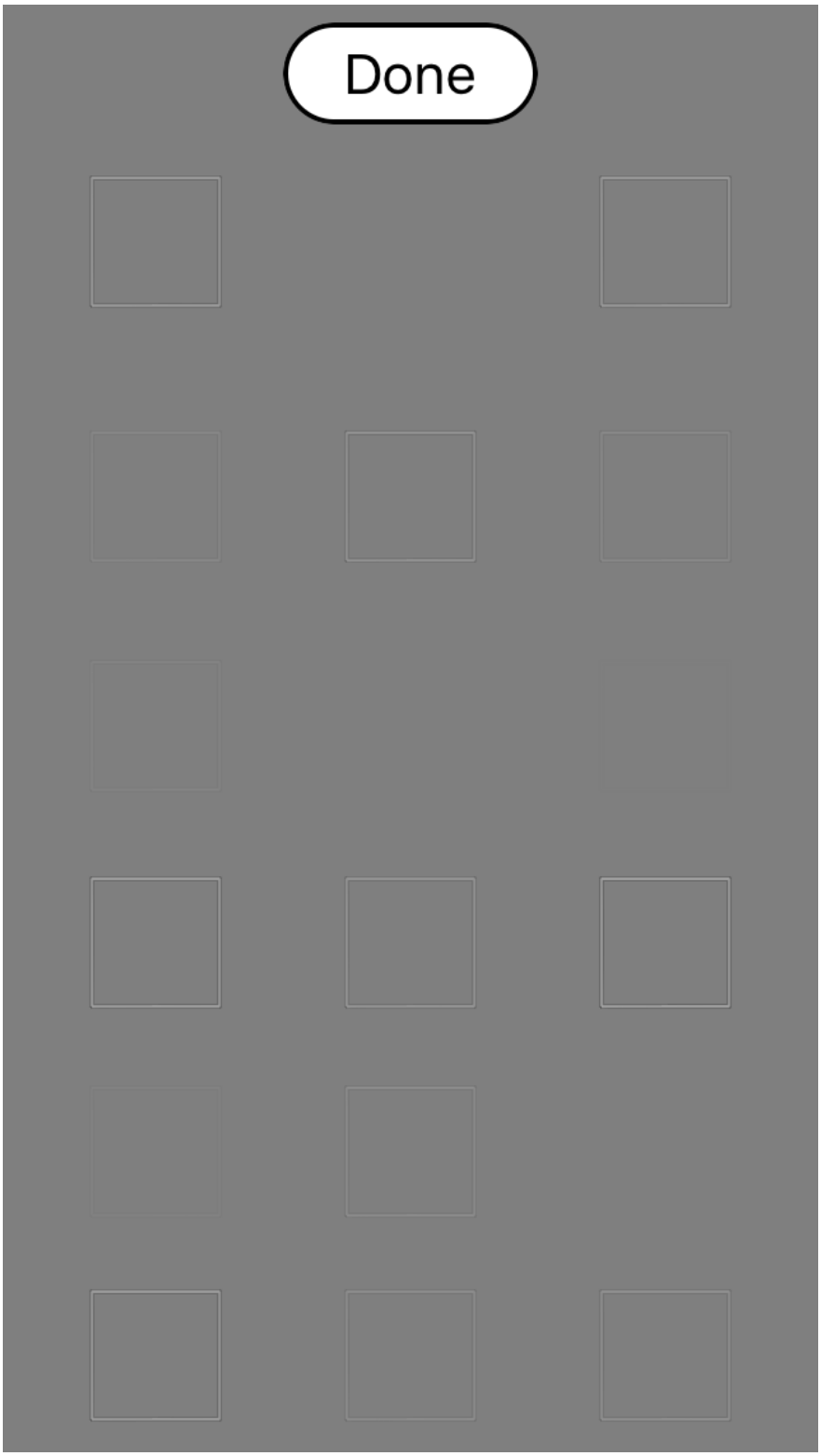

Figure 4.8.2: The user interface of the second step of the eyeVanish vanishing optotype test, where the second step samples across the contrast range using high spatial frequency targets.

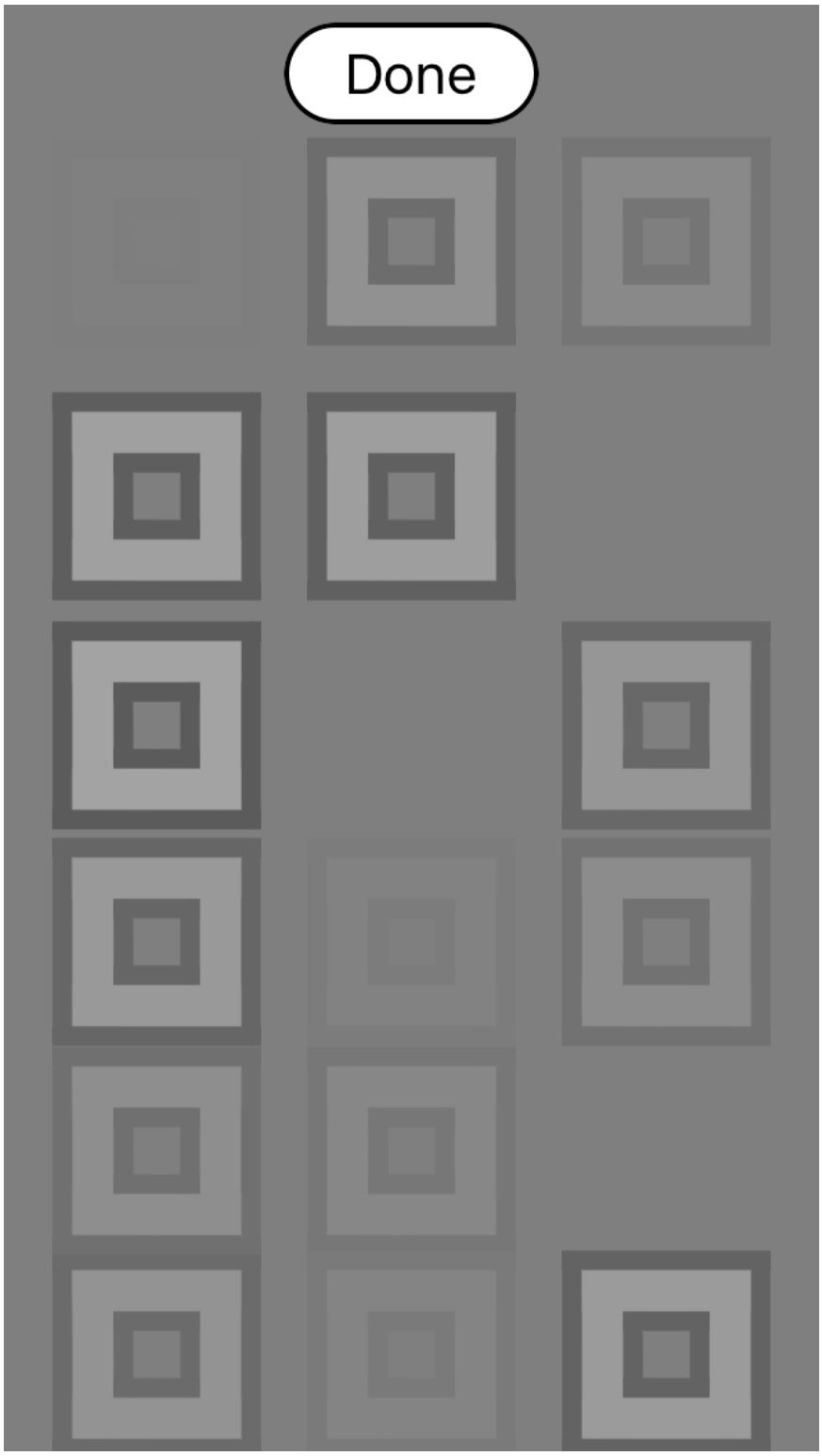

Figure 4.8.3: The user interface of another step of the eyeVanish vanishing optotype test, where the this step samples across the contrast range using low spatial frequency targets.

It is worth noting that there are limitations to the current implementation of the vanishing optotype test (as will be discussed in the subsequent chapter), namely that the complete contrast sensitivity function cannot be quantified and recreated. Furthermore, the current implementation does not apply a filter to the optotypes, and thus, the high frequency component created by edges is not diminished or avoided entirely (this is of particular concern for the lower spatial frequency targets). Iterations of the vanishing optotype test are being re-implemented with the idea of presenting a grid of sine-wave, gratings, either rectangular bars or circles, filtered with a low-pass filter to solve this problem.

The newer proposed design contrasts with the existing implementation in that it does not make use of square optotypes, but it maintains the similarity of utilizing varying combinations of contrast and spatial frequencies for each target with the intention of sampling as many points as possible on the contrast sensitivity function without making the test excessively long or arduous. Future work will be directed to assess whether this approach can be used to quantify contrast sensitivity as the lowest contrast grating detected by the observer, plot a contrast sensitivity function for the observer using the contrast sensitivity at each spatial frequency.

4.5 Vernier Visual Acuity Application (eyeAcuity)

Vernier acuity is commonly referred to as hyperacuity (for example, the precision of a sliding caliper), because the higher dynamic range of resolution that can be tested is five to ten times higher than that of visual acuity.

The developed Vernier acuity test implements the “Vernier Figure” that consists of two lines atop each other with a varied horizontal offset (Figure 4.9). A test subject

must judge which way, to the right or left, the top Vernier line is offset from the bottom one. The top Vernier line is randomly repositioned to the right or left of the bottom line with each modulation of the horizontal offset.

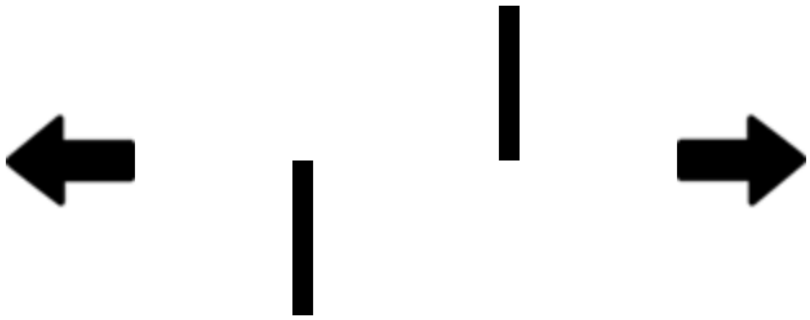

Figure 4.9.1: The eyeVernier hyperacuity testing interface - the initial presentation of the Vernier figure at a starting horizontal offset. The subject selects the arrow which moves the two bars closer together, until one can no longer determine if there is an offset.

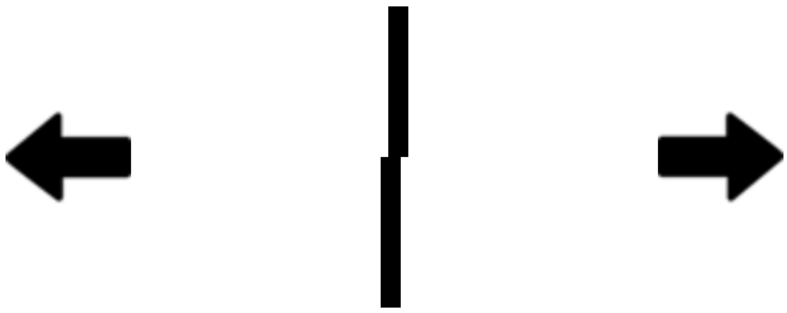

Figure 4.9.2: The eyeVernier hyperacuity testing interface at a later step in the testing protocol where the Vernier figure has a decreased horizontal offset.

The testing paradigm implemented utilizes a 1-up-1-down paradigm where each correct response results in a 1.5-fold decrease in the horizontal offset of the Vernier lines, and each incorrect response results in a 1.5-fold increase in the horizontal offset of the Vernier lines (subject to the spatial limits of the device screen). Similar to the reasons described for visual acuity (i.e. a good measure of visual acuity being defined as the smallest size at which the orientation is identified half the time), the 1-up-1-down paradigm, when coupled with the average of four response reversals provides a reasonable estimate of hyperacuity.

One of the challenges of implementing a hyperacuity test on a smartphone is the need to use anti-aliasing tricks to achieve sub-pixel resolution. Future work related to the Vernier Acuity test developed will focus, in part, on the inclusion of anti-aliasing effects to add sub-pixel horizontal offsets within the Vernier Figure.

4.6 Mojon Chart Application

The Mojon chart is an optotype chart designed for the detection of nonorganic vision loss. Historically, subjects with organic visual loss have been able to see all optotype sizes, while patients with nonorganic visual loss claim only to see the larger optotypes. This particular optotype chart offers a different function (i.e. the ability to differentiate between cases of organic and nonorganic visual loss) not directly provided by the aforementioned implemented psychophysical tests, and is valuable to include in a comprehensive suite of smartphone applications. As described in the original publication, the Mojon chart was implemented for the smartphone (Figure 4.10).

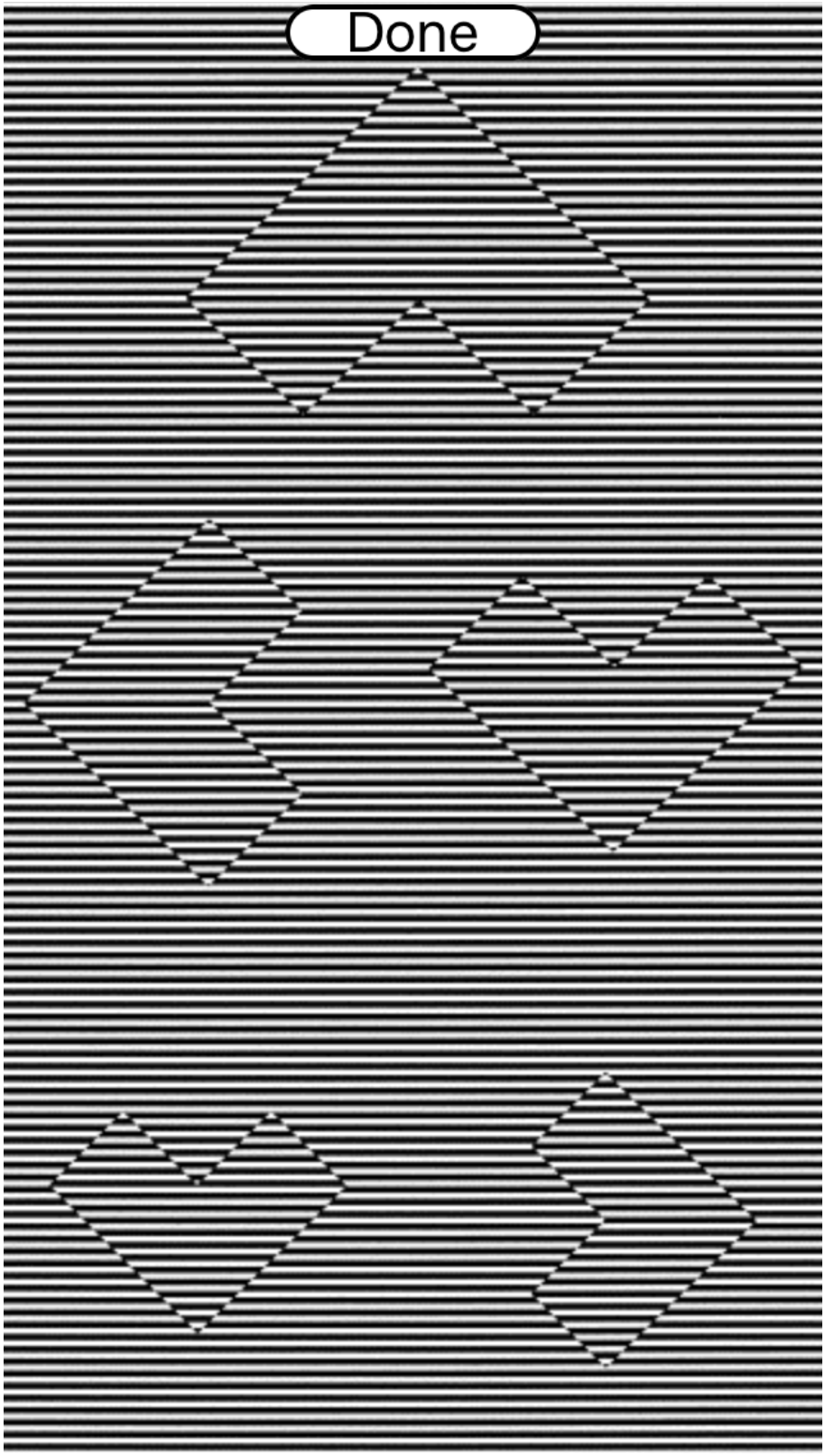

Figure 4.10.1: The first set of targets of the Mojon chart.

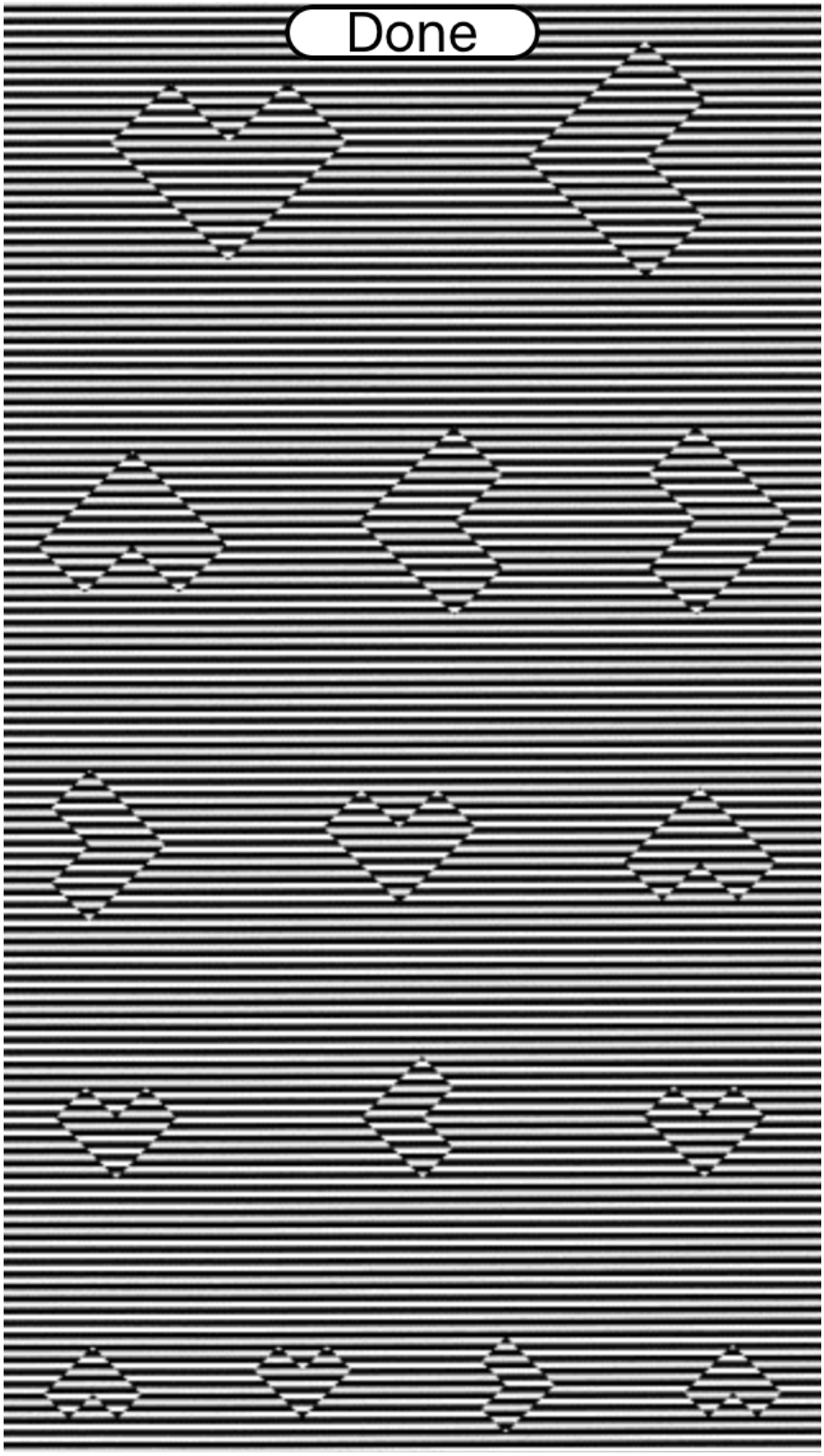

Figure 4.10.2: The second set of targets of the Mojon chart.

4.7 Hearing-in-Noise Application (HearMe)

The Hearing-in-Noise Test (HINT) measures an individual's ability to hear speech in quiet and in noise [43]. HINTs are traditionally done testing both ears together as binaural hearing ability is key in noisy settings and everyday, functional hearing. Traditional HINTs take advantage of testing in four different situations: sentences presented with 1) no noise, 2) competing noise presented 0 degrees azimuth or front, 3) noise presented 90 degrees azimuth or right, and 4) noise presented 270 degrees azimuth or left.

Adaptive procedures are regularly used to determine speech reception thresholds (SRT) in dB signal-to-noise ratio threshold (SNR). Specifically, SRT records the faintest speech that can be heard half of the time (or an intelligibility of 50%), and is more representative of a patient's hearing ability in real-life situations than pure-tone audiometry. For this reason, SRT is considered a supra-threshold test with applications to quantify "hidden-hearing loss". For HINTs, the (white) noise is usually kept fixed (between 50-60 dB) and the signal is modulated. The noise must be set at an audible level for the user

Current HINTs use digit-triplets (digits in noise test), phonemes, or full-sentences presented with competing noise. Sentence tests are reported to be more efficient and provide more reliable SRT measurements than single-word tests. During the tests, subjects must repeat or select digits/words/sentences, typically from a closed set. Each stimulus is scored as either correct or incorrect and the intensity of the stimulus is adjusted using a 1-up-1-down paradigm.

A 1-up-1-down paradigm is historically reliable and efficient. Stimulus levels chosen at a 1-up-1-down paradigm will oscillate about a mean level at which the stimulus is audible 50% of the time. However, a 1-up-1-down paradigm is not the best procedure for estimating additional parameters of the psychometric response curve including slope, although mathematical/logistic functions can fit these curves and estimate slopes. Alternatively, 2-up-1-down paradigms provide an estimate of the SRT corresponding to a 70.7% positive response. With 3-up-1-down paradigms, the user typically achieves a SNR where 80% accuracy is obtained. Commonly, a step-size of 1-2 dB is used for testing.

HearMe takes the above information in consideration and models the implementation from the study described by Koole et al [43]. Specifically, HearMe uses a 1-up-1-down paradigm with a signal step size of 2-dB. Thus with each correct response, the SNR of the presented audio decreases by 2 dB and with each incorrect response, the SNR of the presented audio increases by 2 dB. The user can test their hearing-in-noise function in a variety of programmed noises including white noise, and simulated noises corresponding to environments such as airports, subways, trains, cars, etc. The implemented testing protocol requires users to sign-in with their authenticated Gmail or Facebook accounts. Users also have the option of entering their demographic information and completing the Better Hearing Institute survey. Once a testing instance has been began, the user must identify 24 consecutive three-digit stimuli, presented in noise with modulated amplitudes according to a 1-up-1-down paradigm, beginning at 0 SNR. For ease of use, the user can replay the stimuli as many times as needed.

Spoken digits were recorded (with a male speaker) at a sampling rate of 8000 samples per second in a sound booth with an ear and head simulator, high-precision microphone, and sound level meter. One of the extensive components of developing an auditory test as a smartphone application is the sound processing and calibration required. In fact, current smartphone-based auditory tests lack technical validation purely because they test absolute frequencies as opposed to using the inherent advantage of relative differences (i.e. signal-to-noise ratios). All audio processing was performed in Adobe Audition (2015). The spoken digits were all normalized based on the root mean square amplitude. To achieve a signal-to-noise ratio of 0 SNR, all audio files were incremented by the same dB that avoids any window clipping. One this maximum dB level was achieved, the sound level of each was decreased by 30 dB. The audio files for all human speech signals and noises at 0 SNR were spectrally matched to each noise spectrum according to the top one-third octave, and merged with each corresponding type of noise. To construct the stimuli of varying SNR, the speech signals were amplified by even dB increments or decrements, and then merged with the corresponding type of noise. Finally, digits were concatenated to form triplets of digits and stored in a backend cloud storage through Firebase.

A complete illustration of the implemented hearing-in-noise test (HearMe) and application interface is depicted in Figure 4.11.

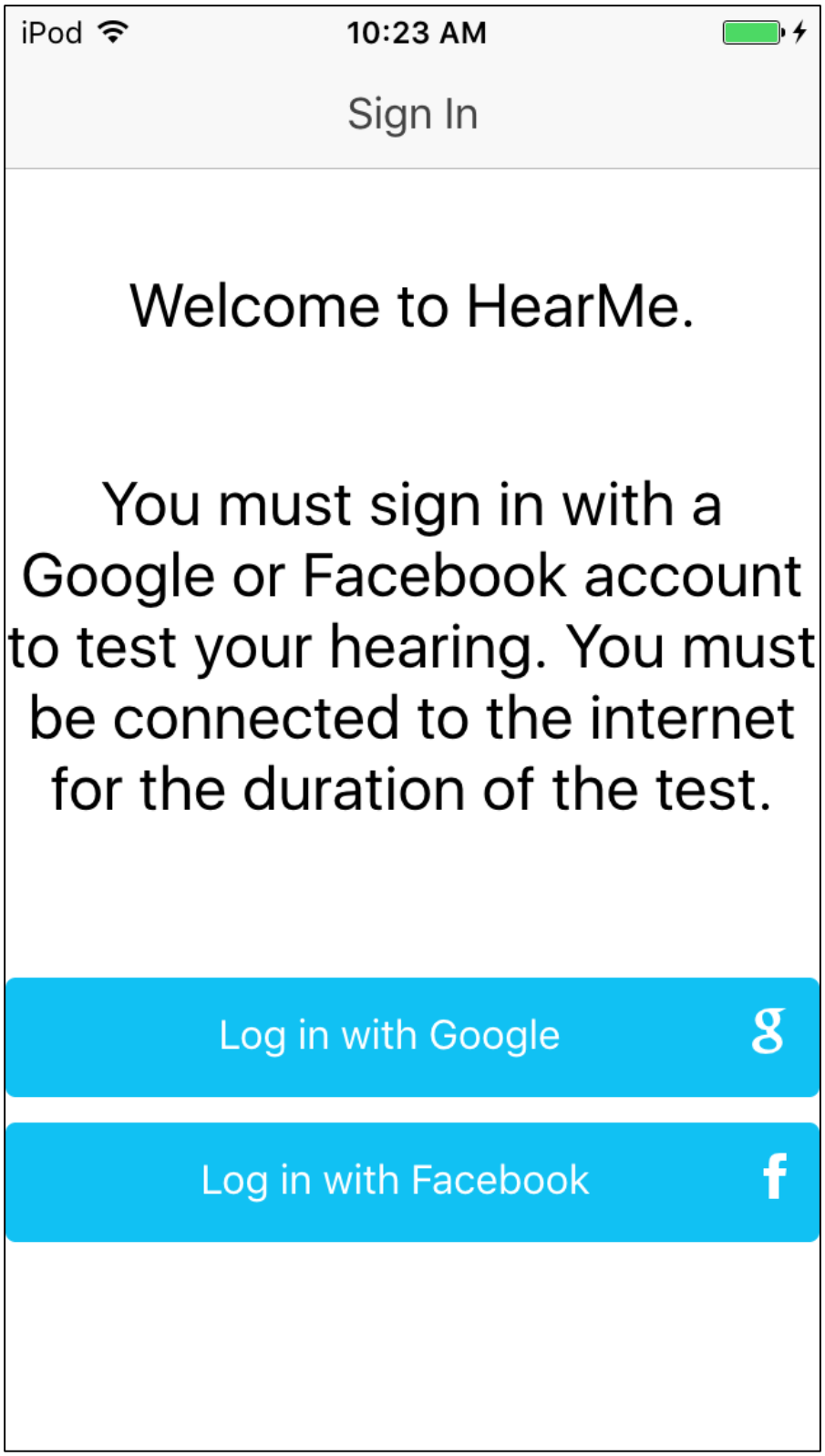

Figure 4.11.1: HearMe sign-in page that requires an authenticated google or facebook account to login.

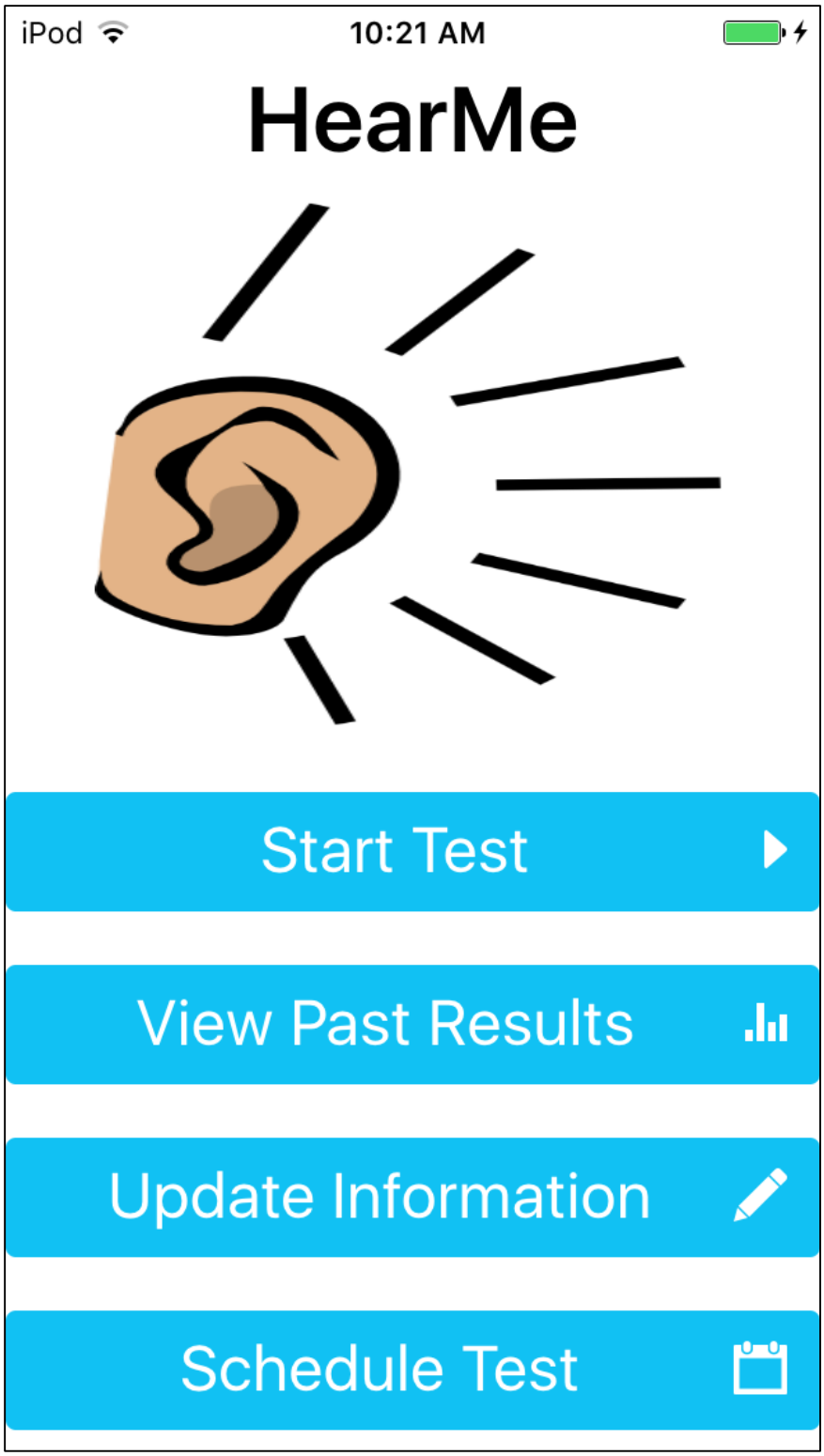

Figure 4.11.2: HearMe menu screen with options to start or schedule a test, visual previous results, and update personal information and complete a survey-based hearing check.

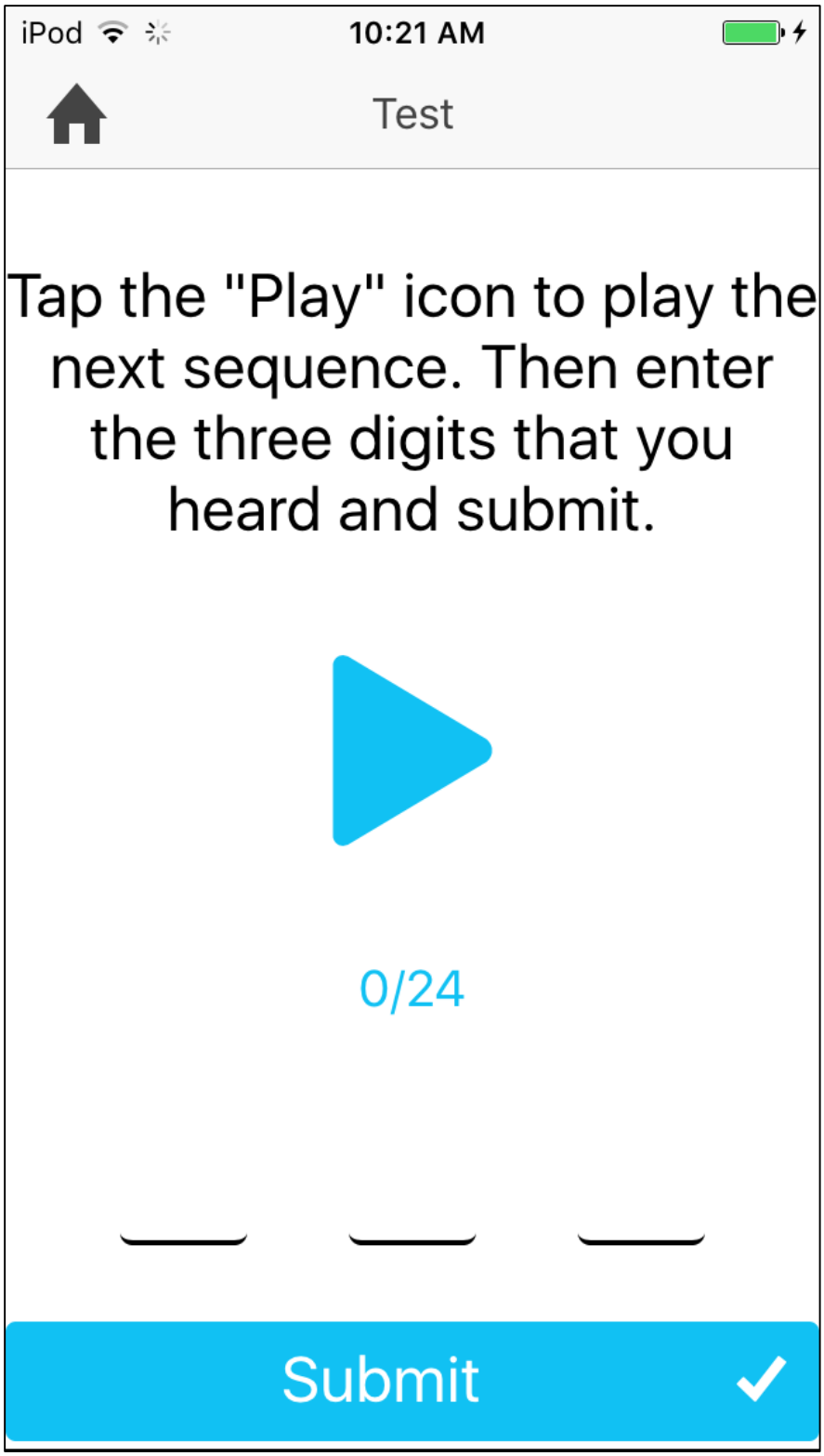

Figure 4.11.3: HearMe testing interface that prompts subjects to play digit triplets and respond with the three digits they could hear.

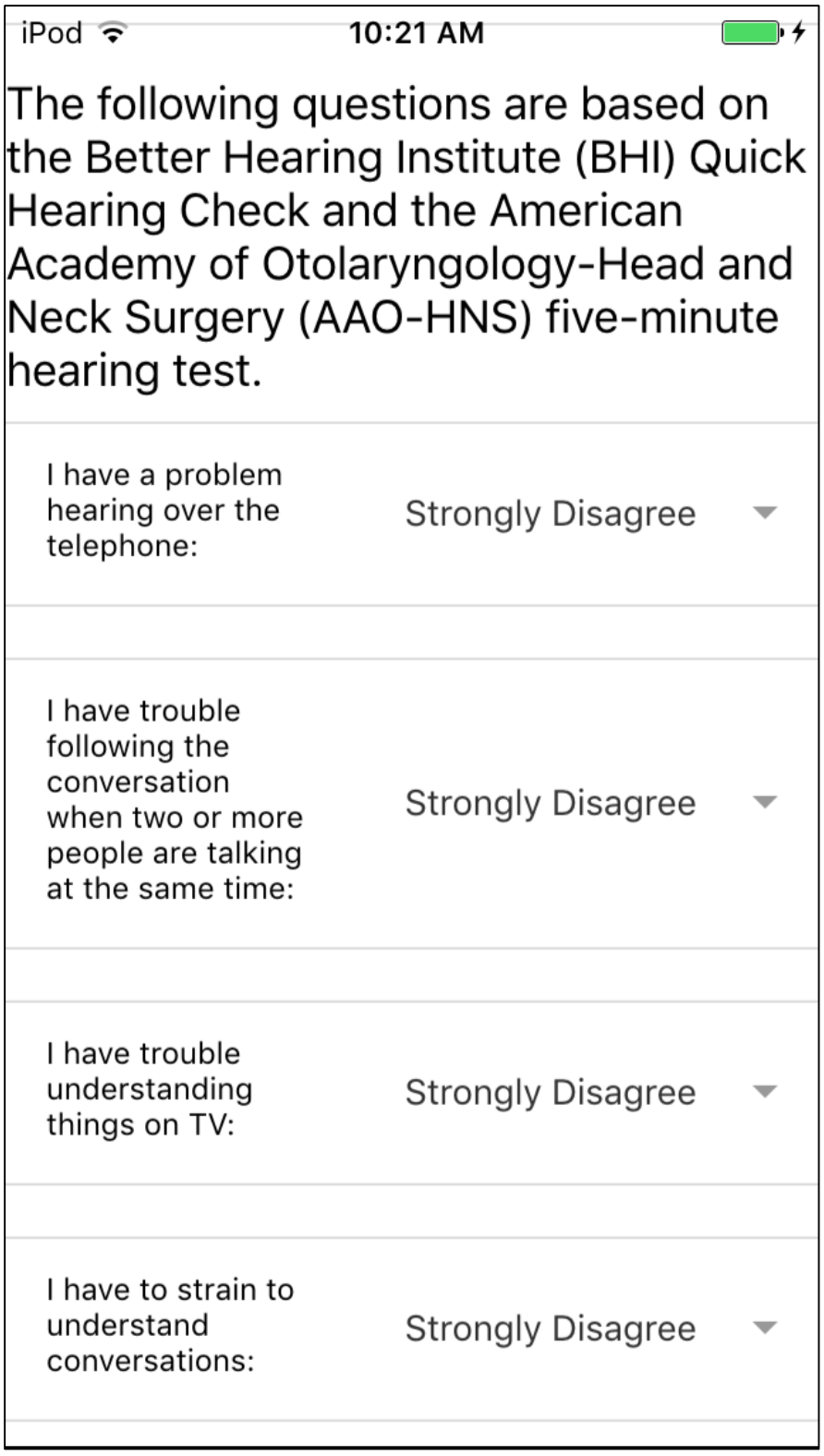

Figure 4.11.4: The Quick Hearing Check survey test that can be completed within HearMe.

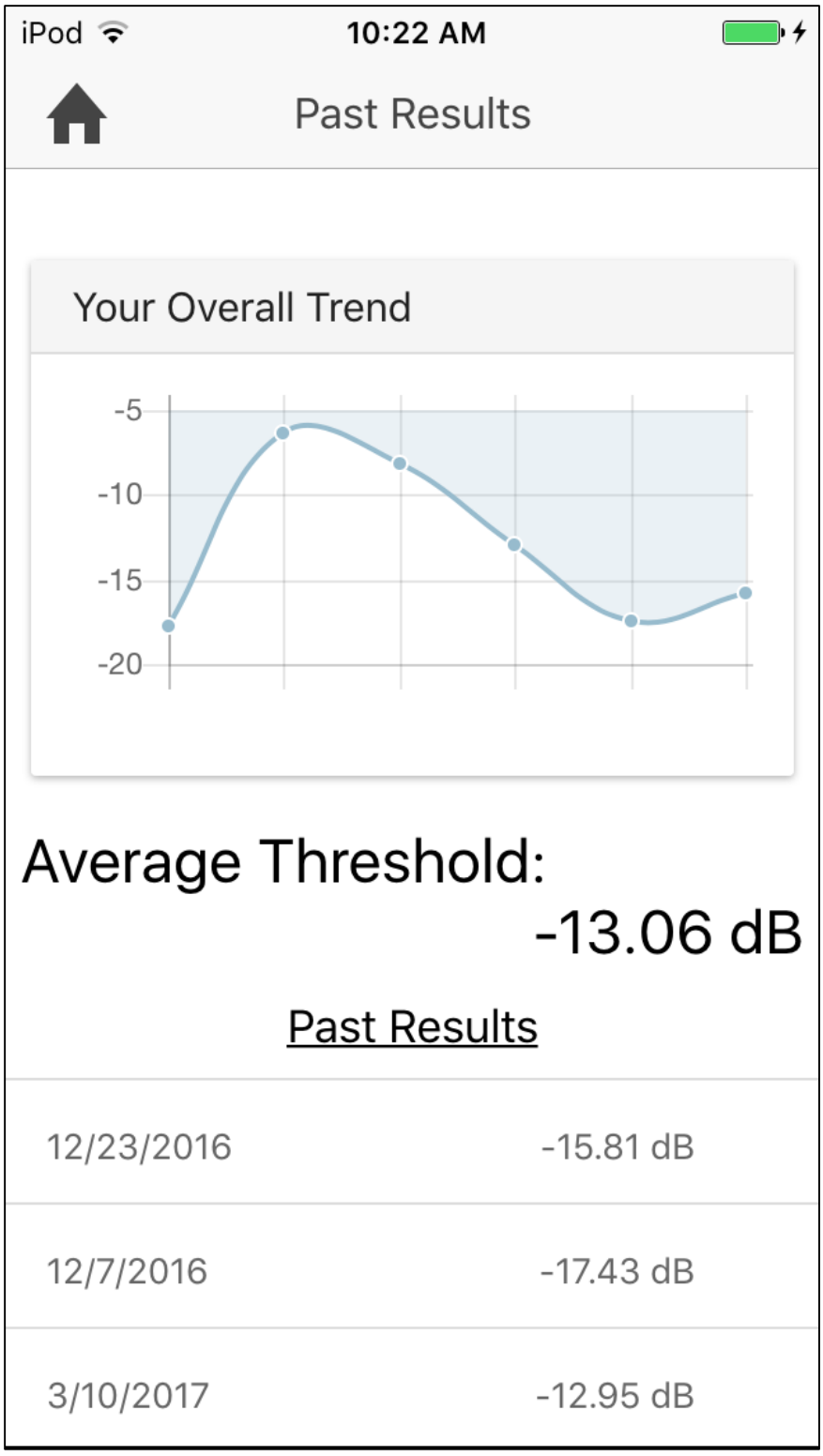

Figure 4.11.5: HearMe user interface that allows subjects to view past results and their overall and average trends.

To date, HearMe is the only smartphone application in the suite of tests developed in this work that is compatible with both iOS and Android platforms, as presenting relative audio intensity differences and signal-to-noise ratios on smartphones is agnostic of the device used (the same argument does not extend to relative differences in contrast and pixel intensity). To implement HearMe as an application that is compatible with both iOS and Android platforms, a hybrid application development technology, called Ionic, was used. Ionic is a powerful solution as a complete, open-source SDK for hybrid mobile app development, and is built on top of Angular JS and Apache Cordova.

4.8 General Implementation Features

The suite of smartphone applications developed share a set of common implementation features. Specifically, all applications, if exited at any point through use of the home button, will return to the menu screen of the application when re-started. The rationale for this design feature is simple: all testing instances must be carried out to completion, as pauses are unwanted due to potential intra-subject variation that can be introduced by a multitude of factors.

Furthermore, landscape orientations are eliminated and cannot be used within the applications. The rationale for this design feature is that landscape orientations will dynamically alter the presentation of the interface and can potentially distract users even with subtle changes in position. Additionally, to avoid unwanted alterations of the luminance of the smartphone devices, the background brightness of the device is fixed at maximum brightness.

Beyond the HearMe application, the remaining smartphone applications developed make use of the iOS Software Development Kit (SDK), particularly SpriteKit,

a graphics rendering and animation infrastructure built on top of Open Graphics Library (GL), for the flicker sensitivity test, and the Core Graphics framework for rendering non-flickering or static stimuli.

4.9 Calibration and Technical Validation Experiments

One of the central weaknesses of existing smartphone applications, beyond the absence of clinical validation, is the lack of thorough calibration. In the earlier section, the audio processing and calibration was discussed. In this section, the discussion will focus on the calibration performed as part of the technical assessment of the limitations of smartphone devices. A comprehensive calibration of the smartphone displays has thus been performed that will extend to all existing and future visual smartphone tests developed.

First, a photodiode was used to measure the true temporal frequency presented at programmed temporal frequencies of 1, 7.5, 15, and 30 Hz (as these are four frequencies that sample across the range of frequencies that can be programmed on an iOS device) on three iOS devices: the iPhone 5c, iTouch 5, and iPad Air. The discrete Fourier transform was computed to characterize the frequency response of each measured signal. Each signal was fitted for a square wave, the desired non-sinusoidal periodic waveform used in flicker perimetry tests and used in the implementation of eyeFusion, with the correlation coefficients measured. This measure is crucial to understanding the shape and consistency of the produced waveform across multiple temporal frequencies, and whether such stimuli can be used for clinical testing.

Secondly, a standard radiometer with a fixed spot size was used to quantify device calibration curves and assess the relationship between the programmed standard RGB

value displayed on an iOS device (grayscale intensity on a scale from 0 to 1) and the luminance measured by the radiometer (candela / meter^2). The target grayscale intensity was modulated in 15 points that sample across the entire grayscale intensity range (0 to 1.0 which corresponds to 0-255 grayscale pixel values). This experiment was repeated to generate calibration curves for five locations (the bottom and top right and left corners of the device, and the center region as illustrated in Figure 4.12), again for three iOS devices: the iPhone 5c, iTouch 5, and iPad Air.

The linear and quadratic model fits and correlations between grayscale target setting and luminance for each location on each device were quantified. The purpose of this calibration step is to determine exactly which RGB values must be programmed (for a given stimulus within an application) above and below a median grayscale background intensity, to program a desired contrast according to luminance – in simpler words, the calibration curves generated can serve as a look-up table when programming testing values for contrast and luminance.

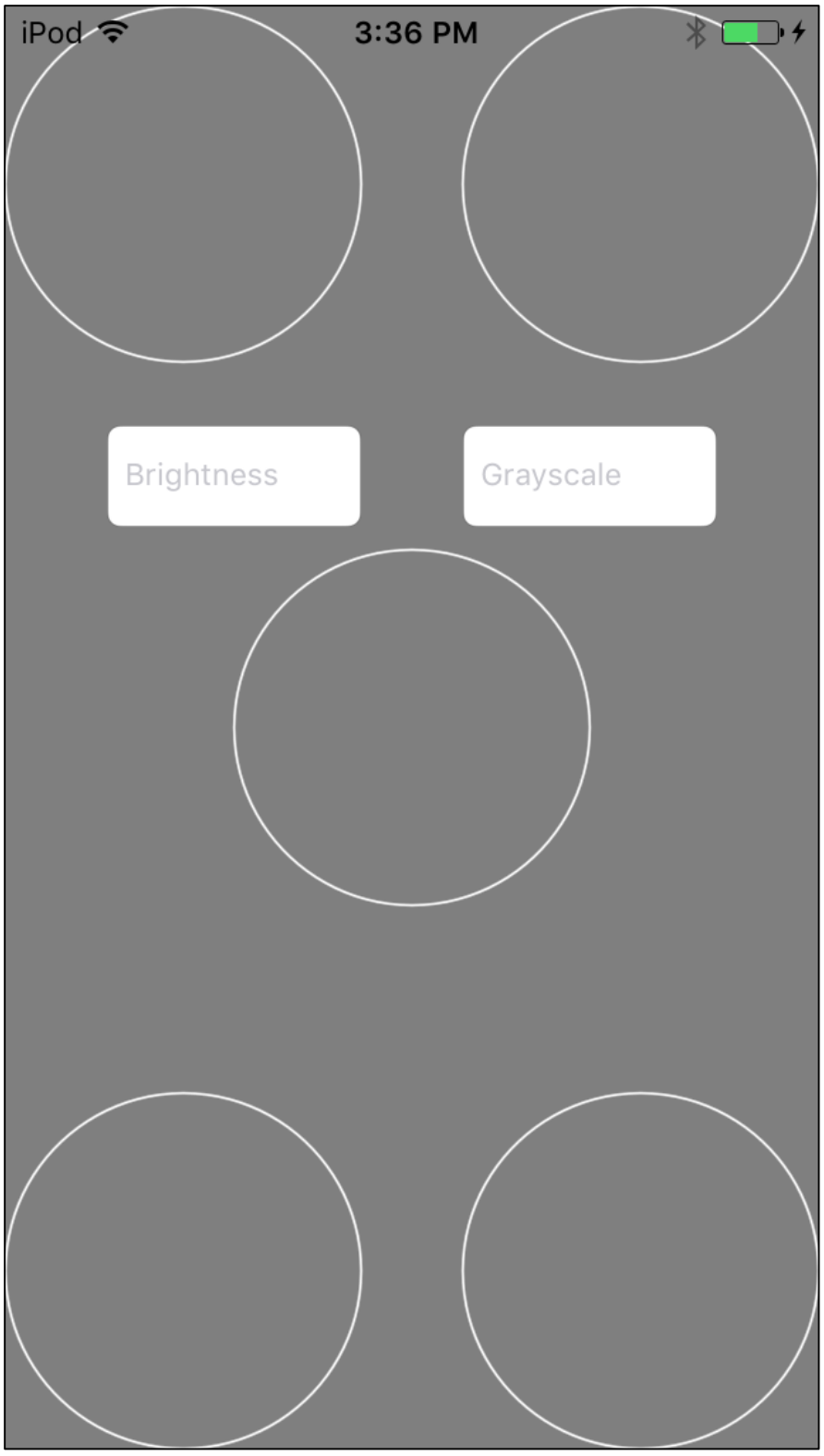

Figure 4.12: A schematic that illustrates the location of the five targets used for measuring and constructing the calibration curves.

4.10 Clinical Validation Experiments

The focus of all human-subject testing will be limited to the flicker fusion, Landolt C visual acuity, and contrast sensitivity applications. The scope of testing was limited to only these three applications as the total testing duration for just the three core applications (that measure flicker sensitivity, visual acuity, and contrast sensitivity) exceeded 10 minutes per subject (accounting for the time required to obtain consent, and test the eyes of each subject separately and together). To prevent the backflow of patients in clinic and to avoid general cases of subject fatigue, for this preliminary testing phase, all the remaining smartphone application tests were temporarily excluded form data collection.

Flicker fusion thresholds at 15 and 7.5 Hz, Landolt C visual acuity (degrees visual angle), and contrast sensitivity were quantified for each subject. All subjects were tested with the right and left eye separately, and both eyes binocularly (while wearing any personal, corrective lenses). The effects of binocular summation were evaluated by comparing performance measures (flicker fusion threshold, contrast sensitivity, and visual acuity) obtained using both eyes to the same measures for the right and left eyes separately. Beyond the three smartphone applications tested on each subject, a standard eye chart was provided to the patients to obtain a standard measure of their visual acuity (as minutes of arc at 0.4 meters). All tests were conducted on subjects at a fixed distance of 0.4 meters – this distance was measured and monitored for each subject using a string of a fixed distance of 0.4 meters. All testing was conducted in rooms with standard lighting and devoid of windows and sunlight that produce glare on the device screen.

The flicker fusion, visual acuity, and contrast sensitivity tests were all assessed for resistance to blurring effects through using a set of Bangerter occlusion filters which blur vision using varying amounts of diffusion filters (0, < 0.1, 0.2, 0.4, 0.6, 0.8, and 1.0 LP), and comparing intra-subject performance across the different occlusion filters. An authentic, visual representation of the blur created by the set of Bangerter filters (on a standard eye chart) is provided below in Figure 4.13.

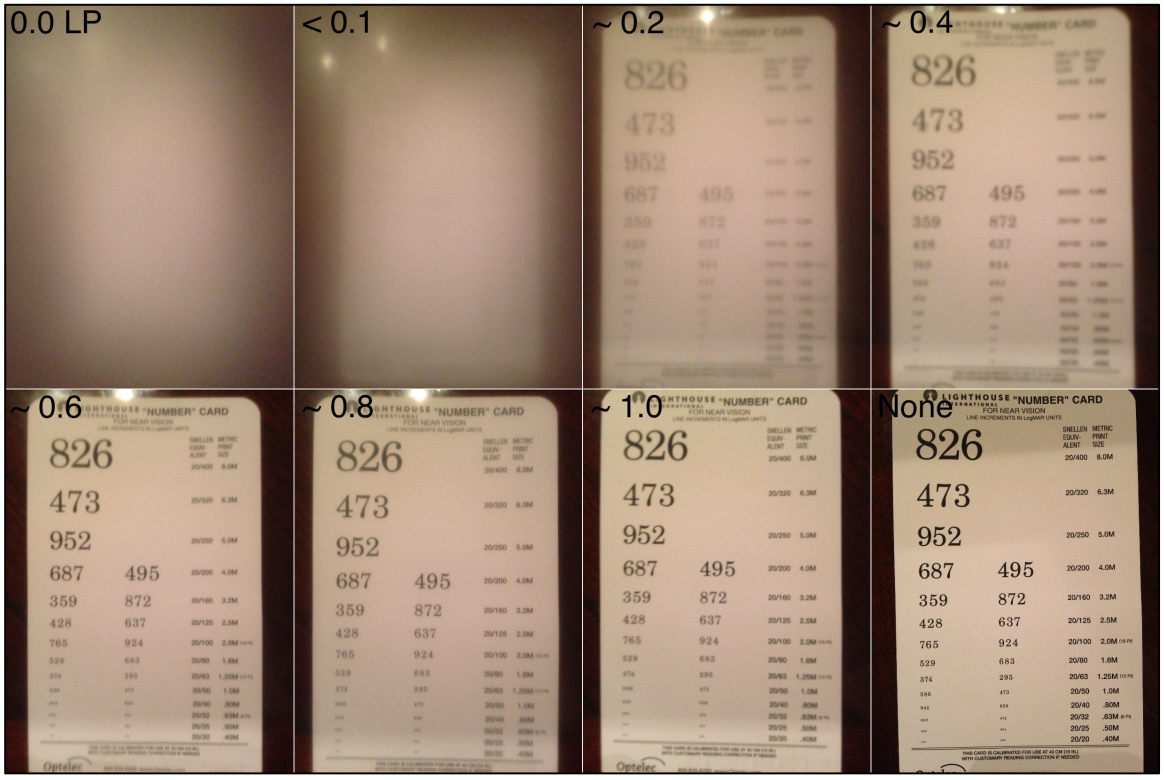

Figure 4.13: Visual representation of the blur create by the set of Bangerter filters, with the corresponding acuity of each filter noted in the top left of each sub-panel. The last sub-panel visually represents the absence of a Bangerter filter.

Normative subjects were recruited from any location on the University of Iowa campus. Non-normative subjects were recruited from the neuro-ophthalmology clinic in the University of Iowa Hospitals and Clinics, who were clinically evaluated and expected to have visual conductance deficits due to their diagnosis of optic neuropathy of various

causes. Local Institutional Board Approval was obtained to test the developed applications. Appendix 1 describes, in full detail, the written instructions provided to individual subjects through the corresponding smartphone applications at the start of testing each application. Appendix 2 consists of the full IRB study form that was created for this project and approved for testing. Finally, Appendix 3 consists of the consent form used for obtaining signed consent from each study participant.

Normative data was collected so that data from non-normative subjects could be compared to preliminary normative ranges. Non-normative subjects recruited in the clinic are routinely evaluated for other measures of visual function including retinal nerve fiber layer thickness measured through optical coherence tomography imaging of the retina, visual field testing, and traditional forms of testing flicker fusion by varying the temporal frequency at a fixed, high contrast of a reds light emitting diode on a diffuse background. Correlations were examined between standard clinical measures of visual function and measures collected with the smartphone. Test-retest reliability was also quantified in a subset of the normative subjects recruited.

CHAPTER 5

RESULTS

5.1 Technical Validation Results

5.1.1 iOS Device Signal Characteristics

For the 1, 7.5, 15, and 30 Hertz signal respectively, the dominant peak frequencies (Hz) computed were 0.98, 7.49, 15, and 30.01 Hz on the iPhone, 0.98, 7.50, 14.99, and 29.98 Hz on the iTouch, and 0.99, 7.50, 15, and 30 Hz on the iPad. Correlations of the 1 Hz signals with the fitted square wave were $r^2 = 0.98$ for all three devices. For the iPhone, iTouch, and iPad respectively, r^2 for the 7.5 Hz signals were 0.87, 0.84, and 0.85; 0.72, 0.65, and 0.64 for the 15 Hz signals, and 0.46, 0.35, and 0.42 for the 30 Hz signals. Furthermore, 30 Hz flicker stimuli on average only reached 90.6% of the value of the intended contrast. A summary of the statistics from this calibration experiment is displayed in Table 5.1, with the characterized flicker waves illustrated in Appendix 4. The signals illustrated in Appendix 4 suggest potential future preference of implementing a sinusoidal wave over a square wave instead.

Table 5.1: The signal characteristics measured from standard iPad, iPhone, and iTouch devices.

Device	Frequency (Hz)	Peak Frequency from FFT (Hz)	Square Wave Correlation (R^2)
iPad	1	0.99	0.98
	7.5	7.5	0.85
	15	15	0.64
	30	30	0.42
iPhone	1	0.98	0.98
	7.5	7.49	0.87
	15	15	0.72
	30	30.01	0.46
iTouch	1	0.98	0.98
	7.5	7.5	0.84
	15	14.99	0.65
	30	29.98	0.35

5.1.2 iOS Device Calibration Curve Construction

Calibration curves (candela/m^2 vs. target grayscale intensity) were created for each of the five targets and the composite of the five targets (as a function of grayscale) and the background (as a function of brightness) for all three iOS devices. In all cases, the findings were the same: although linear fits (of the form Luminance = Slope x Grayscale Value + Y-intercept) were strong for each calibration curve, non-linear trends (second order polynomials of the form Luminance = B_2 x $Grayscale^2$ + B_1 x Grayscale + B_0, where B_2, B_1, and B_0 represented the fitted model coefficients) were observed and quadratic model fits produced even stronger correlations.

All the calibration curves and linear model fits (for all five targets, the mean of the targets, and background) are depicted in Appendix 5. Figure 5.1 provides an example illustrative schematic of the calibration curves and linear model fits on their respective locations on the smartphone device. Tables 5.2-5.7 provide the comprehensive set of summary statistics that quantify the linear and quadratic model fits for each calibration curve.

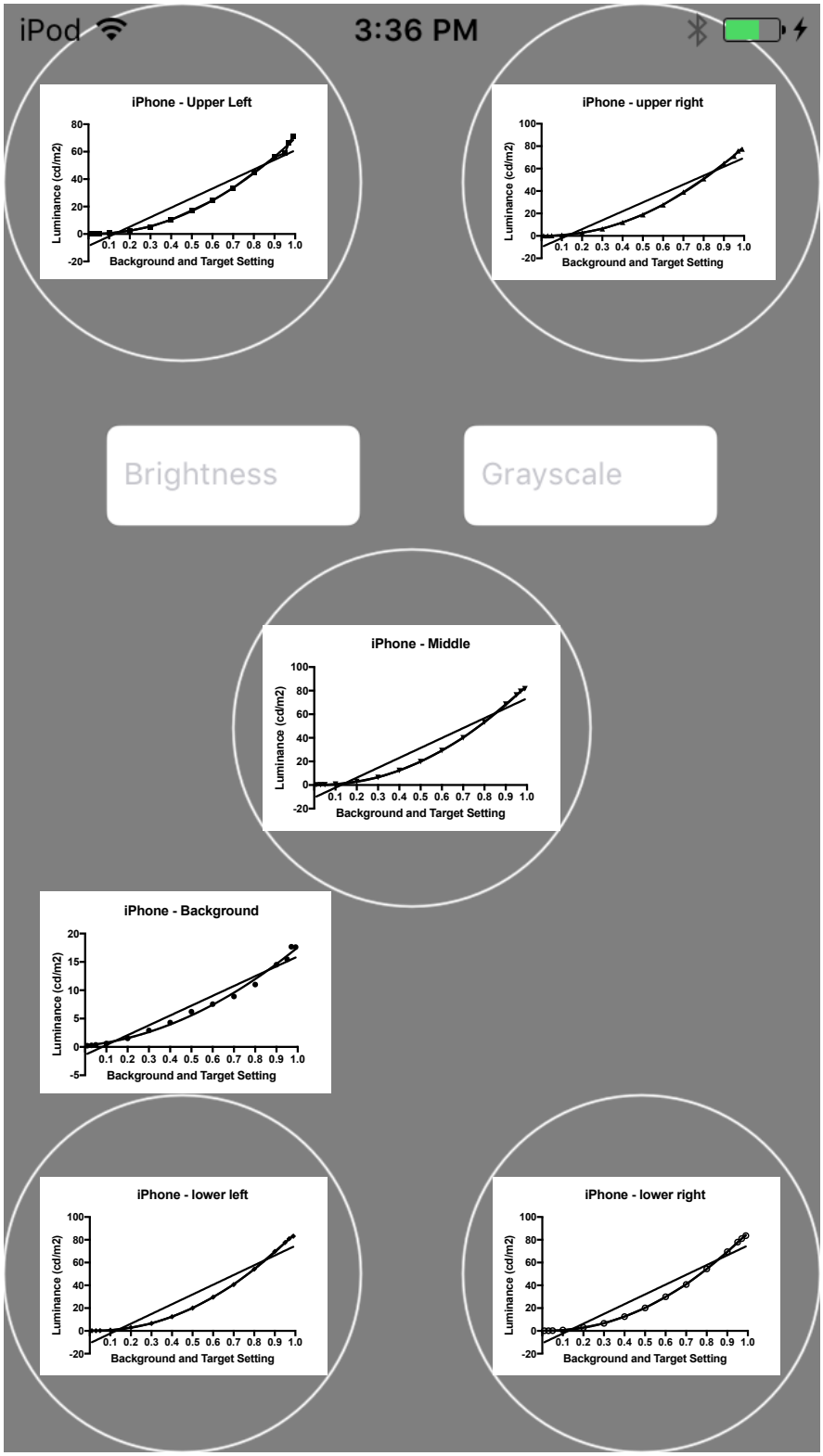

Figure 5.1: Example calibration curves and linear model fits for all five targets and the background of the calibrated iPhone device. Each result is superimposed on the respective, localized area analyzed by the radiometer during calibration.

Table 5.2: The iPad calibration summary statistics for a linear model fit.

	Tablet Background	Upper left	Upper Right	Middle	Lower Left	Lower Right	Tablet Target mean	Tablet Target SD
Best-fit values ± SE								
Slope	11.47 ± 0.5999	54.83 ± 4.137	54.16 ± 3.784	54.66 ± 4.141	57.47 ± 4.162	57.08 ± 4.166	55.64 ± 4.077	1.37 ± 0.07779
Y-intercept	-0.7034 ± 0.369	-6.713 ± 2.545	-6.577 ± 2.328	-7.02 ± 2.548	-7.099 ± 2.56	-7.192 ± 2.563	-6.918 ± 2.508	-0.02185 ± 0.04786
X-intercept	0.0613	0.1224	0.1214	0.1284	0.1235	0.126	0.1243	0.01595
1/slope	0.08715	0.01824	0.01846	0.0183	0.0174	0.01752	0.01797	0.7297
95% Confidence Intervals								
Slope	10.18 to 12.77	45.89 to 63.77	45.99 to 62.34	45.71 to 63.6	48.48 to 66.46	48.08 to 66.08	46.83 to 64.45	1.202 to 1.538
Y-intercept	-1.501 to 0.09389	-12.21 to -1.215	-11.61 to -1.548	-12.52 to -1.516	-12.63 to -1.568	-12.73 to -1.655	-12.34 to -1.5	-0.1252 to 0.08154
X-intercept	-0.009012 to 0.1203	0.0255 to 0.1987	0.03252 to 0.1927	0.03194 to 0.2045	0.0312 to 0.197	0.0332 to 0.1997	0.03089 to 0.1985	-0.06624 to 0.08335
Goodness of Fit								
R square	0.9657	0.9311	0.9403	0.9305	0.9362	0.9352	0.9348	0.9598
Sy.x	0.8327	5.743	5.253	5.749	5.777	5.783	5.659	0.108
Is slope significantly non-zero?								
F	365.9	175.7	204.9	174.2	190.7	187.7	186.2	310.3
DFn, DFd	1, 13	1, 13	1, 13	1, 13	1, 13	1, 13	1, 13	1, 13
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Deviation from zero?	Significant	Significant	Significant	Significant	Significant	Significant	Significant	Significant
Equation	Y = 11.47*X - 0.7034	Y = 54.83*X - 6.713	Y = 54.16*X - 6.577	Y = 54.66*X - 7.02	Y = 57.47*X - 7.099	Y = 57.08*X - 7.192	Y = 55.64*X - 6.918	Y = 1.37*X - 0.02185

Table 5.3: The iPad calibration summary statistics for a quadratic model fit.

	Tablet Background	Upper left	Upper Right	Middle	Lower Left	Lower Right	Tablet Target mean	Tablet Target SD
Second order polynomial (quadratic)								
Best-fit values								
B0	0.2756	0.5895	0.1139	0.3062	0.2612	0.1778	0.2924	0.09068
B1	3.419	-5.254	-0.8895	-5.628	-3.092	-3.562	-3.693	0.4445
B2	8.056	60.09	55.05	60.28	60.56	60.64	59.33	0.9259
Std. Error								
B0	0.19	0.2438	0.1299	0.08891	0.1245	0.09955	0.1122	0.03671
B1	1.004	1.289	0.6866	0.47	0.6584	0.5263	0.5934	0.1941
B2	0.9749	1.251	0.6665	0.4562	0.6391	0.5109	0.576	0.1884
95% CI (profile likelihood)								
B0	-0.1383 to 0.6896	0.0583 to 1.121	-0.1691 to 0.3969	0.1124 to 0.4999	-0.01017 to 0.5325	-0.03912 to 0.3947	0.04784 to 0.537	0.01069 to 0.1707
B1	1.231 to 5.608	-8.062 to -2.446	-2.385 to 0.6065	-6.652 to -4.604	-4.527 to -1.658	-4.708 to -2.415	-4.986 to -2.4	0.02162 to 0.8673
B2	5.931 to 10.18	57.36 to 62.81	53.6 to 56.51	59.29 to 61.28	59.17 to 61.96	59.53 to 61.75	58.08 to 60.59	0.5154 to 1.336
Goodness of Fit								
Degrees of Freedom	12	12	12	12	12	12	12	12
R square	0.9949	0.9996	0.9999	1	0.9999	0.9999	0.9999	0.9867
Absolute Sum of Squares	1.348	2.219	0.6298	0.2951	0.5791	0.37	0.4704	0.05032
Sy.x	0.3351	0.43	0.2291	0.1568	0.2197	0.1756	0.198	0.06475

Table 5.4: The iPhone calibration summary statistics for a linear model fit.

	iPhone Background	Upper left	Upper Right	Middle	Lower Left	Lower Right	iPhone Target mean	iPhone Target SD
Best-fit values ± SE								
Slope	17.35 ± 0.9881	69.68 ± 5.123	79.53 ± 5.716	84.11 ± 6.17	85.6 ± 6.315	85.86 ± 6.32	80.96 ± 5.908	6.801 ± 0.7326
Y-intercept	-1.396 ± 0.6079	-8.7 ± 3.152	-9.922 ± 3.517	-10.62 ± 3.796	-10.84 ± 3.885	-10.88 ± 3.888	-10.19 ± 3.634	-0.9107 ± 0.4507
X-intercept	0.08045	0.1249	0.1247	0.1263	0.1267	0.1267	0.1259	0.1339
1/slope	0.05765	0.01435	0.01257	0.01189	0.01168	0.01165	0.01235	0.147
95% Confidence Intervals								
Slope	15.21 to 19.48	58.61 to 80.74	67.18 to 91.88	70.78 to 97.44	71.95 to 99.24	72.21 to 99.51	68.2 to 93.72	5.219 to 8.384
Y-intercept	-2.709 to -0.08226	-15.51 to -1.891	-17.52 to -2.324	-18.82 to -2.419	-19.24 to -2.451	-19.28 to -2.477	-18.04 to -2.342	-1.884 to 0.06301
X-intercept	0.005268 to 0.1427	0.03112 to 0.1992	0.03339 to 0.1976	0.03296 to 0.2003	0.03284 to 0.2011	0.03307 to 0.2009	0.03312 to 0.1996	-0.01143 to 0.2373
Goodness of Fit								
R square	0.9595	0.9343	0.9371	0.9346	0.9339	0.9342	0.9353	0.8689
Sy.x	1.372	7.112	7.935	8.565	8.767	8.773	8.201	1.017
Is slope significantly non-zero?								
F	308.2	185	193.6	185.8	183.7	184.6	187.8	86.18
DFn, DFd	1, 13	1, 13	1, 13	1, 13	1, 13	1, 13	1, 13	1, 13
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Deviation from zero?	Significant	Significant	Significant	Significant	Significant	Significant	Significant	Significant
Equation	Y = 17.35*X - 1.396	Y = 69.68*X - 8.7	Y = 79.53*X - 9.922	Y = 84.11*X - 10.62	Y = 85.6*X - 10.84	Y = 85.86*X - 10.88	Y = 80.96*X - 10.19	Y = 6.801*X - 0.9107

Table 5.5: The iPhone calibration summary statistics for a quadratic model fit.

	iPhone Background	Upper left	Upper Right	Middle	Lower Left	Lower Right	iPhone Target mean	iPhone Target SD
Second order polynomial (quadratic)								
Best-fit values								
B0	0.2216	0.1972	0.1771	0.2891	0.3212	0.3017	0.2551	0.05645
B1	4.041	-3.533	-3.561	-5.649	-6.276	-6.112	-5.014	-1.156
B2	13.31	73.21	83.09	89.75	91.87	91.97	85.97	7.958
Std. Error								
B0	0.308	0.8061	0.275	0.2218	0.2263	0.1682	0.1643	0.3997
B1	1.629	4.261	1.454	1.173	1.196	0.8892	0.8684	2.113
B2	1.581	4.137	1.411	1.138	1.161	0.8631	0.8429	2.051
95% CI (profile likelihood)								
B0	-0.4496 to 0.8927	-1.559 to 1.953	-0.422 to 0.7762	-0.1942 to 0.7725	-0.1719 to 0.8142	-0.06473 to 0.6682	-0.1028 to 0.613	-0.8144 to 0.9273
B1	0.4931 to 7.59	-12.82 to 5.752	-6.728 to -0.3937	-8.204 to -3.093	-8.883 to -3.67	-8.049 to -4.174	-6.906 to -3.122	-5.76 to 3.447
B2	9.861 to 16.75	64.2 to 82.22	80.02 to 86.17	87.27 to 92.24	89.34 to 94.4	90.09 to 93.85	84.14 to 87.81	3.489 to 12.43
Goodness of Fit								
Degrees of Freedom	12	12	12	12	12	12	12	12
R square	0.9941	0.9976	0.9998	0.9999	0.9999	0.9999	0.9999	0.9419
Absolute Sum of Squares	3.543	24.26	2.823	1.837	1.912	1.056	1.007	5.964
Sy.x	0.5434	1.422	0.485	0.3913	0.3992	0.2967	0.2897	0.705

Table 5.6: The iTouch calibration summary statistics for a linear model fit.

	iTouch Background	Upper left	Upper Right	Middle	Lower Left	Lower Right	iTouch Target mean	iTouch Target SD
Best-fit values ± SE								
Slope	17.52 ± 1.262	74.99 ± 5.483	77.51 ± 5.882	84.93 ± 6.63	78.88 ± 6.067	81.94 ± 6.369	79.65 ± 6.085	3.775 ± 0.4151
Y-intercept	-1.776 ± 0.7763	-9.45 ± 3.373	-10.11 ± 3.619	-11.19 ± 4.079	-10.34 ± 3.732	-10.78 ± 3.918	-10.37 ± 3.743	-0.535 ± 0.2554
X-intercept	0.1014	0.126	0.1304	0.1317	0.1311	0.1316	0.1302	0.1417
1/slope	0.05706	0.01333	0.0129	0.01177	0.01268	0.0122	0.01255	0.2649
95% Confidence Intervals								
Slope	14.8 to 20.25	63.15 to 86.84	64.81 to 90.22	70.61 to 99.26	65.77 to 91.98	68.18 to 95.7	66.5 to 92.79	2.879 to 4.672
Y-intercept	-3.453 to -0.09916	-16.74 to -2.163	-17.93 to -2.29	-20 to -2.377	-18.4 to -2.275	-19.24 to -2.315	-18.46 to -2.285	-1.087 to 0.01669
X-intercept	0.006475 to 0.1765	0.03304 to 0.1999	0.03401 to 0.2064	0.03237 to 0.2095	0.03328 to 0.2079	0.03266 to 0.2091	0.03307 to 0.2067	-0.00548 to 0.246
Goodness of Fit								
R square	0.9369	0.935	0.9303	0.9266	0.9286	0.9272	0.9295	0.8642
Sy.x	1.752	7.611	8.166	9.204	8.422	8.841	8.446	0.5762
Is slope significantly non-zero?								
F	192.9	187.1	173.6	164.1	169	165.5	171.4	82.72
DFn, DFd	1, 13	1, 13	1, 13	1, 13	1, 13	1, 13	1, 13	1, 13
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Deviation from zero?	Significant	Significant	Significant	Significant	Significant	Significant	Significant	Significant
Equation	Y = 17.52*X - 1.776	Y = 74.99*X - 9.45	Y = 77.51*X - 10.11	Y = 84.93*X - 11.19	Y = 78.88*X - 10.34	Y = 81.94*X - 10.78	Y = 79.65*X - 10.37	Y = 3.775*X - 0.535

Table 5.7: The iTouch calibration summary statistics for a quadratic model fit.

	iTouch Background	Upper left	Upper Right	Middle	Lower Left	Lower Right	iTouch Target mean	iTouch Target SD
Second order polynomial (quadratic)								
Best-fit values								
B0	0.3869	0.249	0.3002	0.5375	0.3945	0.4894	0.3951	0.166
B1	-0.2738	-4.816	-8.123	-11.55	-9.432	-10.78	-8.94	-1.993
B2	17.8	79.81	85.64	96.48	88.31	92.72	88.59	5.768
Std. Error								
B0	0.2567	0.1278	0.1012	0.192	0.1408	0.0985	0.07813	0.1016
B1	1.357	0.6756	0.5351	1.015	0.7446	0.5208	0.4131	0.537
B2	1.317	0.6557	0.5194	0.9853	0.7228	0.5055	0.4009	0.5213
95% CI (profile likelihood)								
B0	-0.1723 to 0.9461	-0.02945 to 0.5274	0.07965 to 0.5207	0.1192 to 0.9559	0.08761 to 0.7014	0.2747 to 0.704	0.2248 to 0.5653	-0.05529 to 0.3874
B1	-3.23 to 2.683	-6.288 to -3.344	-9.289 to -6.957	-13.76 to -9.341	-11.05 to -7.81	-11.92 to -9.647	-9.84 to -8.04	-3.163 to -0.8228
B2	14.93 to 20.67	78.38 to 81.24	84.5 to 86.77	94.34 to 98.63	86.73 to 89.88	91.62 to 93.82	87.72 to 89.46	4.632 to 6.904
Goodness of Fit								
Degrees of Freedom	12	12	12	12	12	12	12	12
R square	0.9961	0.9999	1	0.9999	0.9999	1	1	0.9879
Absolute Sum of Squares	2.459	0.6096	0.3825	1.377	0.7406	0.3623	0.2279	0.3853
Sy.x	0.4527	0.2254	0.1785	0.3387	0.2484	0.1737	0.1378	0.1792

5.2 Clinical Validation Results

Flicker fusion, contrast sensitivity, and Landolt C visual acuity data was collected on 15 normative subjects (M = 8, F = 7; mean age = 33.4 years) and 6 non-normative subjects (M = 2, F = 4, mean age = 67.8 years) who provided consent and completed the full study. While multiple other smartphone applications were implemented and described earlier, the discussed results focus only on experiments involving these three smartphone application tests.

5.2.1 Occlusion Filter Tests

Five subjects were tested (using their dominant eye only) with the flicker fusion, contrast sensitivity, and Landolt C visual acuity tests using all seven of the Bangerter filters and under normal conditions (without any filters). Using the 0 LP and < 0.1 LP occlusion filters, none of the tests could be completed for all subjects, but flicker fusion threshold, visual acuity, and contrast sensitivity could all be quantified with the 0.2, 0.4, 0.6, 0.8, and 1.0 LP filters. Flicker fusion thresholds did not significantly change when measured across different occlusion filters ($P > 0.05$). However, visual acuity and contrast sensitivity were significantly altered using the 0.2, 0.4, 0.6, and 0.8 occlusion filters ($P < 0.05$). Thus, while the contrast sensitivity and visual acuity tests (as well as a traditional eye chart) are not resistant to blur, the implemented flicker fusion test is resistant to blur. Both results are expected. Additionally, the presence of a target boarder did not significantly alter flicker fusion threshold measurements ($P > 0.05$).

Figures 5.2.1-5.2.5 depicts a plot of the five measures (flicker fusion at 7.5 Hz, flicker fusion at 15 Hz, Weber contrast sensitivity, visual acuity in degrees visual angle, and visual acuity in distance of five minutes of visual arc) vs. the level of acuity indicated

by the corresponding Bangerter filter used (n = 5). Error bars denote standard errors for each measure.

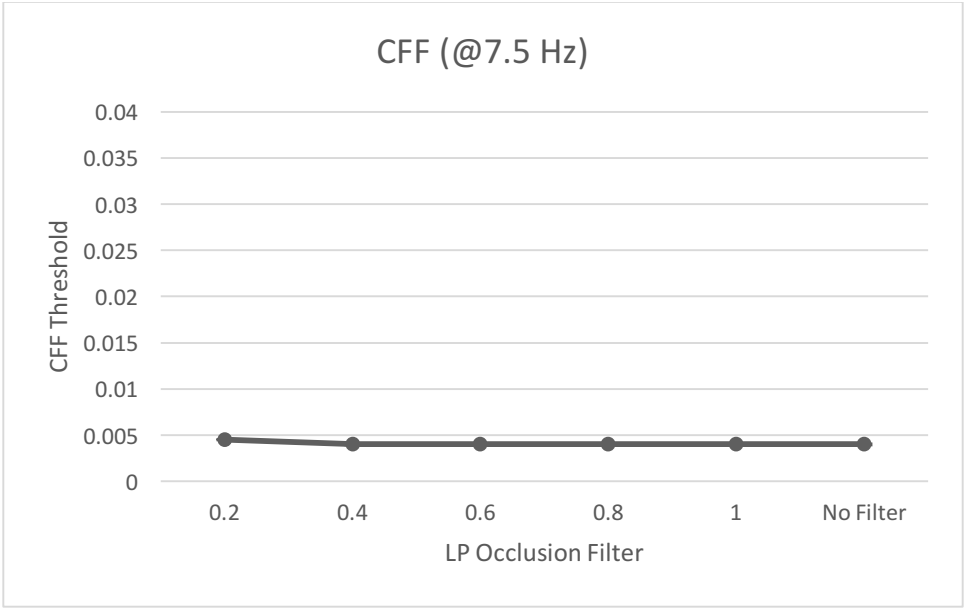

Figure 5.2.1: A plot of flicker fusion thresholds at 7.5 Hz vs. Bangerter filter visual acuity (n = 5 subjects). The standard errors and error bars are negligible and not illustrated.

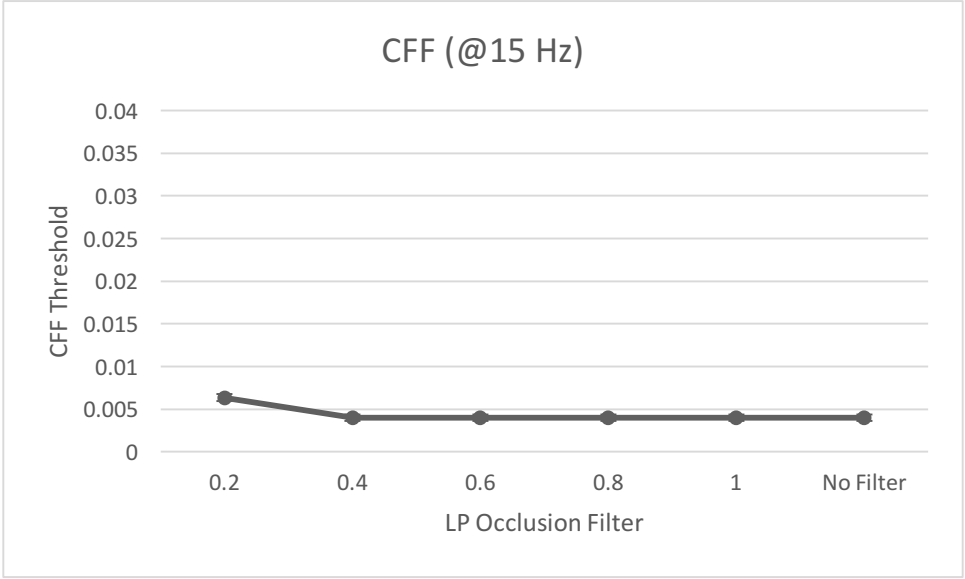

Figure 5.2.2: A plot of flicker fusion thresholds at 15 Hz vs. Bangerter filter visual acuity (n = 5 subjects). The standard errors and error bars are negligible and not illustrated.

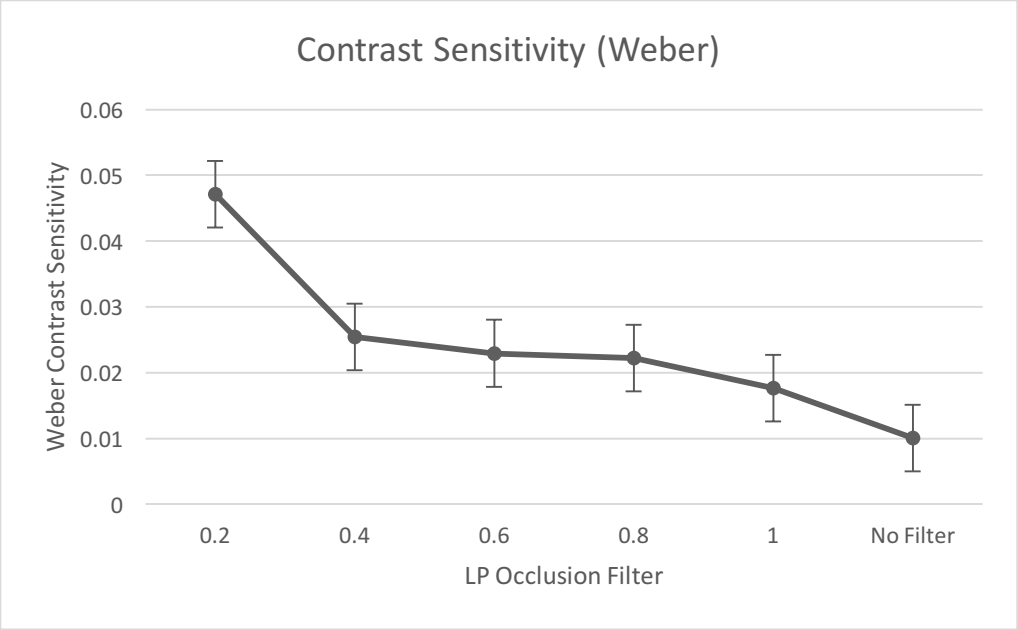

Figure 5.2.3: A plot of Weber contrast sensitivity vs. Bangerter filter visual acuity (n = 5 subjects). Error bars denote standard errors.

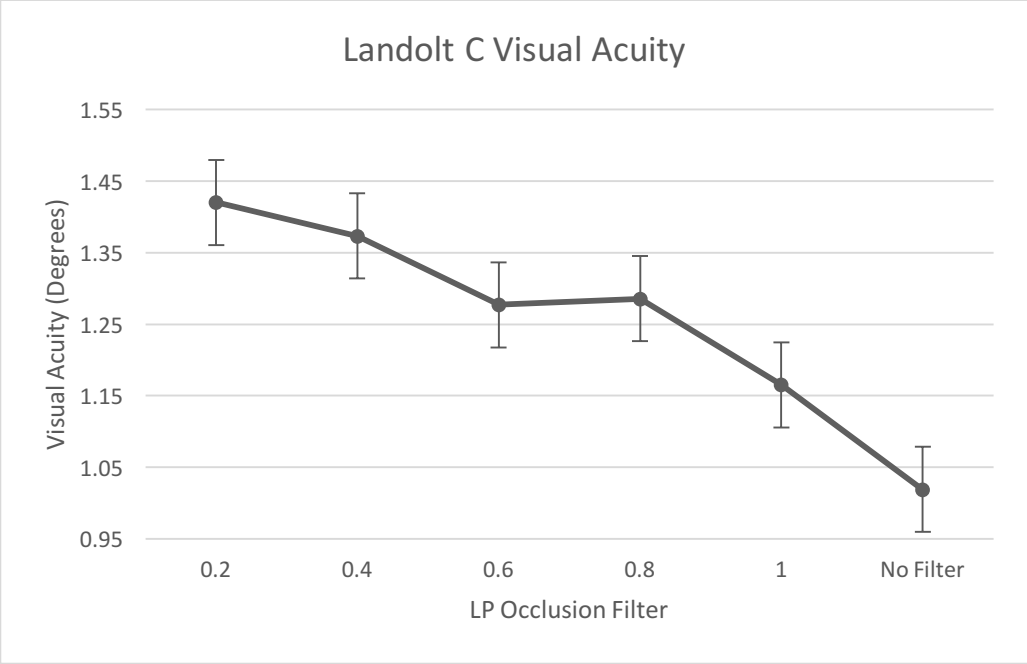

Figure 5.2.4: A plot of Landolt C Visual acuity (degree visual angle) vs. Bangerter filter visual acuity (n = 5 subjects). Error bars denote standard errors.

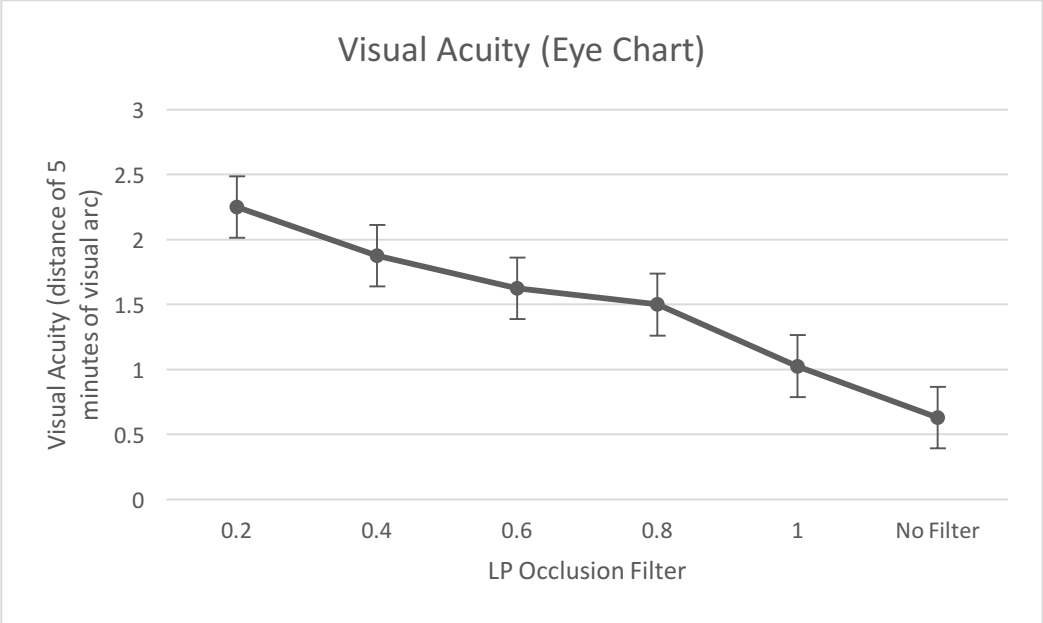

Figure 5.2.5: A plot of Visual acuity (pocket eye chart) vs. Bangerter filter visual acuity (n = 5 subjects). Error bars denote standard errors.

5.2.2 Test-Retest Reliability

Preliminary measures of test-retest reliability measured binocularly (n = 15 normative subjects) were strong for the flicker fusion, contrast sensitivity, and Landolt C visual acuity tests: $R^2 = 0.97$ for flicker fusion at 15 Hz, $R^2 = 0.99$ for flicker fusion at 7.5 Hz, $R^2 = 0.99$ for contrast sensitivity, and $R^2 = 0.96$ for Landolt C visual acuity. Visual acuity measures obtained using the eyeAcuity smartphone application was weakly correlated with visual acuity measures acquired with the standard LogMAR pocket eye chart at the same distance (n = 31, $R^2 = 0.64$).

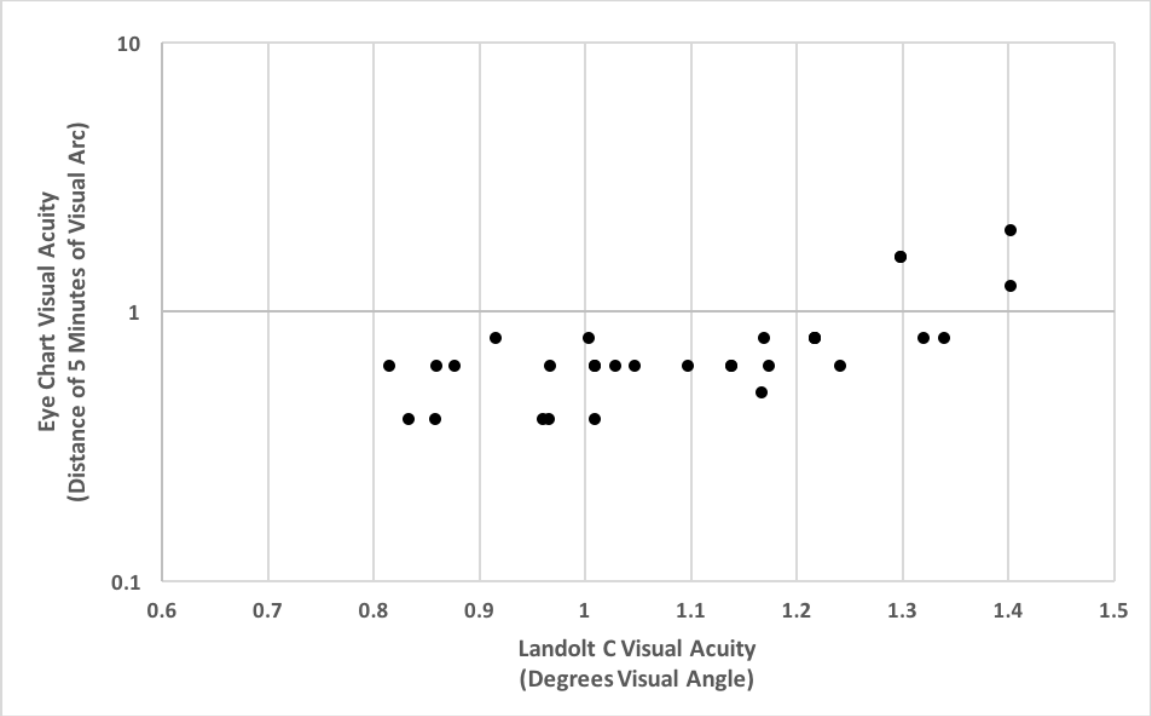

Figure 5.3: The correspondence (n = 31, $R^2 = 0.64$) between two visual acuity measures acquired by a LogMAR pocket eye chart and the Landolt C visual acuity test (eyeAcuity).

5.2.3 Effects of Binocular Summation

The effects of binocular summation were evaluated for the flicker fusion, contrast sensitivity, and Landolt C visual acuity smartphone applications. Subjects who exhibited a ceiling effect during testing, which is common in normative subjects for the flicker fusion and contrast sensitivity tests, were excluded from the respective analysis to determine the effects of binocular summation.

Using a two-tailed t-test for independent samples, binocular flicker fusion at 15 Hz showed statistically significant improvement compared to the average of individual eye flicker fusion thresholds from the same subject (n = 5, P = 0.044), while binocular flicker fusion at 7.5 Hz showed a strong (but non-significant) indication of improvement

(n = 5, P = 0.054). Binocular contrast sensitivity also showed statistically significant improvement (two-tailed t-test for independent samples) compared to the average of individual eye contrast sensitivity measures from the same subject (n = 4, P = 0.015). Finally, binocular Landolt C visual acuity also showed statistically significant improvement (two-tailed t-test for independent samples) compared to the average of individual eye contrast visual acuity measures from the same subject (n = 9, P = 0.002).

5.2.4 Comparison to Normative Data Ranges

Ranges of performance and inter-eye variation were quantified for the normative and non-normative subjects for the three smartphone applications, illustrated as a series of boxplots (Figures 5.4.1 – F.4.8). Enough non-normative data has not been collected, according to the two-sample t-test power analysis (Appendix 2), to perform statistically significant high-powered comparisons between abnormal and normal subjects. Although the non-normative range collected thus far is limited by the sample size, flicker fusion thresholds, visual acuity, and contrast sensitivity of individual subjects with clinically evaluated abnormal visual function collected so far lie outside the normative range (or towards the end of the spectrum corresponding to abnormal function), showing the promise of the measures collected to capture abnormalities of any of the measures.

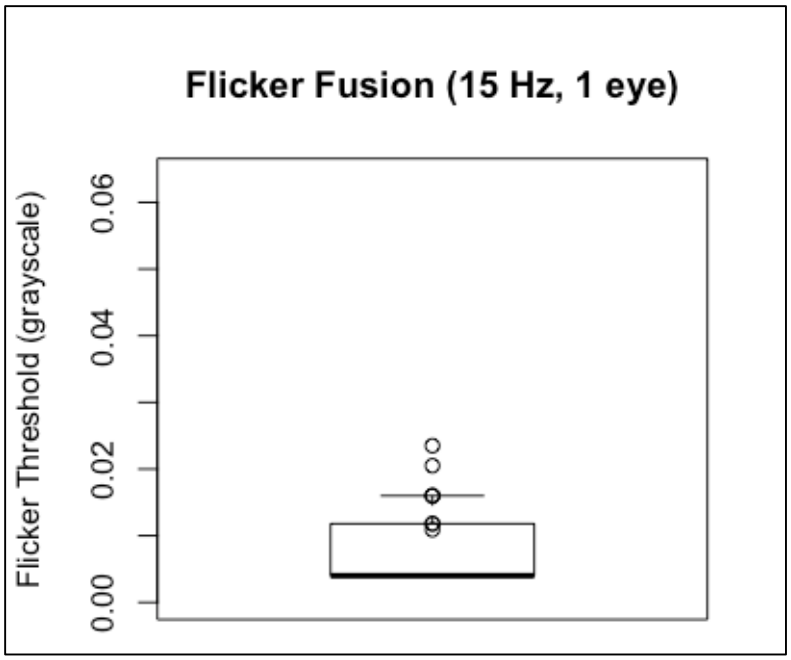

Figure 5.4.1: Normative range of one-eye flicker fusion thresholds at 15 Hz. Individual data points marked indicate the eyeFusion flicker fusion thresholds of clinically evaluated patients with flicker sensitivity deficits assessed in a clinical setting. The 75th percentile, median, and 25th percentile limits are depicted. A total of 30 normal eyes were tested.

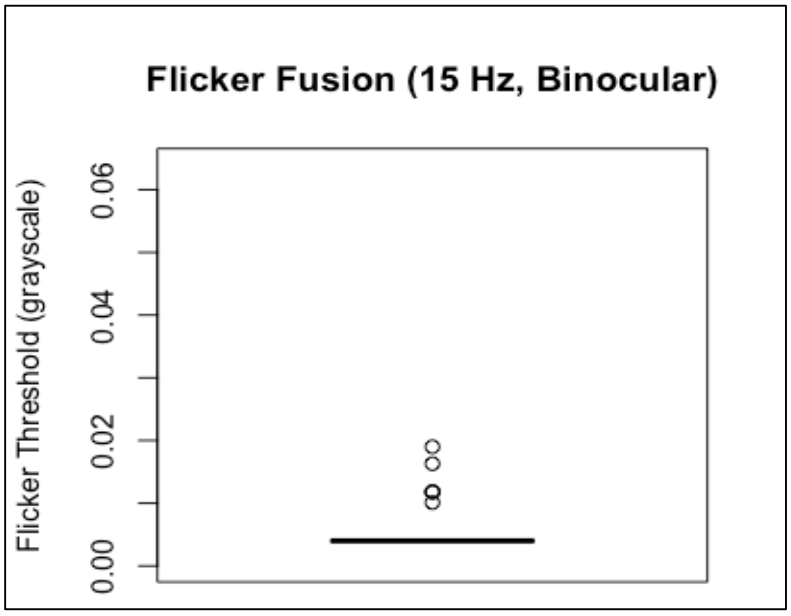

Figure 5.4.2: Normative range of binocular flicker fusion thresholds at 15 Hz. Individual data points marked indicate the eyeFusion flicker fusion thresholds of clinically evaluated patients with flicker sensitivity deficits assessed in a clinical setting. The 75th percentile, median, and 25th percentile limits are depicted. A total of 15 normal subjects were tested.

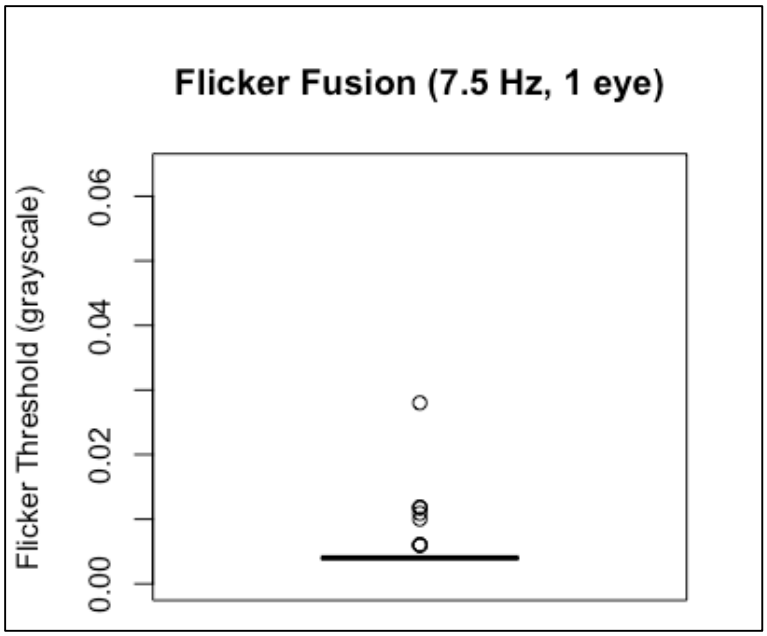

Figure 5.4.3: Normative range of one-eye flicker fusion thresholds at 7.5 Hz. Individual data points marked indicate the eyeFusion flicker fusion thresholds of clinically evaluated patients with flicker sensitivity deficits assessed in a clinical setting. The 75th percentile, median, and 25th percentile limits are depicted. A total of 30 normal eyes were tested.

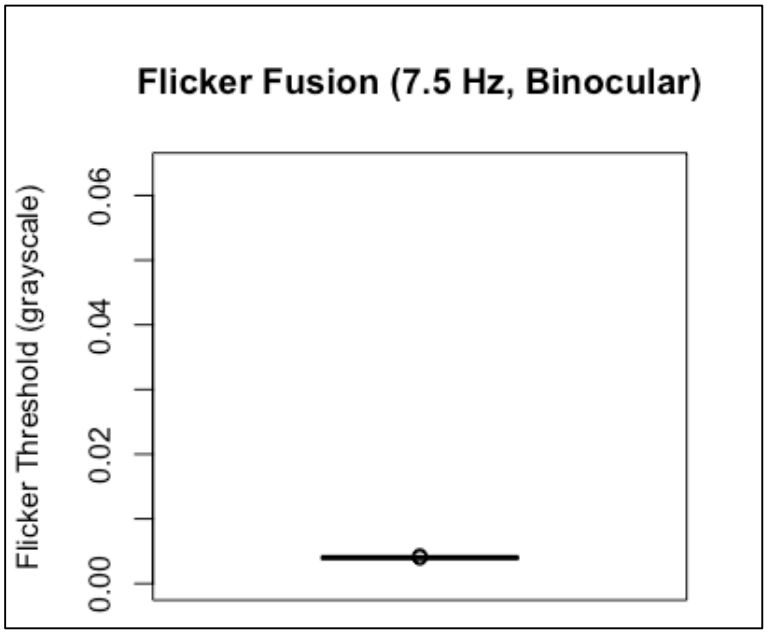

Figure 5.4.4: Normative range of binocular flicker fusion thresholds at 7.5 Hz. Individual data points marked indicate the eyeFusion flicker fusion thresholds of clinically evaluated patients with flicker sensitivity deficits assessed in a clinical setting. The 75th percentile, median, and 25th percentile limits are depicted. A total of 15 normal subjects were tested.

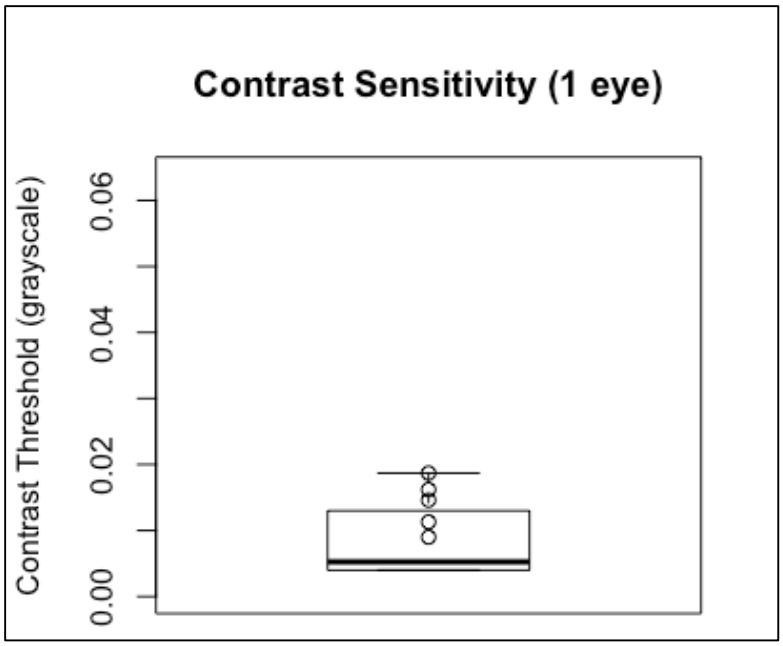

Figure 5.4.5: Normative range of one-eye contrast sensitivity. Individual data points marked indicate the eyeContrast contrast sensitivity thresholds of clinically evaluated patients with contrast sensitivity deficits assessed in a clinical setting. The 75th percentile, median, and 25th percentile limits are depicted. A total of 30 normal eyes were tested.

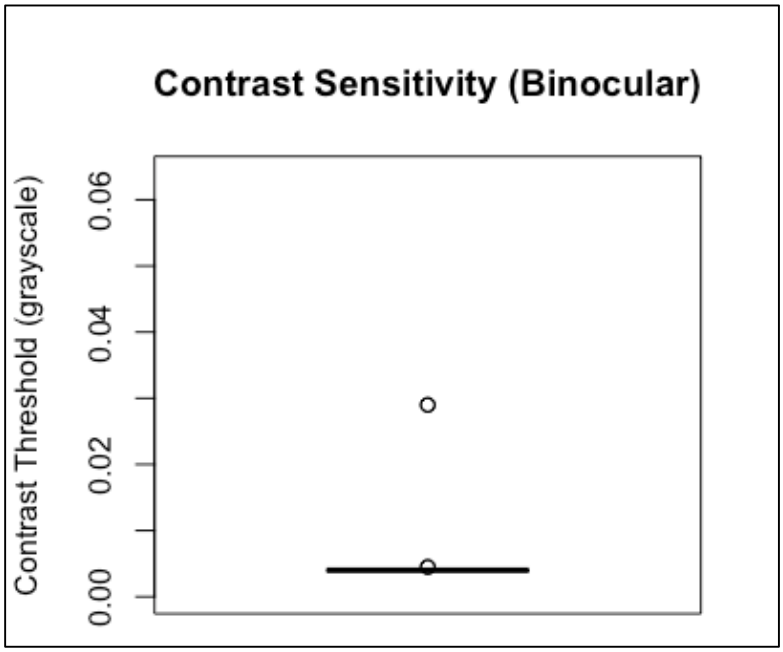

Figure 5.4.6: Normative range of binocular contrast sensitivity. Individual data points marked indicate the eyeContrast contrast sensitivity thresholds of clinically evaluated patients with contrast sensitivity deficits assessed in a clinical setting. The 75th percentile, median, and 25th percentile limits are depicted. A total of 15 normal subjects were tested.

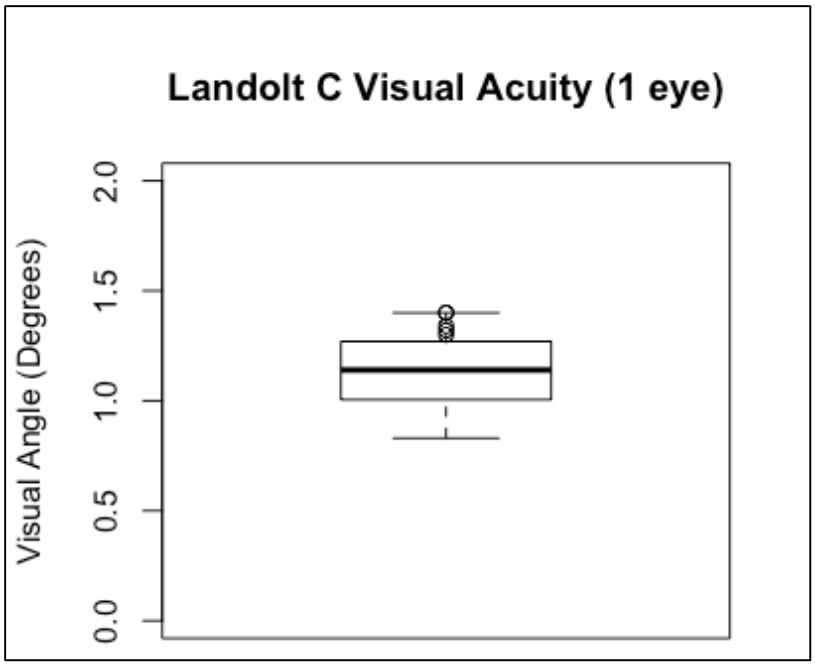

Figure 5.4.7: Normative range of one-eye Landolt C visual acuity. Individual data points marked indicate the eyeAcuity visual acuity of clinically evaluated patients with visual deficits assessed in a clinical setting. The 75th percentile, median, and 25th percentile limits are depicted. A total of 30 normal eyes were tested.

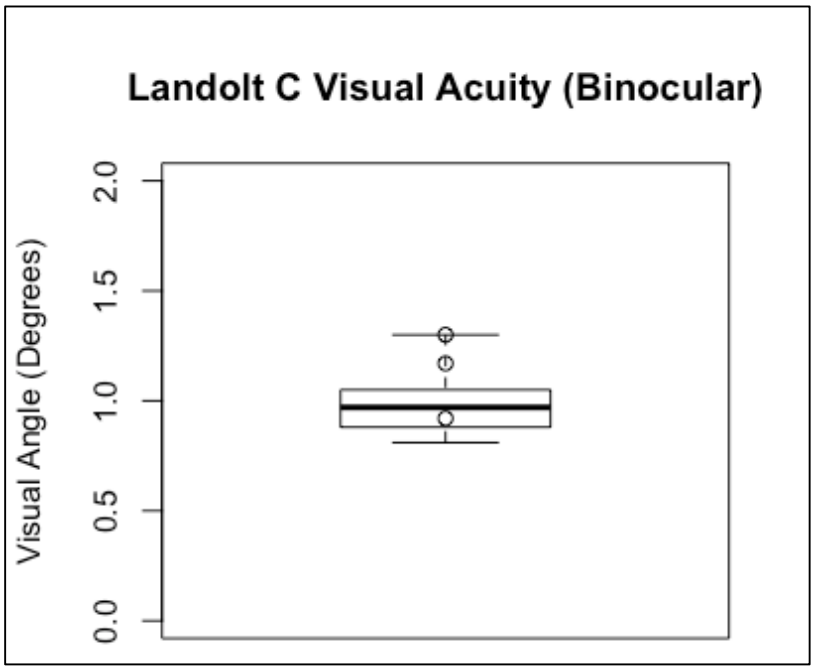

Figure 5.4.8: Normative range of binocular Landolt C visual acuity. Individual data points marked indicate the eyeAcuity visual acuity of clinically evaluated patients with visual deficits assessed in a clinical setting. The 75th percentile, median, and 25th percentile limits are depicted. A total of 15 normal subjects were tested.

CHAPTER 6

CONCLUSIONS AND DISCUSSION

6.1 Evaluation

The results from measuring the frequency of the signals using the pin diode demonstrate the technical feasibility of flicker fusion testing with smartphone and tablet devices. Hardware limitations restrict the temporal frequencies that can be presented. Overall, increases in the intended temporal frequency to be used to produce the flicker correspond with decreases in accuracy in both the temporal and intensity domain of pixel presentation across all iOS devices. For instance, for the iPad, iPhone, and iTouch devices, 30 Hz oscillations have the least accuracy in the temporal and intensity domain of pixel presentation, in respect to presenting a square wave stimulus, while 1 Hz oscillations produce the most accurate square wave flicker (Appendix 4). Unless demonstrated to provide clinically significant measurements, flicker oscillations at temporal frequencies that do not consistently produce a representative square or sinusoidal wave should be excluded from testing as they lack the technical validity met by other tests of flicker fusion.

With confirmation that a robust signal can be presented at frequencies less than 7.5 Hz, and even to an acceptable level at 15 Hz, eyeFusion provides a useful approach to efficiently quantify flicker fusion thresholds in this range of frequncies in large populations. Furthermore, the calibration curves of pixel intensity, acquired from all three types of iOS devices (iPhone, iTouch, and iPad), produced all consistently exhibited strong linear trends and even stronger quadratic (non-linear) trends. Model fits tend to be weaker at the lower grayscale intensities, revealing the subtle inaccuracies introduced

when presenting stimuli at lower luminance levels. Future work will be directed towards determining the exact grayscale settings that must be programmed to produce the desired contrasts. Together, these results demonstrate, in a general sense that any visual stimulus presented on an iOS device is agnostic of the device model used.

As described earlier, the flicker fusion test was resistant to blur (excluding severe levels of diffusion/occlusion) while the visual acuity and contrast sensitivity tests were not resistant to blur. The resistance to blur is expected and necessary for any form of flicker fusion test as certain medical conditions produce visual blur, but not alterations or abnormalities in flicker fusion thresholds. An implemented flicker fusion test that could confuse blurred vision with abnormalities in visual conduction would most likely lead to some inaccurate clinical findings.

Preliminary measures of test-retest reliability, binocular summation effects, and correlations to standard measures of visual acuity, flicker fusion, and other elements of visual function have been encouraging, but require the recruitment of additional subjects with visual abnormalities to capture a wide range of visual function and build the normative data models generated to date with larger number of normal subjects of varying age so that these measures can be age-corrected if there are changes as a function of subject age. The motivation to expand data collection efforts in terms of quantity and application will be discussed in greater detail in the following section.

6.2 Addressing the Functional Requirements

The underlying aims driving the development of eyeApps and HearMe was to develop rapid, intuitive smartphone-based tools that allow health-care workers and researchers to obtain objective quantifications of multiple components of visual and

hearing function. The design and implementation of these tools required careful consideration of the aforementioned functional requirements. The psychophysical tests were designed in a simple manner that would minimize the cognitive requirements of test-takers. In certain cases, at least for the novel visual tests developed (such as the flicker fusion and vanishing optotypes), a concept of "clearing the screen" by tapping all identified targets was employed as it provides immediate feedback to the observer and reduces the confusion associated with cluttered interfaces. Additionally, the cognitive load of the user was minimized by only requiring taps as the form of interaction and input with the interface. However, the elimination of learning effects was still a priority, and the overall design of the test (the number of responses in a closed set, the testing paradigm, the method for computing thresholds, etc.) was constructed in such a way that would limit the impact of chance on the objective functional quantifications.

Testing durations were also minimized without compromising the level of detail and precision of the measurements taken. This necessitated an iterative process of designing and testing to derive the optimal balance between acquiring precise objective measurements and implementing rapid test paradigms, as well as simplifying the interface to intuitively facilitate rapid responses by the observer. The secure transfer of data was accomplished by adhering to existing standards and regulations, and existing platforms that allow the ease of implementation of backend databases and data transfer protocols that are in accordance with these standards.

CHAPTER 7

FUTURE DIRECTIONS

With a rigorous technical evaluation of iOS smartphone and tablet devices performed, the primary focus of continued work should be directed towards collecting additional data of patients across a range of ocular and neurological disorders to both strengthen preliminary forms of clinical validation and answer clinically relevant questions.

Multiple diseases of interest for the smartphone visual measures of interest include multiple sclerosis and different forms of optic neuropathies that reduce visual conductance speed in patients and produce daily and weekly variations. Environments that affect core body temperatures and thus, alter conduction velocities are of interest, as well as new drugs that are designed to increase nerve conduction speed by altering potassium ion channels in nerves. Specifically, one is 4-aminopyridine which has been shown to improve clinical signs in MS. It remains unanswered how the layer thickness of the ganglion cell layer,(which corresponds to nerve density in the retina) measured with OCT of the macula nerve, correlate with flicker fusion. This area work can be important in determining the structural underpinnings of flicker fusion, and study diseases in which there are reports of impaired flicker fusion thresholds but no alterations in ganglion cell layer thickness (and vice-versa). Two-sample t-test power analyses performed to date project, on average, a minimum of 50 controls and 50 abnormal subjects needed for high-powered analyses related to answering disease specific questions.

Data collection efforts need to efficiently be extended to the entire suite of applications developed and discussed in the present work. There is a strong interest in

expanding the current suite of smartphone applications. Additional applications to add to this battery of objective tests include (but are not limited to) applications that can measure the pupil response, photoadaptation and visual acuity in noise. The latter test for instance would potentially involve modifying the Landolt C visual acuity test to present target stimuli at a non-maximum contrast with a patterned noise as illustrated in the Pelli-Levi Dual Acuity Chart. Nowadays, many medical devices have been created that can communicate and integrate with smartphone devices. An example of these devices is the Muse™ ("the brain sensing headband"), a meditation device that can provide a set of EEG measurements. The muse has a developer kit that allows the transfer and real-time analysis of accurate EEG data on smartphone technologies. The technology behind smartphones is also used to power virtual and augmented reality devices (a rapidly developing area) thus adding further value to smartphone-based testing.

Beyond collecting data in the clinic, the Apple ResearchKit is a valuable platform that can enable national and international collection of data with health-related smartphone applications. Data collection on a large-scale is valuable for a wide range of scientific foci, specifically genotype-phenotype correlations and endophenotype discovery in ocular and neurological disorders.

Another application of the developed technology relates to at-home testing of visual and hearing function. This form of independent testing is especially important to screen for sensory deficits earlier and on a larger scale. One example of an existing at-home test for macular degeneration, though not developed for the smartphone, is the Amsler grid [47]. This grid (Figure 7.1.1) consists of dark lines that form a square grid, similar to graph paper.

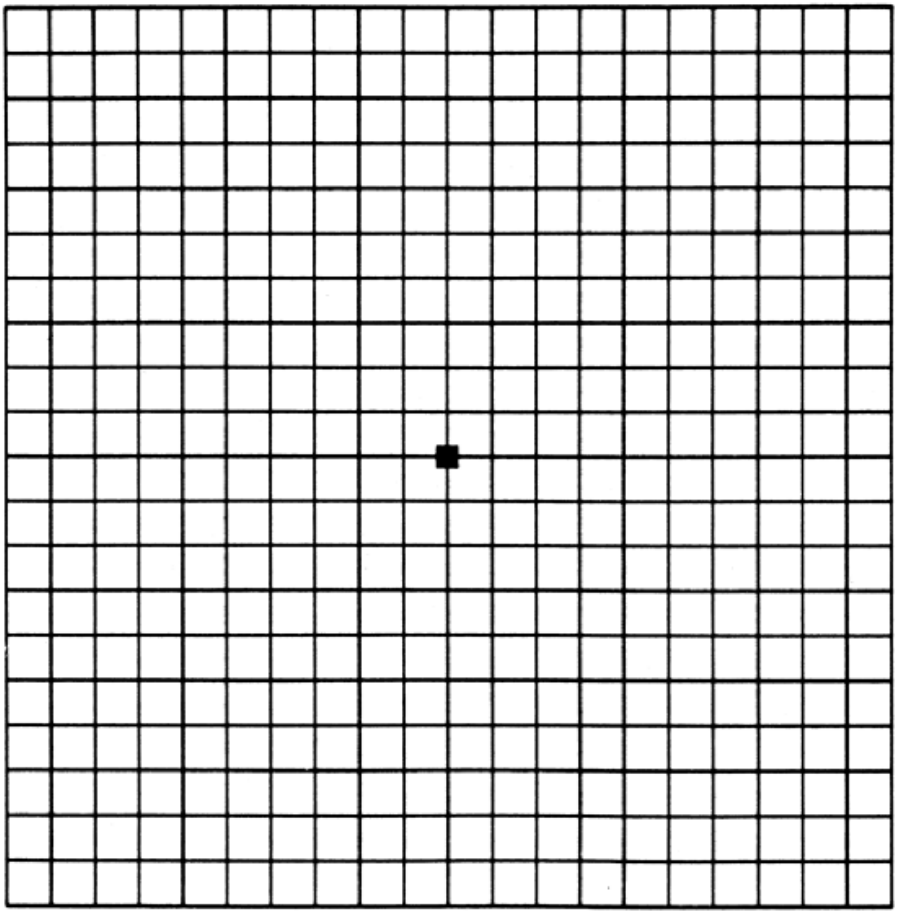

Figure 7.1.1: The Amsler grid consists of dark lines that form a square grid, and is commonly used as a simple test to indicate a problem with macular degeneration. Image courtesy of the National Eye Institute, National Institutes of Health.

The Amsler grid is used to detect early signs of macular degeneration through experiencing missing or blurred areas of vision, or broken, distorted, or wavy lines. An observer with macular degeneration would notice distorted or broken lines (Figure 7.1.2) or blurred areas while looking at the dot at the center of the grid.

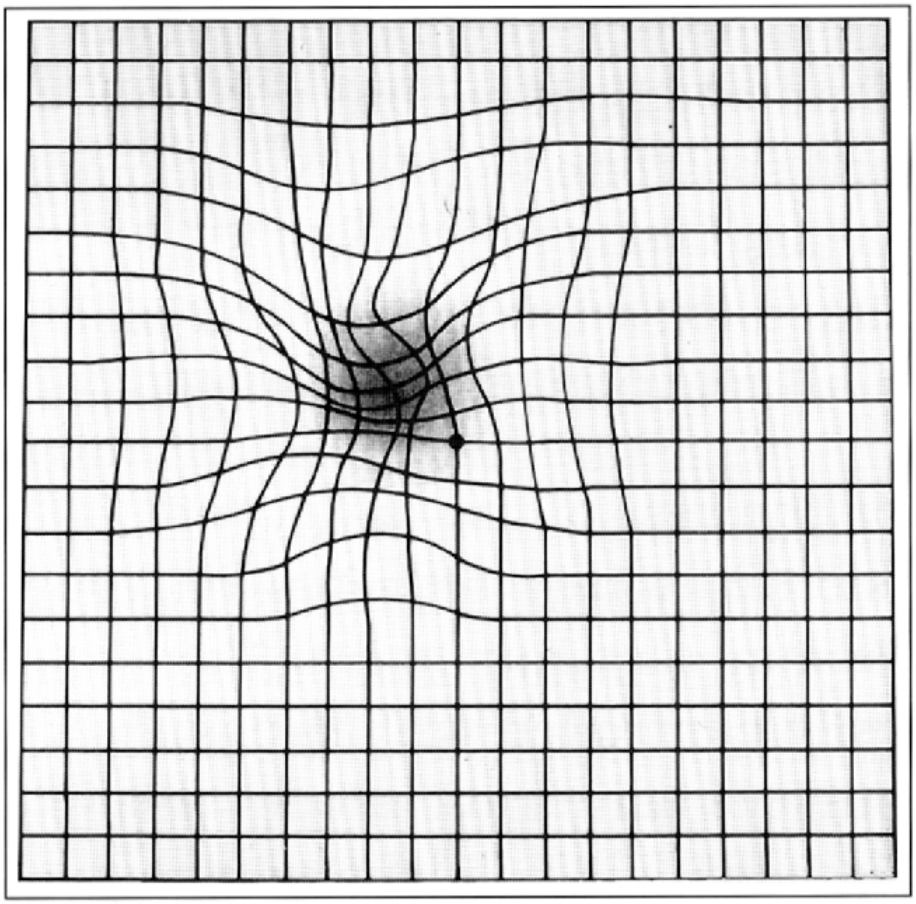

Figure 7.1.2: An illustration of the distorted appearance of the Amsler grid, commonly observed by subjects with macular degeneration. Image courtesy of the National Eye Institute, National Institutes of Health.

Beyond general health screening, at-home, objective testing can be used to monitor sensory function post operations (i.e. before and after cataract surgeries) and interventions. For instance, the functional effects of novel pharmaceutical treatments or forms of alternative medicine can be monitored and assessed for efficacy in unprecedented detail. Furthermore, it is common for subjects to experience elevated blood pressures and levels of anxiety when in a clinical setting [48, 49]. This phenomenon, often referred to as white coat hypertension or white coat syndrome, is not exhibited by subjects in non-clinical settings such as at home [48, 49]. The advantage of

smartphone-driven approaches of functional assessment is that it removes or limits the confounding effects of anxiety and elevated blood pressure, among other factors, when measuring sensory function.

Finally, given the rapidly changing technological landscape, no piece of software is complete. Not only must the suite of smartphone applications be expanded to include other psychophysical tests, but the currently implemented tests must be routinely modified to be kept up-to-date to fully utilize the capabilities of software and hardware updates. Additionally, audio-based instructions were not included in the current implementation, but must be incorporated in the future to assist subjects who are visually impaired and unable to read instructions for at-home, independent testing.

Nevertheless, the presented work, in its entirely, showcases a foundation and procedure to design, implement and test standard and novel psychophysical tests to objectively measure sensory function using smartphone and mobile technology. The ability of this technology to objectively quantify sensory behavior is a reality in the current era of medical mobile applications, and one that must be pursued to develop a comprehensive, low-cost suite of bulletproof tests that extend the work discussed. The entirety of the work presented has far reaching clinical and research applications, as has been discussed and motivated throughout this thesis. The potential of this technology to answer a plethora of scientific questions, save millions of healthcare dollars, and reduce the prevalence of sensory disorders worldwide has not been fully tapped, and must be further pursued through collaborations of engineers, scientists, and physicians.

REFERENCES

1. Wallace, S., M. Clark, and J. White, *'It's on my iPhone': attitudes to the use of mobile computing devices in medical education, a mixed-methods study.* BMJ Open, 2012. 2(4).
2. Ventola, C.L., *Mobile devices and apps for health care professionals: uses and benefits.* P T, 2014. 39(5): p. 356-64.
3. Yoshiyama, K.K. and C.A. Johnson, *Which method of flicker perimetry is most effective for detection of glaucomatous visual field loss?* Invest Ophthalmol Vis Sci, 1997. 38(11): p. 2270-7.
4. Tyler, C.W., *Specific deficits of flicker sensitivity in glaucoma and ocular hypertension.* Invest Ophthalmol Vis Sci, 1981. 20(2): p. 204-12.
5. Daley, M.L., R.L. Swank, and C.M. Ellison, *Flicker fusion thresholds in multiple sclerosis. A functional measure of neurological damage.* Arch Neurol, 1979. 36(5): p. 292-5.
6. Salmi, T., *Critical flicker frequencies in MS patients with normal or abnormal pattern VEP.* Acta Neurol Scand, 1985. 71(5): p. 354-8.
7. Lachenmayr, B.J., et al., *The different effects of aging on normal sensitivity in flicker and light-sense perimetry.* Invest Ophthalmol Vis Sci, 1994. 35(6): p. 2741-8.
8. Kim, C.B. and M.J. Mayer, *Foveal flicker sensitivity in healthy aging eyes. II. Cross-sectional aging trends from 18 through 77 years of age.* J Opt Soc Am A Opt Image Sci Vis, 1994. 11(7): p. 1958-69.
9. Mayer, M.J., et al., *Foveal flicker sensitivity in healthy aging eyes. I. Compensating for pupil variation.* J Opt Soc Am A, 1988. 5(12): p. 2201-9.
10. Casson, E.J., C.A. Johnson, and J.M. Nelson-Quigg, *Temporal modulation perimetry: the effects of aging and eccentricity on sensitivity in normals.* Invest Ophthalmol Vis Sci, 1993. 34(11): p. 3096-102.
11. Lachenmayr, B.J., *The role of temporal threshold criteria in psychophysical testing in glaucoma.* Curr Opin Ophthalmol, 1994. 5(2): p. 58-63.
12. Lachenmayr, B.J. and M. Gleissner, *Flicker perimetry resists retinal image degradation.* Invest Ophthalmol Vis Sci, 1992. 33(13): p. 3539-42.
13. Kelly, D.H., *Visual responses to time-dependent stimuli. III. Individual variations.* J Opt Soc Am, 1962. 52: p. 89-95.
14. Kelly, D.H., *Visual responses to time-dependent stimuli. IV. Effects of chromatic adaptation.* J Opt Soc Am, 1962. 52: p. 940-7.
15. Van Toi, V., P.A. Grounauer, and C.W. Burckhardt, *Artificially increasing intraocular pressure causes flicker sensitivity losses.* Invest Ophthalmol Vis Sci, 1990. 31(8): p. 1567-74.
16. Accornero, N., et al., *Critical fusion frequency in MS during mild induced hyperthermia.* Acta Neurol Scand, 1989. 79(6): p. 510-4.
17. Casson, E.J., C.A. Johnson, and L.R. Shapiro, *Longitudinal comparison of temporal-modulation perimetry with white-on-white and blue-on-yellow perimetry in ocular hypertension and early glaucoma.* J Opt Soc Am A Opt Image Sci Vis, 1993. 10(8): p. 1792-806.

18. Hill, S.Y., *Further evidence for critical flicker fusion as an objective measure of alcohol tolerance in alcoholics.* J Nerv Ment Dis, 1975. 161(5): p. 345-6.
19. Bisht, B., et al., *A multimodal intervention for patients with secondary progressive multiple sclerosis: feasibility and effect on fatigue.* J Altern Complement Med, 2014. 20(5): p. 347-55.
20. Bailey, I.L. and J.E. Lovie, *New design principles for visual acuity letter charts.* Am J Optom Physiol Opt, 1976. 53(11): p. 740-5.
21. Hetherington, R., *The Snellen chart as a test of visual acuity.* Psychol Forsch, 1954. 24(4): p. 349-57.
22. Danilova, M.V. and V.M. Bondarko, *Foveal contour interactions and crowding effects at the resolution limit of the visual system.* J Vis, 2007. 7(2): p. 25 1-18.
23. Bach, M., *The Freiburg Visual Acuity test--automatic measurement of visual acuity.* Optom Vis Sci, 1996. 73(1): p. 49-53.
24. Rover, J., et al., *[The Freiburg Vision Test before and after cataract operation].* Klin Monbl Augenheilkd, 1996. 209(5): p. 315-6.
25. Bach, M., et al., *[Contrast vision-definitions, conversions, and equivalence tables].* Ophthalmologe, 2016.
26. in *Emergent Techniques for Assessment of Visual Performance*. 1985: Washington (DC).
27. *The measurement of contrast sensitivity function.* Ophthalmic Physiol Opt, 1985. 5(1): p. 1-3.
28. Reeves, B.C., J.M. Wood, and A.R. Hill, *Vistech VCTS 6500 charts--within- and between-session reliability.* Optom Vis Sci, 1991. 68(9): p. 728-37.
29. Wakayama, A., C. Matsumoto, and Y. Shimomura, *Binocular summation of detection and resolution thresholds in the central visual field using parallel-line targets.* Invest Ophthalmol Vis Sci, 2005. 46(8): p. 2810-5.
30. Anderson, R.S. and F.A. Ennis, *Foveal and peripheral thresholds for detection and resolution of vanishing optotype tumbling E's.* Vision Res, 1999. 39(25): p. 4141-4.
31. Frisen, L., *Vanishing optotypes. New type of acuity test letters.* Arch Ophthalmol, 1986. 104(8): p. 1194-8.
32. Shah, N., et al., *Vanishing Optotype acuity: repeatability and effect of the number of alternatives.* Ophthalmic Physiol Opt, 2011. 31(1): p. 17-22.
33. Adoh, T.O. and J.M. Woodhouse, *The Cardiff acuity test used for measuring visual acuity development in toddlers.* Vision Res, 1994. 34(4): p. 555-60.
34. Stigmar, G., *Blurred visual stimuli. II. The effect of blurred visual stimuli on vernier and stereo acuity.* Acta Ophthalmol (Copenh), 1971. 49(3): p. 364-79.
35. Foley-Fisher, J.A., *The effect of target line length on Vernier acuity in white and blue light.* Vision Res, 1973. 13(8): p. 1447-54.
36. Westheimer, G., *Editorial: Visual acuity and hyperacuity.* Invest Ophthalmol, 1975. 14(8): p. 570-2.
37. Flueckiger, P. and D.S. Mojon, *Detection of nonorganic visual loss with a new optotype chart in simulated malingerers.* Klin Monbl Augenheilkd, 2003. 220(3): p. 89-92.
38. Mojon, D.S. and P. Flueckiger, *A new optotype chart for detection of nonorganic visual loss.* Ophthalmology, 2002. 109(4): p. 810-5.

39. Levitt, H., *Adaptive procedures for hearing aid prescription and other audiologic applications.* J Am Acad Audiol, 1992. 3(2): p. 119-31.
40. Brand, T. and B. Kollmeier, *Efficient adaptive procedures for threshold and concurrent slope estimates for psychophysics and speech intelligibility tests.* J Acoust Soc Am, 2002. 111(6): p. 2801-10.
41. Nilsson, M., S.D. Soli, and J.A. Sullivan, *Development of the Hearing in Noise Test for the measurement of speech reception thresholds in quiet and in noise.* J Acoust Soc Am, 1994. 95(2): p. 1085-99.
42. Cadieux, J.H., J.B. Firszt, and R.M. Reeder, *Cochlear implantation in nontraditional candidates: preliminary results in adolescents with asymmetric hearing loss.* Otol Neurotol, 2013. 34(3): p. 408-15.
43. Koole, A., et al., *Using the Digits-In-Noise Test to Estimate Age-Related Hearing Loss.* Ear Hear, 2016. 37(5): p. 508-13.
44. Potgieter, J.M., et al., *Development and validation of a smartphone-based digits-in-noise hearing test in South African English.* Int J Audiol, 2015. 55(7): p. 405-11.
45. Wooten, B.R., et al., *A practical method of measuring the human temporal contrast sensitivity function.* Biomed Opt Express, 2010. 1(1): p. 47-58.
46. Kelley, D.H., *Spatio-temporal frequency chracteristics of color-vision mechanisms.* J Opt Soc Am, 1974. 64(7): p. 983-90.
47. Amsler, M., *Earliest symptoms of diseases of the macula.* Br J Ophthalmol, 1953. 37(9): p. 521-37.
48. Helvaci, M.R. and M. Seyhanli, *What a high prevalence of white coat hypertension in society!* Intern Med, 2006. 45(10): p. 671-4.
49. Pickering, T.G., et al., *How common is white coat hypertension?* JAMA, 1988. 259(2): p. 225-8.

APPENDICES

APPENDIX A – TEST INSTRUCTIONS

The following set of instructions were read verbally to the test subjects, and programmed directly into the respective smartphone applications for the extension of at-home self-testing.

A.1 eyeFusion Instructions

You will test each eye one at a time. Leave all corrective lenses, etc. on for the duration of the test. Start with the right eye, and then repeat the procedure for the left eye. Prior to starting the test, use a small piece of cloth to wipe the screen to remove fingerprints and smudges.

Protocol (test right and left eyes separately, and then together):

1. Begin by holding the device at reading distance, or approximately 0.4 meters from your eyes. Try and keep the device in the same orientation and distance away from your eyes.
2. You will be presented with a grid of 12 circles, flickering at 15 Hz at varying contrast levels. Your objective is to tap all the flickering circles that you can see. The circles will vanish once tapped. Note: only tap the circles that are FLICKERING.
3. After you have tapped all the flickering circles that you can see, press the 'Done' Button in the center.
4. You will be presented with another grid of 12 circles, flickering at 15 Hz except at a narrower range of contrast levels. Again, tap all the flickering circles that you can see and press 'Done'

5. Select if you want to continue the test at 7.5 Hz (easier) or 30 Hz (harder), depending on your ease at completing the test at 15 Hz.

6. Repeat steps 2-4 for the new temporal frequency

7. Complete the exit survey.

A.2 eyeAcuity Instructions

You will test each eye one at a time. Leave all corrective lenses, etc. on for the duration of the test. Start with the right eye, and then repeat the procedure for the left eye. Prior to starting the test, use a small piece of cloth to wipe the screen to remove fingerprints and smudges.

Protocol (test right and left eyes separately, and then together):

Begin by holding the device at reading distance, or approximately 0.4 meters from your eyes. Try and keep the device in the same orientation and distance away from your eyes. You will be presented with a series of Landolt "C" rings. Tap the arrows on the side of the screen that indicate the direction of the opening of the ring.

A.3 eyeContrast Instructions

You will test each eye one at a time. Leave all corrective lenses, etc. on for the duration of the test. Start with the right eye, and then repeat the procedure for the left eye. Prior to starting the test, use a small piece of cloth to wipe the screen to remove fingerprints and smudges.

Protocol (test right and left eyes separately, and then together):

Begin by holding the device at reading distance, or approximately 0.4 meters from your eyes. Try and keep the device in the same orientation and distance away from your eyes. You will be presented with a series of Landolt "C" rings. Tap the arrows on the side of the screen that indicate the direction of the opening of the ring.

A.4 eyeVanish Instructions

You will test each eye one at a time. Leave all corrective lenses, etc. on for the duration of the test. Start with the right eye, and then repeat the procedure for the left eye. Prior to starting the test, use a small piece of cloth to wipe the screen to remove fingerprints and smudges.

Protocol (test right and left eyes separately, and then together):

Begin by holding the device at reading distance, or approximately 0.4 meters from your eyes. Try and keep the device in the same orientation and distance away from your eyes. Tap all the stimuli in the 6 x 3 grid, consisting of squares, that you can see. Press done once finished. You will then be presented with another 6 x 3 of stimuli, again consisting of squares. Again, tap all the ones that you can see, and press done once finished.

A.5 eyeVernier Instructions

You will test each eye one at a time. Leave all corrective lenses, etc. on for the duration of the test. Start with the right eye, and then repeat the procedure for the left eye. Prior to starting the test, use a small piece of cloth to wipe the screen to remove fingerprints and smudges.

Protocol (test right and left eyes separately, and then together):

Begin by holding the device at reading distance, or approximately 0.4 meters from your eyes. Try and keep the device in the same orientation and distance away from your eyes. You will be presented with two lines. These two lines atop each other with a slight horizontal offset. You have to judge which way the top line is offset from the bottom one, to the left or right, using the arrows on either side of the screen. Keep on clicking to make the lines aligned as best as you can.

A.6 Mojon Chart Instructions

You will test each eye one at a time. Leave all corrective lenses, etc. on for the duration of the test. Start with the right eye, and then repeat the procedure for the left eye. Prior to starting the test, use a small piece of cloth to wipe the screen to remove fingerprints and smudges.

Protocol (test right and left eyes separately, and then together):

Begin by holding the device at reading distance, or approximately 0.4 meters from your eyes. Try and keep the device in the same orientation and distance away from your eyes. Tap all the optotypes you can see in the first screen. Then press Done. You will be presented with a second screen of optotypes. Tap all the targets that you can see.

A.7 HearMe Instructions

You can stop the test at anytime by pressing the home button at the upper left corner of the screen to take you back to the main menu, or the home button on your phone to exit the app. An incomplete test will not be saved.

The test consists of sequences (24 total) of three digits spoken over background noise. You will determine which digits are spoken in each sequence (that is, how well can you 'hear me'). The signal-to-noise ratio of the sequences will increase and decrease according to your incorrect and correct responses respectively. At higher, more positive signal-to-noise ratios, digits are easier to hear compared to lower, more negative signal-to-noise ratios. Before starting the test, you must press the button (right) to play a sample noise. Adjust the volume on your phone so that you can comfortably hear the noise. When the volume is at a comfortable level, press the button below to start the test in any of the simulated noises/environments listed (note: white noise is recommended to measure your most reliable and accurate performance).

After completing the test, you will be provided with your speech reception threshold (a signal-to-noise hearing threshold in decibels). Be sure to update your information, compare your performance to past results, and schedule a calendar reminder for your future test.

APPENDIX B – IRB PROJECT SUMMARY

PI: Randy Kardon

IRB ID #: 201610703

Project Details

I. Project Introduction

I.1 *Project to be reviewed by:*

IRB-01

I.2 *Project Title:*

Validation of a Smartphone-Based Flicker Fusion Test

I.3 *Short Title (optional):*

eyeFusion

I.4 *Provide a short summary of the purpose and procedures of the study proposed in this IRB application.*

- *DO NOT include information on studies not proposed in this application.*
- *Use LAY terminology only. This must be easily understandable by IRB community members and nonscientists.*
- *DO NOT cut and paste technical abstracts from funding applications that may not be understood by a general audience.*

The purpose of this project is to validate a quick, easy-to-use and administer smartphone flicker fusion test. The app (called eyeFusion) can potentially be used to easily and quickly collect critical flicker fusion measurements on patients admitted with optic disorders as part of the clinical care process.

The smartphone app developed is a flicker fusion that presents the subject with a series of stimuli consisting of a flickering pattern of bars above or below a static rectangle. For each stimulus presentation, the user has to tap the region that is flickering. The duration of the app is less than 2 minutes. The software has been developed and is owned by the research team members listed on this IRB.

For this pilot project we will test at least 50 subjects with scotomas and 50

control subjects between the ages of 18-80. The subjects will be invited to take the app. Our approach for this pilot study is to characterize flicker fusion thresholds (as measured by the app)in both subject groups, and relate it to the phenotype of each group as a preliminary validation test for the app.

The study will assess the validity of the test construct in measuring flicker fusion thresholds, and serve as a foundation for further iterative designs of the app and future validation and characterization studies.

I.5 *Specify your research question(s), study aims or hypotheses (do not indicate "see protocol")*

Flicker perimetry in all of its forms has made it possible to evaluate peripheral visual function in an efficient manner, provides greater sensitivity for detecting early pathologic changes, and provides the opportunity to evaluate the visual field of individuals that otherwise may not be accessible. This proposal seeks to validate a developed smartphone flicker fusion test on an initial cohort of patients and controls. It is anticipated that patients with scotomas will display lower flicker fusion thresholds (as measured by the iPhone app) compared to controls.

I.6 *Background and significance and/or Preliminary studies related to this project.*
(do not indicate "see protocol")

The ability to detect intermittent light and dark alternations of a visual stimulus (flicker or temporal visual processing) is an important component of visual function throughout the field of view. Rapid changes in the luminance or contrast of a stimulus can be important for detecting environmental changes, motion, and awareness of objects in peripheral vision. A thorough description of the variables influencing and mechanisms underlying flicker sensitivity is beyond the scope of this presentation, but there are several references that can provide a comprehensive review. Flicker sensitivity has been a topic of interest to many investigators for nearly 200 years.

Flicker perimetry is a visual field test procedure that evaluates an observer's ability to detect light/dark stimulus alternations (flicker) at various locations in the field of view. Contrast modulation flicker uses a stimulus that is matched in luminance to the background and is the type of flicker test that eyeFusion adopts. The contrast of the stimulus is then modulated temporally according to a fixed frequency, and the amplitude of flicker modulation needed for detection of the stimulus is determined for different rates of flicker. From a clinical perspective, flicker perimetry in its various forms has been reported to be a sensitive indicator of early functional damage for a

variety of disorders, including age- related macular degeneration and retinal diseases, glaucoma, and other ocular and neurologic disorders (namely Alzheimer's Disease).

For many years, psychophysical flicker sensitivity has been reported to be diminished in glaucoma and ocular hypertension. It is important to recognize that the ability to detect flicker is a sensitive and early indicator of functional loss in glaucoma, and subsequent studies have confirmed this result. It is critical to apply test procedures that are robust to non-pathologic influences on flicker sensitivity, and to implement test procedures that are best designed to provide stable, reproducible test results. In view of the many stimulus parameters that can influence the sensitivity to flicker, this represents a challenging and formidable task.

I.7 *Literature cited / references (if attaching a grant or protocol enter N/A).*

1. Kelly DH: Flicker. In Handbook of Sensory Physiology, Vol VII/4 (L Hurvich and D Jameson, eds), Chapter 11, Berlin: Springer-Verlag, 1972, pp. 273-302.
2. McKendrick AM, Johnson CA: Temporal Properties of Vision. In Adler's physiology of the Eye (P. Kaufman and A Alm, eds), Chapter 20, St. Louis: CV Mosby, 2002, pp 511-530.
3. Kelly DH: Visual responses to time-dependent stimuli: 1. Amplitude sensitivity measurements. J Opt Soc Am, 1961, 51: 422-429.
4. Kim CB, Mayer MJ: Foveal flicker sensitivity in healthy aging eyes. II. Cross- sectional aging trends from 18 through 77 years of age. J Opt Soc Am, 1994, 11: 1958-1969.
5. Casson EJ, Johnson CA and Nelson-Quigg JM: Temporal modulation perimetry: the effects of aging and eccentricity on sensitivity in normals, Invest Ophthalmol Vis Sci, 1993, 34: 3096-3102.
6. Tyler CW: Specific deficits of flicker sensitivity in glaucoma and ocular hypertension. Invest Ophthalmol Vis Sci, 1981, 20: 204-212.
7. Casson EJ and Johnson CA: Temporal modulation perimetry in glaucoma and ocular hypertension. Perimetry Update 1992/93,(RP Mills, ed), New York: Kugler Publications, 1993, pp 443-450.
8. Casson EJ, Johnson CA and Shapiro LR: A longitudinal comparison of Temporal Modulation Perimetry to White-on-White and Blue-on-Yellow Perimetry in ocular hypertension and early glaucoma. Journal of the Optical Society of America, 1993, 10: 1792-1806.
9. Yoshiyama K, Johnson CA: Which method of flicker perimetry is most effective for detection of glaucomatous visual field loss ? Invest Ophthalmol Vis Sci, 1997, 38: 2270-2277.
10. Horn FK, Jonas JB, Korth M, Junemann A, Grundler A: The full-field

flicker test in early diagnosis of chronic open-angle glaucoma. Am J Ophthalmol, 1997, 123: 313-319.
11. Delaney SM, Dobson V, Mohan KM, Harvey EM: The effect of flicker rate on measured visual field extent in very young children. Optom Vis Sci, 2001, 78: 846-852.
12. Delaney SM, Dobson V, Mohan KM: Measured visual field extent varies with peripheral stimulus flicker rate in very young children. Optom Vis Sci, 2005, 82: 800-806.
13. Lachenmayr BJ, Kojetinsky S, Ostermaier N, Angstwurm K, Vivell PM, Schaumberger M: The different effects of aging on normal sensitivity in flicker and light-sense perimetry, Invest Ophthalmol Vis Sci, 1994, 35: 2741-2748.
14. Lachenmayr BJ: The role of temporal threshold criteria in psychophysical testing in glaucoma. Curr Opin Ophthalmol, 1994, 5: 58-63.
15. Lachenmayr BJ, Gleissner M: Flicker perimetry resists retinal image degradation. Invest Ophthalmol Vis Sci, 1992, 33: 3539-3542.
16. Lachenmayr BJ, Drance SM: Diffuse field loss and central visual function in glaucoma. Ger J Ophthalmol, 1992, 1: 67-73.
17. Lachenmayr BJ, Drance SM, Airaksinen PJ: Diffuse field loss and diffuse retinal nerve fiber loss in glaucoma. Ger J Ophthalmol, 1992, 1: 22-25.
18. Lachenmayr BJ, Drance SM, Chauhan BC, House PH, Lalani S: Diffuse and localized glaucomatous field loss in light-sense, flicker and resolution perimetry. Graefes Arch Clin Exp Ophthalmol, 1991, 229: 267-273.
19. Lachenmayr BJ, Drance SM, Douglas GR, Mikelberg FS: Light-sense, flicker and resolution perimetry in glaucoma: a comparative study. Graefes Arch Clin Exp Ophthalmol, 1991, 229: 246-251.
20. Anderson AJ, Vingrys AJ: Interactions between flicker thresholds and luminance pedestals. Vision Res, 2000, 40: 2579-2588.
21. Anderson AJ, Vingrys AJ: Multiple processes mediate flicker sensitivity. Vision Res, 2001, 41: 2449-2455.
22. Anderson AJ, Vingrys AJ: Effect of eccentricity on luminance-pedestal flicker thresholds. Vision Res, 2002, 42: 1149-1156.
23. Anderson AJ, Vingrys AJ: Effect of stimulus duration in flicker perimetry. Clin Experiment Ophthalmol, 2000, 28: 223-226.
24. Matsumoto C, Takada S, Okuyama S, Arimura E, Hashimoto S, Shimomura Y: Automated flicker perimetry in glaucoma using Octopus 311; a comparative study with the Humphrey Matrix. Acta Ophthalmol Scand, 2006, 84: 210-215.
25. Austin MW, O'Brien CJ, Wishart PK: Flicker perimetry using a luminance threshold strategy at frequencies from 5-25 Hz in glaucoma, ocular hypertension and normal controls. Curr Eye Res, 1994, 13: 717-723.
26. Stavrou EP, Wood JM: Central visual field changes using flicker perimetry in type 2 diabetes mellitus. Acta Ophthalmol Scand, 2005, 83: 574-

580.
27. Phipps JA, Dang TM, Vingrys AJ, Guymer RH: Flicker perimetry losses in age- related macular degeneration. Invest Ophthalmol Vis Sci, 2004, 45: 3355-3360.
28. Phipps JA, Guymer RH, Vingrys AJ: Temporal sensitivity deficits in patients with high-risk drusen. Aust NZ J Ophthalmol, 1999, 27: 265-267.
29. Vingrys AJ, Pseudovs K: Localized scotomata detected with temporal modulation perimetry in central serous chorioretinoapthy. Aust NZ J Ophthalmol, 1999, 27: 109-116.
30. Mayer MJ, Spiegler SJ, Ward B. Glues A, Kim CB: Mid-frequency loss of foveal flicker sensitivity in early stages of age-related maculopathy. Invest Ophthalmol Vis Sci, 1992, 33: 3136-3142.
31. Mayer MJ, Spiegler SJ, Ward B. Glues A, Kim CB: Foveal flicker sensitivity discriminates ARM-risk from healthy eyes. Invest Ophthalmol Vis Sci, 1992, 33: 3143-3149.
32. Mayer MJ, Ward B, Klein R, Talcott JB, Dougherty RF, Glues A: Flicekr sensitivity and fundus appearance in pre-exudative age-related maculopathy. Invest Ophthalmol Vis Sci, 1994, 35: 1138-1149.

II. Research Team

II.1 *Principal Investigator*

Name	E-mail	College
Randy Kardon	randy-kardon@uiowa.edu	Carver College of Medicine

II.2 *Team Members*

Name	E-mail	College
Randy Kardon, PHD, MD	randy-kardon@uiowa.edu	Carver College of Medicine
Jan Full, BSN	jan-full@uiowa.edu	Carver College of Medicine
Mona Garvin, BSE, MS, PHD, BS	mona-garvin@uiowa.edu	College of Engineering
Pieter Poolman, PHD	pieter-poolman@uiowa.edu	Carver College of Medicine
Kasra Zarei, High School	kasra-zarei@uiowa.edu	Graduate College

II.3 *The Principal Investigator of this study is:*

Faculty

II.6 *Identify the key personnel.*

Name	Is Key Personnel
Randy Kardon, PHD, MD	Yes
Jan Full, BSN	No
Mona Garvin, BSE, MS, PHD, BS	Yes
Pieter Poolman, PHD	Yes
Kasra Zarei, High School	Yes

III. Funding/Other Support

III.1 *Funding Sources*

Type	Source	Grant Title	Name of PI on Grant	Status	Status Description
Departmental					

III.3 *Does any member of the research team have a financial conflict of interest related to this project according to the Conflict of Interest in Research policy? If yes, please indicate which members below.*

Name	Has Conflict of Interest
Randy Kardon, PHD, MD	No
Jan Full, BSN	No
Mona Garvin, BSE, MS, PHD, BS	No
Pieter Poolman, PHD	No
Kasra Zarei, High School	No

IV. Project Type

IV.1 *Do you want the IRB to give this project*

Regular (expedited or full board) review

IV.2 *Enter the date you will be ready to begin screening subjects/collecting data for this project.*

09/01/2016

IV.3 *Are you requesting a waiver of informed consent/authorization (subjects will not be given any oral or written information about the study)?*

No

V. Other Committee Review

V.1 *Does this project involve any substance ingested, injected, or applied to the body? Do not answer yes, if the involvement includes a device, wire, or instrument.*

No

V.2 *Are any contrast agents used for any purpose in this study?*

No

V.9 *Will any subject be asked to undergo a diagnostic radiation procedure (including radiographic, nuclear medicine, DEXA)?*

No

V.14 *Will any subject be asked to undergo a radiation therapy procedure (including external beam therapy, brachytherapy, or nuclear medicine therapy)?*

No

V.20 *Does this project involve the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into one or more human research participant?*

No

V.21 *Will any portion of this project be conducted in the CRU, or does it use any CRU resources?*

No

V.22 *Will this project use any resource/patients of the HCCC?*

No

V.25.a *Will the study involve any of the following activity at UI Health Care, even if subjects or their insurance will not be billed for the item or service, and regardless of the study funding source (including studies with departmental*

or no funding)?

- *Procedures, tests, examinations, hospitalizations, use of Pathology services, use of clinic facilities or clinical equipment, or any patient care services, including services conducted in the Clinical Research Unit; or*
- *Physician services or services provided by non-physicians who are credentialed to bill (ARNPs, Physician Assistants, etc.)*

Yes

V.25.b *Will there be any procedures or services that may happen as part of a subject's regular medical care and as part of the study?*

No

V.25.c *Will any study equipment or devices be supplied by a study sponsor?*

Yes

V.25.d *Please describe the equipment or device(s) being provided and what it will be used for*

Two handheld iTouch devices will be used to deploy the software developed.

V.25.e *Is there or will there be an internal budget for this study?*

No

V.25.f *Is there or will there be an external budget for this study?*

No

V.26 *The study involves nursing, nursing resources or evaluates nursing practices.*

No

VI. Subjects

VI.1 *How many adult subjects do you expect to consent or enroll for this project?*

100

VI.2 *What is the age of the youngest adult subject?*

18.0

VI.3 *What is the age of the oldest adult subject?*

80.0

VI.4 *What is the percentage of adult male subjects?*

50

VI.5 *What is the percentage of adult female subjects?*

50

VI.6 *How many minor subjects do you expect to consent or enroll for this project?*

0

VI.13 *Describe EACH of your subject populations*

- *Include description of any control group(s)*
- *Specify the Inclusion/Exclusion criteria for EACH group*
- *Studies under IRB-03 enrolling non veterans as part of the subject population must present a compelling argument to the IRB for the inclusion of non-Veterans (e.g., insufficient number of Veterans; survey of VA employees; study of active duty military; study involving Veterans' family members), and the research is relevant to the care of Veterans or active duty military personnel.*

1) Control subjects age matched to scotoma subjects

Inclusion Criteria:
1. Age matched (18-80)
2. Healthy normal controls with no known eye disorders
Exclusion Criteria:
1. Scotoma or any ocular disorder

2) Scotoma subjects
Inclusion Criteria:
1. Age 18-80
2. Clinically assessed scotoma
Exclusion Criteria:
1. Any other ocular disorder

VI.14 *Provide an estimate of the total number of subjects that would be eligible for inclusion in each of your study populations (include your control*

population if applicable)

Control population = 50
Scotoma subjects = 50

VI.15 *Describe how you will have access to each of your study populations in sufficient number to meet your recruitment goals.*

Subjects will be recruited from the UIHC Department of Ophthalmology neuro-ophthalmology, plastics, cornea, comprehensive clinics and the Neurology and Neurosurgery clinics.
Healthy Controls will be recruited through word-of-mouth - specifically, individuals (non-patients) in the waiting room who are accompanying friends and family members for their appointments will be approached about participating in the study.

VI.16 *Do you plan to recruit/enroll non-English speaking people?*

No

VI.18 *Do you propose to enroll any of the following in this study as subjects?*

- *Employee of the PI or employee of a research team member*
- *Individual supervised by PI or supervised by member of research team*
- *Individual subordinate to the PI or subordinate to any member of the research team*
- *Student or trainee under the direction of the PI or under the direction of a member of the research team*

No

VI.20 *Will subjects provide any information about their relatives?*

No

VI.23 *Will anyone (other than the subject) provide you with information about the subject (e.g. proxy interviews)?*

No

VI.26 *Is this project about pregnant women?*

No

VI.27 *Will this project involve fetuses?*

No

VI.28 *Does this project involve adult subjects who may be incompetent or have limited decision-making capacity on initial enrollment into the study?*

No

VI.32 *Does this project involve subjects whose capacity to consent may change over the course of the study?*

No

VI.37 *Does this project involve prisoners as subjects?*

No

VII.A. Project Description (A)

VII.A.1 *Where will project procedures take place (check all that apply)?*

UIHC - Department of Ophthalmology, Eye Exam Room

VII.A.2 *Is this project also being conducted by other researchers at their own sites (e.g. a multi-site collaborative project)?*

No

VII.B. Project Description (B)

VII.B.1 *Does this project involve any of the following (Check all that apply):*

☐ Registry – The collection and maintenance of data (not including biologic samples) in which: (1) the individuals in the registry have a common or related condition(s), and/or (2) the individuals in the registry are interested in being contacted for future studies by investigators other than those listed in Section II of this project.(UI Guide)

☐ Repository – The collection, storage, and distribution of human biologic samples and/or data materials for research purposes. Repository activities involve three components: (i) the collection of data and/or specimens such as blood, tissue, saliva, etc.; (ii) the storage of data or specimens, and data management function; and (iii) the sharing of data/specimens with recipient investigators other than the original investigators. (paraphrased from OHRP)

☐ Expanded Access – A process regulated by the Food and Drug Administration (FDA) that allows manufacturers to provide investigational new drugs to patients with serious diseases or conditions who cannot participate in a clinical trial. Examples of expanded access include non-protocol access to experimental treatments, including protocol exception,

single-patient IND, treatment IND, compassionate use, emergency use, continued access to investigational drug, and parallel track (ClinicalTrials.gov & FDA).

☐ Clinical (or Treatment) trial – A prospective biomedical or behavioral research study of new treatments, new drug or combinations of drugs, new devices, or new approaches to surgery or radiation therapy. (NIH and ClinicalTrials.gov & FDA)

☑ Physiology intervention/study – A pharmacologic or measurement study aimed at understanding basic mechanisms of disease and/or of normal human physiology, often without any therapeutic intent (though a clinical trial could include such components, often labeled as "translational" or "basic science" aims.) Measurements in such studies could include, but are not limited to, a blood draw, EKG, EEG, MRI, auditory or sensory testing, checking vital signs, DEXA scans, eye tracking, specimen collection, exercise, fasting, special diets, etc.

☐ Behavioral intervention/study – May be used to refer to studies of individual or group behavior. This option does not include drugs, biologics, or devices but could include psychotherapy, lifestyle counseling, behavior modification, etc.

☐ Diagnostic trial – Protocol designed to evaluate one or more interventions aimed at identifying a disease or health condition (ClinicalTrials.gov & FDA)

☐ Other

VII.B.1.b *Provide the NCT (National ClinicalTrials.gov Identifier) number*

VII.B.2 *Does this project involve a drug washout (asking subject to stop taking any drugs s/he is currently taking)?*

No

VII.B.11 *Is there a separate, written protocol that will be submitted in addition to this IRB New Project form? (Note: a grant application is not considered to be a protocol)*

No

VII.B.18 *Does this project involve testing the safety and/or efficacy of a medical device?*

Yes

VII.B.19 *Describe in detail procedures in place for maintaining device shipment and receipt records:*

The shipment and receipts for handheld iTouch devices will be stored in

a secure, locked file cabinet with all pertinent documents related to this study.

VII.B.20 *Who will be responsible for maintaining these shipment and receipt records?*

A research team member (KZ) will be responsible for maintaining these shipment and receipt records short-term and long-term.

VII.B.21 *Describe in detail procedures in place for tracking use and disposition of devices described in this study:*

A paper/hard-copy log has been created and will be stored in a secure, locked file cabinet with the other pretaining documents of the study. Each day in the clinic when the devices are used, the device ID (i.e. iTouch #1 or iTouch #2) will be noted as well as the number of patients seen that day, and the hours that the devices were used on the particular day.

At the conclusion of the study, the iTouch devices will be returned to their original factory settings (with iOS devices this entails going to the device settings and selecting general --> reset --> erase all content and settings)

VII.B.22 *Who will be responsible for maintaining these use and disposition tracking records?*

A research team member (KZ) will be responsible for maintaining these shipment and receipt records short-term and long-term.

VII.B.23 *Describe in detail procedures in place to limit access to authorized study personnel for the storage, control, and dispensing of the investigational devices. (For example, investigational devices are kept in a locked area away from approved devices or have a keyed interlock, and only study personnel authorized to dispense the device have the keys)*

Investigational devices are kept in a locked area away from approved devices, and only study personnel authorized to dispense the device have the keys. The investigational devices are kept in a secure file cabinet, along with the additional documents related to this study, that only the research team members listed on this IRB will have access to.

VII.B.24 *Is the device FDA-approved for the way it will be used in this study?*

No

VII.B.25 *Is there an IDE (Investigational Device Exemption) for this device in this research project?*

No

VII.B.29 *Indicate the appropriate FDA status you and/or the sponsor are requesting for the use of this device in this study.*

Non-Significant Risk (NSR) device/software

VII.B.31 *Provide a detailed rationale for why this device meets the FDA definition of a Non-Significant Risk Device (NSR)*

Smartphones do not present a potential for serious risk to the health, safety, or welfare of a subject. The subject will not need to undergo an additional procedure as part of the study. The duration of the interaction between the subject and the smartphone will last no more than 2 minutes. The device is not invasive in anyway and only presents a stimulus on a screen that is not harmful to the eye or human body in any way.

VII.B.32 *Provide a summary of prior investigations with this device.*

1. https://www.ncbi.nlm.nih.gov/pubmed/27092927
2. https://www.ncbi.nlm.nih.gov/pubmed/26206531
3. https://www.ncbi.nlm.nih.gov/pubmed/25931170
4. https://www.ncbi.nlm.nih.gov/pubmed/25132717
5. https://www.ncbi.nlm.nih.gov/pubmed/23706608

VII.B.33 *Have there been any prior IRB reviews (at UI or elsewhere) and/or determinations made with regard to this device?*

No

VII.B.35 *Has the FDA made an assessment of risk with regard to this device?*

No

VII.B.36 *Has this device/software been approved by the FDA for another indication or in another form from its use in this project?*

No

VII.C. Project Description (C)

VII.C.1 *Does this project involve any research on genes or genetic testing/research?*

No

VII.D. Project Description (D)

VII.D.1 *Check all materials/methods that will be used in recruiting subjects (you will need to attach copies of all materials at the end of the application):*

- Use of any information available to the researchers or their colleagues because this person is a patient OR use of any information considered to be Protected Health Information (PHI) OR review of patient/clinic records - The neuro-ophthalmology, plastics, cornea, comprehensive clinics in the Ophthalmology clinic have patient clinic records (patient clinic notes in EPIC) for all patients, and we will review these records to see if the patients meet the criteria for the study. The departments also has a diagnosis list that we will use. We may also use the UIHCS database for retrieving patients by diagnostic code.
- Other - Word-of-mouth recruitment (for controls only) in the neuro-ophthalmology, plastics, cornea, comprehensive clinics in Ophthalmology

VII.D.2 *List the individual data elements you will need to access/use from the patient or clinic records to identify potential subjects for recruitment*

Date of Birth for ages 18-80
Address(miles from clinic) and phone number
Diagnosis for scotoma and diagnosis of any ocular disease, including their corresponding performances on other tests of visual function (to quality check diagnoses) done as part of their routine visit (visual field, visual acuity, etc.)

VII.D.3 *Describe why you could not practicably recruit subjects without access to and use of the information described above*

We are looking at a specific disease (scotoma) and need to identify it. There is no way to identify them without reviewing chart notes.

VII.D.4 *Describe why you could not practicably obtain authorization from potential subjects to review their patient or clinic records for recruitment purposes.*

It would not be practicable to approach all subjects presenting at the clinic to ask if their medical record could be reviewed to determine eligibility for the research study

VII.D.5 *Describe plans to protect the identifiers from improper use or disclosure*

When a potential subject is referred from the ophthalmology clinic, a research team member will meet with the subject in the exam room. If they are interested, the process continues, otherwise there is no more communication with them and no information is kept. If they continue, their information will be kept on password protected computers in the lab or offices in the eye clinic at UIHC. During the medical record review confidential measures are in place.

VII.D.6 *Describe plans to destroy identifiers at the earliest opportunity consistent with conduct of the research*

During the recruitment process, confidential measures are in place. Nothing is documented unless we enroll the subjects in the study.

VII.D.7 *Does the research team agree that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research for which the use or disclosure of the requested information would be permitted by the HIPAA Privacy Rule*

Yes

VII.D.8 *Will a member of the research team discuss the study with the subject in person prior to the subject agreeing to participate?*

Yes

VII.D.9 *Describe the physical location where the consent process will take place:*

The consent process will be conducted at the UIHC location, the Department of Ophthalmology. The individual will be taken to a private room for testing. The location will provide the subject privacy to ask questions and discuss the details of the study. Informed consent will take place in the UIHC eye clinic exam room or in the pupil lab.

VII.D.10 *Will a member of the research team discuss the study with the subject by phone prior to the subject agreeing to participate?*

No

VII.D.12 *Who will be involved in the consent process (including review of consent document, answering subjects' questions)?*

Name	Consent Process Involvement
Randy Kardon, PHD, MD	No

Jan Full, BSN	Yes
Mona Garvin, BSE, MS, PHD, BS	No
Pieter Poolman, PHD	No
Kasra Zarei, High School	Yes

VII.D.15 *Check all materials that will be used to obtain/document informed consent:*

Consent Document

VII.D.16 *Are you requesting a waiver of documentation of consent (either no subject signature or no written document)?*

No

VII.D.19 *Before the subject gives consent to participate are there any screening questions that you need to directly ask the potential subject to determine eligibility for the study?*

No

VII.D.25 *After the subject agrees to participate (signs consent), are there any screening procedures, tests, or studies that need to be done to determine if the subject is eligible to continue participating?*

No

VII.D.27 *Discuss how much time a potential subject will have to agree to consider participation and whether or not they will be able to discuss the study with family/friends before deciding on participation.*

A potential subject will have as much time as they require to agree to consider participation. The potential subject will be able to discuss the study with family/friends before deciding on participation.

VII.D.28 *How long after the subject agrees to participate do study procedures begin?*

After the subject agrees to participate, the start of study procedures immediately follows after the informed consent document has been signed.

VII.D.29 *Provide a description of the enrollment and consent process for adult subjects*

- *Describe each study population separately including control*

population

- *Include when recruitment and consent materials are used*
- *Use 3rd person active voice "The Principal Investigator will identify subjects. For example, the principal investigator will identify potential subjects, the study coordinator will discuss the study with subjects over the telephone and schedule the first study visit, etc..."*
- *Describe the steps that will be taken by the research team to minimize the possibility of coercion or undue influence during the consent process*

Study Population:
The control group will include healthy individuals without any known eye disease (glasses are fine). If they have corrective lenses, the participants should use them. Participants can be excluded if they have a severe visual abnormality.

The scotoma group will include subjects at the UIHC clinically assessed to have a scotoma, using medical records in EPIC.

Recruitment Materials:
The research team members listed on this IRB will identify potential subjects. The only recruitment method used for this study is word-of-mouth recruitment. The research team members will inform friends, classmates, colleagues, and other acquaintances about the ongoing study and ask if them if they are interested in participating and would like to discuss the study further in private.

Procedures to Obtain Consent Process:
The interested participant will be taken to a private room in the Ophthalmology clinic at UIHC. The participant will be provided a copy of the consent document. The research team member will discuss the consent document with the potential participant. Potential subjects will be adequately informed about the study (purpose and testing procedures) and have an opportunity to ask questions. Participants will be given time to think about their decision to participate, and discuss with family members and friends.

The potential subject will be informed the decision whether to participate will not affect the clinical care he/she receives so as to minimize the possibility of feelings of coercion

VII.D.37 *Does the study include any form of deception (e.g., providing participants with false information, misleading information, or*

withholding information about certain study procedures)?

Examples:

- *Procedure includes a cover story that provides a plausible but inaccurate account of the purposes of the research.*
- *Participants will be provided with false information regarding the particular behaviors of interest in the research.*
- *Procedures include a confederate pretending to be another participant in the study.*
- *Participants will be told that the research includes completion of a particular task, when in fact, that task will not be administered.*
- *Study is designed to introduce a new procedure (or task) that participants are not initially told about.*
- *If yes, a waiver of informed consent must be requested under question IV.3.*

No

VII.E. Project Description (E)

VII.E.1 *Will subjects be randomized?*

No

VII.E.3 *Will any questionnaires, surveys, or written assessments be used to obtain data directly from subjects in this study?*

No

VII.E.5 *Does this project involve creating any audiotapes, videotapes, or photographs?*

No

VII.E.6 *Provide a detailed description in sequential order of the study procedures following the consent process - DO NOT cut and paste from the Consent Document.*

Describe study populations separately if they will be participating in different procedures - include CONTROL population if applicable.

DESCRIBE:

- *What subjects will be asked to do/what happens in the study (in sequential order)*
- *The time period over which procedures will occur*

- *The time commitment for the subject for individual visits/procedures*
- *Long-term followup and how it occurs*

Project Description

The research procedures will begin immediately after obtaining consent.

The following procedure will be performed:
The subjects will be asked to complete the Flicker Fusion on a portable iOS device provided by the research team members. The subjects will be handed an iTouch and provided instructions to complete the test. The subject will then complete the Flicker Fusion test, following the protocol described as follows:

Flicker Fusion Test Protocol

The subject will test each eye one at a time (starting with the right eye, then the left eye) by covering the other eye not used with their hand, followed by testing both eyes together. All corrective lenses, etc. will be left on for the duration of the test.
The subject will begin by holding the device at reading distance, or approximately one-third of a meter from the eyes.
The subject will be presented with a grid of approximately 12 circles (screenshot shown below), flickering at 7.5 Hz at varying contrast levels. The objective is to tap all the flickering circles that they can see. The circles will vanish once tapped. The subject will be presented with another grid of circles, flickering at 7.5 Hz except at a narrower range of contrast levels. Again, the objective is to tap all the flickering circles that they can see. The circles will vanish once tapped. The threshold is quantified as the minimum contrast they can detect across the two presentations. This part of the protocol (i.e. the two presentations) will be repeated for a second temporal frequency, 15 Hz. Standard measures of visual acuity and contrast sensitivity must also be determined on the smartphone (the same time and device used while the subject is taking the flicker fusion test) to serve as reference data. To determine these measures, we also want to present a series of 4 additional displays that contain varying types of stimuli (squares, landolt rings, optotypes, etc.). The objective of the user is to tap everything they can see on the screen (the optotypes, squares, or arrows on the side of the screen that correspond to the opening of the landolt ring). In total, there are 8 presentations per test which will be done for the right and left eyes

separately, and both eyes together. The test will be administered three times (left eye, right eye, and both eyes).

After completion the vision tests, an email containing the results of the participant's performance on both tests will be sent to a secure email account, iowa.vision.testing@gmail.com. The email and data will be deidentified. Only the research team members listed on this IRB have access to the email account.

Patients evaluated in the neuro-ophthalmololgy clinic will also have standard critical flicker fusion testing that is part of their regular evaluation during their clinic visit. The standard critical flicker fusion test (using an instrument specifically designed for the test and which has been used for over 25 years in the ophthalmology clinic). In the subset of patients that undergo this test, we will have this standard critical flicker fusion test result compared to the smartphone enabled test. By comparing to their relevant normative data, we will determine the proportion of patients that are abnormal at the 5% and 1% level of normal subjects for the two tests in the patients that had both done on the same day.

The time period to check-in, complete the applications (no more than 1 minute), and related instructions is 15 minutes total for the entire visit.

VII.E.7 *Will you attempt to recontact subjects who are lost to follow-up?*

No - followup is not required in this study

VII.E.9 *Will subjects be provided any compensation for participating in this study?*

No

VIII. Risks

VIII.1 *What are the risks to subjects including*
- emotional or psychological
- financial
- legal or social
- physical?

There is a potential risk of fatigue due to completing a physical tests, and loss of confidentiality due to performing the tests in a clinical setting. There are no legal, social, emotional, or psychological risks associated with validating these mobile-phone vision tests. There are no

financial risks as test requires zero costs for the participants.

VIII.2 *What have you done to minimize the risks?*

- *If applicable to this study ALSO include:*
  - *How you (members of your research team at Iowa) will monitor the safety of individual subjects.*
  - *Include a description of the availability of medical or psychological resources that subjects might require as a consequence of participating in this research and how referral will occur if necessary (e.g. availability of emergency medical care, psychological counseling, etc.)*

We have minimized the risks by developing portable visual tests that require no complicated apparatuses. Our visual tests utilize common iOS devices like iTouches, thus, making our tests easy and safe to use.

To minimize the risk of loss of confidentiality, we use a randomized number with each subject, and this data is stored in a secure, password-protected email that only the research team members listed on this IRB have access to.

VIII.3 *Does this study have a plan to have an individual or committee review combined data from all subjects on a periodic basis (such as summary or aggregate safety and/or efficacy data)?*

No

IX. Benefits

IX.1 *What are the direct benefits to the subject (do not include compensation or hypothesized results)?*

There are no direct benefits to the subject

IX.2 *What are the potential benefits to society in terms of knowledge to be gained as a result of this project?*

The knowledge that is hoped to be gained from the conduct of this study includes information about novel visual tests that can be validated. Specifically, information regarding whether these visual tests yield reproducible results on the same participant and whether there is a normal distribution among participants from the sample group (i.e. individual differences) can be obtained. Existing methods to measure the same phenotype that our visual tests seek to measure require large amounts of time and are thus, inconvenient as they require the patients to

come to clinic. Our protocols are implemented as iOS applications and are publicly accessible (available on the Apple App Store).

X. Privacy & Confidentiality

X.1 *What are you doing to protect the privacy interests of the subjects?*

Results of the visual tests are no way associated with individual health information. Furthermore, no personal identification information is recorded for this study. After a participant completes one of the vision test applications, an email containing the results is displayed for the participant to see. The email is then sent to a fixed email (iowa.vision.testing@gmail.com). Login access to the email is shared only by the research team members included on the this IRB form. Only data necessary to answer the research question will be collected as a manner in which the subject's privacy is protected. The record of consent will be scanned into the hospital records.

X.2 *Are you collecting the Social Security Number of any subjects for any purpose?*

No

X.4 *How will information/data be collected and stored for this study (check all that apply):*

- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - Hard copy records will be enclosed in a binder for transport and transfer from the testing room to the storage room. The binder and all pertaining hard copy records will be stored in an office cabinet (in room 01134-0 PFF) that is locked and only accessible by the study coordinator.
- Electronic records (computer files, electronic databases, etc.) - The results of the visual test applications will be sent (via email) to the reading/data analysis center. The email account (iowa.vision.testing@gmail.com) was set up specifically for this study. Only the data collected from the applications will be viewed by the research team with no link to the participant (using de-identified number acronyms). Login access to the email is only accessible by the research team members included on this IRB form. The research database will be password-protected and will be on a stand-alone hard drive. Considering the fact that the primary developer/owners of the software application are primary member of this study/IRB, the data on the secure email will be available to them.

X.5 *Do the confidentiality protections indicated above allow only members of the research team to access the data/specimens?*

Yes

X.7 *Are you seeking a Certificate of Confidentiality from NIH for this study?*

No

XI. Data Analysis

XI.1 *Describe the analysis methods you will use, including, if applicable, the variables you will analyze*

To assess the reproducibility of the results, the flicker fusion visual test will be administered to each participant twice. Flicker fusion thresholds for the first and second administration of the test will be correlated using a scatter and correlation coefficient.

Average flicker fusion thresholds will be compared between the control and case groups using a student's t-test.

XI.2 *Provide the rationale or power analysis to support the number of subjects proposed to complete this study.*

The results from the power analysis indicated 50 cases and 50 controls as an overestimate for testing (alpha = 0.05, beta = 0.8)

We need a large, but doable sample size to maximize the statistical power of this study. Since the visual tests are costless, the entire protocol lasts only a few minutes of time, and participants are easily accessible due to the lack of risks, the propose sample sizes are feasible. A similar rationale/power analysis and validation was provided in the presentation "Objective Quantification of Color Vision Function" (given by a member of the Stone and Scheetz laboratory) at the 2014 Engineering Open House.

XII. Future Research

XII.1 *Do you wish to keep any information about subjects involved with this research project so that members of the current research team may contact them in the future for your own research projects?*

No

XII.2 *Do you wish to keep any information about subjects involved with this*

research project so that other researchers may contact them for future research?

No

XII.4 *Does this project involve storing any data, tissues or specimens for future research?*

No

APPENDIX C – INFORMED CONSENT DOCUMENT

INFORMED CONSENT DOCUMENT

Project Title: Validation of a Smartphone-Based Flicker Fusion Test

Principal Investigator: Randy Kardon

Research Team Contact: Kasra Zarei; Phone: (319) 430-0869; email: kasra-zarei@uiowa.edu

This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you are a healthy adult without eye disease, or were clinically assessed to have a scotoma. A scotoma is a condition referred to as partial loss of vision or a blind spot in an otherwise normal visual field.

The purpose of this research study is to validate a new (flicker fusion) vision test implemented as an iOS application that can be used to improve screening of vision electronically and with convenient access. We hope that in the future these tests can be applied for use in research studies with a variety of eye diseases, after being correlated to other measures of visual function

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 100 people will take part in this study conducted by investigators at the University of Iowa.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for 15 minutes over one visit.

WHAT WILL HAPPEN DURING THIS STUDY?

If you agree to participate, you will be asked to complete the tests described below at the Department of Ophthalmology. You may stop the test at any time during the testing procedures. Your total involvement time for the entire visit is 15 minutes, which will take place after obtaining consent. This study will not require the use of any health information or clinical procedures during the course of the study. The procedure for this study will take place directly after signing the consent following your scheduled appointment in the Department of Ophthalmology & Visual Sciences. The results from these tests will be used for research purposes only.

Flicker Fusion Test
The Flicker Fusion Test uses a portable iOS hand held device. The research team member will give you an iTouch (iOS device) with instructions on how to complete the test. You will test each eye one at a time (starting with the right eye, then the left eye) by covering the other eye not used with your hand, followed by testing both eyes together. Thus, you will take the test three times. All corrective lenses, etc. should be left on for the duration of the test.

You will begin by holding the device at reading distance, or approximately one-third of a meter from the eyes.

You will be presented with a grid of approximately 12 circles, flickering at 7.5 Hz at varying contrast levels. The objective is to tap all the flickering circles that you can see. The circles will vanish once tapped. You will be presented with another grid of circles, flickering at 7.5 Hz except at a narrower range of contrast levels. Again, the objective is to tap all the flickering circles that you can see. The circles will vanish once tapped. This part of the protocol (i.e. the two presentations) will be repeated for a second temporal frequency, 15 Hz. Standard measures of your sharpness of vision and your ability to distinguish between finer and finer increments of light versus dark must also be determined on the smartphone (the same time and device used while you are taking the flicker fusion test) to serve as reference data. To determine these measures, you will also be presented with a series of 4 additional displays that contain varying types of stimuli (squares, landolt rings, optotypes, etc.). Your objective is to tap everything you can see on the screen (the optotypes, squares, or arrows on the side of the screen that correspond to the opening of the landolt ring). In total, there are 8 presentations per test which will be done for the right and left eyes separately, and both eyes together. The test will be administered three times (left eye, right eye, and both eyes).

Upon completing the iOS device vision test, your performance results will be sent by a secure email account, iowa.vision.testing@gmail.com. The email and your data will be de-identified.. Only the research team members have access to the email account. After you have completed working with the portable iOS device applications, you will be given sufficient time to rest.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study. You may get tired or your eyes may fatigue due to completing the tests. You will be given breaks and encourage to blink your eyes between tests.

WHAT ARE THE BENEFITS OF THIS STUDY?
You will not benefit from being in this study. However, we hope that, in the future, other people might
benefit from this study because the knowledge that is gained from this study may help establish more convenient ways to complete visual tests. Existing methods to measure visual tests require long test times and require patients to come to clinic. Our protocol is implemented as an iOS application and will be made publicly accessible (available on the Apple App Store).

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?
You will not have any costs for being in this research study.

WILL I BE PAID FOR PARTICIPATING?
You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?
The University and the research team are receiving no payments from other agencies, organizations, or companies to conduct this research study.

WHAT ABOUT CONFIDENTIALITY?
We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality, we will de-identify your information and use a code. Hard copy records will be stored in an office cabinet that is locked and only accessible by the study coordinator. The research database will be password-protected and will be on a stand-alone hard drive. If we write a report or article about this study or

share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document in your medical record chart that you are participating in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed consent document in our research files; it will not be placed in your medical record chart.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?
The Federal Health Insurance Portability and Accountability Act (HIPAA) requires University of Iowa Health Care (UIHC) to obtain your permission for the research team to access or create "protected health information about you for purposes of this research study". Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study. Once University of Iowa Health Care has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes University of Iowa Health Care to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written notice to Randy Kardon, MD, PhD, Department of Ophthalmology and Visual Science, 200 Hawkins Dr.-PFP University of Iowa Hospitals and Clinics, Iowa City, IA, 52242. However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

Will I Receive New Information About the Study while Participating?
If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

WHAT IF I HAVE QUESTIONS?
We encourage you to ask questions. If you have any questions about the research study itself, please contact: Randy Kardon at 319-356-2260 or Kasra Zarei at 319-430-0869. If you experience a research-related injury, please contact: Dr. Randy Kardon at 319-356-2260 or Kasra Zarei at 319-430-0869.

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name
(printed): _____

Do not sign this form if today's date is on or after EXPIRATION DATE: 01/12/18.

_____

_____

(Signature of Subject) (Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____

_____

(Signature of Person who Obtained Consent) (Date)

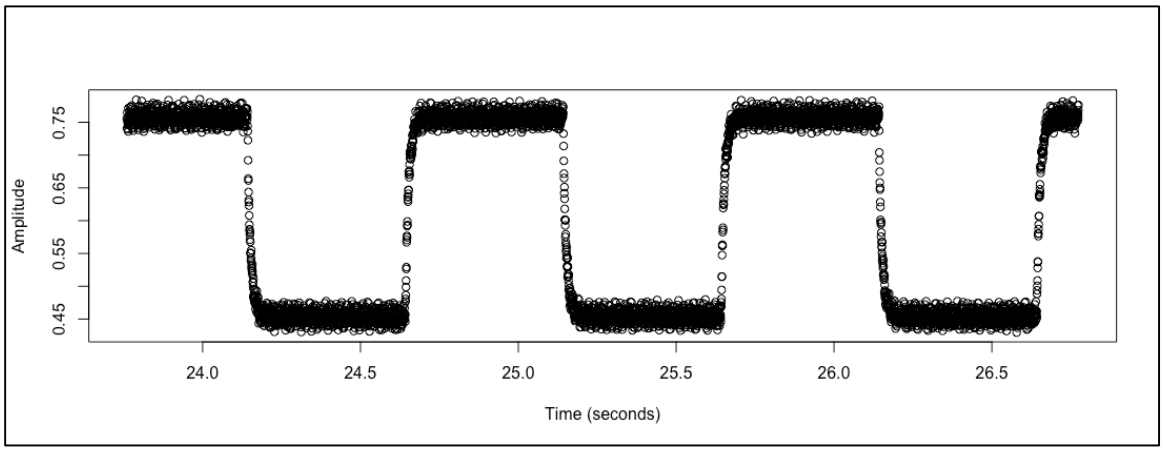

Figure D1: iPad Flicker Wave at a Temporal Frequency of 1 Hz.

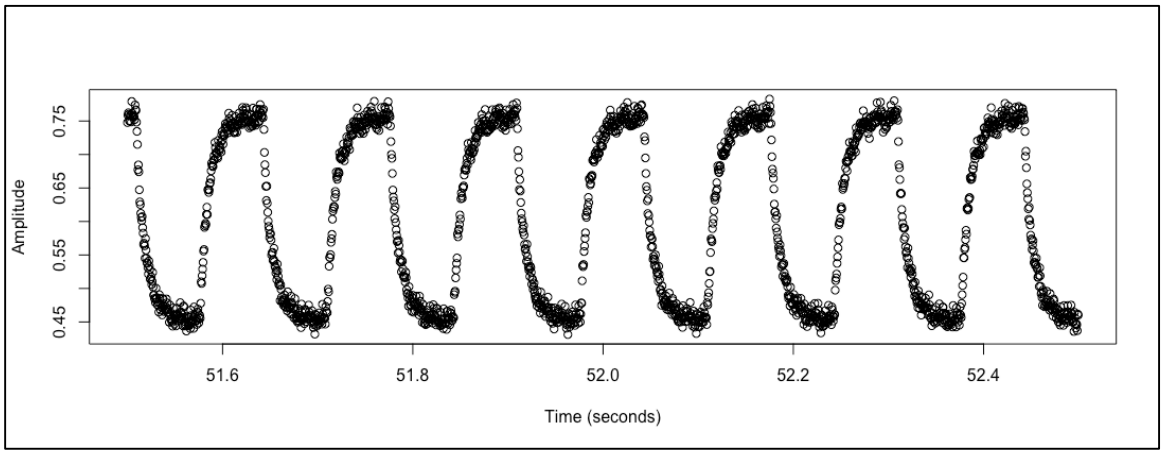

Figure D2: iPad Flicker Wave at a Temporal Frequency of 7.5 Hz.

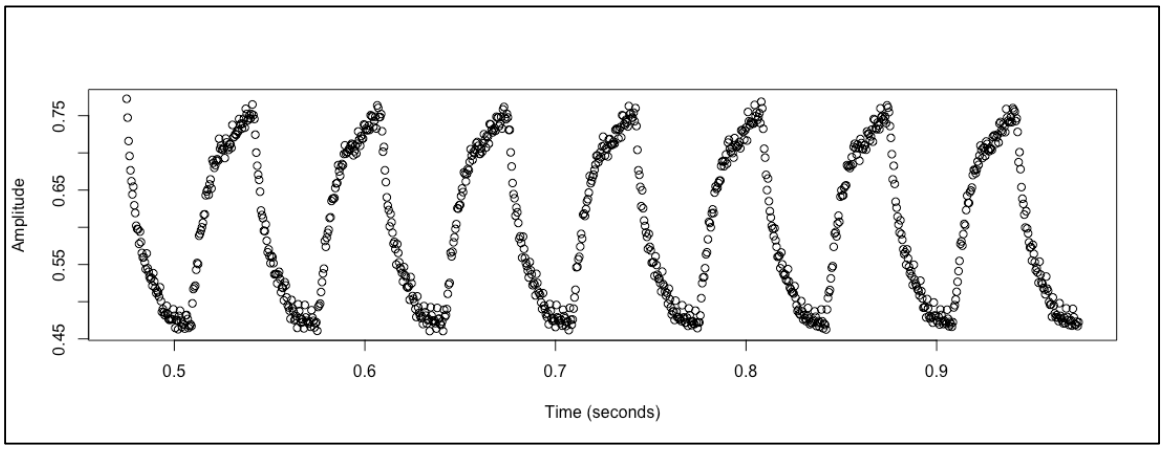

Figure D3: iPad Flicker Wave at a Temporal Frequency of 15 Hz.

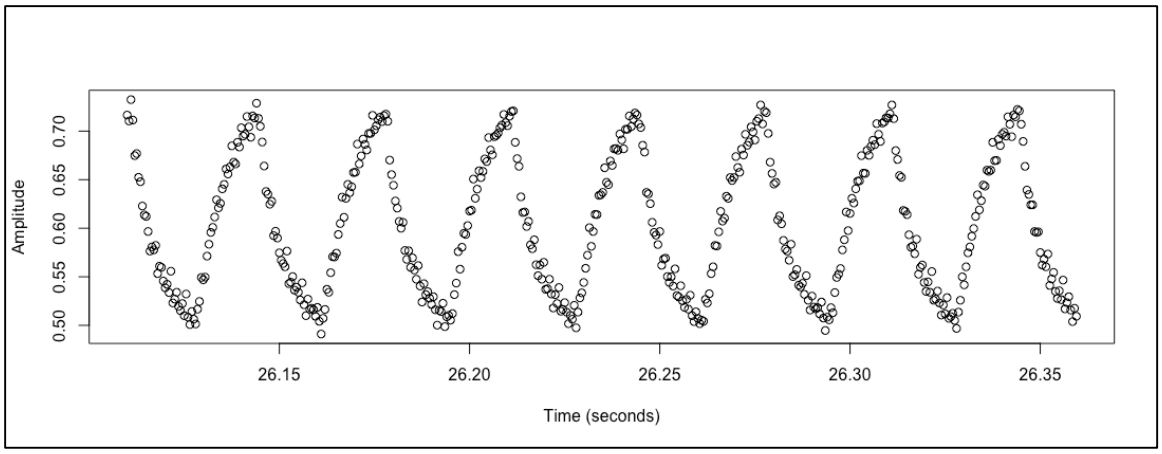

Figure D4: iPad Flicker Wave at a Temporal Frequency of 30 Hz.

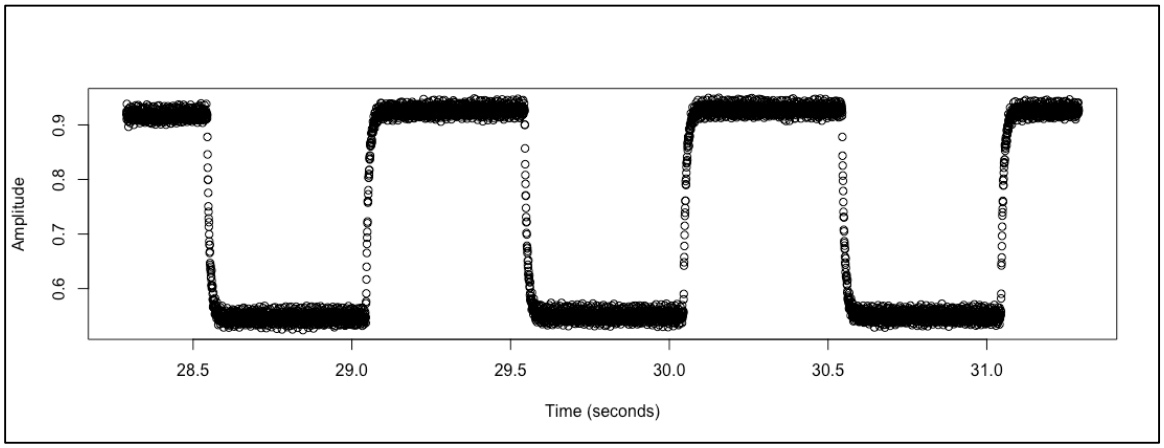

Figure D5: iPhone Flicker Wave at a Temporal Frequency of 1 Hz.

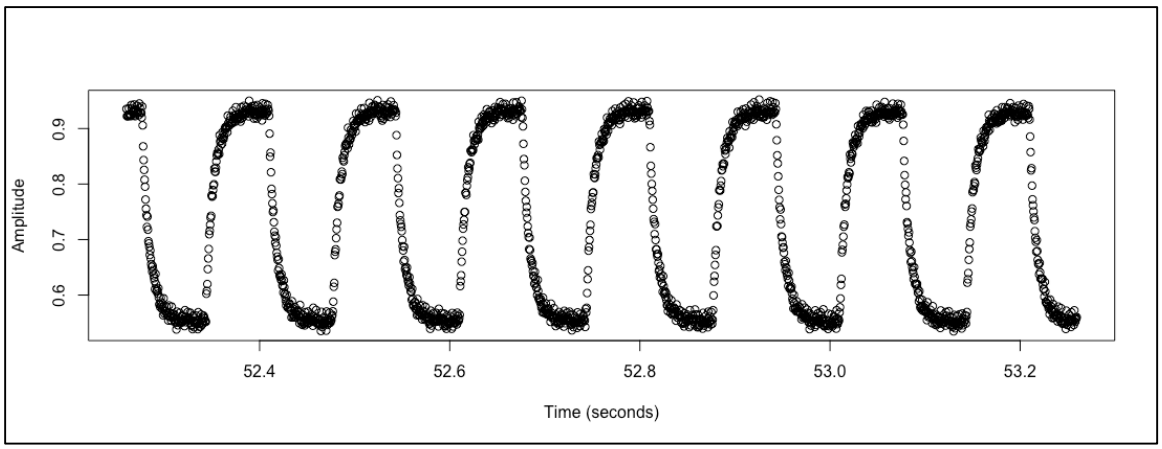

Figure D6: iPhone Flicker Wave at a Temporal Frequency of 7.5 Hz.

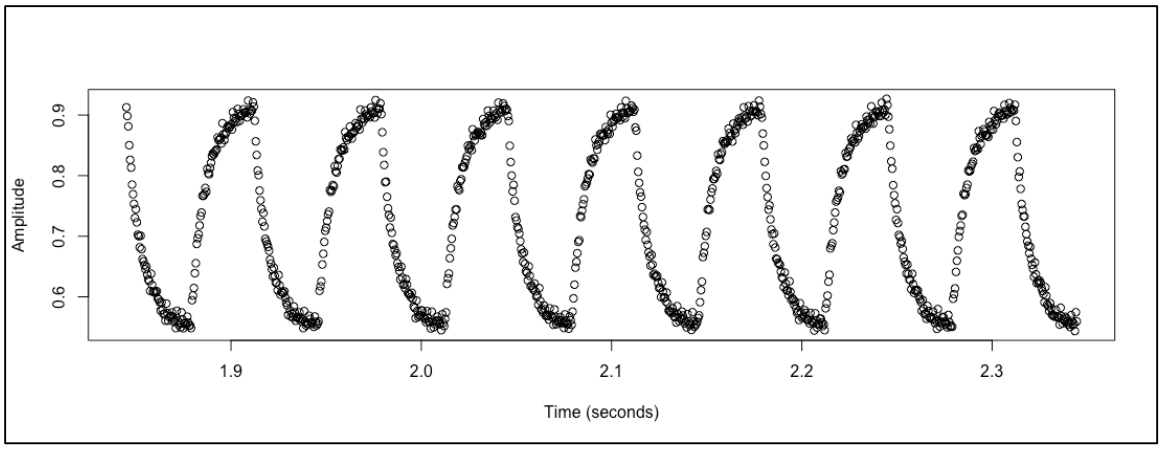

Figure D7: iPhone Flicker Wave at a Temporal Frequency of 15 Hz.

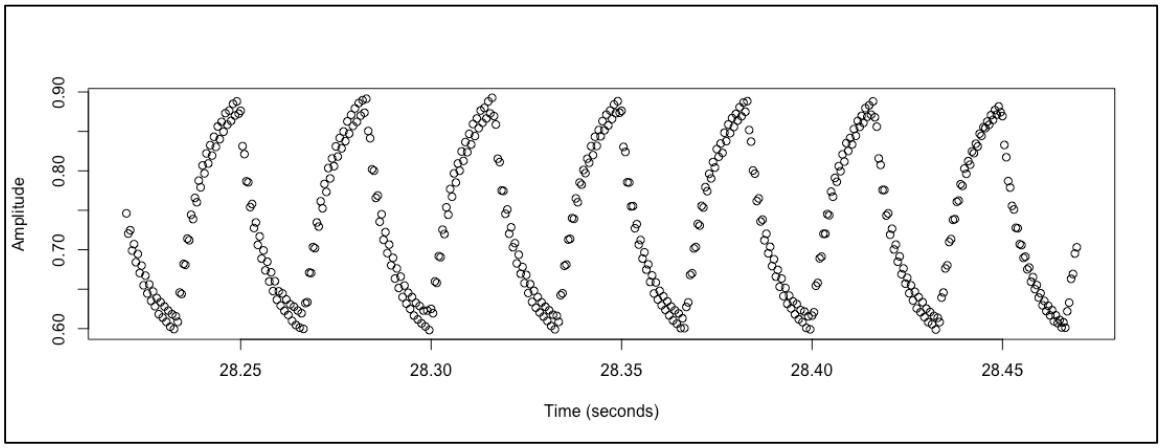

Figure D8: iPhone Flicker Wave at a Temporal Frequency of 30 Hz.

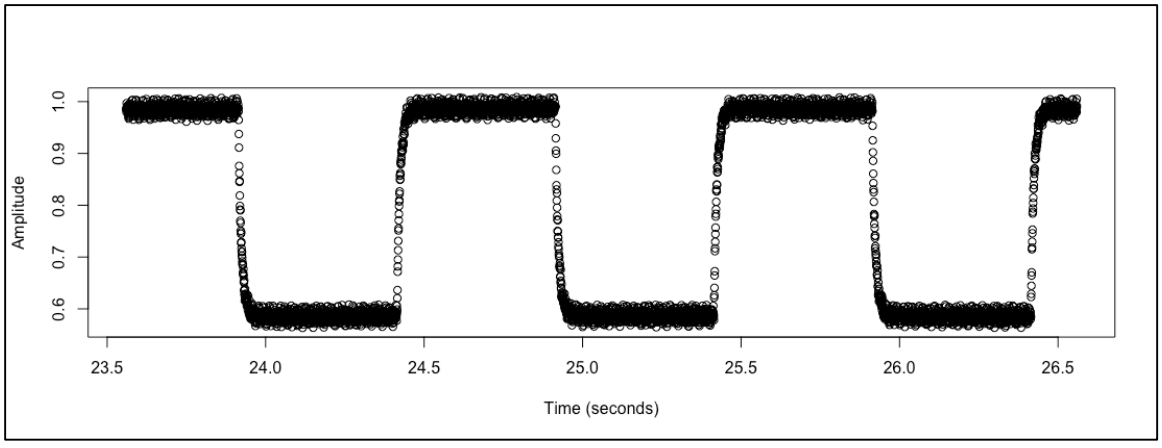

Figure D9: iTouch Flicker Wave at a Temporal Frequency of 1 Hz.

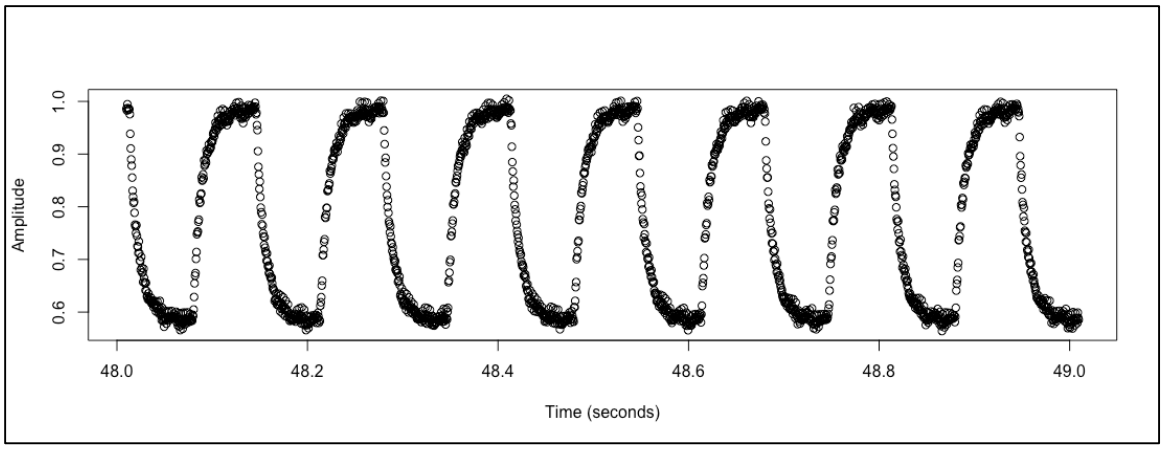

Figure D10: iTouch Flicker Wave at a Temporal Frequency of 7.5 Hz.

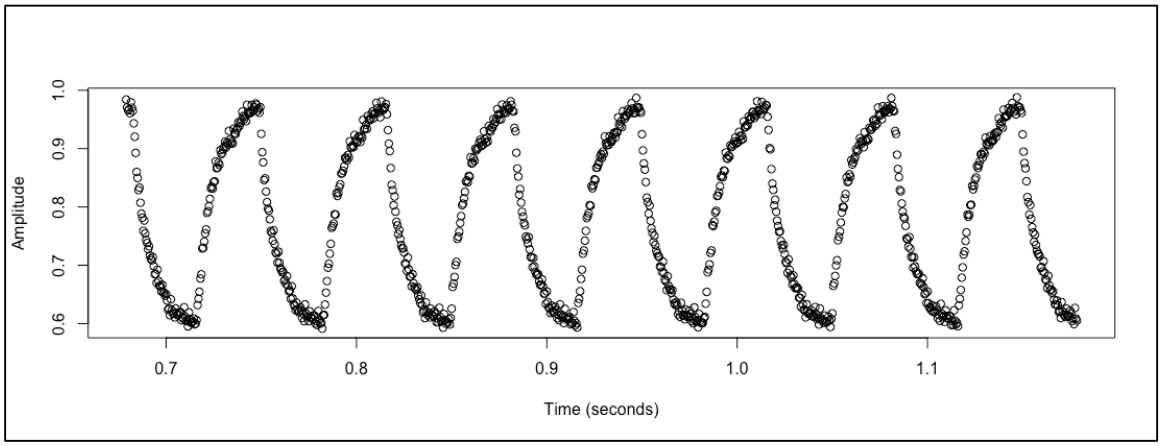

Figure D11: iTouch Flicker Wave at a Temporal Frequency of 15 Hz.

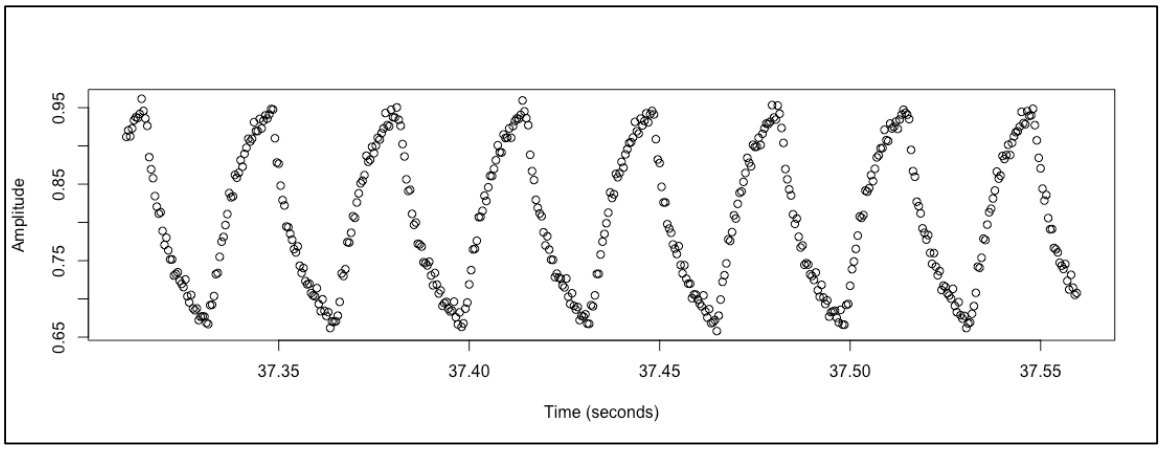

Figure D12: iTouch Flicker Wave at a Temporal Frequency of 30 Hz.

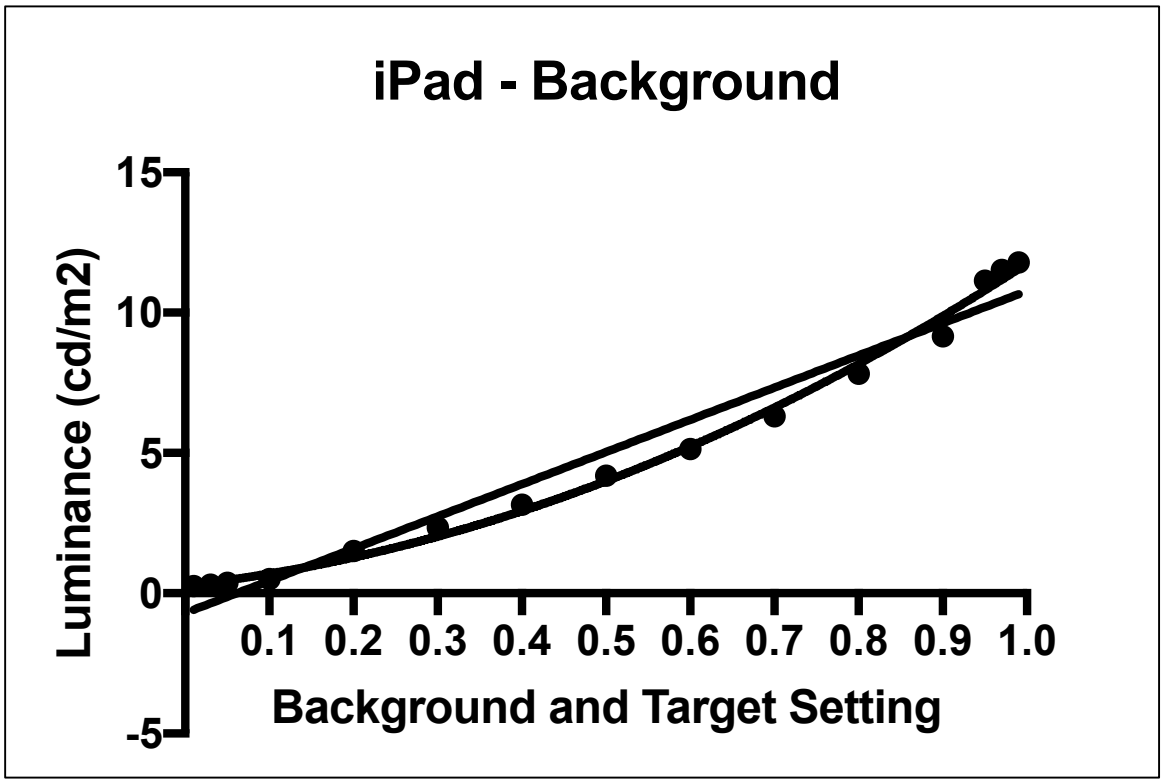

Figure E1: iPad Background Calibration Curve and Linear Fit.

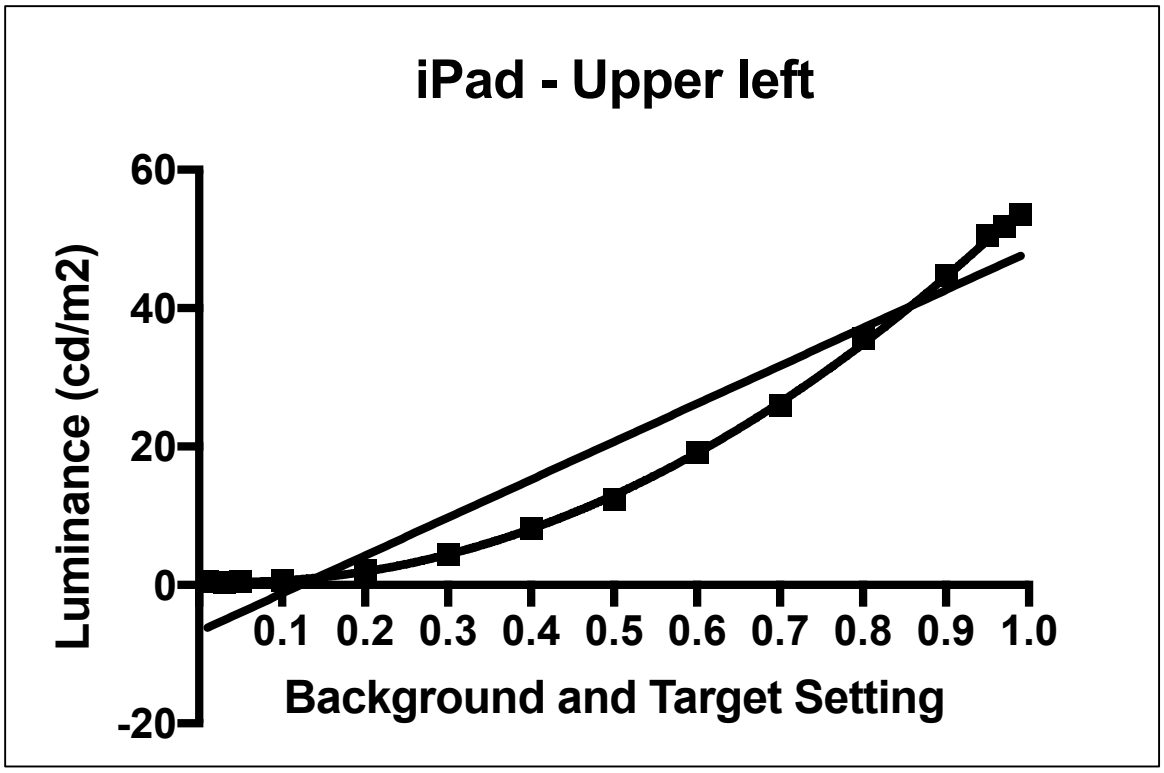

Figure E2: iPad Upper Left Target Calibration Curve and Linear Fit.

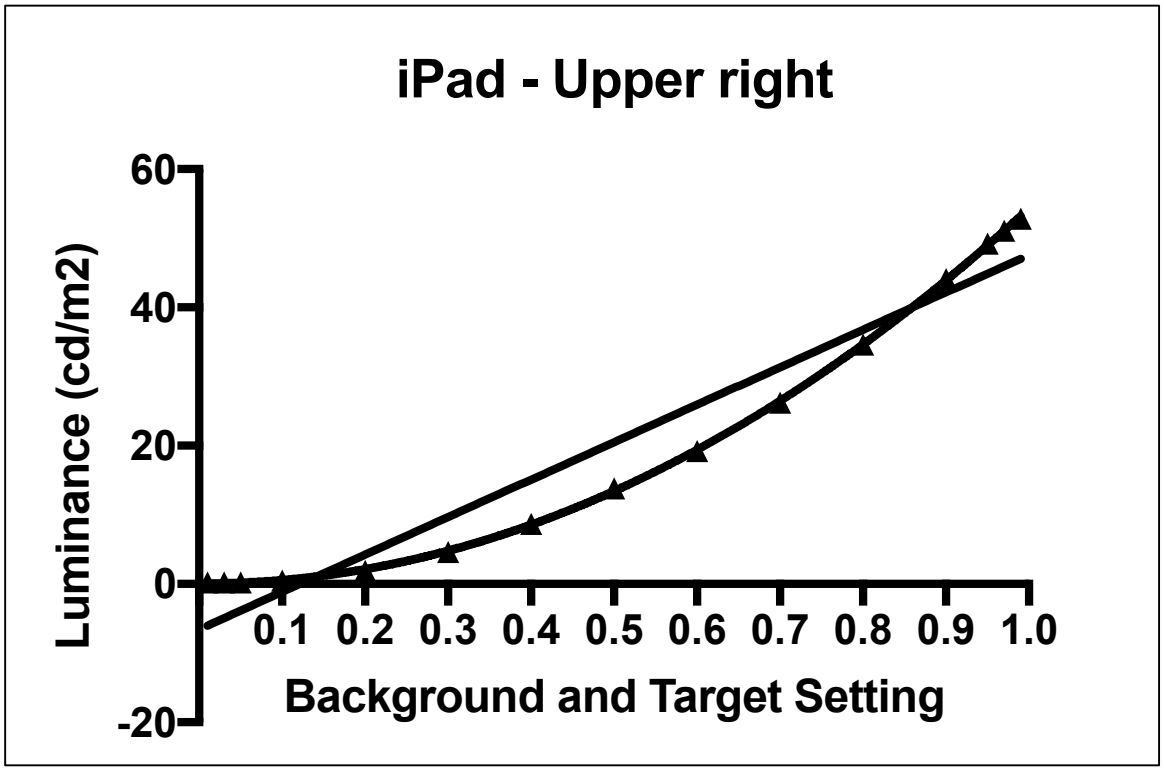

Figure E3: iPad Upper Right Target Calibration Curve and Linear Fit.

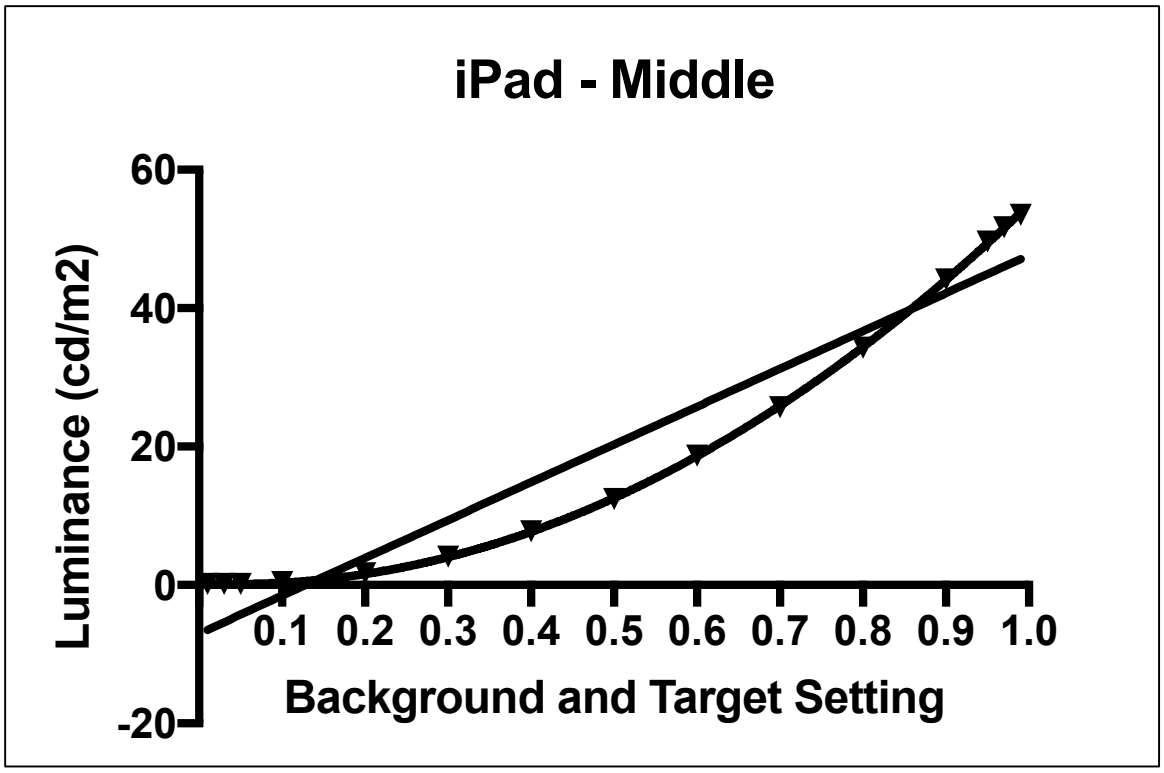

Figure E4: iPad Middle Target Calibration Curve and Linear Fit.

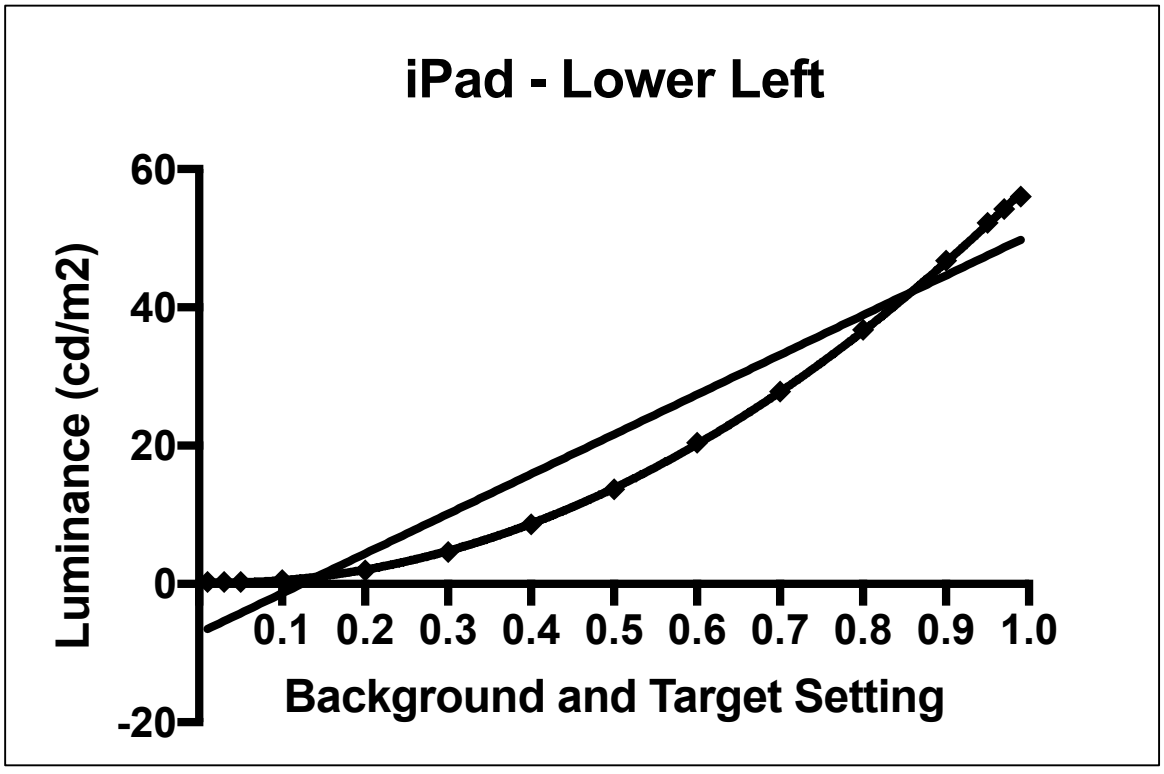

Figure E5: iPad Lower Left Target Calibration Curve and Linear Fit.

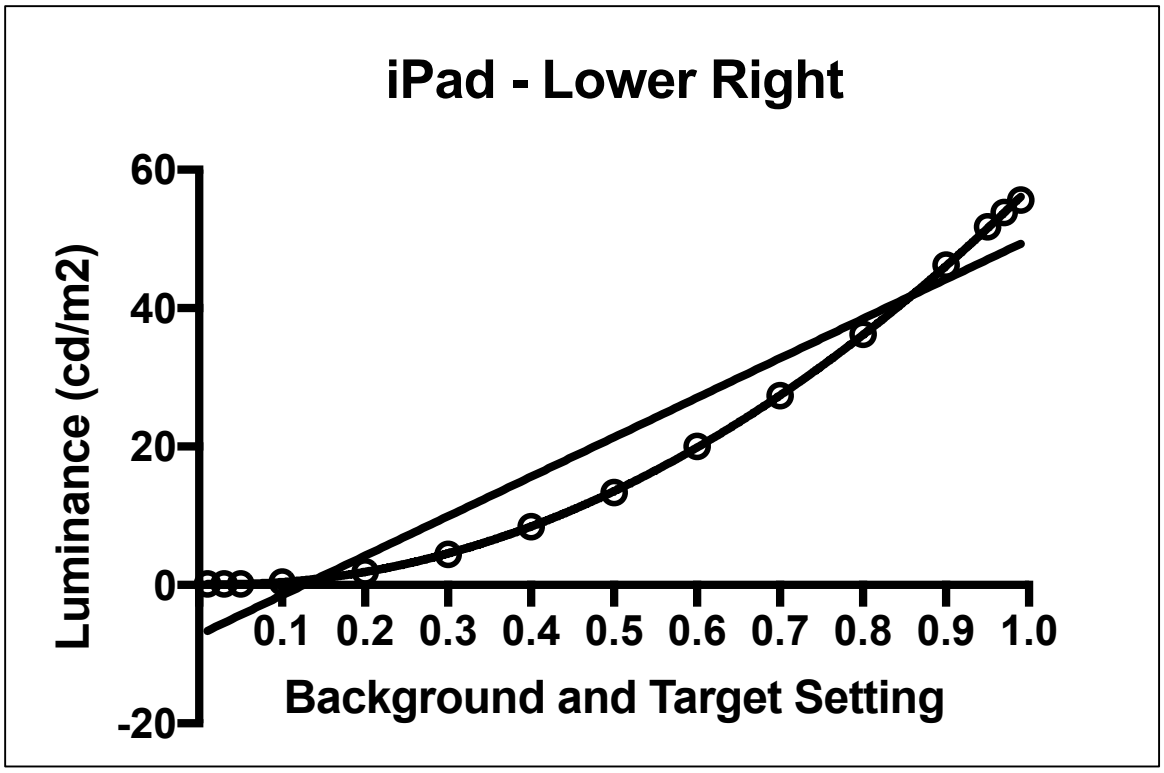

Figure E6: iPad Lower Right Target Calibration Curve and Linear Fit.

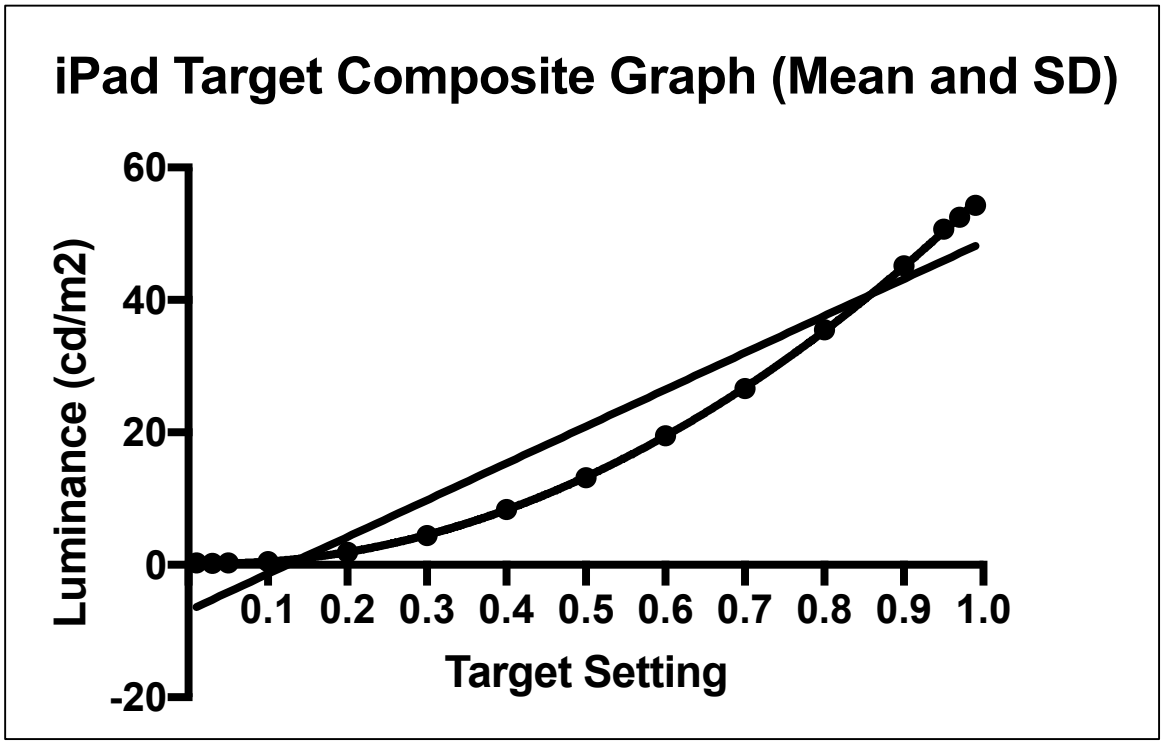

Figure E7: iPad Composite Targets Calibration Curve and Linear Fit.

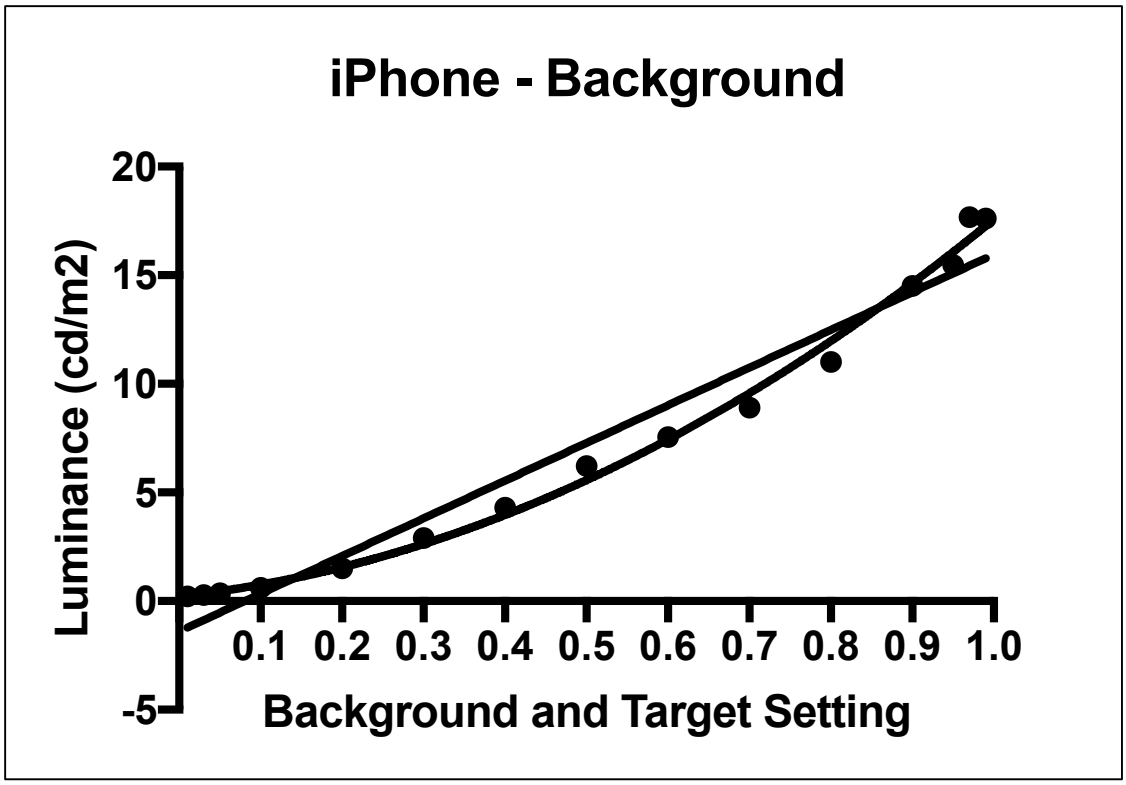

Figure E8: iPhone Background Calibration Curve and Linear Fit.

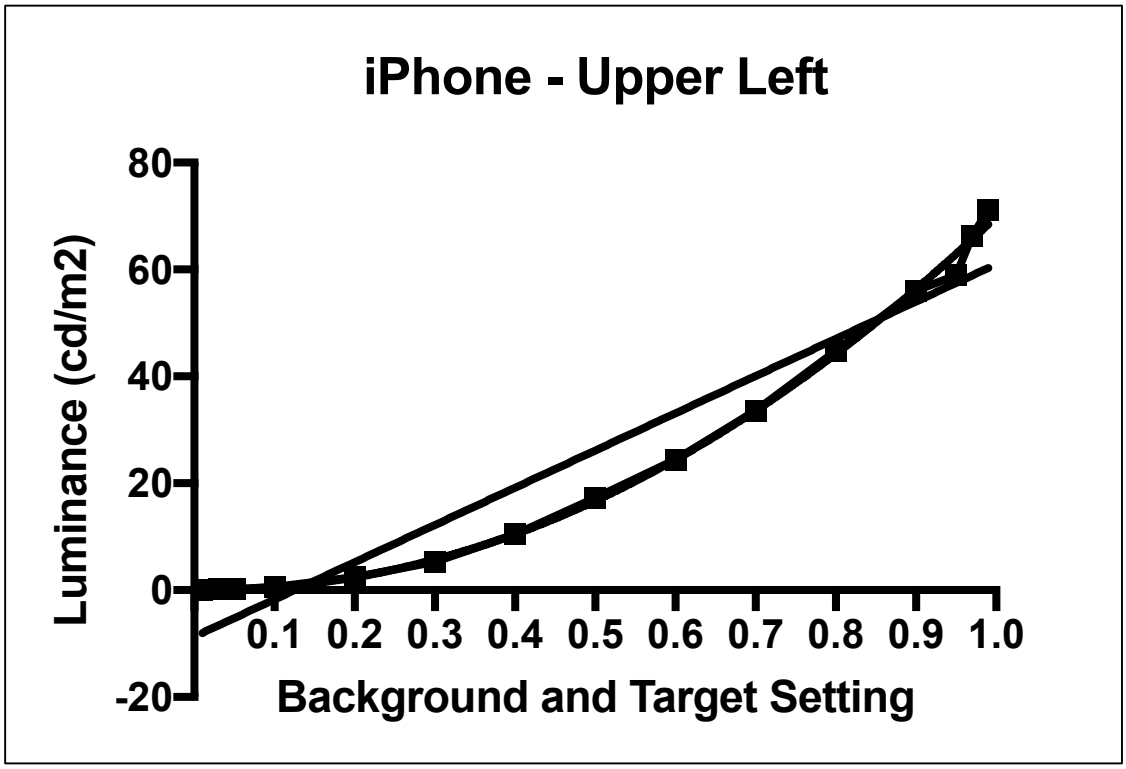

Figure E9: iPhone Upper Left Target Calibration Curve and Linear Fit.

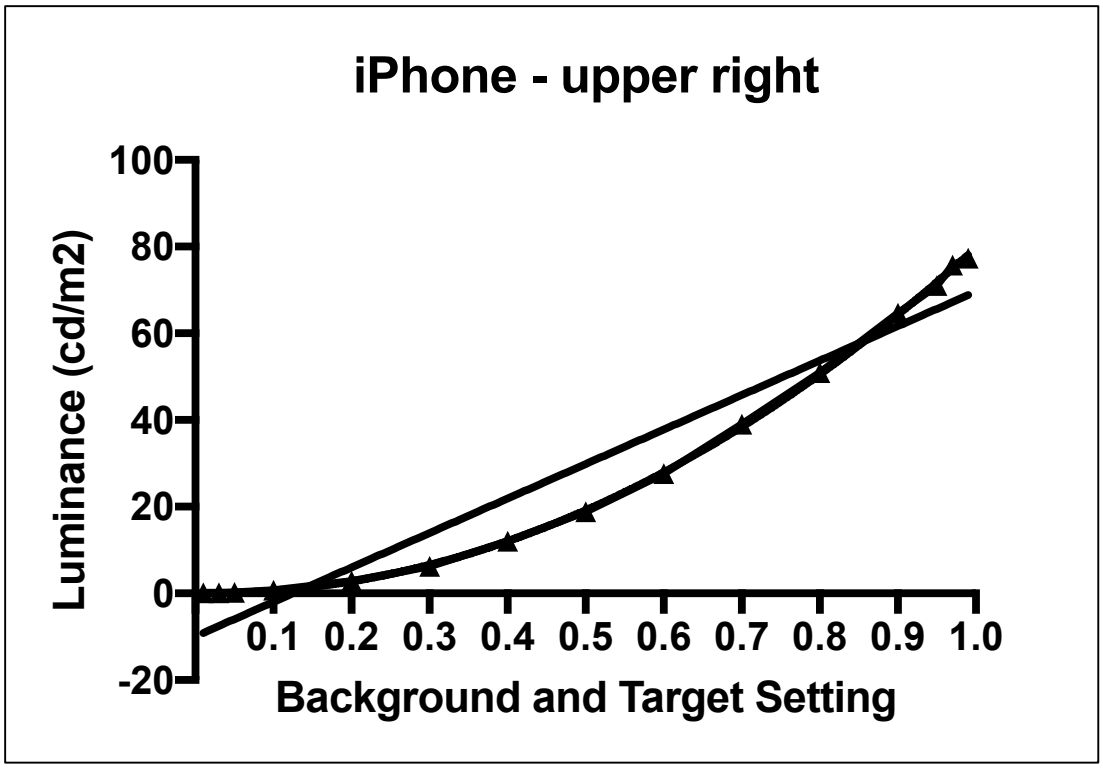

Figure E10: iPhone Upper Right Target Calibration Curve and Linear Fit.

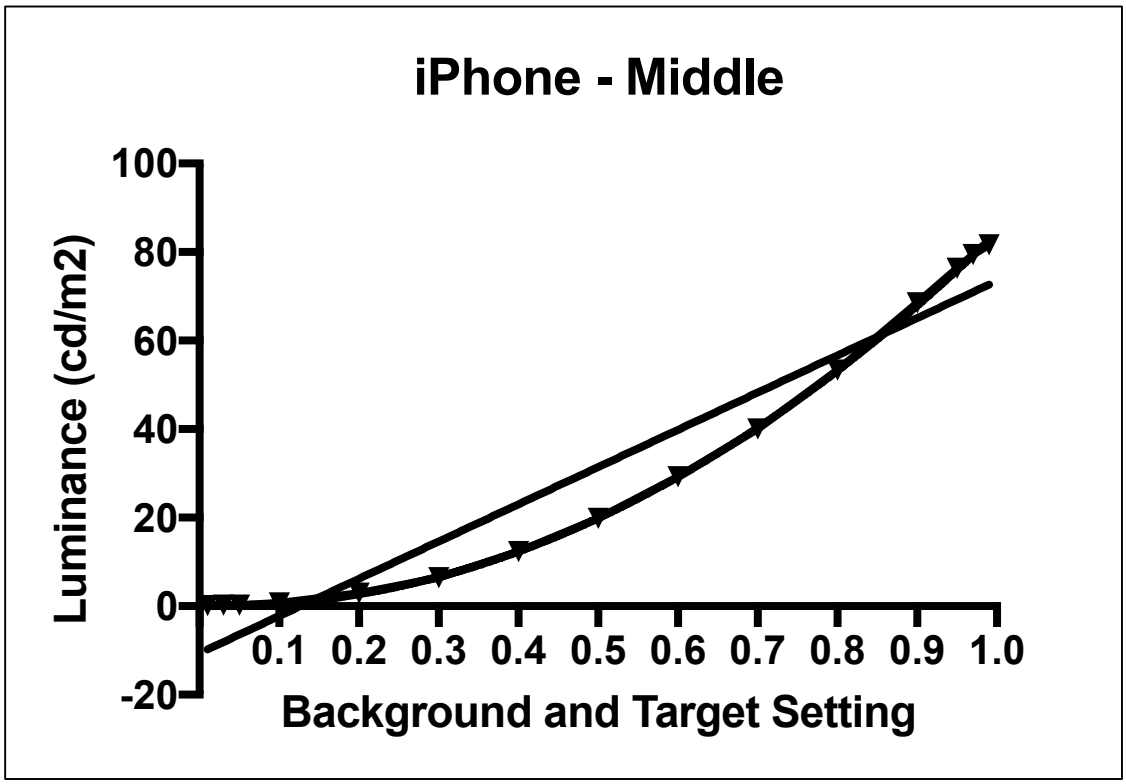

Figure E11: iPhone Middle Target Calibration Curve and Linear Fit.

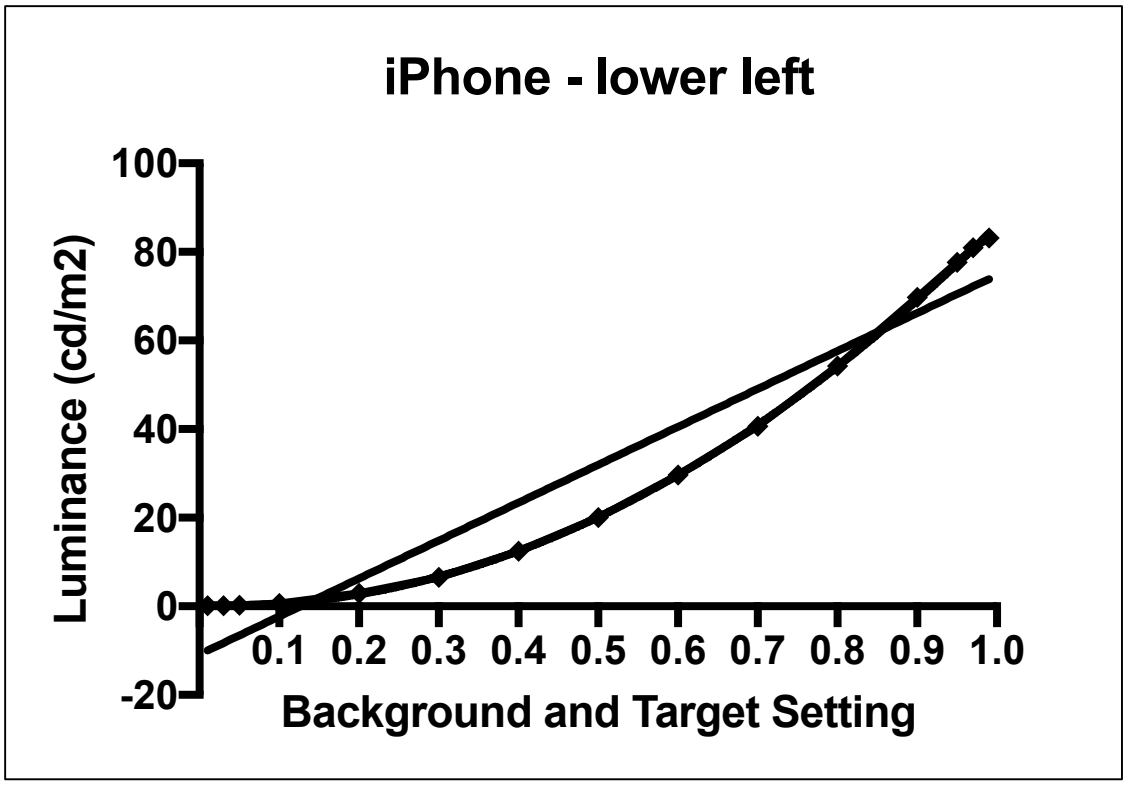

Figure E12: iPhone Lower Left Target Calibration Curve and Linear Fit.

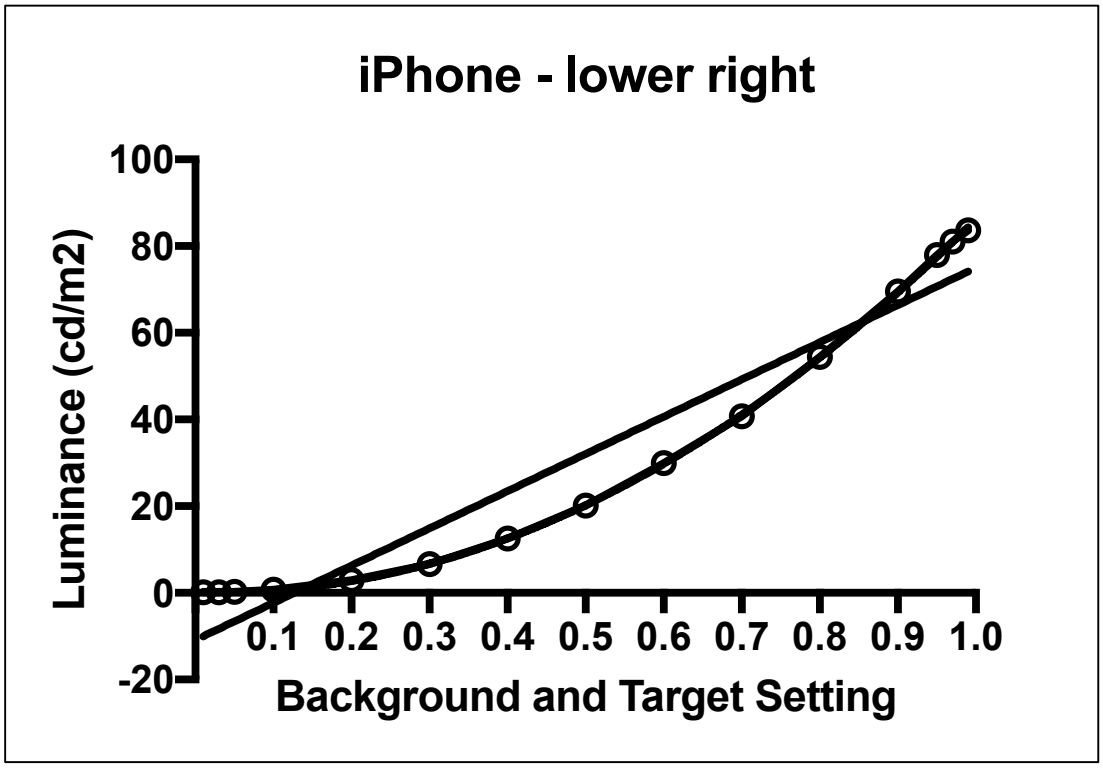

Figure E13: iPhone Lower Right Target Calibration Curve and Linear Fit.

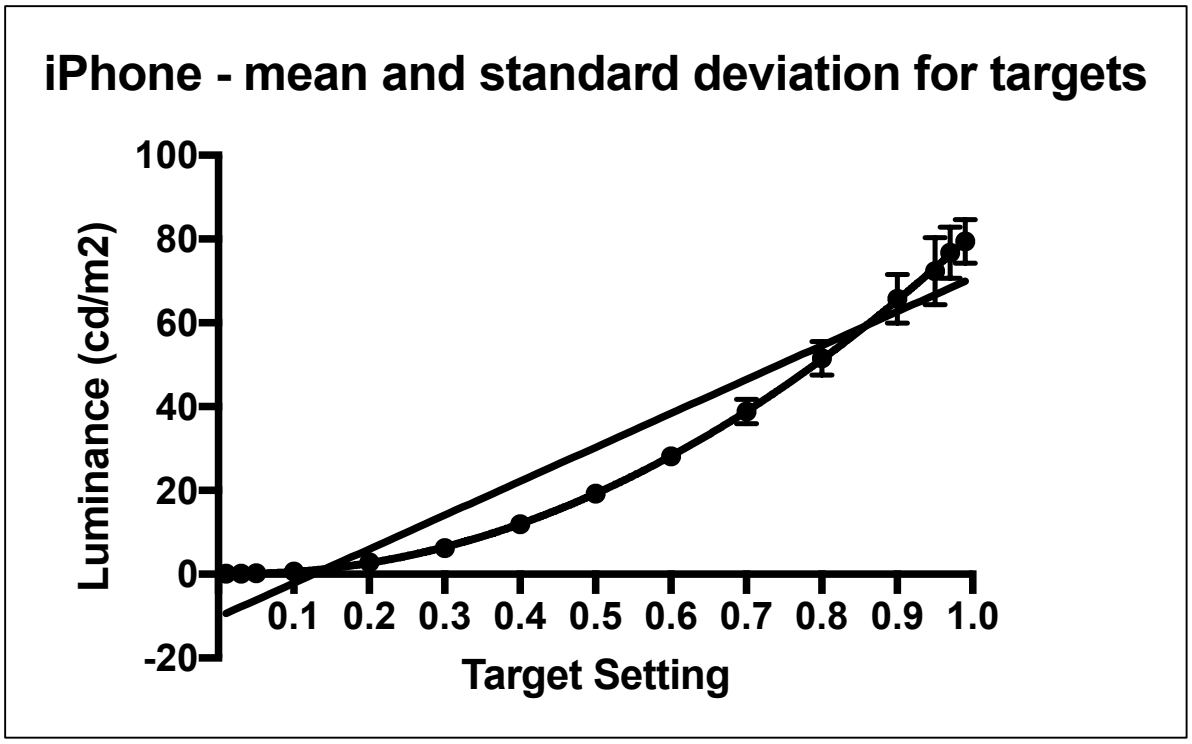

Figure E14: iPhone Composite Targets Calibration Curve and Linear Fit.

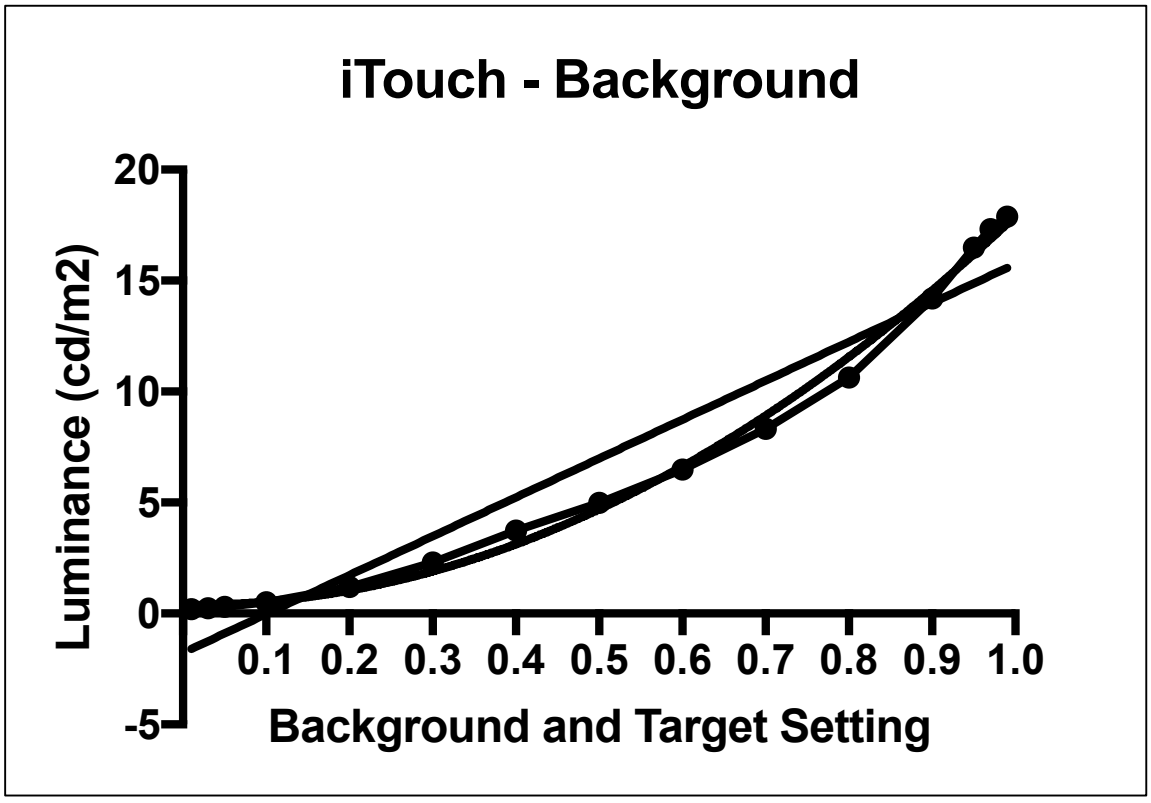

Figure E15: iTouch Background Calibration Curve and Linear Fit.

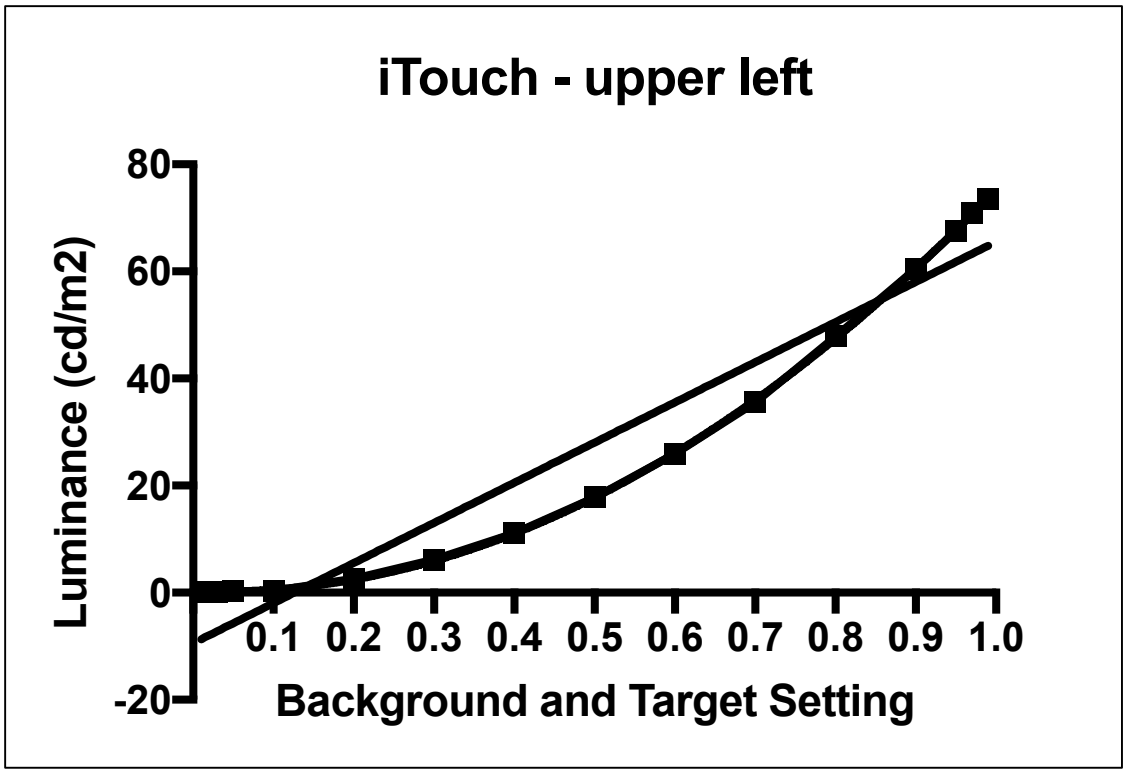

Figure E16: iTouch Upper Left Target Calibration Curve and Linear Fit.

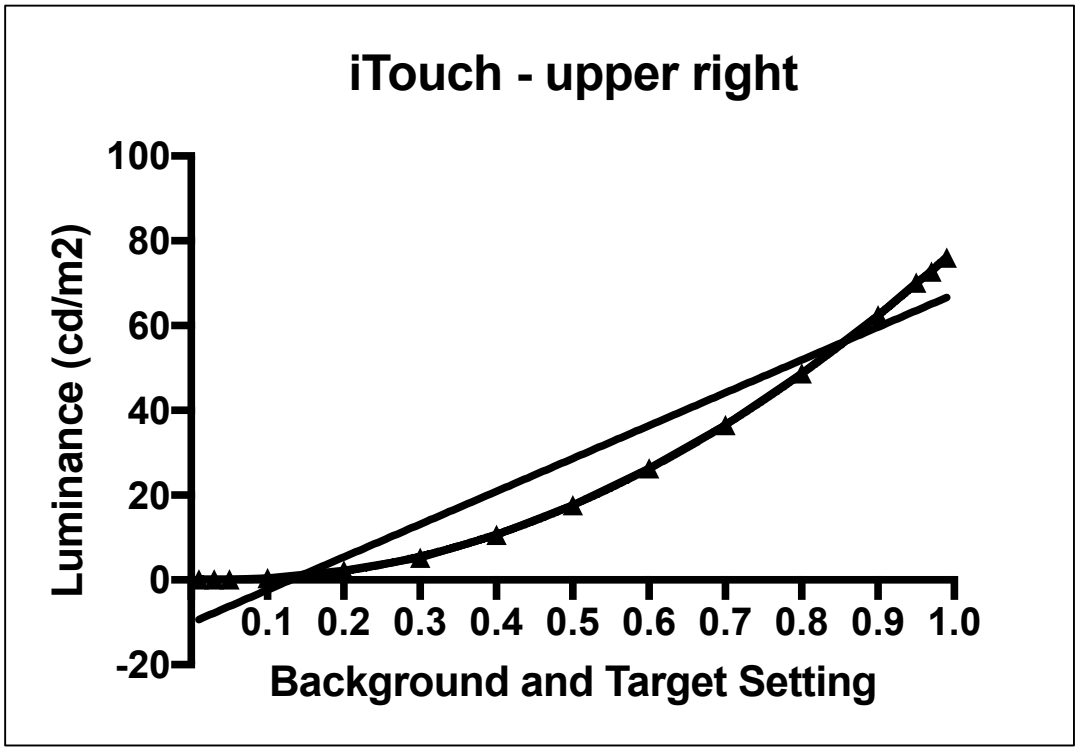

Figure E17: iTouch Upper Right Target Calibration Curve and Linear Fit.

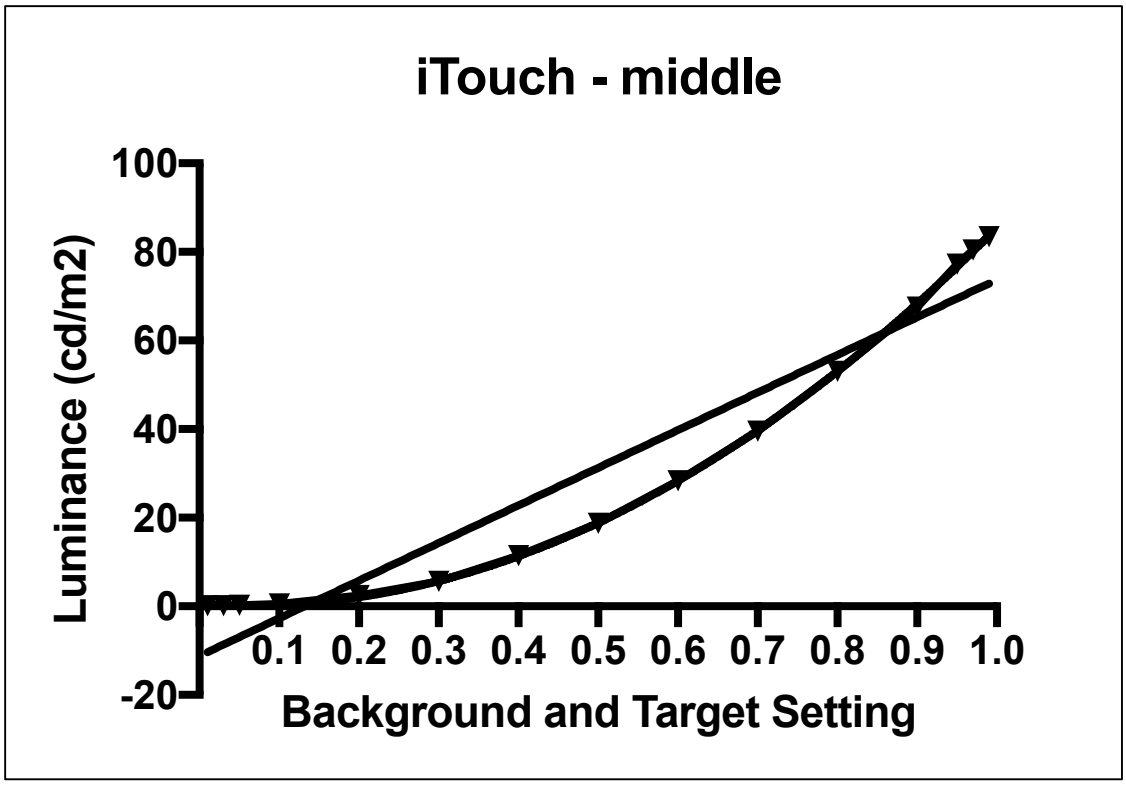

Figure E18: iTouch Middle Target Calibration Curve and Linear Fit.

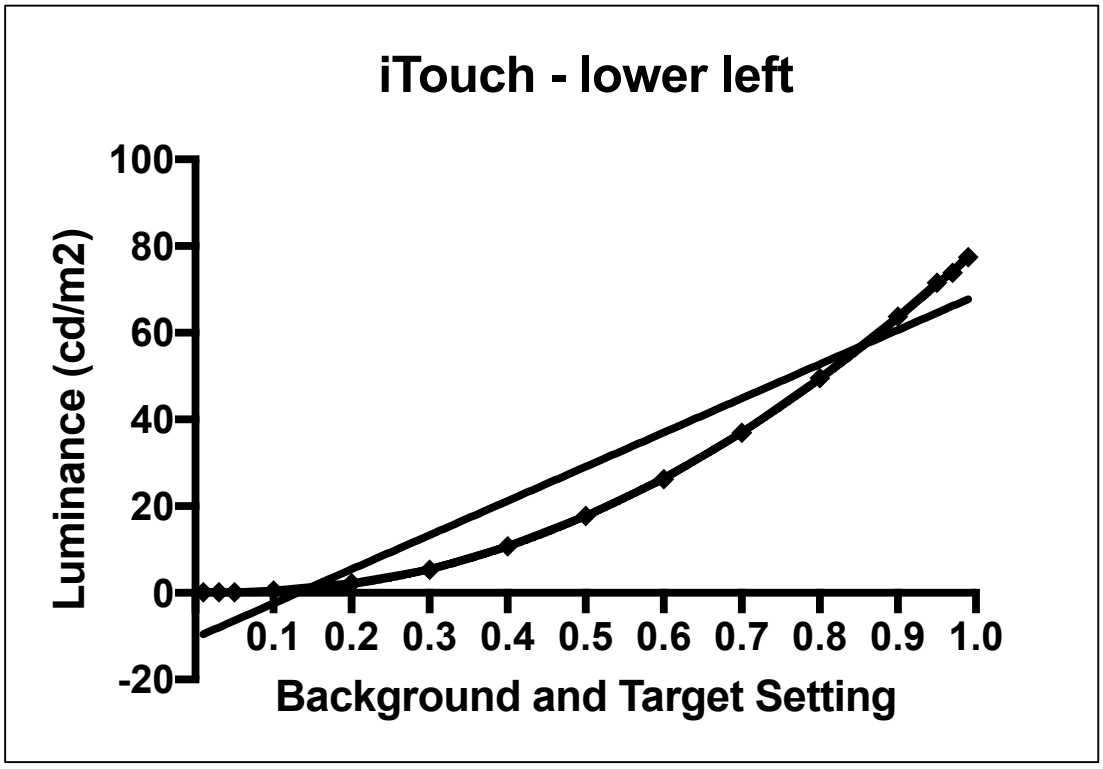

Figure E19: iTouch Lower Left Target Calibration Curve and Linear Fit.

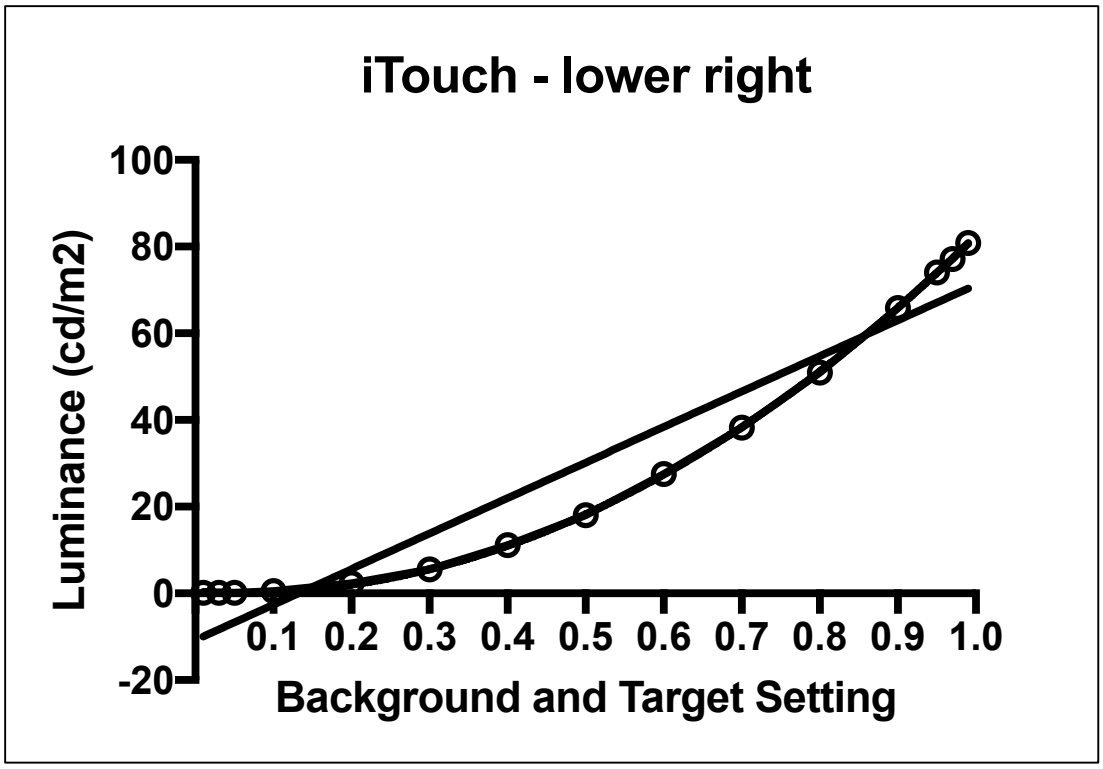

Figure E20: iTouch Lower Right Target Calibration Curve and Linear Fit.

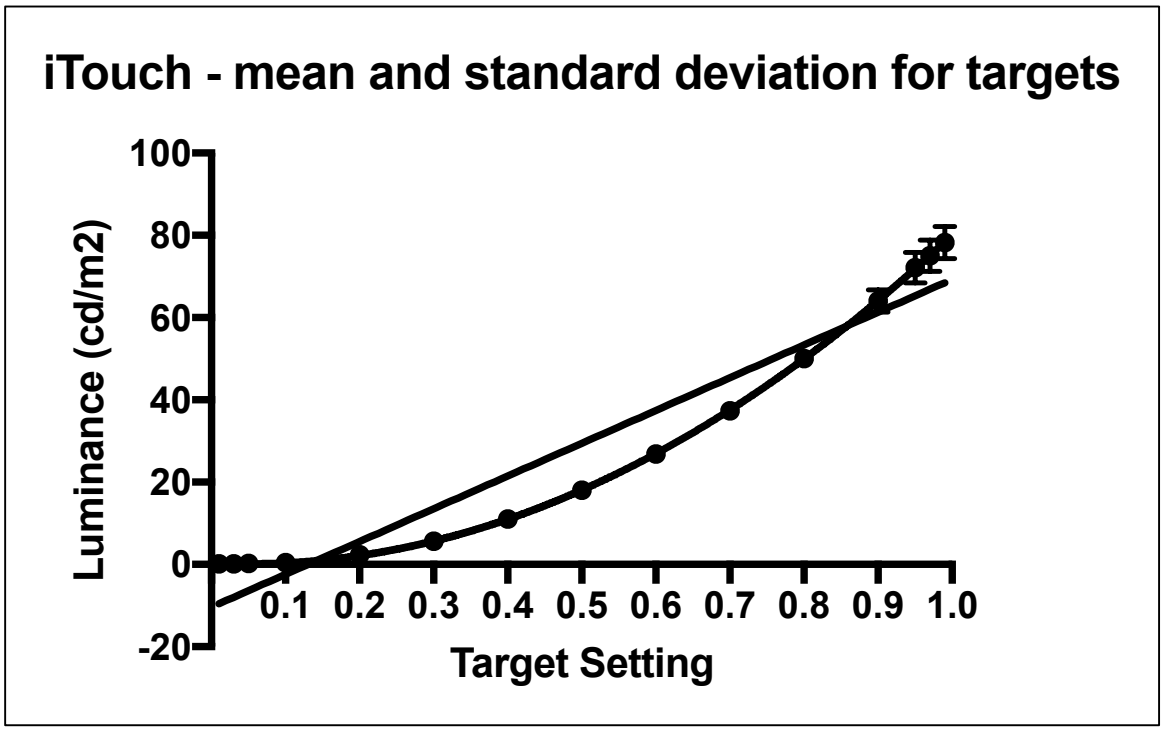

Figure E21: iTouch Composite Targets Calibration Curve and Linear Fit.