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# The Importance of Contrast Sensitivity, Color Vision, and Electrophysiological Testing In Clinical and Occupational Settings

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# THE IMPORTANCE OF CONTRAST SENSITIVITY, COLOR VISION, AND ELECTROPHYSIOLOGICAL TESTING IN CLINICAL AND OCCUPATIONAL SETTINGS

by

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Frances M. Silva

# DEDICATION

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# THE IMPORTANCE OF CONTRAST SENSITIVITY, COLOR VISION, AND ELECTROPHYSIOLOGICAL TESTING IN CLINICAL AND OCCUPATIONAL SETTINGS

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Visual acuity (VA) is universally accepted as the gold standard metric for ocular vision and function. Contrast sensitivity (CS), color vision, and electrophysiological testing for clinical and occupational settings are warranted despite being deemed ancillary and minimally utilized by clinicians. These assessments provide essential information to subjectively and objectively quantify and obtain optimal functional vision. They are useful for baseline data and monitoring hereditary and progressive ocular conditions and cognitive function. The studies in this dissertation highlight the value of contrast sensitivity, color vision, and cone specific electrophysiological testing, as well as the novel metrics obtained with potential practical clinical applications for visual function and perception evaluation in patients in various settings.

The first study aimed to design a clinically expedient method to combine color CS and color naming (CN) into a single, multi-metric test of color vision, the Color Contrast Naming Test (CCNT). This was accomplished by comparing and validating it with the standardized computerized Cone Contrast Test (CCT; Innova Systems, Inc.). Color vision deficient (CVD) and color vision normal (CVN) findings showed a strong correlation between the CCNT CS and the standard CCT. Furthermore, CCT CS showed distinct scores in 50% of CVDs, while the CCNT composite score (mean of CS and CN) showed distinct scores in 70% of CVDs, showing better potential discrimination of CVD color abilities. This novel metric has potential applications for identifying hereditary or progressive CVD severity and capabilities.

The second study focused on electrophysiological diagnostics, specifically cone specific visual evoked potentials (VEPs), to objectively measure long-term neural adaptive responses to color-correcting lenses (CCLs), also called EC. Dr. Werner and colleagues determined that extended wear (for 12 days) of color-correcting lenses improved red-green color perception in hereditary CVD even without wearing CCLs. Furthermore, Dr. Rabin and colleagues were able to objectively measure both immediate short-term (baseline, 4, 8, 12 days) and long-term (3, 6, 12 months) improvements of color perception status post-CCL removal with cone specific VEPs – something that has never been done before. The novel findings from both studies support the notion that neural adaptive changes can occur over short- and longer-term periods despite minimal daily wear time. More importantly, this further supports the value of suprathreshold cone VEPs to objectively assess color vision function in both clinical and occupational settings.

Most dry eye studies use measures of tear quality and volume coupled with standard clinical tests such as high contrast visual acuity (VA), while fewer studies have investigated the effects of dry eyes on low contrast vision. The final study was designed to determine the impact of Meibomian Gland Dysfunction (MGD) dry eye on high and low-contrast vision, including both black/white (luminance) and cone specific color vision. A primary intent was to determine if these novel metrics improved following minimal meibomian gland (MG) expression. The computerized CCNT and CCT (cone and black/white) tests used in this study confirmed that minimal MG expression improved low contrast performance for long (L cone) and short (S cone) wavelength-sensitive cones. These improvements were most significant using throughput (CS/response time) and CCNT composite scores, both novel metrics for potential use in dry eye diagnosis, treatment, and management. Physical optics, including decreased destructive interference in the stroma, most detrimental with red light, and increased scattering by subtle

epithelial, endothelial, and/or tear film defects, most detrimental for blue light, could each decrease retinal image contrast most evident with L and S cone CS.

Contrast sensitivity, color vision, and cone specific electrophysiological testing are non-optimally and infrequently utilized in basic, clinical, applied, and translational research or occupational settings. These studies showed provocative results within their respective categories and confirmed their validity and importance for identifying and monitoring ocular conditions and neural adaptive or cognitive functions. Furthermore, novel metrics such as throughput and CCNT composite scores serve as potential tangible and practical visual function and perception assessment standards.

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# Chapter 1: A New Metric of Color Vision Combining Threshold and Suprathreshold Performance

Color vision perception and function can be measured subjectively and objectively in multiple environments for distinct purposes that vary among individuals.[1-4] Some applications include but are not limited to diagnosis, type, and severity of hereditary color vision deficiency (CVD) and detecting and monitoring acquired CVD in ocular, system, and neurological diseases.[5-9] Existing tests reveal threshold sensitivity but provide no information about the accuracy of color identification critical in many occupations. Computerized color contrast sensitivity (CS), cone specific visual evoked potential (VEP) testing, and neuroimaging coupled with well-established color vision tests (e.g., pseudoisochromatic plates, arrangement cap tests, anomaloscope) enhance color vision functional assessment crucial in clinical, occupational, and translational vision research disciplines.[9,10]

Whereas visual acuity (VA) is generally deemed the "gold standard" for vision assessment, one must add color vision functional evaluation for early congenital or acquired CVD detection.[11] Combining function tests such as VA, CS, color, depth, and motion perception allows proper measurement of an individual's level of functional vision in real-world scenarios.[12-16] Timely comprehensive functional vision assessment is vital to patients from the youth navigating their academic career, to young adults learning how to drive, and adults seeking visually demanding occupations that require specific color vision standards.[12,17,18]

The fundamental property of trichromatic color vision requires the presence of three distinct cone photopigments specialized to respond to long wavelength light (red), medium wavelength light (green), and short wavelength light (blue).[19] Hereditary or congenital CVDs typically affect 8-10% of males and 0.5% of females and are classified as dichromatic or

anomalous trichromacy where the former has loss of the specific wavelength and the latter has a shift in one of their wavelengths resulting in a mild CVD.[19,22,25] Furthermore, acquired CVD can be seen in conditions such as glaucoma, multiple sclerosis, Alzheimer's, Parkinson's and schizophrenia.[5-9] Acquired CVD can impact different stages of visual processing such as pre-receptoral filters, cone photopigments, and post-receptoral processes.[23] This makes detecting acquired CVD difficult with conventional threshold tests warranting measurement of suprathreshold performance as seen with cone contrast sensitivity (CS) testing.

As scientists seek gene therapy solutions to this incurable condition, various tests have been designed to help screen, diagnose, and monitor color vision deficiencies.[13-18,19-25] Coupling these tests with objective neuroimaging can further enhance functional color vision evaluation and cognitive function associated with color vision.[5-9] Most importantly, standard protocols with a battery of color vision tests can be useful in CVD diagnosis, treatment, and management.[14]

***Existing Color Vision Testing in Clinical and Occupational Settings***

A variety of standard color vision testing exists; however, there is noticeable limited standardization with variable utilization within these tests.[17-21,27] Ishihara and Hardy Rand & Rittler (HRR) are well-known pseudoisochromatic plates commonly used for screening CVDs in research and clinical settings, respectfully. Both are efficient tests that detect the presence, severity, and type of CVD, with Ishihara designed to detect hereditary red-green defects and HRR designed to detect rare hereditary and acquired blue-yellow cone defects.[26,27]

Arrangement tests are another category of color vision tests typically used for specific occupations where the observer arranges colors sequentially. The benchmark test for hue discrimination is the Farnsworth Munsell 100 Hue Test, which provides specific metrics of red, green, and blue color discrimination based on color confusion lines.[25,28] The abridged version of

the test, the standard Farnsworth Panel D-15 test and desaturated version are much more rapid to administer and score, typically using a computer program which analyzes the sequence of colors arranged by the observer as well as type and severity.[19] While the FM 100 Hue offers precise quantification of hue discrimination, it requires considerable time, shows an overlap between CVNs and CVDs, and can be tiresome for patients and is hence less commonly used.[15,17]

The anomaloscope is the gold standard for diagnosing X-linked hereditary red-green color vision deficiency.[1] The observer identifies the relative amount of red and green needed in the top hemifield to achieve a perceptual match to the yellow in the bottom hemifield to determine the Rayleigh match point and the range across which matching occurs to determine any deviation from this mixture.[19-21] While the anomaloscope remains a gold standard, it is not widely available for clinical testing and requires skill to administer and interpret.

More recently, color CS tests, which can be administered from a calibrated computer display using rapid staircase algorithms, have been utilized for diagnosis of type and severity of hereditary and acquired CVD. Some examples include the Cone Contrast High-Definition (CCT HD®, Konan Medical), the Rabin Cone Contrast Test (CCT, Innova Systems, Inc.), the Color Assessment and Diagnosis (CAD) test, and the Waggoner Computerized Color Vision Test (WCCVT).[18,29,30]

Color naming combined with validated suprathreshold testing such as cone specific CS can further enhance existing computerized testing to detect color vision deficiencies that impact particular visually demanding tasks specific for certain occupations and monitor progressive color vision loss and/or cognitive dysfunction.[31] The ability of CVDs to recognize and accurately name surface color codes is crucial for individuals whose quality of life is negatively impacted by color vision deficiency.[32] Color naming and categorization depend on functional brain

networks at various neurological levels and are currently studied and mapped out with functional magnetic resonance imaging during specific color vision tasks.[33,34] Psychological and behavioral factors such as experience must be considered when evaluating color vision with a battery of particular tests. Individuals have various educational and experiences levels, cultures, and languages that can contribute to their functional color vision performance and perception.

Studies have shown distinct neural pathways involved in color vision, coding, naming, and/or categorization processes.[32-37] Siuda-Krzywicka et al. determined that color categorization and color naming rely on different neural mechanisms with minimal overlap in the cortex. More specifically, color naming involved a connective network between the left posterior color region, the left middle temporal gyrus, and the left angular gyrus.[32] Color categorization involved a network between the bilateral posterior color regions and left frontal, right temporal, and bilateral parietals areas.[32] Gaining more knowledge of these neural networks can provide a better understanding between color vision performance and cognitive and/or behavioral processes.

### *Purpose of Current Study*

This study aimed to add another dimension to color contrast testing for better specificity and sensitivity. It combined cone specific color CS and color naming (CN) to establish a novel metric that enhanced the existing and validated Innova CCT. This novel method qualitatively and quantitatively measures threshold and suprathreshold color vision performance.

## Methodology

### *Subjects*

Participants (N = 38) were recruited students, interns, staff, faculty, administrators, patients, colleagues, and/or family members from the University of the Incarnate Word Broadway, Rosenberg School of Optometry, and School of Osteopathic Medicine campuses.

Color vision status was confirmed by the Ishihara and Oculus HMC Anomaloscope. Exclusion criteria included a history of ocular, neurological or systemic disease not controlled medically. All subjects provided written informed consent in accordance with our IRB-approved protocol, and all data were collected in accordance with the Declaration of Helsinki and its revisions.

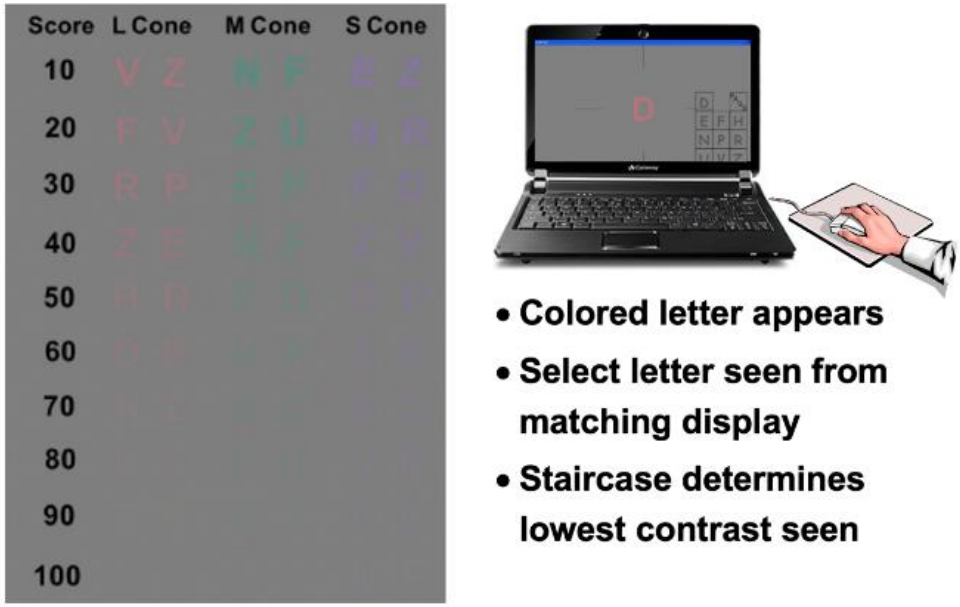
***Procedures and Materials***

Twenty hereditary CVDs (age ± SD, 32 ± 12: 14 deuteranomalous and six protanomalous confirmed by Ishihara, anomaloscope, and cone CS) and 26 CVNs (26 ± 5 YO) participated after providing written informed consent in accordance with our IRB-approved protocol.

A calibrated Microsoft Surface tablet displayed single letters centered in a crosshair on a grey background for 5 seconds per trial (Figure 1). Letters stimulated only L, M, or S cones or luminance (Lum; lighter grey on grey background). Weber contrasts varied from one to sixteen percent in 2x steps (1%, 2%, 4%, 8%, 16%) for L, M, Luminance (Lum) and eight to one hundred and twenty-eight percent in 2x steps (8%, 16%, 32%, 64%, 128%) for S cone letters. Subjects were directed to name each letter and its color, stating the color first, followed by the letter types (L, M, S, Lum) were randomly presented twice at each of the five contrasts per session. Cone CS and CN were each based on the number correct using a scale of 100.

**Figure 1**

Red, Green, and Blue Cone Contrast Sensitivity Testing




Both Innova CCT and CCNT use calibrated Microsoft Surface Display with a central target. The CCT requires the subject to match the letter to a target, while the CCNT requires the subject to verbally state the color and letter when presented. The Innova CCT automatically measures the CS score and reaction time, while the test administrator manually records the CS (letter) and CN (color) responses on a record sheet for the CCNT.

***Statistical Analysis***

CS and CN scores were normally distributed for CVNs and CVDs (Jarque-Bera skewness-kurtosis test). ANOVA, post-hoc t tests, regression, and Bland Altman analyses were conducted to assess within and between group differences, agreement with established testing, and predictive modeling.

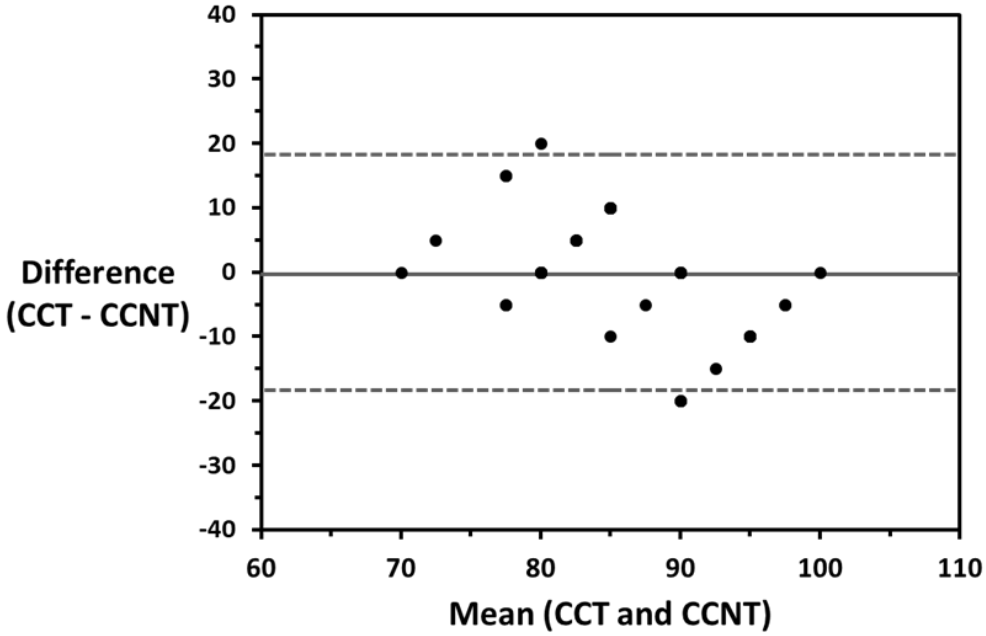
**Results**

CVD CCNT CS was highly correlated with standard CCT CS (Innova Systems, Inc.; $r^2$ = 0.8, $P < .001$) as did CVN CS ($r^2$ = 0.3, $P < .001$). These findings were confirmed and validated with Bland Altman analyses (Figures 2a & 2b). Figure 2a shows the difference between the standard CCT CS score and new CCNT color naming score for each subject plotted against their

mean for CVNs. Most points fall within the 95% confidence interval (CI) for agreement, the discrepancies are likely due to the separate nature of the tasks. Figure 2b shows the difference between standard CCT CS and CCNT CS for CVDs plotted against their means showing good agreement, consistent with the regression analyses. Notably, the gold standard Rayleigh anomaloscope matching range was correlated with both CCNT CS ($r^2 = 0.3$, $P < .03$) and CCT CS ($r^2 = 0.2$, $P < .03$) as seen in Figure 3.

**Figure 2a**

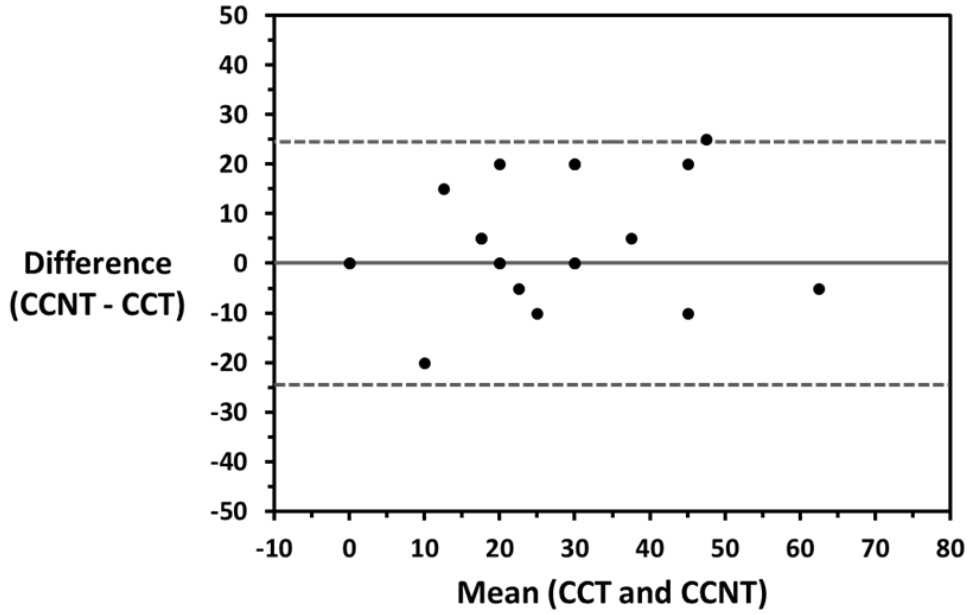
Bland Altman Analysis: CCT vs CCNT Scores for Color Vision Normals (CVNs)




Bland Altman analyses show agreement between CCNT color naming and CS with Innova CCT CS for CVNs (see text for further details).

**Figure 2b**

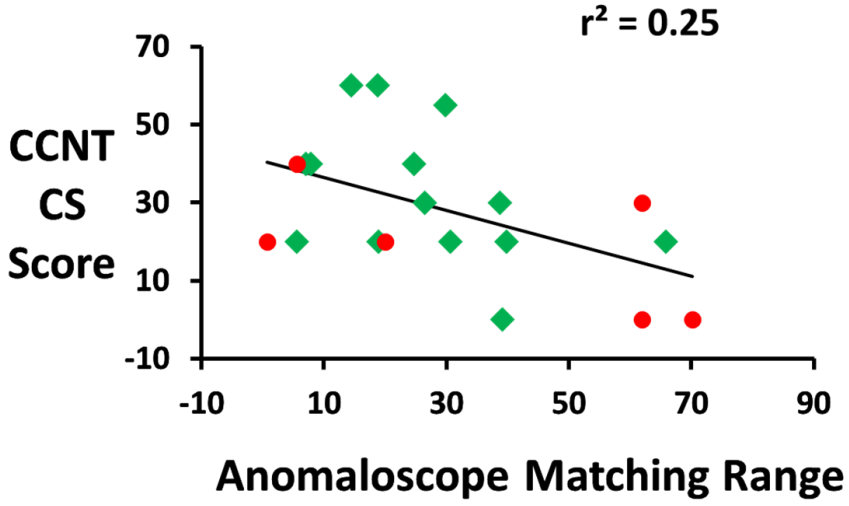
Bland Altman Analysis: CCT vs CCNT Scores for Color Vision Deficients (CVDs)




Bland Altman analyses show agreement between CCNT color naming and CS with Innova CCT CS for CVs (see text for further details).

**Figure 3**

Anomaloscope Predicts Cone CS in CVDs

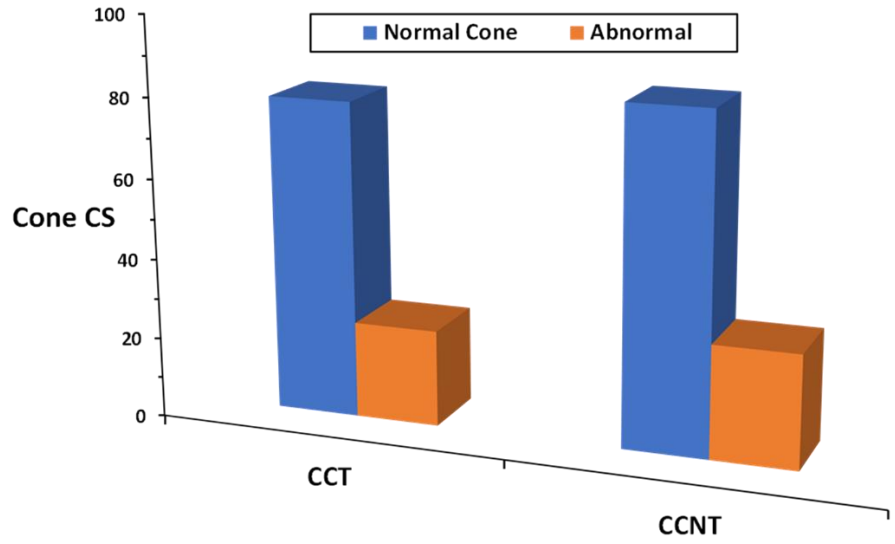



CCNT is further validated with the gold standard Rayleigh Anomaloscope. Protan L-cone CS was significantly lower than deutan M-cone CS for both CCNT and CCT.

The sensitivity of CCNT CS for detecting the type and severity of CVD was 100% (mean CVN CS: 84, mean CVD CS: 28, $P < .001$; CVD CS was 6.1 standard deviations below CVD normal cone CS, $P < .001$). The specificity for confirming normal color vision in CVNs and CVD normal cone type was also 100% (mean CVN = CVD CS: 84, $P > .89$). This demonstrates that the CCNT is comparable to Innova CCT (Figure 4). Additionally, protan L cone CS was significantly lower than deutan M cone CS for both CCNT and CCT ($P < .003$). It is important to note that CVDs CN was decreased considerably for the CVD cone type, normal cone, and luminance stimulus (mean 39) compared to CVNs (mean 82, $P < .001$). This prompted the notion that a mean of CS and CN composite scores might better detect and identify CVD severity. Standard CCT CS showed distinct scores in 50% of CVDs, while a composite CCNT score (mean of CS and CN) showed distinct scores in 70% of CVDs, exemplifying its superior ability to discriminate different levels of performance among CVDs (Figure 5). In addition, the FM 100 Hue Total Error Score decreased systematically with the log of CCNT composite score (Figure 6). No difference was observed between protans and deutans, emphasizing the multifaceted importance of composite scores for occupational and clinical applications for hereditary and acquired CVD.

**Figure 4**

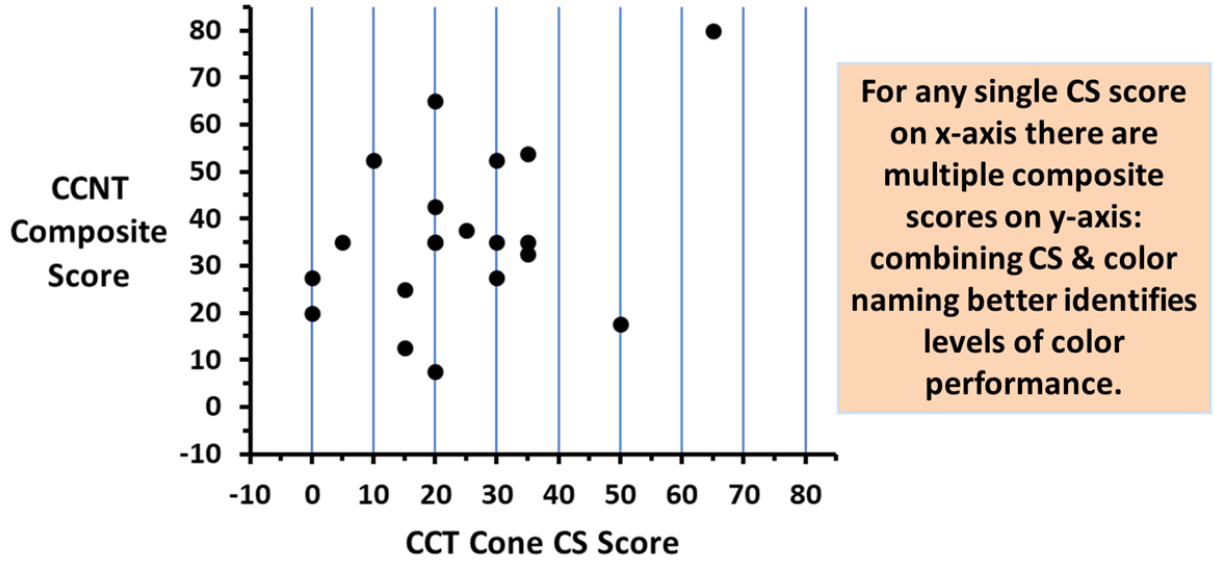
Cone CS: CCT vs CCNT




CCNT is comparable to Innova CCT for the normal (blue) and deficient (orange) cones.

**Figure 5**

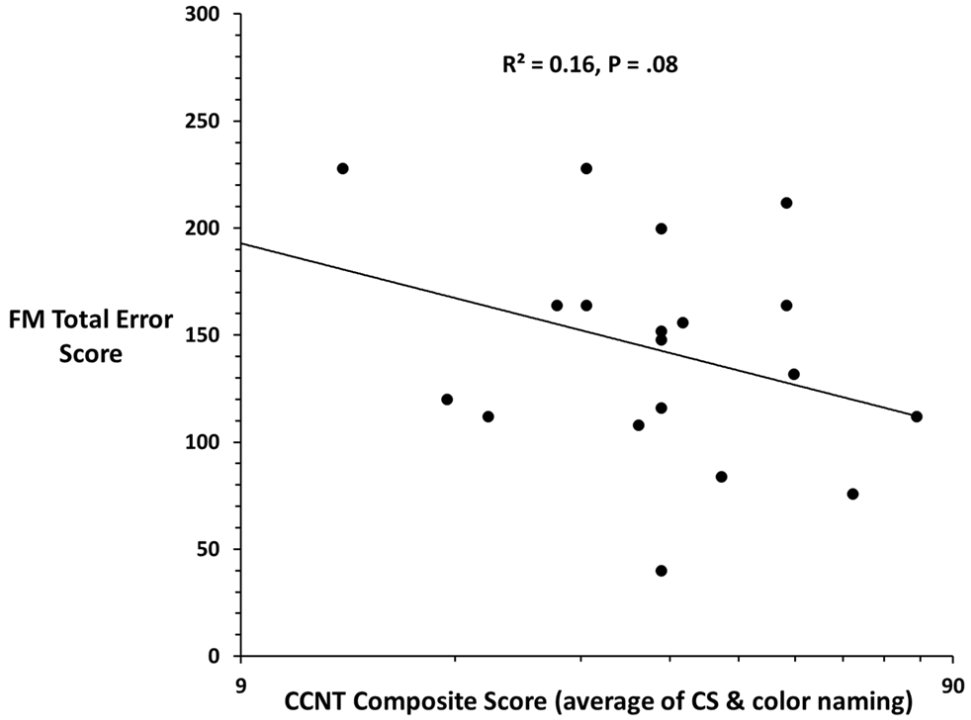
CCNT Composite Scores vs CCT CS Scores




CCNT composite scores plotted against CCT cone CS scores shows enhanced capability for identifying levels of color performance by combining CS and CN.

**Figure 6**

FM 100 Hue Error Score and CCNT Composite Score




FM 100 Hue error scores plotted against CCNT composite scores show a positive trend (lower total error scores with higher composite scores approaching statistical significance ($P$ = .08)) suggesting CCNT composite score's potential role for predicting hue discrimination.

## Discussion

Cone CS and CN expand the scope of color vision assessment for all CVD types. While protanomalous CVDs generally perform lower on cone CS, the CCNT composite score eliminates this difference and enhances the ability to identify levels of color performance. Applications include occupational assessment and detection of acquired CVD.

The CCNT offers a novel combined metric for better identifying both hereditary and acquired CVD and the progression of acquired CVD. Limitations include relatively small sample sizes and a need for automated data entry and scoring to optimize speed and efficiency. It is also possible that fatigue may mitigate sensitivity; hence we developed a more rapid version of the CCNT. We intend to create an abbreviated version that requires half the time to complete with voice-activated responses and automated reaction times recorded per stimulus.

CCNT has a promising future as it is clinically expedient with a wide array of utilization. Further studies with functional magnetic resonance testing during the CCNT are warranted and valuable to determine the neural pathways involved as the patient identifies each letter and verbally names the color. CCNT has potential clinical, occupational, and vision research applications for various hereditary or acquired ocular and cognitive disorders.

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## Chapter 2: The Longitudinal Impact of Color Correcting Lenses

Hereditary X-linked red-green color vision deficiency (CVD) impacts 8% of males and 1 in 200 females.[1] Many attempts have been made to improve color vision with spectrally selective filters with limited success and have yet to be approved for occupational applications to improve color vision in individuals with specific inherent color vision deficiencies (CVD).[1,2] Three primary photopigments (L-, M-, and S-cones) are required for optimum color vision, with the difference in stimulation between at least two cone types being the basis for color hue discrimination (Figure 1a: difference in the stimulation of L and M normal cones is different for green, yellow and orange sending separate signals to the brain for discriminating these colors).[3] However, of the 8% of males with CVD, 6% have anomalous trichromacy in which either the M cone absorption spectrum is shifted toward the normal L cone function (deuteranomaly, 5%) or the L cone function is shifted toward the normal M (protanomaly; Figure 1b shows the typical 15 nm shift of M cone peak such that the three vertical arrows indicating the difference in L and M cone stimulation are now the same length rendering colors discriminable). Finally, 1% of males either lack the M cone photopigment (deutan dichromacy) or the L cone photopigment (protan dichromacy).[3]

Previous studies have indicated that commercialized specialty-filtered glasses or color vision correcting lenses (CCLs) had various and minimal impacts on color saturation, contrast, and color perception overall with minimal improvements.[4-11] Stockman et al. found that the filters impaired color perception of cyan stimuli during color naming tasks.[4] Bastien et al. observed improvement in Optical Hardy-Rand-Rittler (AO HRR) measurements was only seen with protan participants.[5] Gomez-Robles et al. found that the CCLs did not reveal any improvement in recognition and arrangement with screening and sorting color vision tests.[6]

Varikuti et al. determined that most patients reported a subjective increase in color perception as seen with protans only with Ishihara and Farnsworth tests.[12] Alvaro et al. found that pattern similarity exists across hue for discrimination thresholds and naming errors but no significant improvement in these metrics for CVDs.[13] Meta-analysis reviews have found few studies showing chromatic discrimination improvement with CCLs for individuals with known color-vision phenotypes.[8-11] Most of these studies had small sample sizes with subjective testing methods such as Ishihara, HRR, FM 100 Hue, Farnsworth D-15, and color naming or color sorting tasks.[4-11]

More recent studies aimed to better understand the chromatic response to CCLs with objective psychophysical measurements such as cone contrast sensitivity, cone specific or spatio-chromatic VEPs.[14-18] Patterson et al. used psychophysical tests measuring chromatic contrast and threshold stimuli (CAD) to determine color vision enhancement of CCLs specific VEPs allows for more accurate assessment of functional color vision and thorough CCL research and development.

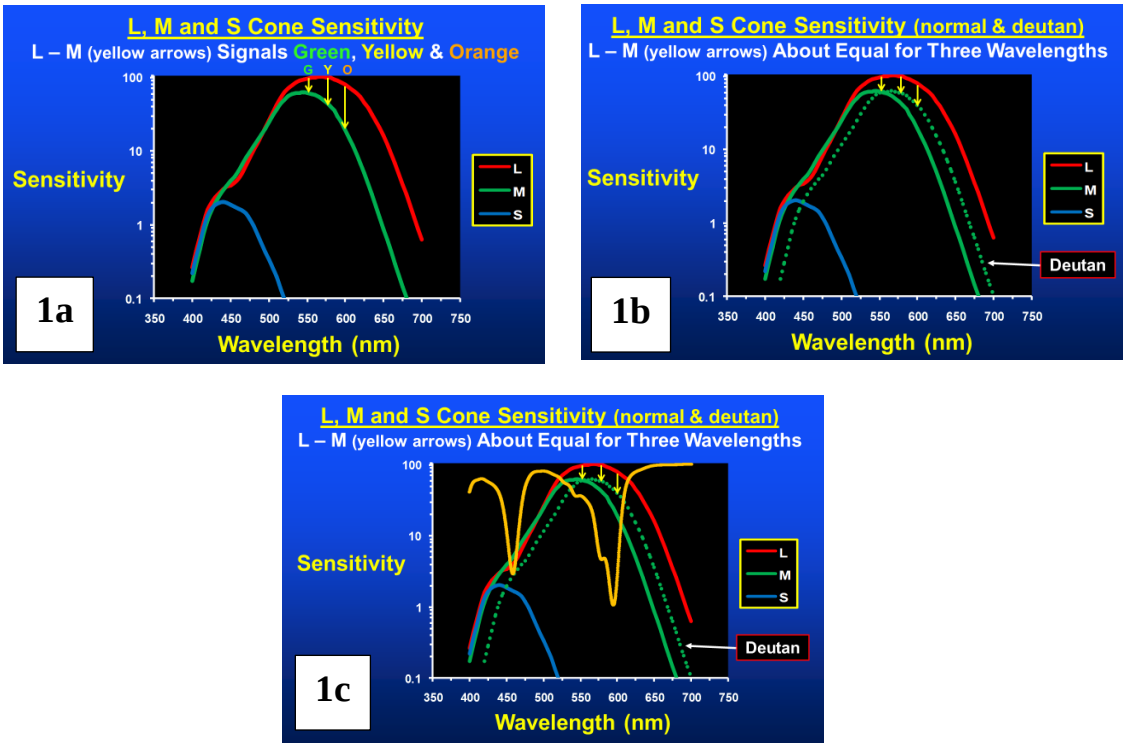
Most recently, CCLs have been designed to address the shift in photopigment peaks by introducing notch filters which better separate the anomalous and normal peaks producing more significant differences in stimulation to L and M cones thereby enhancing color vision (shown diagrammatically in Figure 1c). Werner et al.[2] used a suprathreshold red-green discrimination task to show that eight CVDs who wore the new CCLs for one week showed significant improvement in this task even when not wearing the CCLs, indicating a possible neural adaptive change, possibly due to amplification of the cone signals. Rabin et al.[17,18] replicated these findings for cone specific stimuli both at threshold and suprathreshold levels in a diverse group

of 13 subjects with CVD (Figure 2) and extended it up to 1 year to assess longer-term effects of CCL wear with a variation of daily wearing times.

These neural adaptive findings obtained with objective psychophysical methods such as cone CS, color naming, and cone specific VEPs have re-revitalized CCL research. Coupling these methods with well-established standardized color vision and/or electrophysiology tests and functional neuroimaging extends our functional color vision performance and perception assessment scope.[19-21] Overall, a better understanding of neural pathways involved with these color-specific tasks can have future clinical, occupation, and research applications.[22]

**Figure 1**

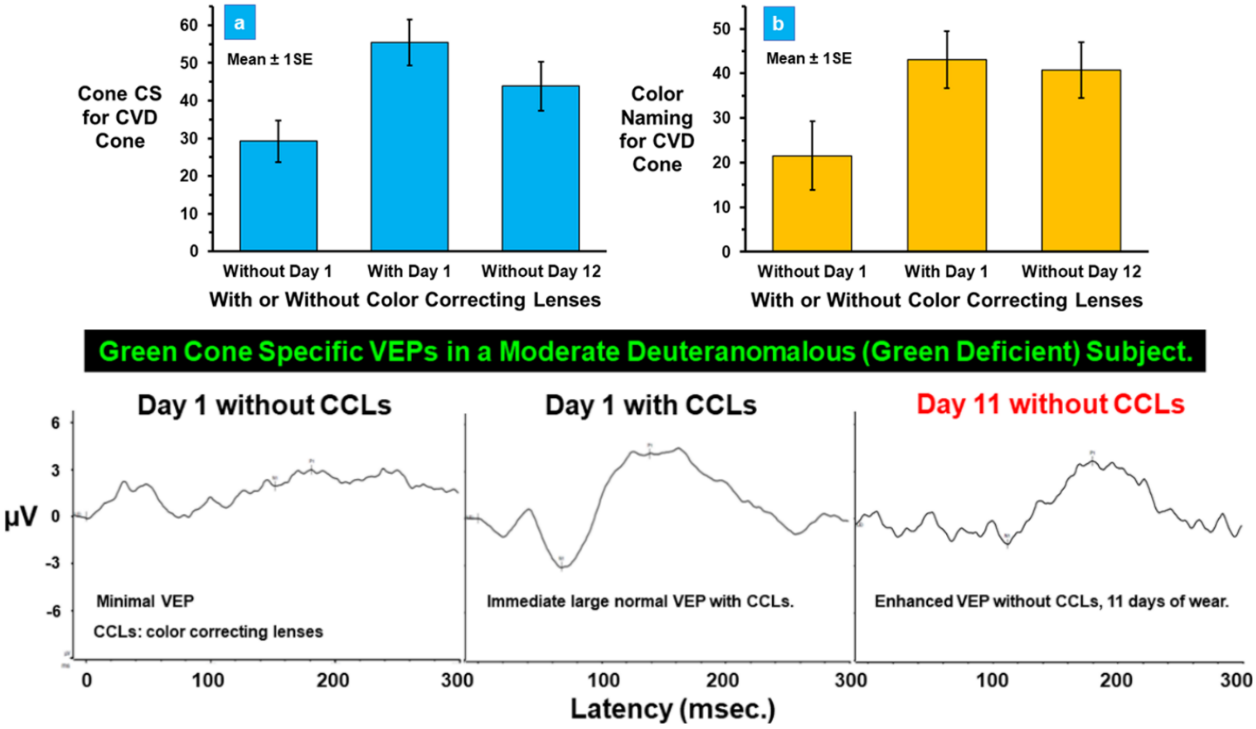
Cone Sensitivity in CVNs and CVDs with Superimposed Notch Filter




1a: Color perception depends on the difference in the stimulation of at least two cone types indicated by different differences (L-M, vertical arrows) for three colors (G, Y, O). 1b: The M-cone is shifted toward the L cone as in deuteranomaly. The arrows are now the same size, and the colors cannot be discriminated. 1c: The CCL introduces notch filters that exaggerate differences between anomalous and normal cones improving color vision.

**Figure 2**

Immediate and Long-Term Neuro-adaptive Effects of Color Correcting Lenses




Immediate and 12-day improvement in cone specific threshold and suprathreshold testing with CCLs (Rabin J, Silva F, Trevino N, et al.). The left top panel (a) shows the immediate improvement in cone CS with CCLs and the long-term improvement even without wearing CCLs. The top right panel (b) shows similar findings for color naming (CN). The bottom panel shows the immediate and long-term improvement in green cone VEPs for a deuteranomalous (green cone deficient) CVD. Performance enhancement in color deficiency with color-correcting lenses. Eye (Lond). 2022;36(7):1502-1503. doi:10.1038/s41433-021-01924-0).[17]

### *Purpose of Current Study*

This longitudinal study focused on long-term impacts of CCLs on hereditary CVDs cone contrast, color naming, and cone specific VEPs[14,15] for one year with minimal habitual wear.

## Methodology

### *Subjects*

Nine CVD subjects (age 34±16; 14-67 years old; 6 deuteranomalous, 3 protanomalous) from our thirteen existing CVD subjects in the short-term study (age 32±14, 13 – 66 years old; 9 deuteranomalous, 4 protanomalous) volunteered to participate in the one-year longitudinal study. Subjects' color vision status was confirmed by the Ishihara, Oculus HMC Anomaloscope (put in site for Oculus), and cone CS. All subjects provided written informed consent in accordance with our IRB-approved protocol, and all data were collected in accordance with the Declaration of Helsinki and its revisions.

### *Procedures and Materials*

Each participant was given CCLs appropriate for their CVDs (and was tested without and with CCLs at baseline, 4, 8, and 12 days followed by 3, 6, and 12 months). Each participant was provided a log sheet to document daily hours worn and any subjective observations during the extended wearing period. The mean wear time at 12 days was approximately 2.5 ± 1.8 hours per day and about 1.1 ± 0.9 hours per day at the one-year mark. Not all subjects could complete all follow-up visits (Table 1) due to schedule conflicts, unforeseen circumstances, and/or no perceived improvement/benefits with CCLs (subject dropout).

**Table 1**

Subject Visits for Longitudinal Study of Color Correcting Lenses

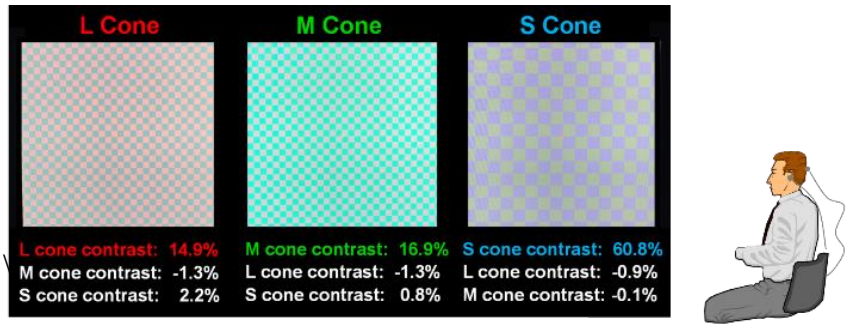
| | Day 1 | Day 4 | Day 8 | Day 12 | 3 Months | 6 Months | 12 Months | |
|---|---|---|---|---|---|---|---|---|
| EC1 | | X | X | | | | X | 57% |
| EC2 | | | | | | X | | 85.70% |
| EC6 | | | | | | | | 100% |
| EC7 | | | | | | | | 100% |
| EC9 | | | | | | X | X | 71.42% |
| EC14 | | | | | | | | 100% |
| EC5 | | | | | | | | 100% |
| EC8 | | | | | | | | 100% |
| EC13 | | | | | X | X | | 71.42% |
| | 100% | 88.90% | 88.90% | 100% | 88.90% | 66.70% | 77.80% | |
| | | | | | | | | |
| X = Missed Visits | | | | | | | | |

9 out of 13 participants volunteered for the longitudinal study with variable visits.

Cone CS was measured binocularly with the cone contrast test (CCT, Innova Systems, Inc.), the newly developed Cone Contrast Naming Test (CCNT, Ch. 1), color naming (CN) with the CCNT, and cone specific visual evoked potentials (VEPs, Figure 3). The test sequence and wear of CCLs during testing were randomized across subjects and testing.

**Figure 3**

Pattern Onset Cone-Specific VEPs




Pattern onset cone specific VEPs (75 onsets, 2x/sec.) were recorded from each subject over the course of one year with and without CCLs. L-, M- and S-cone specific checks appear on a grey field 2x/sec. and both VEP latency to the first negative trough and amplitude of the trough to subsequent peaks quantified the VEP response (doi:10.1167/tvst.5.3.8,[14] doi:10.1111/cxo.12567[15]).

### *Statistical Analysis*

ANOVA, post-hoc paired t tests, and regression analyses were conducted to show trends across time, both with and without CCLs.

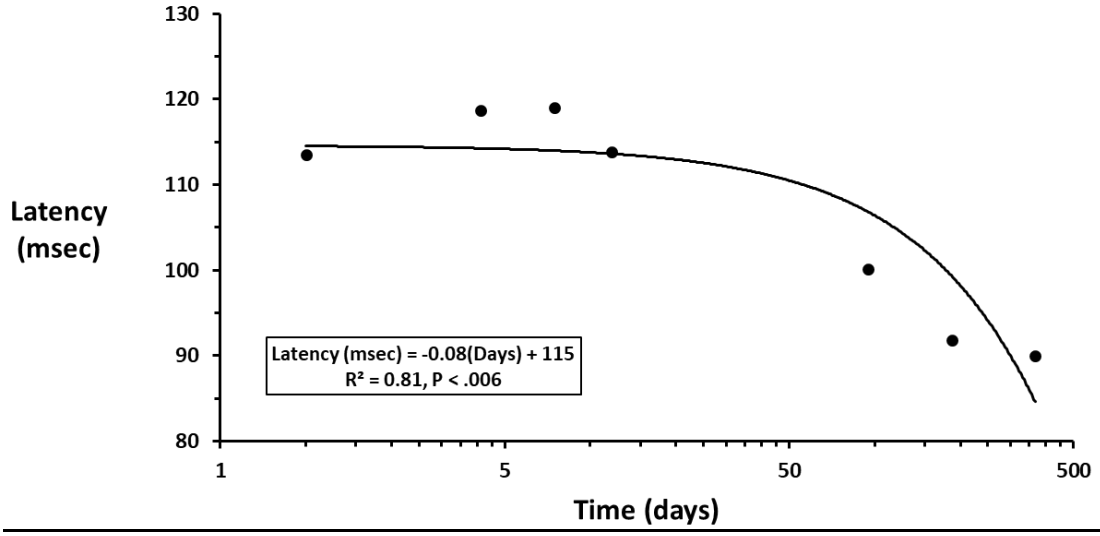
## Results

Our short-term study found both immediate and long-term color threshold (cone contrast) and suprathreshold (color naming and cone specific VEPs) improvement even after CCL removal (Figure 2).[7,8] This trend steadily increased during the year. More specifically, overall VEP latency decreased (Figure 4a-c) and VEP amplitude increased (Figure 5a-c) for the CVD deficient cone but remained constant for their respective normal cone. This supports Werner and colleagues' finding that wearing CCLs can improve color vision over time (12 days) even when tested without CCLs,[2] extends this improvement over a considerable duration (1 year) and adds cone specificity, which did not change for CVD normal cones serving as a within-subject control for findings reported herein.

Importantly, even without wearing the CCLs, mean cone specific VEP latency decreased with time over the course of one year for the deficient cone type (e.g., M cone in deutans, L cone in protans; $r^2 = 0.81$, $P < .006$) as seen in Figure 4a. These findings without CCLs point to a neural adaptive effect over an extended period. A similar effect was observed while wearing CCLs, but this did not reach significance ($r^2 = 0.60$, $P = .13$), suggesting a ceiling effect with the present CCLs as seen in Figure 4b.

**Figure 4a**

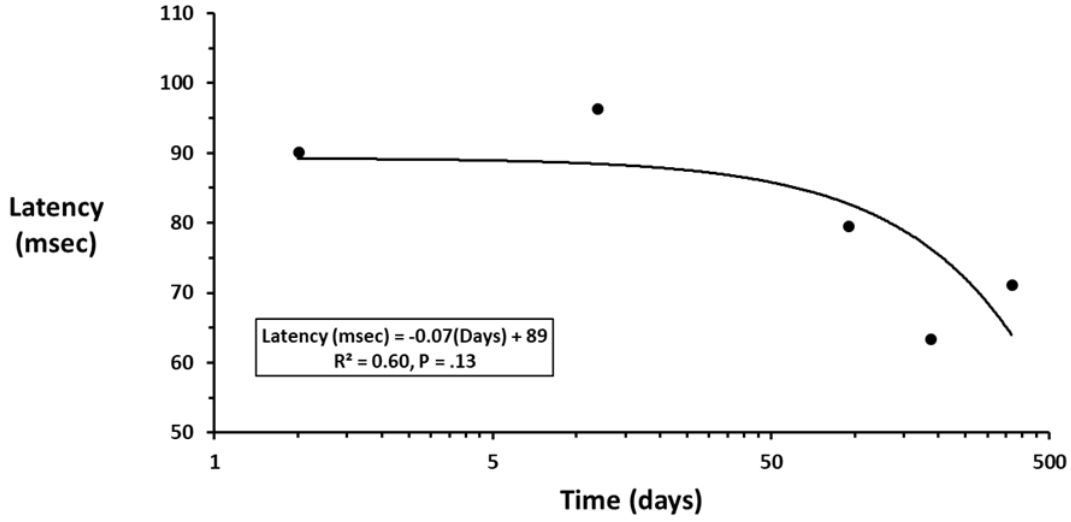
VEP Latency vs Time without CCLs




VEP latency decreased significantly over a period of one year even when tested without CCLs at each time interval.

**Figure 4b**

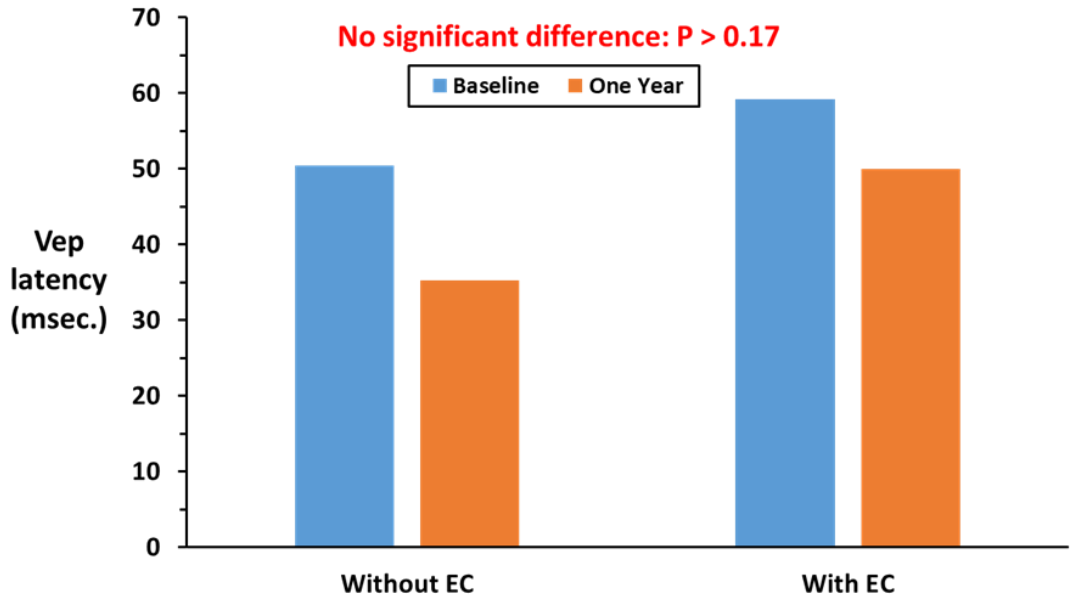
VEP Latency vs Time with CCLs




Cone-specific VEP latency decreased when tested at each interval while wearing CCLs but did not reach significance, perhaps due to a latency decrease saturation effect.

**Figure 4c**

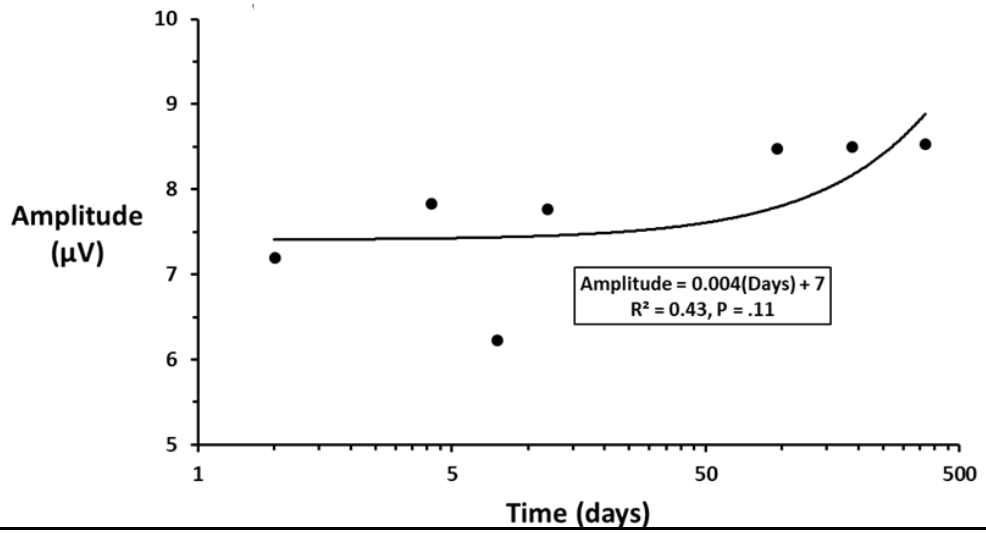
Mean CVD Normal Cone VEP Latency: Baseline vs 1 Year




The mean CVD normal cone VEP latency showed some decrease after one year of various degrees of CCL wearing time, but these results did not achieve statistical significance indicating normal cones were not impacted by the CCLs for each participant.

**Figure 5a**

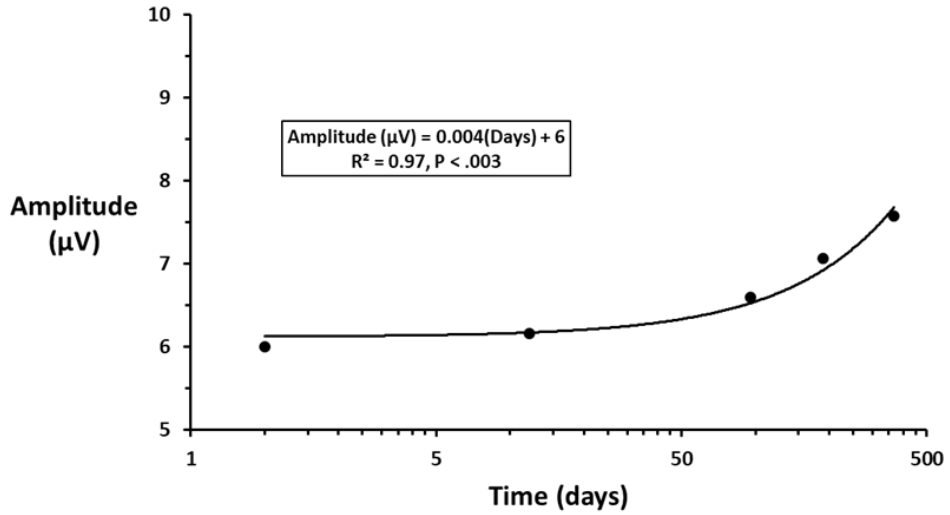
VEP Amplitude vs Time Without CCLs




Cone-specific VEP amplitude increase for CVD deficient cones without CCLs with results approaching but not achieving statistical significance.

**Figure 5b**

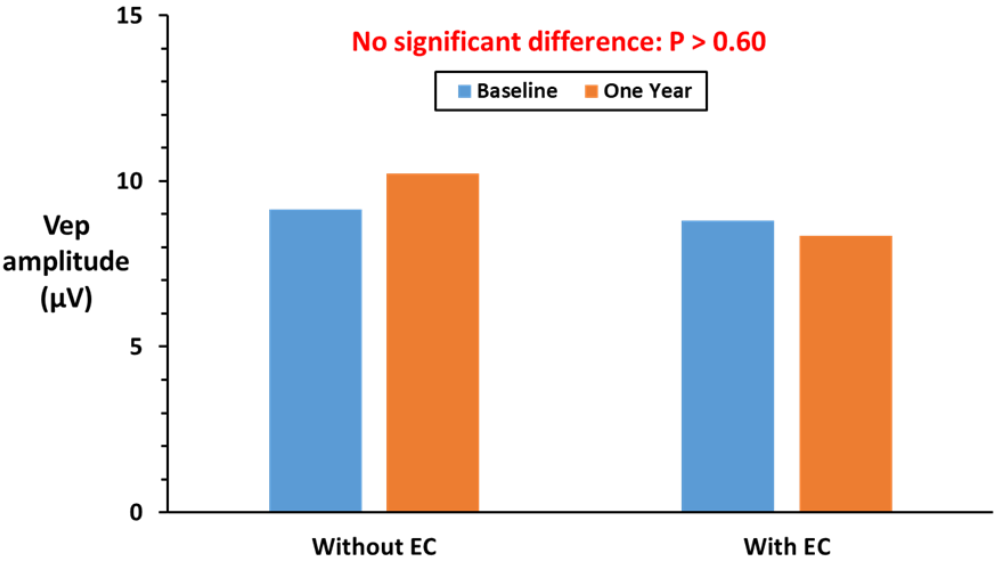
VEP Amplitude vs Time With CCLs




VEP amplitude showed significant improvement when tested with CCLs suggesting that CVDs continue to learn how to utilize the boosted contrast from the CCLs.

**Figure 5c**

Mean CVD Normal Cone VEP Amplitude: Baseline vs 1 Year

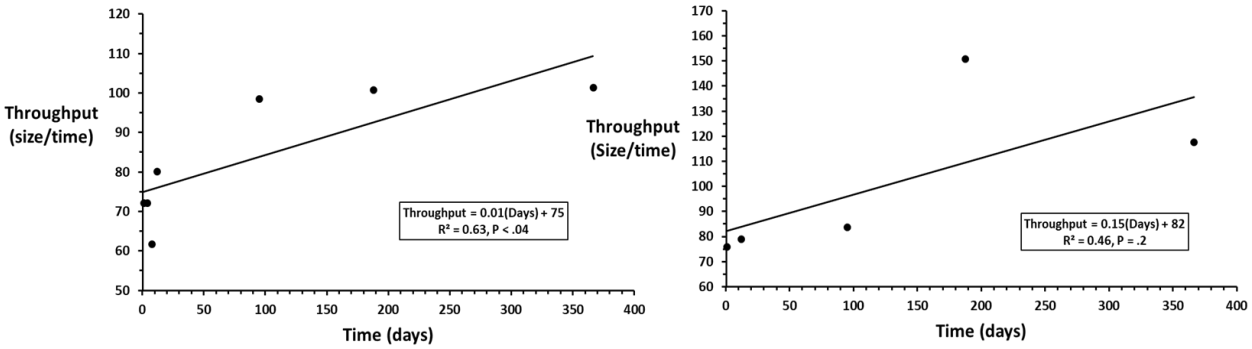



Mean VEP amplitude showed no significant change between baseline and one year for the normal cone type in CVDs.

Figure 6 combines VEP amplitude and latency into a single metric: throughput = VEP amplitude/latency; the higher the throughput, the larger and faster the response. Throughput increased significantly over a period of one year even when tested without wearing CCLs ($r^2$ = 0.63, $P$ < .04). With CCLs throughput increased as well over time but the increase did not reach statistical significance ($r^2$ = 0.46, $P$ = .2). Indeed, this novel metric revealed a positive trend 4-, 8-, and 12-days and 3-, 6-, and 12-month visits without CCLs. The steady increase in throughput during the year with minimal habitual CCL wear suggests neuro-adaptive cone specific changes well beyond the 12 days reported by Werner et al.[2] and in our initial report.[17] This objective suprathreshold metric exemplifies its utility in clinical, occupational, and research settings.

**Figure 6**

VEP Throughput vs Time Without and With CCLS



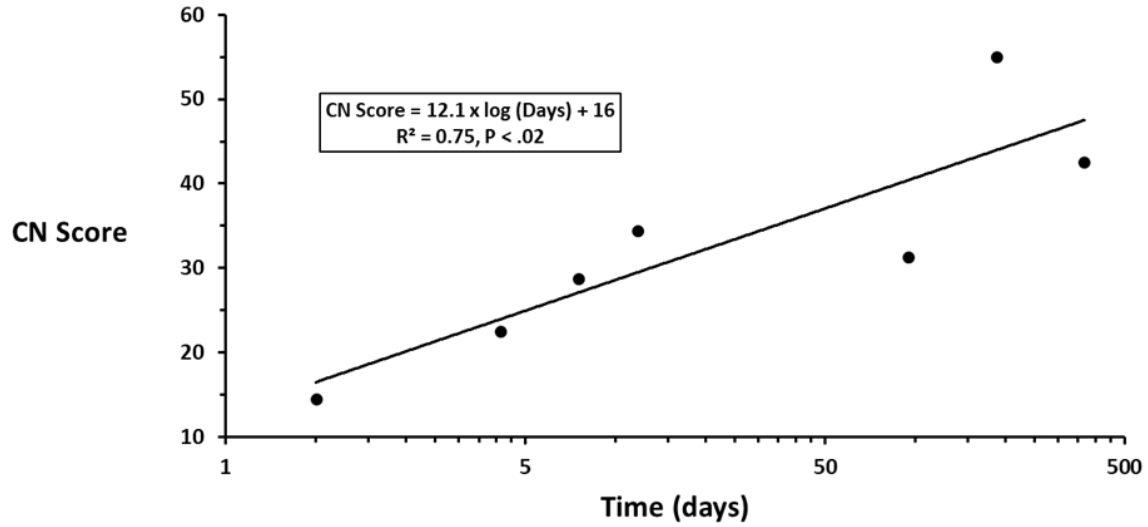

VEP Throughput as a metric to monitor neural adaptive effects over time without (left panel) and with (right panel) CCLs indicates significant positive trends during the one-year study.

In addition to VEPs, CVDs showed significant improvements over the one-year period in color naming on the CCNT test with greater improvement without wearing CCLs during testing ($r^2$ = 0.75, $P$ < .02) and a positive trend with CCLs but no improvement in color naming for the normal cone type (Figure 7). Similarly, CCNT CS showed significant improvement with time ($r^2$ = 0.67, $P$ < .03) without CCLs, a positive trend with CCLs but no improvement in CCNT CS for the normal cone type (Figure 8). The standard CCT showed increased CS with time, but the

results did not achieve statistical significance. CCT throughput (CS/average response time) improved during the one-year period approaching statistical significance (Figure 9).

**Figure 7a**

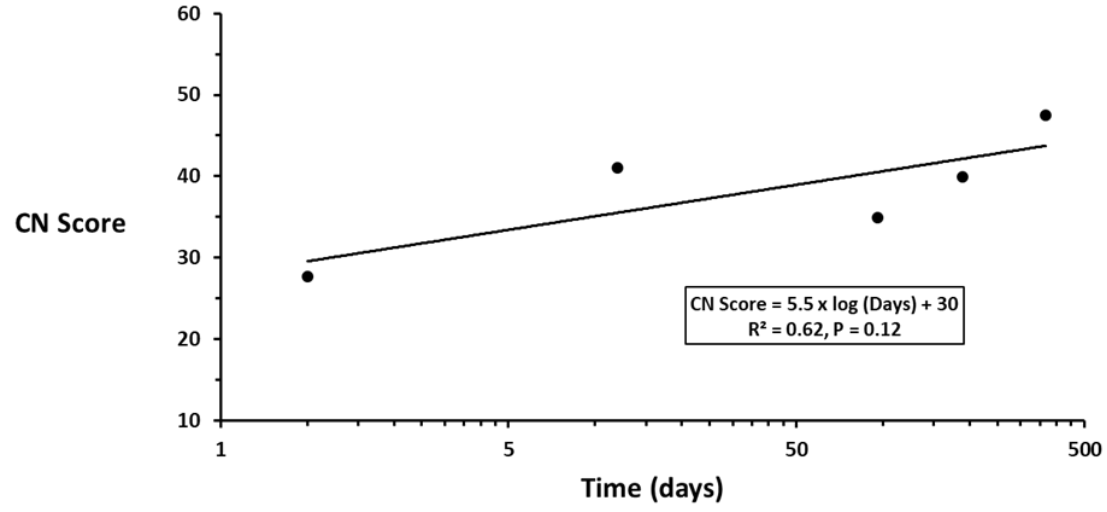
Color Naming Test CN Score vs Time Without CCLs




Improvement was observed in color naming without wearing CCLs during testing.

**Figure 7b**

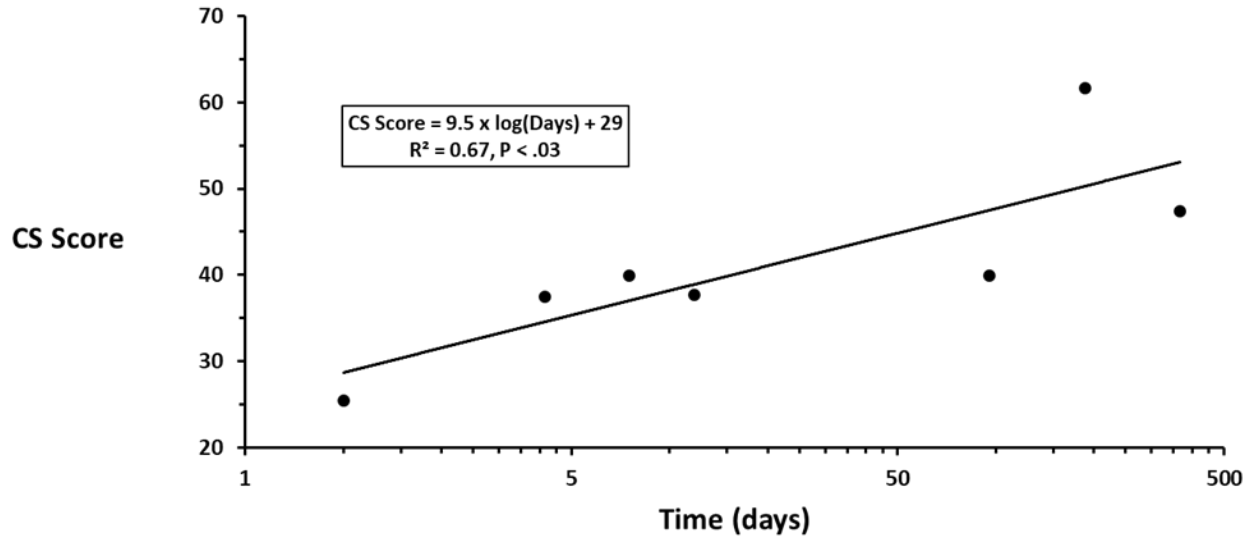
Color Naming Test CN Score vs Time With CCLs




Improvement in color naming with time approached significance while wearing the CCLs.

**Figure 8a**

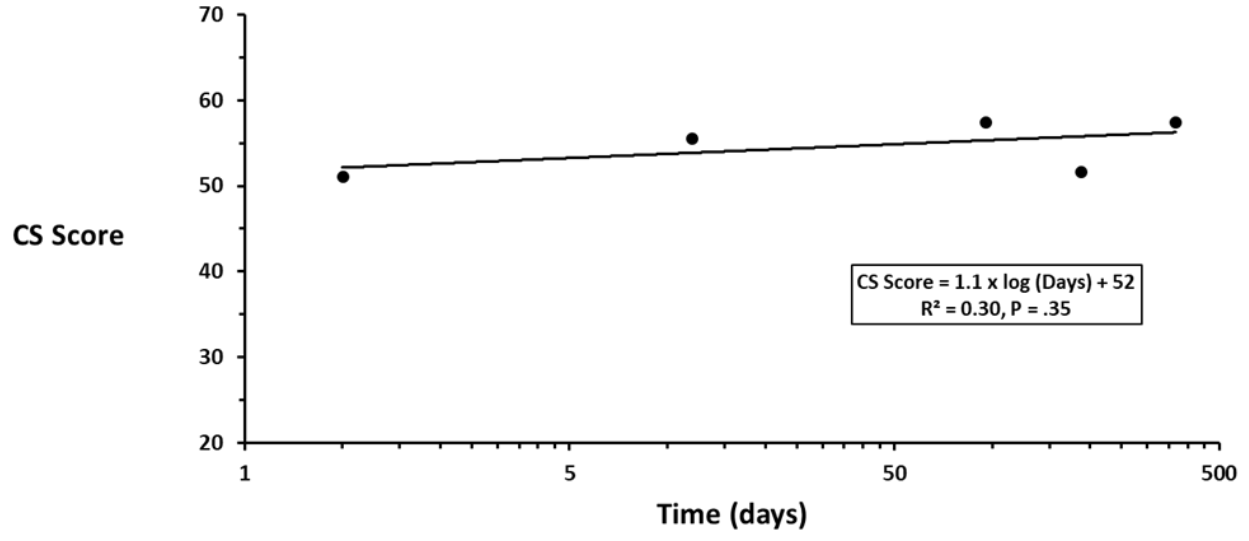
Color Naming Test CS Score vs Time Without CCLs




CCNT CS score increases significantly with time without wearing CCLs during testing.

**Figure 8b**

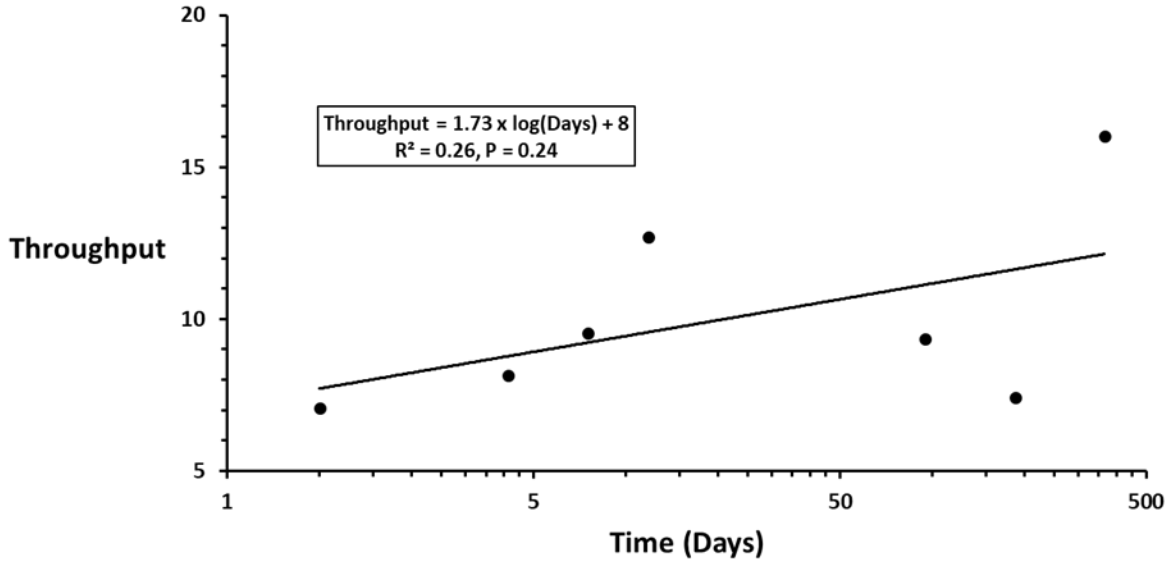
Color Naming Test CS Score vs Time With CCLs




CCNT CS score increases slightly with time when tested with CCLs, but the increase does not achieve statistical significance.

**Figure 9**

Cone Contrast Test (CCT) Throughput vs Time Without CCLs




CCT throughput (CS/response time) shows a positive trend with response without being tested with CCLs emphasizing the importance of this new metric which shows high sensitivity for detection of CVD and providing a finer gradation in visual performance than CS alone.

**Discussion**

This research aimed to extend the short-term study beyond the 2-week period to see the long-term impacts of CCLs with minimal habitual wear. Our results supported Werner's findings of higher cone contrast gain amplification after CCL wear and removal and objectively confirmed persistent long-term effects with cone specific VEPs.[2,17,18] This is consistent with the proposed existing neural compensatory mechanisms that preserve the binocular visual field for in glaucoma, cognition in Alzheimer disease, and motor function in Parkinson disease.[15]

Whereas our study had a small sample size with an unequal number of protanomalous and deuteranomalous subjects, we employed objective and subjective cone specific threshold and suprathreshold measurements (CCT, CCNT, Cone specific VEPs) throughout a long-term period. Eliminating the variety of lenses for CVD-specific CCLs would have been more advantageous. This could have been accomplished with standardized CVD-specific CCLs for only indoor or outdoor use, as the outdoor CCLs decreased display luminance, potentially impacting results. Variable patient wear time, compliance, follow-up visits, dropout, and data log entry were noticeable limitations in our study that have been addressed with a double-blind, randomized clinical trial in our laboratory to be complete by 15 July 2023.

An additional protocol extending the use of CCLs for improving vision and quality of life in patients with acquired CVD from eye disease will expand our knowledge and database for real-world CCL applications. Coupling our novel composite CS + CN score metrics and throughput with functional MRI could enhance disease detection and management for a wide range of progressive acquired CVDs and diseases associated with cognitive function. Interprofessional collaborative research is essential to achieve these goals.

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## Chapter 3: The Impact of Dry Eye and Meibomian Gland Expression on Low Contrast Vision Performance

Dry eye disease (DED) is a multifactorial disease that is further divided into aqueous deficient and evaporative dry eye.[1] Meibomian gland dysfunction (MGD) significantly contributes to evaporative dry eye, resulting in tear film lipid layer abnormalities and its sequelae (i.e., visual disturbances, ocular discomfort, dryness, etc.). While visual disturbances affect the quality of life and are commonly reported by patients, there is no current gold standard for DED diagnosis, treatment, and management.[2,3]

The Tear Film and Ocular Surface Society (TFOS) broadly defined "dry eye as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which the tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles".[4] Furthermore, the International Workshop on Meibomian Gland Dysfunction recommends the following definition for MGD, "Meibomian gland dysfunction is a chronic, diffuse abnormality of meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease."[5]

Ocular surface disease (OSD) results in poor optical integrity and clarity of the cornea and is caused by many ocular conditions that impact the tear film and corneal or glandular structures.[5] Disruption of these structures can lead to poor visual acuity, contrast sensitivity, photophobia, glare, and eye fatigue.[3] The cornea is highly transparent to light in the visible range with a short-range ordering of fibril arrangement and structure that maintains corneal regularity.[6]

The corneal stroma is also crucial in regulating optimal optical clarity, and any disruptions in this process could result in light scatter.[7] Ocular signs and symptoms from DED could result in irregular astigmatism and higher-order aberrations that impact quality of life, such as night-time driving.[8] Overall, dry eye disease is a debilitating disease with extensive research focus on tear osmolarity, and inflammatory and abnormal neurological functions.[9]

Some studies have focused on standard high-contrast visual acuity, but very few on low and color cone contrast performance. Basic dry eye testing typically includes tear break up time and corneal fluorescein staining. Additional assessments such as eyelid imaging (meibography) and matrix metalloproteinase-9 (MMP-9) detection can further assist with classification of DED.[10] Proper characterization of the condition is crucial in treatment and management as everyone varies with signs and symptoms.

MMP-9 testing is rapid, with 85% sensitivity and 94% specificity.[11] It indicates the presence of the inflammatory biomarker for both symptomatic and asymptomatic patients. This combined with meibography, can provide a holistic view of the individual and better guide treatment and management per case. Over the past 50 years, meibography has undergone significant development in clinical and research practice.[12] It is non-invasive and relatively easy to use with a computer software option to reduce grading variability.[12] Meibography provides photographic documentation of the meibomian gland under specialized illumination techniques with additional features such as tear break up time (TBUT) and videography.[12,13]

Meibomian gland dropout is only a fraction of MGD, as MGD is an umbrella term that encompasses several meibomian gland disorders, ranging from congenital to acquired.[14] It is believed that MG dropout is irreversible and that dry eye therapy with warm compresses helps both the quality and quantity of lipid secreted.[14] A prospective evaluation of intense pulsed light

and MG expression showed significant improvement in signs and symptoms of DED.[15] Most studies use patient surveys, TBUT, biomicroscopy evaluation, and standard high-contrast visual acuity as outcomes, but minimal studies focus on low and cone contrast performance.[16]

Dry eye disease research for diagnosis, treatment, and management is constantly evolving.[17] MG grading with meibography, MMP-9 testing, and other novel techniques provide a holistic approach for each patient suffering from DED.[18] Such diagnostic tools can provide more individualized and precise treatment.[19-23] More studies should be conducted focusing on contrast sensitivity, glare, and issues impacting low and color contrast performance in everyday activities.

### *Purpose of Current Study*

This study focused on the impact MGD secondary to MG dropout has on visual acuity and low achromatic and chromatic contrast performance. Most importantly, a goal was to determine if minimal gland expression improved these outcomes despite MG dropout.

## Methodology

### *Subjects*

Participants (N = 40; age 36 ± 11.4; 22-60 years old; 25 females; 15 males) were students, interns, staff, faculty, administrators, patients, colleagues, and/or family members of the University of the Incarnate Word (UIW) Main Broadway and Rosenberg School of Optometry (RSO) campuses. Color vision status was confirmed by Ishihara. Inclusion criteria were 18 years or older and best corrected visual acuity 20/25 or better in the patient's preferred eye. Exclusion criteria included a history of ocular, neurological or systemic disease not controlled medically. Subjects in concurrent dry eye studies were also excluded. Subjects completed a 5-minute survey to determine eligibility criteria. All subjects provided written informed consent in accordance with our IRB-approved protocol, and all data were collected in accordance with the Declaration

of Helsinki and its revisions. Insofar as the study was prospective with an intervention, it was registered as a clinical trial (ClinicalTrials.gov Identifier: NCT05713981).

### *Procedures and Materials*

The test order for the DES with the preferred eye only before and after minimal MG expression included: high and low contrast VA (Precision Vision ®), Ishihara, CCNT, Innova CCT (cone specific color contrast sensitivity), Innova B/W CS (achromatic CS), and low contrast (6%) small (20/25) and large (20/100) VA on a calibrated Microsoft surface display at 91.44 cm in scotopic conditions. This within-subject before-after clinical trial was a single visit that lasted approximately forty-five minutes to complete.

### *Statistical Analysis*

CCT color, CCT black/white (B/W), and CCNT data scores were normally distributed (Jarque-Bera skewness-kurtosis test). Repeated-measures ANOVA, post-hoc paired t-tests, and regression analyses were conducted to compare data outcomes before and after the MGD intervention and to establish predictive relationships. Data analyses were completed for twenty-nine study participants with a summation of the upper lid (MGUL) and lower lid (MGLL) MG dropout grades greater than two. The CCNT composite score was then applied to both the subset (n = 29) and total sample size (n = 40) for validation.

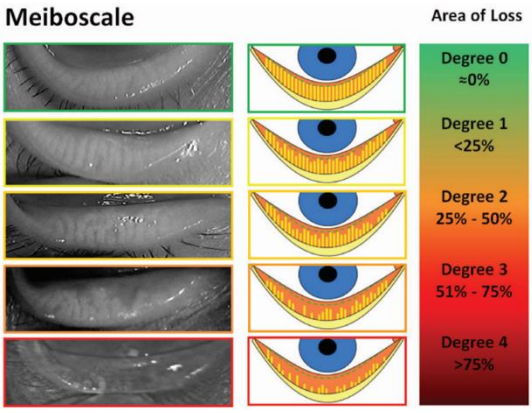
## Results

High contrast visual acuity, small letter CS, and all relevant data, including L and S cone CS, color naming composite scores, and throughput (CS/average response time), were distributed normally (Jarque-Bera skewness-kurtosis test). While the total participants (n = 40) yielded improvements in these metrics, statistical significance was limited to subjects with a composite MGD score greater than 2 for upper and lower lids (n = 29). This was based on the established

Pult 5-Grade scale for MG dropout, as seen in Figure 1.[16] Further analysis showed the well-established correlation between decreased tear break up time (TBUT) and increased meibomian gland dropout and dysfunction (Figure 2).

**Figure 1**

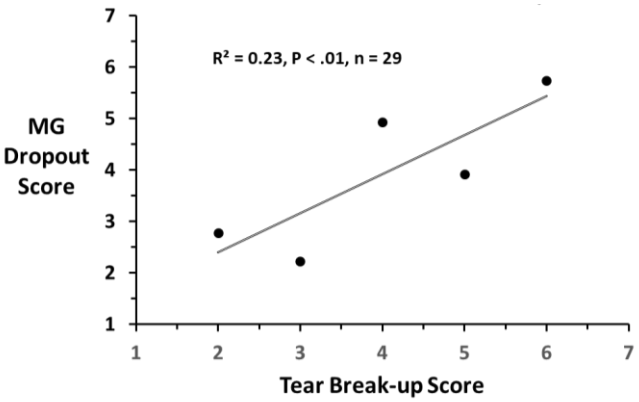
Pult 5-Grade Scale for MG Dropout




Pult H, Riede-Pult B. Comparison of subjective grading and objective assessment in meibography. Cont Lens Anterior Eye. 2013 Feb;36(1):22-7. doi: 10.1016/j.clae.2012.10.074. Epub 2012 Oct 27.[17]

**Figure 2**

MG Dropout vs Tear Break Up Time Scores

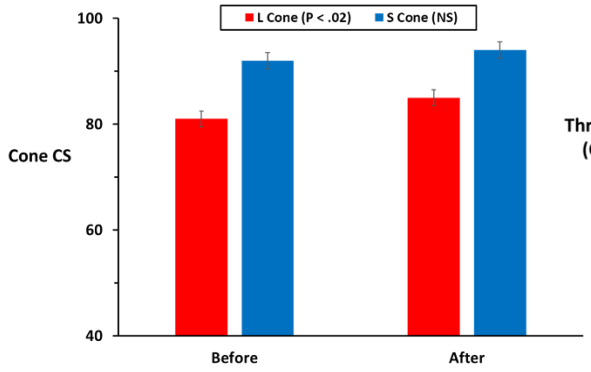



MGUL and MGLL grading scores were added with data analyses completed for those with summation scores greater than 2.

CCT L cone CS was lower before (81) compared to after MG treatment (85; mean difference = 4, 95% CI = 1-7, $P < .02$) while CCT S Cone CS differences were non-significant. However, throughput (TP: CS/average response time) was significant for both L and S cones. The mean L cone TP was 34 before and 38 post-MG expression (mean difference = 4, 95% CI = 0.6 – 6.77, $P < .03$). The mean S cone TP was 46 before and 50 post-MG expression (mean difference = 4, 95% CI = 0.1 – 8.0, $P < .05$). See Figures 3 and 4.

**Figure 3**

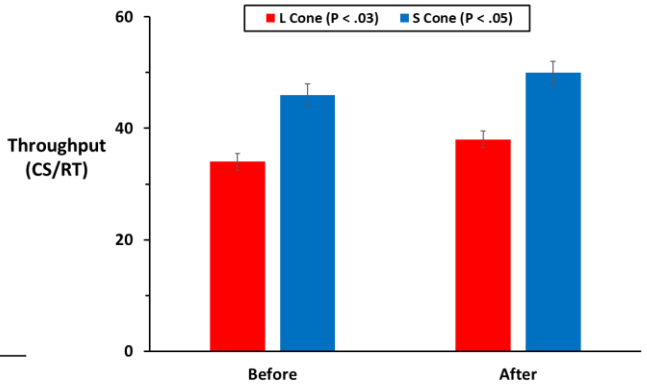
Mean L and S Cone CS
Before and After MG Expression




Improvement was observed in mean L but not S cone CS after MG expression.

**Figure 4**

Mean L and S Cone Throughput (TP)
Before and After MG Expression

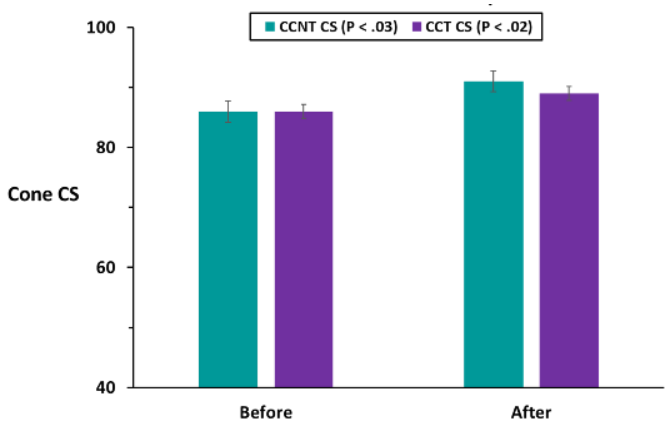



Improvement was observed in mean L and S cone TP after MG expression.

The mean of L and S cone CS was also lower for CCNT CS before (86) compared to post-MG expression (91) (mean difference 5, 95% CI = 1-8, *P* < .03). Further evaluation also revealed that the mean of L and S cone CS for CCT CS was 86 pre-MG expression and 89 post-MG expression (mean difference = 3, 95% CI = 0.5 – 5.2, *P* < .02). See Figure 5.

**Figure 5**

Mean L and S Cone CCNT vs CCT CS Before and After MG Expression

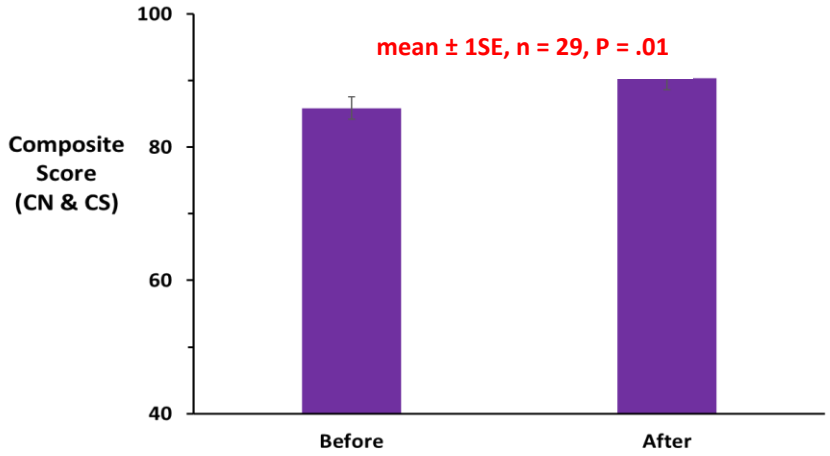



Both Mean L and S Cone CCNT and CCT CS showed improvement after MG expression.

More importantly, the CCNT composite score (mean of CS and CN) was significantly lower before (85.9) as compared to after MG treatment (90.4) with mean difference = 4.5, 95% CI = 1 – 8, *P* = .01 for our 29 subjects (Figure 6). This novel metric was further applied to the entire subject sample revealing significant improvement after MG expression (*P* = .03, Figure 7). Hence the CCNT composite score was an adequate metric to assess ALL 40 participants.

**Figure 6**

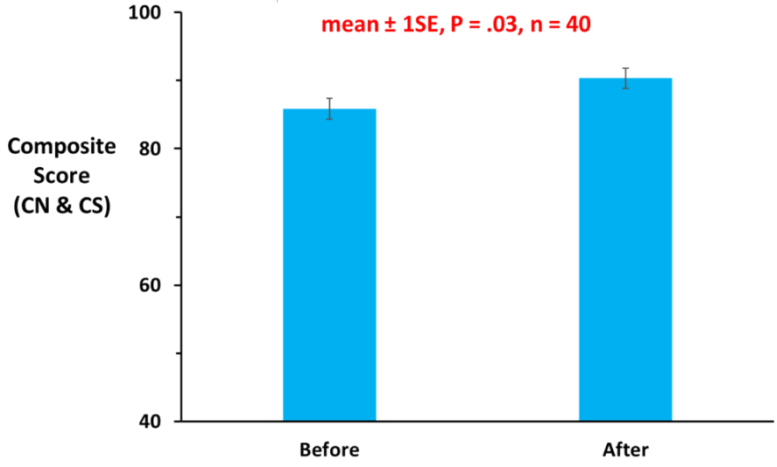
CCNT Composite Score Before and After MG Expression (n = 29)




The mean CCNT composite score is shown before and after MG expression in the 29 subjects confirmed to have MG dropout.

**Figure 6**

CCNT Composite Score Before and After MG Expression (n = 29)




The mean CCNT composite score is shown before and after MG expression in all 40 subjects.

**Discussion**

A single MG expression can improve low contrast performance in subjects identified with definitive dry eye based on MG dropout/dysfunction. Threshold chromatic contrast sensitivity (Cone CS), throughput (CS/average response time), suprathreshold color naming (CCNT) accuracy, and composite score (average of CS and CN) add another dimension to dry eye disease assessment. This, in conjunction with clinical tools such as TBUT, meibography, and InflammaDry® can provide a more comprehensive approach to dry eye assessment, treatment, and management.

Although many findings were improved after treatment, significance was minimal in the overall sample (n = 40). Identifying subjects with more definitive dry eye based on MG dropout revealed significant outcomes: correlation between TBUT and MG dropout and improvement in L and S cone CS and CN after treatment with considerable impact on throughput and the CCNT composite score. CCT Cone CS TP and CCNT composite scores have potential applications in future dry eye research.

Our relatively small sample size (n = 29), reflecting a variety of ages and genders, limits the applicability of this initial study. Moreover, the single, brief intervention with limited time between pre- and post-testing limits the relevance to the conditions of this study. It would be beneficial to conduct studies controlling for age and gender as well as additional quantitative verification of MGD dry eye compared to other sources of dry eye. The inclusion of additional MGD interventions and/or the persistence of low contrast improvements over time are needed. Nevertheless, the novel results provide a basis for utilizing color contrast as a sensitive metric of dry eye symptoms and disease, mainly when physical optical effects such as interference and scattering are considered.

The most intriguing finding is that the L and S cone sensitivity functions were impacted by MGD and improved post-MG expression. The human eye is optimized to focus wavelength at the peak of the photopic luminosity function (555 nm).[22] Dry eye impacting tear film or corneal epithelium may increase minute disruptions increasing Rayleigh scattering of light which is 10x greater for blue vs. red light,[6] a possible basis for the sensitivity of blue (S cone) metrics. Subtle stromal edema from MGD or other DED may impair destructive interference effects by altering collagen fibril separation, presumed to maintain corneal clarity. Since interference effects would be most compromised by long wavelength red light,[6] this may explain the efficacy of red (L cone) metrics. The two physical optical effects could selectively decrease the contrast of the retinal image for blue and red stimuli. Hence L and M cone CCT and CCNT testing may offer a unique metric for DED evaluation.

More importantly, the CCNT composite score that was useful in CVD color vision function evaluation is also applicable to dry eye research with advanced clinical applications for other conditions impacting low and color contrast vision function and performance. Future studies using a more diverse subject pool, including CVDs and the impact of various interventions, are needed to substantiate the efficacy of the novel results reported herein. There is vast potential to improve our understanding of DED using more sensitive and diverse metrics, as illustrated. This baseline study establishes a foundation for potential studies to incorporate a step-by-step approach for dry eye research, intervention, and management.

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# DISSERTATION DISCUSSION

The present dissertation focused on contrast sensitivity, color vision, and electrophysiology testing for functional vision assessment.[1-8] Cone-contrast, color naming, cone specific VEP tests have been shown to be useful in clinical, occupational, and vision research settings.[9-23] These extensive studies revealed novel tests that measure optimal function vision with metrics such as throughput and composite CCNT scores that enhance vision assessment.

Color vision testing is warranted and should be incorporated as an essential element of a comprehensive functional vision evaluation.[24-25] These contemporary studies highlight that computerized cone contrast testing is expedient, efficient, and easy to use in real-world scenarios. Most importantly, these metrics extend clinical applications for hereditary to acquired CVD detection, dry eye disease and management, and cognitive function evaluation capabilities.

Specific color vision metrics such as cone contrast, cone specific VEPs, VEP/CCT CS throughput, and composite CCNT score are crucial for comprehensive visual function testing. This research demonstrates the value of contrast sensitivity, color vision, and electrophysiological testing across clinical, occupational, and vision research disciplines.

It is worthwhile to repeat these studies encompassing larger sample sizes, with more evenly distributed sample demographics such as CVD to CVN ratios, male to female ratios, and age groups, to obtain more specific and precise outcomes. Coupling cone-contrast, color vision metrics (composite CCNT score, color naming), and cone specific VEPs with functional MRIs could outline the neural pathways involved in hereditary or acquired CVDs and cognitive function. Clinical applications are limitless as these studies expand color vision functional assessment and fundamental understanding of color vision perception.

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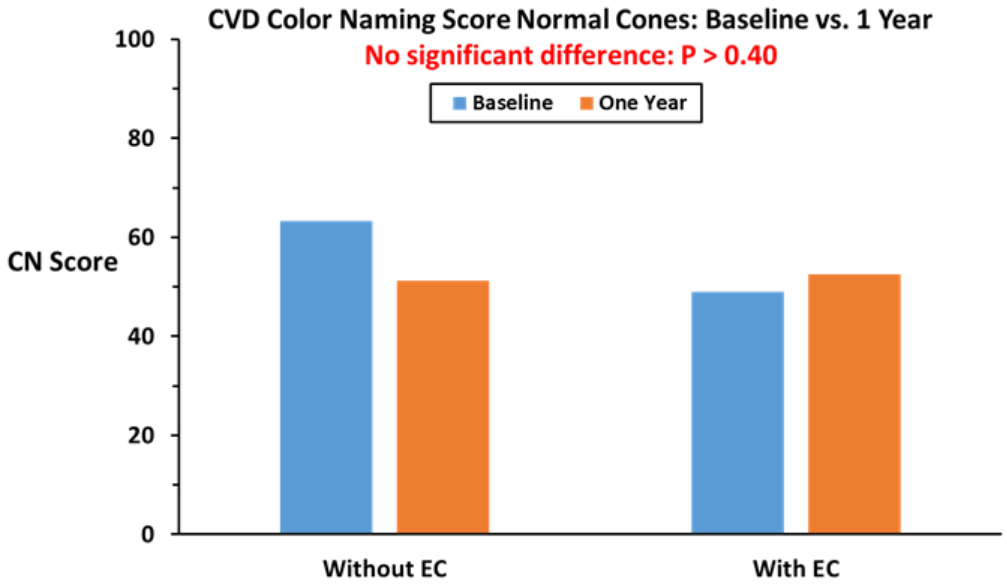
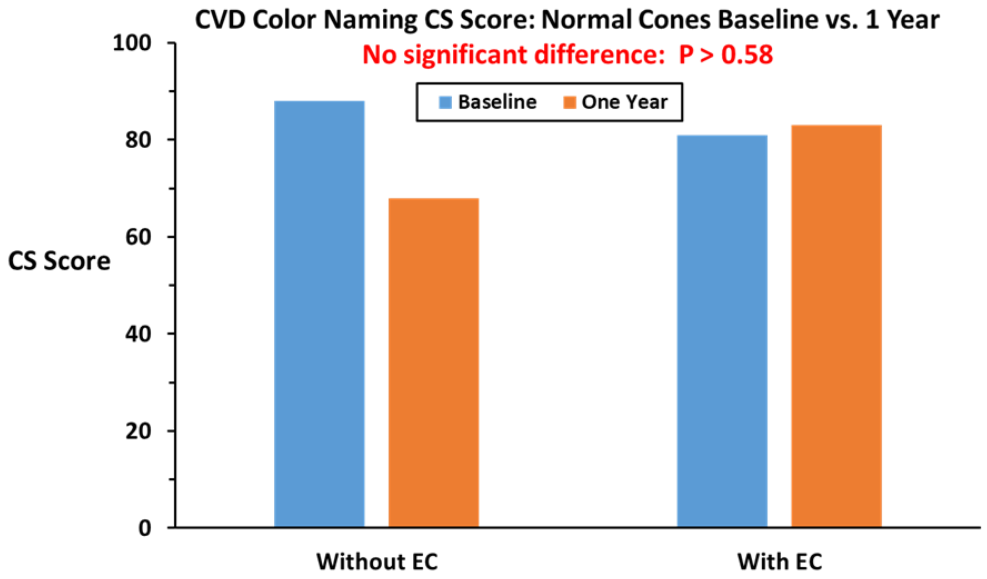
# Appendices

APPENDIX A: Chapter 2 Supplementary Figures

The figures show mean color naming and cone CS for the normal cone of CVDs at baseline and 1 year after CCL wear (e.g., L cone for deutans, M cone for protans). There is no impact on the normal cone type substantiating the importance of cone specificity in the assessment of color vision correcting lenses.



# APPENDIX B: IRB Approval Letter Short-Term CCL Protocol

UNIVERSITY OF THE INCARNATE WORD

June 22, 2021

To: Dr. Jeffrey Rabin

From: University of the Incarnate Word Institutional Review Board, FWA00009201

Jeffrey :

Your request to conduct the study titled Can Colored Glasses Improve Color Vision in Color Blindness? was approved by expedited review on 06/22/2021. Your IRB approval number is 21-06-005. You have approval to conduct this study through 6/22/2022.

**The stamped informed consent document is uploaded to the Correspondence section in the Research Ethics Review system. Please use only the stamped version of the informed consent document**.

Please keep in mind the following responsibilities of the Principal Investigator:

1. Conducting the study only according to the protocol approved by the IRB.
2. Submitting any changes to the protocol and/or consent documents to the IRB for review and approval prior to the implementation of the changes. Use the **IRB Amendment Request** form.
3. Ensuring that only persons formally approved by the IRB enroll subjects.
4. Reporting immediately to the IRB any severe adverse reaction or serious problem, whether anticipated or unanticipated.
5. Reporting immediately to the IRB the death of a subject, regardless of the cause.
6. Reporting promptly to the IRB any significant findings that become known in the course of the research that might affect the willingness of the subjects to participate in the study or, once enrolled, to continue to take part.
7. Timely submission of an annual status report (for exempt studies) or a request for continuing review (for expedited and full Board studies). Use either the **IRB Study Status Update** or **IRB Continuing Review Request** form.
8. Completion and maintenance of an active (non-expired) CITI human subjects training certificate.
9. Timely notification of a project's completion. Use the **IRB Closure** form.

Approval may be suspended or terminated if there is evidence of a) noncompliance with federal regulations or university policy or b) any aberration from the current, approved protocol.

If you need any assistance, please contact the UIW IRB representative for your college/school or the Office of Research Development.

Sincerely,

Mary Jo Bilicek
Research Compliance Coordinator
University of the Incarnate Word
(210) 805-3565
bilicek@uiwtx.edu

# APPENDIX C: IRB Approval Letter Longitudinal CCL Protocol

UNIVERSITY OF THE INCARNATE WORD

September 23, 2021

PI: Dr. Jeffrey Rabin

Protocol title: Can Colored Glasses Improve Color Vision in Color Blindness?

Jeffrey :

Your request for revisions to expedited protocol 21-06-005 was approved. The following revisions to your protocol have been approved:

- Number of approved subjects
- Duration of study

Please keep in mind these additional IRB requirements:

- Either a study status update (for exempt studies) or a request for continuing review (for expedited and full Board studies) must be completed for projects extending past one year, and closure of completed studies must be reported. Use either the **IRB Study Status Update**, **IRB Continuing Review Request** or **IRB Closure** form.
- Changes in protocol procedures must be approved by the IRB prior to implementation except when necessary to eliminate apparent immediate hazards to the subjects. Use the **IRB Amendment Request** form.
- Any unanticipated problems involving risks to subjects or others must be reported immediately.

Approved protocols are filed by their number. Please refer to this number when communicating about this protocol.

Approval may be suspended or terminated if there is evidence of a) noncompliance with federal regulations or university policy or b) any aberration from the current, approved protocol. Congratulations and best wishes for successful completion of your research. If you need any assistance, please contact the UIW IRB representative for your college/school or the Office of Research and Sponsored Projects Operations.

Sincerely,

Mary Jo Bilicek
Research Compliance Coordinator
University of the Incarnate Word
(210) 805-3565
bilicek@uiwtx.edu

# APPENDIX D: IRB Approval Letter CCNT Protocol

UNIVERSITY OF THE INCARNATE WORD

June 22, 2021

To: Dr. Jeffrey Rabin

From: University of the Incarnate Word Institutional Review Board, FWA00009201

Jeffrey :

Your request to conduct the study titled Development and Validation of the Cone Contrast Naming Test (CCNT) was approved by expedited review on 06/22/2021. Your IRB approval number is 21-06-006. You have approval to conduct this study through 6/22/2022.

**The stamped informed consent document is uploaded to the Correspondence section in the Research Ethics Review system. Please use only the stamped version of the informed consent document**.

Please keep in mind the following responsibilities of the Principal Investigator:

1. Conducting the study only according to the protocol approved by the IRB.
2. Submitting any changes to the protocol and/or consent documents to the IRB for review and approval prior to the implementation of the changes. Use the **IRB Amendment Request** form.
3. Ensuring that only persons formally approved by the IRB enroll subjects.
4. Reporting immediately to the IRB any severe adverse reaction or serious problem, whether anticipated or unanticipated.
5. Reporting immediately to the IRB the death of a subject, regardless of the cause.
6. Reporting promptly to the IRB any significant findings that become known in the course of the research that might affect the willingness of the subjects to participate in the study or, once enrolled, to continue to take part.
7. Timely submission of an annual status report (for exempt studies) or a request for continuing review (for expedited and full Board studies). Use either the **IRB Study Status Update** or **IRB Continuing Review Request** form.
8. Completion and maintenance of an active (non-expired) CITI human subjects training certificate.
9. Timely notification of a project's completion. Use the **IRB Closure** form.

Approval may be suspended or terminated if there is evidence of a) noncompliance with federal regulations or university policy or b) any aberration from the current, approved protocol.

If you need any assistance, please contact the UIW IRB representative for your college/school or the Office of Research Development.

Sincerely,

Mary Jo Bilicek
Research Compliance Coordinator
University of the Incarnate Word
(210) 805-3565
bilicek@uiwtx.edu

# APPENDIX E: IRB Approval Letter DES Protocol

UNIVERSITY OF THE INCARNATE WORD

December 16, 2022

PI: Dr. Frances Silva
Protocol Title: The Impact of Dry Eye Syndrome on Novel Metrics of Low Contrast Vision before and after Therapeutic Meibomian Gland Expression
Review Category: Expedited
Expiration Date: 12/16/2023

Project Link: https://uiw.forms.ethicalreviewmanager.com/ProjectView/Index/1283
Reference Number: 2022-1283-EXP

Hello,

Your request to conduct the above study has undergone Expedited review and is approved. The following expedited categories apply:

- Category 4: Collection of data through noninvasive procedures.

Project team:

| Team Name | Team Email | Team CITI Expiration Date | Team Role - value |
|---|---|---|---|
| Dr. Jeff C. Rabin | rabin@uiwtx.edu | 05/31/2025 | Access, obtain, or analyze identifiable private information about the subjects of the research, Co-PI or Site PI, Obtain data about the subjects of research through intervention or interaction, Obtain the informed consent of the subjects of the research |

Approved documents:

| Document Type | File Name | Date | Version |
|---|---|---|---|
| Recruitment Materials | Dry Eye Study Silva FINAL | 12/06/2022 | 2nd |
| Instruments for Data Collection | Dry Eye Study Survey | 12/06/2022 | First |
| Consent Documents | Silva MGD Cone CS and Low CS Consent Form Final Revisions | 12/06/2022 | 2nd |

Please keep in mind the following responsibilities of the Principal Investigator:

1. Conduct the study only according to the protocol approved by the IRB.
2. Submit any changes to the protocol and/or consent documents to the IRB for review and approval prior to the implementation of the changes. Use the **IRB Amendment Request** form.
3. Ensure that only persons formally approved by the IRB enroll subjects.
4. Report immediately to the IRB any severe adverse reaction or serious problem, whether anticipated or unanticipated, using the **Unanticipated Problem/Protocol Deviation Report**.
5. Report immediately to the IRB the death of a subject, regardless of the cause.
6. Report promptly to the IRB any significant findings that become known in the course of the research that might affect the willingness of the subjects to participate or continue to take part in the study.
7. Submit a request for annual continuing review when notified. Use the **IRB Continuing Review Request** form.
8. Ensure completion and maintenance of an active (non-expired) CITI human subjects training certificate for all individuals on the protocol.
9. Prompt closure of the project after completion. Use the **IRB Closure** form.
10. Data must be retained for a minimum of **3 years** after study completion.

Approval may be suspended or terminated if there is evidence of a) noncompliance with federal regulations or university policy or b) any aberration from the current, approved protocol.

If you need any assistance, please contact us.

Sincerely,

Office of Research and Graduate Studies
Research Compliance
University of the Incarnate Word
(210) 805-3565
irb@uiwtx.edu

APPENDIX F: ClinicalTrials.gov PRS Approval Letter DES Protocol

ClinicalTrials.gov PRS
Protocol Registration and Results System

**ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt**
Release Date: February 1, 2023

**ClinicalTrials.gov ID: NCT05713981**

## Study Identification

| | |
|---|---|
| Unique Protocol ID: | 2022-1283-EXP |
| Brief Title: | The Impact of Dry Eye Syndrome on Metrics of Low Contrast Vision Before and After Meibomian Gland Expression |
| Official Title: | The Impact of Dry Eye Syndrome on Novel Metrics of Low Contrast Vision Before and After Therapeutic Meibomian Gland Expression |
| Secondary IDs: | |

## Study Status

| | |
|---|---|
| Record Verification: | February 2023 |
| Overall Status: | Not yet recruiting |
| Study Start: | February 6, 2023 [Anticipated] |
| Primary Completion: | October 16, 2023 [Anticipated] |
| Study Completion: | December 16, 2023 [Anticipated] |

## Sponsor/Collaborators

| | |
|---|---|
| Sponsor: | University of the Incarnate Word |
| Responsible Party: | Principal Investigator<br>Investigator: JEFFREY CARL RABIN [rabin]<br>Official Title: Professor and Assistant Dean for Graduate Studies, Research and Assessment and Chief, Visual Neurophysiology Service<br>Affiliation: University of the Incarnate Word |
| Collaborators: | |

## Oversight

| | |
|---|---|
| U.S. FDA-regulated Drug: | No |
| U.S. FDA-regulated Device: | No |
| U.S. FDA IND/IDE: | No |
| Human Subjects Review: | Board Status: Approved<br>Approval Number: 2022-1283-EXP<br>Board Name: U of the Incarnate Word IRB #1<br>Board Affiliation: University of the Incarnate Word<br>Phone: 2108053565<br>Email: koaustin@uiwtx.edu<br>Address: |

4301 Broadway, CPO 1216
San Antonio, TX 78209

Data Monitoring: No

FDA Regulated Intervention: No

## Study Description

Brief Summary: The study aims to determine the impact of Meibomian Gland Dysfunction (MGD) dry eye on low contrast black/white (luminance) and cone color sensitivity performance and improvement in these functions after in-house non-invasive Meibomian gland (MG) expression.

Detailed Description: This study offers possible benefits from gland expression to patients and subjects in terms of clinical measurements and care associated with meibomian gland dysfunction impacting all age ranges. Prior studies show that these interventions improve dry eye symptoms with intent to improve vision, low contrast color, and B/W vision after intervention in this study.

## Conditions

Conditions: Meibomian Gland Dysfunction

Keywords:

## Study Design

Study Type: Interventional

Primary Purpose: Supportive Care

Study Phase: N/A

Interventional Study Model: Single Group Assignment

Number of Arms: 1

Masking: None (Open Label)

Allocation: N/A

Enrollment: 40 [Anticipated]

## Arms and Interventions

| Arms | Assigned Interventions |
|---|---|
| Experimental: non-invasive Meibomian gland (MG) expression<br>Baseline testing of visual acuity, contrast sensitivity, color vision, and Innova, Inc. cone and B/W low contrast vision will be measured.<br>The intervention will be standard clinical expression of Meibomian superior and inferior glands (MG) using a sterile cotton tip applicator to apply gentle pressure in a rolling motion in the direction of the MGs along the upper and lower eyelid margins to allow oil secretion of the tested eye. One drop of sterile saline will be instilled following the intervention to | Procedure/Surgery: Meibomian gland (MG) expression<br>The procedure is performed with a sterile cotton tip applicator once in the upper and lower eyelids of the subject's choosing. |

| Arms | Assigned Interventions |
|---|---|
| remove debris. The subject's visual acuity, contrast sensitivity, color vision, and Innova, Inc. cone and B/W low contrast vision will be measured before and after this intervention. | |

## Outcome Measures

Primary Outcome Measure:

1. Change in Cone Contrast Sensitivity on the Cone Contrast Test (CCT, Innova Systems, Inc.)
   This computer test measures the lowest contrast (contrast sensitivity) to see red, green and blue cone specific letters.

   [Time Frame: This test will occur prior to the intervention (Meibomian gland expression) and immediately after this intervention.]
2. Change in Response Time on Cone Contrast Test (CCT, Innova Systems, Inc.)
   This computer test measures average response time in seconds to see red, green and blue low contrast letters.

   [Time Frame: This test will occur prior to the intervention (Meibomian gland expression) and immediately after this intervention.]

Secondary Outcome Measure:

3. Change in Black White Contrast Sensitivity (Innova Systems, Inc)
   This computer test measures the lowest contrast (contrast sensitivity) to see black/white letters.

   [Time Frame: This test will occur prior to the intervention (Meibomian gland expression) and immediately after this intervention.]
4. Change in Response Time on Black White Contrast Sensitivity Test (Innova Systems, Inc) Response Time
   This computer test measures average response time in seconds to see low contrast black/white letters

   [Time Frame: This test will occur prior to the intervention (Meibomian gland expression) and immediately after this intervention.]
5. Change in Visual Acuity Test at Low Contrast (Innova Systems, Inc)
   This computer test measures the smallest low contrast letters which can be seen.

   [Time Frame: This test will occur prior to the intervention (Meibomian gland expression) and immediately after this intervention.]
6. Change in Response Time on Visual Acuity Test at Low Contrast (Innova Systems, Inc)
   This computer test measures average response time in seconds to see low contrast visual acuity letters

   [Time Frame: This test will occur prior to the intervention (Meibomian gland expression) and immediately after this intervention.]
7. Change in Sensitivity on Cone Contrast Color Naming test (CCNT)
   This computer test measures the lowest contrast (contrast sensitivity) to see red, green, blue and grey letters.

   [Time Frame: This test will occur prior to the intervention (Meibomian gland expression) and immediately after this intervention.]
8. Change in Color Naming Accuracy on Cone Contrast Color Naming test (CCNT)
   This computer test measures the accuracy of naming (number correct) low contrast red, green, blue and grey letters.

   [Time Frame: This test will occur prior to the intervention (Meibomian gland expression) and immediately after this intervention.]

Other Pre-specified Outcome Measures:

9. Change in High Contrast Visual Acuity
   The Precision Vision, Inc. Super Vision Chart will be used to measure visual acuity (smallest black letters on a white background that can be seen).

[Time Frame: This test will occur prior to the intervention (Meibomian gland expression) and immediately after this intervention.]

10. Change in Small Letter Contrast Sensitivity
The Precision Vision, Inc. Super Vision Chart will be used to measure the lowest contrast (contrast sensitivity) which can be seen using small (20/25) letters.

[Time Frame: This test will occur prior to the intervention (Meibomian gland expression) and immediately after this intervention.]

## Eligibility

| | |
|---|---|
| Minimum Age: | 18 Years |
| Maximum Age: | |
| Sex: | All |
| Gender Based: | No |
| Accepts Healthy Volunteers: | Yes |
| Criteria: | Inclusion Criteria: |

- Individuals over the age of 18 years
- Healthy individuals with reported symptoms of dry eye such as burning, stinging, fluctuating vision, inappropriate tearing, and feelings of grittiness particularly with prolonged near work

Exclusion Criteria:

- Under the age of 18
- Individuals currently using prescription eye medications for dry eye / MGD / inflammation / Infections or any other treatments.

## Contacts/Locations

Central Contact Person: Jeffery Rabin, OD, PhD
Telephone: 2108831197
Email: rabin@uiwtx.edu

Central Contact Backup: Karoline Austin, BA
Telephone: 2108053565
Email: koaustin@uiwtx.edu

Study Officials: Jeffery Rabin, OD, PhD
Study Chair
University of the Incarnate Word

Locations: **United States, Texas**
University of the Incarnate Word Rosenberg School of Optometry
San Antonio, Texas, United States, 78229
Contact: Frances Silva, OD 210-792-0033 fmsilva@uiwtx.edu
Contact: Rabin Jeffery, OD, PhD 210-883-1197 rabin@uiwtx.edu
Principal Investigator: Frances Silva, OD

## IPDSharing

Plan to Share IPD: Yes

Share IPD will facilitate data analysis and understanding for current and future research. We will share outcome and results and potentially present to local, national, and international faculty during conferences.

Supporting Information:
Study Protocol
Informed Consent Form (ICF)

Time Frame:
Data will become available upon conclusion of the study and for approximately 1 year.

Access Criteria:
URL:

## References

Citations: Gao Y, Liu R, Liu Y, Ma B, Yang T, Hu C, Qi H. Optical quality in patients with dry eye before and after treatment. Clin Exp Optom. 2021 Jan;104(1):101-106. doi: 10.1111/cxo.13111. PubMed 32618024

Szczotka-Flynn LB, Maguire MG, Ying GS, Lin MC, Bunya VY, Dana R, Asbell PA; Dry Eye Assessment and Management (DREAM) Study Research Group. Impact of Dry Eye on Visual Acuity and Contrast Sensitivity: Dry Eye Assessment and Management Study. Optom Vis Sci. 2019 Jun;96(6):387-396. doi: 10.1097/OPX.0000000000001387. PubMed 31116166

Narayanan S, Miller WL, Prager TC, Jackson JA, Leach NE, McDermott AM, Christensen MT, Bergmanson JP. The diagnosis and characteristics of moderate dry eye in non-contact lens wearers. Eye Contact Lens. 2005 May;31(3):96-104. doi: 10.1097/01.icl.0000140907.45705.e2. PubMed 15894874

Thulasi P, Djalilian AR. Update in Current Diagnostics and Therapeutics of Dry Eye Disease. Ophthalmology. 2017 Nov;124(11S):S27-S33. doi: 10.1016/j.ophtha.2017.07.022. PubMed 29055359

Yeh TN, Lin MC. Meibomian Gland Contrast Sensitivity and Specificity in the Diagnosis of Lipid-deficient Dry Eye: A Pilot Study. Optom Vis Sci. 2021 Feb 1;98(2):121-126. doi: 10.1097/OPX.0000000000001636. PubMed 33534375

Links:

Available IPD/Information: