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Al-Otaibi M. et al: 'Validity, Usefulness and Cost of RETeval System for Diabetic Retinopathy Screening' in TVST, 2017, Vol. 6., No. 3

PURPOSE: The purpose of our study was to evaluate the RETeval as a screening tool in (sight-threatening) DR compared to conventional digital retinal photographs. We further evaluated the ease of use and cost-effectiveness of DR screening using RETeval.

METHOD: Patients with diabetes attending the screening unit of King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia were evaluated by "RETeval", Amsler grid, and digital dilated fundus photography. Fundus images were evaluated by a retina specialist to determine grade of DR. The sensitivity and specificity of STDR and DR screening compared to photography were calculated, as well as "RETeval" combined with Amsler grid testing.

RESULTS/CONCLUSION: RETeval is a rapid screening device with excellent sensitivity for detecting STDR. It has potential as a first level screening tool to detect patients who require further evaluation.

Asakawa K. et al: 'New Mydriasis-Free Electroretinogram Recorded with Skin Electrodes in Healthy Subjects' in Hindawi BioMed Research International, Volume 2017, Article ID 8539747

PURPOSE: To evaluate the reproducibility and consistency of the new mydriasis-free electroretinogram (ERG) with a skin electrode (RETeval) device, to determine the normative values of parameters, and to clarify the usefulness of pupil records to colored-light stimulus

METHOD: A total of 100 eyes of 50 healthy subjects (mean age, 21.4 years) were enrolled. The diagnostic parameters obtained by the RETeval device were examined under the following conditions. The reproducibility was determined with the coefficient of variation (CV). The consistency was examined by intraclass correlation coefficients (ICCs). The mean value and the normal range were analyzed with a 95% confidence interval as the normative values of parameters. The correlation of parameters to pupil records (area ratio, constriction ratio) and flicker ERG was also examined in the diabetic retinopathy assessment protocol.

RESULTS/CONCLUSION: From the CV for each of the two measurements, the amplitude has a low reproducibility compared with the implicit time. Generally good consistency was obtained with both ERG parameters (ICCs = 0.48–0.92). Moderate correlations were found for the white-, red-, and blue-light stimulus in the area ratio and the constriction ratio, respectively ($r = 0.44–0.62$; $P = 0.010–<0.0001$). No correlation was observed between pupil and flicker parameters ($r = 0.06–0.34$; $P = 0.646–0.051$). The RETeval device was suggested as a possible screening device to detect the visual afferent diseases by evaluating in combination with the ERG recording and the colored-light pupil response.

Biswas P. et al: 'A mutation in IFT43 causes non-syndromic recessive retinal degeneration' in Human Molecular Genetics, 2017, Vol. 26, No. 23 4741–4751

PURPOSE: The aim of this work is to identify the molecular cause of autosomal recessive early onset retinal degeneration in a consanguineous pedigree

METHOD: Seventeen members of a four-generation Pakistani family were recruited and underwent a detailed ophthalmic examination. Exomes of four affected and two unaffected individuals were sequenced. Variants were filtered using exomeSuite to identify rare potentially pathogenic variants in genes expressed in the retina and/or brain and consistent with the pattern of inheritance. Clinical analysis including electroretinography (ERG), fundus photography, and color vision was performed on four affected members (III: 1, III: 2, III: 7 and III: 8) and two unaffected members of this pedigree (III: 4 and III: 5). Patients' ERG responses were measured at 0 dB while the 30 Hz flicker responses were recorded at 0 dB to a background illumination of 17 to 34 cd/m² using LKC Technologies, Inc (Gaithersburg, MD).

RESULTS/CONCLUSION: Our studies identified a novel homozygous mutation in the ciliary protein IFT43 as the underlying cause of recessive inherited retinal degeneration. This is the first report demonstrating the involvement of IFT43 in retinal degeneration.

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Davis Q.C. et al: 'Constant luminance (cd*s/m²) versus constant retinal illuminance (Td*s) stimulation in flicker ERGs' in *Doc Ophthalmol* (2017) 134:75–87

PURPOSE: To compare the effect of variable pupil size on the flicker electroretinogram (ERG) between a stimulus having constant luminance and a stimulus having constant retinal illuminance (constant Troland) that compensates for pupil size.

METHOD: Subjects (n = 18) were tested with 12 pairs of the stimuli. The stimulus pair consisted of the ISCEV standard constant luminance stimulus (3 cd*s/m² with a 30 cd/m² background) and a constant retinal illuminance stimulus (32 Td*s with a 320 Td background) selected to provide the same stimulus and background when the pupil diameter is 3.7 mm. Half the subjects were artificially dilated, and their response was measured before and during the dilation. The natural pupil group was used to assess intra- and inter-subject variability. The artificially dilated group was used to measure the flicker ERG's dependence on pupil size.

RESULTS/CONCLUSION: With natural pupils, intra-subject variability was lower with the constant Troland stimulus, while inter-subject variability was similar between stimuli. During pupil dilation, the constant Troland stimulus did not have a dependence on pupil size up to 6.3 mm and had slightly larger amplitudes with longer implicit times for fully dilated pupils. For the constant luminance stimulus, waveform amplitudes varied by 22% per mm change in pupil diameter, or by 48% over the 2.2 mm diameter range measured in dilated pupil size. There was no difference in inter-subject variability between constant Troland natural pupils and the same subjects with a constant luminance stimulus when dilated (i.e., the ISCEV standard condition).

These results suggest that a constant Troland flicker ERG test with natural pupils may be advantageous in clinical testing. Because of its insensitivity to pupil size, constant Troland stimuli should produce smaller reference ranges, which in turn should improve the sensitivity for detection of abnormalities and for monitoring changes. In addition, the test can be administered more efficiently as it does not require artificial dilation.

Degirmenci M.F.K. et al: 'Role of a mydriasis-free, full-field flicker ERG device in the detection of diabetic retinopathy' in *Doc Ophthalmol* 2018

PURPOSE: To determine if the RETeval system can be used for the screening of diabetic retinopathy (DR) to provide early diagnosis.

METHOD: The subjects were 42 diabetic patients selectively recruited by examination of their medical records to have varying severities of DR.

We compared the DR assessment protocol results and the macular RNFL thickness among four groups.

As this study aimed to recognize patients with the risk of progressive DR, the eyes with moderate and severe nonproliferative DR (NPDR) were evaluated as a single group.

RESULTS/CONCLUSION: Our results suggest that the RETeval full-field ERG system can be used as an adjunctive tool for the mass screening of DR, while macular RNFL thickness would not be useful.

Fry E.L. et al: 'The coma in glaucoma: Retinal ganglion cell dysfunction and recovery' in *Progress in Retinal and Eye Research* 65 (2018) 77–92

PURPOSE: Retinal ganglion cell (RGC) degeneration causes vision loss in patients with glaucoma, and this has been generally considered to be irreversible due to RGC death. We question this assertion and summarise accumulating evidence that points to visual function improving in glaucoma patients with treatment, particularly in the early stages of disease. We propose that prior to death, RGCs enter periods of dysfunction but can recover with relief of RGC stress. Detecting RGC dysfunction and augmenting recovery of such 'comatosed' RGCs holds clinical potential to improve early detection of glaucoma and improve visual function.

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METHOD: Aspects of RGC injury and recovery can be broadly divided into functional and structural changes. Here, clinical and pre-clinical studies that investigate changes to RGC function and structure in glaucoma are discussed. We present evidence to address three primary questions: (1) do RGCs demonstrate dysfunction prior to cell death?; (2) if so, do RGCs have the capacity recover from dysfunction?; and (3), what factors affect RGC recovery and how might this be modulated? We then highlight directions for future work.

RESULTS/CONCLUSION: While the concept of the injured ganglion cell has been present in the glaucoma literature for decades (Spaeth, 1985), we now possess the technology to interrogate RGCs experimentally at the cellular level and use these findings to develop clinically relevant tools to diagnose and

treat RGC dysfunction in glaucoma. Clinical studies have identified that RGC dysfunction occurs early in both patients with OHT and glaucoma. This is detectable with electroretinography and may be reversible with reduction in IOP.

There is less evidence to suggest that reduction in IOP results in improved functional or structural outcomes commonly measured in the clinical setting including visual fields, ONH appearance and RNFL thickness. However, evidence that recovery does occur, in at least some patients, suggests that it may be possible to improve RGC function and improve vision with IOP lowering and points to the potential of other neuroprotective interventions.

[Fukuo M. et al: 'Screening for diabetic retinopathy using new mydriasis-free, full-field flicker ERG recording device' in *Scientific Reports* 6:36591, 2016](#)

PURPOSE: The purpose of this study was to determine whether a small, hand-held, mydriasis-free, full-field flicker electroretinographic (ERGs) device called RETeval can be used to screen for DR.

METHOD: This was a prospective, cross sectional, single-center study,(...). One hundred and eighteen eyes of 118 patients with DM and 48 eyes from 48 normal subjects were studied. The results of only the right eye were used for the statistical analyses. (...) we recorded full-field flicker ERGs with this device from 48 normal eyes and 118 eyes with different severities of DR in patients with diabetes mellitus (DM).

All of the patients with DM had comprehensive ocular examinations including measurements of the best-corrected visual acuity (BCVA), refractive error by autorefractometry, and intraocular pressure (IOP) with a non-contact tonometer. In addition, they had anterior segment examination by slit-lamp biomicroscopy. After mydriasis, fundus examinations were performed by indirect ophthalmoscopy, and color fundus photographs were recorded.

RESULTS/CONCLUSION: Our results showed that there were significant correlations between the severity of DR and the implicit times ($P < 0.001$; $r = 0.55$) and the amplitudes ($P = 0.001$; $r = -0.29$). These results suggest that the implicit times of the flicker ERGs recorded by the small, mydriasis-free ERG system can be used as an adjunctive tool to screen for DR.

[Grewal MK, Sivapathasuntharam C, Chandra S, et al. A Pilot Study Evaluating the Effects of 670 nm Photobiomodulation in Healthy Ageing and Age-Related Macular Degeneration. *JCM*. 2020](#)

PURPOSE:.. we aimed to establish the possible therapeutic effect of 670 nm light exposure on multiple visual functions and anatomical structures in healthy ageing and AMD with and without SDD to assess whether any of the tests could be reliably used in a future definitive randomized controlled trial on photobiomodulation in AMD.

METHOD: We evaluated the functional and structural effects of applying 670 nm light to 31 patients with intermediate AMD and 11 people aged 55 years or above with normal retina. The study eyes were treated daily in the morning with a 670 nm hand-held light source housed in a torch-like tube that emitted energy equivalent to 40 mW/cm² or 4.8J/ cm² for 2 min at the viewing aperture. Visual function in terms of best-corrected visual acuity, low luminance visual acuity, scotopic thresholds and rod-intercept time were compared between baseline and 1, 3, 6 and 12 months. Structural changes on optical coherence tomography OCT and colour photographs were also assessed.

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RESULTS/CONCLUSION: In normal ageing, there was an improvement in scotopic thresholds in the group with no AMD by 1.77dB ($p = 0.03$) and no other parameters showed any clinically significant change. In eyes with intermediate AMD, there was no significant improvement in any functional or structural changes at any time point up to 12 months although the compliance was good. This pilot study shows that photobiomodulation with 670 nm has no effect in patients who have already progressed to intermediate AMD.

Grace S.F. et al: 'Nonsedated handheld electroretinogram as a screening test of retinal dysfunction in pediatric patients with nystagmus' in *Journal of AAPOS* 2017

PURPOSE: To assess the feasibility, sensitivity, and specificity of nonsedated handheld cone flicker electroretinogram (ERG) as a screening tool to detect retinal dysfunction in children with nystagmus.

METHOD: A total of 71 children were enrolled.

(...) three age-matched groups: normal, nystagmus with a retinal dystrophy, and nystagmus without a retinal dystrophy. Unsedated 30 Hz cone flicker ERG responses were obtained using a handheld device (RETeval) from both eyes of each patient using skin electrode sensors after pupillary dilation.

(...) children were dilated because the device's pupil-tracking function requires cooperative fixation during examination to deliver constant retinal luminance.

(...) amplitudes and implicit times were successfully obtained in 65 (92%): 31 (mean age SD, 5.6 2.7 years; range, 1-12 years) without nystagmus and 34 with nystagmus.

RESULTS/CONCLUSION: Unsedated handheld cone flicker ERG is a feasible screening test that effectively detects retinal dysfunction in children with nystagmus. In conjunction with clinical findings, the test helps reduce the need for sedated ERG in children.

Hobby A.E. et al: 'Effect of varying skin surface electrode position on electroretinogram responses recorded using a handheld stimulating and recording system' in *Doc Ophthalmol* (2018) 137:79–86

PURPOSE: A handheld device (the RETeval system, LKC Technologies) aims to increase the ease of electroretinogram (ERG) recording by using specially designed skin electrodes, rather than corneal electrodes. We explored effects of electrode position on response parameters recorded using this device.

METHOD: Healthy adult twins were recruited from the Twins UK cohort and underwent recording of light adapted flicker ERGs (corresponding to international standard stimuli).

In Group 1, skin electrodes were placed in a "comfortable" position, which was up to 20 mm below the lid margin. For subsequent participants (Group 2), the electrode was positioned 2 mm from the lid margin as recommended by the manufacturer.

Amplitudes and peak times (averaged from both eyes) were compared between groups after age matching

and inclusion of only one twin per pair. Light-adapted flicker and flash ERGs were recorded for an additional 10 healthy subjects in two consecutive recording sessions: in the test eye, electrode position was varied from 2 to 10–20 mm below the lid margin between sessions; in the fellow (control) eye, the electrode was 2 mm below the lid margin throughout. Amplitudes and peak times (test eye normalised to control eye) were compared for the two sessions.

RESULTS/CONCLUSION: Flicker ERG amplitudes were significantly lower for Group 1 than Group 2 participants ($p = 0.0024$). However, mean peak times did not differ between groups ($p = 0.54$).

For the subjects in whom electrode position was changed between recording sessions, flash and flicker

amplitudes were significantly lower when positioned further from the lid margin ($p < 0.005$), but peak times were similar ($p > 0.5$).

Moving the skin electrodes further from the lid margin significantly reduces response amplitudes, highlighting the importance of consistent electrode positioning. However, this does not significantly affect peak times. Thus, it may be feasible to adopt a more comfortable position in participants who cannot tolerate the recommended position if analysis is restricted to peak time parameters.

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Hui F. et al: 'Optimizing a Portable ERG Device for Glaucoma Clinic: The Effect of Interstimulus Frequency on the Photopic Negative Response' in TVST, Vol 8, No 6, 2018

PURPOSE: The purpose of this study was to investigate the effect of interstimulus frequency on the photopic negative response (PhNR) in glaucoma and healthy eyes. (...). Here we show the importance of considering flash interstimulus frequency when designing ERG.

METHOD: Participants (n=20 controls, n=15 glaucoma) were recruited from the glaucoma and surgical outpatient clinics at the Royal Victorian Eye and Ear Hospital. The PhNR amplitude was measured in three ways: (1) as a minimum from the baseline to trough (BT), (2) from the b-wave peak to PhNR trough (PT), and (3) as a ratio to the b-wave (ratio).

RESULTS/CONCLUSION: An interstimulus frequency of 2 Hz was optimal for recording the PhNR, creating a good balance between testing time and signal quality. A higher frequency could be used to further shorten clinical testing times; however, this may compromise its clinical utility by dampening the PhNR.

Hui F. et al: 'Improvement in Inner Retinal Function in Glaucoma 1 in Response to Nicotinamide (Vitamin B3) Supplementation: A Crossover Randomized Clinical Trial' in medRxiv preprint, 2020

PURPOSE: To determine whether nicotinamide supplementation taken in conjunction with 48 conventional IOP-lowering therapy leads to early improvement in retinal ganglion cell 49 function in people with glaucoma.

METHOD: Crossover, double-masked, randomized clinical trial conducted between October 2017 to January 2019. Adults diagnosed and treated for primary glaucoma. Ninety-four participants assessed for study eligibility. Primary endpoint was change in inner retinal function determined a-priori as change in photopic negative response (PhNR) parameters: saturated PhNR amplitude (Vmax), ratio of PhNR/b-wave amplitude (Vmax ratio).

RESULTS/CONCLUSION: Fifty-seven participants (65.5 ± 10.0 years, 39% female) enrolled. PhNR Vmax improved beyond 95% coefficient of repeatability (COR) in 23% of participants following 12 weeks of nicotinamide versus 9% on placebo. Conversely, PhNR Vmax deteriorated in 9% on placebo and 7% on nicotinamide. Overall, Vmax improved by 14.8% [95% CI: 2.8%, 26.9%], (p=0.02) on nicotinamide and 5.2% [-4.2%, 14.6%], (p=0.27) on placebo. Vmax ratio improved on average by 12.6% [5.0%, 20.2%], (p=0.002) following nicotinamide and 3.6% [-3.4%, 10.5%], (p=0.30) on placebo. A concomitant trend for improved visual field mean deviation was observed with 27% improving ≥1dB on nicotinamide and fewer deteriorating ≥1dB (4%) compared to placebo (p=0.02). Moderate correlation was observed between PhNR and visual field change with treatment. Participants demonstrated excellent treatment adherence rates (>94%) and nicotinamide was well tolerated with minimal side effects.

Ji X. et al: 'Hand-held, dilation-free, electroretinography in children under 3 years of age treated with vigabatrin' in Doc Ophthalmol 2019

PURPOSE: The anti-epileptic drug vigabatrin is associated with reduction in light-adapted 30-Hz flicker

electroretinogram (ERG) amplitude. Ophthalmological assessments, including ERGs, monitor retinal health during vigabatrin treatment. RETeval is a hand-held ERG device adapted for dilation-free ERG assessment. To evaluate the usefulness of RETeval for vigabatrin ERG assessment, we evaluated intra-visit

reliability and clinical feasibility of RETeval ERG assessment in children under 3 years of age undergoing vigabatrin treatment.

METHOD: In this prospective study, children underwent 30-Hz flicker ERG assessment with RETeval before routine vigabatrin monitoring including sedated-ERG using the Espion E2 Colour Dome.

RESULTS/CONCLUSION: RETeval demonstrated high intra-visit reliability with responses consistent with the standard Espion ERG. RETeval may be beneficial for assessment of retinal toxicity in young children treated with vigabatrin.

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Kato K. et al: 'Effect of Pupil Size on Flicker ERGs Recorded With RETeval System: New Mydriasis-Free Full-Field ERG System' in The Association for Research in Vision and Ophthalmology, Inc.
iovs.arvojournals.org j ISSN: 1552-5783

PURPOSE: We studied whether pupil size affects the flicker electroretinograms (ERGs) recorded by RETeval, a new mydriasis-free full-field flicker ERG system.

METHOD: We studied 10 healthy subjects. The RETeval manufacturer claims that the system delivers a constant flash retinal illuminance by adjusting the flash luminance to compensate for changes in the pupil size. Two experiments were performed. First, the flicker ERG was recorded every 3 minutes after the instillation of mydriatics. Second, the flicker ERG was recorded while the subjects wore soft contact lenses with two different artificial pupil sizes.

RESULTS/CONCLUSION: The first experiment showed that as pupil size increased, the amplitudes of the fundamental component of the flicker ERG did not change significantly, but the implicit times of the fundamental component were significantly prolonged for larger pupil sizes. There was a significant positive correlation between the pupillary area and implicit time of the fundamental component ($r=0.93$, $P < 0.001$). The second experiment showed that the implicit times of the fundamental component in the flicker ERG were significantly longer with larger artificial pupil.

The results suggest that the effective retinal illuminance of the stimulus delivered by the RETeval system decreases for large pupil sizes. However, in most clinical testing situations, patients' undilated pupils will likely be sufficiently small to fall within the range for which the system delivers a stimulus of constant retinal illuminance.

Kato K. et al: 'Factors Affecting Mydriasis-Free Flicker ERGs Recorded With Real-Time Correction for Retinal Illuminance: Study of 150 Young Healthy Subjects' in IOVS ISSN: 1552-5783, 2017

PURPOSE: The purpose of this study was to determine what factors affect the fundamental components of the flicker ERGs recorded by RETeval in young healthy subjects.

METHOD: Flicker ERGs were recorded with the RETeval system from 150 eyes of 150 young healthy subjects (age, 20–29 years). Univariate and multivariate linear regression analyses were performed to identify the factors that affected the implicit times and amplitudes of the fundamental component of the flicker ERGs. The independent variables included age, sex, refractive error, axial length, and pupillary area.

RESULTS/CONCLUSION: Multivariate regression analyses indicated that a longer axial length ($P = 0.03$) and larger pupillary area ($P = 0.008$) were independent factors that were significantly associated with longer implicit times of the fundamental component of the flicker ERGs. Multivariate regression analyses also showed that the female sex ($P = 0.03$) was an independent factor, which was significantly associated with larger amplitude fundamental component of the flicker ERGs. These results indicate that the fundamental components of the RETeval flicker ERGs are significantly affected by the axial length, pupillary area, and sex of young healthy subjects.

Kita Y et al. RETeval Portable Electroretinogram Parameters in Different Severity Stages of Glaucoma. J Glaucoma. April 2020.

PURPOSE: To investigate the RETeval full field electroretinogram (ERG) parameters for accuracy of separating glaucoma and normal eyes, and correlation with glaucoma severity

METHOD: Sixty-two eyes of 62 primary open-angle glaucoma patients (visual field mean deviation [MD] range: -0.44 to -31.15 dB) and 39 eyes of 39 healthy controls underwent one RETeval test (photopic negative response protocol), optical coherence tomography (OCT) imaging, and Humphrey 30-2 visual field testing

RESULTS/CONCLUSION: Significant correlations were found between the best-performing 4 RETeval ERG parameters and the glaucoma severity measures (MD and OCT thickness parameters) for all eyes, Except for P-ratio, there was no significant difference between the AUROC values of the OCT thickness parameters (range: 0.927 to 0.938) and the 4 best-performing RETeval ERG parameters (range: 0.839 to 0.905) in the early glaucoma vs. control separation. [...] differentiating the control

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and the moderate-to-advanced glaucoma eyes, the AUROC values of the 4 best-performing RETeval ERG parameters ranged between 0.924 and 0.958, and no significant difference was found between them and those of the OCT parameters.

Liu H. et al: 'Evaluation of light- and dark-adapted ERGs using a mydriasis-free, portable system: clinical classifications and normative data' in *Doc Ophthalmol* 2018

PURPOSE: The purpose of this study was to determine the intra-visit reliability and diagnostic capability of a handheld, mydriasis-free ERG, RETeval, in comparison with the standard clinical ff-ERG by measuring responses recommended by the International Society for Clinical Electrophysiology of Vision (ISCEV). Assessing the diagnostic accuracy of the RETeval was the primary question of this study.

METHOD: 35 patients recruited (median age = 17, range 11 months–69 years) who had undergone a clinical ff-ERG according to ISCEV standards. Fifty-seven control participants (median age = 22, range 8–65 years) with no known retinal disease were recruited from the general population and underwent RETeval ERG.

RESULTS/CONCLUSION: Our study supports the finding that RETeval has a reasonable diagnostic accuracy in comparison with the clinical ff-ERG while exhibiting a high degree of sensitivity (1.00) and specificity (0.82).

The portable ERG possesses remarkable clinical reliability given adequate testing compliance, as the results demonstrated reproducibility among the control participants as well as their patient counterparts.

Maa A.Y. et al: 'A novel device for accurate and efficient testing for vision-threatening diabetic retinopathy' in *Journal of Diabetes and Its Complications* 30 (2016)

PURPOSE: To evaluate the performance of the RETeval device, a handheld instrument using flicker electroretinography (ERG) and pupillography on undilated subjects with diabetes, to detect vision-threatening diabetic retinopathy (VTDR).

METHOD: Performance was measured using a cross-sectional, single armed, non-interventional, multi-site study with Early Treatment Diabetic Retinopathy Study 7-standard field, stereo, color fundus photography as the gold standard. The 468 subjects were randomized to a calibration phase (80%), and a validation phase (20%).

RESULTS/CONCLUSION: With a sensitivity of 83%, the specificity was 78% and the negative predictive value was 99%. The average testing time was 2.3 min. (...) the RETeval device will identify about 75% of the population as not having VTDR with 99% accuracy. The device is simple to use, does not require pupil dilation, and has a short testing time.

Mahroo O. et al 'Comparison of peak times of photopic flicker electroretinogram responses recorded using conventional and portable systems in Birdshot chorioretinopathy' in *Acta Ophthalmologica, Abstracts from the 2019 European Association for Vision and Eye Research Conference 2019*

PURPOSE: Assessing disease activity in Birdshot uveitis can be challenging. The peak time of the 30 Hz flicker photopic electroretinogram (ERG) was shown to be sensitive for detecting retinal dysfunction. ERG testing is not readily available in many eye units. We investigated use of a portable device to obtain recordings in the clinic setting and compared these with conventional recordings.

METHOD: Patients underwent testing with the portable device (RETeval, LKC Technologies) and conventional equipment (Espion ColorDome, Diagnosys). For portable recordings pupils were undilated and skin electrodes used; for conventional recordings a conductive fibre electrode was used with mydriasis. Flicker ERG peak times were recorded and were deemed abnormal if they exceeded the 95th centile from a healthy cohort (>190 healthy volunteers).

RESULTS/CONCLUSION: 18 patients with Birdshot uveitis underwent recordings. Recordings with the portable device took c. 3 min and were well-tolerated. Mean (SD) age was 56.3 (12.8) years. For portable recordings, mean (SD) peak times were 30.1 (3.7) and 30.2 (3.9) ms for right and left eyes

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respectively. For conventional recordings mean (SD) peak times were 31.4 (3.9) and 31.8 (4.0) ms respectively. Peak times were significantly shorter with the portable device ($p = 0.026$ and 0.002 for right and left eyes). Correlation between devices was high (0.83 and 0.89 for right and left eyes) and highly significant ($p < 0.0001$). Strength of agreement between the two methods was good (kappa statistic 0.64; 95% CI, 0.36-0.92).

Correlation between the portable and conventional ERG recordings was high with a good level of agreement. Recordings were rapid and well-tolerated. There were significant differences in peak times between the two methods highlighting the importance of normative data specific to each device.

[Maranhao B. et al: 'Investigating the Molecular Basis of Retinal Degeneration in a Familial Cohort of Pakistani Decent by Exome Sequencing' in PLOS ONE, DOI:10.1371, 2015](#)

PURPOSE: To define the molecular basis of retinal degeneration in consanguineous Pakistani pedigrees

with early onset retinal degeneration.

METHOD: A cohort of 277 individuals representing 26 pedigrees from the Punjab province of Pakistan was analyzed. Exomes were captured with commercial kits and sequenced on an Illumina HiSeq 2500. Candidate variants were identified using standard tools and analyzed using exomeSuite to detect all potentially pathogenic changes in genes implicated in retinal degeneration.

RESULTS/CONCLUSION: We identified a total of nine causal mutations, including six novel variants in RPE65, LCA5, USH2A, CNGB1, FAM161A, CERKL and GUCY2D as the underlying cause of inherited retinal degenerations in 13 of 26 pedigrees.

We identified causal mutations associated with retinal degeneration in nearly half of the pedigrees investigated in this study through next generation whole exome sequencing. All novel variants detected in this study through exome sequencing have been cataloged providing a reference database of variants common in, and unique to the Pakistani population.

[Miura G. et al: Effects of cataracts on flicker electroretinograms recorded with RETeval™ system: new mydriasis-free ERG device' in BMC Ophthalmology \(2016\) 16:22](#)

PURPOSE: The purpose of this study was to evaluate the effects of cataracts on the flicker Electroretinograms (ERGs) recorded with the RETeval™ system under mydriatic-free conditions.

METHOD: This was a retrospective study of 82 eyes of 60 patients with cataracts and 52 eyes of 38 patients who were pseudophakic. Flicker ERGs were recorded with the RETeval™ system (LKC Technologies, Gaithersburg, MD) under mydriatic-free condition with skin electrodes. Flicker ERGs were elicited by white light delivered at a frequency of 28.3 Hz and intensity of 8 Td-s. The implicit times and amplitudes of the ERGs recorded from the Grade 2 cataract, Grade 3 cataract, and pseudophakic groups were compared.

RESULTS/CONCLUSION: The mean amplitude was significantly smaller in both cataract groups than the pseudophakic group (Grade 2 cataract vs pseudophakic group, $P < 0.0001$; Grade 3 cataract vs pseudophakic group, $P < 0.0001$; Grade 2 cataract vs Grade 3 cataract, $P = 0.027$).

The mean implicit times was significantly longer in both cataract groups than the pseudophakic group (Grade 2 cataract vs pseudophakic group, $P = 0.046$; Grade 3 cataract vs pseudophakic group, $P = 0.0004$; Grade 2 cataract vs Grade 3 cataract, $P = 0.0084$).

The results indicate that the presence of Grade 2 or more cataracts will affect both the amplitude and

the implicit time of the flicker ERGs. The presence of cataracts should be taken into consideration when interpreting the flicker ERG recorded with RETeval™.

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Miura G. et al: 'Flicker electroretinograms recorded with mydriasis-free RETeval system before and after cataract surgery' in *Eye* (2017) 1-5

PURPOSE: The purpose of this study is to compare the amplitudes and peak times of the flicker electroretinograms (ERGs) recorded before and after cataract surgery with the RETeval from eyes without dilation.

METHOD: Thirty-two eyes of 32 patients (77.3 ± 6.5 years) that had grade 2 Emery–Little nuclear or cortical cataract without any other abnormalities were studied. Flicker ERGs were recorded with the RETeval system under mydriatic-free conditions. Skin electrodes were used to pick-up the ERGs that were elicited by white light delivered at a rate of 28.3 Hz and intensity of 2, 8, and 32 Td-s. The amplitudes and peak times of the flicker ERGs before and after cataract surgery were compared.

SUMMARY/CONCLUSION: These results indicate that the presence of cataracts will affect both the amplitudes and the peak times of the flicker ERGs even if the cataract is mild.

The effect of lens opacity on the peak time decreased as strengthen the light intensity increased. The effect will be essentially eliminated when the stimulus intensity was equal to 32 Td-s.

Miura G. et al: 'Flicker electroretinograms of eyes with cataract recorded with RETeval system before and after mydriasis' in *Clinical Ophthalmology* 2018;12 427–432

PURPOSE: The aim of this study is to determine the effect of pupil size of eyes with cataracts on the flicker electroretinograms (ERGs) elicited and recorded with the RETeval system.

METHOD: Forty-one eyes of 41 patients (mean age, 76.5 ± 7.3 years) that had grade 2 nuclear or cortical cataract without any other abnormalities were studied. Flicker ERGs were recorded before and after mydriatic drops instillation. The ERGs were elicited by the white light delivered at the frequency of 28.3 Hz and intensities of 2, 8, and 32 Td-s. The amplitudes and the implicit times of the flicker ERGs before and after mydriasis were compared.

RESULTS/CONCLUSION: There were no significant differences between the amplitudes before and after mydriasis ($P=0.35$, 2 Td-s; $P=0.31$, 8 Td-s; $P=0.50$, 32 Td-s). There were also no significant differences between the implicit times before and after mydriasis ($P=0.86$, 2 Td-s; $P=0.98$, 8 Td-s; $P=0.95$, 32 Td-s). The mean amplitudes and implicit times of the nuclear and cortical cataracts groups before the mydriasis were also not significantly different from those after mydriasis for all stimulus intensities.

The lack of significant differences in the amplitudes and the implicit times of the flicker ERG of cataractous eyes before and after mydriasis indicated that the RETeval flicker ERGs in cataractous eyes is less affected by the pupil diameter. With our earlier study, it was assumed that the effect of cataracts on the RETeval flicker ERGs was due to the opacity of the crystalline lens, and the influence of the cataract would not be reduced or increased by mydriasis.

Miyata et al: 'Supernormal Flicker ERGs in Eyes With Central Retinal Vein Occlusion: Clinical Characteristics, Prognosis, and Effects of Anti-VEGF Agent' in *IOVS* 2018;59

PURPOSE: To determine the clinical characteristics, prognosis, and effect of anti-vascular endothelial growth factor (VEGF) agents on eyes with a central retinal vein occlusion (CRVO) with and without supernormal flicker ERG amplitudes.

METHOD: Forty-eight eyes of 48 patients with a CRVO were studied. Flicker ERGs were recorded from fully dilated eyes with the RETeval system. The amplitudes and implicit times of the fundamental component were analyzed. "Supernormal flicker ERGs" were defined as those whose amplitudes were $\pm 117\%$ of the unaffected fellow eyes. To determine the clinical characteristics of eyes with super-normal flicker ERG amplitudes, we separated the 48 CRVO eyes into three groups: nonischemic CRVO with supernormal flicker ERGs (Group A, $n=10$), nonischemic CRVO without supernormal flicker ERG (Group B, $n=28$), and ischemic CRVO (Group C, $n=10$). Then, we compared the different clinical factors among the three groups

RESULTS/ CONCLUSION: These results indicated that the supernormal flicker ERGs can be a sign of a mild degree of ischemia, and these eyes have a better prognosis. The results also suggest that the

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supernormal flicker ERG may be caused by changes in the electrical activities of retinal cells following a mild increase in the VEGF levels in eyes with CRVO.

Motz C.T. et al ' Novel detection and restorative levodopa treatment for pre-clinical diabetic retinopathy' in *Diabetes* (published online) 2020

PURPOSE: In this study, we proposed two goals: (1) to determine if a hand-held ERG device with a skin recording electrode had the sensitivity to measure OP delays in response to dim flash stimuli in persons with diabetes, without clinically detectable retinopathy and (2) to evaluate whether levodopa treatments could restore OP implicit time delays in persons with diabetes, without clinically detectable retinopathy.

METHOD: We recruited 15 control participants (male, n=12; female, n=3) between the ages of 37-69 years that had not been diagnosed with diabetes and without any confounding ocular diseases (i.e. retinitis, glaucoma, vitreous degeneration, high myopia, etc.) as verified by an eye exam within the last 6 months. To avoid difficulties when recording ERGs without dilation, patients with cataracts documented greater than 1+ nuclear sclerosis were also not included. We recruited participants with diabetes between the ages of 29-71 years (n=44, all male, Table 1) that had been identified as not having signs of retinopathy based on diabetic teleretinal screening fundus photographs from the Atlanta VA Eye Clinic in the last six months. Persons with diabetes were not included if they had any dopamine dysregulating diseases such as restless leg syndrome, Parkinson's disease, or major depressive disorder. Additionally, to avoid confounding effects as well as prevent drug interactions once treated with Sinemet, participants were excluded if they were on any dopamine enhancing drugs, such as DA agonists (i.e. bromocriptine, ropinirole, etc.) or monoamine oxidase inhibitors. Participants were tested at baseline, two days (DM group only), two weeks, and four weeks. Testing consisted of ERG recordings, uncorrected visual acuity testing, and drifting spatial contrast sensitivity thresholds. Fundus photographs of eyes from the diabetic group included in the study were over-read by a comprehensive ophthalmologist (AYM), masked to the treatment groups, and confirmed that no signs of retinopathy were present.

RESULTS/ CONCLUSION: Our results show that early retinal dysfunction in persons with diabetes is detectable prior to clinically-recognized vascular changes using a hand-held ERG device with a novel dim stimulus, a skin electrode, and no dilating drops. These data indicate that recording dim flash OP delays could be used as a screening method to detect pre-clinical diabetic retinal dysfunction. Although contrast sensitivity as well as visual acuity deficits have been shown to be decreased in diabetic rodent models as well as humans, we did not observe any changes in our study for either test. (...). The lack of visual acuity and contrast sensitivity deficits in this study may be due to the fact that the study population had no clinically detectable DR, and visual acuity changes are often not seen until after clinical DR onset

In summary, these results show that early retinal dysfunction is detectable in the diabetic retina prior to clinically recognized retinopathy using a hand-held ERG system with skin electrodes. This ERG testing approach could be used to screen persons with diabetes in primary care clinics and other non-specialty eye clinics. These findings also show that early retinal dysfunction is reversible using levodopa treatments, suggesting reduced dopamine levels underlie early retinal function deficits. The recovery of dim OP delays within two weeks of treatment demonstrate that OP delays may be sensitive to early stage retinal dysfunction and provide a means to monitor both systemic and retinal-specific treatments for DM.

Nakamura, N. et al: 'Evaluation of cone function by a handheld non-mydratic flicker electroretinogram device' in *Clinical Ophthalmology* 2016:10

PURPOSE: Determine whether a new, handheld, portable ERG device, RETeval™, can be used to screen patients for cone dysfunction.

METHOD: Thirty-five eyes of 35 patients who had reduced cone responses ascertained by a conventional ERG system using contact lens electrodes were studied. The causative diseases included achromatopsia, cone dystrophy, cone-rod dystrophy, retinitis pigmentosa, choroidal dystrophy,

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autoimmune retinopathy, and Stargardt disease. The flicker ERGs were recorded with the RETeval™ under undilated conditions with skin electrodes (stimulus strength, 3.0 cd·s/m²; frequency, 28.3 Hz), and the responses were compared to that of 50 healthy eyes.

RESULTS/ CONCLUSION: The RETeval™ has a potential of being used to screen for cone dysfunction. The entire examination takes <5 minutes and does not require pupil dilatation or a contact lens electrode. Although the flicker responses do not provide information on the scotopic functions, the RETeval™ device can be used to determine which patients require additional full-field ERG testing with dilated pupils under both scotopic and photopic conditions.

[Osigian C.J. et al: 'Assessing nonsedated handheld cone flicker electroretinogram as a screening test in pediatric patients: comparison to sedated conventional cone flicker electroretinogram' in J AAPOS 2019](#)

PURPOSE: To assess the RETeval (LKC Technologies, Gaithersburg, MD) handheld electroretinogram (ERG) device as a screening tool for cone dysfunction in pediatric patients by comparing it to conventional ERG.

METHOD: Patients scheduled for ERG under general anesthesia (GA) underwent three tests: (1) RETeval

standard 30 Hz cone flicker ERG using skin electrodes prior to GA, (2) E3 Diagnosys (Diagnosys LLC, Lowell, MA) conventional complete standard protocol full-field ERG using bipolar contact lens electrodes and handheld stimulus under GA, and (3) repeat RETeval testing under GA. The 30 Hz cone flicker amplitudes and implicit times from the three methods were compared. Negative and positive predictive values were calculated by applying a previously established 5 mV amplitude cut-off.

RESULTS/ CONCLUSION: Thirty patients ≤ 18 years of age were enrolled. Impaired conventional ERGs were found in 18 patients. Compared to conventional ERG under GA, RETeval cone flicker amplitudes were smaller before GA (mean difference, -42.2 ± 45.3 mV) and under GA (-37.1 ± 44.5 mV), likely due to skin electrode; and implicit times were shorter before GA (-1.06 ± 2.83 ms) and longer under GA (1.28 ± 4.12 ms), likely due to GA. Comparing RETeval responses before and under GA, the amplitudes were lower (-3.05 ± 6.82 mV), and implicit times were shorter (-2.25 ± 3.28 mV) before GA. Overall, the positive predictive value of the RETeval was 85%; the negative predictive value, 90%. The unsedated handheld RETeval 30 Hz cone flicker ERG is a feasible screening test for detecting cone dysfunction in pediatric patients. Full-protocol ERG is needed when screening ERG is reduced, equivocal, or clinically warranted.

[Ozaki K. et al: 'Electroretinograms recorded with skin electrodes in silicone oil-filled eyes' in PLOS ONE, May 31, 2019](#)

PURPOSE: To assess the physiology of the retina by electroretinography (ERG) with skin electrodes in eyes that had undergone vitrectomy with silicone oil (SO) tamponade.

METHOD: ERGs were recorded from eleven eyes with complex vitreoretinal disorders and from the normal fellow eyes. The affected eyes underwent pars plana vitrectomy (PPV) with SO tamponade. ERGs were recorded before and after the SO was removed. The amplitudes and implicit times of the a- and b-waves of the affected eyes were compared to those of the normal fellow eyes. In addition, the ratios of the amplitudes of the b-waves of the affected eyes to those of the fellow eyes were compared before and after the SO was removed.

The RETeval system (LKC Technologies Inc., Gaithersburg, MD; (...)) is a handheld, portable ERG device that uses skin electrodes to pick up the ERGs. The recordings can be done rapidly, and the skin electrodes reduce the risk of corneal abrasion and infections. Thus, it allows clinicians to assess the physiology of the retina shortly after any type of intraocular surgery.

These properties prompted us to evaluate the retinal function by the RETeval system in eyes filled with SO before and after the silicone oil was removed. The relationships of the ERG findings to the clinical conditions were determined.

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RESULTS/ CONCLUSION: ERGs were recordable from 7 eyes (63.6%) before the SO was removed and 11 eyes (100%) after the SO was removed. The a- and b-wave amplitudes were significantly smaller in the affected eyes than those of the fellow eyes at the baseline. The b-wave amplitude before the removal of the SO was significantly and positively correlated with that after the SO removal. The ratios of the b-waves of the affected/normal fellow eye significantly increased after the SO was removed.

The results indicate that ERGs picked up by skin electrode can be used to assess the physiology of the retina in eyes with a SO tamponade. The amplitude of the b-waves of the ERGs in silicone-filled eyes can be used to predict the amplitude after the silicone is removed.

Özmert E. et al 'Management of retinitis pigmentosa by Wharton's jelly derived mesenchymal stem cells: preliminary clinical results' in *Stem Cell Research and Therapy*, 2020 11:25

PURPOSE: The aim of this study is to determine if umbilical cord Wharton's jelly derived mesenchymal stem cells implanted in sub-tenon space have beneficial effects on visual functions in retinitis pigmentosa patients by reactivating the degenerated photoreceptors in dormant phase.

METHOD: This prospective, open-label, phase-3 clinical trial was conducted between April of 2019 and

October of 2019 at Ankara University Faculty of Medicine, Department of Ophthalmology. 32 RP patients (34 eyes) were included in the study. The patients were followed for 6 months after the Wharton's jelly derived mesenchymal stem cell administration, and evaluated with consecutive examinations. All patients underwent a complete routine ophthalmic examination, and best corrected visual acuity, optical coherence tomography angiography, visual field, multifocal and full-field electroretinography were performed. The quantitative results were obtained from a comparison of the pre-injection and final examination (6th month) values.

RESULTS/ CONCLUSION: RP is a genetic disorder that can result in blindness with outer retinal degeneration. Regardless of the type of genetic mutation, sub-tenon Wharton's jelly derived mesenchymal stem cell administration appears to be an effective and safe option. There are no serious adverse events or ophthalmic / systemic side effects for 6 months follow-up. Although the long-term adverse effects are still unknown, as an extraocular approach, subtenon implantation of the stem cells seems to be a reasonable way to avoid the devastating side effects of intravitreal/submacular injection. Further studies that include long-term follow-up are needed to determine the duration of efficacy and the frequency of application.

(...)

The mean amplitude improved in 16 Tds from 2.4 to 5.0 nv/deg² ($p = 0.01$) and in 32 Tds from 2.4 to 4.8 nv/deg² ($p = 0.01$) in the full-field flicker electroretinography results. Full field flicker electroretinography mean implicit time also improved in 16 Tds from 43.3 to 37.9 ms ($p = 0.01$).

Sheikh S.A. et al: 'Homozygous Variant in ARL3 Causes Autosomal Recessive Cone Rod Dystrophy' in *IOVS*, 2019

PURPOSE: Cone rod dystrophy (CRD) is a group of inherited retinopathies characterized by the loss of cone and rod photoreceptor cells, which results in poor vision. This study aims to clinically and genetically characterize the segregating CRD phenotype in two large, consanguineous Pakistani families.

METHOD: Funduscopy, optical coherence tomography (OCT), electroretinography (ERG), color vision, and visual acuity assessments were performed to evaluate the retinal structure and function of the affected individuals. Exome sequencing was performed to identify the genetic cause of CRD. Furthermore, the mutation's effect was evaluated using purified, bacterially expressed ADP-ribosylation factor-like protein 3 (ARL3) and mammalian cells.

RESULTS/ CONCLUSION: Fundus photography and OCT imaging demonstrated features that were consistent with CRD, including bull's eye macular lesions, macular atrophy, and central photoreceptor thinning. ERG analysis demonstrated moderate to severe reduction primarily of photopic responses in all affected individuals, and scotopic responses show reduction in two affected

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individuals. The exome sequencing revealed a novel homozygous variant (c.296G>T) in ARL3, which is predicted to substitute an evolutionarily conserved arginine with isoleucine within the encoded protein GTP-binding domain (R99I). The functional studies on the bacterial and heterologous mammalian cells revealed that the arginine at position 99 is essential for the stability of ARL3. Our study uncovers an additional CRD gene and assigns the CRD phenotype to a variant of ARL3. The results imply that cargo transportation in photoreceptors as mediated by the ARL3 pathway is essential for cone and rod cell survival and vision in humans.

Shibuya M. et al 'Electroretinographic recordings with skin electrodes to assess effects of vitrectomy gas tamponade on eyes with rhegmatogenous retinal detachment' in Scientific Reports, nature.com, (9:19948), 2019

PURPOSE: The purpose of this study was to evaluate the retinal function by electroretinograms (ERGs) recorded with the RETeval system using skin electrodes after pars plana vitrectomy (PPV) with gas tamponade in eyes with a rhegmatogeneous retinal detachment (RRD).

METHOD: Flicker ERGs were recorded from 17 eyes with an RRD before (baseline), within 2 weeks after the PPV when the size of the tamponade gas was approximately one-half of the vitreous cavity (P1), and when the gas had been completely absorbed (P2). The amplitudes of the flicker ERGs at each phase were compared to that at the baseline.

RESULTS/ CONCLUSION: We conclude that recordings the flicker ERGs with skin electrodes can be used to assess the physiology of eyes even with the vitreous cavity half-filled with the gas used to tamponade the retina.

Because ERG recordings takes only a few minutes, we believe that it is practical for the clinical use to obtain

clinically relevant information.

Another of our significant findings was that the amplitudes of the flicker ERGs at Phase 1 were positively

and significantly correlated with the amplitudes at Phase 2.

In conclusion, our results indicate that skin electrodes with the RETeval system can be used to assess the

physiological status eyes half-filled with SF6 gas. The findings can provide information on the degree of recovery of the retina a short time after the PPV. This is significant because the amplitudes of the ERGs at Phase 1 were significantly correlated with the ERGs at Phase 2.

Tang G. et al: 'Baseline Detrending for the Photopic Negative Response' in TVST, 2018, Vol. 7, No. 5

PURPOSE: The photopic negative response (PhNR) of the light-adapted electroretinogram (ERG) holds promise as an objective marker of retinal ganglion cell function. We compared baseline detrending methods to improve PhNR repeatability without compromising its diagnostic ability in glaucoma.

METHOD: Photopic ERGs were recorded in 20 glaucoma and 18 age-matched control participants. A total of 50 brief, red-flashes (1.6 cd.s/m²) on a blue background (10 photopic cd/m²) were delivered using the RETeval device. Detrending methods compared were: (1) increasing the high-pass filter from 1 to 10 Hz and (2) estimating and removing the trend with an increasing polynomial (order from 1–10) applied to

the prestimulus interval, prestimulus and postsignal interval, or the whole ERG signal. Coefficient of repeatability (COR%), unpaired Student's t-test, and area under the receiver operating characteristic curve (AUC) were used to compare the detrending methods.

RESULTS/ CONCLUSION: Most detrending methods improved PhNR test–retest repeatability compared to the International Society for Clinical Electrophysiology of Vision (ISCEV) recommended 0.3 to 300 Hz band-pass filter (COR% ± 200%). In particular, detrending with a polynomial (order 3) applied to the whole signal performed the best (COR% ± 44%) while achieving similar diagnostic ability as ISCEV band-pass (AUC 0.74 vs. 0.75, respectively). However, over-correcting with higher orders of processing can cause waveform distortion and reduce diagnostic ability.

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Baseline detrending can improve the PhNR repeatability without compromising its clinical use in glaucoma.

Tang J. et al: 'A Comparison of the RETeval Sensor Strip and DTL Electrode for Recording the Photopic Negative Response' in TVST, Vol 7, No 6, 2018

PURPOSE: To compare the RETeval sensor strip and Dawson-Trick-Litzkow (DTL) electrodes for recording the photopic negative response (PhNR) using a portable electroretinogram (ERG) device in eyes with and without glaucoma.

METHOD: Twenty-six control and 31 glaucoma or glaucoma-suspect participants were recruited. Photopic ERGs were recorded with sensor strip and DTL electrodes in random order using the LKC RETeval device.

RESULTS/ CONCLUSION: Sensor strip electrodes are a viable alternative for recording reproducible PhNRs, especially when values are normalized to the b-wave. However, DTL electrodes should be considered in cases of attenuated PhNR, or in elevated noise levels, due to its better signal-to-noise quality. Sensor strip electrodes can simplify PhNR recordings in the clinic, potentially eliminating the need for an experienced operator.

Tekavcic Pompe M., et al: 'Flicker electroretinogram recorded with portable ERG device in prematurely born schoolchildren with and without ROP' in Doc Ophthalmol 2019

PURPOSE: The purpose of this study was to compare electroretinographic (ERG) responses of preterm schoolchildren, with and without a history of retinopathy of prematurity (ROP) with those of full-term schoolchildren by using a portable ERG device (RETeval system).

METHOD: Twenty five prematurely born schoolchildren with a mean gestational age of 27 + 1/7w (range 23–30w) and a mean birth weight of 1030 g (range 580–1700 g) who were 6.9 ± 2.2 years old participated in the study (premature group). A further subdivision according to a history of ROP (ROP+ group) or its absence (ROP- group) was introduced. Twenty eight healthy full-term schoolchildren with an average age of 8.6 ± 1.9 years participated as the control group. 30-Hz flicker ERG responses were obtained, and implicit times and amplitudes were compared between the groups.

RESULTS/ CONCLUSION: Prematurely born schoolchildren exhibit longer implicit time of the 30-Hz flicker ERG response compared to controls, suggesting a possible abnormality of the retinal cone system function. Under such circumstances, portable ERG device might be used clinically as a screening tool for retinal function evaluation in prematurely born children.

Terauchi G. et al: 'Retinal function determined by flicker ERGs before and soon after intravitreal injection of anti-VEGF agents' in BMC Ophthalmology (2019) 19:129

PURPOSE: To evaluate the retinal function before and soon after an intravitreal injection of an anti-vascular endothelial growth factor (anti-VEGF) agents.

METHOD: Seventy-nine eyes of 79 patients that were treated by an intravitreal injection of an anti-VEGF agent for age-related macular degeneration (AMD), diabetic macular edema (DME), or retinal vein occlusion (RVO) with macular edema (ME) were studied. The RETeval® system was used to record 28 Hz flicker electroretinograms (ERGs) from the injected and non-injected eyes before (Phase 1, P1), within 2 h after the injection (P2), and 2 to 24 h after the injection (P3).

RESULTS/ CONCLUSION: The results indicate that an intravitreal anti-VEGF injection will increase the implicit times not only in the injected eye but also in the non-injected eye soon after the intravitreal injection.

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Ullah I. et al: 'Mutations in phosphodiesterase 6 identified in familial cases of retinitis pigmentosa' in Human Genome Variation (2016) 3, 16036; 2016

PURPOSE: In the pursuit of determining the genetic basis of autosomal recessive RP, we have collected a large cohort of volunteer participants from highly inbred families, all affected by retinal dystrophies.

METHOD: To delineate the genetic determinants associated with retinitis pigmentosa (RP), a hereditary retinal disorder, we recruited four large families manifesting cardinal symptoms of RP. We localized these families to regions on the human genome harboring the α and β subunits of phosphodiesterase 6 and identified mutations that were absent in control chromosomes.

RESULTS/ CONCLUSION: In conclusion, we report four causal mutations present in consanguineous RP families recruited from the Punjab province of Pakistan. PDE6 is necessary for regulating the concentrations of cyclic guanine monophosphate in the retina and mutations in its subunits have been associated with RP, including a pathogenic connection between PDE6B and congenital stationary night blindness. We have previously reported mutations in both PDE6A and PDE6B that are responsible for RP in our cohort of Pakistani families. We have recruited 4350 families, and of these, we have now localized 11 familial cases to PDE6 genes (PDE6A and PDE6B), suggesting that they contribute approximately 3% of the total genetic load of autosomal recessive RP in our cohort. Determining the genetic cause of RP contributes to our understanding of the disease itself and of the normal physiological function of the retina. A better understanding of the physiology and its underlying pathology will hopefully lead to improved diagnosis and treatment of RP.

Wu Z. et al: 'Photopic Negative Response Obtained Using a Handheld Electroretinogram Device: Determining the Optimal Measure and Repeatability' in TVST, Vol 5, No 4, 2016

PURPOSE: This study therefore sought to determine the test-retest repeatability of the PhNR using the novel handheld ERG system under various testing conditions (including both intra- and intersession) in normal participants, and to determine the optimal measure of the PhNR for minimizing the degree of variability after normalizing its magnitude of repeatability by its EDR. It also sought to determine whether increasing the number of recordings could improve the repeatability of the PhNR.

METHOD: Multiple ERG recordings (using 200 sweeps each) were performed in both eyes of 20 normal participants at two different sessions to compare its coefficient of repeatability (CoR; where 95% of the test-retest difference is expected to lie) between different PhNR measures and under different testing conditions (within and between examiners, and between sessions).

RESULTS/ CONCLUSION: The PhNR/B ratio was the measure that minimized variability, and its measurements using a novel handheld ERG system with self-adhering skin electrodes and the protocols described in this study were comparable under different testing conditions and over multiple recordings.

The PhNR can be measured for clinical and research purposes using a simple-to-implement technique that is consistent within and between visits, and also between examiners.

Yasuda S. et al: 'Flicker electroretinograms before and after intravitreal ranibizumab injection in eyes with central retinal vein occlusion' in Acta Ophthalmologica 2015

PURPOSE: To compare the amplitudes and implicit times of the flicker electroretinograms before and after an intravitreal injection of ranibizumab (IVR) in eyes with a central retinal vein occlusion (CRVO).

METHOD: We reviewed the medical records of 15 consecutive patients who had macular oedema secondary to CRVO and had received an IVR at the Nagoya University Hospital from November 2013 to July 2014. Flicker ERGs were recorded with both the RETeval™ system and a conventional ERG system before the IVR. One month after the IVR, recordings were repeated with only the RETeval™ system.

RESULTS/ CONCLUSION: The mean implicit times of the flicker ERGs of the affected eyes recorded with the RETeval™ system were significantly longer than that of the fellow eyes (32.2 ± 2.6 msec

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versus 28.1 ± 1.2 msec, $p < 0.001$). One month after the IVR, the implicit times of the flicker ERGs of affected eyes were significantly shortened from 32.2 ± 2.6 to 30.6 ± 2.2 msec ($p < 0.001$).

Zeng Y. et al: 'Early retinal neovascular impairment in patients with diabetes without clinically detectable retinopathy' in Br J Ophthalmol 2019

PURPOSE: To investigate the function and the corresponding neurovascular structures in patients with diabetes and without clinically detectable retinopathy.

METHOD: Sixty-six patients with type 2 diabetes without retinopathy (NOR) and 62 healthy controls were recruited. The 16 and 32 Tds flicker electroretinography (ERG) was performed using a mydriasis-free, full-field flicker ERG recording device (RETeval). The vessel density (VD) of superficial capillary plexus (SCP) and deep capillary plexus (DCP), FD300 and ganglion cell complex (GCC) thickness in the macula were quantified using optical coherence tomography angiography (OCTA). The retinal nerve fibre layer (RNFL) thickness and the radial peripapillary capillary (RPC) density in the peripapillary area were also measured with OCTA.

RESULTS/CONCLUSION: Functional and structural impairments have already started in diabetic retina even in the absence of visible retinal lesions.

After Bonferroni correction, increased implicit time of 16 and 32 Tds light stimuli was significantly correlated with decreased VD of SCP in both parafovea and perifovea regions, and increased implicit time of 32 Tds light stimuli was significantly correlated with VD of DCP in perifovea area.

Zeng Y. et al: 'Retinal vasculature–function correlation in nonproliferative diabetic retinopathy' in Doc Ophthalmol. 2019

PURPOSE: To compare and correlate retinal microcirculation and function in patients with non-proliferative diabetic retinopathy (NPDR).

METHOD: Thirty-three healthy controls (33 eyes), 36 diabetic patients with no clinically detectable retinopathy (NDR, 36 eyes) and 101 patients (101 eyes) with NPDR (35 mild NPDR, 34 moderate NPDR, 32 severe NPDR) were involved in the study. We used optical coherence tomography angiography (OCTA) to quantify the macular vessel density (VD) of superficial capillary plexus (SCP), deep capillary plexus (DCP) and foveal density in a 300 μ m region around foveal avascular zone. Retinal function was assessed by a mydriasis-free, full-field flicker electroretinogram (FERG) recording device, and the amplitudes and implicit time were recorded. The association between microvascular parameters and FERG results was analyzed with stepwise multiple linear regression model.

RESULTS/ CONCLUSION: Decreased amplitudes and delayed implicit time, as well as lower parafoveal/perifoveal VD in both SCP and DCP, were found in NDR group and NPDR groups compared with the control group (all $p < 0.05$). Specifically, the FERG parameters and microvascular indices were comparable between NDR group and mild NPDR group (all $p > 0.05$). However, compared to mild NPDR, the reduction in FERG amplitude was more pronounced than the reduction in parafoveal VD (both SCP and DCP) in severe NPDR. Stepwise multiple linear regression analyses showed that delayed implicit time was significantly correlated with increased age and decreased VD of parafoveal region in both SCP and DCP in patients with NPDR. Meanwhile, decreased amplitude was significantly associated with decreased VD of parafoveal region in both SCP and DCP in patients with NPDR. Macular VD in both superficial and deep capillary plexus correlated with ERG implicit time and amplitude in mild-to-severe NPDR. OCTA and FERG may both be useful in detection of preclinical DR and early DR, but once the disease deteriorates, FERG may be more sensitive to discern progression of DR.

PUBLICATION HUMAN MODELS

Zeng Y. et al 'Screening for diabetic retinopathy in diabetic patients with a mydriasis-free, full-field flicker electroretinogram recording device' in *Doc Ophthalmol*, <https://doi.org/10.1007/s10633-019-09734-2>

PURPOSE: To investigate the accuracy of the RETeval full-field flicker ERG in the screening of diabetic retinopathy (DR) and vision-threatening diabetic retinopathy (VTDR) and to determine a suitable range of DR diagnostic reference for patients with type 2 diabetes mellitus (T2DM).

METHOD: This was a cross-sectional study involving 172 subjects with T2DM, including 71 subjects without clinically detectable DR (NDR), 25 subjects with mild non-proliferative diabetic retinopathy (NPDR), 24 subjects with moderate NPDR, 27 subjects with severe NPDR and 25 subjects with proliferative diabetic retinopathy (PDR). All the subjects underwent a full-field flicker ERG using the RETeval device (DR assessment protocol), which is a mydriasis-free, full-field electroretinogram (ERG) recording system. The performance of the DR assessment protocol in detecting the DR (including mild NPDR, moderate NPDR, severe NPDR and PDR) and VTDR was analyzed with the receiver operating characteristic (ROC) curve.

RESULTS/ CONCLUSION: For the detection of DR (mild NPDR, moderate NPDR, severe NPDR, PDR), the area under the ROC curve was 0.867 ($p < 0.001$, 95% CI 0.814–0.920), and the best cutoff value for DR was determined to be 20.75, with a sensitivity of 80.2% and specificity of 81.7%. Meanwhile, for the detection of VTDR, the area under the ROC curve was 0.965 ($p < 0.001$, 95% CI 0.941–0.989), and the best cutoff value was set to 23.05, with a sensitivity of 94.6% and a specificity of 88.8%. The DR assessment protocol in RETeval device was effective in screening for DR (mild NPDR, moderate NPDR, severe NPDR, PDR) and VTDR in patients with diabetes. It could be helpful in referring and managing patients with T2DM in primary health-care setting. However, caution should be taken that optimal cutoff value of DR assessment protocol may vary in different ethnic populations.

ANIMAL MODELS

Hwang C. J. et al 'Role of Retrobulbar Hyaluronidase in Filler-Associated Blindness: Evaluation of Fundus Perfusion and Electroretinogram Readings in an Animal Model' in Ophthal Plast Reconstr Surg, Vol. 35, No. 1, 2019

PURPOSE: Hyaluronic acid gel filler-associated blindness is an uncommon but devastating complication. Hyaluronidase can potentially dissolve intravascular filler and improve perfusion; however, its role in filler-associated blindness has yet to be determined. The purpose of this study is to determine the effect of retrobulbar hyaluronidase on hyaluronic acid gel-induced ophthalmic artery occlusion in a rabbit model.

METHOD: New Zealand red rabbits were used to simulate hyaluronic acid gel filler-associated vascular occlusive blindness. Ophthalmic artery occlusion and subsequent ischemia were confirmed by both retinal fundus photography and electroretinogram changes. Retrobulbar hyaluronidase 1,000 IU was injected 30 minutes after occlusion. Fundus photography and electroretinogram changes were recorded at 30, 60, 90, and 120 after administration of retrobulbar hyaluronidase.

RESULTS/ CONCLUSION: A total of 6 rabbits were used, for a total of 12 eyes. Four eyes were used as controls. Of the 8 experimental eyes, 2 eyes had recorded partial occlusion and 6 eyes had fully occluded ophthalmic arteries by angiographic evaluation. One of the partially occluded eyes demonstrated some improvement in perfusion 60 minutes after injection of retrobulbar hyaluronidase; however, electroretinogram readings remained flat over the 120-minute period of observation. Six eyes with completely occluded ophthalmic arteries showed no improvement in retinal perfusion with corresponding flat electroretinogram readings at 120 minutes following retrobulbar hyaluronidase injection. In this rabbit model, 1,000 IU of retrobulbar hyaluronidase administered 30 minutes after occlusion failed to reverse obstruction or restore function following hyaluronic acid gel occlusion of the ophthalmic artery.

Kim S et al. Safety and Biocompatibility of Aflibercept-Loaded Microsphere Thermo-Responsive Hydrogel Drug Delivery System in a Nonhuman Primate Model. 2020

PURPOSE To evaluate the safety and tolerability of a microsphere thermo-responsive hydrogel drug delivery system (DDS) loaded with aflibercept in a nonhuman primate model.

METHOD: A sterile 50 µL of aflibercept-loaded microsphere thermo-responsive hydrogel-DDS (aflibercept-DDS) was injected intravitreally into the right eye of 10 healthy rhesus macaques. A complete ophthalmic examination, intraocular pressure (IOP) measurement, fundus photography, spectral-domain optical coherence tomography (SD-OCT), and electroretinogram were performed monthly for 6 months.

RESULTS/ CONCLUSION: No abnormalities were observed in the anterior segment, and IOP remained within normal range during the study period. A small number of cells were observed in the vitreous of some macaques, but otherwise the remainder of the posterior segment examination was normal. No significant changes in retinal architecture or function as assessed by SD-OCT and histology or full-field electroretinography, respectively, were observed.

Ikeda Y. et al 'Discovery of a Cynomolgus Monkey Family With Retinitis Pigmentosa' in iovs.arvojournals.org, ISSN: 1552-5783

PURPOSE: To accelerate the development of new therapies, an inherited retinal degeneration model in a nonhuman primate would be useful to confirm the efficacy in preclinical studies.

In this study, we describe the discovery of retinitis pigmentosa in a cynomolgus monkey (*Macaca fascicularis*) pedigree.

METHOD: First, screening with fundus photography was performed on 1443 monkeys at the Tsukuba Primate Research Center. Ophthalmic examinations, such as indirect ophthalmoscopy, ERGs using RETeval, and optic coherent tomography (OCT) measurement, were then performed to confirm diagnosis.

RESULTS/ CONCLUSION: Retinal degeneration with cystoid macular edema was observed in both eyes of one 14-year-old female monkey. In her examinations, the full-field ERGs were nonrecordable and the outer layer of the retina in the parafoveal area was not visible on OCT imaging. Moreover, less frequent pigmentary retinal anomalies also were observed in her 3-year-old nephew. His full-field ERGs were almost nonrecordable and the outer layer was not visible in the peripheral retina. His father was her cousin (the son of her mother's older brother) and his mother was her younger half-sibling sister with a different father. The hereditary nature is highly probable (autosomal recessive inheritance suspected). However, whole-exome analysis performed identified no pathogenic mutations in these monkeys.

ANIMAL MODELS

Moshiri A. et al 'A nonhuman primate model of inherited retinal disease' in Clin Invest. 2019

PURPOSE: (...) well-defined NHP models of heritable retinal diseases, particularly cone disorders that are predictive of human conditions, are necessary to more efficiently advance new therapies for patients

METHOD: We have identified 4 related NHPs at the California National Primate Research Center with visual impairment and findings from clinical ophthalmic examination, advanced retinal imaging, and electrophysiology consistent with achromatopsia.

RESULTS/ CONCLUSION: Inherited retinal degenerations are a common cause of untreatable blindness worldwide, with retinitis pigmentosa and cone dystrophy affecting approximately 1 in 3500 and 1 in 10,000 individuals, respectively. A major limitation to the development of effective therapies is the lack of availability of animal models that fully replicate the human condition.

Particularly for cone disorders, rodent, canine, and feline models with no true macula have substantive limitations. By contrast, the cone-rich macula of a nonhuman primate (NHP) closely mirrors that of the human retina.

Genetic sequencing confirmed a homozygous R565Q missense mutation in the catalytic domain of PDE6C, a cone-specific phototransduction enzyme associated with achromatopsia in humans. Biochemical studies demonstrate that the mutant mRNA is translated into a stable protein that displays normal cellular localization but is unable to hydrolyze cyclic GMP (cGMP).

This NHP model of a cone disorder will not only serve as a therapeutic testing ground for achromatopsia gene replacement, but also for optimization of gene editing in the macula

CASE REPORTS

Asakawa K. et al 'Electroretinography and Pupillography in Unilateral Foveal Hypoplasia' in Journal of Pediatric Ophthalmology and Strabismus, Volume 53 · E26-E28, Posted June 7, 2016

PURPOSE: The authors describe a 3-year-old boy with unilateral foveal hypoplasia and an absence of other ocular or systemic findings. Electroretinography obtained predominantly affecting cones. Laterality of pupil constriction to red but not to blue light was observed. The colored-light pupil response can be used to predict the retinal state.

METHOD: We have recorded the pupil light response in a patient with unilateral foveal hypoplasia in the absence of other ocular or systemic findings.

RESULTS/ CONCLUSION: One hypothesis for the laterality of pupil constriction to red light is a potential effect on melanopsin-containing retinal ganglion cells in the eye with predominantly affecting cones. Our results provide the functional data supporting this hypothesis. However, the differential diagnosis may include early retinal degeneration and retinopathy of prematurity.⁸ Consequently, these results indicate that the colored-light pupil response can be used to predict the retinal state in patients with foveal hypoplasia.

Eda S. et al 'A Case of Hydranencephaly in Which Ophthalmic Examinations Were Performed' in Case Rep Ophthalmol 2016;7:142–147

PURPOSE: We performed ophthalmic examinations, including optical coherence tomography (OCT), on a case diagnosed with hydranencephaly

METHOD: This case involved a female infant born at the gestational age of 35 weeks and 4 days, with the birth weight of 2,152 g, who was one of monochorionic diamniotic twins, and the identical twin died in utero at the gestational age of 24 weeks. After that, examination by fetal echo indicated that she had microcephaly and ventriculomegaly. Postnatal magnetic resonance imaging (MRI) of her head indicated microcephaly and significant enlargement of the lateral ventricle on both sides, with no obvious signs of elevated intracranial pressure. Ophthalmic examinations indicated that both of her eyes had slight light reflex, attributed to optic nerve atrophy. Examination by use of a hand-held OCT system indicated a layered structure of the retina and thinning of the ganglion cell layer. Flicker electroretinogram (ERG) examination by use of a hand-held ERG system indicated an almost normal wave. However, no clear visual reaction was observed when she was 10 months old.

RESULTS/ CONCLUSION: Our findings in this case of hydranencephaly revealed that even though the outer layer functions of the patient's retina were maintained, extensive damage to her cerebral cortex resulted in poor visual function.

Endres D. et al 'Heteroplasmic Point Mutation in the MT-ND4 Gene (m.12015T>C; p.Leu419Pro) and Comorbid Polyglandular Autoimmune Syndrome Type 2' in Frontiers in Immunology March 2019, Volume 10, Article 412

PURPOSE: To our knowledge, this is the first case report of a patient with MELAS syndrome with comorbid autoimmune polyglandular syndrome type 2. This aspect is clinically important, as shown in the patient's history. Addison's disease and MELAS syndrome (lactate acidosis/myopathy) share clinical features with respect to weakness, fatigue, and abdominal complaints such as nausea or diarrhea. Hence, it is important to think of both diseases when considering the differential diagnosis. Additionally, our patient was tested positive for further antibodies. It is important to recognize these immunological changes to prevent end organ damage.

METHOD: We present the case of a 25-year-old female patient with dysexecutive syndrome, muscular fatigue, and continuous headache. Half a year ago, she fought an infection-triggered Addison crisis. As the disease progressed, she had two epileptic seizures and stroke-like episodes with hemiparesis on the right side. [Following diagnostic steps were done] Psychiatric examination, Psychiatric examination, Family history, Genetic testing, Basic blood/urine analyses, Immunological blood testing, Cerebrospinal fluid analyses, Cerebral magnetic resonance imaging, magnetic resonance spectroscopy, Electroencephalography, Electromyography, Lactate ischemia test, Magnetic resonance imaging of thigh and lower leg, Muscle biopsy, Ophthalmological examinations: For visual electrodiagnostic testing light adapted electroretinogram was recorded from both eyes

CASE REPORTS

using RETeval device from LKC-Technologies. Both eyes showed normal cone function in response to the photopic-flash protocol and normal ganglion cell function with the stimulation protocol for the photopic negative response. Normative data were provided by LKC-Technologies. Heart examinations, Otorhinolaryngologic examination, Ultrasound of the carotids, Thyroid sonography, Gastroscopy, Neuropsychological tests

RESULTS/ CONCLUSION: In summary, to our knowledge this is the first case presentation of a patient with atypical MELAS syndrome presenting with a neuropsychiatric syndrome of predominantly executive dysfunction, together with a polyglandular autoimmune syndrome type 2, and a heteroplasmic point mutation in the MT-ND4 gene. The recognition of such constellations is important for further research and clinical differential diagnosis in complex neuropsychiatric cases. Screening for autoimmune alterations in those patients is important to prevent damage to end organs.

Katagiri S, Hayashi T, Nakamura M, et al. RDH5 -Related Fundus Albipunctatus in a Large Japanese Cohort. 2020

PURPOSE: To investigate clinical characteristics of *RDH5*-related fundus albipunctatus (FAP) in a Japanese cohort.

METHOD: Twenty-five patients from 22 pedigrees with *RDH5*-related FAP were studied. Ophthalmic medical records were reviewed. For genetic analysis, either Sanger sequencing of the *RDH5* gene or whole-exome sequencing was performed.

RESULTS/ CONCLUSION: In optical coherence tomography, macular involvement was observed in 12 patients (24 eyes). Ten patients (83.3%) who had good BCVA (0.10 or better) exhibited diffuse disruption of the outer retina with foveal sparing, and two patients (16.7%) exhibited diffuse disruption throughout the macula and decreased BCVA.[...] Full-field electroretinography showed extinguished or severely decreased rod responses in all 23 examined patients, whereas decreased cone responses were seen in 17 patients (73.9%).

Kumagai, T. et al 'Electroretinograms before and after extraction of large intraocular iron foreign body'

PURPOSE: We present our findings in a case with an intraocular foreign body in which the electroretinographic (ERG) findings were useful.

METHOD: Preoperative ERGs with a contact lens electrode showed reduced responses with many blinking artifacts. Lensectomy and pars plana vitrectomy were performed and a fragment of a wire brush was seen embedded in the superior nasal retina which was removed. The decimal visual acuity improved to 1.2 two weeks later. The postoperative ERG performed with a skin electrode showed reduced responses in the injured eye.

RESULTS/ CONCLUSION: We recommend that the physiology of the retina to be assessed by recording ERGs with a skin-type electrode as soon as possible after a traumatic injury to the eye.

MENTAL HEALTH

Constable P.A. et al 'Light - Adapted Electroretinogram Differences in Autism Spectrum Disorder' in Journal of Autism and Developmental Disorders, 2020

PURPOSE: The ERG offers the potential to help our understanding of neurodevelopmental and neurodegenerative conditions as a non-invasive and objective measure of retinal activity in response to brief flashes of light.

There are presently no biomarkers for ASD. Differences in the ERG waveform in ASD may help our understanding of the biology of factors contributing to ASD.

(...) the present study sought to explore the nature and frequency of differences in LA-ERGs with sufficient power in a large group of young individuals with ASD from multiple centers.

METHOD: This study comparison between children and young adults with ASD and the control group was conducted across three sites based in London (UK), New Haven (USA) and Adelaide (Australia). Light-adapted (LA) electroretinograms (ERGs) from 90 individuals with autism spectrum disorder (ASD), mean age (13.0 ± 4.2), were compared to 87 control subjects, mean age (13.8 ± 4.8). LA-ERGs were produced by a random series of nine different Troland based, full-field flash strengths and the ISCEV standard flash at 2/s on a 30 cd m⁻² white background.

RESULTS/ CONCLUSION: A random effects mixed model analysis showed the ASD group had smaller b- and a-wave amplitudes at high flash strengths ($p < .001$) and slower b-wave peak times ($p < .001$). Photopic hill models showed the peaks of the component Gaussian ($p = .035$) and logistic functions ($p = .014$) differed significantly between groups. Retinal neurophysiology assessed by LA-ERG provides insight into neural development in ASD.

The main finding is that the primary outcome, the LA ERG b-wave amplitude was reduced in the ASD group.

For the secondary outcomes, the b-wave time to peak and a-wave amplitude were delayed and reduced at the higher flash strengths respectively, along with a reduced b:a wave amplitude ratio. This large, multicenter study of children shows the LA-ERG is a potential marker for neurodevelopmental conditions such as ASD in children. By providing a reproducible, noninvasive and robust measure of CNS activity the ERG can help our understanding of the impact of genetic interaction and complexity in ASD and aid drug discovery that targets CNS development of signaling pathways common to the CNS and retina.

DeBuc D.C. et al 'Investigating Multimodal Diagnostic Eye Biomarkers of Cognitive Impairment by Measuring Vascular and Neurogenic Changes in the Retina' in Frontiers in Physiology, December 2018, Volume 9, Article 1721

PURPOSE: In this pilot study, we investigated the extent to which measures of vascular complexity and neurodegenerative changes in the retinal tissue contribute to differences in cognitive function using a low-cost multimodal approach. Our central hypothesis is that multivariate eye biomarkers reflect distinctive eye-brain signatures of cognitive impairment that might be associated with the onset and progression of cognitive decline.

METHOD: Prospective subjects with cognitive impairment were identified in a non-systematic fashion as they appeared in the clinic or identified from a population attending adult care centers and community clinics with a diagnosis of AD.

Quantification of the retinal structure and function were conducted for every subject ($n = 69$) using advanced retinal imaging, full-field electroretinogram (ERG) and visual performance exams.

Of the 69 participants, 32 had CI (46%).

RESULTS/ CONCLUSION: Our preliminary findings show that our multimodal approach to evaluating visual capacities in elderly individuals may add predictive value of early visual pathway injury associated with cognitive decline and facilitate the introduction of novel multimodal eye biomarkers for early detection of cognitive impairment at a low-cost.

(...)Also, drusen-like regions in the peripheral retina along with pigment dispersion were noted in subjects with mild CI. Functional loss in color vision as well as smaller ERG amplitudes and larger peak times were observed in the subjects with CI.

MENTAL HEALTH

Demmin D.L. et al ' Electoretinographic Anomalies in Schizophrenia' in Journal of Abnormal Psychology 2018, Vol. 127, No. 4, 417–428

PURPOSE: In this study, we recorded light- (photopic) and dark-adapted (scotopic) fERG data from 25 schizophrenia patients and 25 healthy control subjects to (1) determine if past key findings on abnormal photoreceptor and bipolar cell signaling could be replicated; (2) for the first time, examine retinal ganglion cell functioning using the photopic negative response of the fERG; (3) also for the first time, determine responsiveness of schizophrenia patients to a flickering stimulus, as an additional method to isolate cone photoreceptor function; and (4) determine if schizophrenia-related changes in the fERG could be detected using a portable hand-held ERG device.

METHOD: ERG data were collected on 25 patients with schizophrenia and 25 healthy controls. At the time of testing all but one patient was prescribed psychiatric medication. All participants were between the ages of 18 and 60 years old.

RESULTS/ CONCLUSION: In both photopic and scotopic conditions, schizophrenia patients demonstrated weakened photoreceptor and bipolar cell activations that were most pronounced in response to the most intense stimuli. A reduced cone response to a flicker stimulus and attenuation in ganglion cell activity were also observed in the schizophrenia group. In general, groups did not differ in implicit time of retinal cell responses. These findings (1) replicate and extend prior studies demonstrating reduced photoreceptor (both rod and cone) and bipolar cell functioning in schizophrenia; (2) indicate that retinal ganglion function abnormality can also be detected using fERG; and (3) indicate that these anomalies can be detected using a portable testing device, thereby opening up possibilities for more routine administration of ERG testing.

Demmin D.L. et al People with current major depression resemble healthy controls on flash Electoretinogram indices associated with impairment in people with stabilized schizophrenia' in Schizophrenia Research (Article in Press) 2019

PURPOSE: In this study we directly compared the fERG performance of MDD patients experiencing a current major depressive episode to that of stabilized, but not symptom free, schizophrenia patients, and that of healthy controls, in order to clarify the extent of changes in acute MDD relative to both groups, thereby addressing both the issues of presence of MDD-related abnormality and diagnostic specificity.

METHOD: ERG data were recorded from 25 patients with schizophrenia (SCZ), 25 patients with major depressive disorder (either single episode or recurrent; MDD) in a current major depressive episode, and 25 healthy controls (HC). At the time of testing, all MDD patients and all but one SCZ patient were prescribed psychiatric medication. In the MDD group, 72% of patients (n = 18) had recurrent major depressive episodes and 28% (n = 7) met criteria for a single episode. All patients in the MDD group were experiencing a current major depressive episode (past month). No patients in the MDD group reported experiences of psychotic symptoms. Healthy control participants were recruited from the community. All participants were between the ages of 18 and 60 years old.

RESULTS/ CONCLUSION: These data indicate that MDD patients currently experiencing a major depressive episode requiring hospitalization resemble psychiatrically healthy controls on fERG indices that have previously been shown to discriminate stabilized schizophrenia patients from controls. While we cannot rule out the possibility that MDD is associated with retinal functioning anomalies on other fERG indices or test parameters, prior research on this issue suggests that if/when such anomalies exist they are likely to be less severe than those observed in schizophrenia, and possibly much less severe if compared to a schizophrenia group with an equal proportion of hospitalized cases.

Demmin D.L. et al ' Retinal functioning and reward processing in schizophrenia' in Schizophrenia Research (Article in Press) 2019

PURPOSE: We aimed to determine whether ERG amplitudes would be sensitive to the well-documented reward processing impairment in schizophrenia.

MENTAL HEALTH

METHOD: Flash ERG data from 15 clinically stable people with schizophrenia or schizoaffective disorder and 15 healthy controls were collected under three conditions: baseline, anticipation of a food reward, and immediately after consuming the food reward. At the group level, data indicated that controls' ERG responses varied as a function of salience of the food reward (baseline vs. anticipation vs. consumption) whereas patients' ERG responses did not vary significantly across conditions.

RESULTS/ CONCLUSION: These data suggest that flash ERG amplitudes may be a sensitive indicator of the integrity of reward processing mechanisms. However, several differences in the direction of findings between this and a prior study in controls point to the need for further investigation of the contributions of a number of key variables to the observed effects.

Kazakos C.T. et al Retinal Changes in Schizophrenia: A Systematic Review and Meta-analysis Based on Individual Participant Data' in Schizophrenia Bulletin 2019

PURPOSE: In this study, we aimed to investigate the potential role of 3 non-invasive retinal evaluation methods in SZ detection: OCT, fundus photography, and electroretinography (ERG).

METHOD: e searched MEDLINE, SCOPUS, clinicaltrials.gov, PSYINDEX, Cochrane Controlled Register of Trials (CENTRAL), WHO International Clinical Trials Registry Platform, and Google Scholar, up to October 30, 2018. Authors were contacted and invited to share anonymized participant-level data. Aggregate data were pooled using random effects models. Diagnostic accuracy meta-analysis was based on multiple cut-offs logistic generalized linear mixed modeling. This study was registered with PROSPERO, number CRD42018109344.

RESULTS/ CONCLUSION: Pooled mean differences of peripapillary retinal nerve fiber layer thickness in micrometer between 694 eyes of 432 schizophrenia patients and 609 eyes of 358 controls, from 11 case-control studies, with corresponding 95% confidence intervals (CIs) by quadrant were the following: -4.55, 95% CI: -8.28, -0.82 (superior); -6.25, 95% CI: -9.46, -3.04 (inferior); -3.18, 95% CI: -5.04, -1.31 (nasal); and -2.7, 95% CI: -4.35, -1.04 (temporal). Diagnostic accuracy, based on 4 studies, was fair to poor, unaffected by age and sex; macular area measurements performed slightly better.

The notion of structural and functional changes in retinal integrity of patients with schizophrenia is supported with current evidence, but diagnostic accuracy is limited. The potential prognostic, theranostic, and preventive role of retinal evaluation remains to be examined.