Assessing Residual Visual Function in Severe Vision Loss

Lauren N. Ayton, Nicholas V. Apollo, Mary Varsamidis, Peter N. Dimitrov, Robyn H. Guymer, and Chi D. Luu

Centre for Eye Research Australia, The University of Melbourne, Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria, Australia

Correspondence: Lauren N. Ayton, University of Melbourne, Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Macular Research Unit, Level 1, 32 Gisborne Street, East Melbourne, VIC 3002, Australia; lnayton@unimelb.edu.au.

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Purpose. Vision restoration is a fast-approaching reality for some people with profound vision loss. In order to reliably determine treatment efficacy, accurate assessment of baseline residual visual function is critical. The purpose of this study was to compare residual function as detected on Goldman visual field (GVF) and full-field ERG (ffERG), and correlate with the remaining photoreceptor layer as determined by spectral-domain optical coherence tomography (SD-OCT), in subjects with severe vision loss.

Methods. Fifty-four subjects with advanced retinitis pigmentosa and no discernible signal on ffERG were included. Trace residual function was assessed using discrete Fourier transform (DFT) analysis of the 30-Hz flicker ffERG and the percentage of remaining GVF. The horizontal extent of the outer nuclear layer (ONL) on SD-OCT was assessed.

Results. Thirty percent of the study eyes had a 30-Hz flicker response after DFT analysis of the ffERG, and 57% had a measurable GVF. Thirty-five percent had a visible ONL on SD-OCT. There was no significant correlation between the magnitude of the 30-Hz flicker response and the percentage of remaining GVF ($r = 0.172$, $P = 0.213$) or the extent of remaining central photoreceptors ($r = 0.258$, $P = 0.06$). Only 17% of the eyes had all three parameters detected.

Conclusions. Discrete Fourier transform analysis of the 30Hz-flicker ffERG response and GVF can detect trace residual function. Evidence of this residual function is not always supported by the structural correlate of a measurable ONL. Our findings highlight the importance of completing a multimodal assessment to accurately define the important parameters of retinal structure and function in people with profound vision loss.

Keywords: low vision, visual function, vision regeneration, retinitis pigmentosa, electroretinography

Advances in medical technology have led to early clinical trials for vision restoration therapies such as gene therapy,[1,2] stem cell transplantation,[3] and retinal prostheses.[4,5] There is now a real chance that we will soon be able to restore vision to people with profound vision loss.

The likely potential recipients of early vision restoration treatments will have visual function at a level that is very difficult to accurately assess.[6,7] Historically, studies of people with such poor vision have not needed significant rigor around their measurement. However, when implementing interventions that aim to improve visual function, which at first are likely to be small gains, it becomes extremely important to develop strategies for more accurate and reliable measures of residual function. A baseline vision assessment must have the ability to determine the extent of any residual functional vision before claims can be made about improvements post intervention. In addition, these measures must be sensitive enough to detect small levels of improvement after the intervention. Traditional terms of visual acuity such as "hand movements" or "counting fingers" are completely inadequate in this setting.

In subjects with low vision, it is well accepted that subjective Goldmann kinetic perimetry gives the most accurate and repeatable results of residual visual field.[8] Full field ERG (ffERG) gives an objective quantitative measure of retinal function; however, in moderate to advanced RP, the ffERG is usually undetectable, even when subjective islands of vision can be detected on Goldman kinetic perimetry.[9] By using a common signal processing method, discrete Fourier transform (DFT) analysis, it is possible to detect some residual signal in the ffERG.[10–12] Discrete Fourier transform analysis is commonly used in mathematics, biology, and engineering fields to analyze signals and decompose those signals into component frequencies for simplified analysis. Whilst both the DFT and its analog equivalent (narrow-band filtering) have been used in patients with retinal degeneration previously,[10,13–18] neither are routinely used to quantify the ffERG responses, particularly the flicker ffERG signals, in a clinical setting. In a review of the DFT technique for visual electrophysiology by Bach and Meigen[11] in 1999, they concluded that this technique can "increase the reliability of physiologic or pathologic interpretations."

In addition, with the availability of high-resolution spectral domain optical coherence tomography (SD-OCT), it is now possible to identify discrete layers of the retina within the living eye. This enables us to make correlations between detection of residual visual function and residual retinal layers such as the outer nuclear layer (ONL), which contains the nuclei of the photoreceptors.

The aim of this study was to accurately document residual visual function in participants with very low levels of vision, in

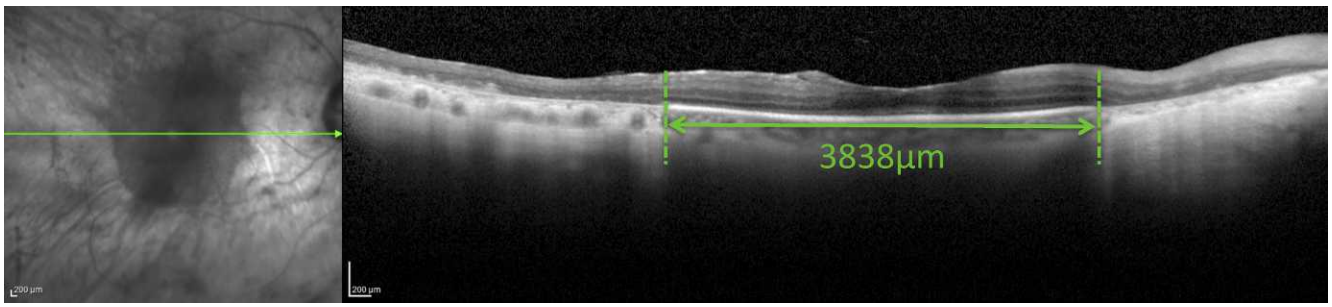

FIGURE 1. An example of the ONL horizontal extent measurement using the Heidelberg HEYEX software in a patient with advanced retinitis pigmentosa.

whom the standard ffERG waveform parameters were undetectable. In this population of patients with an undetectable ffERG, we used Goldman visual field (GVF) and DFT analysis of the flicker ffERG response to assess residual function and then correlated with the structural measurement of the ONL on SD-OCT.

METHODS

Subjects with moderate to profound vision loss from RP were recruited as part of a natural history study at the Centre for Eye Research Australia. Moderate to profound vision loss was defined as vision of less than 20/80 and/or visual fields of less than 60° diameter, as stated by the International Council of Ophthalmology guidelines.[19] Written informed consent was obtained for all participants. The research study was approved by the Human Ethics Committee of the Royal Victorian Eye and Ear Hospital, and was carried out in accordance with the tenets of the Declaration of Helsinki.

Diagnosis of RP was confirmed from medical records, clinical examination, ffERG, and review of fundus photography. Visual acuity was measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart[20,21] for vision to the level of 20/400 (logMAR 1.3) and the Berkeley Rudimentary Vision Test[22] for vision less than 20/400.

All subjects underwent retinal imaging and functional testing. Infrared and SD-OCT images were taken using the Spectralis OCT (Heidelberg Engineering GmbH, Heidelberg, Germany). Subjects were asked to fixate on the internal fixation light or, if not possible, were directed to look straight ahead. Using a single line raster scan through the fovea, the presence of a central ONL was determined by an experienced OCT examiner. The presence of an ONL was determined by the clear delineation of the hyporeflective band on the OCT. An example of the ONL measurement in an advanced case of RP is shown in Figure 1. If present (>20 µm), the horizontal extent of the layer was measured using the inbuilt HEYEX software.

Visual fields were assessed using Goldmann manual kinetic perimetry.[23] The Goldmann field was completed with the smallest target that the subject could identify. The field testing was completed by one experienced examiner, who measured each of the 24 meridians at least twice to check for consistency. The edges of any islands or scotomas were further probed with tangential movements to accurately map the remaining field. Patient fixation was monitored using the viewfinder in the Goldmann equipment. Unreliable field tests were defined as frequent fixation losses during testing and/or intermittent measures (i.e., where the edge of the island or scotoma was not repeatable on the second measure). Unreliable fields were excluded from this analysis. To quantify the remaining field, the hard copy Goldmann fields were scanned into ImageJ image processing software (National Institute of Mental Health, Bethesda, MD). The percentage of field seen was determined by comparing the field seen to the total possible field area. For the purposes of this study, the total visual field remaining included both central field (within 10° from fixation) and peripheral islands.

Retinal function was assessed by ffERG using the 2008 International Society for Clinical Electrophysiology of Vision (ISCEV) standard protocol, including measurement of the scotopic (0.01 cd·s/m^2), maximal (3.0 cd·s/m^2), photopic, and 30-Hz flicker responses (3.0 cd·s/^{2}).[24] Pupils were dilated to at least 7 mm using 1 drop of 0.5% tropicamide and 1 drop of 2.5% phenylephrine hydrochloride (Chauvin Pharmaceuticals, Surrey, UK). Scotopic ERGs were recorded after 20 minutes dark adaption, and the photopic ERGs were performed after 10 minutes of light adaptation with 30 cd·s/m^2 background luminance. For the scotopic, maximal, and photopic measures, an average of 3 to 5 sweeps was taken, and 30 sweeps were averaged for the 30-Hz stimuli. The recording window was 300 ms, which allowed for the measurement of 9 cycles for the 30-Hz flicker response. The flash stimuli were generated using a ColorDome Ganzfeld (Diagnosys LLC, Lowell, MA), and all signals were acquired using an Espion system (E2; Diagnosys LLC). Recorded signals were band-pass filtered between 0.15 and 100 Hz, with no amplification (gain set to ×1). All of the recordings were made using Dawson-Trick-Litzkow (DTL) electrodes.[25]

For inclusion into this study, participants needed to record an undetectable ffERG response, defined as indiscernible response waveforms in all ISCEV standard ffERG components (scotopic, maximal, photopic, and 30-Hz flicker) or a response amplitude of less than 10 µV. The response of each of the components was an average of at least three trials.

Full field ERG test results were assessed in two ways: first, assessment of the waveform parameters were made using standard clinical assessment protocols and, if eligible, the ffERG was then assessed using the DFT analysis. Only subjects with undetectable ffERGs were eligible for this study. The ffERG was classified as undetectable if the response waveforms were indiscernible, with the amplitude of the b-wave or trough-peak amplitude of the flicker ffERG on all measurements being less than 10 µV. In these participants, the flicker responses were analyzed using the DFT analysis method. The 30-Hz flicker data of the average waveform of each eye were exported for offline DFT analysis using IgorPro software (WaveMetrics, Portland, OR). From the Fourier spectrum, the signal-to-noise ratio (SNR) was calculated as the amplitude of the main frequency divided by the average amplitude of the two neighboring signals (between 27 and 33 Hz). In this study, an SNR $\geq$ 2 (corresponding to a P value of 0.12) was determined to be indicative of a residual retinal response. We have chosen this SNR cutoff level because the study cohort had minimal ERG responses.

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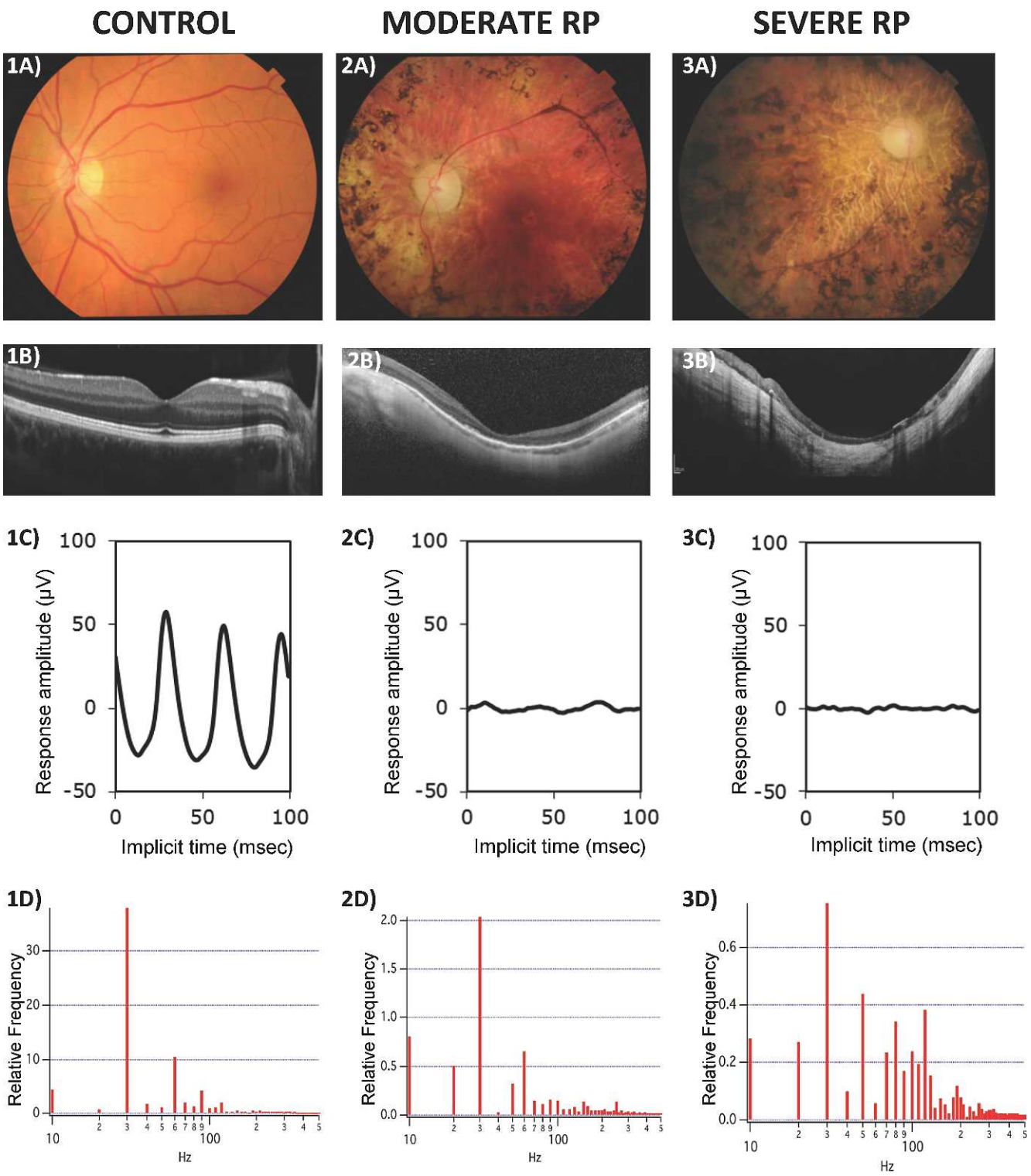

FIGURE 2. Representative results from a control (No. 1), a subject with moderate RP (No. 2), and a subject with severe RP (No. 3). This figure shows representative fundus photos (**A**), SD-OCT scans (**B**), 30-Hz flicker ffERG trace (**C**), and DFT analysis histogram (**D**). Note that for subject 3 (severe RP), DFT analysis showed a detectable 30-Hz flicker (**3D**), although the ffERG trace (**3C**) was undetectable.

RESULTS

Eighty-five subjects with RP were screened for this study, with 54 subjects having an undetectable ffERG and thus meeting the eligibility criteria. Measurements were taken in both eyes and analyzed separately and, as they showed similar results, we have reported the results for the right eye in this study. The age range of the included subjects was 33 to 80 years (average, 54 ± 12 years). Subjects had visual acuity from 20/40 (logMAR 0.3) to light perception only (logMAR 3.8). We did not have any participants with no perception of light.

Figure 2 shows an example of a fundus photo, SD-OCT scan, standard 30-Hz flicker ffERG trace, and DFT histogram

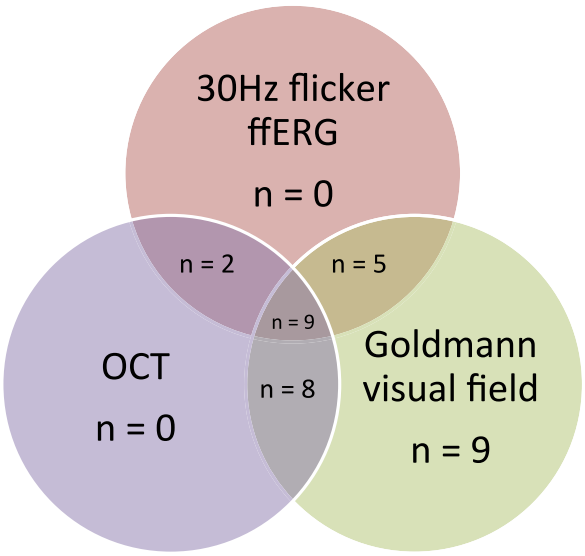

FIGURE 3. Summary of positive results for the DFT-analyzed 30-Hz flicker ffERG ($n = 16$), SD-OCT ($n = 19$), and GVF ($n = 31$) from 54 eyes.

for a normal subject, one with moderate RP, and one with severe RP.

Goldmann Kinetic Visual Fields

Of the 54 eyes, 31 (57%) had a measurable GVF. The target size used was V-4-e in 72% of eyes, II-4-e in 26%, and I-4-e in 2%. In these eyes, the remaining field was classified as a severe restriction (<20° diameter)[19] in all cases, with an average remaining field percentage of 1.39% (range, 0.12%–9.64%).

DFT Analysis of 30-Hz Flicker ffERG

Of the 54 eyes assessed, 16 (30%) were found to have a 30-Hz flicker response (≥2 SNR) on DFT analysis.

Spectralis OCT

Nineteen (35%) of the 54 eyes had a measurable ONL on the SD-OCT images. The average horizontal extent of the ONL was 671 μm (range, 471–3645 μm).

Correlations Between the Three Tests

A Venn diagram of the relationships between the results from the three tests is shown in Figure 3.

Only 9 of the 54 eyes had all three measured parameters (i.e., 30-Hz flicker response after DFT analysis, GVF, and a detectable photoreceptor layer on SD-OCT). When the GVF was detected, only 45% (14 of 31) had a detectable 30-Hz flicker response and 54% (17 of 31) had a measurable ONL on SD-OCT. Conversely, it was nearly always possible to detect the remaining Goldmann field when either a 30-Hz flicker response was recorded (88% of cases) or when the ONL was measurable (90% of cases).

The lack of correlation between the SNR of the 30-Hz flicker response and the percentage of remaining visual field ($r = 0.172$, $P = 0.213$) and a similar lack of correlation between the SNR of the 30-Hz ffERG response and the horizontal extent of the ONL ($r = 0.258$, $P = 0.06$) are shown in Figures 4A and 4B, respectively. As can be seen in Figure 4B, there is a trend toward significance in the relationship between the OCT and ffERG measures, but this trend is removed ($r = 0.096$, $P = 0.494$) with the exclusion of one outlier (Fig. 4C).

DISCUSSION

As the field of vision restoration progresses, robust patient selection and assessment will be vital so that evidence of benefit, albeit small in the first instance, can be determined. It is imperative that the baseline visual function of recipients of treatments such as visual prostheses, stem cells, and gene therapy is measured to a high level of accuracy. This will ensure optimal patient selection and an accurate comparison for posttreatment outcomes. Unfortunately, the visual status of people with profound vision loss (often defined as less than 20/400 or logMAR 1.3)[19] is notoriously difficult to measure and, to date, protocols attempting to determine residual function and changes post intervention lack any general consensus among the field.[26]

The use of DFT analysis of the 30-Hz flicker ffERG was able to show trace residual cone function in 30% of our subjects, all of whom had an undetectable ffERG using conventional waveform parameter analysis. Using DFT, therefore, enables the differentiation of two subgroups of patients; those with or without detectable electrical signals of residual retinal function. As such, this technique of ffERG analysis may prove to be useful in identifying a group that might respond differently to those without a detectable response in treatment trials, as well as providing a potential outcome measure post intervention. The strength of the DFT analysis method proposed here is that the analysis can be easily automated using simple computer programming, such as IgorPro (WaveMetrics) and MatLab (MathWorks, Natick, MA). As such, it does not add substantial time to the analysis of ffERG waveforms.

One limitation of the ERG methodology used in this study is that the 30-Hz flicker response mainly reflects cone pathway function.[24] As such, it is possible that we have not detected the full amount of residual rod function to flickering stimuli, which could have been detected by a 9-Hz flicker. We did attempt to measure the rod response to a 9-Hz flicker stimulus, with an epoch time of 300 ms. However, to obtain a reliable DFT, a minimum of four complete cycles is required.[11] A 1-second recording window is required to ensure an integer number of cycles for the 9 Hz. In this study, most subjects had very poor vision with uncontrolled eye movements, so a recording window of 1 second would be heavily contaminated with eye movement and blink artifacts. Therefore, our results of the 9-Hz flicker (300-ms duration) are likely to underestimate the SNR, and thus are uninterpretable and have not been reported here.

Despite no recordable standard ffERG waveforms, a measurable GVF was detected in 57% of the eyes tested in this study, which was the highest positive result of the three tests. However, only approximately 30% of the eyes with a detectable field had a measurable ONL on SD-OCT and a 30-Hz flicker response.

If residual function was detected on ffERG and/or the structure of the ONL was visible on OCT, 92% of these eyes also had a GVF. This finding alone informs us that the somewhat time-consuming and basic test of Goldmann perimetry still provides more sensitive information than the newer, more sophisticated technologies with regard to identifying and describing residual islands of vision. In total, only 9 of the 54 eyes (17%) had a positive result on all three tests.

It is worth noting that owing to time restrictions, the GVF was only completed with one-sized target for each patient. In

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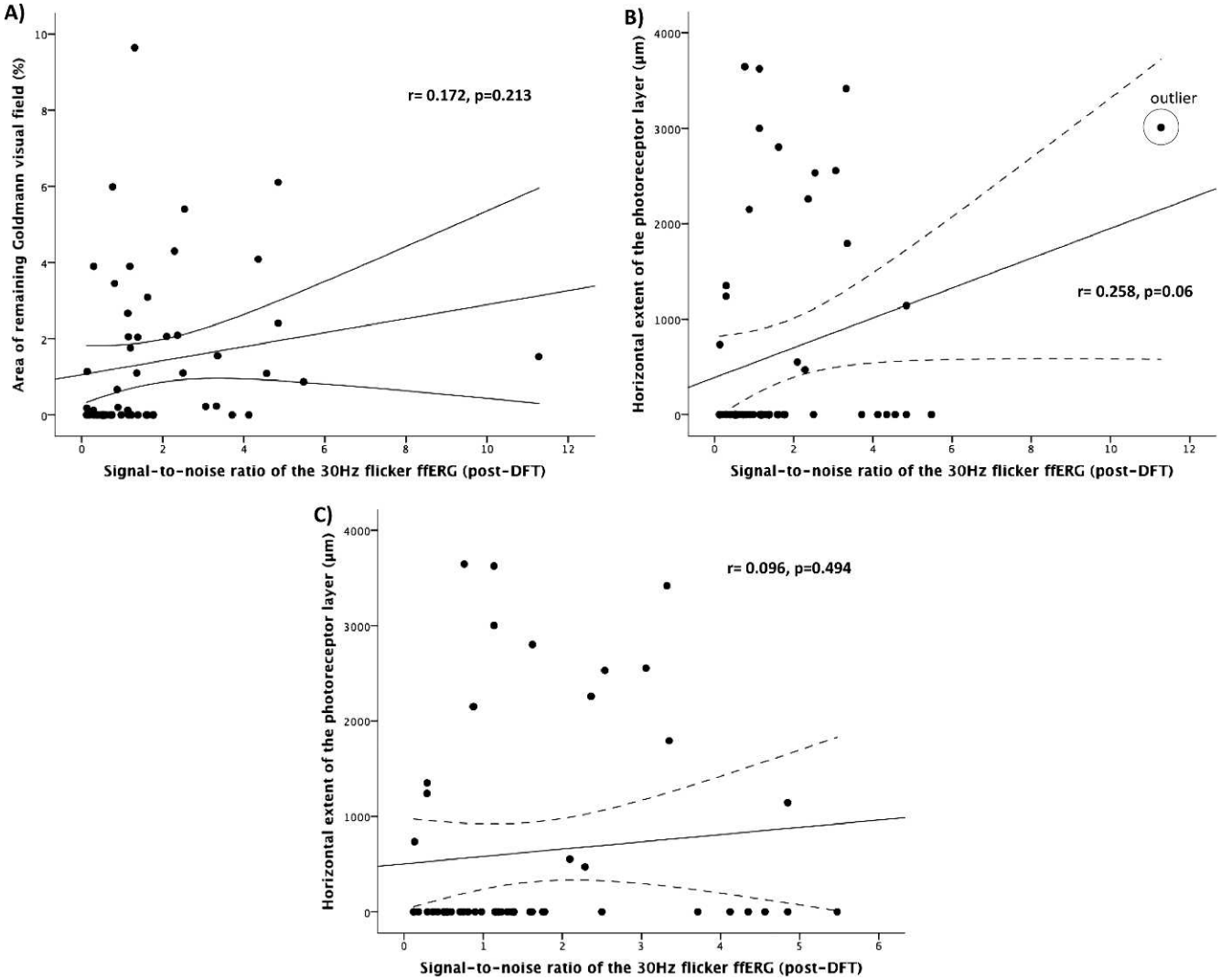

FIGURE 4. Signal-to-noise ratio of the 30-Hz flicker response versus the percentage of remaining visual field (**A**) and the horizontal extent of the ONL (**B**), showing no correlation between the measures. A trend toward significance in the relationship between OCT and ffERG measures (**B**) is removed if one outlier is excluded (**C**). The *solid* and *dotted lines* represent the mean and 95% confidence intervals of the regression, respectively.

total, 72% of the eyes were tested with a V-4-e target, 26% used a III-4-e, and 2% used a I-4-e target. We chose to do this to gain the most sensitive assessment of the boundaries of the remaining central visual field, by using the smallest possible target for each individual.[27]

There are other functional tests that may be used in RP, such as the multifocal ERG (mfERG)[28–34] and the full field VEP (ffVEP) or multifocal VEP (mfVEP).[35–38] The advantage of an mfERG is that it can identify small areas of localized dysfunction, which would be of interest to correlate with GVFs. Unfortunately, an mfERG is not appropriate for our study cohort because of their severe vision loss and uncontrolled eye movements, which result in unreliable recordings. In addition, the ffERG has the benefit of being able to differentiate between rod and cone function. Similarly, the VEP and mfVEP require good patient fixation and are not as good a measure of overall retinal function as the ffERG. Both mfERG and VEP only provide functional results of the central visual pathway, with the signal mainly derived from the macula. Defects beyond the macula will not be picked up by either of these tests. As found in this study, a large proportion of subjects with severe RP have residual visual field islands in the peripheral retina, meaning DFT analysis of the 30-Hz flicker ffERG and GVFs would be more appropriate functional tests.

With regard to the SD-OCT ONL thickness, we chose to assess the central region, as subjects with RP tend to retain their central photoreceptors until the latter stages of their disease progression. It would have been preferable to include a detailed volume scan of the retina, with a larger area to analyze, but this was not possible owing to the poor fixation of the participants, and the subsequent long session times required to get a clear image. As the ffERG is a global measure of the entire retina, it is not surprising that there was no significant correlation with the central ONL. Whilst the original data set suggests a trend of increasing ONL extent with increasing SNR of the 30-Hz flicker ERG, this is no longer the case once an outlier is removed. Similarly, GVF can detect islands of vision anywhere in the field, so it would not necessarily correlate with the remaining central photoreceptors. While it would be ideal to perform SD-OCT scans over a larger area, this would prove difficult owing to the poor fixation ability of subjects with the levels of vision present in our cohort. Also, it is

imperative to acknowledge that the mere presence of the ONL is not indicative of the function of the photoreceptors, thus their presence may not relate directly to retinal function.

The lack of correlation between GVF and the other tests suggests that all three techniques are exposing different elements of retinal health and function and are potentially informing us about different important aspects of the retina. As such, we strongly recommend that researchers undertake a range of structural and functional assessments when embarking on novel interventions in similar groups of participants with profound vision loss.

In conclusion, this study has shown that DFT analysis of the 30-Hz flicker response can detect trace residual retinal function in a significant proportion of patients with severe vision loss. In a cohort selected for an absent ffERG, we were able to identify residual islands of vision on GVF in more than half of the cases. This demonstrates the importance of the GVF technique in capturing residual function that would be missed using other more sophisticated techniques. However, because of the lack of correlation between the percentage of residual visual field, 30-Hz flicker response, and OCT findings, it remains important to complete a multimodal assessment to accurately define all the important parameters of retinal structure and function. This is especially vital for people with profound vision loss taking part in strategies to restore their vision.

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