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Comparison of mfERG waveform components and implicit time measurement techniques for detecting functional change in early diabetic eye disease

Marilyn E. Schneck, Marcus A. Bearse Jr., Ying Han, Shirin Barez, Carl Jacobsen & Anthony J. Adams

Vision Sciences Program, School of Optometry, University of California at Berkeley, Berkeley, CA, USA

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Abstract

This study first compares two methods for measuring first order multifocal electroretinogram (mfERG) implicit time abnormalities in eyes with early diabetic retinopathy. Two analysis methods are used: template stretching (multiplicative scaling) of an 80 msec response epoch and template sliding (cross-correlation or additive scaling) of portions of responses containing the major waveform features. The study also compares the relative sensitivities of N1, P1 and N2 implicit time assessed by cross-correlation. The nature of the change in the mfERG waveform associated with diabetes is also assessed. MfERGs were recorded from 15 eyes of 15 individuals with diabetes and early non-proliferative retinopathy and 20 eyes of 20 healthy control subjects of similar age. Implicit time determined by template stretching is more frequently abnormal in the eyes of the diabetic subjects than the implicit time of any of the components assessed by template sliding. This is attributable to the lower variability of the template stretching implicit time measure in normals. Of the components, P1 is most often abnormal in the eyes of individuals with diabetes. Responses recorded from retinal areas with retinopathic signs are more often abnormal than those from other areas. Later components of the response are not delayed more than earlier ones. We conclude that template stretching is a sensitive measurement technique, but that it does not fully capture the effect of diabetes on the first order mfERG well.

Abbreviation: mfERG – multifocal electroretinogram.

Introduction

The multifocal electroretinogram (mfERG) [1–3] has been used by a number of groups to explore the effects of diabetes and diabetic eye disease on retinal function [4–12]. An association between local retinal damage and local first order mfERG implicit time delays has been demonstrated in eyes with moderate diabetic retinopathy (e.g. [5]) and edema [7]. Such an association is also seen in eyes with early diabetic retinopathy [12, 13]. Amplitude of the mfERG was less affected than implicit time by diabetic retinopathy and shows poor spatial correspondence with retinal damage. These previous studies [5, 7, 12, 13] used a 'template stretching' method to measure local mfERG implicit times [14]. At each stimulated retinal location, this technique multiplicatively scales a template (itself a mean waveform obtained from a group of normals) in amplitude and time dimensions to obtain a least-squares best-fit estimate of the local mfERG's amplitude and implicit time.

To date, alterations of the local mfERG waveforms produced by diabetic retinopathy have not been examined in detail. Specifically, the implicit times of the individual major local waveform features (N1, P1 and N2) have not been measured. In addition, results obtained by measuring these different waveform implicit times

have not yet been compared to results obtained using the template stretching method. Thus, we do not yet know how the mfERG waveform actually changes as a result of diabetic retinopathy or how best to measure and capture any waveform changes.

In the present study, we present evidence for correspondence of first order mfERG implicit time changes with local retinal disease in eyes with very early diabetic retinopathy. We also examine the major local waveform feature implicit times to determine the nature of waveform alterations and compare the abilities of the different measures to detect retinal dysfunction. Measurement of individual waveform feature implicit times is also compared to implicit time determined by the template stretching method to determine their relative abilities to detect retinal dysfunction in the diabetic eyes.

Methods

Subjects

Fifteen eyes of 15 individuals aged 32–60 years (mean 51.7 ± 7.0 years) with early non-proliferative diabetic retinopathy (NPDR; see below) and no other eye or systemic disease affecting vision were tested. The duration of diabetes ranged from 1 to 20 years (mean 10.3 ± 6.3 years). Data from NPDR eyes were compared to that of a normal group comprised of 20 eyes of 20 healthy adults aged 28–66 years (mean 47.2 ± 9.4 years) with no history of eye disease or surgery or systemic disease known to affect vision. All subjects had refractive errors less than ±6.00 D and no ocular media opacities.

Fundus characteristics of NPDR eyes

All diabetic subjects underwent dilated fundus examination and fundus photography within one month of mfERG recording. Fundus photos were graded by a retina specialist (author SB) using ETDRS criteria [15]. NPDR, when present, tends to be mild in this group, even in the study (worse) eye. Six of NPDR eyes had only a few scattered microaneurysms or dot hemorrhages (51 instances in 15 eyes). However, there were a total of 6 areas of edema (6 eyes) in the 15 eyes, and 17 instances of hard exudate (5 eyes), all smaller than an mfERG stimulus element.

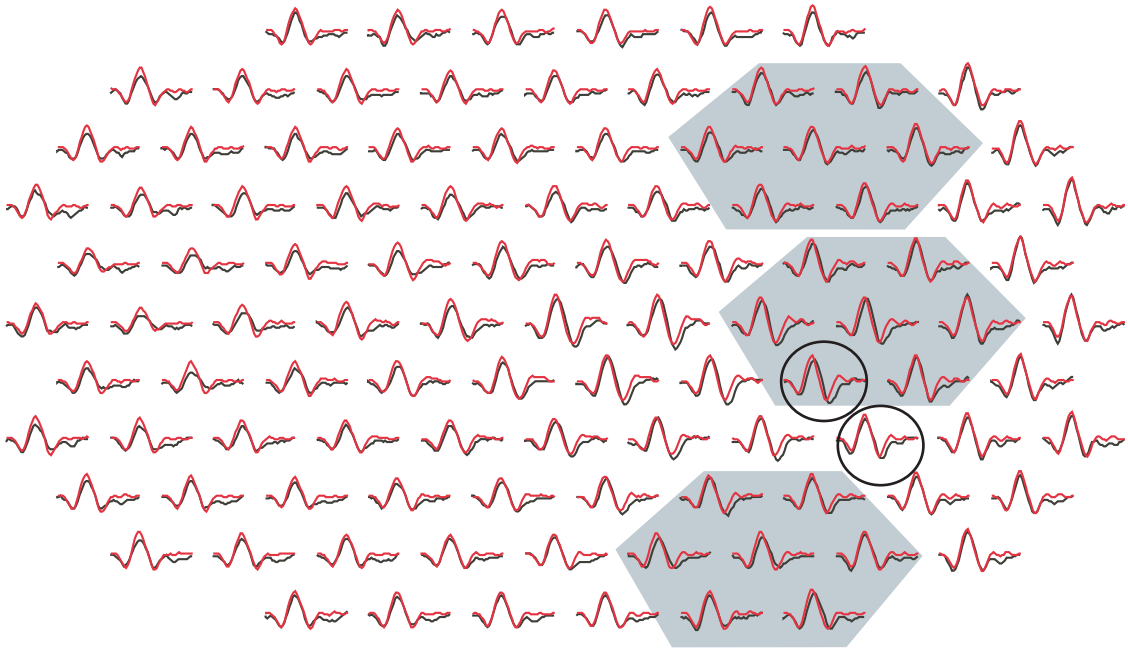

Figure 1. The mfERG trace array recorded from a left eye with mild non-proliferative diabetic retinopathy (NPDR; black). Red traces are the mean of 20 normal (non-diabetic) subjects' eyes. The NPDR eye has three retinal signs visible on the fundus photograph, located at the central responses of the three shaded hexagonal areas, which represent retinopathy zones (RZ). Circled responses are examples in which the diabetic response appears to be a stretched version of the normal response.

The location, type and grade of each retinal finding was mapped by the grader onto a template of the mfERG hexagon stimulus grid for later comparison with mfERG findings. Using the marked template, 'retinopathy zones' (RZ), comprised of any location with a retinal lesion and its immediate neighboring locations (hexagons) were identified. Zones were defined this way (surrounding lesions) for two primary reasons. The first is positional uncertainty of the lesion with respect to the array. There is always the possibility of some small error in mapping, or a lesion may fall near a stimulus border and fall in either element during recording as a result of small eye movements. Second, it is possible that the functional effect of a visible lesion happens some distance away from the lesion itself (e.g. 'downstream' along the vasculature from a hemorrhage). Including neighboring elements without lesions (responses) in RZ, of course, means that there will be many more elements in RZ than there are identified instances of retinopathy. The remainder of the retina was classified as a retinopathy-free (no-disease) zone (NZ).

mfERG recording

Multifocal ERGs were recorded using a VERIS 4.3 system (EDI, San Mateo, CA, Figure 1). Pupils were fully dilated with 1.0% tropicamide and 2.5% phenylephrine. After the cornea was anesthetized with 0.5% proparicaine, a bipolar contact lens electrode (Hansen Ophthalmic, Solon City, IO) was placed on the eye and a ground electrode clipped to the right earlobe. The fellow eye was occluded. An array of 103 hexagonal elements spanning the central 45° was delivered by an eye camera/display/refractor unit (EDI, San Mateo, CA) driven at a 75 Hz frame rate. The hexagons were modulated between white (200 cd/m^2) and black (<2 cd/m^2) according to an m-sequence during recordings. The 7.5 min recordings were made in 16 30-second-long segments. Observers adjusted the stimulus unit for best focus of the central fixation target prior to recording. Recording quality and eye movements were monitored by real-time display and the eye camera, respectively. Contaminated segments were discarded and repeated. Retinal signals were filtered at 10–100 Hz [12] and amplified 100 000 times. mfERGs were processed in the usual way with one iteration of artifact removal and spatial averaging with 1/6 of the surrounding responses.

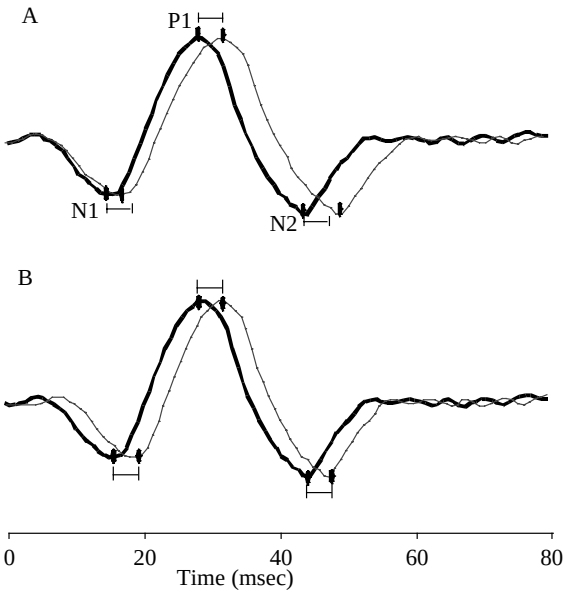

Figure 2. (A) Thin gray trace is an illustration of the effects of multiplicative scaling in time (stretching; by a factor of 1.1 in this example) of the normal response template (heavy black trace). Scale bars: 3 msec. In this example the scale bar fits only the P1 latency difference between the stretched response and the response template. The N1 difference is less and the N2 difference is more than that for P1 as a result of the stretching. The vertical stretching for amplitude is not illustrated. (B) Thin gray trace is shifted from the original template (black trace) by a fixed amount (3 msec). The difference between the template and shifted response is the same for all components of the waveform (N1, P1, N2).

An example of a trace array recorded from one of the eyes with diabetic retinopathy (black) is compared to the template derived from the 20 normal subjects (red traces) in Figure 1. This eye had diabetic retinopathic changes at three locations corresponding to the center traces of the three shaded hexagonal areas, which represent the corresponding retinopathy zones (RZ). One can see that, by and large, amplitudes are not very much affected in the diabetic eye, so that responses are robust. There are, however, implicit time changes apparent.

mfERG data analysis

Four response measures were examined: N1 IT, P1 IT, N2 IT, and response IT determined by the template stretching (Str) method. The template stretching method of Hood and Li [14] multiplicatively scales the entire (80 msec post-flash

epoch) waveform independently in amplitude and time for best fit to a template based on normal data (Figure 2 top). The implicit time of each local response, measured to the first prominent peak (P1), was derived from the scaling factor. Multiplicative scaling effectively shifts later portions of the response template relatively more than earlier features. This has been reported to produce a superior fit to data from eyes of diabetic subjects than does additive scaling ('sliding', Figure 2B) of the entire 80 msec epoch of the local response [5]. Implicit times of three of the first order kernel components of interest (N1, P1 and N2) were determined using the cross-correlation method in the Veris 4.3 software, which assesses the IT of the individual waveform features separately. An epoch containing, and largely restricted to, the feature of interest is selected and then the cross-correlation of the feature and the local waveform is determined. The IT is at the resulting location of the peak (or trough) of the feature**.** Though this method 'slides' a template, because the IT of each component is calculated separately, it also provides very good fits to the data from eyes of persons with diabetes. In further contrast to Hood and Li's stretching procedure, this method uses a template based on the individual's corresponding ring average rather than normal data.

To analyze the local mfERGs in eyes of persons with diabetes, the means and standard deviations of the four response measures of the normal subjects at each of the 103 stimulated locations were first calculated. Distributions of control values did not differ significantly from a normal distribution, permitting the use of Z-scores (the difference, in standard deviation units, between a value and the mean control value) to quantify each of the local response measurements in eyes of diabetics. Responses with IT Z-scores ≥ 2.0 were considered abnormal ($p \leq 0.023$).

Results

Number of abnormalities

Figure 3 shows the total number of abnormal mfERGs across subjects for each of the 4 IT measures. Each of the measures identified many more abnormalities than are expected by chance (2.3% of the $15 * 103 = 1545$ total responses, i.e. 36 responses). The number of abnormalities is lowest for N1 IT (247 or 16% of responses), yet even this is significantly greater than chance ($p < 0.0001$). IT determined by template stretching characterized the greatest number of responses as abnormal (29% (441) of responses; $p < 0.0001$).

Association between mfERG IT measures and local retinopathy

The Z-score distribution for each IT measure for mfERGs from retinopathy zones (RZ; 89 hexagons overlying visible retinal signs and their nearest neighbors, 454 total responses) was compared to the corresponding distribution from areas without visible fundus changes (NZ; 1091 responses; Figure 4). The box plots (white: RZ; gray: NZ) illustrate that the distributions for affected areas and unaffected areas are significantly different for each measure ($p < 0.01$).

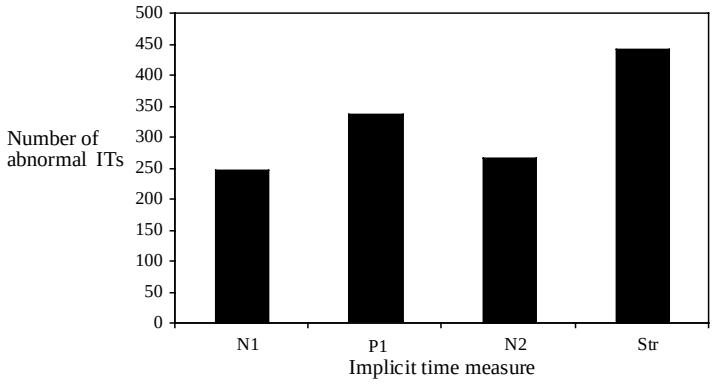

Figure 3. The number of 1545 total mfERG responses (15 eyes × 103 locations) with an abnormal implicit time (IT) for each of three features (N1, P1, N2) or as determined by a template stretching method (Str).

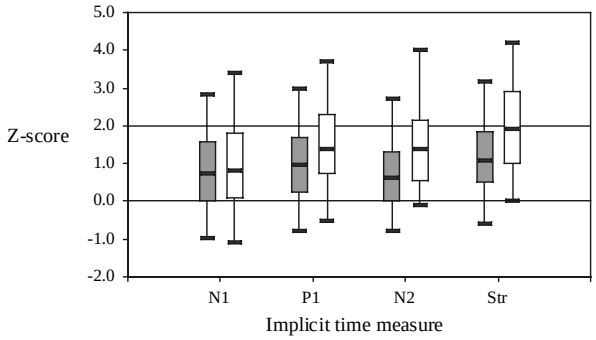

Figure 4. Distribution of implicit times (as Z scores, based on normal data) in diabetic eyes in zones without retinopathy (gray) and in retinopathy zones (white). Horizontal lines at 0.0 and 2.0 denote the normal mean and criterion for abnormality, respectively. Data are shown for 4 measures of implicit time (IT). Heavy horizontal lines in boxes are medians; boxes span the 25–75th percentiles; whiskers span the 5–95th percentiles.

Note that for all measures of IT, the majority ($\geq$75%) of responses in NZ as well as RZ are somewhat delayed with respect to the normal mean *Z*-score (0.0). Twenty percent of ITs determined by the template stretching method are abnormal (*Z*-score $\geq$ 2.0) in NZ compared to nearly half (49.4%) in RZ. P1 and N2 implicit times obtained by template sliding demonstrated similar frequencies of abnormalities in RZ (33.5% and 31.9%, respectively) whereas P1 IT identified more abnormal responses in NZ than N2 IT(17.0% versus 11.1%). Both P1 IT and N1 IT were abnormal in twice as many RZ as NZ responses (33.5% versus 17% and 22.0% versus 11.0%, respectively); this is smaller than the difference between NZ and RZ for N2, which is a factor of 2.9 times.

Association between mfERG IT measures and type of visible retinopathy

As described in 'Methods', there were 51 instances of microaneurysms or dot hemorrhages in the 15 eyes, 17 instances of hard exudate, and 6 areas of edema, each defining a retinopathy zone. What percentage of the RZs associated with these lesion types does each IT measure identify as abnormal? A RZ was considered to be abnormal on a mfERG measure if any (1 or more) of the responses in the zone had abnormal IT (*Z* score $\geq$ 2.0) by that measure. For RZ associated with edema or hard exudate, all of the IT measures do equally well except N1, which tends to identify a lower percentage of areas as abnormal (Table 1). However, only the difference between P1 and N1 identification rates for detection of hard exudate (HE) – with P1 detecting more abnormalities – reached statistical significance ($p = 0.02$, two tailed X^2 test) For more mild lesion types (MA and/or dot hemorrhages), stretching significantly outperforms other IT measures ($p < 0.01$), 'detecting' approximately 75% of these retinal findings. These high percentages of abnormal ITs in areas associated with retinopathy are compelling given that the majority of ITs are normal, and that no more than 20% of responses in NZ are abnormal by any measure.

Table 1. Frequency (and percentage) of abnormal mfERG in retinopathy zones associated with three types of retinopathic sign for each of four implicit time measures

		Implicit time measure			
		Stretching	N1	P1	N2
Retinopathic change	MA/DH	38/51 (75%)	25/51 (49%)	29/51 (57%)	28/51 (55%)
	Hard exudate	11/17 (65%)	7/17 (41%)	12/17 (71%)	11/17 (65%)
	Edema	5/6 (83%)	3/6 (50%)	6/6 (100%)	5/6 (83%)

MA – microaneurysm; DH – dot hemorrhage. A zone was considered abnormal if any response within it was abnormal (*Z*-score $\geq$ 2.0).

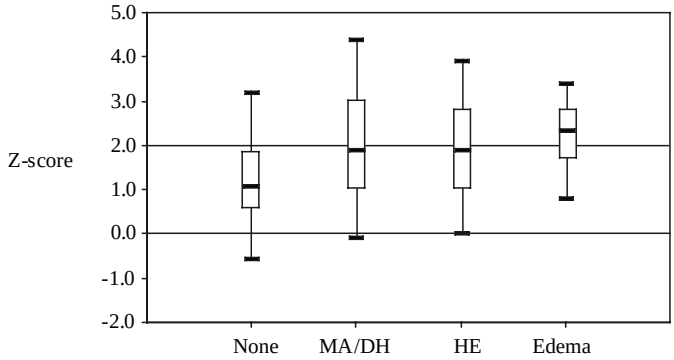

Figure 5. *Z*-score distribution for IT determined by template stretching in zones associated with each of 3 types of retinopathic sign and in areas free of retinopathy. MA/DH: Microaneurysm/dot hemorrhages; HE: Hard exudate, and Edema. Heavy horizontal lines in boxes are medians; boxes span the 25–75th percentiles; whiskers span the 5th and 95th percentiles.

The previous analysis defined an entire zone as functionally abnormal if a single mfERG IT in that zone was abnormal on a given measure, but does not describe the distribution of the IT measures associated with the various lesion types. Given that stretching IT appears to be the most sensitive index and that it is most often abnormal in areas with retinopathy, a closer examination of the association between this measure and local retinopathic signs is presented in Figure 5. Even in areas of retina not yet showing retinopathic change ('none'), the distribution of ITs is shifted away from normal, with approximately 50% of the responses at least 1 standard deviation slower than the normal mean . The distributions of ITs derived by template stretching in areas associated with any type of retinal change are shifted toward larger values compared to ITs of responses in non-retinopathy zones. The distributions of ITs in areas associated with hard exudate (HE) and microaneurysms or dot hemorrhages (MA/DH) are very similar to one another, with approximately half (49.3% and 47.2%, respectively) meeting the 2.0 *Z*-score criterion for abnormality. Responses in zones associated with edema are more often abnormal (64.3% of responses) than mfERGs in areas with MA/DH ($p < 0.02$) or with HE ($p < 0.02$).

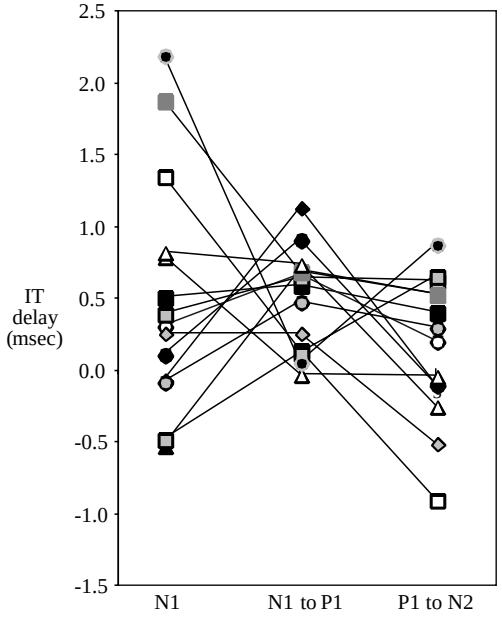

Figure 6. For each diabetic subject, the median deviation of each of the three response components (N1, P1, and N2) from the normals for responses falling within retinopathy zones is plotted. Each subject is represented by a unique symbol. If multiplicative scaling (stretching) described the diabetics' responses in areas associated with retinopathy, each curve should monotonically increase with increasing component implicit time (i.e. from N1 to P1 to N2). This is generally not seen. The results do not differ if mean, rather than median, response delays are used.

Waveform changes associated with diabetic eye disease

Str most often identifies abnormal ITs, but is multiplicative scaling (stretching) descriptive of the change in the diabetics' responses from normal? Stretching assumes that multiple components will be delayed, as indeed we find P1 and N2 to be. It further assumes that later components will be more delayed (with respect to the prior feature) than earlier components by some factor, as illustrated in the top of Figure 2. Slid-

ing (additive scaling) of the waveform as a whole assumes all components are equally affected (Figure 2, bottom) so that the shape of the waveform is not changed.[1] To determine whether stretching or sliding best describes the waveform alterations in diabetes, we did the following: The implicit times of the components of interest (N1, P1, and N2) were separately computed using VERIS. The implicit time with respect to the prior component (N1 from flash onset, P1 from N1, N2 from P1) was then determined (by subtraction) and then averaged at each location for normals. In diabetic eyes, for responses in retinopathy zones (which are most affected), the difference between these derived implicit times and the normal average at that location were compared (subtracted) to calculate a delay. For each diabetic subject, the median delays of the responses in the retinopathy zones for the derived N1, P1–N1, and N2–P1 measures are plotted in Figure 6. If multiplicative scaling (stretching) described the diabetics' responses in areas associated with retinopathy, each curve should monotonically increase with increasing component implicit time (i.e. from N1 to P1–N1 to N2–P1). For most (9 of 15) of the subjects, P1–N1 is more delayed than N1 or N2–P1, producing peaked curves in this Figure. N2–P1 is not more delayed than earlier components. Only 2 of 15 subjects show the trend predicted by stretching.

Discussion

The present results extend to eyes with milder retinopathy the earlier findings [5, 7] that there is an association between local retinopathic changes and mfERG implicit time delays as determined by Hood and Li's [14] template stretching method. The eyes in the present study often had just a few scattered microaneurysms and dot hemorrhages, though there were a few instances of hard exudate and edema. Further, analyses revealed that more 'severe' retinopathic signs were more often associated with mfERG delays than milder disease such as microaneurysms.

[1] The VERIS method for determining latency used here slides individual components, not the whole waveform, and so makes no assumption about relative magnitude of the IT changes of early versus late features of the waveform.

The VERIS method for determining IT of individual components also reveals abnormal implicit times that are associated with local retinal signs of non-proliferative diabetic retinopathy. Of the three components studied, P1 showed the greatest sensitivity and association with local retinopathy. N2 is more often abnormal and more often associated with NPDR lesions than is N1. However, none of the individual components is as 'sensitive' as latency determined by the template stretching method, particularly when associated with microanuerysms. Str IT is abnormal in the presence of MA 75% of the time, compared to less than 60% of the time for any component by template sliding.

Fortune et al. [5] reported that when ITs are significantly delayed, stretching templates provided a better fit to diabetics' mfERG data than did sliding of the entire 80 msec template (fitting by cross-correlation). Nonetheless, we do not find evidence to support the supposition that stretching is descriptive of the underlying response in diabetic eye disease. Later mfERG components are not generally more delayed than early components, though instances in which this is the case do occur. Such instances are apparent, for example, in the circled responses in Figure 1. These observations/conclusions were also obtained in a study using the slow flash mfERG [11].

We believe that the superior sensitivity of the template stretching method is attributable largely to its smaller variability among normals compared to measures of individual component ITs. The mean (across elements) standard deviations of P1 IT and N2 IT in our group of normal subjects are approximately 10% and 38% larger than Str IT, respectively. Thus, if these measures were all equally affected by diabetes, which they may or may not be, we would expect Str IT to identify more responses as abnormal. On the other hand, given that the standard deviation of normal N1 implicit times is as small as that of Str and that the N1 proves relatively insensitive, one may conclude that this component is less delayed in diabetes.

There may be an additional advantage of the Str IT over the other IT measures for identifying local changes associated with disease. We find that the standard deviation of the normal Str ITs is more uniform across the retina than for the other measures. Non-uniformity of variance across the

retina can produce spurious patterns of local sensitivity loss in patients, insofar as responses in areas with low variability among normals require smaller delays to be considered abnormal.

This study has practical implications for researchers and clinicians. As shown previously, implicit time is a more sensitive measure than amplitude in diabetes, as well as other conditions, such as retinitis pigmentosa [16, 17] and cone dystrophy [18]. Implicit time, measured locally, closely relates to retinal complications of diabetes visible on fundus photography. However, evaluating implicit time locally is not as readily implemented as measuring amplitude using, for example, the scalar product method. Determining whether the IT of a response (component) is normal or abnormal must be performed outside the commercial data acquisition software package. Hopefully, and almost certainly, as studies continue to demonstrate the value of IT, the software will evolve to more easily evaluate this parameter. At present, Hood and Li's [14] Matlab (Mathworks, Natick, MA) programs are available from the first author (personal communication) for analyses by template stretching. However, these analyses require the appropriate software as well as further statistical analysis.

Consistent with previous mfERG studies (e.g. [5, 11]) of diabetes, we find that implicit time delays are sometimes present in regions with no visible retinopathy by dilated fundus exam or photography. However, IT abnormalities are more common and more extreme in areas associated with retinopathy. The IT abnormalities not associated with local retinopathy are meaningful. Our recent report demonstrates that these local abnormalities of the mfERG Str IT predict sites of future retinopathy development [19].

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Address for correspondence: M. Schneck, School of Optometry-2020, University of California at Berkeley, Berkeley, CA 94720-2020, USA

Phone: +1-510-642-5904; Fax: +1-510-643-5109; E-mail: mes@berkeley.edu