

Retest variability and diurnal effects in the pattern electroretinogram

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Abstract. Pattern electroretinograms were recorded to phase-reversing checkerboard stimuli with DTL electrodes under conditions close to those of the ISCEV pattern electroretinogram guidelines. Both transient (2 reversals/s) and steady-state (16 reversals/s) stimulation was used. The check sizes were 0.4° , 0.8° and 16° ; the mean luminance 45 cd/m^2 , the contrast 98%, and the field size $32^\circ \times 27^\circ$. In 42 eyes of 21 subjects, measurements were repeated at the same time of day after 1 week. For each eye, the intersession coefficient of variation was calculated as a measure of reproducibility. We found a coefficient of variation (\pm standard deviation) of $7\% \pm 5\%$ for the amplitude of the steady-state pattern electroretinogram, $9.5\% \pm 7\%$ for the transient pattern electroretinogram and $1.5\% \pm 2\%$ for the latency of the transient pattern electroretinogram. To assess the diurnal variability, during a 15-h period, three pattern electroretinograms were recorded in 10 subjects. No relationship was found between the P50 latency and the time of day. However, the mean amplitude showed a maximum in the morning (9:30 am) and a minimum in the afternoon (2:30 pm). This small effect (about 7%, $p < 0.001$) was more pronounced for N95 and steady-state amplitudes than for P50 amplitudes ($p < 0.01$). Diurnal contributions to the pattern electroretinogram ranged between 3% and 10%. We conclude that pattern electroretinogram amplitude reproduces within $\pm 10\%$ with a probability of 70%. The effect size of the diurnal variation is similar and might be relevant for longitudinal studies.

Introduction

Physiological experiments and clinical experience with the pattern electroretinogram (PERG) in recent years indicate that the PERG is a reliable electrophysiological correlate of ganglion cell function and is of clinical use in diagnosis and visual assessment [1-5]. The PERG seems to be especially useful for glaucoma since current findings suggest that PERG amplitude reductions precede the clinical signs of glaucomatous damage [6-8]. The reproducibility of the PERG is clearly a matter of practical interest, especially when therapeutic maneuvers make follow-up studies necessary.

Reports on the reproducibility of the PERG seem contradictory [9-13]. When variability is discussed, *intrasession* and *intersession* variability need to be distinguished, since electrode position plays a major role and can be

assumed to be more stable within a session than between sessions, where reinsertion is necessary.

Investigating the intrasession reproducibility, Odom et al. [12] found an amplitude variability of 5% to 8%, which is a high reproducibility compared to other reports; Bartel et al. [9] presented data about the reproducibility during the same session, calculating a mean coefficient of variation (CV) around 30%.

Not surprisingly, studies of intersession reproducibility have found a higher amount of total amplitude variability. Holopigian et al. [10] reported marked variability of the amplitude between two recordings (30%-67%) and consequently advised caution in the clinical use of the PERG. Prager et al. [13] found a CV of 14% or 21%, depending on the electrode type used. Jacobi et al. [11], who unfortunately did a regression analysis on their results, which is misleading when reproducibility is to be addressed [14], found a high amplitude variability of a factor 2 to 4 between two recordings in several of their subjects. They concluded that the PERG is poorly reproducible and of limited clinical value.

This uncertain situation may partly result from varying experimental conditions. The guidelines for PERG recording, recently published by the International Society for Clinical Electrophysiology of Vision (ISCEV) [15], should clarify the field. This prompted us to reinvestigate the reproducibility of the PERG under conditions close to these guidelines. But what factors can, in principle, affect the reproducibility? A systematic compilation of variance sources (Table 1), though likely to be incomplete, suggests that many sources can be controlled by careful methodology and some sources can be identified by assessing whether the effect is additive or multiplicative, and by analyzing whether the variance is common among several (nearly) simultaneously obtained measures (e.g., P50 versus N95, or various check sizes).

By reducing all technical sources of variability, one can obtain an upper limit for the physiological variability. This, again, is likely to be a mixture of factors, some of which have a circadian rhythm (intraocular pressure [16], shedding of rod and cone outer segment membranes [17], retinal sensitivity to light [18], amplitude of the flash ERG [19] and retinal dopamine level [20], which is known to modulate contrast sensitivity [21]). To unconfound diurnal and other effects, we performed two experiments: (1) repeat measurement after a 1-week interval (intersession variability) and (2) repeat measurement over 1 day (diurnal variability).

Table 1. Possible sources of variability, the type of effect and possible remedies

Cause	Effect	Remedy
Varying electrode position (both 'active' and reference electrodes)	Multiplicative, common to all components	Systematic care
Biological noise	Additive, not correlated between components	Control eye movements, reject artifacts, control glossolaryngeal artifacts, etc.
Technical noise	Additive, not correlated between components	Improve equipment
Pupil size, adaptive state	Multiplicative, common to all components	Control ambient luminance and interleave experimental conditions
Variable amplification, filtering, etc.	Multiplicative, common to all components	Frequent calibration of recording system
Inconstant stimuli, especially luminance and observer distance	Multiplicative, common to all components	Frequent calibration of stimulus setup
Inappropriate analysis (noisy peaks, steady state without Fourier analysis, Fourier analysis with overspill, etc.)	Any	Avoid
Intrinsic physiology	Multiplicative, may differ between components and stimuli	May be the experimental goal

Methods

Subjects

We examined 21 subjects (15 men, six women; mean age, 25.5 years) with no known eye disease and a visual acuity of ≥ 1.0 [22], refracted if necessary for the observation distance. All of them participated in the study of intersession variability, and 10 of them (six men, four women; mean age, 26.3 years) also participated in the diurnal study.

Stimuli

Phase-reversing checkerboards were used as stimuli. These were created with a Cambridge Research VSG2 graphics card and displayed on raster-

scan display [23] with a frame rate of 70 Hz, a stimulus field size of $32^\circ \times 27^\circ$ (larger than the 10° - 16° suggested in the ISCEV guidelines) at an observation distance of 57 cm, a mean luminance of 45 cd/m^2 and 98% contrast. Six stimuli were presented in an interleaved block design: three check sizes (0.4° , 0.8° and 16°), and each in a transient (2 reversals/s) and a steady-state presentation mode. Both eyes were stimulated at the same time, so we were able to record two PERG channels and one binocular visual evoked potential (VEP) channel.

Recording

To record the PERG, DTL electrodes were prepared as follows: A length of about 80 mm of DTL fiber [24, 25] was held by two gold-plated microcrocodile clips, attached to an Ohm meter (and later to the input amplifier). The center of the DTL fiber was pressed on a small adhesive strip. Stable conductance of the crocodile grip and the DTL fiber itself was assessed by shaking the microclips and listening to the audible Ohm meter. Then the adhesive strip was cut in the center, cutting also the DTL fiber, producing two DTL electrodes. These were placed in both eyes near the lower limbus after medial (nasal) fixation with the adhesive strips. Gold cup reference electrodes were placed at the ipsilateral outer canthi. A ground electrode was attached to the earlobe; the electrical impedance for all electrodes was less than $3 \text{ k}\Omega$. VEP signals were recorded simultaneously from Oz versus FPz by means of gold cup electrodes. Electrodes were placed by one investigator only (T.O.).

Signals were amplified, filtered (first-order band pass; upper frequency limit, 70 Hz; time constant, 0.1 s for steady-state and 0.5 s for transient recordings; no 50-Hz notch filter) and digitized at a sampling interval of 2.65 ms over an analysis interval of 412 ms. A sweep was rejected if the signal exceeded $\pm 100 \mu\text{V}$. Two recordings with 80 sweeps each were obtained in one session. The entire amplification chain including the computer interface was semiautomatically calibrated each day.

Subjects reported a random digit that appeared every 8 to 16 s for 300 ms in the center of the display to control for fixation and accommodation.

The averaged responses were digitally low-pass filtered (without introducing a phase shift) with a cutoff frequency of 40 Hz. According to the ISCEV guidelines, peak-to-peak amplitude measurements of the P50 component were measured from N35 to P50, and of the N95 component from P50 to N95. Steady-state responses were subjected to Fourier analysis, and the amplitude was defined as the magnitude at the reversal rate.

To assess intersession variability, measurements were repeated at the same time of day (maximal deviation, 1 hour) after 1 week, following Jacobi et al.

[11]. To assess diurnal variability, we conducted three recording sessions at 5-hourly intervals, starting in the morning.

Data analysis

How can we quantify reproducibility? Regression analysis is not appropriate [14], even though often used: the correlation coefficient is normalized for variance, thus it confounds retest variability and total variance. A better measure might be the ‘coefficient of reproducibility’ [14]. If the means of test and retest are identical, the coefficient of reproducibility collapses into the standard deviation (SD). This index scales with the magnitude of the signal, which is not desirable for the present application. So we used the coefficient of variation ($CV=SD/\text{mean}$), which is a normalized index: from the two measurements for each eye, the mean and the SD were calculated to obtain the individual CV. These individual CVs were averaged over all eyes, separately for all experimental conditions. A high value of CV indicates high variability or poor reproducibility.

When analyzing results from both eyes of the subjects, interocular correlation needs to be considered to avoid faulty significance estimates [26, 27]. One way to avoid this is to average the values from the two eyes. In the present case, however, this reduces the variability. To err on the safe side (i.e., find a higher variability estimate), we did not average across eyes for the intersession variability. For the diurnal variability study, however, we did average the values obtained from the two eyes of each subject, since circadian contributions – if existent – are probably highly correlated in the two eyes. By averaging across the eyes, we avoid erroneous inflation of the significance level.

Results

Intersession variability

First we consider the intersession variability experiment: repeat recording at the identical time of day after a 7-day interval. Figure 1 displays typical raw traces from two subjects, the one with the highest variability (right), and the one with the lowest variability in P50 and N95 (left). Also indicated are the individual P50 and N95 components. The digital smoothing (continuous curves) makes peak identification somewhat independent from noise influences on raw data points (small dots), as suggested by the ISCEV guidelines [15].

Figure 2 presents scatterplots of intersession variability for all experimental conditions. The scatterplots are arranged for check size (top 0.4° ; bottom 16°), and temporal frequency or component (left, steady state; center, P50;

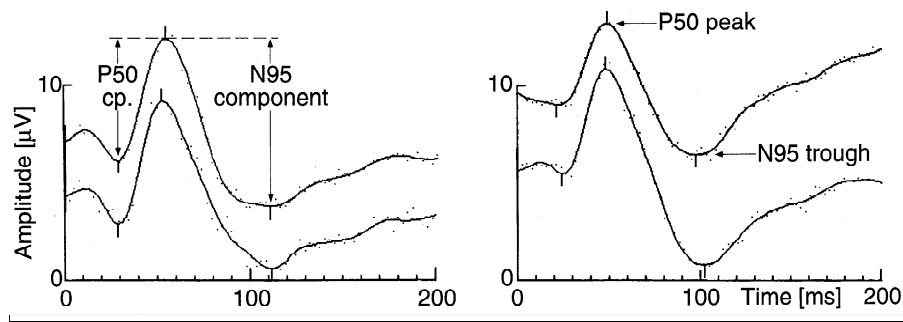


Figure 1. PERG traces from two subjects (right eye), superposition of the first session and the repeat session after one week. Transient stimulation, 0.8° check size. The small dots represent unfiltered data, and the smooth curves result from a digital filter of 0 to 40 Hz. The PERG from subject T.M. (left) is highly reproducible ($CV_{P50} = 0.4\%$, $CV_{N95} = 0.2\%$), and the PERG from subject F.E. (right) had the highest variability in P50 and N95 ($CV_{P50} = 18\%$, $CV_{N95} = 28\%$).

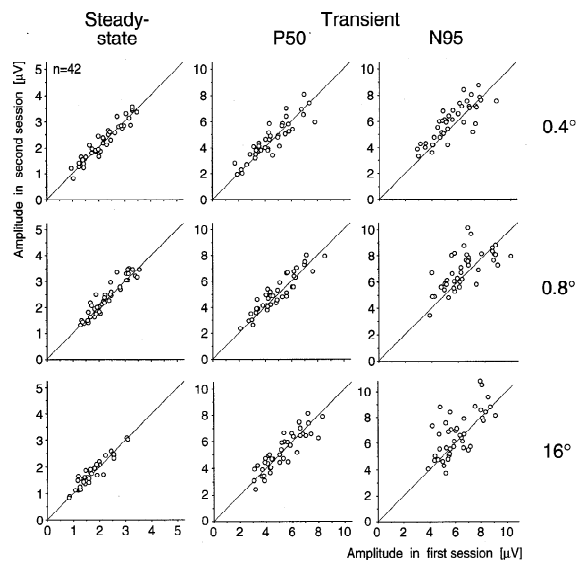


Figure 2. Intersession reproducibility of the PERG amplitude. For each eye, the CV of recording 2 (1 week after recording 1) versus the CV of recording 1 is depicted. Interindividual variability expresses itself along the 45° line, intersession variability perpendicular to the 45° line.

right N95). *Interindividual variability* expresses itself along the 45° line and has considerable magnitude: amplitudes range from 1.5 to $4 \mu\text{V}$ for steady state and from 4 to $10 \mu\text{V}$ for the transient N95. The large discrepancy between steady-state and transient amplitudes results mostly from the defini-

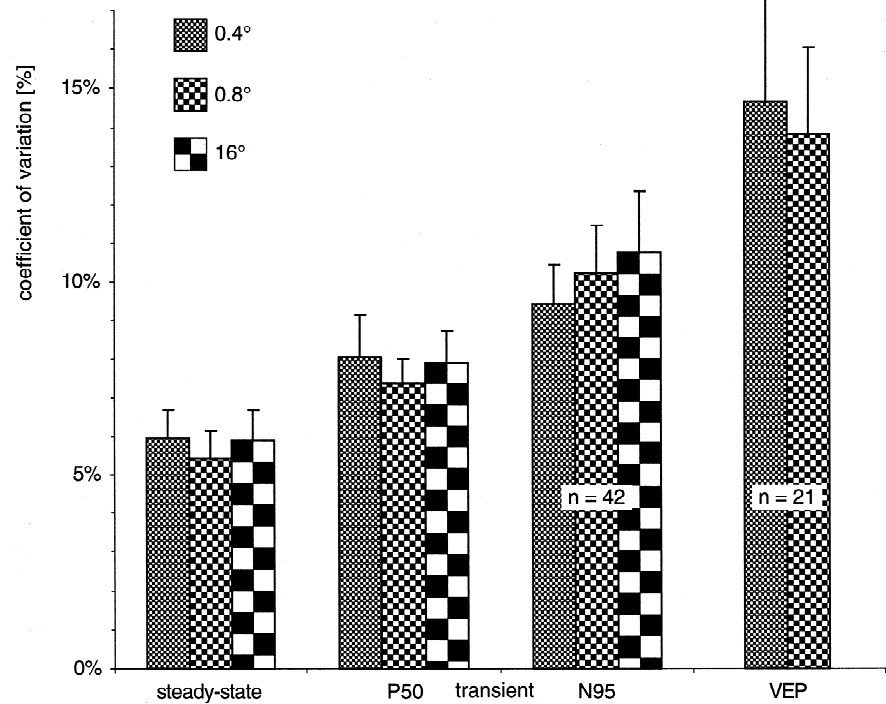


Figure 3. Mean (CV±SD) as a measure of intersession reproducibility for all recording conditions of PERG and VEP. Low values indicate high reproducibility.

tion of Fourier amplitudes; peak trough measures would yield values a factor of two higher. *Intersession variability* expresses itself as the deviation from the 45° line. It was quantified with the CV (see Methods). Figure 3 shows mean CV for all experimental PERG conditions and also the variability of the VEP amplitude. The mean amplitudes did not differ significantly between sessions in any condition (analysis of variance, always >5%). The CV was lowest for steady-state stimulation. Averaged over all conditions, mean CV was approximately 10%; VEP variability was higher, at 14%.

From the considerations compiled in Table 1, some variability sources can have effects common to or separate for each PERG component. In an attempt to unconfound these, we analyzed interrelations of the variability between the various PERG components. We concentrated on the steady-state PERG for the 0.8° and 16° check size condition and the transient P50 and N95 for the 0.8° condition, to reduce complexity. Initially, any effects are masked by the high interindividual variability. To remove this main effect, we normalized the amplitude obtained in the second session against the amplitude in the

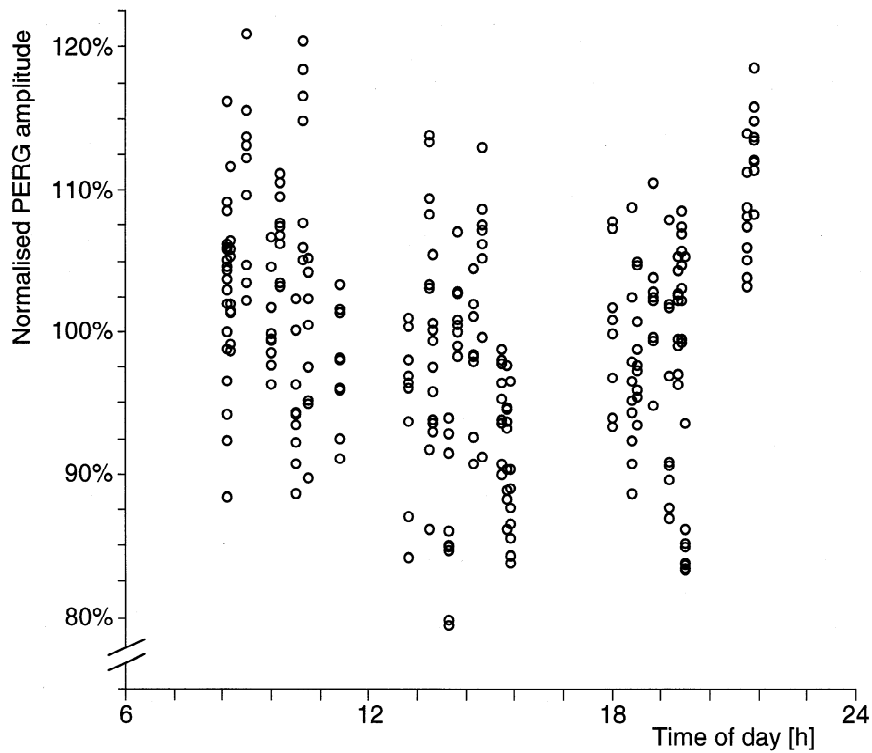


Figure 4. Relation between normalized PERG amplitude and time of day. Data for all check sizes and components collected from all subjects and recordings are plotted to show the central tendency and dispersions characteristics.

first session for each subject and component and analyzed the correlation between the four components with the following results. The two steady-state amplitudes (0.4° and 16°) were significantly correlated ($r^2=0.25$, $p<0.02$), but not significantly correlated with P50 or N95 ($r^2<0.07$, $p>0.5$). The two transient components are highly correlated ($r^2=0.31$, $p<0.01$). Latencies were found to be much less variable than amplitudes. Latency-CV was below 2% for both P50 and N95 and all check sizes.

Diurnal variability

To assess diurnal variability, subjects were recorded three times on one day with a time interval of 5 hours. The time of the first session varied between subjects. Figure 4 illustrates the dependency of individually normalized PERG amplitude on the time of day for all subjects, recordings, components and check sizes. There is a relative maximum of 105% in the morning, a minimum of 95% in the early afternoon and a rise to 102% in the evening. An analysis

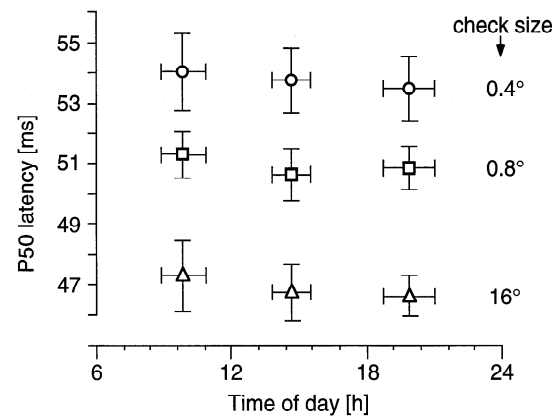


Figure 5. Mean P50 latency and SDs of 10 subjects over a 12-hour period. Latency decreased with increasing check size. No significant relationship between P50 amplitude latency and the time of day could be found for any of the three check sizes.

of variance was performed on the raw PERG amplitude with the factors time, component and check size. Significant effects were obtained for check size ($p=0.024$), component (steady-state, P50 and N95, $p<0.001$) and time of day ($p<0.001$), but no significant interactions were found. Post hoc analysis revealed that the diurnal variation was not significant with a check size of 16° but was significant at the 5% level for 0.4° and 0.8° . Furthermore, the diurnal effect was significant at the 0.1% level for all components, with an effect size of 7% for steady state, 5% for P50 and 9% for the N95 component. There was no significant diurnal effect on latency (Figure 5).

Discussion

Intersession variability

The mean CV across sessions ranged from 6% to 12%. Its value was lowest for steady-state recordings. We assume that the low steady-state variability does not reflect an intrinsic physiological property but rather results from the higher number of averages that can be obtained per unit time in a steady-state situation, combined with the effect that at 16 reversals/s, PERG amplitudes have not begun to decline markedly compared to lower temporal frequencies [28, 29]. Check size does not affect variability to a sizable degree. Interestingly, the variability of the VEP amplitude was found to be markedly higher than that of the PERG. This does not mean that the PERG is clinically much more reliable: the major diagnostic parameter of the VEP is latency, with a

CV of 2%. To date, the diagnostic variable of interest in the PERG is the amplitude.

The values for the amplitude variability of the VEP were found to be about 15%. This is somewhat lower than that in previous reports; for transient VEPs, 20% [30] or 25% [31] was found, and for steady-state VEPs, 20% [32].

Our PERG findings are consistent with those of Odom et al. [12] and Prager et al. [13]. Odom et al. found a CV of 5% to 8% for intrasession reproducibility; Prager et al. reported a CV of 8.5% with DTL and 15% with gold foil electrodes for intersession reproducibility.

It is unclear why Holopigian et al. [10], Bartel et al. [9] and Jacobi et al. [11] found much higher variability. Holopigian et al. [10] reported amplitude variability in three subjects within a single stimulus condition ranging from 30% to 67%. Possibly, their reference electrode position “temple” might account for some of the higher variability. The outer canthi as the reference position are more precisely defined, and amplitude is known to depend on the reference electrode position [33].

If signal-to-noise ratio decreases, variability increases. The high values of CVs for intrasession variability of around 30% found by Bartel et al. [9] may partially be caused by noise intrusion. They reported an average N95 amplitude of $1.7 \pm 0.42 \mu\text{V}$, which is markedly lower than the present average N95 of $5.8 \pm 1.4 \mu\text{V}$, obtained for the same check size. Jacobi et al. [11] sometimes found intersession amplitudes to vary by a factor of 2 to 4, a much higher variability than that in the present study. Again, this may partially be traced to noise intrusion, as only 50 sweeps were recorded per session; we routinely use 160 sweeps per condition.

It is of interest to note that some, but not all, components correlate between sessions, if the main effect (interindividual variability) is factored out. All measures were obtained in an interleaved design, so sequential effects such as fatigue cannot play a role. The finding that P50 and N95 have 31% of variance in common (only analyzed at 0.8°), steady-state 0.8° and steady-state 16° have 25% of variance in common, but only 7% of variance is common between transient and steady state, suggests the following interpretation: part of the variance common to P50 and N95 likely arises from the fact that the N95 amplitude is defined from the peak of the P50. But the 25% common variance between the steady-state measures is likely caused by intrinsic physiological modulators, and these modulators may not be identical for the steady-state and the transient conditions. Furthermore, the low common variance between the transient and the steady-state measures suggests that multiplicative factors, such as electrode position, adaptational state of the eye and pupil size, do not dominate our variability estimates (e.g., Table 1). We also conclude that ‘derived measures’ have some, though limited, value: the N95/P50 ratio [3,

34] could, at best, reduce the variability by 31%, and the PERG index [28], being based on a linear combination of steady-state responses at 0.8° and 16° check size, could, at best, remove 25% of the variability.

Diurnal variability

We were surprised to find a small ($\approx 10\%$) but significant and consistent circadian effect on PERG amplitude, and not on latency. While the effect is small, some speculation on its physiological basis is in order.

Dopamine. It has been suggested that dopamine tunes the contrast sensitivity function in humans [21]. The content of retinal dopamine is maximal around noon [20]. Intravitreal injection of dopamine decreased PERG amplitude in chickens, depending on spatial frequency: down to 25% for 0.8-cpd stimuli, down to 50% for 0.2 cpd, and stable for 0.05 cpd [35]. Human light sensitivity [18] and the magnitude of the ERG b-wave are minimal in the late afternoon [36].

Intraocular pressure. Both intraocular pressure (IOP) and mean arterial blood pressure (MAP) show a circadian minimum around 3 pm [37]. To the degree that PERG amplitudes decrease when IOP increases [38], an increase of PERG amplitude would be expected. However, blood flow in the optic nerve head is also influenced by the MAP, and the PERG responses are impaired when the eye perfusion pressure ($PP = MAP - IOP$) is reduced, disappearing at a critical MAP, irrespective of the absolute value of the IOP [39]. Thus, the circadian effects of IOP and MAP might cancel and not affect the PERG amplitudes.

The circadian amplitude modulation of the PERG might thus be traced mainly to circadian modulation of the dopamine level. The absolute effect is small (less than 10%) but could be taken into account when follow-up tests are scheduled. It is easily avoided by retesting at the same time of day.

We suggest that the following factors play a major role in obtaining a high reproducibility of PERG recordings: (1) precise, intraindividually and interindividually consistent position of the active and reference electrodes; nasal fixture of the recording electrode to ensure a stable location in the eye in the case of the DTL electrode; (2) appropriate and consistent choice of stimulus variables (high mean luminance, high contrast, large stimulus field size, optimal check size [15, 40]) evoking a high PERG amplitude; (3) use of Fourier analytic techniques, where applicable; (4) averaging a sufficient number of sweeps so that the sampling noise plays only a minor role; and (5) general observation of critical technical factors, such as blinking, head movement, eye movement, muscle artifact, amplifier and filter design, etc. [41]; see also Table 1).

Combining the results from the intersessional and diurnal parts of the present study suggests the following rule of thumb: PERG amplitude reproduces within $\pm 10\%$ with a probability of 70%. The effect size of the diurnal variation is of the same size and might be relevant for longitudinal studies.

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