Electroencephalogram-Based Scaling of Multifocal Visual Evoked Potentials: Effect on Intersubject Amplitude Variability

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PURPOSE. The interindividual variability of the visual evoked potential (VEP) has been recognized as a problem for interpretation of clinical results. This study examines whether VEP variability can be reduced by scaling responses according to underlying electroencephalogram (EEG) activity.

METHODS. A multifocal objective perimeter provided different random check patterns to each of 58 points extending out to 32° nasally. A multichannel VEP was recorded (bipolar occipital cross electrodes, 7 min/eye). One hundred normal subjects (age 58.9 ± 10.7 years) were tested. The amplitude and inter-eye asymmetry coefficient for each point of the field was calculated. VEP signals were then normalized according to underlying EEG activity recorded using Fourier transform to quantify EEG levels. High α-rhythm and electrocardiogram contamination were removed before scaling.

RESULTS. High intersubject variability was present in the multifocal VEP, with amplitude in women on average 33% larger than in men. The variability for all left eyes was 42.2% ± 3.9%, for right eyes 41.7% ± 4.4% (coefficient of variability [CV]). There was a strong correlation between EEG activity and the amplitude of the VEP (left eye, r = 0.83; P < 0.001; right eye, r = 0.82; P < 0.001). When this was used to normalize VEP results, the CVs dropped to 24.6% ± 3.1% (P < 0.0001) and 24.0% ± 3.2% (P < 0.0001), respectively. The gender difference was effectively removed.

CONCLUSIONS. Using underlying EEG amplitudes to normalize an individual’s VEP substantially reduces intersubject variability, including differences between men and women. This renders the use of a normal database more reliable when applying the multifocal VEP in the clinical detection of visual field changes.


Recent advances in clinical electrophysiology have extended the possible applications of the visual evoked potential (VEP) to objective visual-field mapping. However, a high level of intersubject variability is one of the major factors limiting clinical use of this technique. This variability has been recognized in standard central field VEPs and has been attributed to many factors, such as age and sex, cortical convolution and position of the calcaneous fissure relative to external landmarks (inion), eccentricity of the visual field tested, conductivity of underlying tissues (bone and subcutaneous fat thickness and blood circulation), general level of brain activity, and stimulus conditions. Although some factors (i.e., cortical convolution) are difficult to eliminate, others (such as age, sex, scalp conductivity, and level of brain activity) when compensated for may reduce the amplitude variation of the VEP.

Basar et al. and Rahl and Basar demonstrated an inverse relationship between amplitudes of the α (8–13 Hz) and θ (4–7 Hz) components of the spontaneous EEG activity measured immediately before stimulation, with subsequent frontal VEP amplitudes. They surmised that a high θ rhythm (which is associated with drowsiness) is associated with a suppressed VEP. When stimuli were applied only if the root mean square value of the ongoing EEG at the lead F4 was below an individual threshold level (so-called selective stimulation) the amplitude of the VEP significantly increased.

With relation to sex, it has been shown that the amplitude of the VEP is larger in women (particularly in older women) than in men. An interesting observation is that the larger amplitude is attributed to unusually high responsiveness of the visual system of older women to patterned stimuli or to the level of estrogen.

With VEP latency, a significant age effect (increasing latency with age) has been demonstrated, but not in relation to gender. The converse holds true for VEP amplitude, however, with no age effect being observed. Dependence of amplitude variability on visual field eccentricity has been demonstrated with the coefficient of variability (CV) of amplitudes of the waveforms in midperipheral locations being larger than those of the more central areas.

There have also been attempts to bypass the problem of between-subject differences in cortical anatomy by inter-eye comparison (asymmetry analysis) in the multifocal VEP interpretation. Underlying cortical convolution and position of the visual cortex relative to external landmarks are major contributors to intersubject VEP variability, but they influence the signals for the two eyes of a subject equally. This can permit the detection of unilateral changes without reference to normal values—for example, in the case of optic neuritis. However, if there is bilateral disease, the technique is less applicable.

In a pilot study we identified a strong correlation between background EEG levels recorded simultaneously with multifocal VEP stimulation, and the mean amplitude of the VEP. We surmised that the amplitudes of the two responses were correlated because the conduction of electrical signals across the skull, skin, subcutaneous tissue and electrodes was altered proportionately for the two signals. Therefore, it may be possible to use the underlying EEG levels to normalize VEP signals for each patient, to minimize influence of the mentioned factors and thus reduce intersubject variability. Because EEG activity is not totally independent of visual activity (for example, α rhythm levels vary between subjects and are suppressed by visual attention), other factors in the raw EEG signal must be taken into consideration.
Reducing intersubject variability is crucial in the identification of normal and pathologic results, whereas low intrasubject variability is important for detection of progression of the disease. The purpose of this study was to investigate variability among subjects for the multifocal VEP, and to determine whether an EEG-based scaling algorithm could be used to effectively reduce this variability.

**MATERIALS AND METHODS**

**Subjects**

One hundred normal subjects (44 men and 56 women) participated in this study. The mean age was 58.9 ± 10.7 years (range 21–80; men, 58.2 ± 11.1 years; women, 59.0 ± 9.9 years). The study protocol was approved by our regional ethics committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects. All participants were examined by an ophthalmologist. They had normal intraocular pressure, normal findings on ophthalmoscopy, and no family history of glaucoma or retinal dystrophy. All performed normal field tests (program 24-2; Humphrey Instruments, San Leandro, CA), confirmed by a normal result on the glaucoma hemifield test analysis. The inclusion criteria for the study required corrected visual acuity of 6/9 or better and pupil diameter of least 2.5 mm without dilation. Subjects with diabetes, previous cataract surgery, or any other ocular disorders were excluded.

**Stimulation and Recording**

A multifocal VEP was recorded using a multifocal objective perimeter (AccuMap; ObjectVision Pty. Ltd., Sydney, Australia), which simultaneously stimulates multiple sites within the visual field and extracts corresponding VEP signals from those sites. The perimeter used a spread-spectrum technique with families of binary sequences used to drive the visual stimulus. Two opposite checkerboard pattern conditions underwent pseudorandom binary exchange at each of 58 sites in the visual field. Each input (stimulation site) was modulated in time according to a different sequence (in contrast to m-sequences for which the same sequence is used but shifted in time). The technique permits computation of the resultant signal by cross-correlation of the response evoked by the sequence stimulation with the sequence itself. Short sequences of 4096 elements were used, which resulted in 55 seconds of recording time for each run. In further runs, different sequences were used for the same stimulation site to reduce the potential for cross-contamination. Results were viewed on screen after each run and then online averaged, and the recording was terminated when stable signals were achieved.

The visual stimulus was generated on a computer screen (22-in. high-resolution display; Hitachi, Tokyo, Japan) with a stimulation rate of 75 Hz. Fifty-six closely packed segments in a dart-board configuration were used, with two additional segments located in the nasal step region. The segments were cortically scaled with eccentricity to stimulate segments with two additional segments located in the nasal step region. Each segment contains a checkerboard pattern (16 checks), with the size of individual checks being proportional to the size of the segment. The central area is used as a fixation monitor.

Subjects were seated comfortably in a chair and asked to fixate on the fixation number at the center of the stimulus pattern. The distance to the screen was 50 cm, corresponding to a radial subtense for the stimulus of 24°, not including the additional nasal step (32°). All subjects had optimal refraction for near and the pupils were not dilated. All recordings were collected using monocular stimulation. Data were recorded using a four-channel amplifier (Grass model 15 Neurodata; Astro-Med, Inc., West Warwick, RI). The signal was amplified 100,000 times and band-pass filtered between 3 and 30 Hz. The upper band-pass filter at 30 Hz was relatively low and outside International Society for Clinical Electrophysiology of Vision (ISCEV) standards for conventional VEP recording. We deliberately chose this, because it removed high-frequency noise that can contaminate some recordings. We have performed comparisons on the same subjects, both healthy persons and subjects with glaucoma, and found minimal differences between the 100- and 30-Hz cutoffs other than a slight (2–3-msec) increase in latency. Fourier analysis showed minimal high-frequency components in the VEP above 30 Hz that have been removed by filtering (authors’ unpublished data, 1999). Although not ideal, it allowed the system to operate in a clinical setting with the effects of muscle noise removed and allowed use of an unshielded room.

The data-sampling rate was 450 Hz. Raw data were scanned in real time, and noise artifacts exceeding 3 SE were excluded from the analysis. Runs contaminated by a high level of noise were also rejected. Usually, eight runs were recorded to provide a good signal-to-noise ratio.

**Electrode Positions**

Gold disc electrodes (Grass; Astro-Med, Inc.) were used. A custom-designed occipital cross electrode holder predetermined the four electrode positions. It was lightweight and comfortable for the patient, and neck muscles remained relaxed. The scalp was cleaned (Nuprep; D. O. Weaver & Co., Aurora, CO) at each site before finalizing the electrode position. All recordings were performed with the level of resistance between electrodes lower than 3 kΩ. Four channels were used, as described previously, to cover different underlying dipole orientations. The vertical channel comprised electrodes 4.5 cm below inion and 2.5 cm above. The horizontal channel linked the two electrodes 4 cm either side of the inion. The oblique channels linked the lower midline with either right or left horizontal electrode. The lower midline electrode was negative for the vertical and oblique channels,
whereas the left horizontal electrode was negative for the horizontal channel.

**Analysis**

VEP traces were analyzed using custom-designed software. Largest peak-to-trough amplitudes for each wave within the interval of 60 to 180 msec were determined and compared among channels for every stimulated segment of the visual field. The VEP waveform was most frequently present as a single wave, simplifying identification of peak-to-trough amplitudes. However, in some cases, a double peak could be seen, which makes it possible that different peaks were measured in some subjects. This may have an influence on determining latency values (not analyzed in this article). The wave of maximal amplitude from each point in the field was automatically selected, and a combined topographic map was created by the software. A combined trace array was then used for further analysis.

The intersubject CV (SD/mean) was calculated for each of the 58 segments of the visual field. The VEP amplitude was averaged over the whole visual field (all 58 segments) for each subject, and variability for the averaged amplitude was calculated.

To quantitatively analyze the relationship between the EEG and VEP, a Fourier power spectrum (fast Fourier transform [FFT]) of the EEG for each recorded channel was calculated (Fig. 2A). It was noted that in some subjects there was a large peak in the FFT at approximately 8 to 10 Hz that was attributed to a rhythm (Fig. 2B). In some subjects there was also a strong electrocardiogram (ECG) contribution. The ECG had previously been noted in several subjects during real-time recording, seen as spikes that were synchronous with the subject’s pulse. These were identified in the FFT (Fig. 2C). To exclude the influence of these two components on scaling, the Fourier power spectrum within the interval 0 to 30 Hz was fitted with a polynomial function of the fourth order, and the integral of the fit was calculated. Average values of the integral from all 100 subjects were obtained for each channel.

**Results**

The mean (±SD) of the VEP amplitude for each segment of the visual field of all 100 subjects is presented in Figure 3. There is a noticeable reduction of the amplitude in the upper part of the visual field of both eyes, which is in agreement with previously reported results. Generally, the amplitude also tended to decrease toward the periphery.

The intersubject variability in amplitude for each segment of the tested visual field for both eyes is shown in Figures 4A and 4B. High intersubject variability was present across the visual field and was similar between the two eyes (Fig. 4A). The mean CVs for all individual segments for left eyes was 42.2% ± 3.9% and for right eyes, 41.7% ± 4.4%. There was no change in variability with eccentricity of the visual field stimulated (Fig. 4B), even though amplitudes were smaller with eccentricity.

The variability among subjects was also calculated for the mean amplitude across the visual field of each subject. The CVs for the mean amplitude of the left and right eyes were 27.5% and 28.5%, respectively.

There was a strong correlation between EEG activity and the amplitude of the VEP. Figures 5A and 5B display the relationship for all subjects tested between VEP amplitude of the vertical channel averaged over all 58 points of the visual field and the related Fourier power spectrum of the raw EEG data of the same channel collected during VEP recording. The integral of the FFT fit was used as an EEG measure. The correlation coefficient defined by linear regression analysis for the left eye was $r = 0.83 (P < 0.001)$ and for the right eye, $r = 0.82 (P < 0.001)$. The high level of correspondence between the amplitudes of two electrophysiological responses measured simultaneously suggests that to a large extent VEP amplitude variability is likely to be attributed to the same factors that influence EEG amplitude.

The amplitude of the individual VEP was then normalized to the average amplitude of the whole group by the Fourier power spectrum of the EEG. Normalization of the VEP signal was performed separately for each channel (before combining) and each run. Raw data (EEG) were initially cross-correlated with the corresponding stimulating sequence to derive the VEP, and then the following formula was applied:

$$V_{\text{normal}} = V_{\text{recorded}} \times \left[ \frac{(F_{\text{average}} - X_{\text{mean}})}{(F_{\text{recorded}} - X_{\text{mean}})} \right]$$

where $V_{\text{normal}}$ is normalized VEP, $V_{\text{recorded}}$ is recorded VEP, $F_{\text{average}}$ is average of FFT from all 100 subjects, $F_{\text{recorded}}$ is the FFT recorded for a particular run of a particular subject, and $X_{\text{mean}}$ is interception of the trend line with horizontal axis.

The results of normalization are presented in Figures 5C, 5D and 6. There was a significant reduction in intersubject variability in both mean VEP amplitude and VEP amplitude of
individual sectors. The CV of mean VEP amplitude averaged across the whole visual field (Figs. 5B, 5C) decreased by more than 46% in both eyes ($P < 0.01$) and reached 15.2% and 14.9% in the right and left eyes, respectively. The amplitudes of the VEP after normalization appeared to be much more closely grouped around the mean value.

CVs of the individual sectors of the visual field were also substantially reduced by normalization. Figure 6 shows a comparison between nonscaled (gray background) and scaled (vertical bars) variability and demonstrates significant improvement in amplitude variability for each stimulated sector of the visual field. CVs after amplitude normalization were 24.6% ± 3.1% in the left eye ($P < 0.0001$) and 24.0% ± 3.2% in the right eye ($P < 0.0001$), representing reductions in variability for individual segments of 41.4% ± 5.2% and 42.2% ± 5.8% in the left and right eyes, respectively.

Examples of EEG scaling of the multifocal VEP are presented in Figure 7. The first subject had a low EEG amplitude and lower than usual VEP signal, which was scaled up by the normalization procedure (Fig. 7A), whereas the second subject had a high VEP amplitude and very high EEG signal. His VEP traces were scaled down by normalization (Fig. 7B). The resultant trace arrays are much more similar in amplitude than they were before EEG-based normalization.

There was practically no relationship between the amplitude of the VEP recorded in this study and the age of the subjects, either before or after scaling (Figs. 8A–D). Age versus amplitude correlation coefficients before scaling were $r = 0.049$ ($P > 0.5$) and $r = 0.0094$ ($P > 0.5$) and after scaling $r = 0.1$ ($P > 0.5$) and $r = 0.05$ ($P > 0.5$) in the left and right eyes, respectively.

There was, however, a significant difference in amplitude between the male and female groups before scaling (Fig. 9). The mean amplitude in the women was 209 nV and 210 nV compared with 158 nV and 156 nV in the men in left and right eyes, respectively ($P < 0.00001$ for both eyes). The variability was slightly less after subjects were separated into gender groups (Table 1). However, when EEG scaling was applied, the gender-based amplitude difference was removed, and the variability declined significantly and approached the variability values for the scaled combined-gender group (Table 1). Mean amplitudes in the female group were reduced to 180 nV for both eyes, whereas mean amplitudes in the male group increased to 182 nV for both eyes, whereas mean amplitudes in the male group increased to 182 nV and 178 nV in the left and right eyes, respectively ($P = 0.69; P = 0.16$, respectively).

**DISCUSSION**

Multifocal VEP recording provides a unique opportunity for objective detection of visual field defects. However, high intersubject variability due to variation in cortical anatomy caused some investigators to conclude that it would not be useful for clinical testing. It was argued that in some locations,
even extreme damage of the visual pathway may not be reliably distinguished from normal values. This study demonstrates that using underlying EEG amplitudes to scale an individual’s VEP response substantially reduces this variability, including differences between men and women. This renders the use of a normal database more reliable when applying the multifocal VEP in the clinical detection of visual field changes.

The intersubject variability assessed after derivation of the VEP by cross-correlation of the raw EEG data with stimulating sequences was evenly distributed across the visual field and very similar between the two eyes. VEP amplitude did not correlate with age, which is in accordance with previous reports. However, there was a well-defined difference in VEP amplitude between genders, with the women demonstrating significantly higher amplitudes than the men. Slight decreases in variability of gender groups compared with the tested population as a whole indicated that some of the intersubject VEP variability was gender based. EEG scaling of the

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**Figure 4.** (A) Intersubject amplitude CVs before EEG scaling for each segment of the visual field (100 subjects) in both eyes. Segment numbers are as for Figure 3C. (B) Intersubject CVs before EEG scaling were averaged over rings of different eccentricity and showed no increase in variability with eccentricity. (C) Ring topography.

**Figure 5.** (A, B) Correlation between EEG activity and the mean VEP amplitude for the vertical recording channel. Fourier power spectrum expressed in arbitrary units; (C, D) amplitude of the mean VEP after EEG-based normalization. (A, C) Left eyes, (B, D) right eyes.
VEP was able to effectively remove the differences between the sexes.

The VEP amplitude was highly correlated with raw EEG data collected during the recording. The high correlation ($r^2 > 0.65$) suggests that similar influences account for the amplitude variability of these two electrophysiological measures. Because the VEP signal is tiny in comparison to the EEG (approximately 1000 times) it does not make a significant contribution to the overall EEG amplitude and is only identified by cross-correlation techniques. We propose that normalization of the VEP by the EEG removes the common source of variability. We suspect that the differences between individuals are to a large extent conductivity differences affecting transmission of the signal from the cortex to the scalp.

The scaling applied in this study to the VEP amplitude reduced intersubject variability greatly. An intersubject CV of the mean VEP amplitude decreased by more than 46%, whereas individual segments of the stimulated visual field improved variability by approximately 40%. The scaling procedure did not affect the independence of the VEP amplitude with age. However, the clear difference in amplitude of the VEP between genders before scaling was eliminated by EEG-based normalization.

It is critical to determine the components of the raw EEG signal before applying any scaling. Some individuals have high $\alpha$ rhythm activity, even when they are visually attentive. If this is included in the scaling, the VEP response is artificially scaled down. High $\alpha$ rhythm may also indicate that the patient is not

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig6}
\caption{Comparison between nonscaled (gray background) and scaled (vertical black bars) CVs for each stimulated segment of the visual field. Segment topography is as shown in Figure 3C. Top: left eyes; bottom: right eyes.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig7}
\caption{Examples of EEG-based scaling of the multifocal VEP. Final trace amplitudes for the two subjects shown are similar after normalization. (A) Small VEP amplitude scaled up based on smaller than average EEG signal in that subject. (B) Large VEP amplitude was scaled down based on a high EEG signal in that subject.}
\end{figure}
concentrating and can provide some real-time feedback to the recording technician, especially if it appears halfway through the recording. It could also be present in malingerers who are deliberately defocusing. Our system cannot differentiate the cause of a high α rhythm, but it should be excluded from any scaling algorithm used.

There are other measures that can be taken to attempt to reduce variability. The randomly changing fixation number in the central screen helps to keep the subject concentrating and mentally alert. It provides a partial index of reliability and reduces the mesmerizing effects of the multifocal display, which can cause fatigue in some patients. Breaks between runs and the presentation of an alternative image between runs (e.g., scenic photographs) also help in relaxation and preventing fatigue during the test. Standardizing distance to the screen may increase reproducibility; a tracking device has been developed for this purpose.

The use of multichannel recording reduces the great variability between individuals that is thought to be a result of underlying convolution of the cerebral cortex, because most dipole orientations are covered by at least one channel. However, because of the significant size of the area of visual field stimulated by a single zone, the visual cortex to which this part of the visual field projects is still not uniformly oriented (otherwise, all differences might be rectified by differently oriented channels) but contains a three-dimensionally curved cortex producing a signal of variable source between subjects. Although reduction of the size of the single stimulated zone may help to reduce the amplitude variability, it would also lead to a reduction in the VEP amplitude and therefore to a reduction in the signal-to-noise ratio, which would further increase variability. Because the VEP amplitude does not seem to depend on the age of the subjects and using EEG scaling removes variability related to conductivity and sex, we believe that the remaining variability is probably due to residual microanatomic differences in the cortical convolutions of the striate cortex between subjects that cannot be overcome by use of multichannel recording. Therefore, we still need to derive a source-localization technique that will accurately pick up responses from all underlying anatomic variations. Several different approaches to this problem are currently under review.

In conclusion, by the application of EEG scaling to VEP responses, a considerable problem in objective visual field mapping can now be largely overcome. Interindividual variability is halved, which allows meaningful comparisons with nor-

### Table 1. VEP CVs for the Whole Group and for Separate Gender Groups, before and after EEG-Based Normalization

<table>
<thead>
<tr>
<th>Groups</th>
<th>Individual Segments before Scaling</th>
<th>Individual Segments after Scaling</th>
<th>Averaged Response before Scaling</th>
<th>Average Response after Scaling</th>
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</thead>
<tbody>
<tr>
<td>Whole Group</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LE</td>
<td>41.4 ± 5.2</td>
<td>24.6 ± 3.1</td>
<td>27.5</td>
<td>15.2</td>
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<tr>
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<td>42.2 ± 5.8</td>
<td>24.0 ± 3.2</td>
<td>28.5</td>
<td>14.9</td>
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<tr>
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<tr>
<td>LE</td>
<td>39.8 ± 5.4</td>
<td>24.2 ± 2.8</td>
<td>25.8</td>
<td>15.0</td>
</tr>
<tr>
<td>RE</td>
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<td>25.9</td>
<td>14.9</td>
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</tr>
<tr>
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<td>24.4 ± 2.9</td>
<td>24.9</td>
<td>14.8</td>
</tr>
<tr>
<td>RE</td>
<td>39.8 ± 4.4</td>
<td>25.8 ± 4.2</td>
<td>25.3</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Data are percentages. Columns 2 and 3 show mean ± SD for CV of individual segments across all subjects. Columns 4 and 5 show mean ± SD CV of VEP mean amplitude. LE, left eye; RE, right eye.
mal databases and increases the sensitivity of the test to the detection of disease.

Acknowledgments

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References