ISCEV extended protocol for estimating visual acuity using VEP spatial frequency thresholds

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Contributor's Statement Page

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

The International Society for Clinical Electrophysiology of Vision (ISCEV) standard for visual evoked potentials (VEP) describes a minimum procedure for clinical VEP testing, but encourages more extensive testing. This ISCEV extended protocol is an extension to the VEP standard. It describes procedures for establishing the VEP spatial frequency (SF) threshold by recording multiple VEPs to pattern stimuli with a range of size to determine a threshold, and relating this threshold to visual acuity.

Introduction

The International Society for Clinical Electrophysiology of Vision (ISCEV) standard for visual evoked potentials (VEPs) describes a minimum set of tests but encourages the use of additional VEP protocols for clinical testing [1]. This extended protocol describes the VEP spatial frequency (SF) threshold, a specialised procedure which is well established and broadly accepted by experts in the field. The protocol was prepared by the authors in accordance with ISCEV procedures (www.iscev.org/standards) and was approved by the ISCEV Board of Directors on [date], following a two-month period of open consultation with the ISCEV membership. The authors have also undertaken a systematic review of VEPs used for SF threshold measurement to inform this extended protocol, to provide a contemporary review of the relevant extensive literature and to examine how associations between VEP SF threshold and visual acuity vary with clinical condition [2].

Scope and applications

VEPs are evoked in the visual cortex and are recorded by processing electroencephalographic (EEG) signals from overlying scalp electrodes. Given the integrity of the central visual field for the specific stimulus, for that stimulus an extant VEP is expected [1]. Therefore, VEPs can be used to measure a SF threshold as an estimate of visual acuity: such techniques have been employed for over 40 years [3, 4]. A VEP SF threshold is objective and requires less cognitive function or cooperation than behavioural tests of vision. VEP SF threshold and visual acuity are not measurements of the same entity due to differences in stimuli, retinal area, fixation duration, level of the visual system assessed, and means of defining a threshold. Nonetheless, agreement between VEP SF thresholds and behavioural measures of acuity can be sufficiently consistent to make VEPs useful for clinical estimation of acuity when behavioural testing is not possible or reliable. The difference between a VEP SF threshold and a behavioural acuity can be handled using an empirical calibration factor or offset which depends on the VEP SF technique, the acuity test, the subject's age, the type of visual

dysfunction and, to a lesser extent, the subject's acuity. The empirical calibration factor is required to infer visual acuity from a VEP SF threshold: it is incorrect to assume that a VEP SF threshold of 30 cycles per degree (cpd) is equivalent to a visual acuity of 0.0 logMAR, i.e. 1.0 (decimal), 6/6 or 20/20 (Snellen) as this relationship typically fails to hold for VEP SF thresholds. As described in our systematic review [2], VEP SF thresholds can be a good proxy for behavioural acuity in patients with media opacities, refractive errors, and primarily retinal dysfunction. In patients whose primary site of dysfunction is the macula, the optic nerve or any cerebral structures, VEP SF thresholds may have poorer accuracy and precision when compared to behavioural measures: this includes amblyopic patients in whom VEP SF thresholds are relatively insensitive to reduced optotype acuity. VEP SF thresholds are particularly helpful in patients with non-organic vision loss providing sufficiently fine[*] SFs are used and all possible organic causes have been ruled out. A VEP SF threshold should be ordered and interpreted only as part of a fuller assessment, and cannot be interpreted without full clinical assessment and history. It should be used for patients who cannot or will not reliably undertake behavioural acuity tests.

Patient populations

Visual acuity is typically measured using subjective tests such as letter charts which require the patient to have adequate cognitive and motor function, and to comply with the test process. VEP SF thresholds are indicated in patients who cannot undertake behavioural acuity tests, or where reliable completion of subjective or behavioural acuity tests is questionable. VEP SF thresholds are useful for estimating acuity in infants and children, particularly those with motor or learning impairments which prevent reliable measurement of behavioural acuity. Typical thresholds increase rapidly over

[*] For clarity, we have described patterns as "fine" or "coarse" and avoided the terms "high" and "low" since SF units, e.g. cycles per degree (cpd), and element size units, e.g. minutes of arc (′) have an inverse relation, and therefore opposite meanings of "high" and "low".

the first year of life and then more slowly, reaching adult levels between 2 and 10 years of age. VEP SF thresholds are much better than behavioural acuity in the youngest typically-developing infants, typically measured with acuity card tests based on fixation preference, but the reverse is found from around 3–5 years onwards. For this reason inferring a visual acuity from an individual infant or child's VEP SF threshold should not use empirical calibrations established for adults.

Technical issues

(a) VEP stimuli. VEP amplitude is tuned to temporal frequency and largest for stimuli which change in the range of 5–12 Hz (on/offsets; 10–24 reversals per s (rps)): within this approximate range, VEP SF thresholds are relatively constant. VEP SF thresholds improve with increasing mean spatial luminance, reaching stability across the range 25–100 cd/m^2. Higher contrast generally improves signal to noise ratio (SNR) and hence VEP SF thresholds, but contrast levels >40% enhances the amplitude notch (reduced amplitude VEPs at intermediate SFs) in the amplitude versus SF tuning curve, risking underestimation of VEP SF threshold. Lower contrast reduces the risk of luminance artefacts and may be more comfortable for patients. VEP SF thresholds remain relatively stable over a large range of field sizes (2–12°); larger field sizes can compensate a little for poor fixation. Checkerboards, sinusoidal gratings and square wave gratings (bars) are widely used. While sinusoidal gratings are spatially simpler, containing a single SF, the sharp edges of square-wave gratings or checkerboards contain multiple finer SFs and may provide a better accommodative stimulus. Grating orientation (horizontal vs vertical) does not affect VEP SF thresholds but oblique orientations give poorer VEP SF thresholds than cardinal orientation: since a checkerboard's fundamental SF (SF_f) is oriented obliquely (see formula below), VEP SF thresholds to checkerboard stimuli may be poorer than those to grating stimuli. Reversing stimuli produce a more marked notch than on/offset stimuli. Brief onsets (e.g. 40 ms) cause the on- and off-responses to overlap, producing a larger and therefore more detectable VEP than longer onsets (e.g. 300 ms [1]).

(b) Stimulus sequencing. True sweep VEPs (continuously changing SFs) is no longer used; rather SF is changed in steps, a 'stepwise sweep'. Extrapolation techniques require adequately dense and extensive sampling of the VEP amplitude versus SF function, especially with reversing stimuli which may produce a notched function. In healthy adults and older children at least, patterns up to 40 cpd may be required in order to approach or bracket the subject's VEP SF threshold and avoid under-estimation errors. Linear sampling of SF produces desirably fine sampling towards the VEP SF threshold of normal adults but linear changes in SF cannot always be achieved for the finest patterns available on a display, e.g. 1×1 to 2×2 to 3×3 pixels. Logarithmic sampling gives equal weight to each octave of SF, as for a psychophysical tuning function, but spatial resolution is reduced towards the acuity limit. For sequential SF presentation, the direction of change (coarse-to-fine or fine-to-coarse) does not incur much hysteresis nor does it affect VEP SF thresholds, although subjects may be more attentive to coarse-to-fine stepwise sweeps.

(c) Acquisition and analysis. Active electrodes close to Oz define VEP SF thresholds well, and closely-positioned reference electrodes, especially in a Laplacian montage, enhance SNR towards threshold by cancelling remote noise. VEPs acquired at rates of 5–12 Hz or 10–24 rps are usually analysed in the frequency domain using a discrete Fourier transform (DFT), sometimes after some time domain averaging. Typically, only the first harmonic (at the stimulus frequency, on/offset stimuli) or second harmonic (at the reversal rate, reversing stimuli) is considered since magnitude is usually lower for higher harmonics, but considering higher harmonics may be useful. Presence or absence of a VEP at the stimulus frequency is determined objectively, for example SNR ≥ 3 with noise defined by magnitude in an adjacent frequency bin or mean of the two adjacent bins, or 95% confidence interval of DFT magnitudes excluding zero. DFT phase data may be incorporated into decision-making by requiring physiologically plausible phase lead or lag with decreasing or increasing SF respectively. Both magnitude and phase can be employed in bivariate techniques such as the circular T^2 statistic or magnitude-squared coherence statistic.

(d) Defining the VEP SF threshold. Extrapolation to 0 μV of a straight line regressed through the final descending portion of detectable VEP magnitudes plotted versus linear SF is most commonly used. Logarithmic SF axes are also used, but may give better VEP SF thresholds than linear scaling. Since some of the magnitude output of a DFT at the stimulus frequency is noise, extrapolating to 0 μV rather than to a noise floor may slightly overestimate VEP SF thresholds unless noise-corrected magnitudes are used. VEP SF threshold can also be defined as the finest SF evoking a significant VEP, which results in thresholds slightly worse than those found by extrapolation: this finest SF technique can be used as an alternative, integrated strategy for occasions when the extrapolation technique fails to define a threshold.

(e) Transient VEPs for SF threshold measurement. Transient VEPs SF thresholds can be used to estimate acuity, but as they are known to be affected by patient fatigue, neural adaptation and subjectivity of analysis, they are not included in this extended protocol: the long recordings required to evoke subjectively-recognisably, reproducible responses to multiple SFs make them less suitable for the target patient population. Furthermore, it is not advisable to attribute an acuity based on presence, absence, or normality of VEPs to ISCEV standard checkwidths of 60’ and 15’ (0.71 and 2.8 cpd): an extant VEP (transient or steady-state) to 2.8 cpd would certainly be in keeping with “good visual acuity” for a baby, but, as a threshold, would be much poorer than typical for any patient aged over 1 year.

Calibration

Calibration of stimulation and recording systems should be verified and re-calibrated if indicated at intervals as specified in the current ISCEV VEP standard and Calibration guideline [1, 5]. Users must ensure absence of any luminance artefact such as transient artefacts created by non-CRT screens or artefacts due to luminance mismatch of grey and pattern for on/offset stimulation. All pattern element sizes, e.g. checkwidths, should be directly measured to verify the visual angle

subtended. Patterns should be expressed in cpd using formulae in [4, Table 1]. In particular, the obliquely-oriented SF_f (cpd) of a checkerboard is expressed as

$$SF_f = \frac{60}{\sqrt{2} \times w_c},$$

where w_c is the visual angle subtended by one checkwidth in minutes of arc.

An empirical calibration factor is required to infer a behavioural acuity from a VEP SF threshold: for details, see section Response evaluation: (b) Inferring a behavioural acuity, below.

Protocol specifications

Patient preparation follows that of the current VEP standard [1], except for a closely placed reference electrode (see below). Measurement of the VEP SF threshold may precede or follow ISCEV standard minimum protocols. Subjects should wear any required refraction and pupils should not be pharmaceutically dilated, although cycloplegia and refraction may be required for some patients suspected to be malingering or with factitious disorders. Binocular stimulation is used when the aim is to gain insight into practical functioning levels. Monocular testing is used to evaluate vision in each eye separately, and any interocular differences. Patients should be physically well-supported which may mean using a carer's lap with heads supported securely for infants or small children, or the patient's own mobility chair. Ambient lighting should be chosen to maximise the subject's attention and fixation on the stimulus screen. It is essential that data acquisition for analysis is suspended if the subject's gaze leaves the stimulus.

Rapidly-altering stimuli, i.e. 5–12 Hz (on/offsets) or 10–24 reversal per s (reversals), are required to evoke steady-state VEPs which can be objectively analysed. Onsets should be brief, e.g. 40 ms and should not exceed 60 ms. Checkerboards, sinusoidal gratings or square wave gratings should be used. Mean luminance should be approximately 50 cd/m^2 (acceptable range 25–100 cd/m^2); contrast of 40% (acceptable range 30–50%) which balances the need to minimise any notch in the SF tuning

curve whilst maintaining reasonable SNR. A field size >15°, as for the VEP standard, is suitable, but may need to be smaller to accommodate increased viewing distances required for fine SFs: field size should not be less than 3° in diameter. The range of SFs should be suited to each patient as far as possible, with the finest SF presented being close to or beyond the subject's VEP SF threshold. Either linear or logarithmic sampling of SF are suitable. SFs are typically evenly distributed across the range employed. Coarse-to-fine or fine-to-coarse SF sequencing are acceptable, as are random, pseudo-random or staircasing sequences A single channel recording with the active electrode at Oz, as for ISCEV standard VEPs, is adequate; the reference electrode is closely-positioned, for example at O1, O2 or Pz. Two or more channels, for example Oz referenced to O1 and Oz referenced to O2, and using whichever has highest SNR is an acceptable option. Using a Laplacian montage to enhance VEP detection is also acceptable and can be implemented using two close reference electrodes, e.g. O1 and O2, and a 'virtual' channel derived as Oz−((O1+O2)/2).

Magnitude and phase of the EEG signal at the first harmonic (i.e. the stimulus frequency for on/offset) or second harmonic (i.e. the reversal rate for reversal) should be determined with a suitable technique, e.g. the DFT. Significance of the signal should be established objectively based on magnitude (e.g. SNR at stimulus frequency relative to neighbouring frequency bin(s)) and/or phase statistics. The VEP SF threshold is defined as the extrapolated threshold or the finest SF evoking a significant VEP.

Response evaluation

(a) VEP SF threshold. During recording, automated artefact rejection and manual suspension of acquisition during poor fixation should be used, and the quality of the EEG signal should be monitored. Both magnitude and phase plots with axes labelled with relevant units (e.g. μV and degrees vs stimulus cycles per degrees) should be inspected for physiologically plausible findings, e.g. reasonable magnitudes and phase lag increasing with SF. Plots should indicate which SFs

evoked significant or non-significant VEPs, and which were used for any regression.

(b) Inferring a behavioural acuity. An empirical calibration factor is required to infer a behavioural acuity from a VEP SF threshold. This should be derived experimentally from an adequately-sized group of subjects from whom both VEP SF thresholds and behavioural acuities have been obtained. Some measure of the spread of values, e.g. limits of agreement, as well as a point estimate of the average offset should be given. Empirical calibration factors derived from adult subjects are not valid for infants or children younger than 2–5 years old. Where a calibration factor from elsewhere is used, e.g. as part of a manufacturer's protocol, its provenance should be given in sufficient detail to allow new users to judge its transferability to their patient population.

Reporting

Full details of all stimulus, acquisition and analysis parameters, pertinent patient details such as quality of fixation, and plots of VEP magnitude and phase vs SF should be included. The plots should indicate all SFs which were employed, and those which evoked significant VEPs. If extrapolation is used, the regression line and the SFs regressed should also be indicated. If extrapolation is not used, the criterion for threshold SF should be stated. Thresholds should be stated in cpd. Reports should state age-appropriate reference intervals, including their provenance, and a statement of normality or otherwise for the patient tested.

There is no requirement for the further step of relating the VEP SF threshold to behavioural acuity measures. If this is undertaken, reports should explicitly state what empirical calibration factor has been applied with access to a reference for its provenance which provides details such as ages of subjects, behavioural acuity tests used, and a measure of variability e.g. limits of agreement. Reports should advise caution with interpreting results for patients whose known or suspected type of visual dysfunction potentially makes their VEP SF threshold an unreliable estimate of acuity.

Acknowledgements

To follow.

Appendix: Justification of the protocol details

The committee was formed of individuals from diverse centres with experience of development and/or use of clinical VEP SF thresholds. To minimise bias, a systematic review was undertaken. In brief, four databases were independently searched using appropriate MeSH terms or equivalent keywords for studies (articles, conference proceedings or dissertations) describing VEPs used to estimate visual acuity in humans. Titles and abstracts, and where necessary, full texts were screened to identify potentially eligible studies for inclusion. Data were extracted from included studies using a standardised template. The protocol was registered with the international prospective register of systematic reviews (PROSPERO), registration number CRD42018085666 and methodology is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6]. This extended protocol is an informed distillation of the findings of the systematic review [2].

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