Factors Affecting Multifocal Electroretinograms: A Mini-Review

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Abstract

Multifocal electroretinogram (mfERG) is an important diagnostic tool in clinical evaluation of electro-retinal functions. Continuous efforts have been put into examining and understanding the internal and external factors that can upset mfERG recordings and clinical interpretations. It is essential to fine-tune the diagnostic values and enhance the accuracy and internal consistency. The objective of this review is to consolidate the potential determinants that affect mfERG measurements. This review process consisted of the identification, screening, and eligibility steps. Scopus and PubMed databases were used to identify articles with pre-determined keywords. Truncation, and phrase searching were employed as the relevant search techniques. The search for literature was carried out based on the titles, abstracts, and related criteria. Sixty-five articles were screened and found to be eligible for data analysis in this study. Contributing factors that affect mfERG measurements were identified, segregated, and analysed through categorisation to facilitate the inference and decision making in developing more concrete guidelines for mfERG. Potential determinants of the mfERG measurements were systematised and were scored into endogenous and exogenous categories, respectively. The endogenous factors were discussed under 'physiological', 'systemic' and 'ocular' subheadings for pragmatic purposes. The exogenous factors were streamlined into 'lighting' and 'setting' subheadings to simplify understanding of these concepts. Lower amplitude was associated with aging, female gender, high blood pressure, hypoxia, smaller pupil size, longer axial length, increasing myopia, or suppressed eyes. Meanwhile, higher amplitude was linked with hyperglycaemia and higher stimulus luminance. Fixation, alignment and stretch factor can affect the accuracy of mfERG measurements. Future experiments should be designed to eliminate confounding elements in order to systematically quantify their impact on clinical interpretations.

Keywords: multifocal electroretinogram, mfERG measurement, clinical interpretation, exogenous factor, endogenous factor, determinants

Introduction

The first clinical recording of a focal electroretinogram (ERG) was conducted using foveal and parafoveal focal stimuli projected on the retina with a handheld ophthalmoscopic stimulator (Sandberg et al., 1977; 1983). Then, only one focal region could be examined at any time. Focal ERG was tailored for assessing central macular diseases. One of its inadequacies was the difficulty in applying multiple focal stimulations to cover a wider retinal area. This shortfall was overcome by the introduction of the multifocal electroretinogram (mfERG). The mfERG employs special binary m-sequence with flash on– and flash off–stimuli in unique orders to map different retinal locations within a short time. This was done over a much larger area of the retina (Bearse & Sutter, 1996; Sutter & Tran, 1992). The mathematical m-sequence model enables the electrical activity of the retina to be recorded as a single time-domain signal to produce a single derived mfERG within 45° in the posterior pole (Bearse & Sutter, 1996).

Clinical evaluation of electro-retinal function using electrophysiology has become a valuable diagnostic tool since the introduction of mfERG. Multifocal ERG is complementary to full-field electroretinography (ffERG) in assessing the peripheral retinal function (Creel, 2019; Hood, 2000; Hood et al., 2003; Tsang & Sharma, 2018). Multifocal ERG has been frequently used by clinicians and scientists to analyse retinal function in combination with other diagnostic techniques such as standardised automated perimetry, optical coherence tomography, fluorescein angiography, and fundus autofluorescence, and has been found to be useful in retinal evaluation in both clinical and research settings.

The International Society for Clinical Electrophysiology of Vision (ISCEV) publishes clinical mfERG guidelines regularly (Hood et al., 2008; 2012; Marmor et al., 2003; Robson et al., 2018). They continuously provide updates on issues affecting mfERG recordings and findings based on clinical experience or experimental evidence (Hood et al., 2008; 2012; Marmor et al., 2003; Robson et al., 2018). To enhance the diagnostic value, accuracy, and internal consistency, it is crucial to carefully examine the internal and external factors that affect mfERG recordings and clinical interpretations. Variables that influence the quality of the mfERG response can be technical, such as the field of view, interference levels and the duration of on-state stimulation. Other factors influencing the results may be due to data acquisition issues, such as electrode type and placement, amplifier specifications and filter bandwidth settings. The mode of stimulation such as Cathode Ray Tube (CRT) and Liquid Crystal Display (LCD) systems can also affect the quality of mfERG responses (Kaltwasser et al., 2009; Keating et al., 2000). In a CRT monitor, each pixel lights up for a duration of a few milliseconds during each frame. In an LCD monitor, meanwhile, each pixel lights up with a certain delay after the trigger but has a constant luminance during the entire length of the frame. These different display characteristics have been reported to affect the mfERG signal. The latencies of mfERG responses recorded with an LCD monitor were significantly increased for N1 and P1 compared with those recorded with a CRT. However, only the N1, and not the P1, amplitude was reported to be higher with an LCD monitor.

Information available on external and internal factors affecting mfERG measurements remains scattered and disorganised. The purpose of this review is to identify, segregate, and analyse the contributing factors that affect mfERG measurements through categorisation to facilitate clinical interpretation. Hence, it is important to guide clinicians on how to mitigate these variables when using mfERGs in patient management.

Methods

A systematic approach was used to perform this review. The review process consisted of four stages: identification, screening, eligibility, and data analysis (see Figure 1). Table 1 summarises the search configuration used in the identification, screening, and eligibility processes.

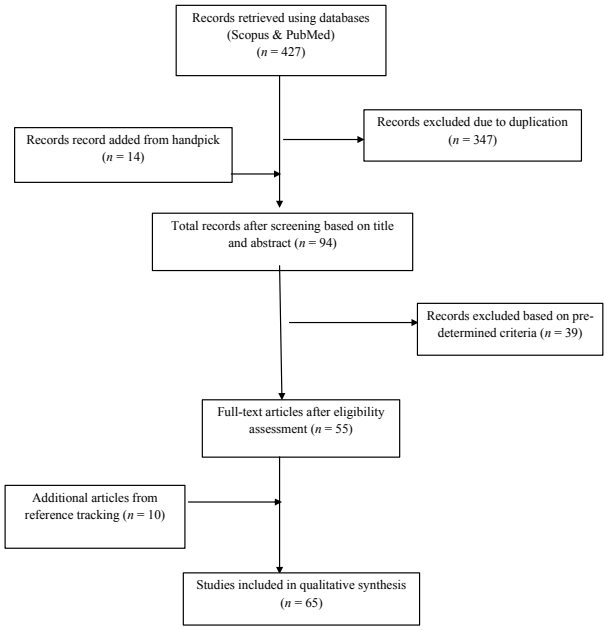

Figure 1: *Flow diagram of the literature search and selection process.*

Table 1: *Summary of search configuration in identification, screening, and eligibility.*

Database	Scopus, PubMed
Search techniques	Truncation and phrase searching
Keywords	Visual electrophysiology, electroretinogram*, multifocal electroretinogram*, exogenous factor*, mfERG
Target fields	Title, Abstract, Keyword, Full Text (Partial matches of key words were allowed for Title, Abstract and Keywords. Explicit match was used for full text search)
Criteria	Literature type: original research articles Language: English

Note: '*' is the wildcard/truncation search operator.

In the identification phase, two electronic databases were used to conduct the literature search, namely Scopus and PubMed. These were chosen due to their large coverage of publications within life sciences and biomedical topics. Medical and healthcare related publications are also covered comprehensively. Keywords ("visual electrophysiology", "electroretinogram*", "multifocal electroretinogram*", "mfERG", where '*' is the wildcard/truncation operator) were used to identify the related articles. The process to determine the main keywords was based on the review objective. The search for synonyms or related terms or variations of the main keywords was attempted using a thesaurus or keywords used in past studies. Truncation, and phrase searching were the search techniques employed to trace articles in both these databases.

In the screening process, 347 records were removed due to duplication. The remaining 94 records were vetted based on their titles and abstracts and a further 39 were excluded using the pre-determined criteria. After the eligibility assessment of full-text articles was conducted 55 articles were found to be eligible. Names of specific authors known to have conducted work on mfERG were also included in the search through a hand-picking process. Additional relevant studies that might have been missed from the databases search were also captured using a 'reference tracking approach'. Relevant studies were subsequently identified based on the articles from the initial search strategy.

In the Data Analysis phase, 65 original articles published in English language were included. Data on contributing factors were either established from articles that directly reported factor investigations or extracted indirectly from multifarious mfERG related studies. In data analysis, elements considered to influence the mfERGs were itemised. The information extracted was then merged to synthesise a pattern of all factors affecting mfERG measurements.

Results

In general, there are many factors that can affect ERG values. The contributing factors have accumulatively influenced the standard for electrophysiology in the vision science community over the years. However, records on contributing factors were found to be quite sparse and unsystematic. After undertaking multiple gap analyses to map the determinants that might potentially affect mfERG measurements, it was found that they were frequently related to factors such as age, gender, axial length, refractive error, pupil size, ambient light, stimulus luminance, fixation, alignment, suppression, stretch factor, blood pressure, and blood oxygen and glucose levels. To consolidate the interrelated data, these contributing factors were systematised and sorted into endogenous and exogenous categories. For the purpose of pragmatic discussion, the endogenous factors were discussed under 'physiological', 'systemic' and 'ocular' subheadings. The exogenous factors were streamlined into 'lighting' and 'setting' subheadings to simplify understanding.

Physiological variation

Physiological variations associated with ERG measurements were frequently linked to age and gender. It is important to understand the normal retinal changes when considering the influence of age on mfERG results. Normal retinal changes that occur with age include gene modulation, and psychophysical, structural, and cellular alterations (Bonnel et al., 2003). It is essential to differentiate the normal aging process from pathological aging (Bonnel et al., 2003) where the aging process changes the retinal function in an abnormal manner (Alavi, 2016; Bonnel et al., 2003). The aging of the eye involves genetic, biochemical, and cellular pathways, called longevity pathways, that regulate lifespan (Alavi, 2016). Retinal degeneration has been reported as the accelerated aging of photoreceptors (Alavi, 2016). Despite a better understanding of hereditary retinal diseases, the changes that occur in the retina as a result of aging remain debatable and are still being explored further (Bonnel et al., 2003). Age-related changes in mfERG results can be due to both optical and neural factors (Gerth et al., 2002; Panorgias et al., 2017). The decline of photopic mfERG responses with age has been reported between the ages of 20 and 70 years, primarily due to preretinal optical factors (Fortune & Johnson, 2002; Nabeshima et al., 2002). Both these studies reported a strong dependence on age for all mfERG responses measured, especially the central first-order retinal responses within 5° eccentricity and second-order response kernels. Meanwhile, another study reported decreases in response density and increases in implicit time with age (9–80 years) across all retinal regions (Keating et al., 2000). Age-related changes in response density were found to be most significant for the central retina and decreased with increasing retinal eccentricity (Gerth et al., 2002). One possible explanation for this is the slower temporal adaptation in the aging retina (Gerth et al., 2002; Jackson et al., 2002). It has been reported that the response densities of the first-order kernel (first positive wave P1) and second-order kernel (second positive wave P2) waves decreased, and the implicit times of the second-order kernel P2 increased among those above 50 years old in a group of subjects aged between 12 and 76 years (Nabeshima et al., 2002). A study carried out to determine age-related changes in the localised response and localised variability of mfERG parameters demonstrated considerable variation between differ-

ent retinal regions with regards to the variability of the response and characteristics of age-related changes (Tzekov et al., 2004). The localised approach revealed patterns of age-related changes that were not apparent in the ring averages generated using hexagons mapped across the retina area (Tzekov et al., 2004). Each localised response showed a decline with age, either in the scalar product or in the N1-P1 amplitude. The decline of the response varied from 3.3% in the periphery to 7.5% in the perifovea (Tzekov et al., 2004). The decline was greater for the superior than for the inferior retina for amplitude parameters, corresponding to larger increases in the P1 implicit time (Tzekov et al., 2004). The relative rate of change with age was similar for the nasal and temporal retina (Tzekov et al., 2004). Tzekov et al. (2004) proposed that the topographic properties of the retina had to be considered when establishing a normative database for clinical and research purposes. Age factor was linked to the diverse amplitude and implicit times of the mfERG in different regions of the retina in addition to the L–to–M-cone ratio disparities (Albrecht et al., 2002; Ziccardi et al., 2014).

A gender effect is apparent in both animal and human research findings. Multifocal ERG was carried out in cynomolgus and rhesus macaques (C. B. Y. Kim et al., 2004). Rhesus males (compared to rhesus females) and cynomolgus females (compared to cynomolgus males) exhibited larger amplitudes and less delayed implicit times in the central retina. In a study using human subjects the relative numbers of L– and M–cones (L–to–M-cone ratio) were found to be lower in females than in males (Jägle et al., 2006). However, the magnitude of the mfERG amplitude differences was larger than predicted by the L–to-M–cone ratio. The direct effect of sex hormones on the ion channel function was proposed as an alternative explanation for this (Jägle et al., 2006). The gender investigation was further probed in another human study into the neuro-retinal function in terms of the first order P1 implicit times and N1–P1 amplitudes obtained from photopic mfERG (Ozawa et al., 2014). It was claimed that hormones played a role in the gender effects. All neuro-retinal functions were found to be lower and shorter in females among those under 50 years old (Ozawa et al., 2014). However, the gender effects disappeared among those over 50 years old.

The effects of age and gender on both amplitudes and implicit times of the mfERG have been indicated in this review. The ERGs were found to decrease in response density but increased in implicit time with age. The responses also varied by regions of the retina. Retinal functions were reported to be lower and shorter in females and were likely linked to sex hormones. However, the clinical relevance, significance, and implication of these findings remain inconclusive. To develop a predictive adjustment for age and gender in clinical interpretation, a strategically polished clinical study with well-defined objectives that specify the relevant parameters and scopes of measurement is greatly needed. A retrospective approach to obtain data from existing multicentre clinical records might be an easy-to-accomplish option to first observe the preliminary inclination before embarking on more sophisticated experiments.

Systemic changes

Hypertension and diabetes are major medical and public health issues worldwide (Mokdad et al., 2003; Pappachan et al., 2011). Variations in mfERG have been linked to systemic changes of the human body in terms of blood glucose, blood pressure, and blood oxygen levels. Blood pressure can affect the retina both through high blood pressure and ocular hypertension (Chan & Brown, 2000; Gundogan et al., 2008; Lu et al., 2011; Michael Nork et al., 2010). Amplitudes of mfERG in hypertensive subjects were reported to be reduced in comparison to normotensive subjects, but no difference was found in the implicit time (Gundogan et al., 2008). The mfERG amplitude was similarly reduced in a study of the effect of ocular hypertension on mfERG (Chan & Brown, 2000). Studies on non-human primates and rats also found reduced mfERG amplitudes as a result of induced high intraocular pressure (Lu et al., 2011; Michael Nork et al., 2010). Intraocular pressure is normally highest in the morning and reduces through the day (Read et al., 2008). However, a study into diurnal variation in mfERG recordings did not reveal any similar trends (Heinemann-Vernaleken et al., 2000).

In a study into the association between the mean ocular perfusion pressure, systemic blood markers and retinal function in subjects with and without vascular disease, the mean ocular perfusion pressure was suggested as one of the sources of mfERG amplitude variation (Harrison et al., 2014). The mean ocular perfusion pressure is a function of systolic, diastolic, and intraocular pressure. It can be abnormal in patients with diabetes and its co-morbidities. Hyperglycaemia was associated with an increase in the amplitudes and a decrease in the implicit times of the mfERG (Klemp et al., 2005). The mfERG values were affected by diabetic retinopathy and the mfERG implicit time was suggested as a good indicator of the diabetic retinopathy onset (Harrison et al., 2014). Patients with type 1 diabetes without retinopathy demonstrated a delayed mfERG response compared with healthy subjects (Klemp et al., 2005). Chronic hyperglycaemia induces an adaptational response that tends to normalise retinal implicit time at a higher level of habitual glycemia (Klemp et al., 2005). During hypoglycaemia, mfERG was found to decrease, both in subjects with type 1 diabetes and subjects without diabetes (Khan et al., 2011). The dominant effect was in the amplitude of the responses in the central macular retina and not in their temporal properties (Khan et al., 2011). Responses from the central region were approximately 1.8-fold lower than from the periphery for both groups (Khan et al., 2011).

The impact of oxygen concentration on mfERG findings has mainly been reported during natural exposure among highlanders and climbers (Feigl et al., 2007; Klemp et al., 2007; Kofoed et al., 2009; Pavlidis et al., 2005). In a study into variation in mfERG during acclimatisation of native highlanders to normobaric normoxia at sea level, the highlanders were reported to display supernormal mfERG amplitudes that continued to increase during a 72-day period of observation whilst their haematocrit normalised. It was suggested that acclimatisation after a change in altitude and in ambient oxygen tension involved intrinsic retinal mechanisms (Kofoed et al., 2009). In another investigation into acclimatisation effects on mfERG among healthy climbers of a trekking expedition, it was found that the mfERG responses decreased a week after high-altitude exposure at 5050 m (compared with 500 m), but recovered the following week (Pavlidis et al., 2005). This oxygenation postulation was further examined in a direct in vivo comparison between normoxia, hypoxia and hyperoxia conditions in healthy human retina (Klemp et al., 2007). Compared with normoxia, hypoxia was associated with a reduction in mfERG amplitude. Hyperoxia had no effect on amplitude. Neither hypoxia nor hyperoxia had any effect on the latency of the P1 implicit times of the mfERG (Klemp et al., 2007). In another unrelated study comparing normoxic and hypoxic conditions, a reduction in mfERG responses was found during hypoxia (Feigl et al., 2007). An increase in mfERG implicit time with higher oxygen concentration might indicate that bipolar and Muller cells were affected (Feigl et al., 2007). However, altered mfERG values among patients with long-term breathing problems such as in chronic obstructive pulmonary disease (COPD) have not been accurately reported (Vogelmeier et al., 2017). Poor airflow in COPD may hypothetically display similar trends of reduction in mfERG values due to lower oxygen concentration, but this would need further confirmation through more research.

The impact of systemic changes on the amplitude of mfERG is apparent, while their impact on the implicit time varies. If the levels of blood glucose, blood oxygen, and blood pressure can affect the amplitude value of the mfERG, it is imperative to incorporate these tests into the preliminary assessment prior to any mfERG measurements.

Ocular changes

Multifocal ERG measures the electrical activities of the retina in response to a light stimulus. Any ocular changes that alter the light transmission and optical quality are likely to have an effect on the mfERG measurements. The pupil size affects the amount of light entering the eye. This has been continually explored in mfERG research. Axial length and refractive error have also been frequently highlighted in mfERG measurements due to retinal structure investigations in myopia research.

Pupil size

Pupil size plays a particularly important role in mfERG as stated in the ISCEV standard (Hood et al., 2008; 2012; Marmor et al., 2003; Robson et al., 2018). The pupil regulates the amount of light entering the eye during mfERG measurements. It is required by ISCEV to be fully dilated and its size must be monitored throughout the mfERG procedure. Pupil size has been found to have significant effects on the amplitude and latency of the mfERG (Gonzalez et al., 2004). There was a reduction in mfERG amplitude with a change in pupil diameter of 7 mm (mfERG P1 amplitude 53 nV at 8 mm to 25 nV at 1 mm), whereas a pupil diameter greater than 8 mm does not contribute significantly to the amplitude and timing of the mfERG (Gonzalez et al., 2004).

Nevertheless, mfERG measurements with non-dilated pupils can sometimes be unavoidable and can become necessary when pupil dilation is contraindicated. Two studies carried out comparisons between mfERG measurements with dilated and non-dilated pupils. The luminance of a screen monitor that was set five times higher than the recommended ISCEV value of 150 cd/m^2 during mfERG recordings with natural pupils was found to give the same mfERG responses as dilated pupils and screen luminance 150 cd/m^2 (Poloschek & Bach, 2009a). The mfERG amplitudes and implicit time in dilated eyes were found to be equal to non-dilated eyes in the central retina (Mohamad-Rafiuddin et al., 2014). Both studies advocated that mfERG values with non-dilated pupils could be used for clinical purposes. Unfortunately, the sample size of the latter study was too small to draw any convincing conclusion. Therefore, to develop a clinical guide on use of mfERG with non-dilated pupils, a well-controlled experimental study which systematically quantifies the impact of various natural pupil sizes on mfERG results is required.

Axial Length and Refractive Error

Refractive error is determined by the relationship between the axial length of the eye and its optical power. Despite the close relationship between refractive error and axial length, variations in mfERG values have been attributed more to axial length rather than refractive error (Sachidanandam et al., 2017). Multifocal ERG amplitudes were reported to reduce with increasing axial length and across eccentricities (Chan & Mohidin, 2003; Man et al., 2013).

Multifocal ERG values for myopic eyes were reported to be different to emmetropic eyes (Chan & Mohidin, 2003; Chen et al., 2006a; Luu et al., 2006; Man et al., 2013; Wolsley et al., 2008). A weaker mfERG response has been recorded due to the morphological changes associated with increased axial length (Chan & Mohidin, 2003). Axial length contributed to 15% of the implicit time total variance. Amplitudes and implicit time mfERG correlated with the severity of myopia in adults. Amplitudes decreased and the implicit time increased as the dioptric power of myopia increased. However, such correlations between refractive error and mfERG results were not found in children with myopia (Luu et al., 2006).

It has been suggested that changes in the mfERG responses in myopes are primarily due to the increased axial length that accompanies myopia development (Chen et al., 2006a). Underlying differences in retinal function resulting from myopia could be one possible explanation. In an investigation using a range of refractive errors (+0.50 to –15.00 D), retinal thinning (reduced thickness of the outer plexiform layer of the nerve fibre layer) in moderate and high myopia correlated with reduced spatial resolution and delayed mfERG timing in the peripheral retina (Wolsley et al., 2008). The structure and function of the post-receptor retina were suggested to be susceptible to disruption in eyes with moderate and high myopia.

Retinal defocus was found to be a contributing factor for mfERG variation (Rosli et al., 2014; Wolsley et al., 2008). In an investigation into the effects of refractive blur (plano, –3 D, +3 D, and +6 D) on mfERG, a significant difference in the density of the mfERG response was suggested for every 2 D change of refraction (Palmowski et al., 1999). When the viewing distance was adjusted to compensate for the induced changes in retinal image size by the refractive lens, no influence due to refraction was observed in either latencies or amplitudes (Palmowski et al., 1999). The effect of optical defocus on mfERG was further examined by ensuring the pupil size remained constant to minimise the aberration factor as it might indirectly affect the results (Chan & Mohidin, 2003). The amplitude was found to be reduced, but the implicit time was not changed by increasing the optical defocus (Chan & Mohidin, 2003). A later investigation found that retinal defocus of up to 3 D did not affect mfERG values (Rosli et al., 2014).

Theoretically, performing mfERG on a subject with an uncorrected refractive error may affect the amplitude or implicit time of the mfERG measurements as the quality of the retinal image is essential. Here, greater optical defocus produces poorer retinal image quality. The ISCEV guideline encourages correction of refractive errors before mfERG measurements (Hood et al., 2008; 2012; Marmor et al., 2003; Robson et al., 2018). A full optical correction is recommended for mfERG measurements to minimise reduction of the retinal response due to optical defocus (Chan & Mohidin, 2003), particularly for patients with high refractive errors (> 6 D) (Hood et al., 2008; 2012; Marmor et al., 2003; Robson et al., 2018). Contact lenses are considered better than correction by spectacles (Hood et al., 2008; 2012; Marmor et al., 2003; Robson et al., 2018). In a recent investigation of the local differences in spherical and astigmatic defocus across the human retina using global-flash mfERG, it was found that responses from different retinal areas varied with local spherical defocus, but were not affected by astigmatic defocus (Turnbull et al., 2020). Further investigation is needed to fill the current gaps in information on the effects of hyperopia, presbyopia, and astigmatism on mfERG.

Lighting

Multifocal ERG values are directly correlated with the amount of light that enters the eye and is projected on the retina. ERGs record the retina's response to a light stimulus. Therefore, any light source, including both stimulus and ambient light, that contributes to retinal illumination can affect the mfERG measurements.

The brightness of the stimulus has been shown to produce direct effects on the mfERG outputs. Luminance contrast between the luminance of a brighter area of interest and that of an adjacent darker area might be another contributing factor in

mfERG variations. In an investigation into the effects of high luminance on the amplitude of the mfERG, luminance was set at three different levels, 150, 300 and 500 cd/m^2 (Schimitzek & Bach, 2006). The mfERG amplitude increased by 20% when the stimulus luminance was increased by a factor of 3.3. Peak times decreased slightly (less than 1.5 ms) with higher stimulus luminance. Contrast adaptation, produced by prolonged viewing of high contrast gratings, was suggested to occur at both retinal and cortical locations within the visual pathway (Chen et al., 2006b). An increase in implicit time but no change to the amplitude of the mfERG waveform was reported in a study into the effect of retinal contrast adaptation on the mfERG response (Chen et al., 2006b).

The ideal illumination for the examination room was loosely described in ISCEV as 'moderate and dim room illumination' close to the stimulus screen (Hood et al., 2012). ISCEV recommends pre-adaptation in light for 15 minutes (Hood et al., 2008; 2012; Marmor et al., 2003; Robson et al., 2018). Multifocal ERG has been reported to increase in both amplitude and implicit time in 2 minute subsequent internal recordings for 16 minutes of light adaptation after dark adaptation (Kondo et al., 1999). The most stable mfERG recording condition appears to be a fully lit room (1.6 log cd/m^2) (Chappelow & Marmor, 2002). For clinical application, it would be more helpful if the recommended value was given in Lux (illumination). Although direct measurement would provide a more precise measurement, it can be estimated as 150 lux based on the reported value (1.6 log cd/m^2). The amplitudes and times-to-peak were found to be disturbed by increasing the ambient room luminance (Chappelow & Marmor, 2002). The exaggerated attenuation of signals in the blind spot with room lighting indicated that mfERGs recorded in the dark might be contaminated by the light scattered in the dark-adapted peripheral retina (Chappelow & Marmor, 2002). Stray light was reported to affect the ERG responses to local stimuli (Boynton, 1953; Shimada & Horiguchi, 2003; Wirth & Zetterstrom, 1954). The same issue of stray light-induced response in the mfERG (elicited by a stimulus falling on the disc) was found in a comparison study revealing that an optic disc with high reflectance scattered stimulus light to create a weak full-field stimulus (Shimada & Horiguchi, 2003). Investigations of the subsequent usage of equipment involving flashes of light as stimuli reported a negligible effect on the mfERG measurements (Suresh et al., 2016). A more explicit statement on lighting for mfERG practitioners would be beneficial in standardising mfERG procedures.

Setting

Fixation, Alignment and Suppression

A fixation-monitoring system was widely used to monitor the integrity of any acquired data in electronic ocular instruments (Chu et al., 2006). Fixation is also used to monitor mfERG (Rudolph et al., 2002). Reliable data usually have less than 10–20% fixation loss during measurements. The accuracy of mfERG measurements for subjects with poor fixation might be difficult to interpret (Chu et al., 2006). Small eye movements during the mfERG measurement generate noise and contaminate the input signals. The central mfERG amplitude is most affected by unsteady fixation. A lower amplitude is anticipated for unsteady fixation of 4° and beyond. High resolution stimuli of less than 2.4° are reported to be more susceptible to fixation fluctuations during the mfERG recording process (Chisholm et al., 2001). The depth of depression at the blind spot area has been suggested as an alternative to interpret the accuracy of mfERG results in patients with poor fixation (Chu et al., 2006).

Interocular differences in mfERG were not apparent when measurements were taken under monocular and binocular stimulation conditions in healthy subjects with good binocular vision (Pálffy et al., 2010). Fixation errors in a patient with asymptomatic intermittent exotropia can affect the mfERG measurements (Bellmann et al., 2004). The near reflex is a triad which consists of accommodation, convergence and miosis for adjustment to fixate on a near object. Convergence errors may happen in patients with high heterophoria due to the proximity of the stimuli which demands prolonged near fixation and may cause fatigue. The misalignment may affect the mfERG comparisons by pairing the erroneous fixation locus between the two eyes. When measuring mfERG in subjects with eccentric fixation, fixation locus is crucial to ensure that equivalent retinal areas are compared (Seiple et al., 2006). If the fixation is maintained within the central stimulus hexagon (2°), the mfERG amplitude will not be substantially affected (Chu et al., 2006).

Suppression is a significant factor that must be addressed during mfERG measurements because the amplitude is reduced and the implicit time shortened in a suppressed eye (Vrabec et al., 2004). The possibility of performing mfERG recordings in the clinic using more flexible, natural techniques such as watching movies has been demonstrated (Saul & Still, 2017). However, an alternative stimulation strategy is needed to handle the difficulties in the presence of temporal-spatial correlations and eye movements to achieve results that are comparable to those routinely obtained with conventional methods. Clinical use of binocular mfERG in patients with monocular macular disease is thus recommended (J. W. Kim et al., 2013).

Fixation, alignment, and suppression are vital factors that must be equally considered during mfERG measurement to enhance the accuracy and repeatability of the mfERG values for retinal disease monitoring and visual rehabilitation follow-up.

Stretch factor

Multifocal ERG ring measurements are generated using hexagons mapped across the retina. The values of mfERG in each of the rings represent the total amount of responses from the photoreceptors within that defined retinal area. Hypothetically, the mfERG data generation for each ring is based on the presumption using hexagons of the same size across the field of stimulation. However, the volume of photoreceptors in the central retina is different to that in the periphery. If the same size of hexagon is used for the calculation, it will result in a systematic error due to these differences. The number of photoreceptors in the peripheral retina is too small to be detected with the same hexagon size as that used in the central retina (Poloschek & Bach, 2009b). This stimulus distortion from the central to the peripheral ring of the mfERG is called the stretch factor. The topographical distribution of photoreceptors plays a huge role in determining the most accurate stretch factor, which can be affected by the distance between the subject and the monitor, the size of the stimulus, and the stimulus resolution. The size of the hexagons should not be the same throughout the field of view (Poloschek & Bach, 2009b). The electrical activity of the peripheral retina cannot be represented by the same hexagon size as the central retina because the variabilites between the different eccentricities are too small to detect or differentiate (Poloschek & Bach, 2009b). Another possible error is the overlapping or sharing of the hexagon in the adjacent ring during the analysis of the ring responses. However, the stretch factor investigation was restricted to the VERIS multifocal ERG application (Poloschek & Bach, 2009b). Diagnosys mfERG takes a different approach to control the stretch factor in terms of scaling, sizing, and elongation. Different models employ different calculations to generate the outputs. The variation in stretch factors used in different apparatuses should be probed further with a view to standardise procedures and aid clinical comparison between different models.

The impacts of endogenous and exogenous factors on mfERG

values and measurements discussed in this mini-review are summarised in Table 2.

Table 2: *Impact of endogenous and exogenous factors on mfERG measurements.*

Endogenous factors	
Age	lower amplitude with age
	higher implicit time with age
	varies by retinal region
Gender	lower amplitude in female
	shorter implicit time in females
Blood pressure level	lower amplitude with higher blood pressure
	no effect on implicit time
	no diurnal variation
Glucose level	higher amplitude in hyperglycaemia
	shorter implicit time in hyperglycaemia
Oxygen level	lower amplitude in hypoxia
	no effect on implicit time in hypoxia
	no effect on amplitude in hyperoxia
	two conflicting data on implicit time in hyperoxia (no effect and increment)
Pupil size	lower amplitude with smaller pupil size
Axial length	lower amplitude with longer axial length
Refractive error	lower amplitude with increasing myopia
	higher implicit time with increasing myopia
Exogenous factors	
Stimulus	higher amplitude with higher stimulus luminance
	lower implicit time with higher stimulus luminance
Ambient light	a brightly lit room (1.6 log cd/m^2) is the most stable mfERG recording condition
Fixation	reject data with > 20% fixation loss
Alignment	precise binocular alignment is crucial to ensure that equivalent retinal areas are compared
Suppression	lower amplitude in suppressed eye
	shorter implicit time in suppressed eye
Stretch factors	values of the mfERG ring measurements in different brands or models of equipment should be interpreted together with the knowledge of stretch factors being used

Conclusion

In this mini-review, the contributing factors that affect mfERG measurements have been identified, segregated, and analysed through categorisation. Potential determinants of the mfERG measurements were organised into endogenous and exogenous categories. Relevant data were combined and discussed under five different subheadings (physiological, systemic, ocular, lighting, and setting) to simplify the information for easy comprehension. The nullifying effects of various contributing factors stated in this mini-review should be carefully examined in designing any factor-related mfERG studies in the future. Quality data would lead to more accurate clinical interpretations and comparable data worldwide. An in-depth investigation into these contributing factors of the mfERG can be used as a future guide in the revision of the mfERG standard.

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Faktorer som påvirker multifokal elektroretinogram: En oversiktsartikkel

Sammendrag

Multifokal elektroretinogram (mfERG) er et nyttig diagnostisk verktøy ved klinisk utredning av retinafunksjonen. Mye arbeid er blitt lagt ned i å undersøke og forstå de ulike interne og eksterne faktorer som kan påvirke mfERG målinger og klinisk tolkning. Det er viktig å forbedre diagnostisk nytteverdi, og øke nøyaktighet og repeterbarhet.

Målet med denne oversiktsartikkelen er å sammenholde mulige faktorer som kan påvirke mfERG målinger. Prosessen besto av identifisering, screening og vurdering av relevans. Databasene Scopus og PubMed ble brukt til å identifisere artikler ved hjelp av bestemte nøkkelord. Trunkerte søk og frasesøk ble brukt. Litteratursøket ble foretatt i titler, sammendrag og relaterte kriterier. Til sammen 65 artikler ble gjennomgått og funnet passende for analyse i dette studiet. Faktorer som kan påvirke mfERG målinger ble identifisert, skilt ut, analysert og sortert for å forenkle tolkning og avgjørelser ved utvikling av retningslinjer for bruk av mfERG. Potensielle faktorer ble kategorisert som interne eller eksterne. Interne faktorer ble diskutert under de følgende overskriftene: «fysiologiske», «systemiske» og «okulære». Interne faktorer ble plassert under «belysning» og «setting».

Lavere amplituder kan knyttes til aldring, kvinnelig kjønn, forhøyet blodtrykk, hypoksi, mindre pupillediameter, større aksial lengde, økende myopi, eller supprimerte øyne. Høyere amplituder kan knyttes til høyt blodsukker og høyere stimulus luminans. Fiksasjon, øyeposisjon og strekkfaktor kan påvirke nøyaktigheten av mfERG målinger.

I fremtidige studier bør forvirrende elementer reduseres for å forenkle klinisk tolkning.

Nøkkelord: multifokal elektroretinogram, mfERG målinger, klinisk tolkning, ytre faktorer, indre faktorer, bestemmende faktorer

I fattori che influiscono sull'elettroretinogramma multifocale: una mini revisione

Riassunto

L'elettroretinogramma multifocale (mfERG) e' un importante strumento diagnostico della diagnosi clinica delle funzioni elettro-retiniche. Continui sforzi sono stati fatti nell'esaminare e comprendere i fattori interni ed esterni i quali possono influenzare le misure mfERG e la loro interpretazione clinica. E' essenziale rifinire i valori diagnostici e migliorarne l'accuratezza e la consistenza interna. L' obiettivo di questa revisione e' di consolidare i potenziali determinanti che influiscono sulle misure della mfERG. Questo processo di revisione ha consistito nell'identificazione, screening e criteri di eligibilita'. I database di Scopus e PubMed sono stati utlizzati per identificare gli articoli con predeterminate parole chiave. Troncamenti e parole di ricerca sono state utilizzate cosiccome le piu' rilevanti tecniche di ricerca. La ricerca della letteratura scientifica e' stata condotta attraverso i titoli, i sommari e i relativi criteri. Sessantacinque articoli sono stati controllati e considerati idonei per l'analisi dei dati di questo studio. I fattori che influenzano le misure con la mfERG sono stati identificati, separati ed analizzati grazie ad una categorizzazione per facilitare l'inferenza e la decisione nello sviluppo di concrete linee guida per la mfERG. I fattori endogeni sono stati discussi all'interno di sottocategorie quali "psicologiche", "sistemiche" e "oculari" per ragioni di pragmaticita'. I fattori esogeni sono stati separati tra "illuminazione" e "settaggi" come sottocategorie per semplificare la comprensione di questi concetti. La ridotta ampiezza e' stata associata con l'invecchiamento, sesso femminile, pressione sanguigna alta, ipossia, diametro pupillare ridotto, lunghezza assiale aumentata, miopia aumentata o ambliopia. Invece, ampiezza aumentata e' stata collegata a iperglicemia ed elevato stimolo alla luminosita'. Fissazione, allineamento e fattore di compressione possono influenzare l'accuratezza delle misure con mfERG. Esperimenti futuri dovranno essere disegnati considerando l'eliminazione di questi elementi di confusione per evitare l'impatto sistematico sull'interpretazione clinica.

Parole chiave: elettroretinogramma multifocale, misure mfERG, interpretazione clinica, fattori esogeni, fattori endogeni, determinanti