What’s New:
Where are we going with approaches such as PERG, VEP, SWAP and FDT?

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Core Concepts
• Standard automated perimetry (SAP) with white on white stimulus remains the gold standard for functional testing.
• Pattern electroretinogram (PERG) can be used where perimetry is not possible; it is valuable to investigate unexplained visual loss.
• Scotopic threshold response (STR) has not been found useful for clinical detection of glaucoma.
• Photopic negative response (PhNR) has not been shown to be a good discriminator to detect disease.
• Multifocal visually evoked potential (mfVEP) has been found useful to investigate patients with visual field loss that does not match the clinical picture.
• Short wavelength automated perimetry (SWAP) has been shown useful in younger patients who are good observers, without nuclear sclerosis, where there is high suspicion of early damage.
• Frequency doubling technology (FDT) matrix is at least as sensitive as SAP for detection of damage.
• Flicker defined form (FDF) may detect glaucomatous defects similarly to SAP. More data is needed to determine sensitivity/specificity and ability to detect early disease.
• Alternative strategy subjective tests SWAP, FDT matrix and perhaps HeP can be used in “pre-perimetric glaucoma” patients, as they may detect changes earlier.

Is anything new in functional testing?
There have been many attempts to refine psychophysical and electrophysiological techniques over the last 20 years to enable earlier detection and/or possibly provide an objective means for monitoring function. While a few techniques survive in clinical practice, there has generally not been any major breakthroughs in recent times in the functional testing area. Standard automated perimetry (SAP) with white on white stimulus still remains the gold standard despite all its well known limitations.

PERG/STR/PhNR
The pattern electroretinogram (PERG) consists of an averaged response to a uniformly reversing checkerboard pattern, and is derived from the central visual field. It has been described as abnormal in glaucoma in many studies dating back as far as the 1980’s. Reduction of the two main components P50 (positive wave at 50 ms) and N95 (negative wave at 95ms) has been reported, but in glaucoma there may be more significant effects on the N95. The Freiburg group use a PERG ratio comparing responses at 0.8 degree check size (which are more affected in early glaucoma) to 16 degree checks. Latency changes are also reported, although not as substantial as that seen in demyelinating diseases (optic neuritis).

The PERGLA (Lace Elettronica, Pisa, Italy) is a system designed to provide more rapid investigation using a short protocol steady state PERG. While many animal and human studies agree that the PERG is reduced by ganglion cell loss, and source analysis confirms it to be generated in the inner retina, clinical correlations have not been accurate enough for it to become widely used for diagnostic or monitoring purposes. There is a wide range of variability in normal and disease with considerable overlap. Also it is subject to reductions from any other pathology

Figure 1. Binocular simultaneous mfVEP (dichoptic). Shows reduction of signal in scotoma areas in both eyes compared to corresponding SITA field.
affecting visual acuity and retinal function, so like so many of our functional tests, it is non-specific for glaucoma. It can be of use in cases where perimetry is not possible and is of value in investigating unexplained visual loss. The fact that there appears some generalised loss which does not correspond topographically, has confounded the possibility of adapting a multifocal PERG.

The scotopic threshold response (STR) is a signal recorded to a dim stimulus at the depths of dark adaptation. It appears to be generated in inner retina and is sensitive to optic nerve damage in animal models, and regularly used in lab based research. In humans it has not been found to be useful for clinical detection of glaucoma.

The photopic negative response (PhNR) is a slow negative response following the b wave peak. It is easier to record than the STR, and seems to be dependent on retinal ganglion cell function. However while there are reports of its reduction in human glaucoma, it also has not been shown to be a good discriminator for detecting disease.

mfVEP

The conventional pattern VEP (visually evoked potential) represents a single summed response that is mainly derived from the macular region, and due to cortical anatomy, it is dominated by the inferior hemifield. In fact, a dense superior field defect can go undetected on conventional VEP testing.

To evaluate local VEP responses from the visual cortex and to map them topographically the multifocal VEP (mfVEP) has been developed. Using a multifocal mfVEP technique it is possible to objectively detect visual field defects. Multifocal stimulation is now available commercially in several different electrophysiological systems. The visual stimulus is usually generated on a CRT screen (eg, 22-inch high-resolution display), but with faster refresh rates, LCD flat screens can now be used. We have also used virtual reality goggles and twin LCD screens to present the stimulus dichoptically (see Figure 1). A blue-on-yellow mfVEP has also been described using a sparse blue pattern-onset stimulus (instead of pattern reversal) on a yellow-adapting background. The goal was to target the koniocellular pathway. This approach showed good sensitivity and displayed more extensive scotomata than the conventional black-white mfVEP (92.2% sensitivity), and it correlated well with SAP. The advantage of the blue on yellow stimulus over standard mfVEP, however, was probably more likely related to the fact that the pattern onset stimulus was spatially sparse (likely due to less lateral inhibition) and was of low luminance, both of which we have demonstrated may increase sensitivity.

The mfVEP is particularly useful for investigating patients with field loss that does not match the clinical picture, either because they are poor performers on subjective tests or there is a suspicion of other pathology. It supplements but does not replace the findings of subjective SAP and does not have the suitable follow up capability to compare with SITA or Octopus progression analysis software.

Pupil perimetry has also been reported, as a form of objective perimetry and uses a multifocal type stimulus with sophisticated pupil tracking to capture responses. It has the issues associated with pupil variability to deal with and requires an intact efferent pathway (in at least one eye) to give meaningful results, but does seem to work well as a screening tool and is completely non-invasive.

SWAP (short wavelength automated perimetry), and FDT (frequency doubling technology)

The SWAP technique for perimetry presents a 440nm blue size V target on a bright yellow background to attempt to selectively test the koniocellular pathway. Initial studies had reported favourable early detection of glaucoma, despite some of the limitations including greater fluctuation of responses, lens absorption of the blue light stimulus, and generally lower patient acceptance of the test. Some more recent reports suggest no clinical advantage in detection over SITA white-on-white. It may still be useful in younger patients who are good observers where there is a high index of suspicion of early damage, but despite the introduction of SITA SWAP it has generally not been as widely adopted as once anticipated.

The FDT technique was also introduced as a means of attempting to target a subpopulation of ganglion cells, in this case the magnocellular pathay, to...
Figure 3. Structure function correlation map produced by Heidelberg Retinal Tomograph and HEP. Inner coloured ring represents Moorfield’s classification, while outer ring represents HEP visual field result for corresponding sector of disc.

Flicker defined form (FDF)

Flicker defined form is a recently adapted technique in the Heidelberg Edge Perimeter (HEP, Heidelberg Engineering) which presents as a stimulus counter-phase dots to discrete areas within the field. In my early experience it seems to be well received by patients and detects glaucomatous defects with similar distribution to SAP.

Further studies are needed to test its sensitivity/specificity and ability to detect early disease. The addition of a combined structure-function map by combining the test results of the HEP with the HRT (Heidelberg Retina Tomograph) scan structural data has been a nice addition for clinicians. However, like all structure-function correlations, there appears to be many cases where the two simply do not match. Figure 2 shows an example of HEP where there is quite reasonable correlation with SAP findings. Figure 3 shows an example of a structure-function correlation map.

Clinical applications

Electrophysiology testing using either PERG or mfVEP can be helpful in patients who are poor perimetrists, in cases where there is disproportionate field loss compared to the clinical picture, and in other cases of unexplained vision loss including functional overlay.

The alternative strategy subjective tests SWAP, FDT Matrix and perhaps now HEP also, can be used in investigating patients with suspect early disease, as they may be able to detect changes earlier in some cases. However SWAP is quite variable and better reserved for younger patients who are good observers.

I have found the Matrix FDT sometimes works well for patients who fatigue on SAP, and it can be easier for those with back problems due to easier positioning, however none of the alternate strategies have the same follow up software capabilities for progression analysis.

References