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MULTIFOCAL OBJECTIVE PUPIL PERIMETRY (mfPOP) IN MULTIPLE SCLEROSIS

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Background

- MRI scanning in multiple sclerosis (MS) is well correlated with inflammation but less so with disability
- secondary degeneration in MS may continue after inflammation is controlled
- our recent study of *sparse* mfVEPs in MS[1] indicated that the method was well correlated with degeneration, not inflammation:
  - high sensitivity and specificity for RRMS, *even in persons with no history of optic neuritis (see figure 3b)*
- dichoptic multifocal stimuli test many parts of both optic nerve and the brain concurrently:
  - mfVEPs are time-consuming and associated with large between-subject variability due to different cortical anatomy
- we have recently demonstrated a technique in which the record of brain activity is obtained from *pupil responses* to multifocal stimuli:
  - good diagnostic power in glaucoma and diabetic retinopathy.[2,3]
- the multifocal pupil perimeter is much easier to use than mfVEP:
  - minimal setup time (*see figure 1*)
  - not influenced by cortical anatomy

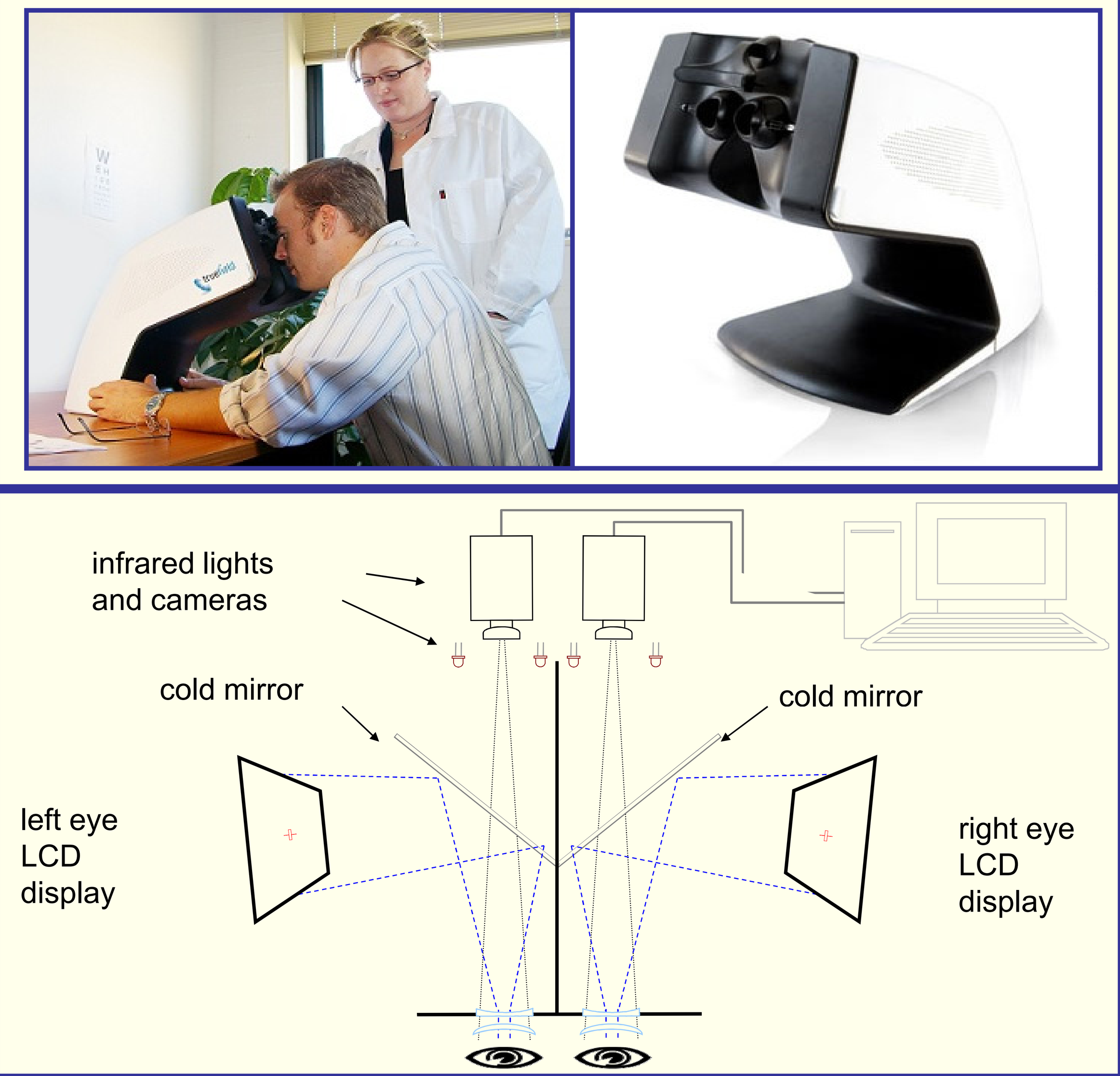


Figure 1. The multifocal objective pupil perimeter

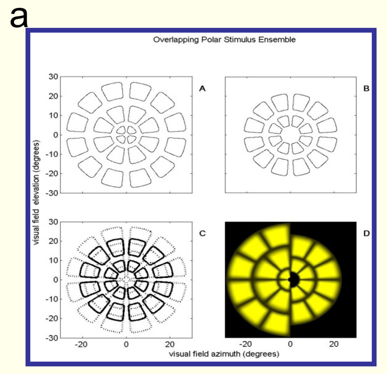
Background (contd.)

- **multifocal pupillometry** (*see figure 1*):
  - electrodes of ERG or VEP replaced with infrared cameras
  - pupils monitored for contractions at 30 frames/s:
    - (only one working pupil needed)
    - changes in *relative pupil diameter* measured, not absolute pupil diameter (so small pupils are OK)
    - lower 75% of pupil recorded to avoid problems of ptosis
  - gaze tracking automatically discards data from fixation losses or blinks:
    - up to 15% data loss from blinks/fixation losses permitted
    - (if > 15%, then a 30 s segment is repeated)

Methods

- basic stimulus parameters of multifocal pupil perimeter:
  - 60º diameter field
  - 44 stimulus regions/eye (*see figure 2a*)
  - each stimulus persists for 33 ms
  - background luminance 10 cd/m²
- stimulus protocol:
  - divided into 8 segments of 30 s duration, including short rest breaks
  - total stimulus duration 4 minutes (i.e. 2 minutes/eye)

a



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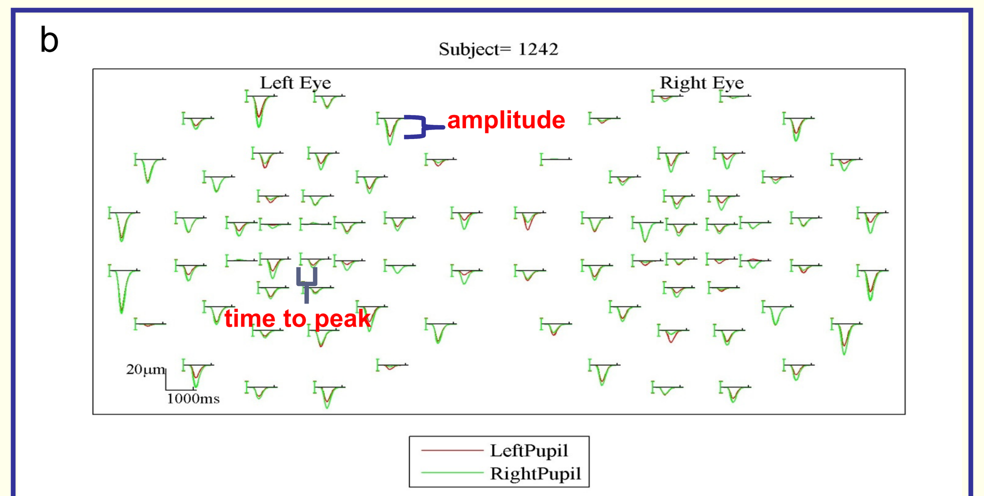

(results combined in a linear model as a unified ("discriminant") measure)

Figure 2. (a) Stimulus pattern: small overlap may improve reproducibility[4] (b) example output from multifocal pupil perimeter

Methods (Contd.)

Subjects

- 85 patients with MS (49.8 ± 11.3 years; 73% female) compared with 35 age-matched controls (47.9 ± 16.8 years; 63% female):
  - refractive error not greater than (±) 9D or 2D of cylinder
  - acuity better than 6/12
- diagnosis of MS confirmed on history, examination and MRI scan:
  - 72 relapsing-remitting (RRMS)
  - 2 primary and 11 secondary progressive (PorS)
  - patient records examined to determine if there was a history of optic neuritis (ON) or not (NoON) and, if so, which eye
  - EDSS performed at time of pupillometry

Data Analysis

- absolute deviations from normal calculated for **amplitude asymmetry**, **time to peak**, and **"discriminant"** (combination of amplitude and time to peak) measure[2] for each region:
  - **"single"** eyes
  - between-eye **"asymmetry"**
- for each of 44 stimulus regions of **"single"** and "**asymmetry**":
  - worst 20 most deviating regions/field sorted
  - receiver-operator curves calculated for N regions
- comparisons made:
  - **RRMS vs. control** and **PorS vs. control**
  - **ON vs. control** and **NoON vs. control**

Methods (Contd.)

Area under Receiver-Operator Curves

- sensitivity (e.g. patients vs. normal controls) plotted against false-positive rate (= 1-specificity)
- Area Under Curve (AUC) measured (see examples in *figure 3*)
- AUC of 1.0 equals perfect diagnostic power

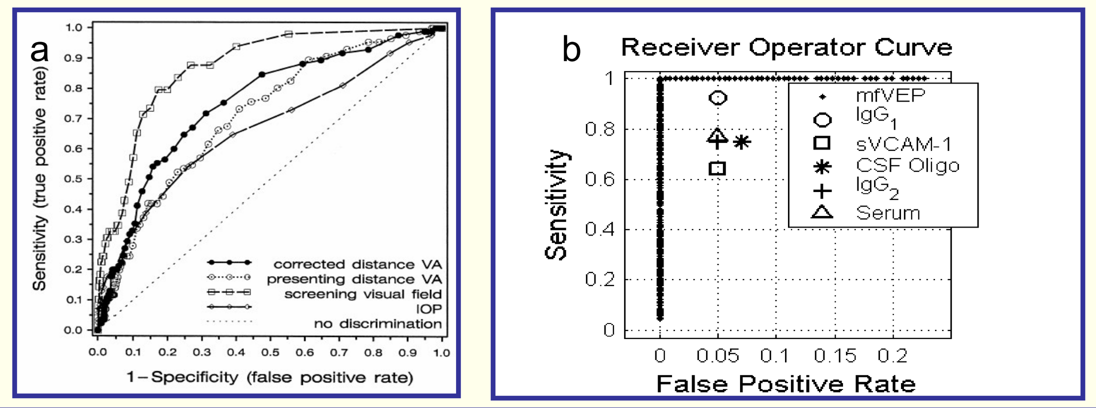

Figure 3. ROCs for (a) tests for glaucoma and (b) tests for MS[1]

Results

- the area under ROC curves correlated:
  - inversely with number of deviations from normal (*see figure 4*)
  - directly with EDSS
- results for **72 RRMS patients**:

Area under ROC ± SE				
Response measure (Between eyes)	EDSS 1-3 (N = 18)	EDSS 3-4 (N = 26)	EDSS 4-5 (N = 21)	EDSS ≥ 5 (N = 7)
Amplitude Asymmetry	71.3 ± 8.0	73.8 ± 6.0	94.3 ± 7.6	91.0 ± 4.9
Time to Peak	72.0 ± 8.5	81.4 ± 7.5	77.3 ± 4.0	91.4 ± 8.1
Discriminant	69.4 ± 8.9	75.9 ± 6.8	85.4 ± 6.1	80.8 ± 11.9

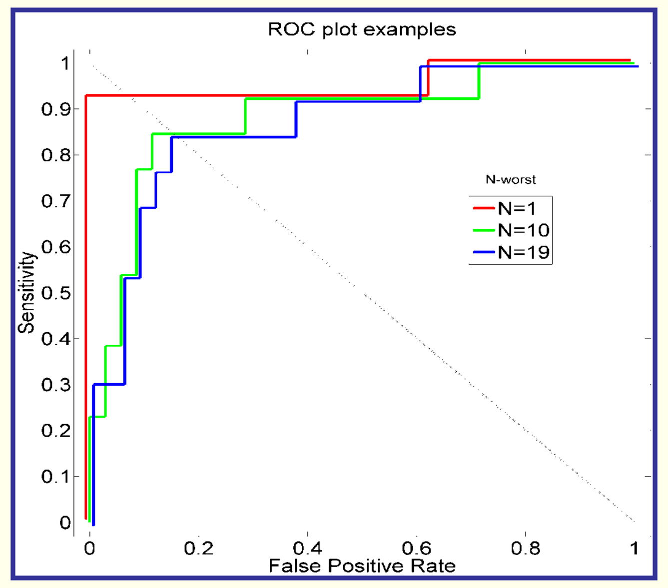

Figure 4. Changes in the area under ROC plots (AUC) as a function of the number of points in the field considered. N indicates a selection of the N-worst deviations from normal performance. The curves are for PS patients using a combination of amplitude and delay data ("discriminant" measure).[2] In this case the single worst deviation from normal was the most diagnostic (N=1, red curve)

Results

PorS and RRMS vs. control

- discriminant analysis performed best overall
- comparison between eyes performed better than single eye alone
- diagnostic power followed the EDSS

Area under ROC ± SE (discriminant analysis)		
	PorS vs. Control	RRMS vs. Control
EDSS (MS pts.)	5.90	3.53
Single Eye	87.7 ± 4.39	68.2 ± 3.79
Between Eyes	94.8 ± 3.55	75.0 ± 3.31

NoON and ON vs. control

- no obvious difference between NoON and ON
- [therefore performance not relevant to history of inflammation]
- 72 RRMS patients

Area under ROC ± SE (discriminant analysis)		
	NoON vs. Control	ON vs. Control
EDSS (MS pts.)	3.87	3.93
Single Eye	75.9 ± 3.93	71.6 ± 5.03

Conclusions

- as in our earlier mfVEP study[1] (also using sparse stimuli) diagnostic power of multifocal pupil perimetry (mfPOP) followed EDSS, not history of acute inflammation of the optic nerve
- this suggests that the results are more consistent with secondary degeneration than inflammation *per se*
- mfPOP is a possible fast, low-cost adjunct to MRI with which to follow progressive disease:
  - separate efferent and afferent information[2,5]
  - alternatively only one pupil needs to be operating
  - blinks, fixation losses, small pupils not a problem
  - stimuli tolerant of mis-refraction

Author Disclosure Information

CJ Lueck: None. C Voicu: None.
AC James: Seeing Machines patents and consultancies.
T Maddess: Seeing Machines patents and consultancies; Carl Zeiss Meditec, patents, royalties for the FDT/Matrix perimeters; EyeCo Ltd, consultant, equity.

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