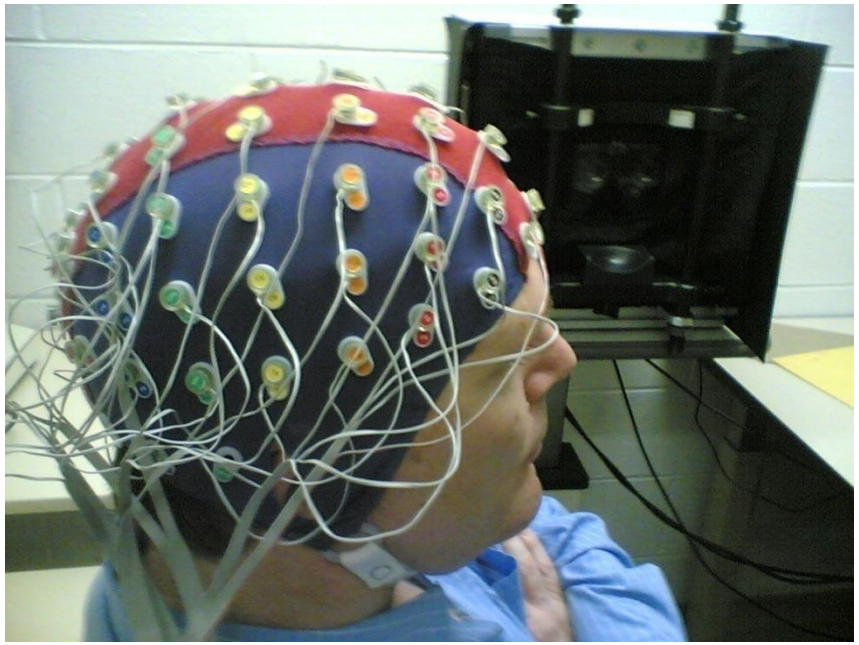
Objective visual field testing to assess MS severity and progression

Ted Maddess, Christian Lueck, Corinne Carle,
Emilie Rohan, Jon Baird-Gunning, Josh van Kleef

Pattern Visual Evoked Potential (**VEP**)



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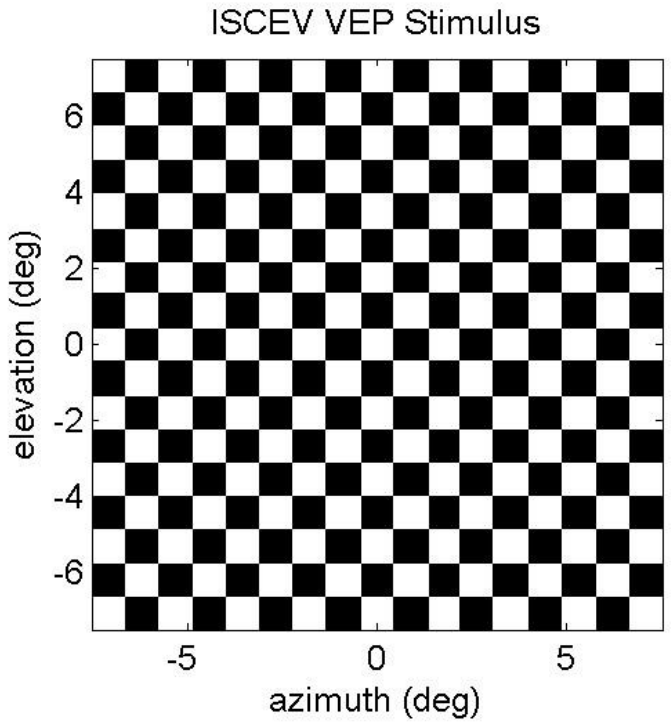

illustration of “pattern reversal”

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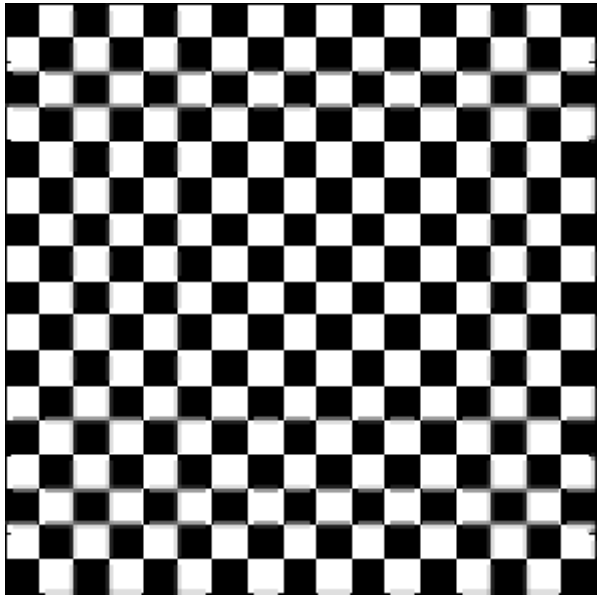
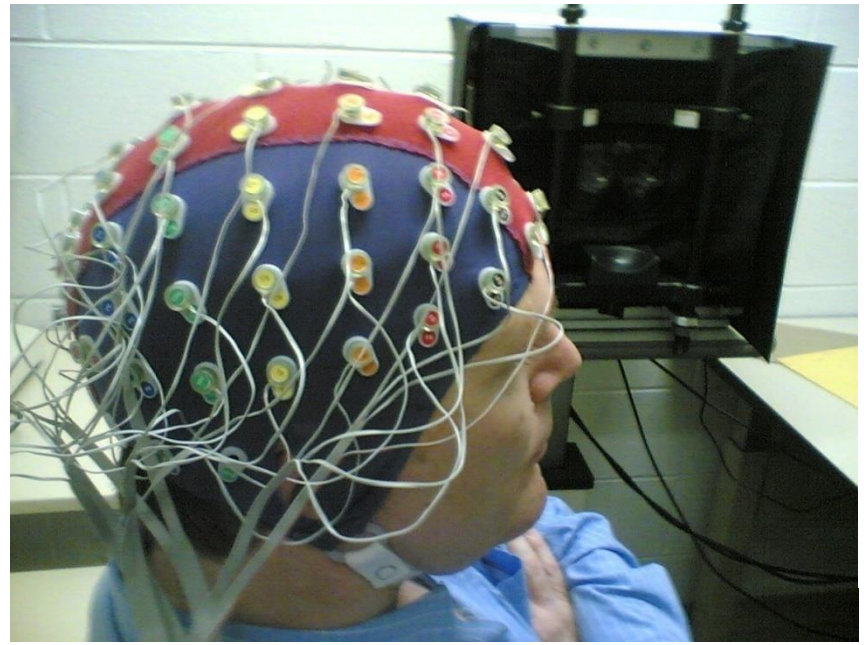
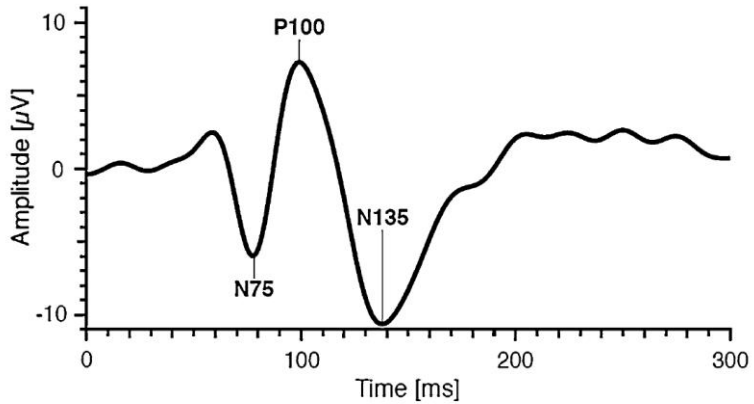


illustration of “pattern reversal”

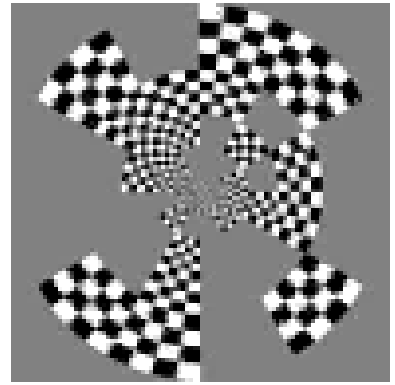




A typical pattern-reversal VEP

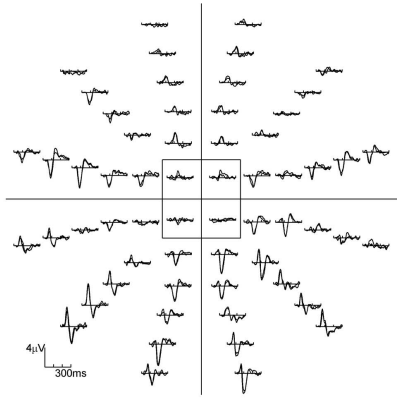
Multifocal VEPs (**mfVEPs**)

- Many independent stimuli
- **Sparse** = each regional stimulus briefly present with longer breaks



Multifocal VEPs (**mfVEPs**)

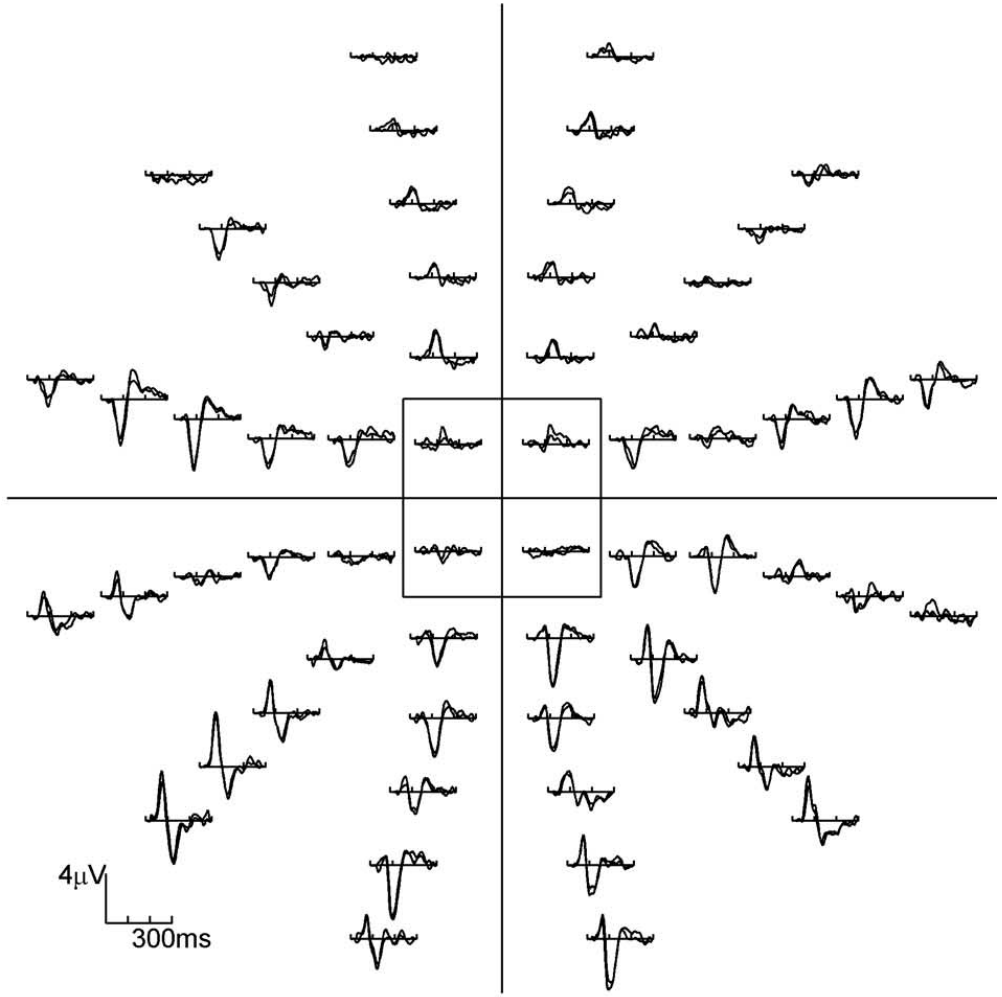
- You get many responses
- One for each stimulus region



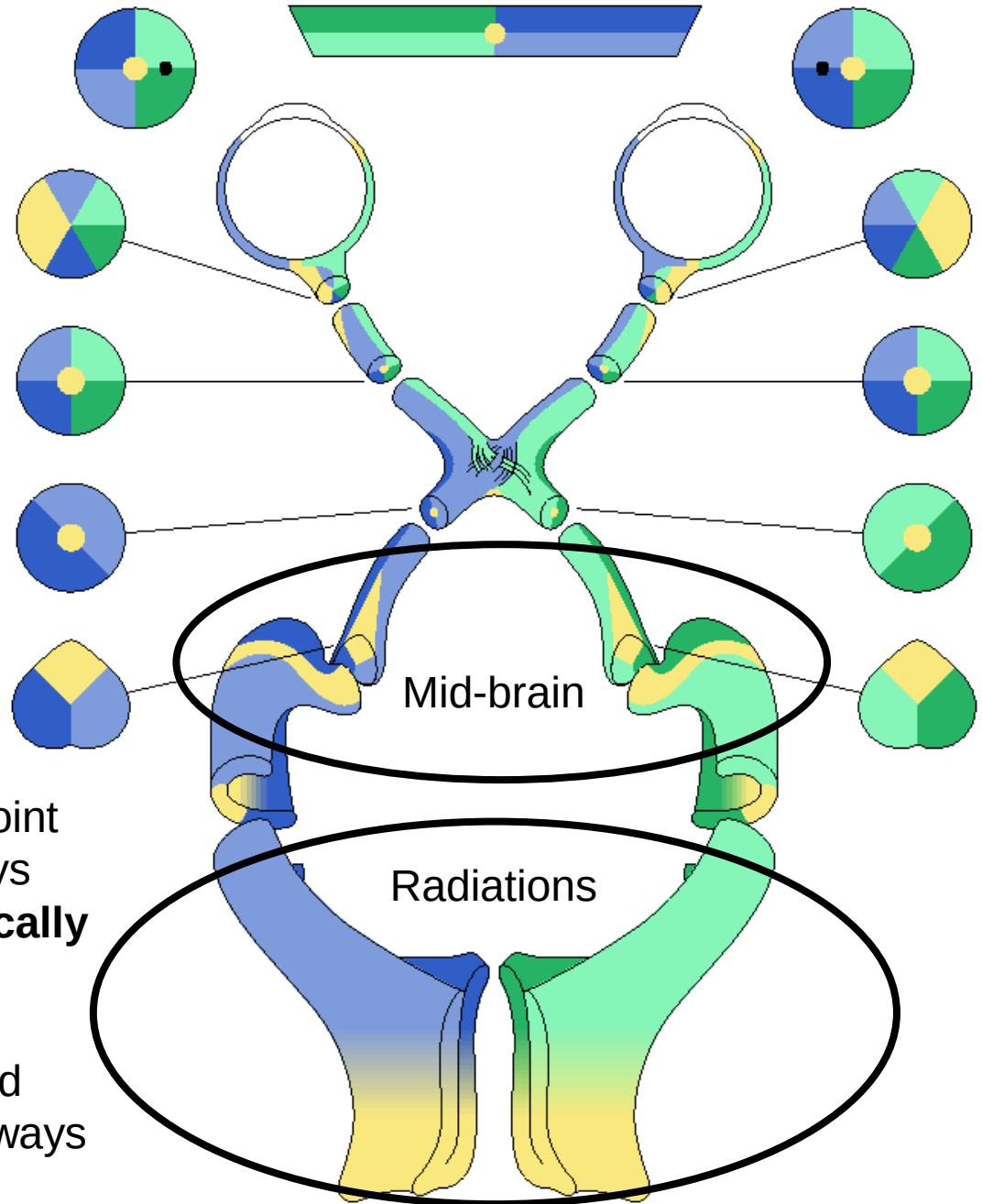
Multifocal VEPs (**mfVEPs**)

- You get many responses
- One for each stimulus region

- i.e. one for each part of the optic nerve and brain



4 quadrant stimulus on a TV



Damage at any point along the pathways will be **retinotopically** expressed
i.e. map of visual space is preserved all along the pathways

Why is the visual system useful in MS?

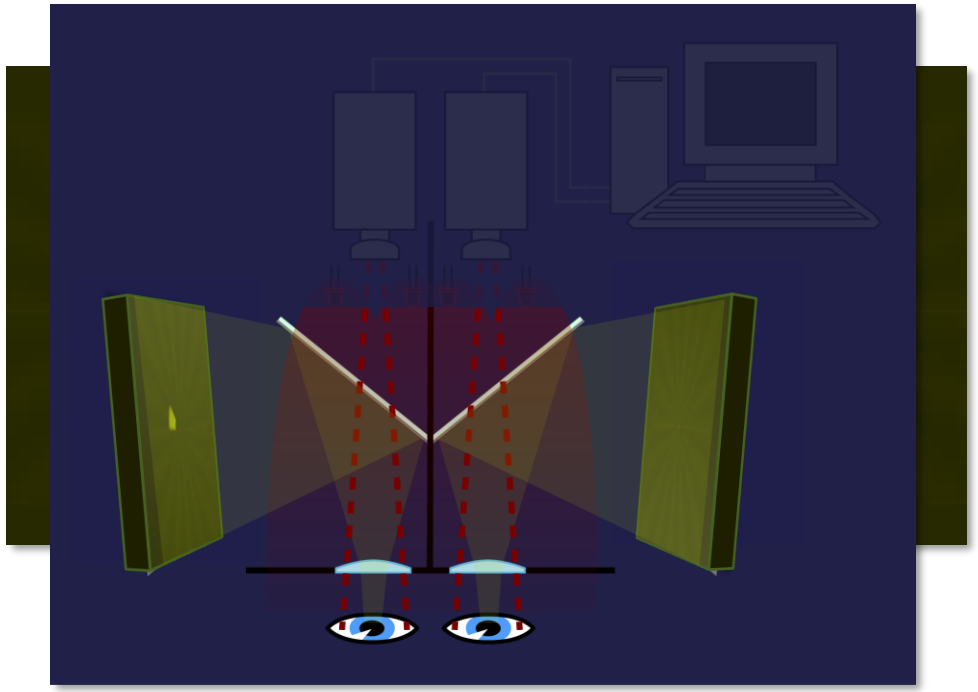
- evoked potential response gain increases up to 15-fold as transient ***mfVEP*** stimuli are made *temporally sparse* (infrequent)*
- increasing gain increases both sensitivity and specificity in discriminating MS patients from controls (92% sensitivity at FPR = 0)*
- there are 4.5x more efferent axons (taking signals from cortex to thalamus) than the afferent path within the optic radiations
- the gain may be regulated in this *cortico-thalmic loop*
- the optic radiations are 1% of white matter but account for 7–10% of all white matter lesions

*Ruseckaite R, Maddess T, Danta G, Lueck CJ, James AC. Sparse multifocal stimuli for the detection of multiple sclerosis. Ann Neurol 2005; 57: 904–13

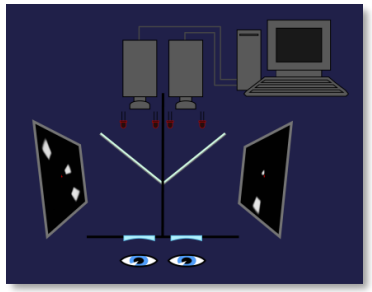
Device explanation

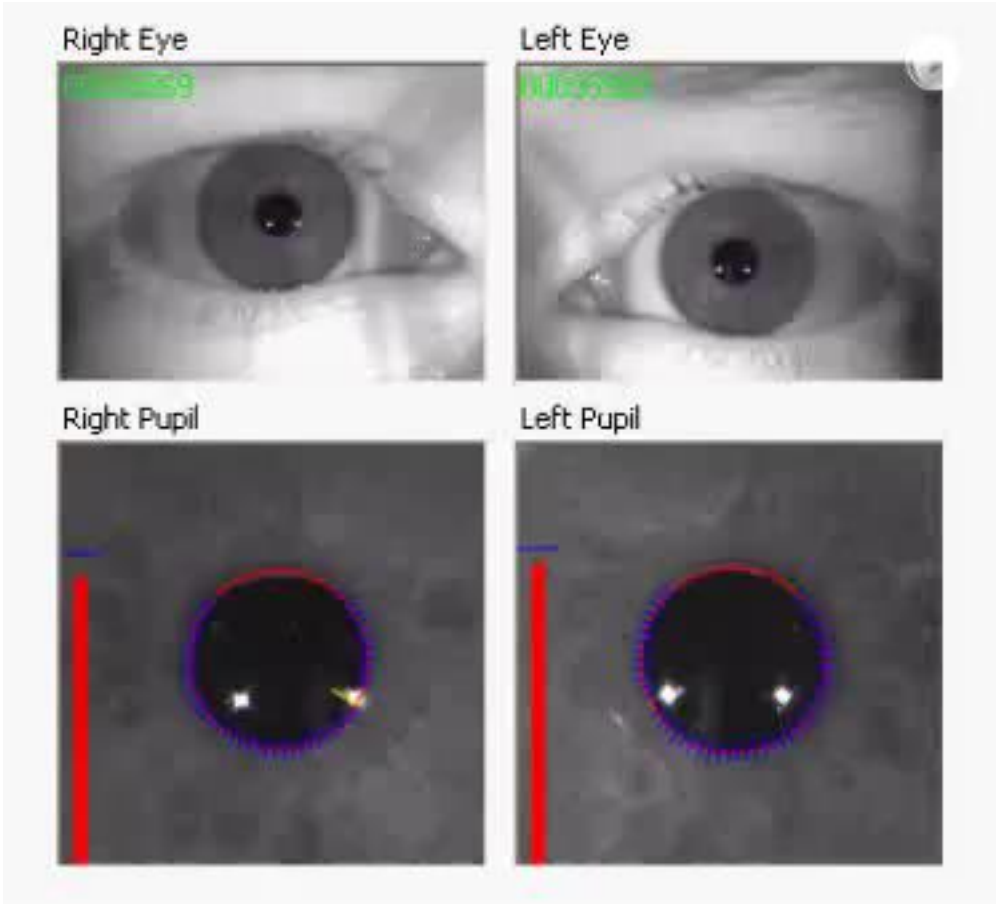
Konan ObjectiveFIELD Analyzer (OFA)

ObjectiveField Analyser



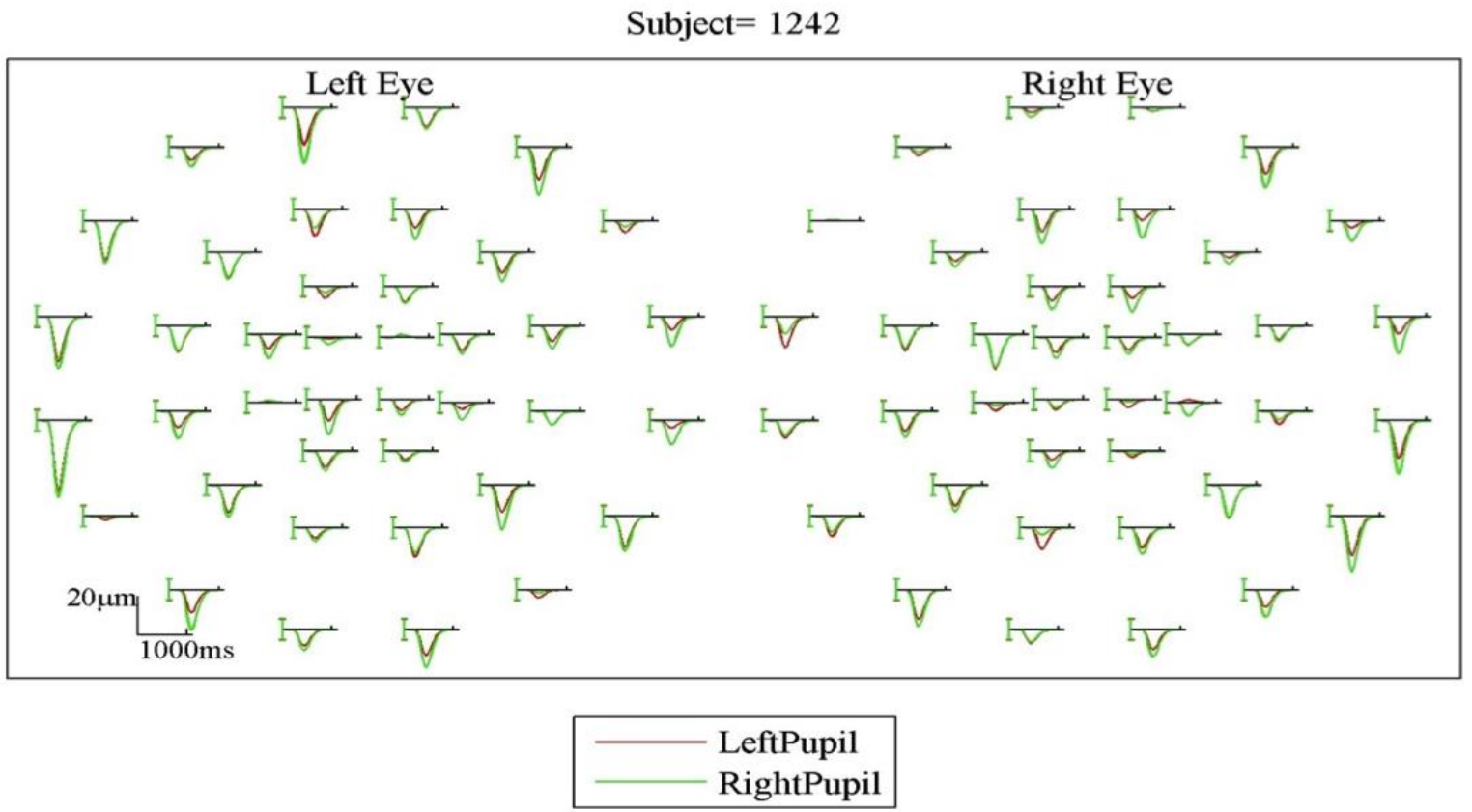
ObjectiveFIELD Analyzer





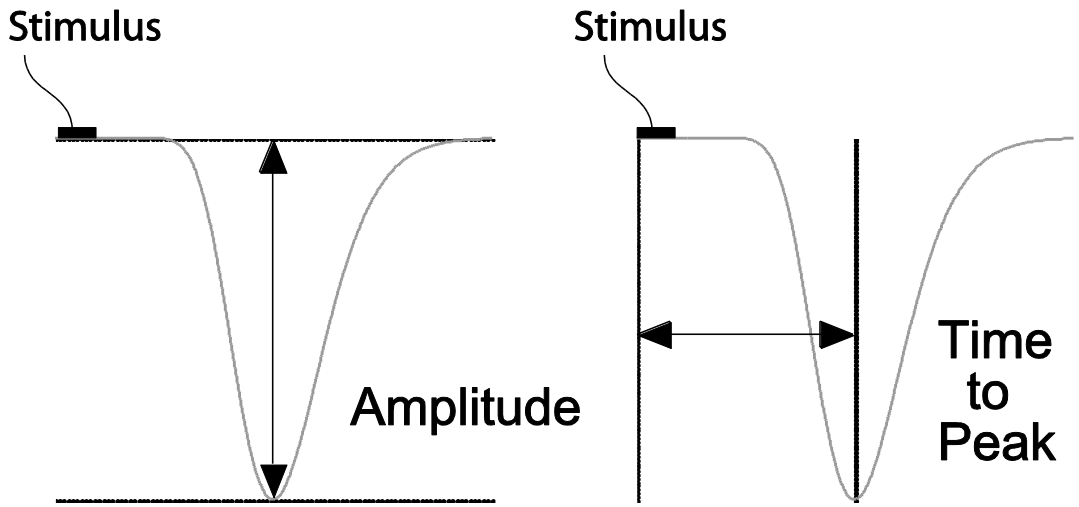
OFA example results

- note there are 4 fields = 176 responses



Data obtained at each region

- Pupil responses, down = contraction
- amplitude = **sensitivity**; also get **delay** (time to peak)



- so 176 sensitivities and 176 delays, and SE for each

2008-9 study of a old OFA method in MS

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
2014, Vol. 20(7) 854–861

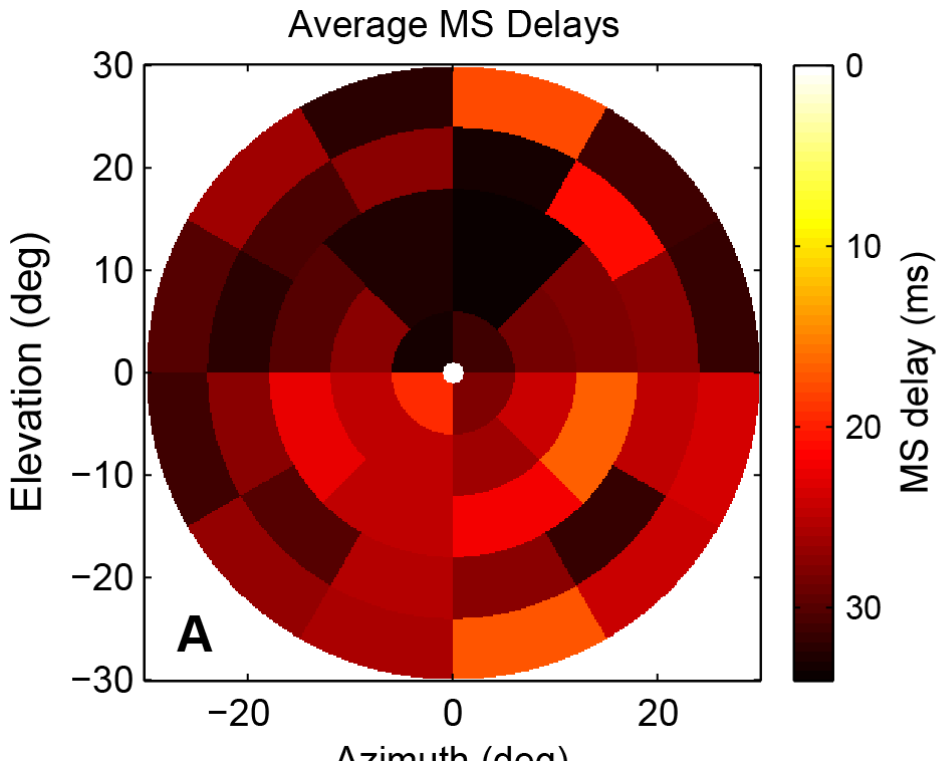
DOI: 10.1177/1352458513512708
msj.sagepub.com
SAGE

Pupillary response to sparse multifocal stimuli in multiple sclerosis patients

EN Ali[1], T Maddess[1], AC James[1], C Voicu[1] and CJ Lueck[2]

Results of 2008-9 study

- reduction of 0.69 ± 0.04 dB (mean ± SE) in per-region sensitivity
- delayed time-to-peak of 25.95 ± 0.89 ms (mean ± SE)
- Figure is mean difference in per-region delays relative to normal of **the 85 MS patients** (n.b. 30 ms delays common)



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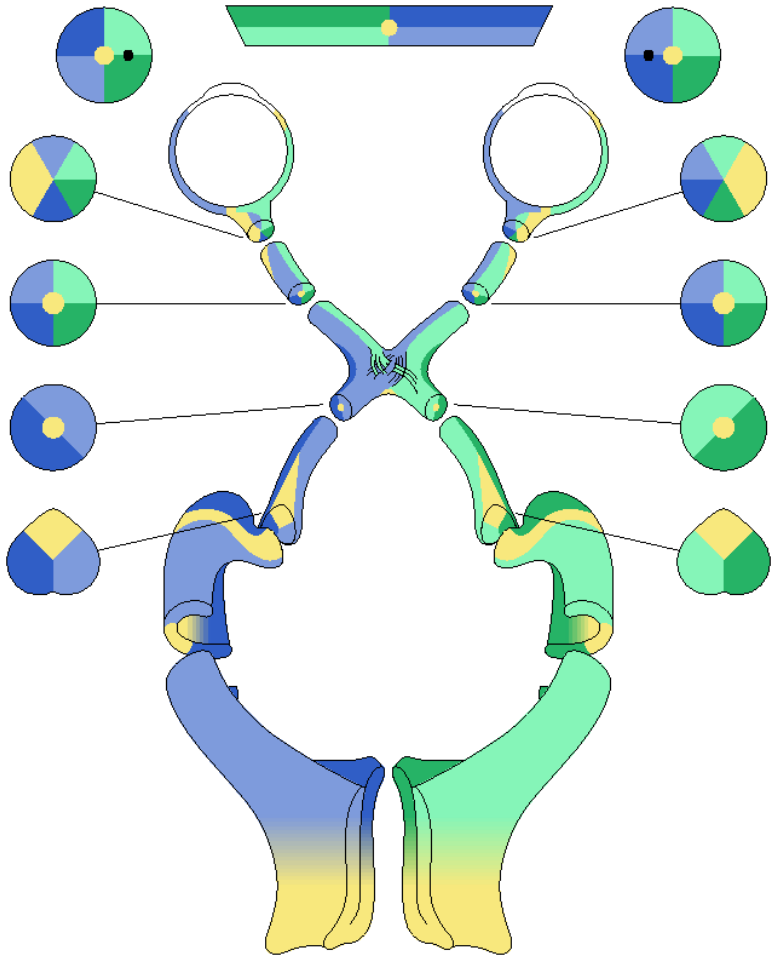
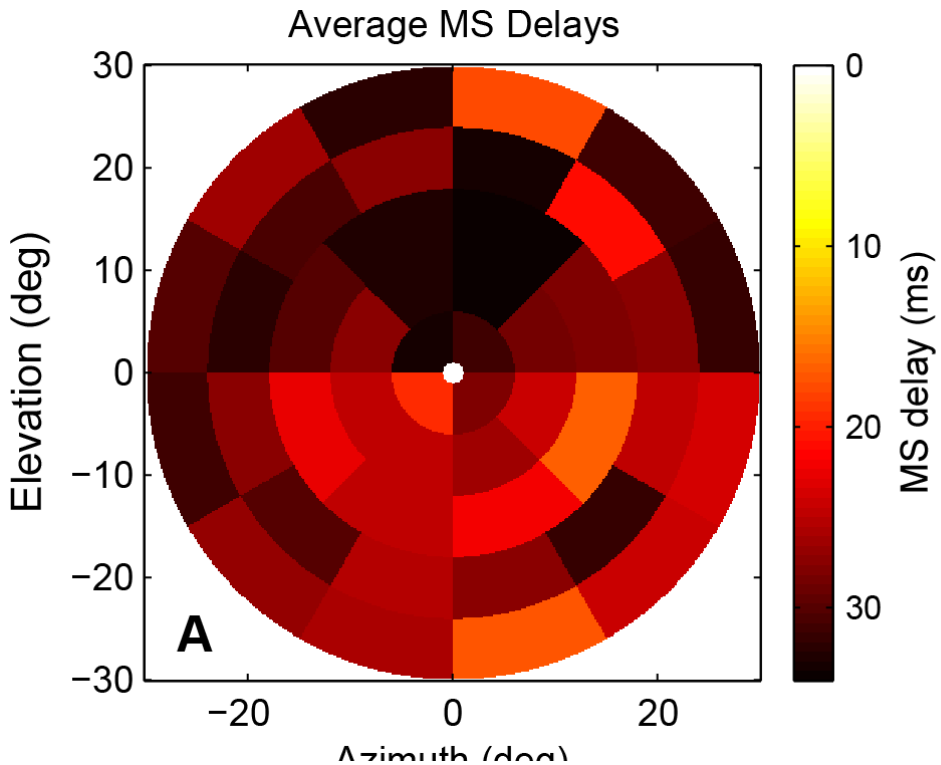
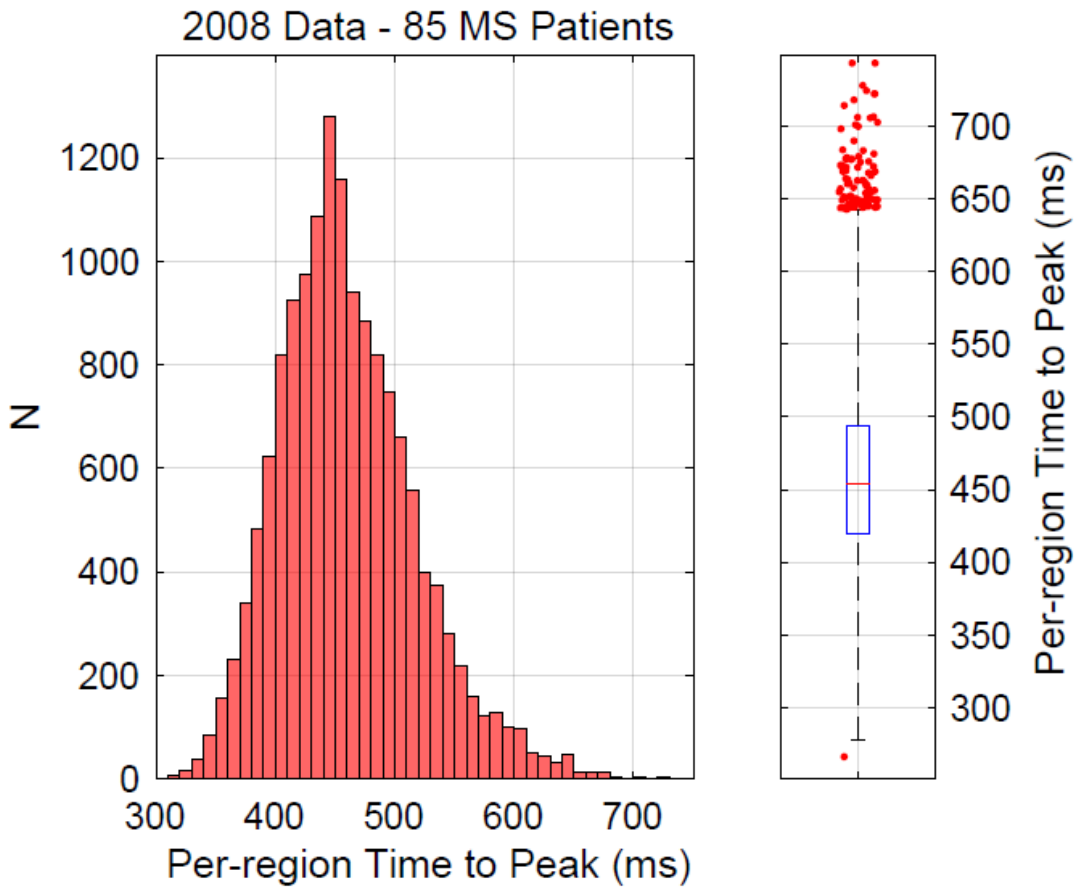




Distribution of 2008-9 MS Patient Delays



SD is about 40 ms

Remember this!

Conclusions of 2008-9 study

- Diagnostic power followed the EDSS scores but *not the history of optic neuritis*
  - *Just like the earlier mfVEP study!*
- Implying that OFA was measuring degeneration rather than something related to acute inflammation
- The most affected ~3 of 44 regions per eye were most diagnostic for MS vs. normal controls
- Provided the starting point for our follow-up study

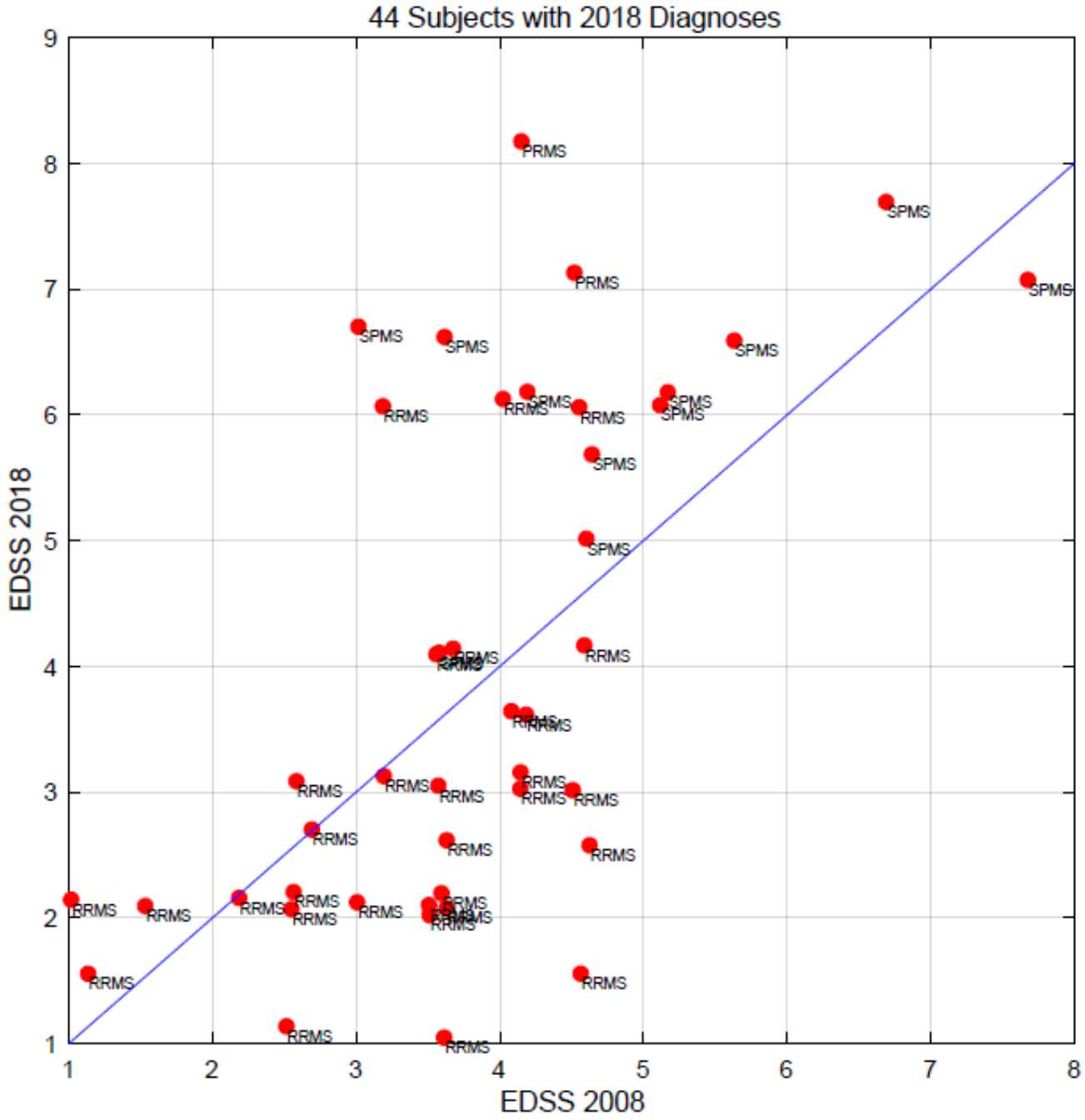
The new follow-up study

- 2008 to 2009
- 85 MS subjects

- 2018 to 2019
- Managed to get 46 subjects back (13 Progressive)

10 year changes

- Disease type was re-assessed
- Nine progressed from RRMS to SPMS
- Two were Progressives and their EDSS got worse
- EDSS and was re-assessed in 2018 (see plot)



Can we predict Progression with 2008 data?

- Progression: RSMS who progressed to SPMS, or PPMS or SPMS whose EDSS progressed by up to 3 steps
- Logistic regression model fitting the log-odds for clinical progression
- Used fitglm in Matlab, one mean per subject of worst 3 regions

Logistic regression model results

	log-Odds	SE	t-stat	P-value
(Intercept)	-1.14	0.40	-2.88	0.004
3 Amplitudes	0.38	0.55	0.70	0.485
3 Delays	**18.0***	8.99	2.00	0.045

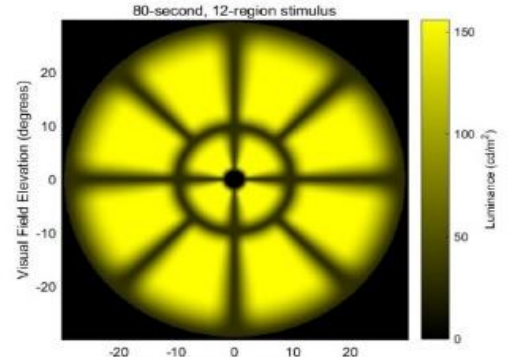
*18.0 is the log-Odds/second of delay in 2008

40 ms longer delay gives: 2.05x higher risk { ±SD = 1.43x : 2.95x }

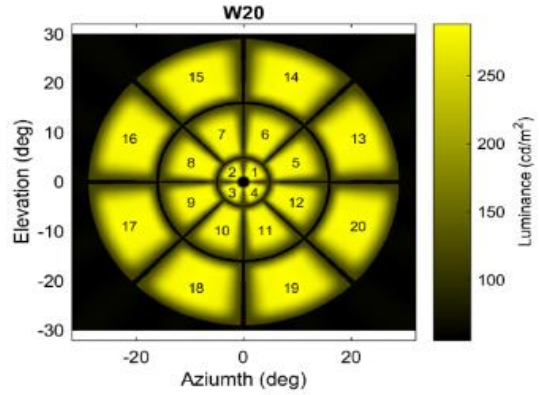
40 ms quicker delays gives: 2.05x lower risk

New stimuli also tested

- In addition to retesting with the 2008 mfPOP method (P117) we tested all the subjects with 3 new mfPOP tests
  - P129 240 seconds per eye
  - W12 new 12-region/eye: 80 seconds for both eyes
  - W20 new 20-region/eye: 80 seconds for both eyes
  - 53 normal control patients



W12



W20

Diagnostic power – Relapsing Remitting

		AUC ± SE		g	
		N=4	N=12	N=4	N=12
P129	Pattern Dev	72.6 ± 5.22	75.6 ± 4.74	1.10	1.16
	Asymm	75.7 ± 5.32	78.6 ± 4.95	1.28	1.46
W12	Pattern Dev	77.3 ± 5.52	77.5 ± 5.47	0.93	0.95
	Asymm	83.0 ± 4.97	82.2 ± 4.81	1.05	0.99
W20	Pattern Dev	79.8 ± 5.51	78.0 ± 5.57	1.11	1.05
	Asymm	86.6 ± 4.72	83.9 ± 4.73	1.35	1.26

Diagnostic power – Progressive MS

		AUC ± SE		g	
		N=4	N=12	N=4	N=12
P129	Pattern Dev	94.7 ± 3.47	93.4 ± 2.86	2.86	2.69
	Asymm	96.2 ± 1.76	97.0 ± 1.75	3.09	3.32
W12	Pattern Dev	93.4 ± 3.52	91.6 ± 6.57	1.93	1.81
	Asymm	96.5 ± 2.30	94.5 ± 3.79	2.07	2.02
W20	Pattern Dev	85.9 ± 6.55	86.6 ± 6.42	1.85	1.87
	Asymm	93.0 ± 3.42	94.3 ± 3.47	2.54	2.49

Diagnostic power – By EDSS

		AUC ± SE		g	
		N=4	N=12	N=4	N=12
	EDSS1	73.9 ± 7.00	77.7 ± 5.80	1.12	1.25
P129	EDSS2	80.5 ± 6.62	82.9 ± 6.48	1.73	2.06
	EDSS3	90.3 ± 6.19	91.1 ± 6.13	2.74	2.93
	EDSS1	75.0 ± 8.33	76.4 ± 7.53	1.12	1.12
W12	EDSS2	**89.8 ± 4.74**	88.4 ± 4.58	**1.70**	**1.62**
	EDSS3	**95.4 ± 2.62**	93.3 ± 3.77	**1.91**	**1.88**
	EDSS1	81.1 ± 6.69	81.5 ± 6.00	1.32	1.26
W20	EDSS2	**86.5 ± 6.26**	84.6 ± 6.03	**1.85**	**1.70**
	EDSS3	**94.1 ± 3.12**	94.4 ± 3.16	**2.37**	**2.35**

Diagnostic power – noON vs. ON

		AUC ± SE		g	
		N=4	N=12	N=4	N=12
P129	no-ON	81.1 ± 6.85	86.2 ± 5.33	1.99	2.02
	ON	82.0 ± 4.89	83.0 ± 4.79	1.63	1.73
W12	no-ON	**86.2 ± 5.77**	86.9 ± 5.24	1.50	1.45
	ON	**87.4 ± 4.62**	86.0 ± 4.46	1.29	1.29
W20	no-ON	**84.5 ± 6.44**	87.2 ± 5.45	1.69	1.75
	ON	**88.7 ± 4.06**	86.8 ± 4.36	1.63	1.50

Conclusions

- Recalling 2008-9 study subjects showed persons with
  - 1 SD slower responses in 2008-9 had a 2.05x greater chance of progressing
  - 1 SD quicker 2.05x lower risk of progression
- The new 80-second stimuli performed as well or better than the older 6-minute stimulus
- Asymmetry between per-region delays in the two eyes performed best
- AUCs for W12 (discriminating controls from patients)
  - RRMS: 83.0 ± 4.97
  - Progressive: 96.5 ± 2.30
- AUCs for EDSS 2-3 high, and also for eyes with **no** Optic Neuritis

Thanks for listening!

OFA also measures brain function

Sabeti F, Carle CF, Jaros RK, Rohan EMF, Lueck CJ, Maddess T. Objective perimetry in sporting-related **mild traumatic brain injury**. **2019** *Ophthalmology;* 126: 1053-1055

Carle CF, James AC, Rosli Y, Maddess T. **Localisation of neuronal gain-control** in the pupillary response. **2019** *Frontiers of Neurol.* **10**(203): 1-9.

Rosli Y, Carle CF, Ho Y, James AC, Kolic M, and Maddess T. Retinotopic effects of **visual attention** revealed by dichoptic multifocal pupillography**. 2018** *Sci Reports*; 8, 2991.

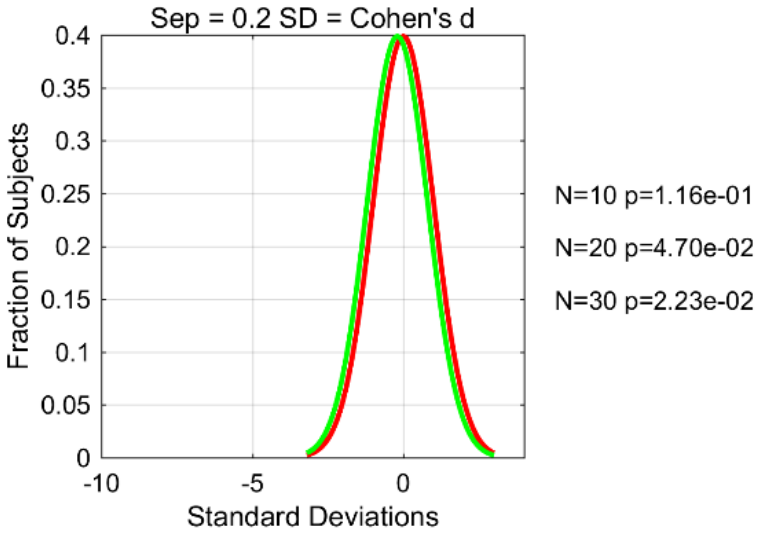
Sabeti F, James AC, Carle CF, Essex RW, Bell A & Maddess T. Comparing multifocal pupillographic objective perimetry (**mfPOP**) and multifocal visual evoked potentials (**mfVEP**) in **retinal diseases**. **2017** *Sci Rep* **7**, 45847

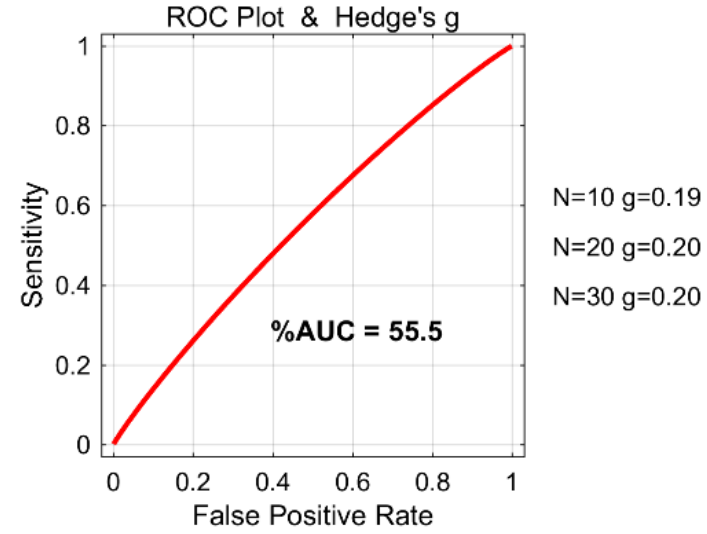
T-tests, ROC, and Effect-size

How to measure diagnostic power

ROCs, Effect Sizes Significance

Small	**0.2**
Medium	0.5
Large	0.8
Very large	1.2
Huge	2.0





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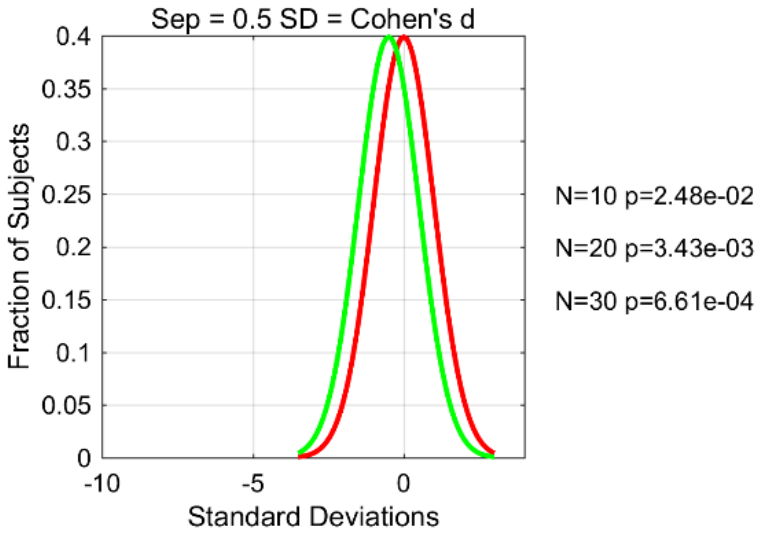

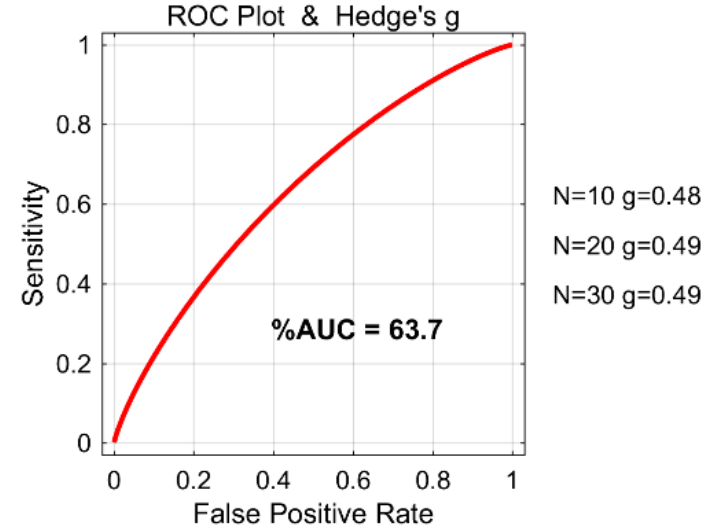

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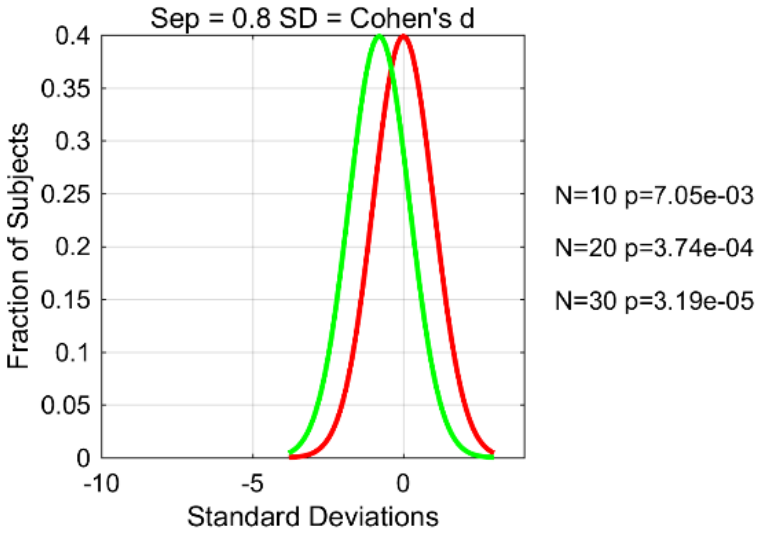

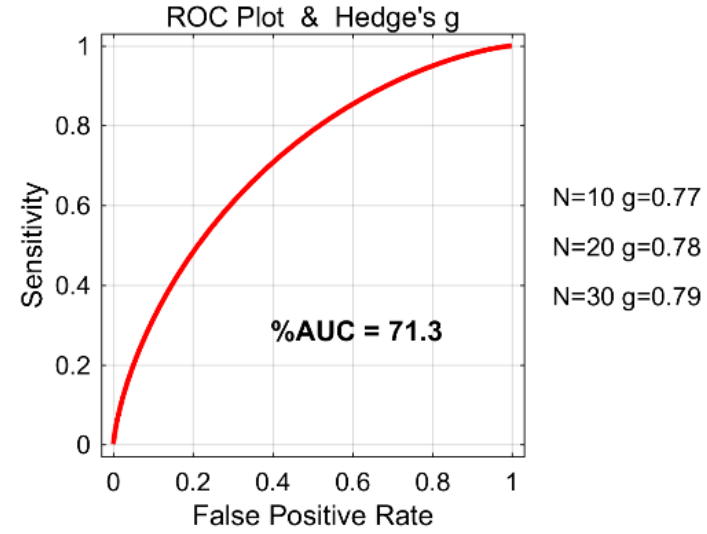

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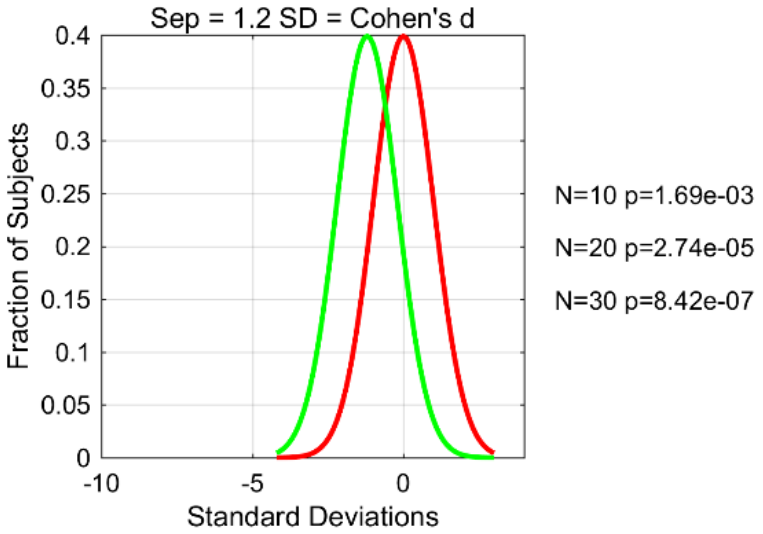

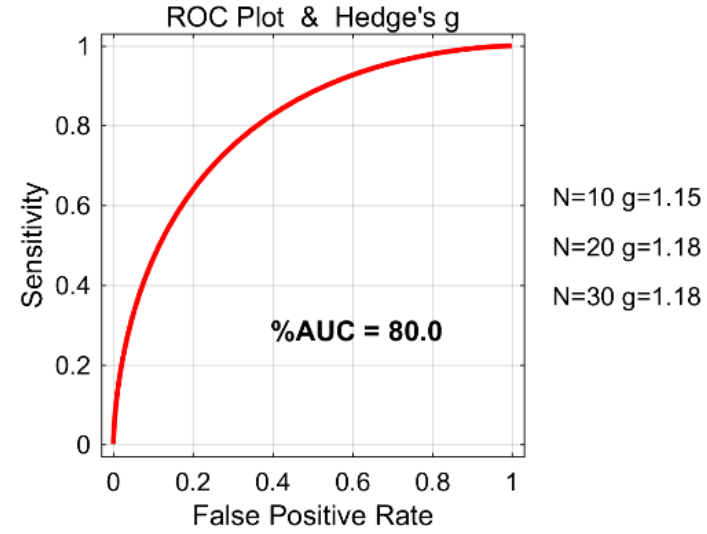

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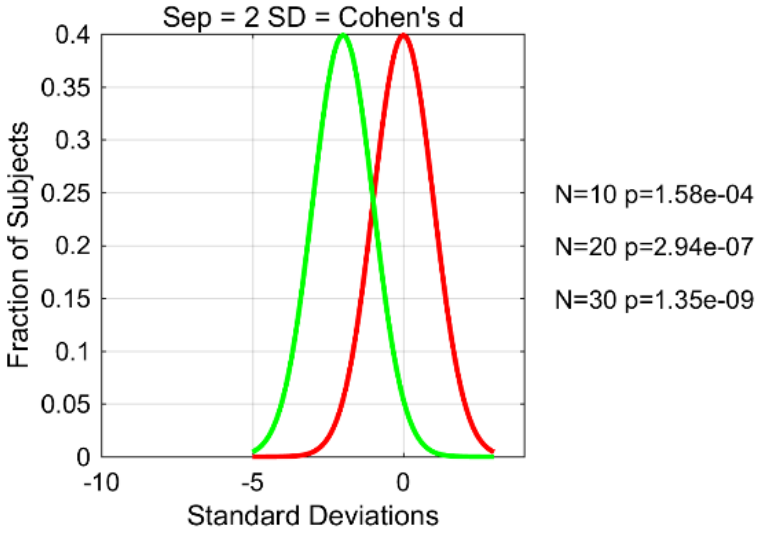

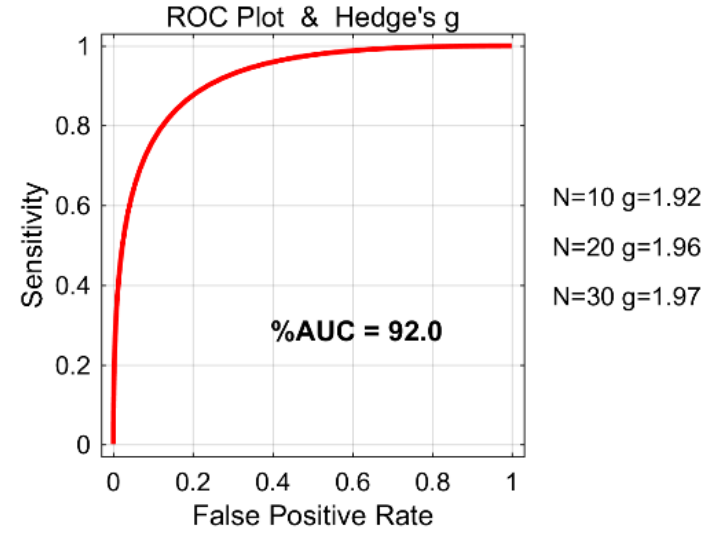

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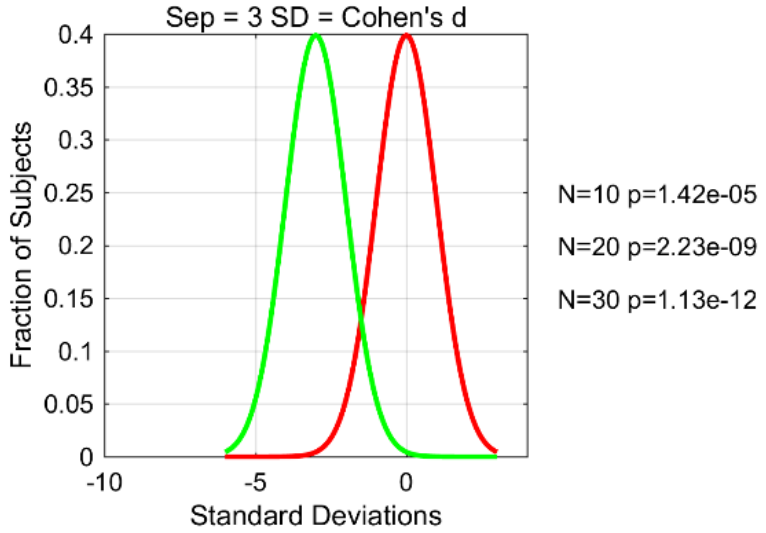

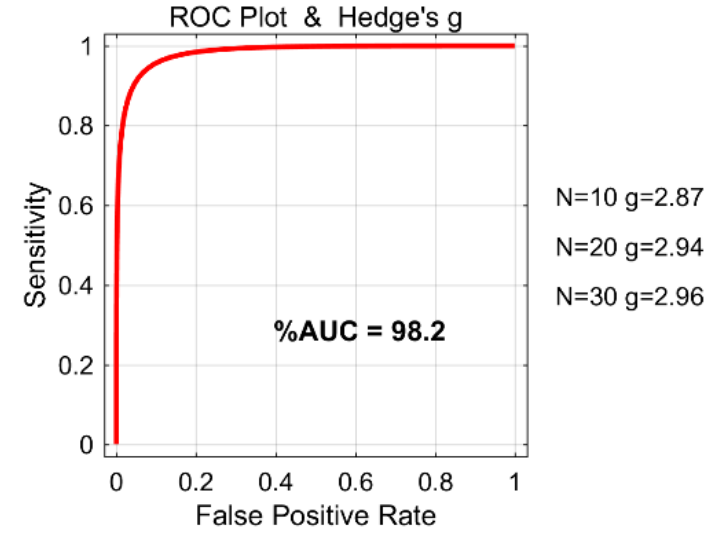

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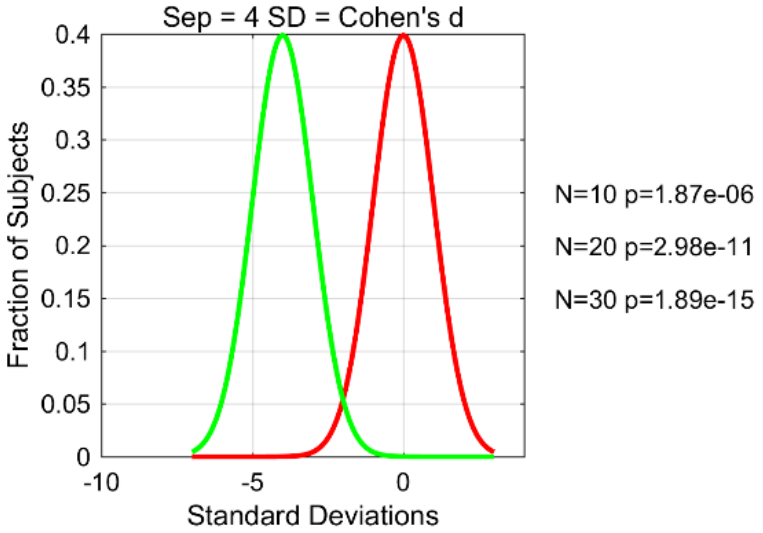
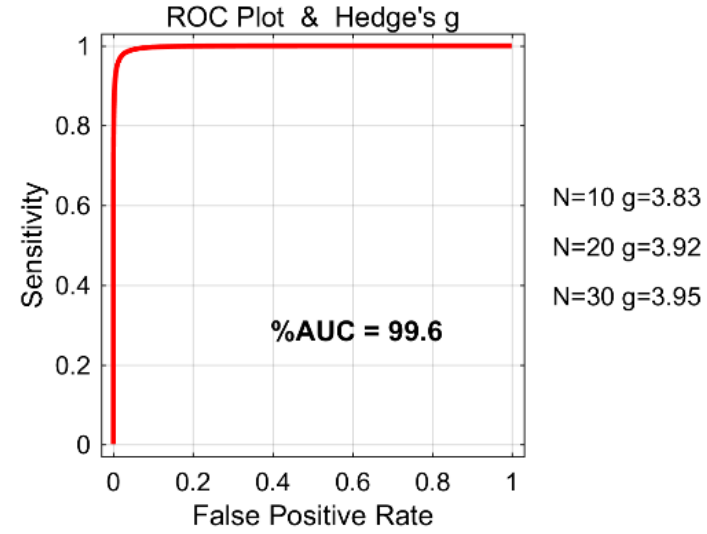
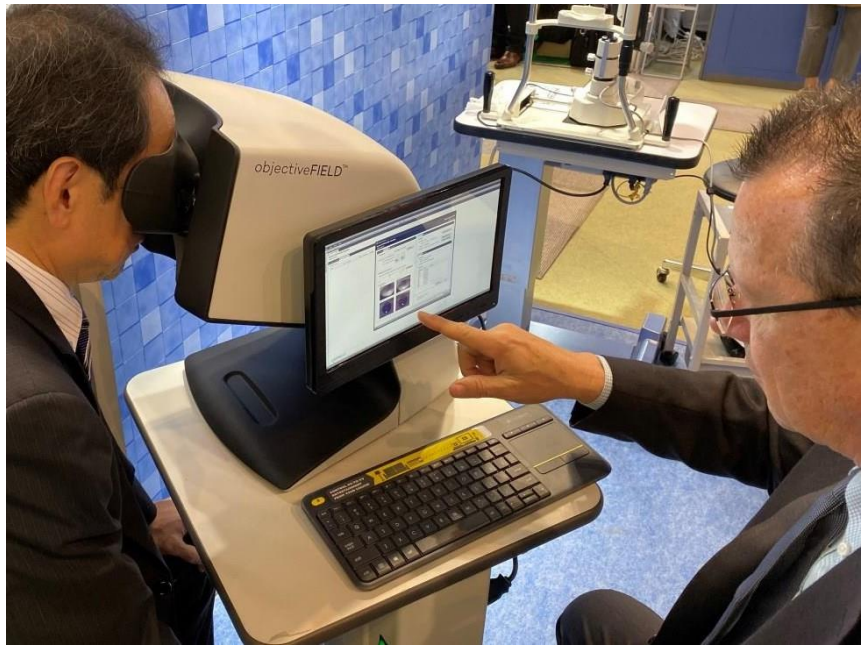
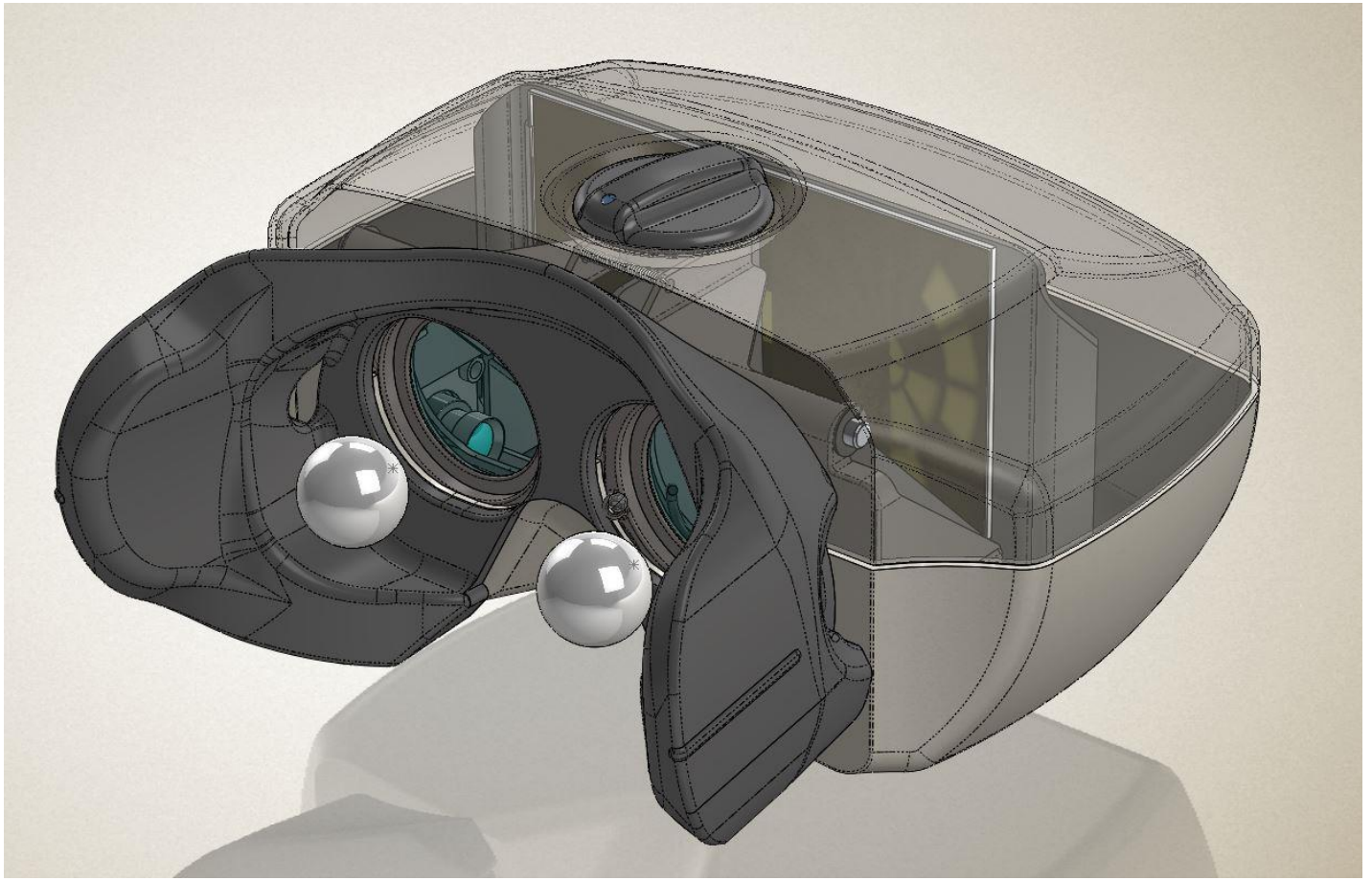




Updated units: 2 weeks



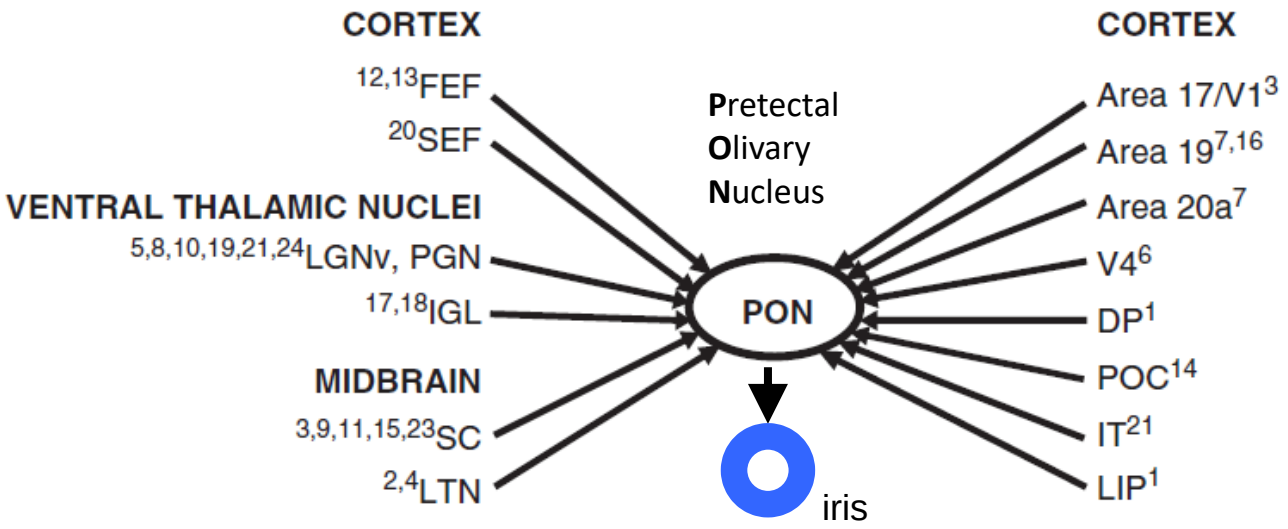
New portable units: 2021



Pupil and Brain

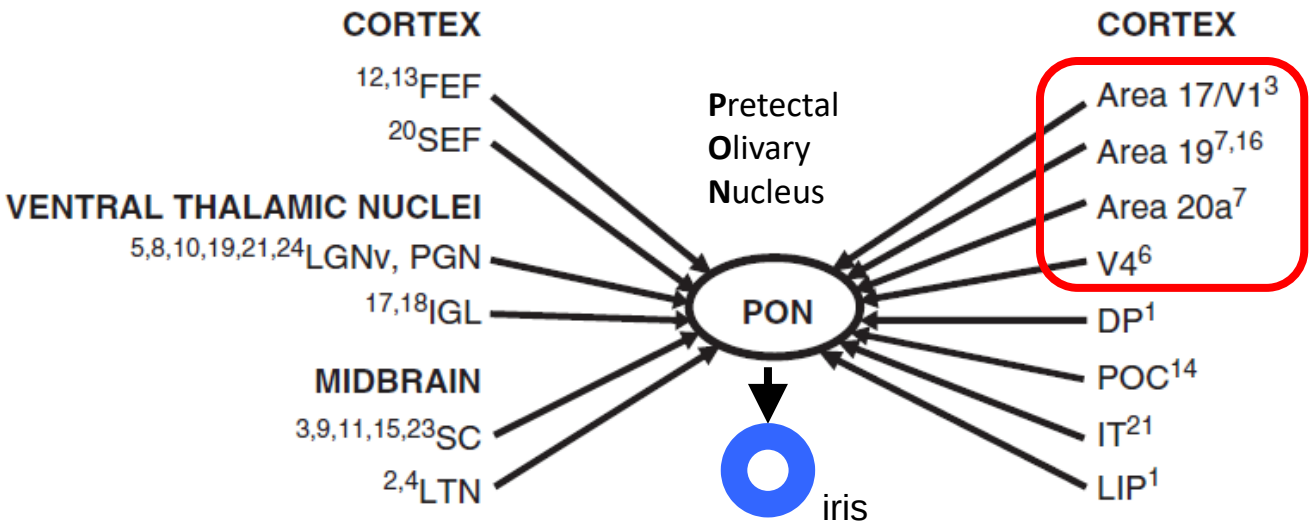
The cortical pathways

Inputs to pupils from brain areas



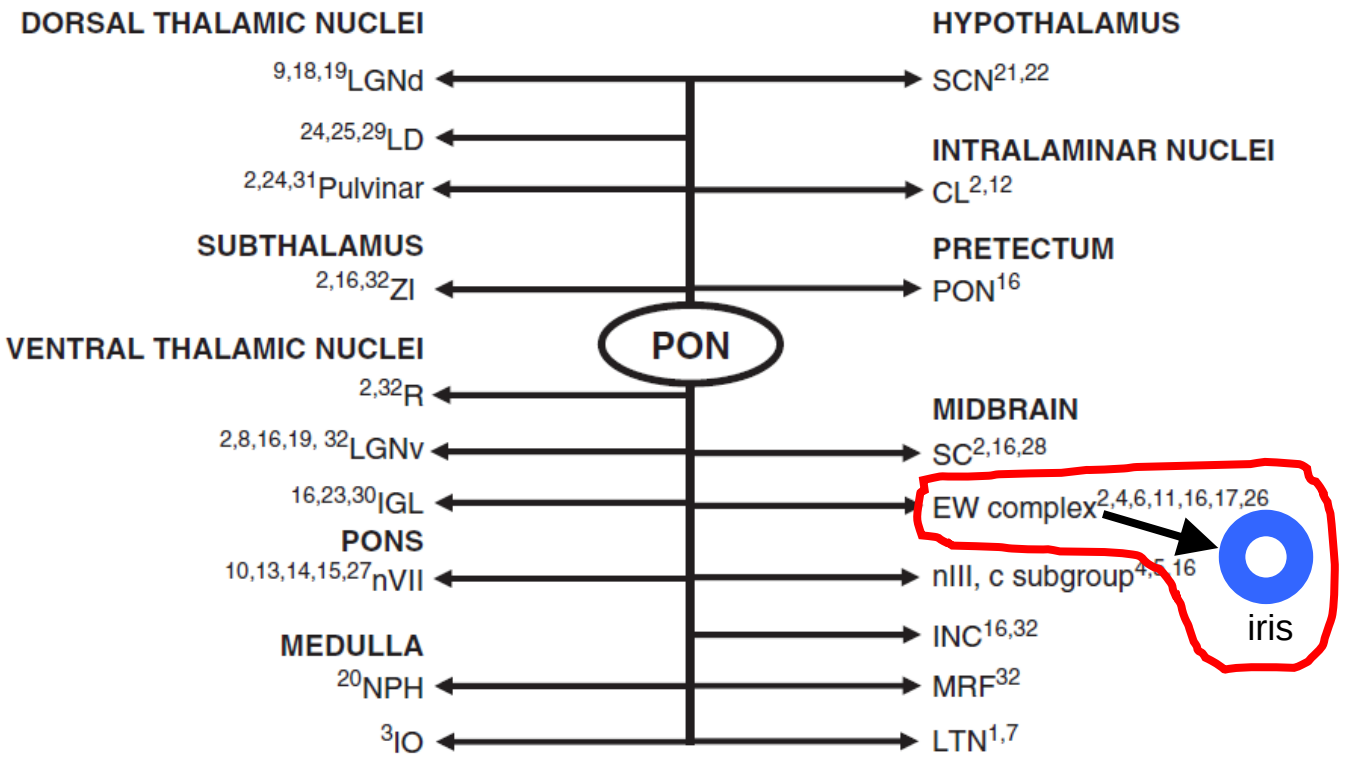
Gamlin PD (2006) *Prog Brain Res* **151,** 379–405

Inputs to pupils from brain areas



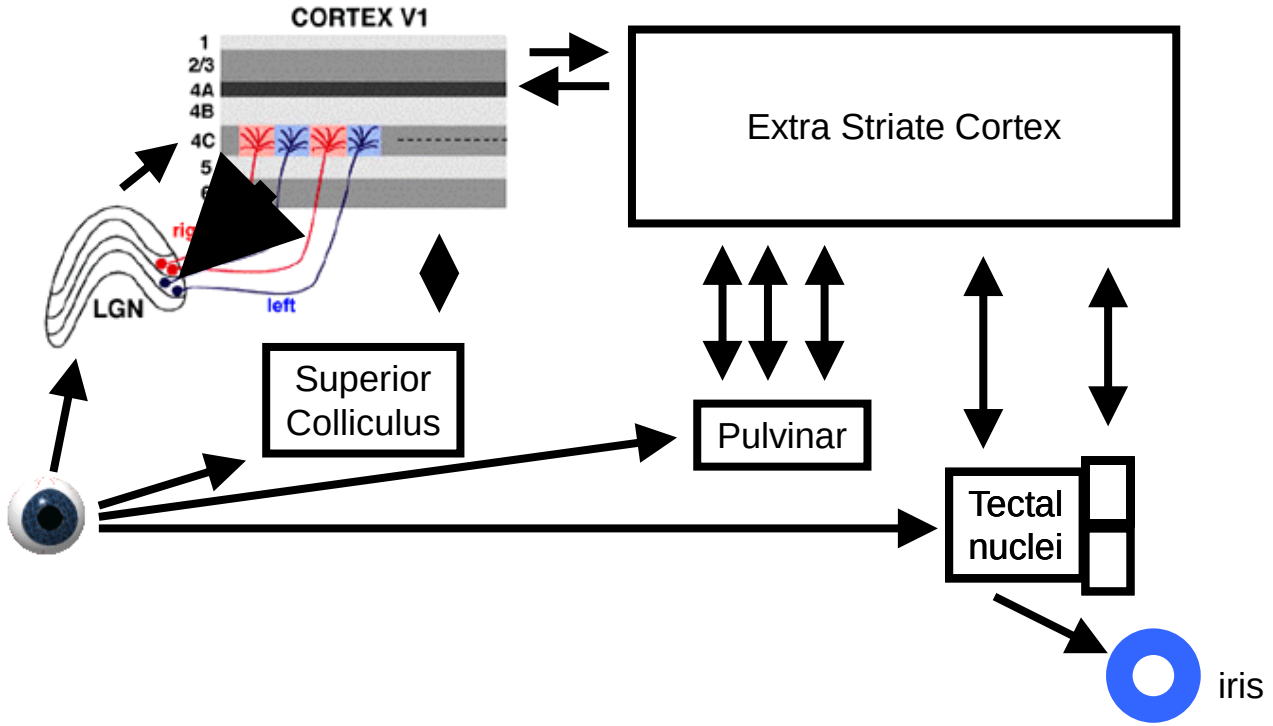
Gamlin PD (2006) *Prog Brain Res* **151,** 379–405

Outputs from pupils to brain areas

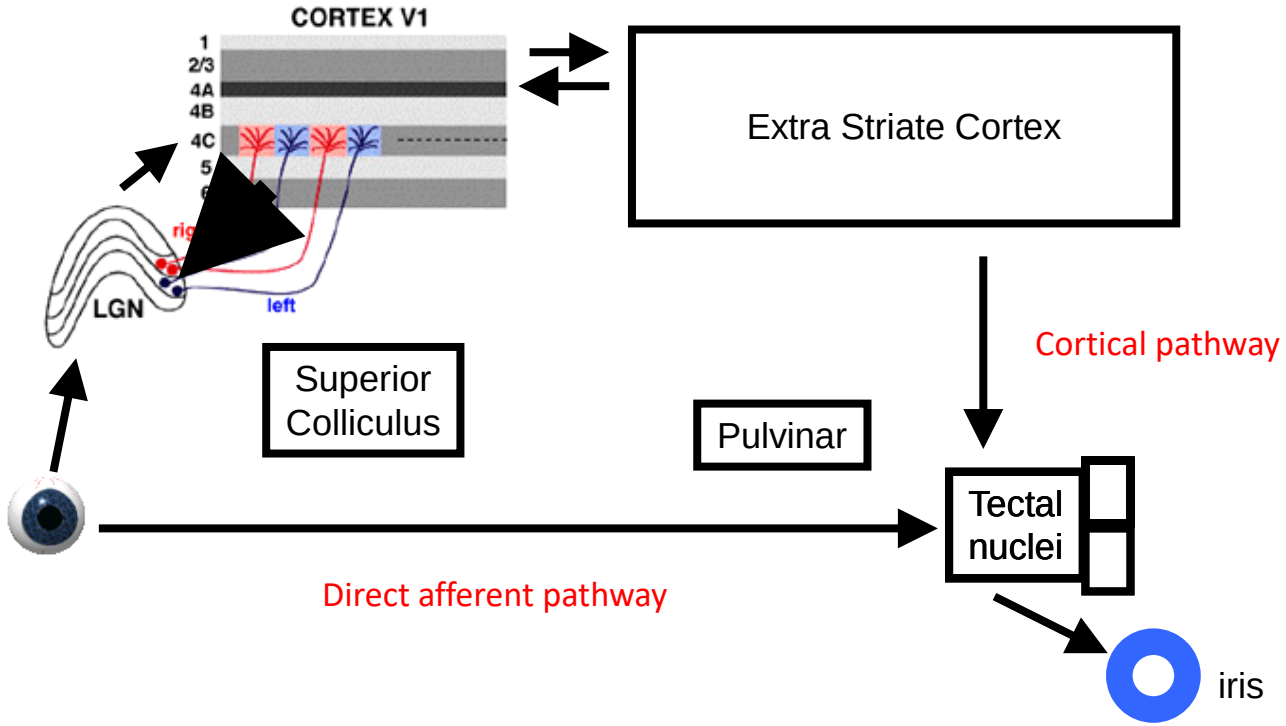


Gamlin PD (2006) *Prog Brain Res* **151,** 379–405

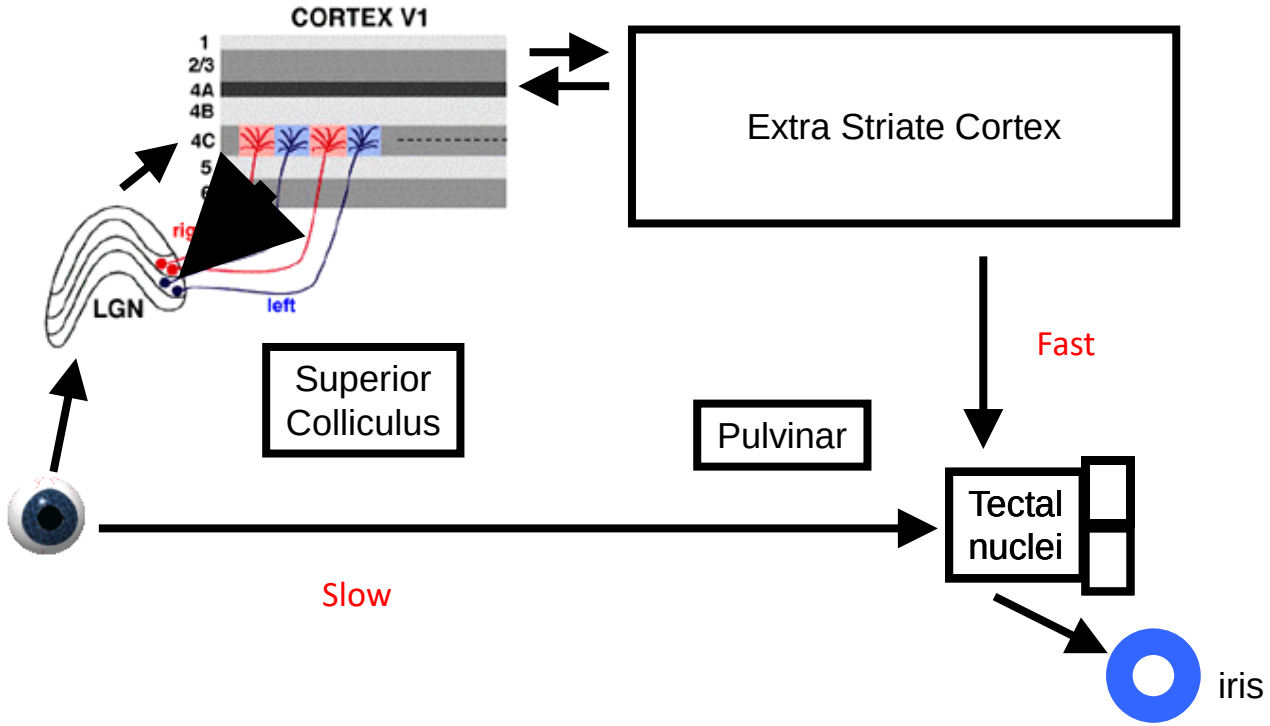
Eye to brain


CORTEX V1
1
2/3
4A
4B
4C
5
LGN
left
Extra Striate Cortex
Superior Colliculus
Pulvinar
Tectal nuclei
iris

Eye to brain


CORTEX V1
1
2/3
4A
4B
4C
5
LGN
left
Extra Striate Cortex
Cortical pathway
Superior Colliculus
Pulvinar
Tectal nuclei
Direct afferent pathway
iris

Eye to brain (a duplex system)



OFA and drive from the cortex

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- Carle CF, James AC, Kolic K, Essex RW, Maddess T. **Blue multifocal pupillographic objective perimetry in glaucoma. 2015** *Invest Ophthalmol Vis Sci* **56**: 6934-6403
- Sabeti F, James AC, Carle CF, Essex RW, Bell A & Maddess T. **Comparing multifocal pupillographic objective perimetry (mfPOP) and multifocal visual evoked potentials (mfVEP) in retinal diseases. 2017** *Scientific Reports* **7**: 45847
- Rosli Y, Carle CF, Ho Y, James AC, Kolic M, and Maddess T. **Retinotopic effects of visual attention revealed by dichoptic multifocal pupillography. 2018** *Scientific Reports* **8**: 2991
- Sabeti F, Carle CF, Jaros RK, Rohan EMF, Lueck CJ, Maddess T. Objective perimetry in sporting-related **mild traumatic brain injury**. **2019** *Ophthalmology;* 126: 1053-1055

- Conclusion: multifocal *transient onset stimuli* provide significant visual cortical drive to the irises