Evoked Potentials for diagnosis and as a marker for the evolution of MS

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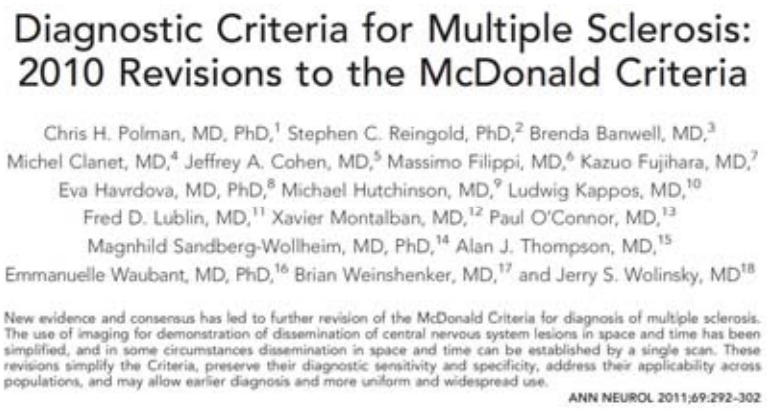
Nothing to disclose in this context

Learning objectives

Evoked potentials can

- Detect silent lesions
  - Pathological VEP without vision disturbance
  - Pathological SEP/MEP without sensory/motor symptoms
- Verify week / uncertain symptoms
  - SEP, VEP, MEP, AEP
- Help to differentiate between axonal and demyelinating lesions
  - Delayed latencies with normal amplitudes
  - Normal latencies with reduced amplitudes



Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,[1] Stephen C. Reingold, PhD,[2] Brenda Banwell, MD,[3] Michel Clanet, MD,[4] Jeffrey A. Cohen, MD,[5] Massimo Filippi, MD,[6] Kazuo Fujihara, MD,[7] Eva Havrdova, MD, PhD,[8] Michael Hutchinson, MD,[9] Ludwig Kappos, MD,[10] Fred D. Lublin, MD,[11] Xavier Montalban, MD,[12] Paul O'Connor, MD,[13] Magnhild Sandberg-Wollheim, MD, PhD,[14] Alan J. Thompson, MD,[15] Emmanuelle Waubant, MD, PhD,[16] Brian Weinshenker, MD,[17] and Jerry S. Wolinsky, MD[18]

New evidence and consensus has led to further revision of the McDonald Criteria for diagnosis of multiple sclerosis. The use of imaging for demonstration of dissemination of central nervous system lesions in space and time has been simplified, and in some circumstances dissemination in space and time can be established by a single scan. These revisions simplify the Criteria, preserve their diagnostic sensitivity and specificity, address their applicability across populations, and may allow earlier diagnosis and more uniform and widespread use.

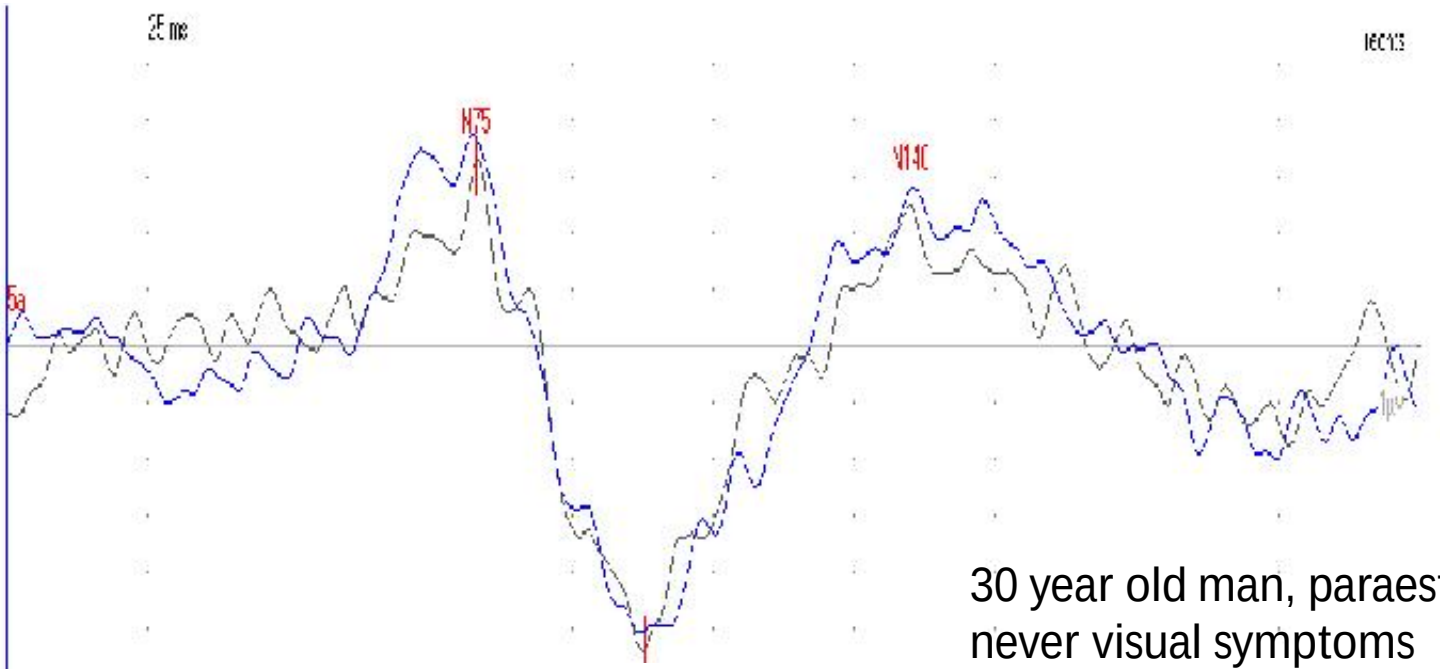
ANN NEUROL 2011;69:292–302

Before diagnosis at least 1 attack must be corroborated by findings either on

- neurological examination,
- visual evoked potential (VEP) response in patients reporting prior visual disturbance, or
- MRI consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

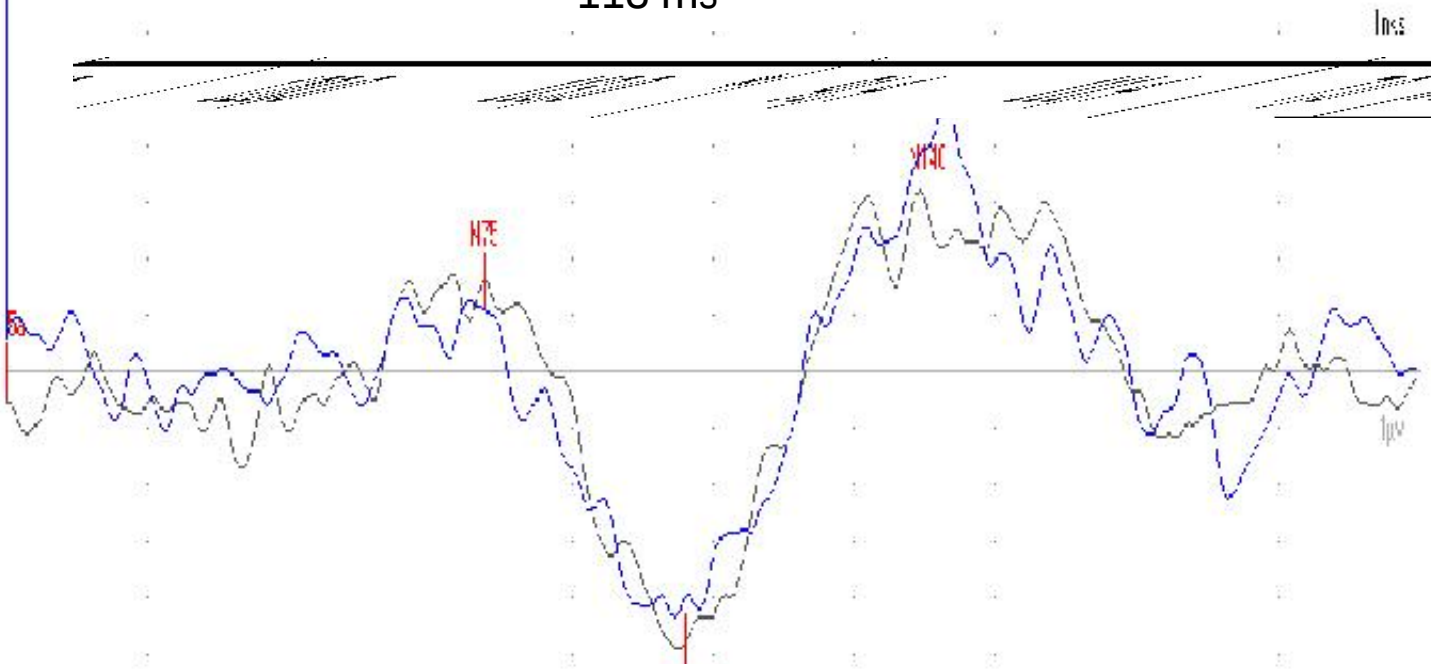
These Criteria were designed for multicentric studies, MR lesion load of high importance for quantification. Evoked potential not considered for this purpose

VEP

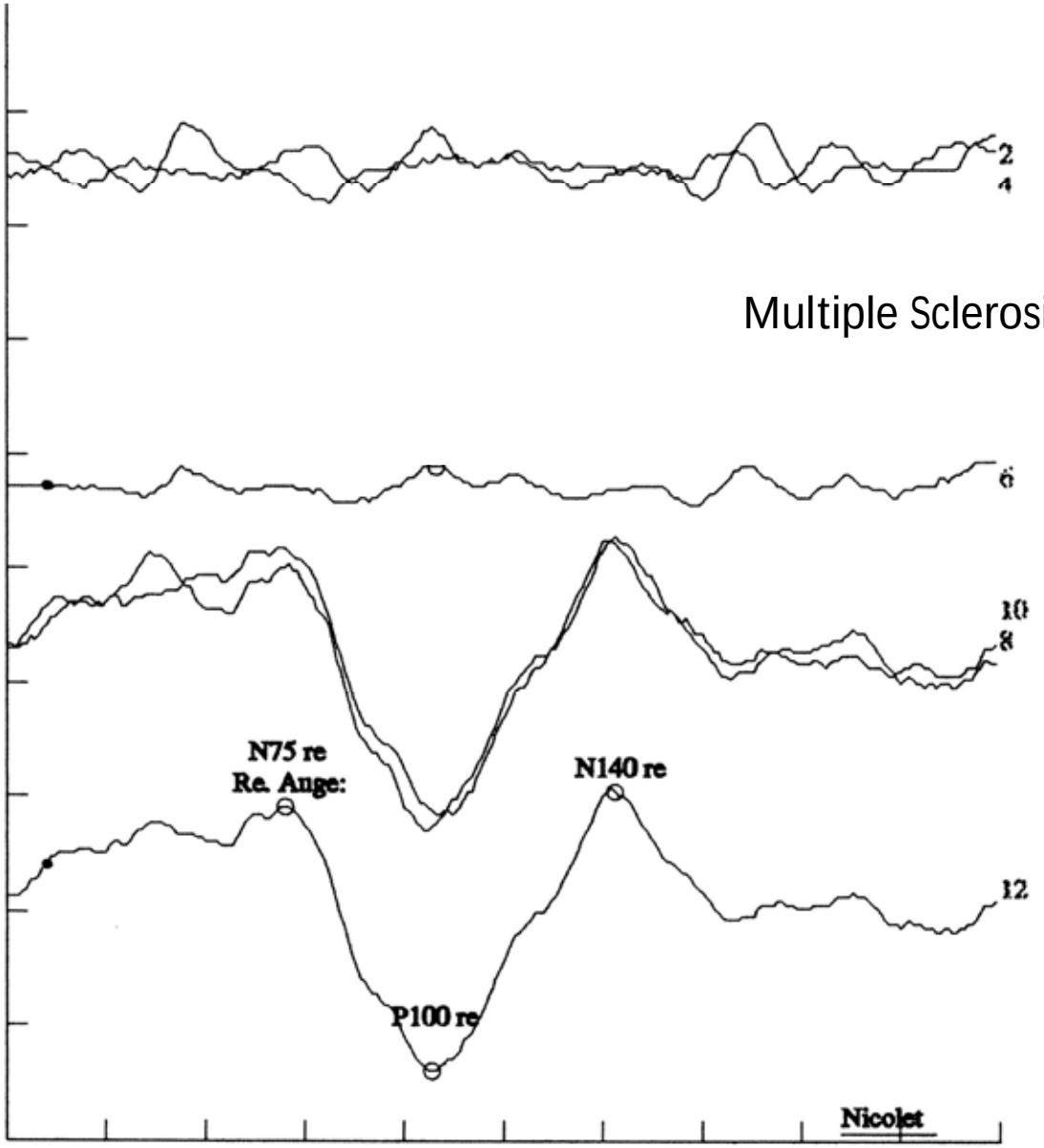


30 year old man, paraesthesia in V2, never visual symptoms

113 ms



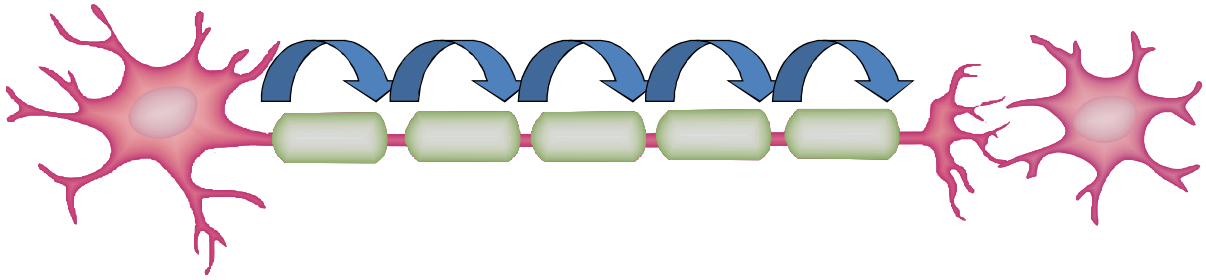
120 ms



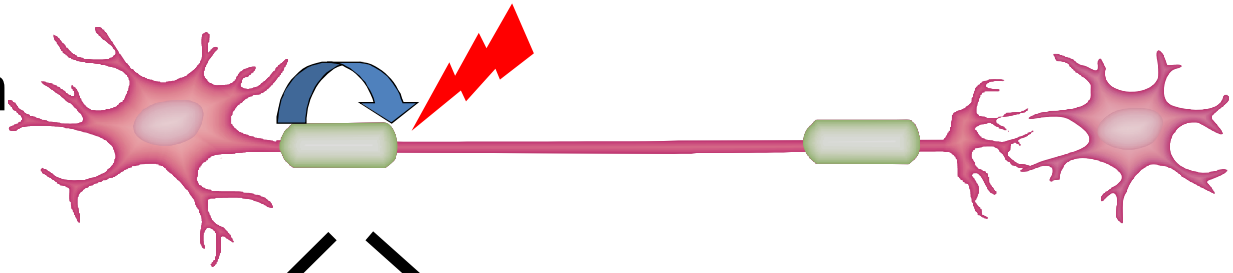
Multiple Sclerosis left eye blind

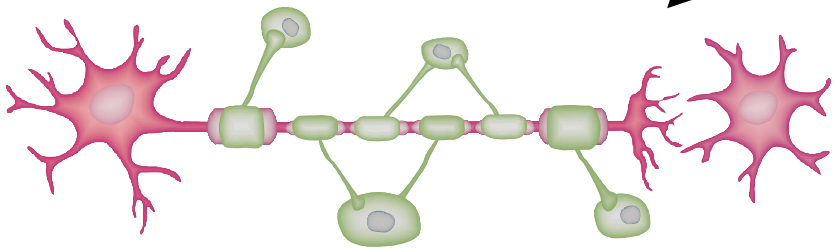
Why delay of Eps in MS

Saltatoy conduction

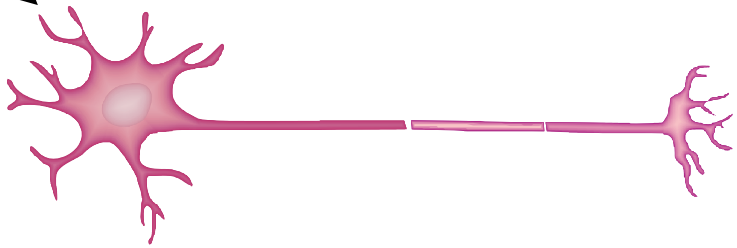


Acute demyelination
Conduction block





Remyelination
slower conduction, P100 delay

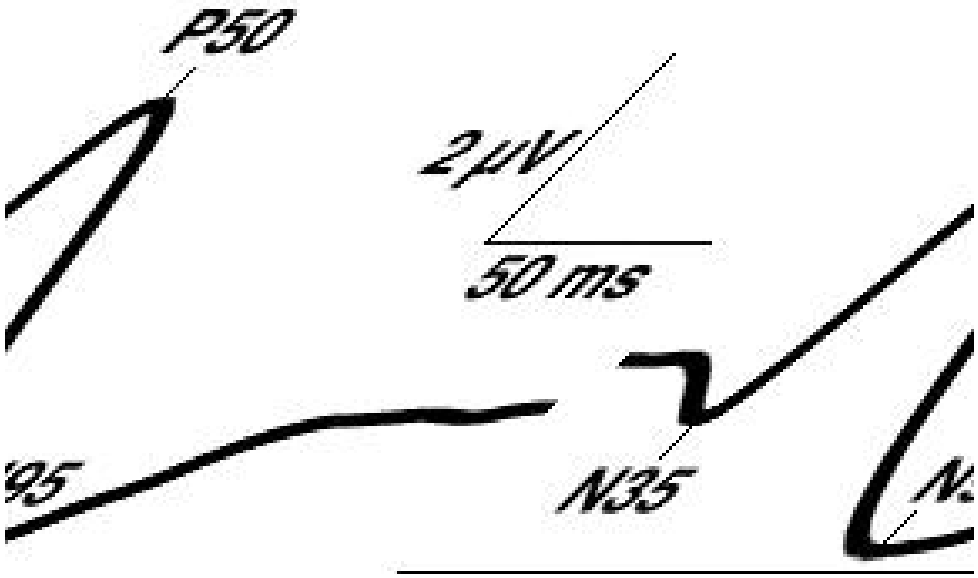


Axonal loss
P100 loss

Why are VEP latencies so much longer than SEP and AEP latencies?

Electroretinography

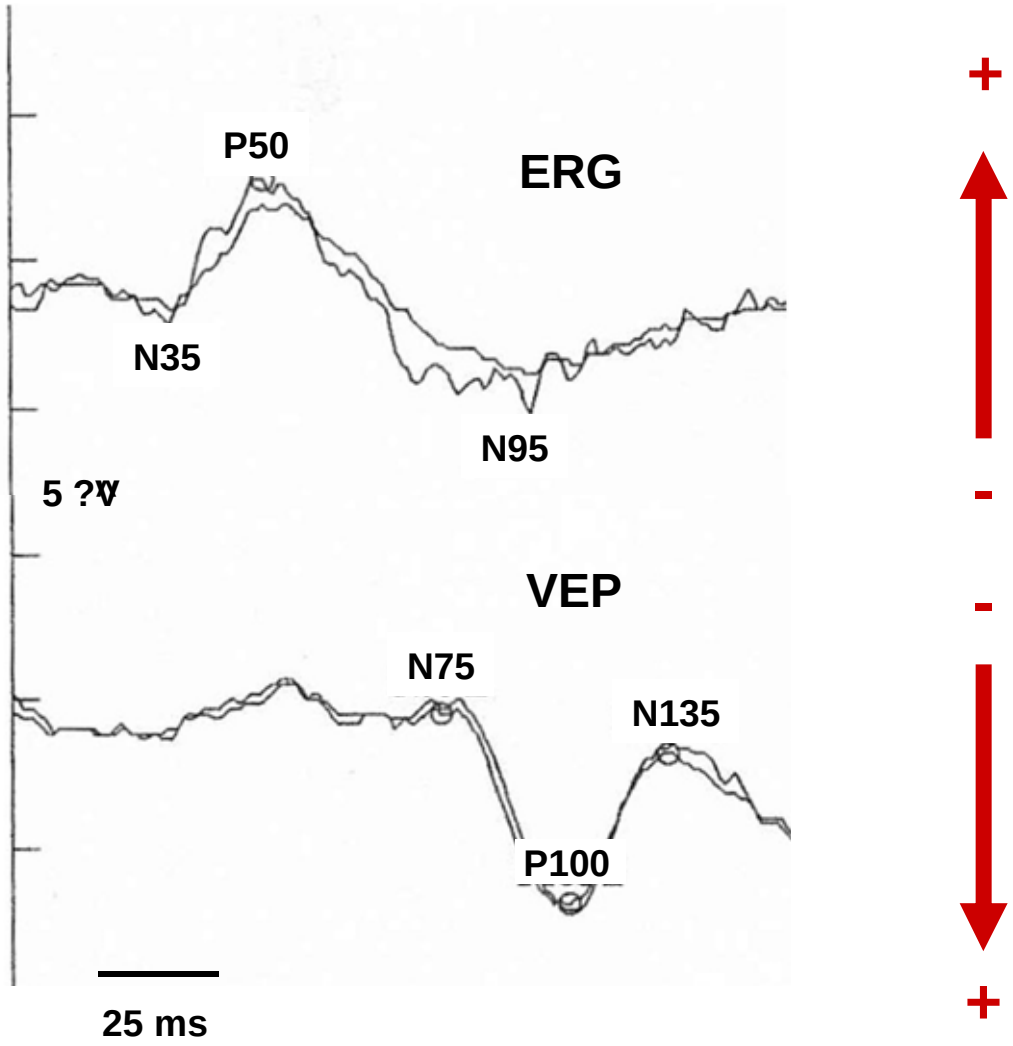
(B-wave)



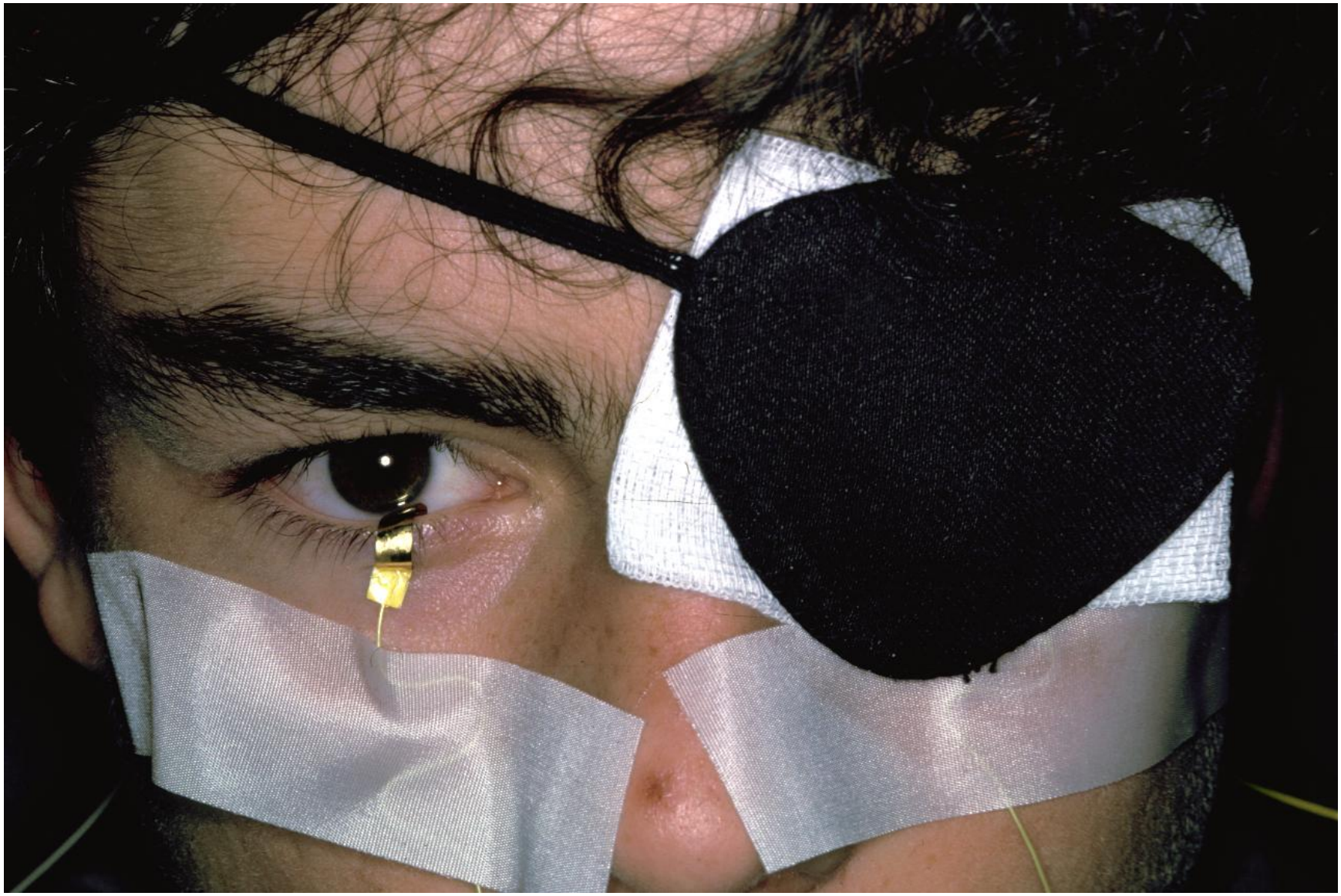
(A-wave)

(C-wave)

transient pattern ERG
Pattern size 0.8°
size 15° x 15°
contrast 98 %
Mean luminance 45 cd/m^2



Time is lost in the retina! Delay P50 – P100 can be used for diagnosis of MS



What is the DTL Electrode?

We should be thankful to the carpeting industry that they tackled the electrostatic charge problems that can arise with carpets made from plastic fibres. A metal-coated fibre was developed, which removes charges when weaved into the carpet due to its good electrical conducting properties. Just by chance this fibre is also well suited to record retinal potentials from the cornea. This was first discovered by Dawson, Trick & Litzkow in 1979, hence the name. Advantages of DTL-electrodes include:

DTL fibre is very flexible, giving little rise to irritation on the cornea, no local anaesthetic necessary

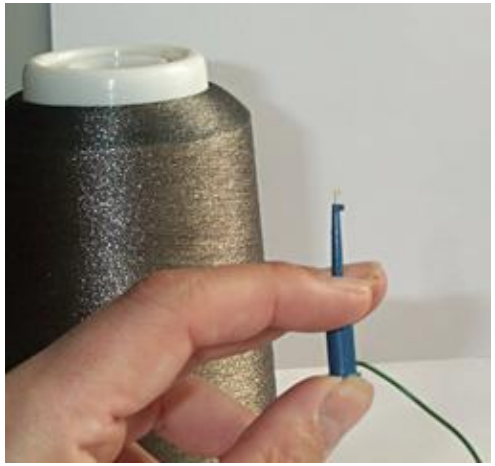
DTL fibre has a low electrical resistance (a few hundred Ohms)

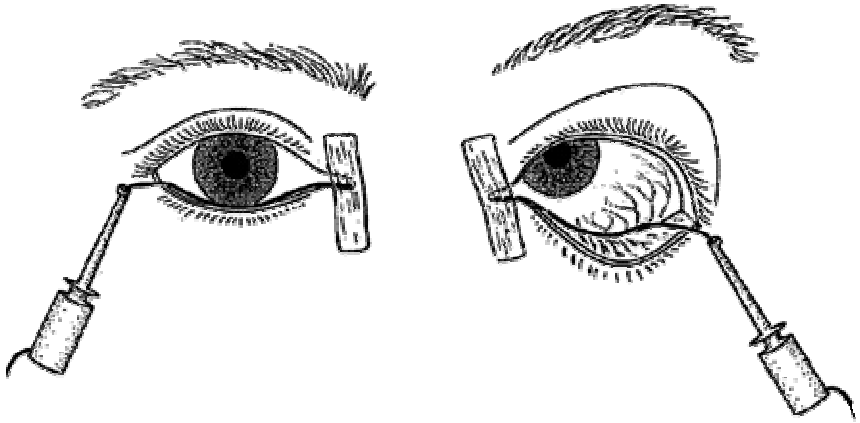
DTL fibre, bought at the right place, is very inexpensive

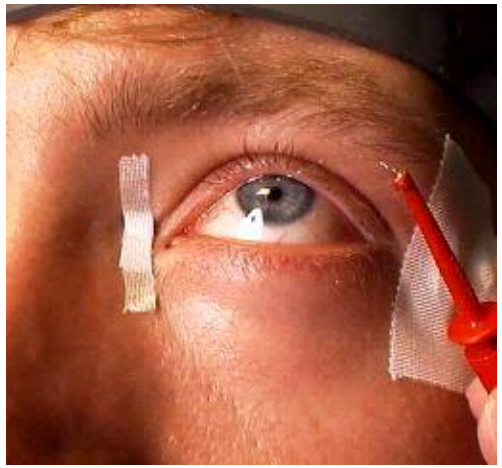
DTL fibre can be discarded after each examination, so no disinfection is necessary afterwards.

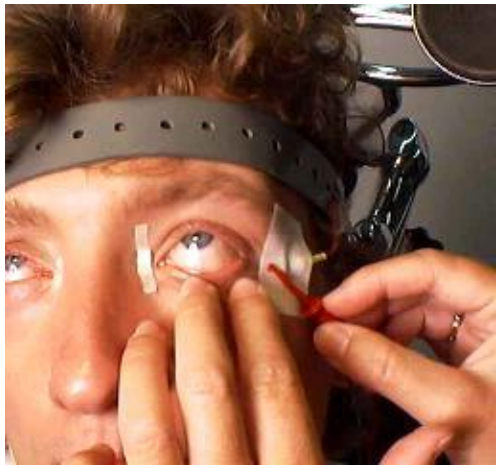
Dawson, Trick & Litzkow 1979: DTL Elektrode

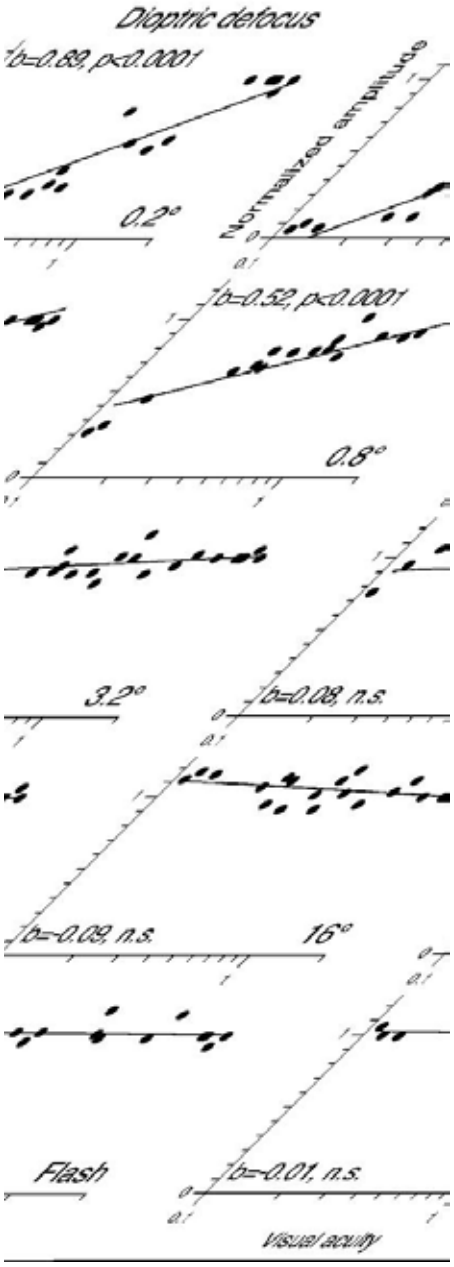
Homepage: Michael Bach, Freiburg











Documenta Ophthalmologica **108:** 99–106, 2004.

Different effect of dioptric defocus vs. light scatter on the Pattern Electroretinogram (PERG)

Michael Bach & Marcel Mathieu
Universitäts-Augenklinik, Killianstr. 5, 79106 Freiburg, Germany

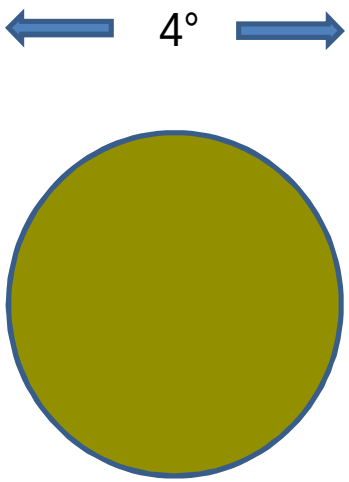
When does visual information arrive in the primary visual cortex?

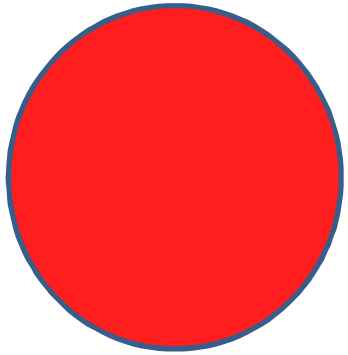
Shortest information transfer periphery:

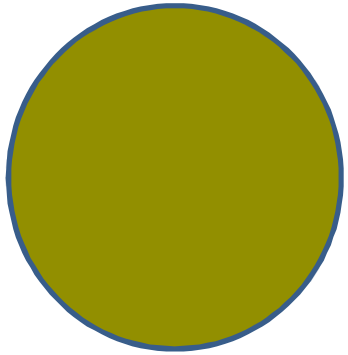
Neuroreport. 1997 Jul 28;8(11):2419-22.
Fast visual evoked potential input into human area V5.
Buchner H, Gobbelé R, Wagner M, Fuchs M, Waberski TD, Beckmann R.

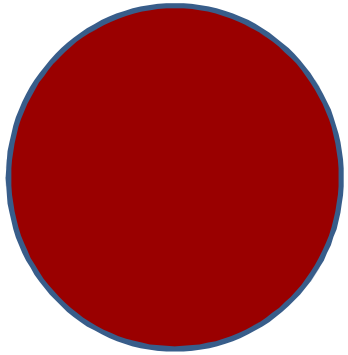
30 ms V5, 50 ms V1

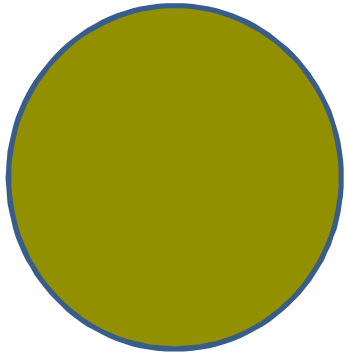
Longest information transfer foveal parvocellular cells (colour vision)

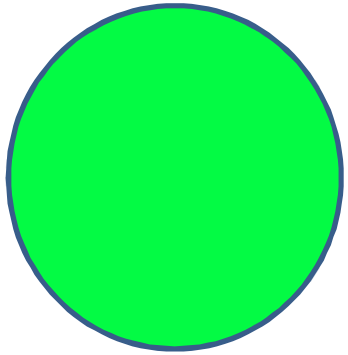

4°

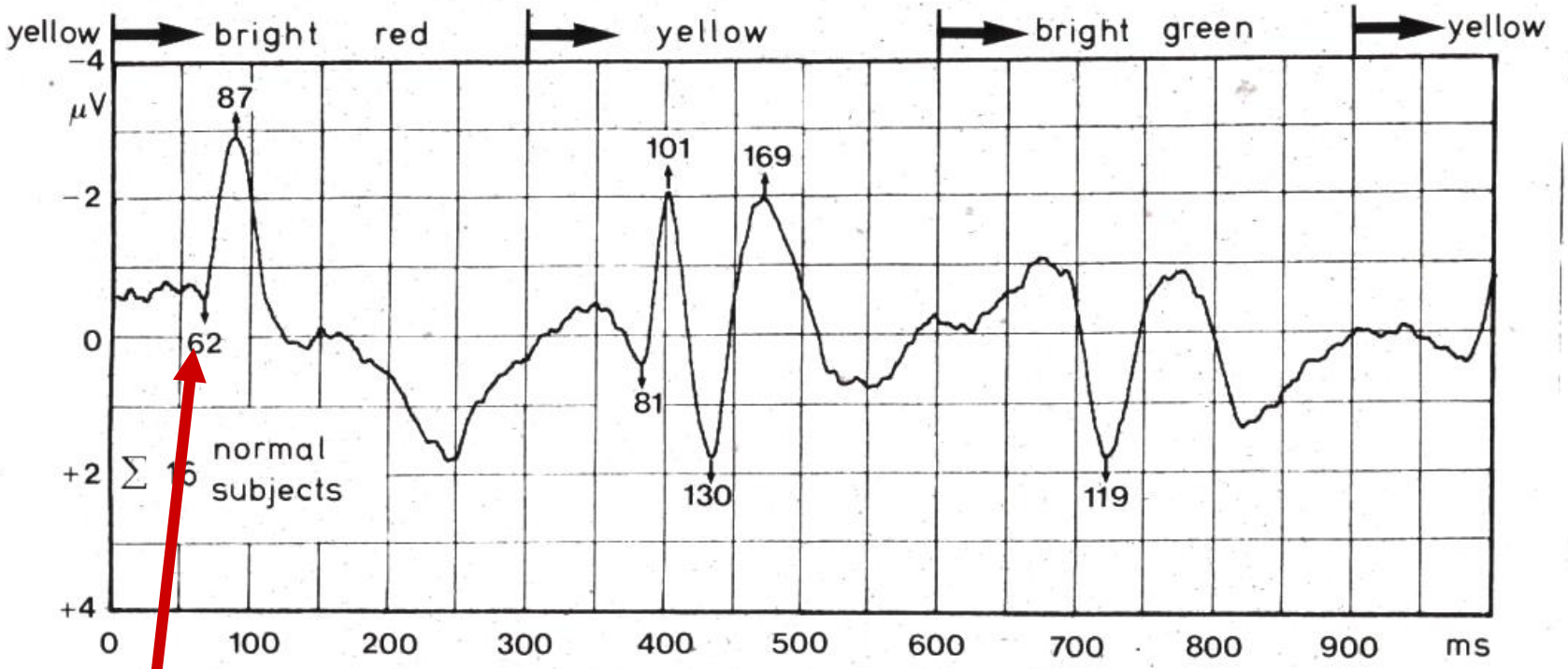






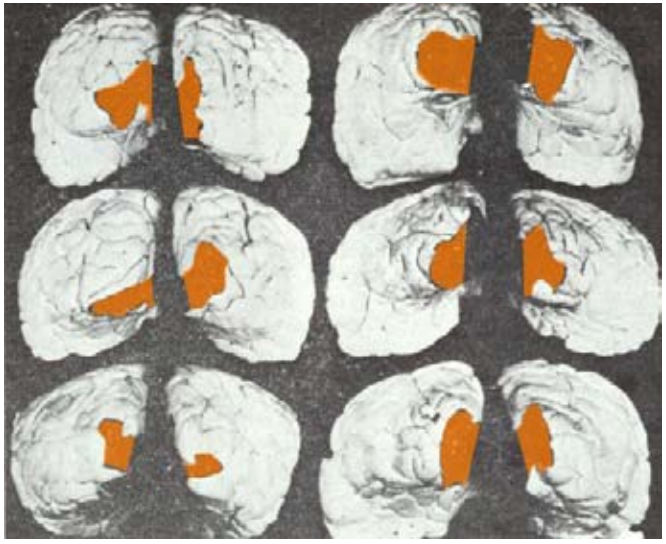






Earliest foveal response after 62 ms

Conclusion: P100 includes at least 40 ms cortical processing time

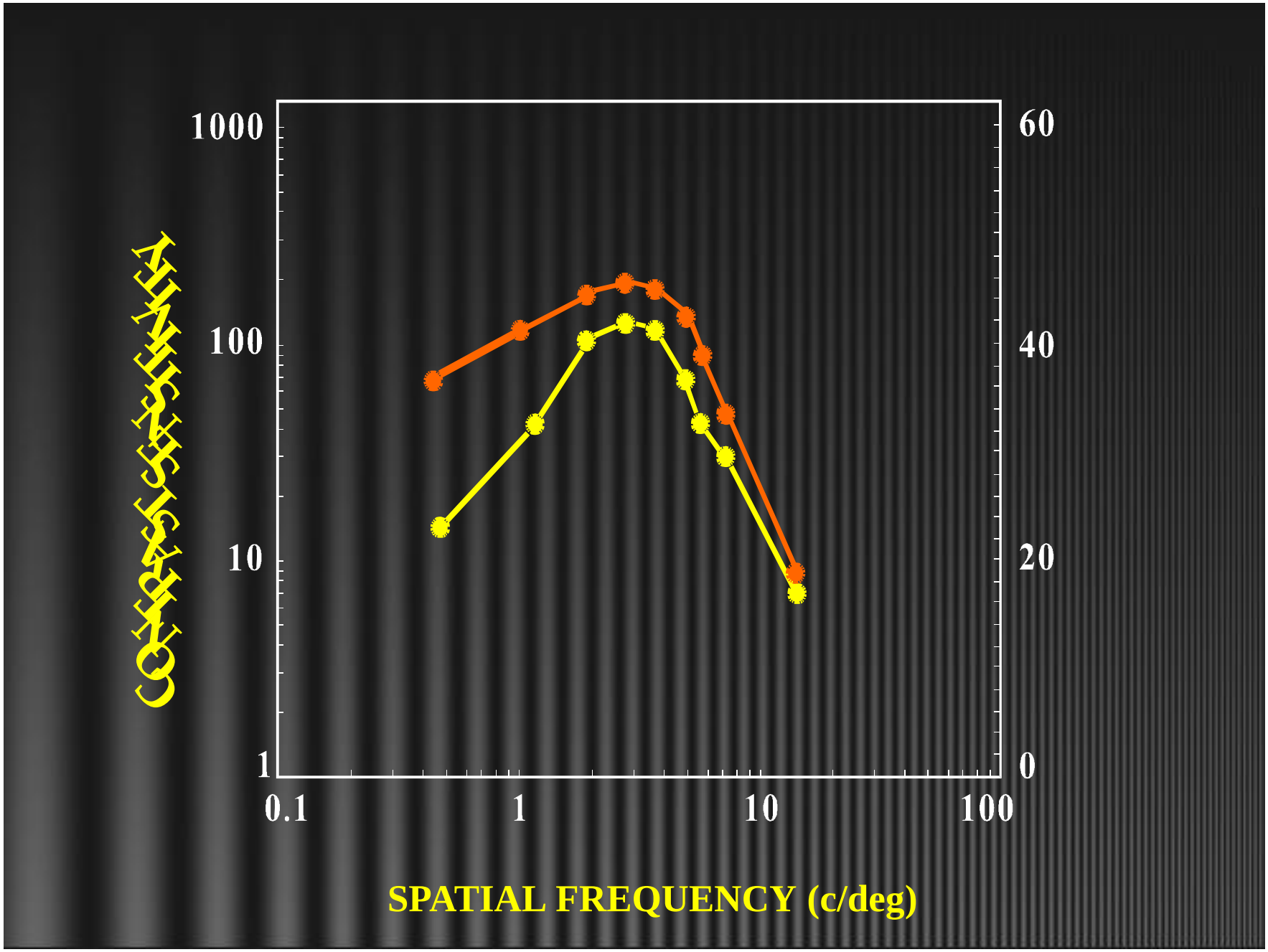


Brindley, 1972

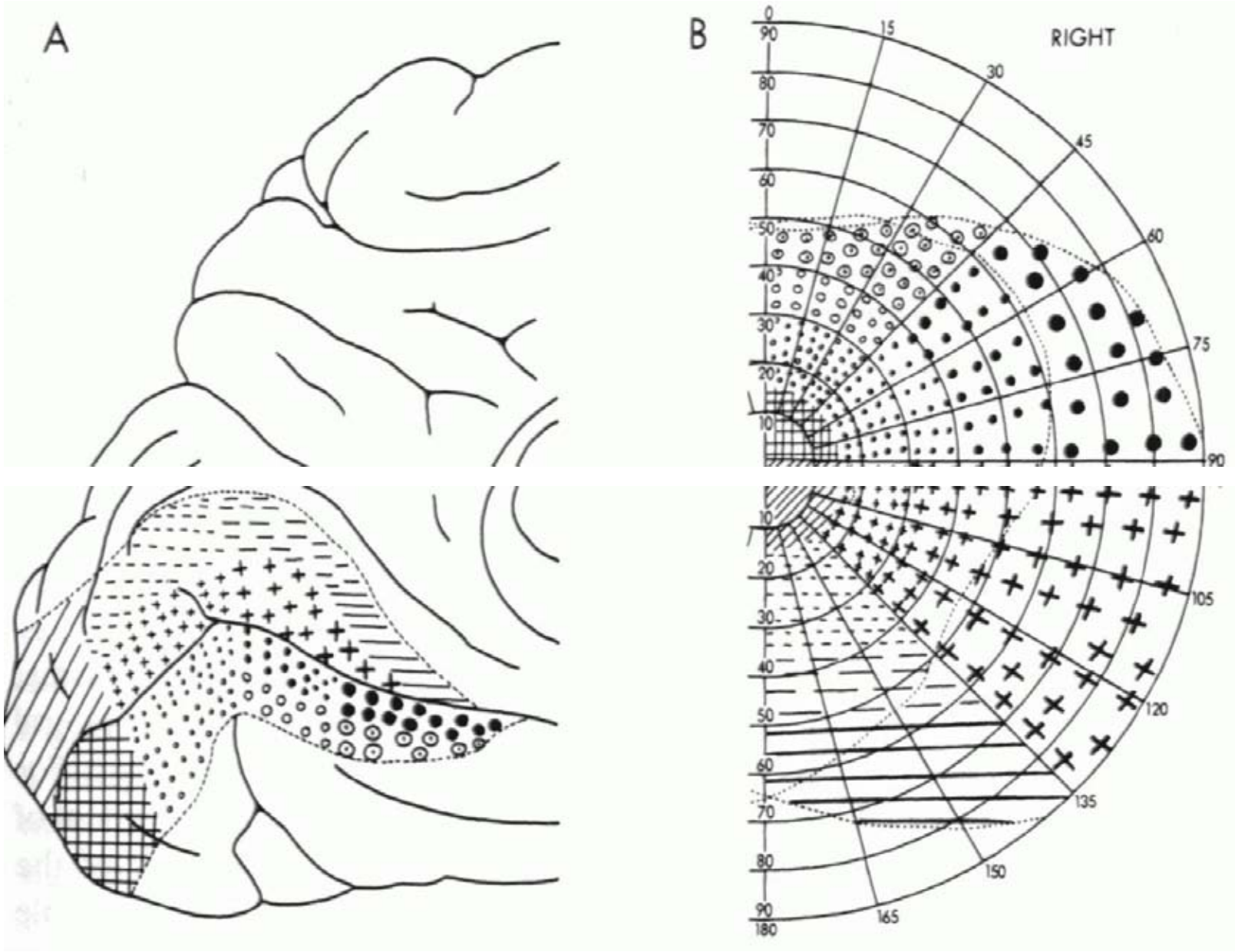
Design of visual stimuli

More (light) is not more (Potential size)

Robustness < > Sensitivity

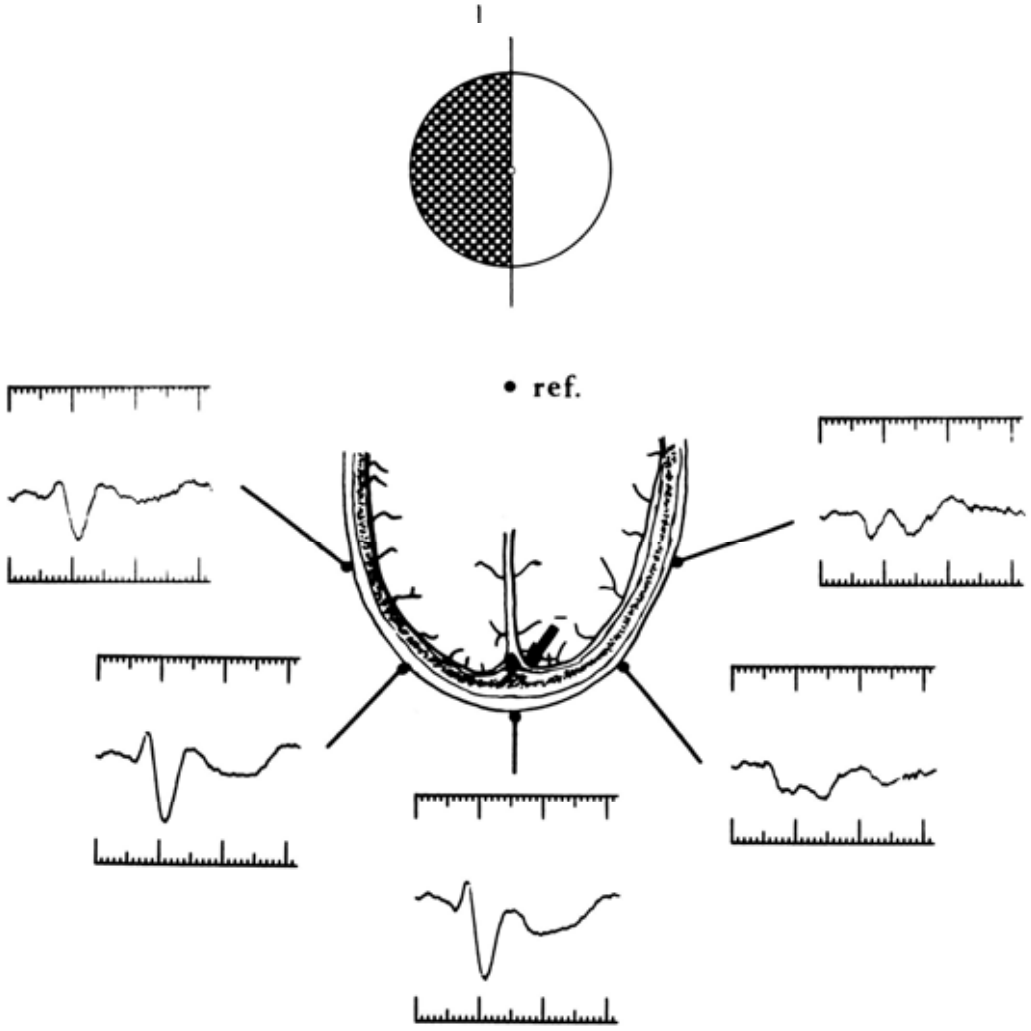

1000
100
10
1
60
40
20
0
0.1
1
10
100
CONTRAST SENSITIVITY
SPATIAL FREQUENCY (c/deg)

Why more than 1 recording electrode for VEP‘s?


A
B
RIGHT
0
15
30
45
60
75
90
90
80
70
60
50
40
30
20
10
105
120
135
150
165
180

Elektrode position

(Halliday montage)

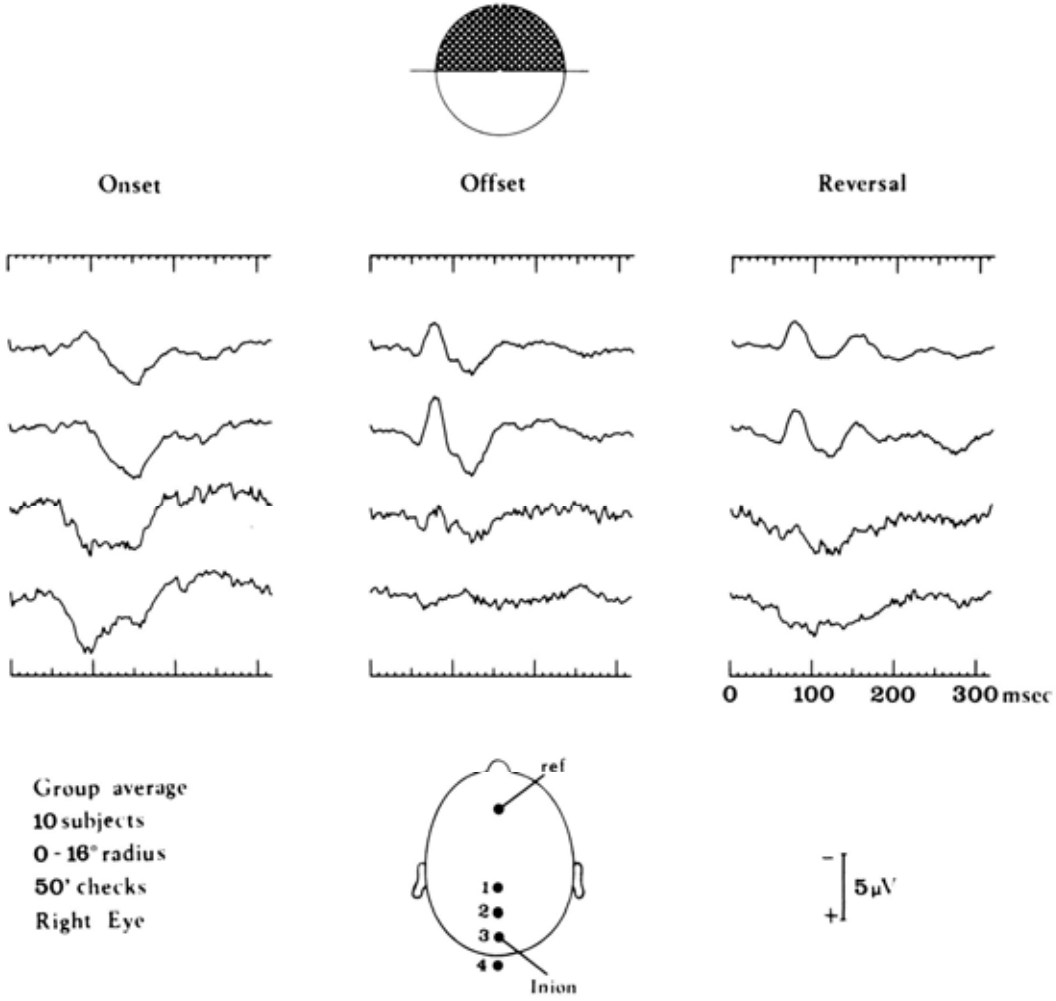


Stimulation
left half field

Fz – Oz, and 5 and
10 cm to each side

Barrett et al., 1976

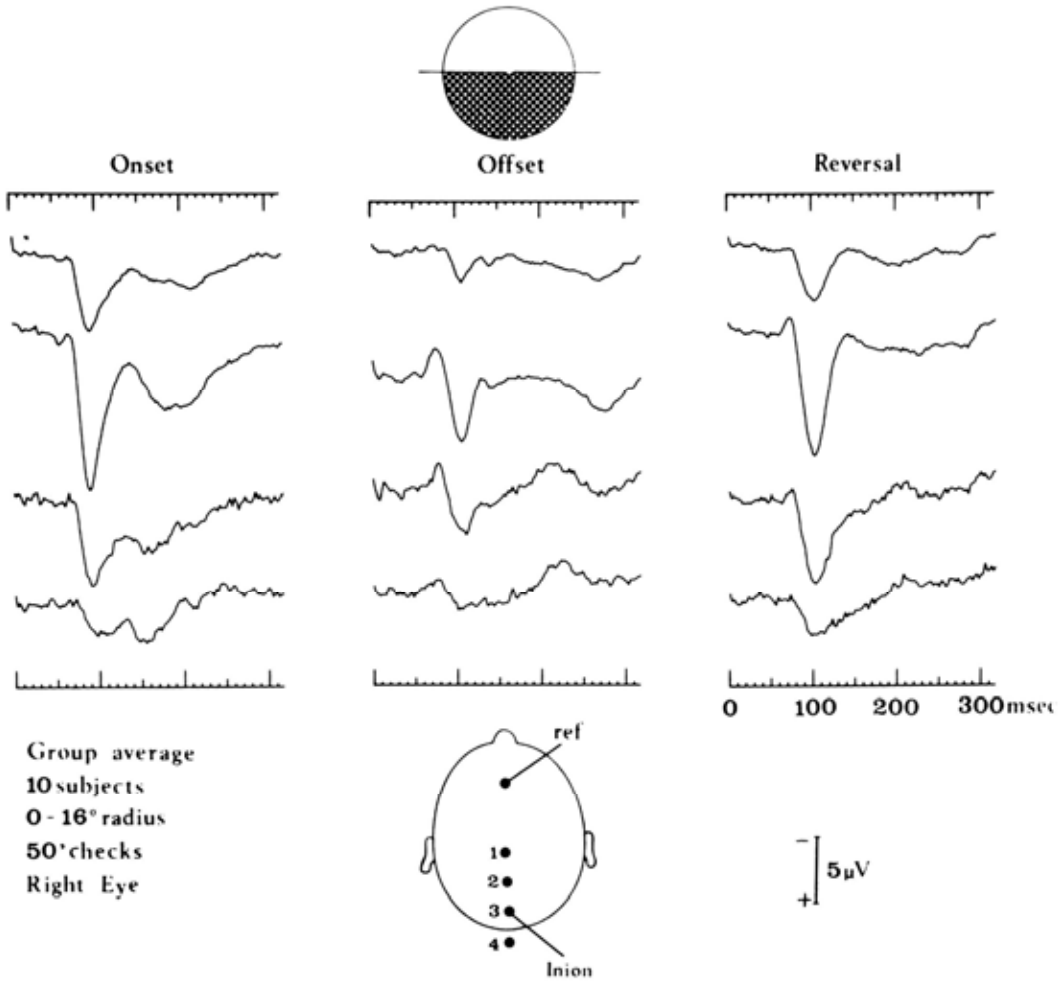
Electrode position and visual field



- Stimulation upper half field
- electrode Oz and 5 resp. 10 cm above and beneath

Chris and Halliday, 1980

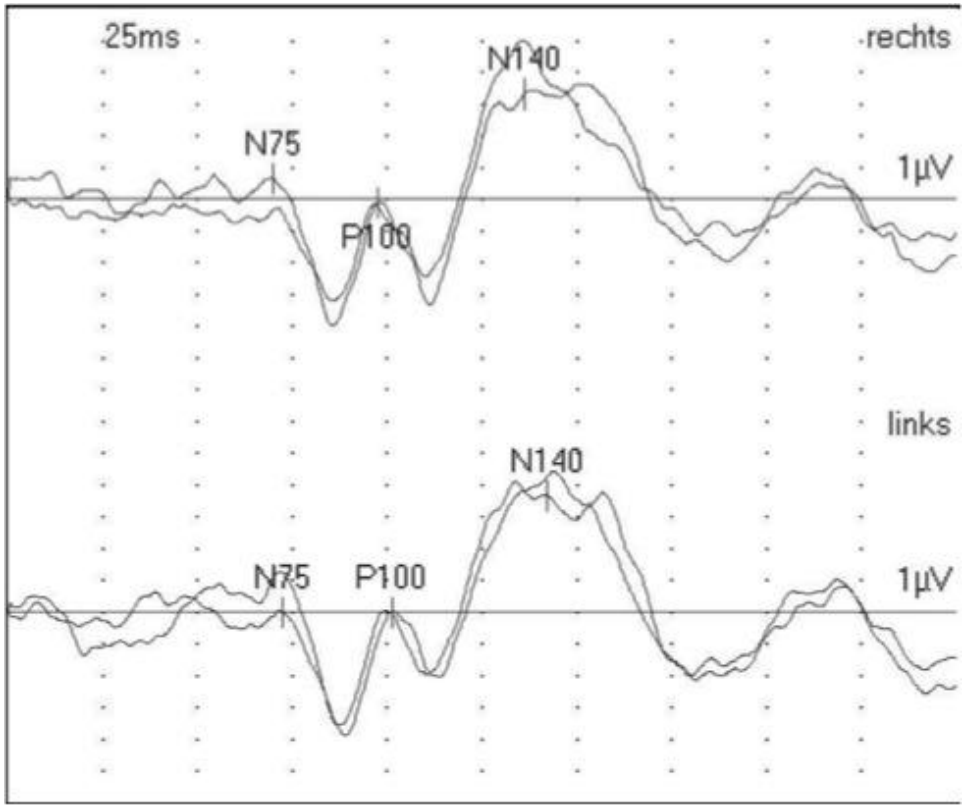
Electrode position and visual field

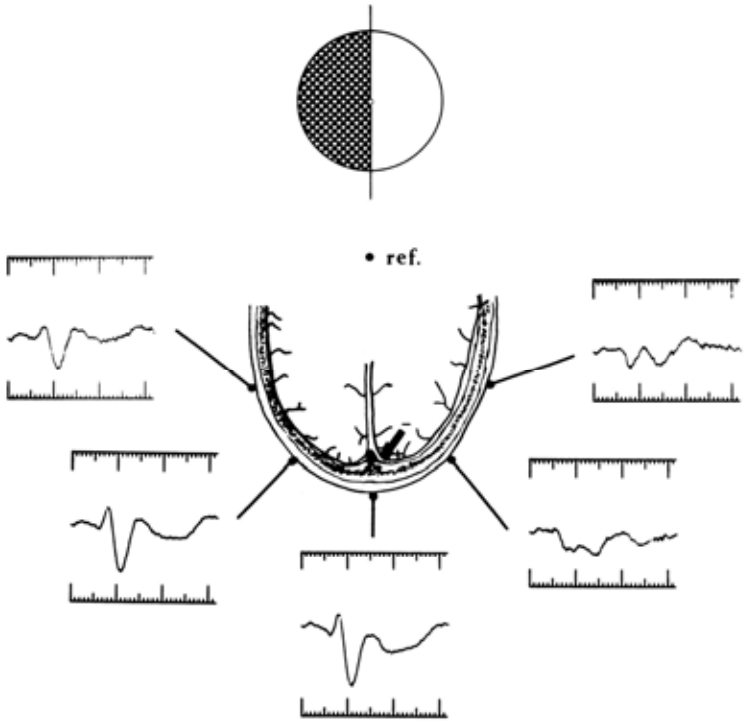


- Stimulation lower half field

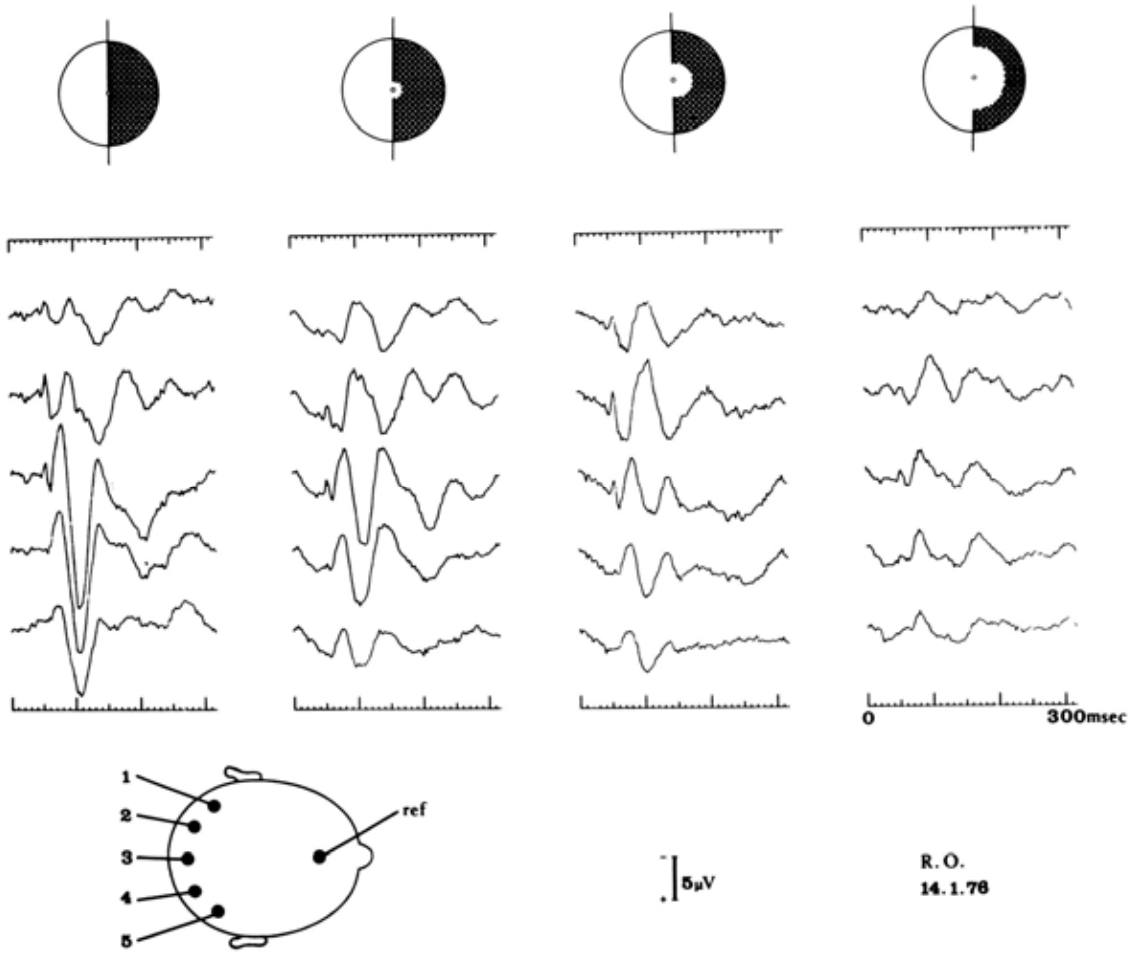
Chris and Halliday, 1980

W-shape





central skotoma and W shape

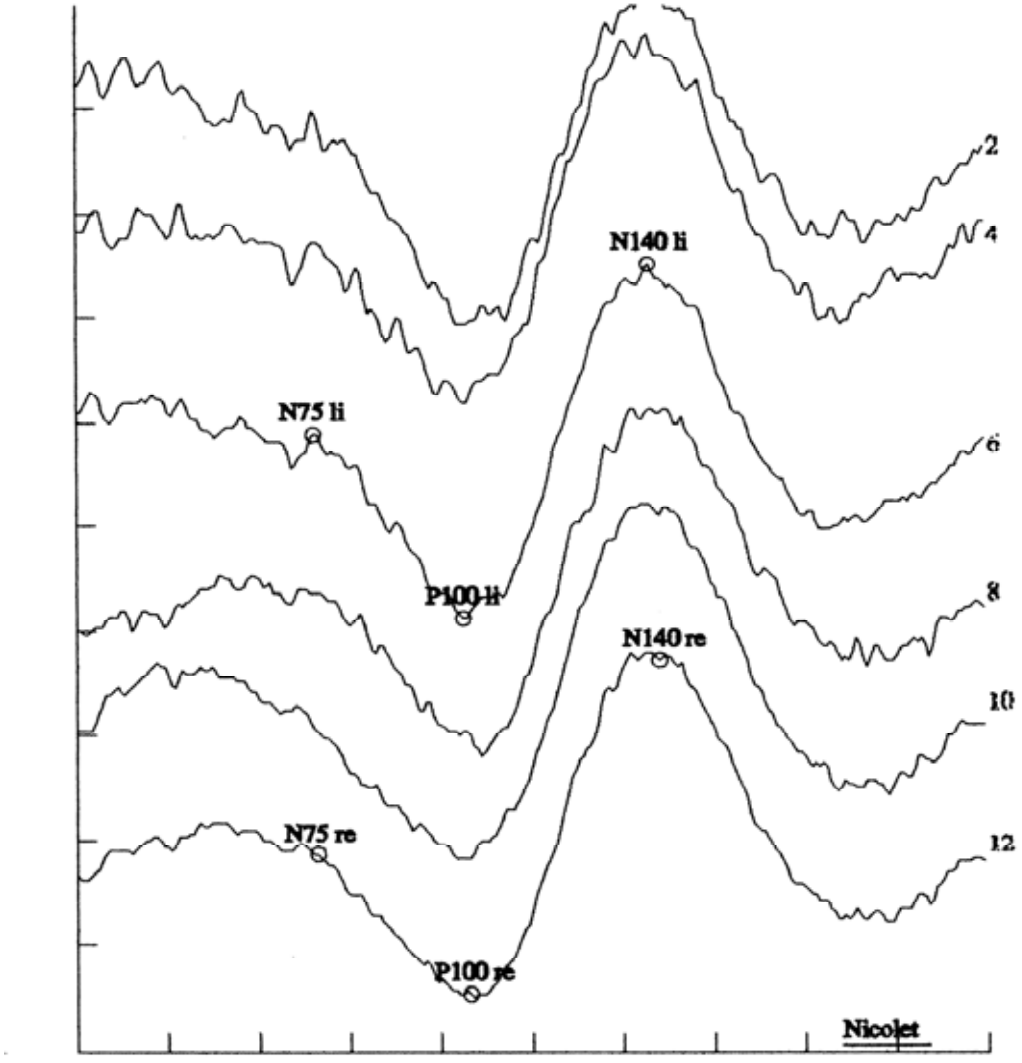


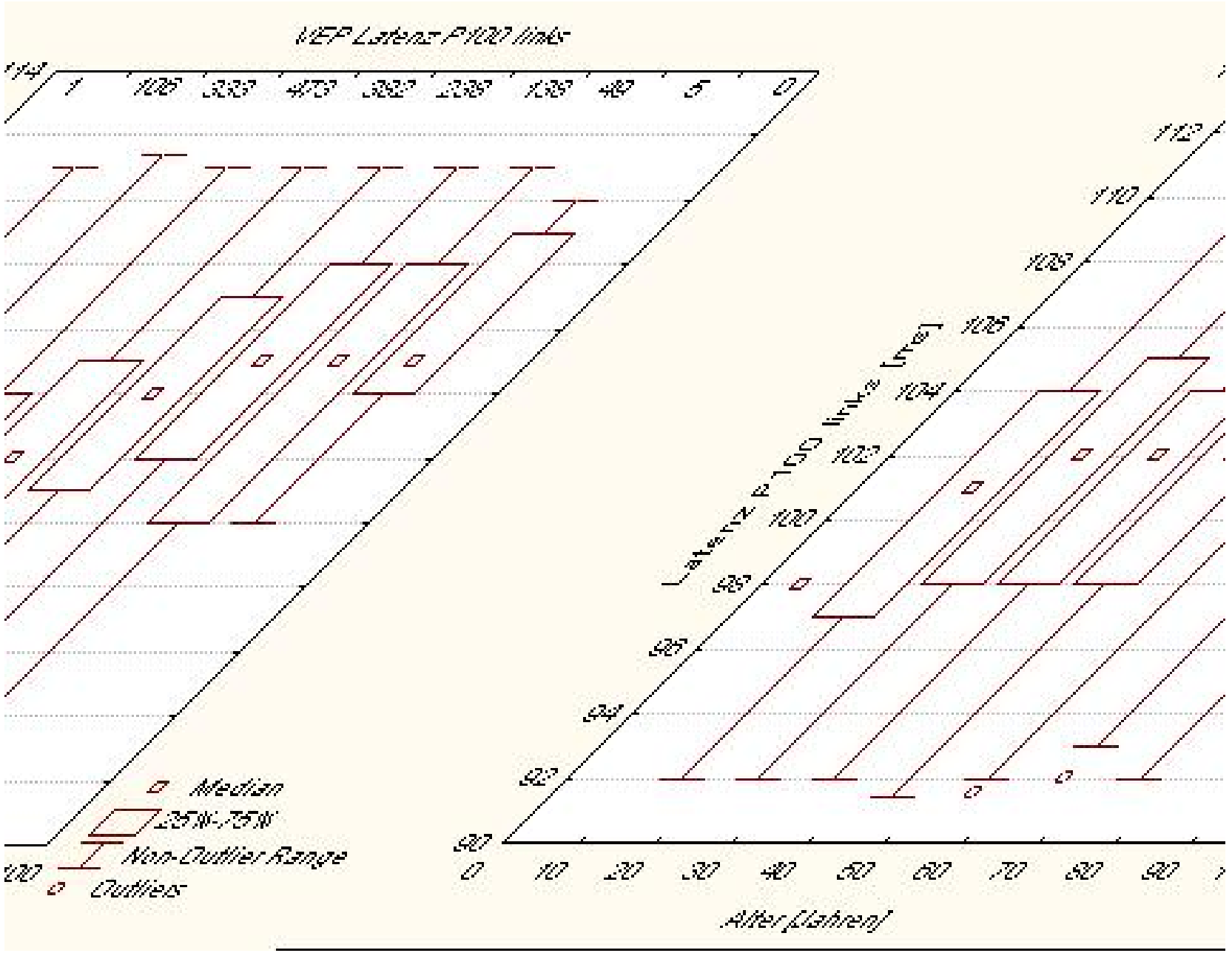
- Stimulation right half field
- 2,5 ° , 5 ° , 10 ° artifical skotoma
- Oz versus Fz

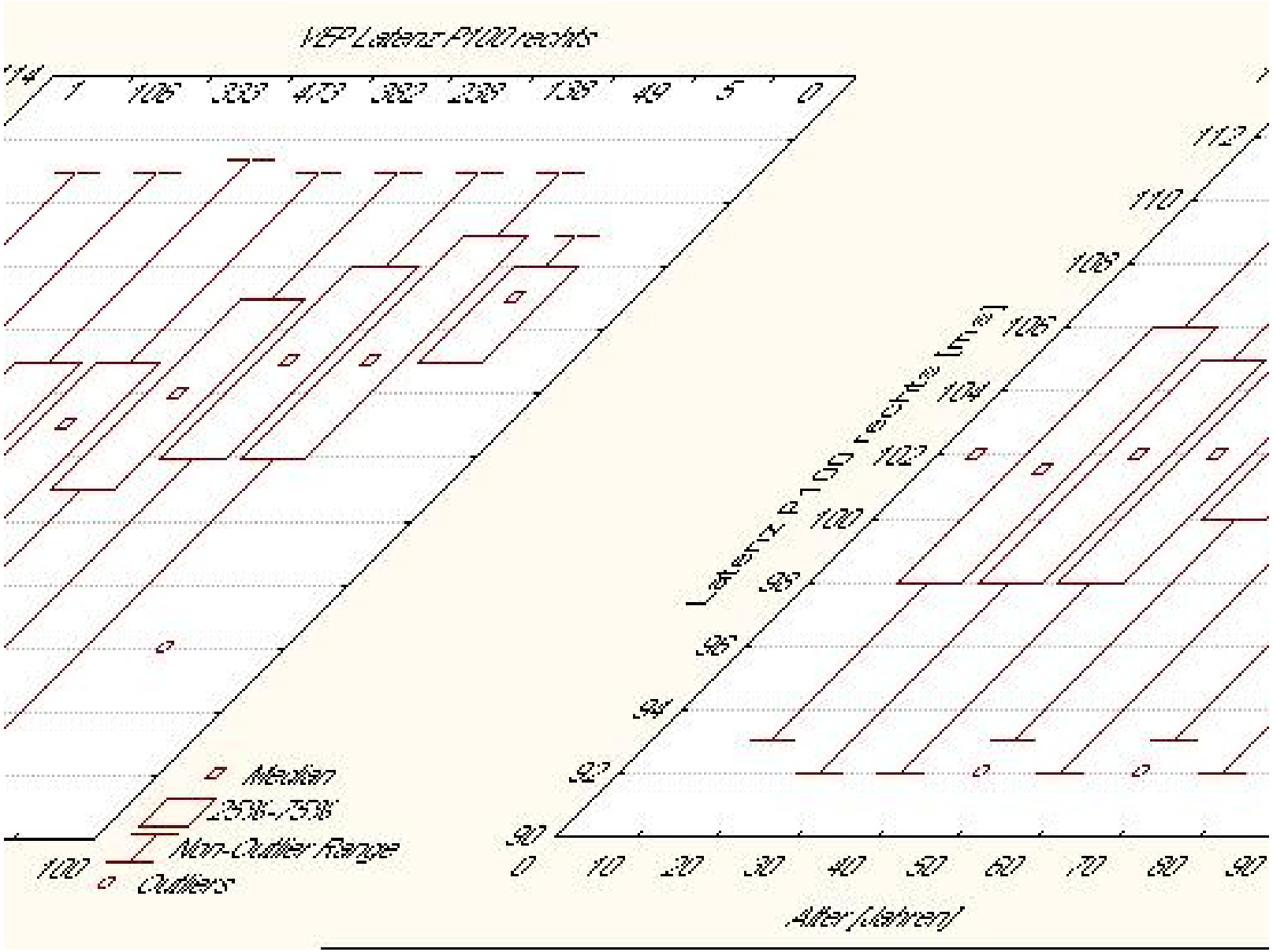
Blumhardt et al., 1978

Conclusion: be aware of claiming a P100 delay in the presence of a central scotoma!
Example: Leber‘s optic atrophy

Sleepy (?/driving)





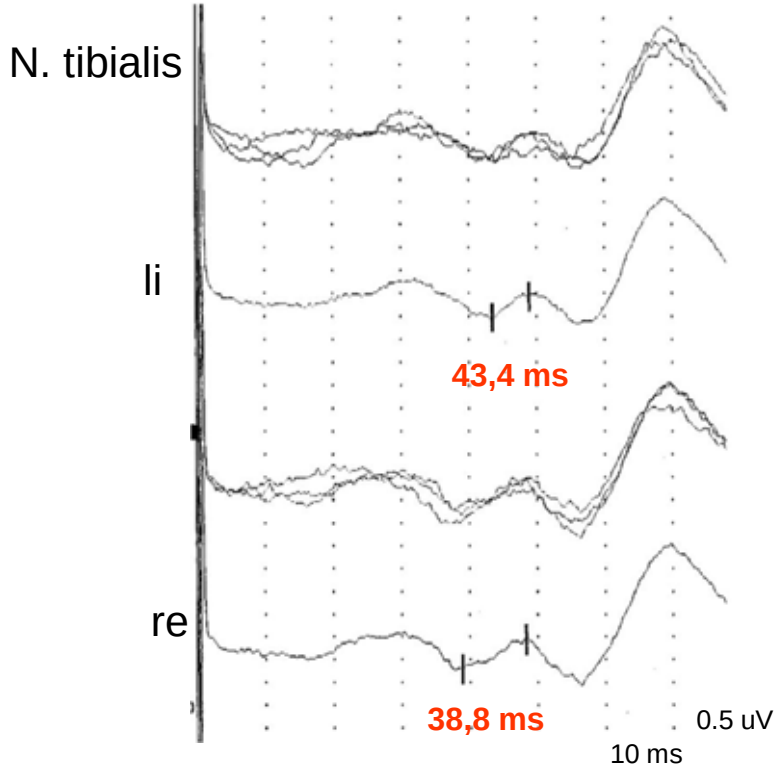


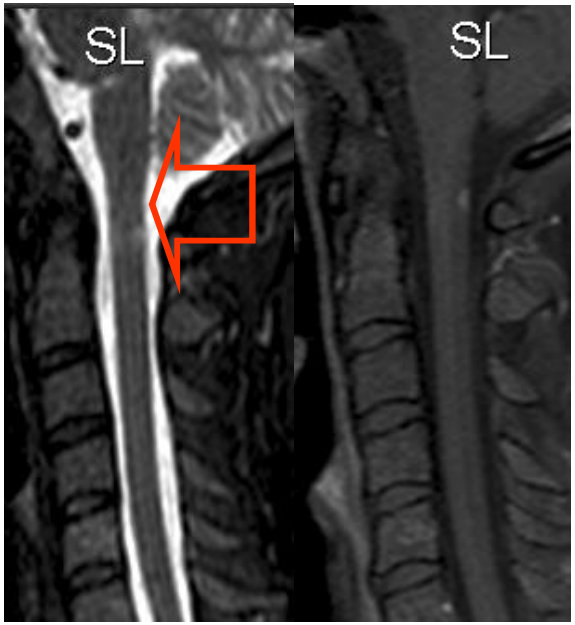
P100: ?ㅏ= 103 ms ?ㅏ= 102 ms

n= 1725

SEP

ø Delayed tibial nerve SEP

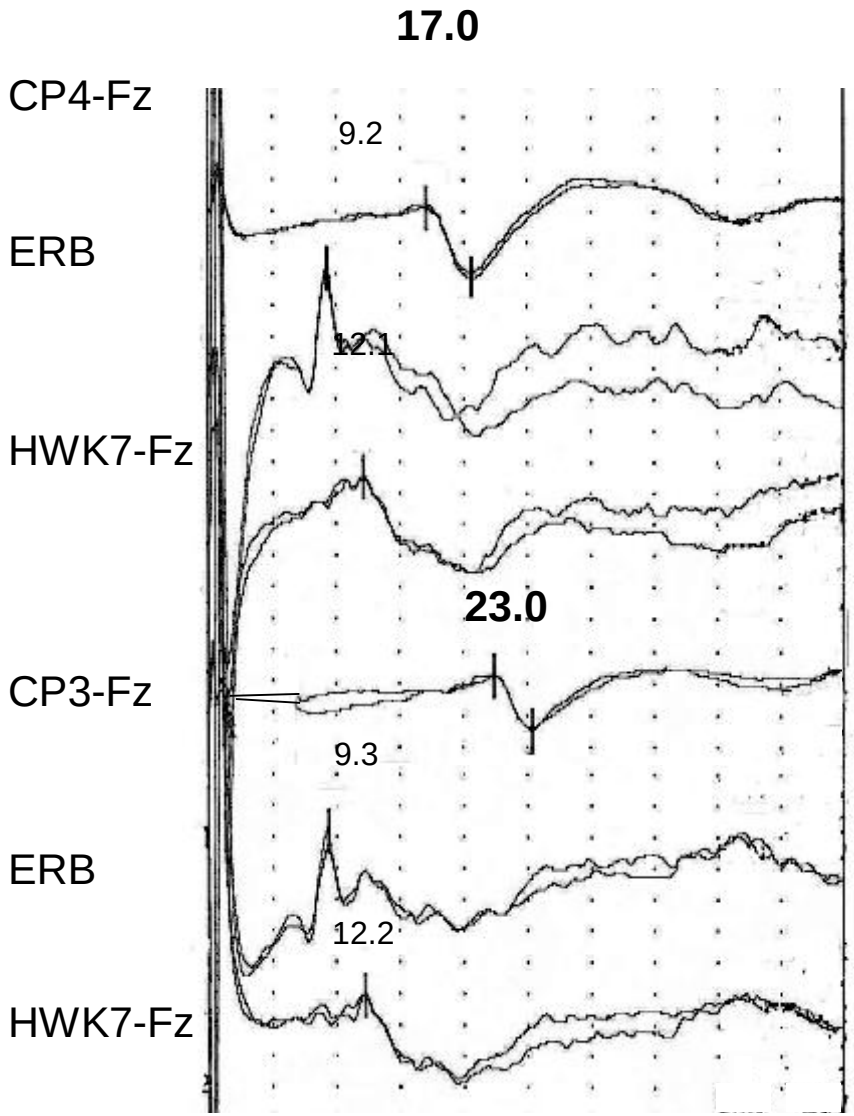




max: 43,9 ms; side differences. max: 2,1 ms

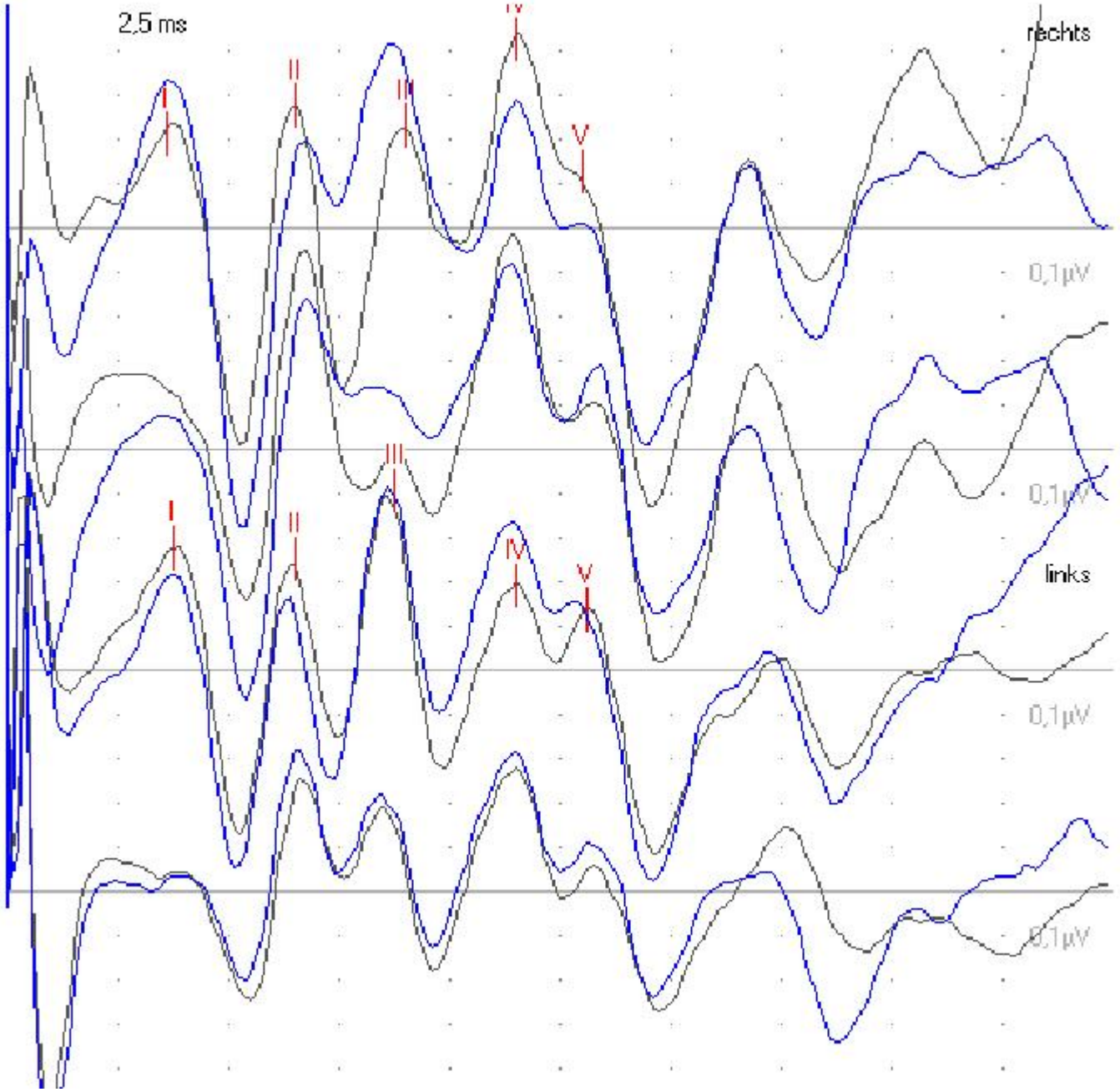
Median nerve SEP

- Delayed N20



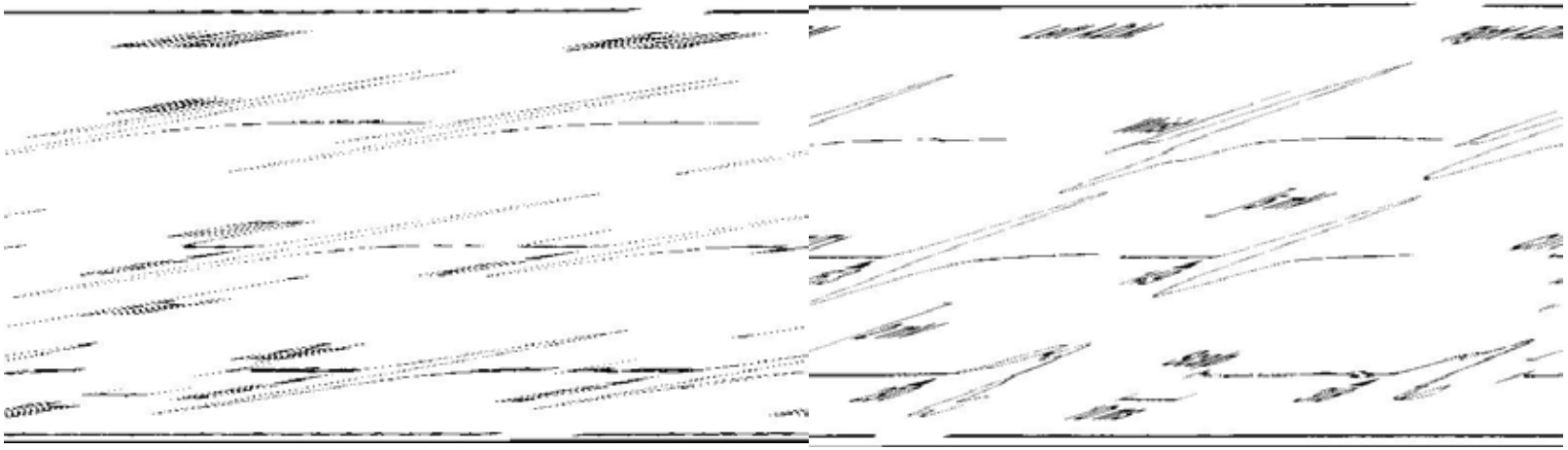
N20 max = 22,3; side difference max = 1,4ms

AEP

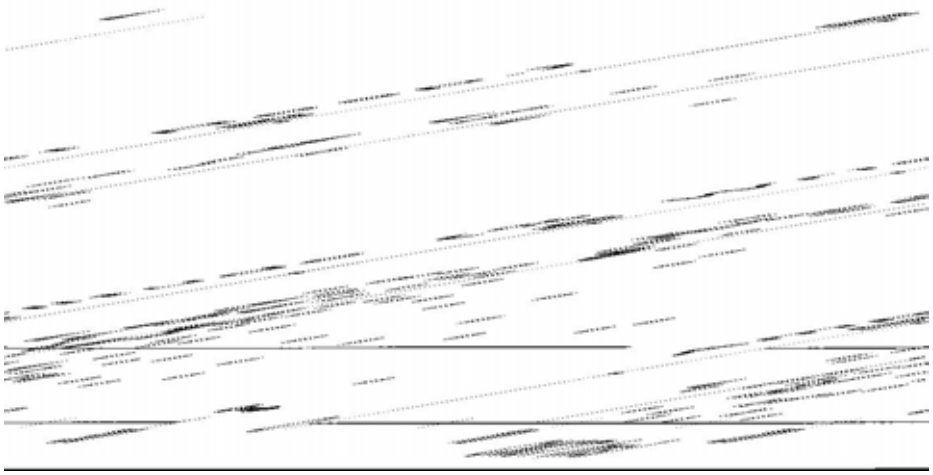

2,5 ms
rechts
links
I
II
III
IV
V
0,1µV
0,1µV
0,1µV
0,1µV

MEP

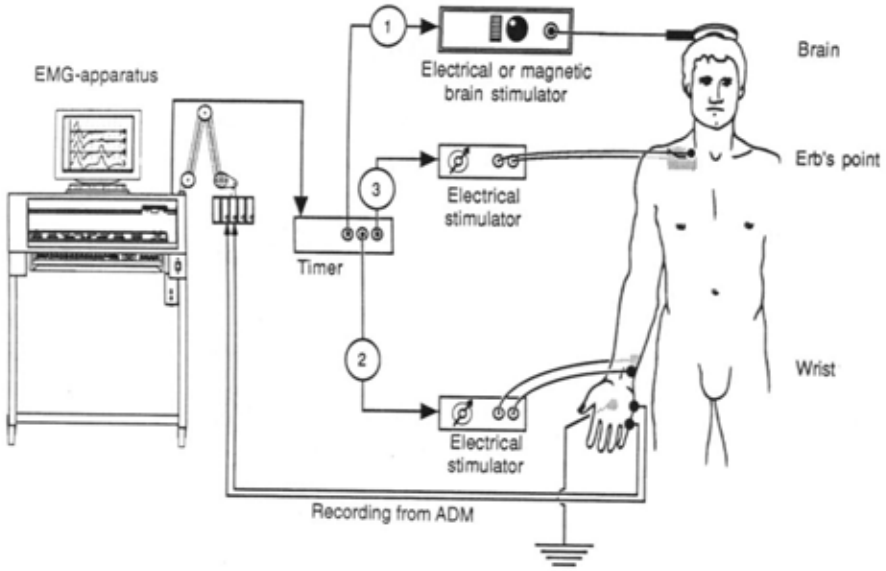
Ann. Neurol 1987



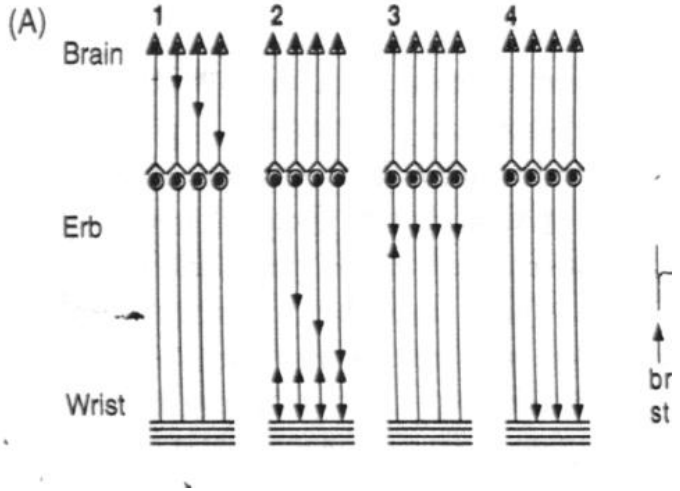
Control MS



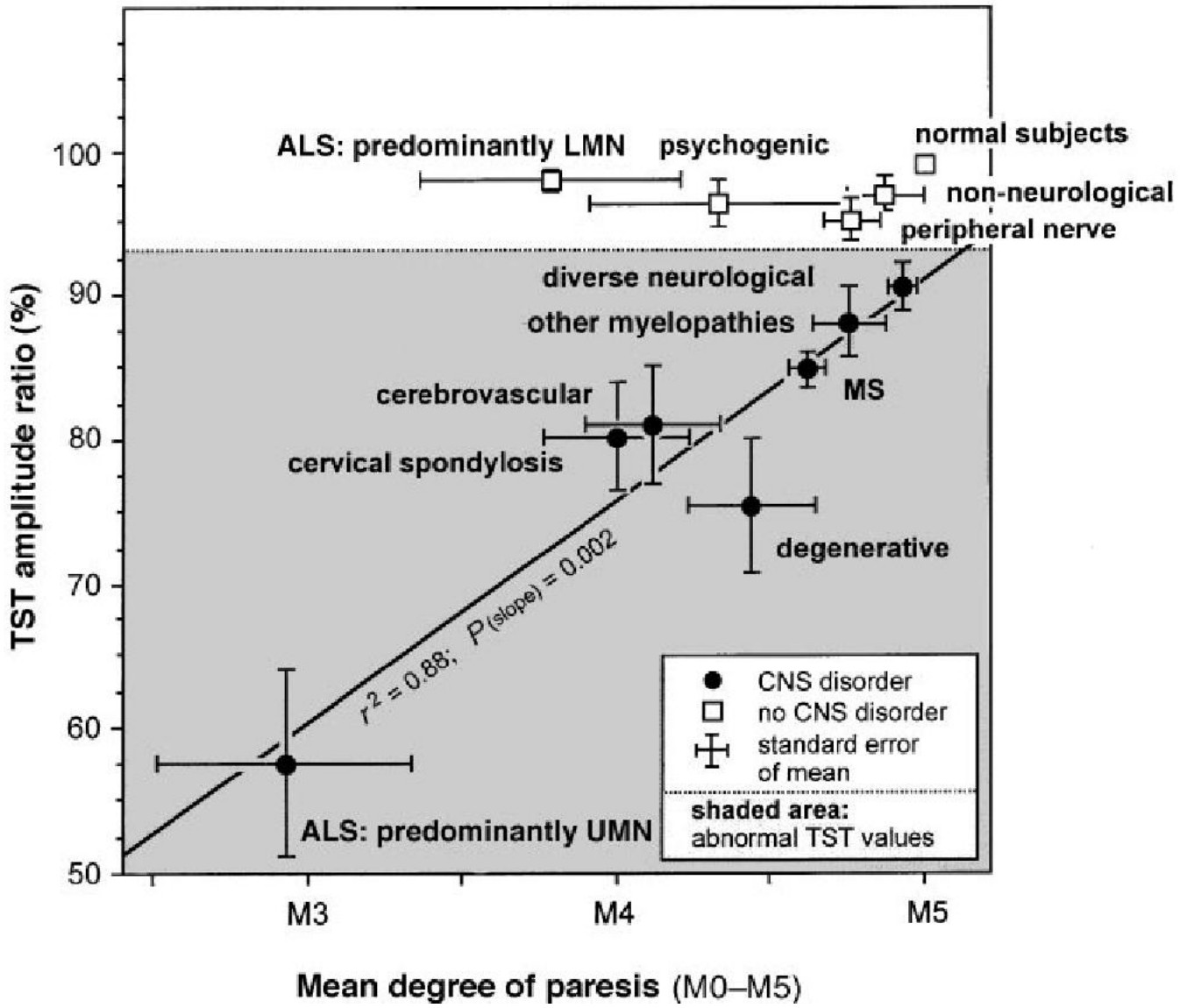
Triple Stimulation Technique (TST) to circumvent phase cancellation and allow to estimate axonal loss



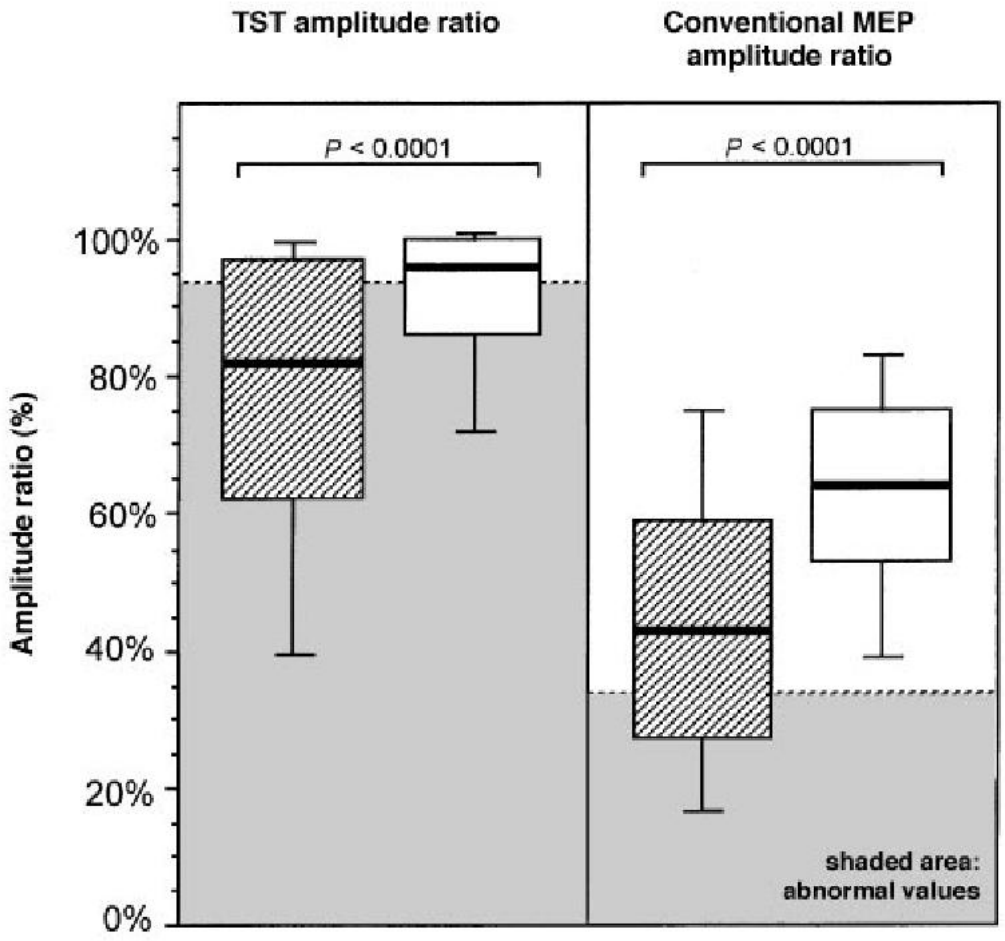
2.75 times more sensitive than conventional TMS



Magistris et al. 1998, Brain 121:437-450


ALS: predominantly LMN
psychogenic
normal subjects
non-neurological
peripheral nerve
diverse neurological
other myelopathies
MS
cerebrovascular
cervical spondylosis
degenerative
$r^2 = 0.88$; $P_{(slope)} = 0.002$
ALS: predominantly UMN
CNS disorder
no CNS disorder
standard error of mean
shaded area: abnormal TST values
TST amplitude ratio (%)
100
90
80
70
60
50
M3
M4
M5
Mean degree of paresis (M0–M5)

Presence versus absence of pyramidal syndrome



Significance of Evoked Potentials for diagnosis of MS?

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Comparison of the 2010 and 2005 versions of the McDonald MRI criteria for dissemination-in-time in Taiwanese patients with classic multiple sclerosis

Chun-Jen Hsueh [a], Hung-Wen Kao [a], Shao-Yuan Chen [b,c], Chung-Ping Lo [d,e,*], Chia-Chun Hsu [d,e], Dai-Wei Liu [e], Wen-Lin Hsu [e]

The new criteria are more sensitive and accurate and specific just as the old criteria. They allow the diagnosis of definite multiple sclerosis in 34.1% patients at first presentation of the clinically isolated syndrome.

Evoked potentials not mentioned here, how do data compare?

Early Diagnosis

- 27 Pat. with CIS (Rot & Mesec 2006 Clin Neurol Neurosurg 108)
  29 % pathological VEP

- 22 Pat. with CIS (Rico et a. 2009 Mult Scler 15)
  50% pathological MEP Amplitude Ratio
  18% pathological MEP CMCT

- 245 Pat. with CIS (Pelayo et al. 2010 Mult Scler 16)
  VEP – SEP – AEP at time of first symptoms
  47 % one EP; 16 % two EP; 8 % three pathological EP
  Risk for conversion into MS after 3 month significantly increased with three pathologial EPs (hazard ratio 7.0) independent from first MRT

Early Diagnosis

- 27 Pat. with CIS – only **optic neuritis** (Simó et al. 2008 Mult Scler 14)

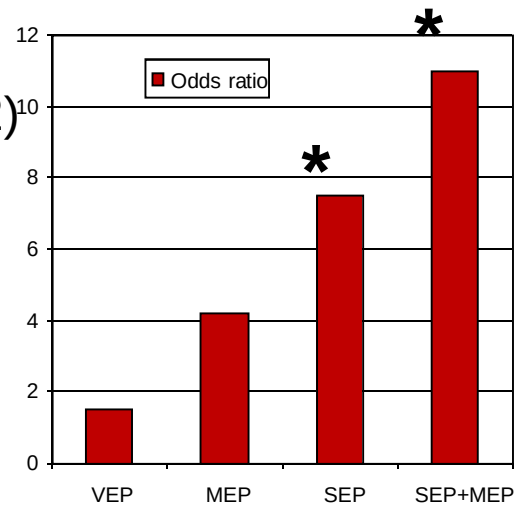
MEP – SEP at presentation, follow-up after 20 months

- **6/27 EPs positive,** MRT Follow-up positive in all pts
- **19/27 normal Eps,** MRT pos. after McDonald, but only **3** converted to MS

- At first symptoms MEP plus SEP more sensitive in the prediction to MS than MRT

Prognosis / course

- 94 pts with MS (Kallmann et al. Mult Scler 2006:12)
  - MEP-SEP SUM-score at baseline
    - sig. correlated with prognosis and EDSS after 5 years - not VEP



- 84 pts, follow-up 64 pts after 2.5 / 5 years

  (Leocani et al. JNNP 2006:77)

  Multimodal EP-Score (MEP, SEP, VEP, AEP)

  Pts. with Score above average 72.5 % risk

  Pts. with Score below average 36.3 % risk of EDSS deterioration by 1 point

  Only changes in SEP scores significantly correlated with changes of sensory function

Prognosis / Course

- 37 Pat. mit RRMS (Jung et al. Mult Scler 2008:14)
  - Multimodal EP-score (mEPS) at baseline
    - sign. correlated with prognosis of EDSS after 24 months, not at baseline

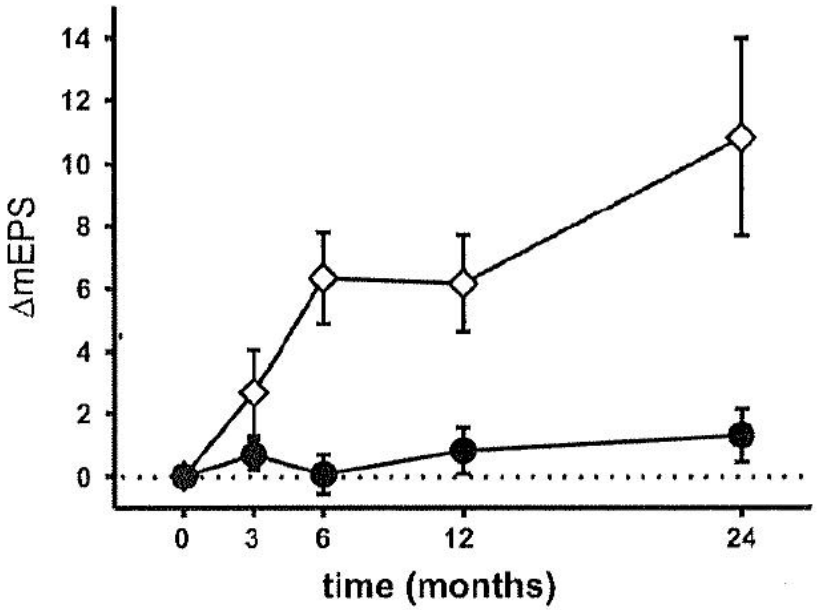


Figure 1 Changes in the multimodal evoked potential score (ΔmEPS) in RRMS patients with (open diamonds, $n = 7$) or without (filled circles, $n = 30$) relevant EDSS progression during the 24-month follow-up. Starting at month 6, ΔmEPS was significantly higher in progressive than stable patients (all $p < 0.01$).

Prognosis / Course

- 143 Pat. with RRMS (Margaritella et al. BMJ Neurol 2012:12)

  High multimodel EP-score at baseline

  bad prognosis of EDSS after 4-5 years,

Prognosis / Course

- 80 pats. 5 year follow-up (Invernizzi 2011)
  - correlation ($p < 0.001$) EP score and EDSS score at the time of neurophysiological study and at 1, 3 and 5 years of follow-up, particularly for MEP and SEP
  - increased risk of disability in pts with EP score higher than the median
  - Higher correlation between EPs abnormalities and EDSS than between conventional MRI and EDSS.

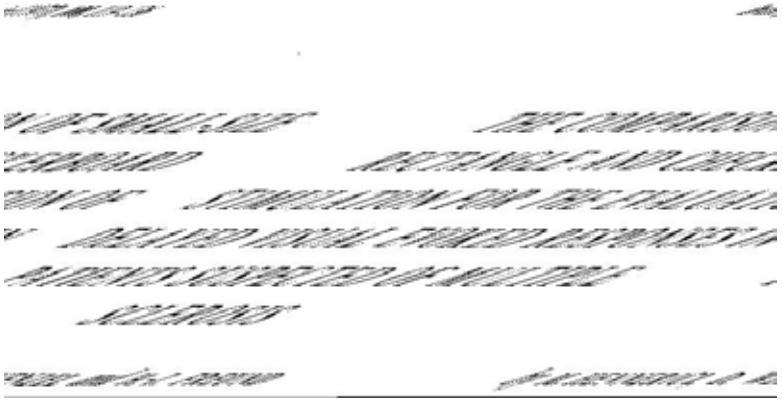
Multiple Sklerosis – Take Home

Which value of evoked potentials right now?

- **Early Diagnosis** (CIS - clinicaly isolated Syndrom)
  - EP can confirm diagnosis
- **Prognosis / Course**
  - EPs maybe superior concerning prognosis to first MRT
  - Length matters, short distance AEP smallest, long distance leg SEP and MEP highest contribution

Clinical Neurophysiology methods: Enhancing sensitivity, but

- loosing robustness
- time consumption

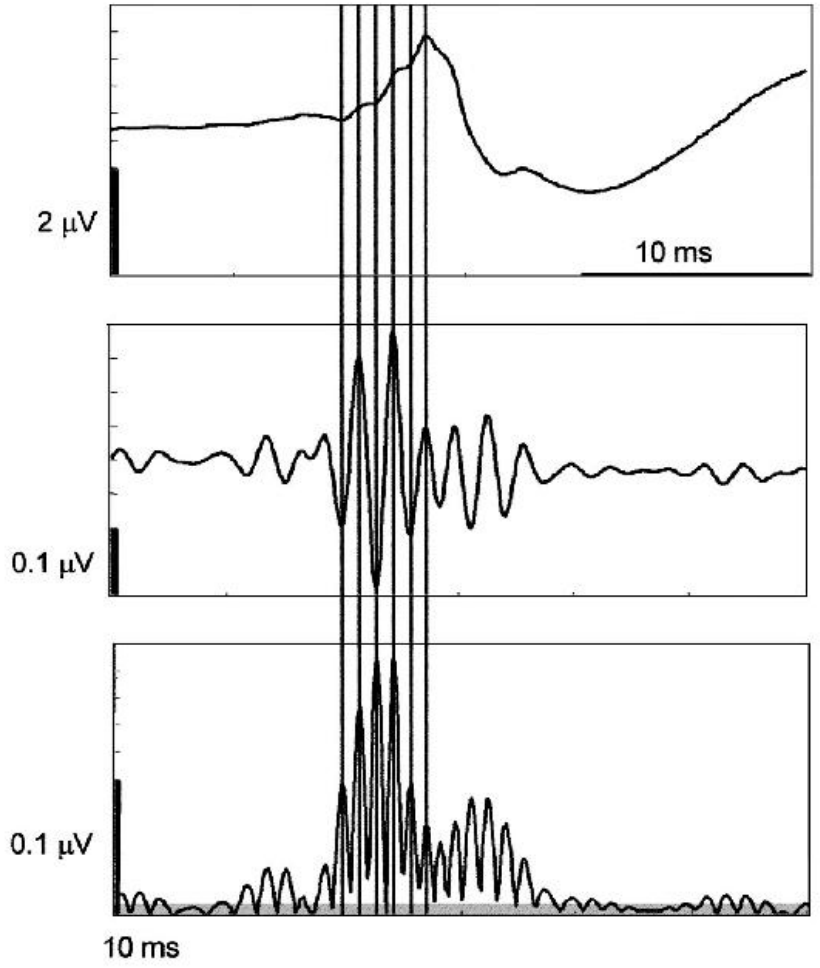


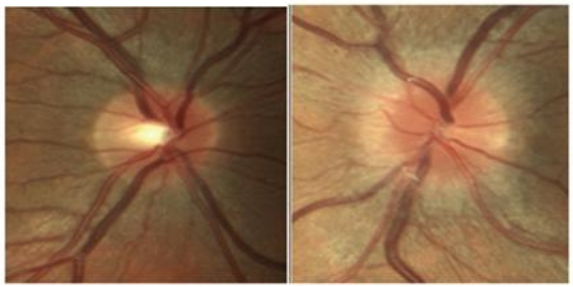
Examples for additional methods

Journal of Clinical Neurophysiology
20(4):283–290, Lippincott Williams & Wilkins, Inc., Philadelphia

Patterns of Disturbed Impulse Propagation in Multiple Sclerosis Identified by Low and High Frequency Somatosensory Evoked Potential Components

*René Gobbelé, *Till Dino Waberski, *Anne Dieckhöfer, *Wolfram
†Fabian Klostermann, †Gabriel Curio, and *Helmut Buchner

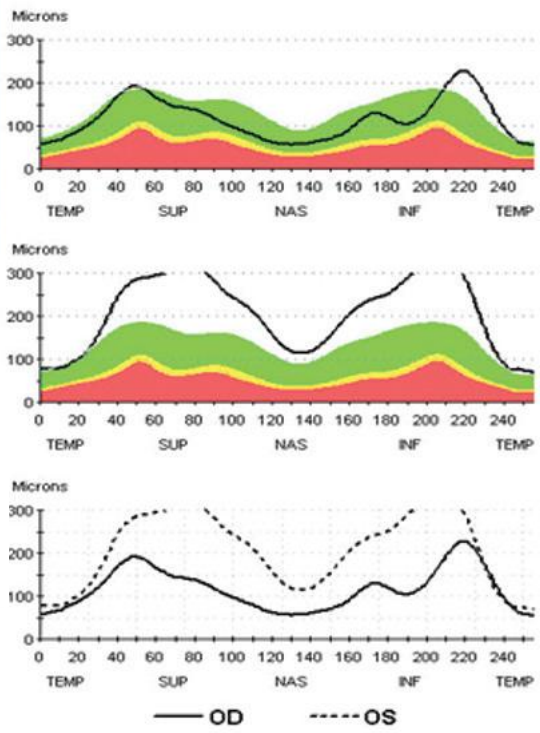


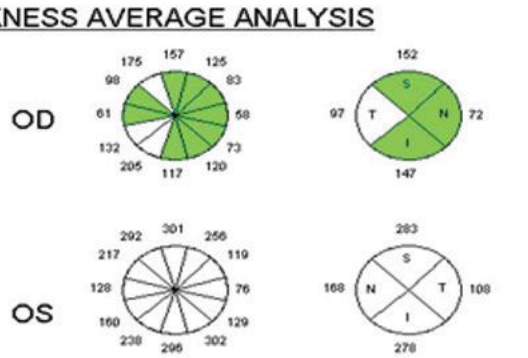


A B

Optical Coherence Tomography in the Diagnosis and Management of Optic Neuritis and Multiple Sclerosis

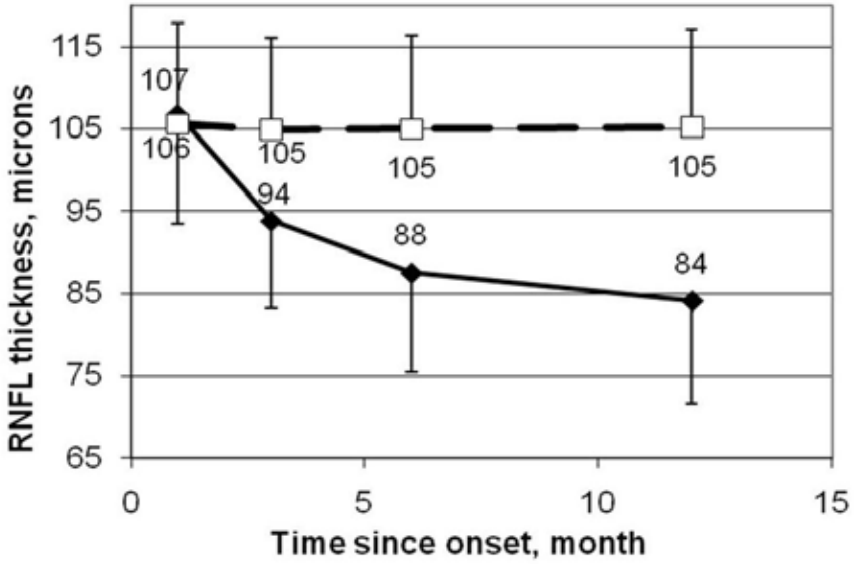
Fiona E. Costello, MD, FRCP; Alexander Klistorner, PhD; Randy Kardon, MD, PhD





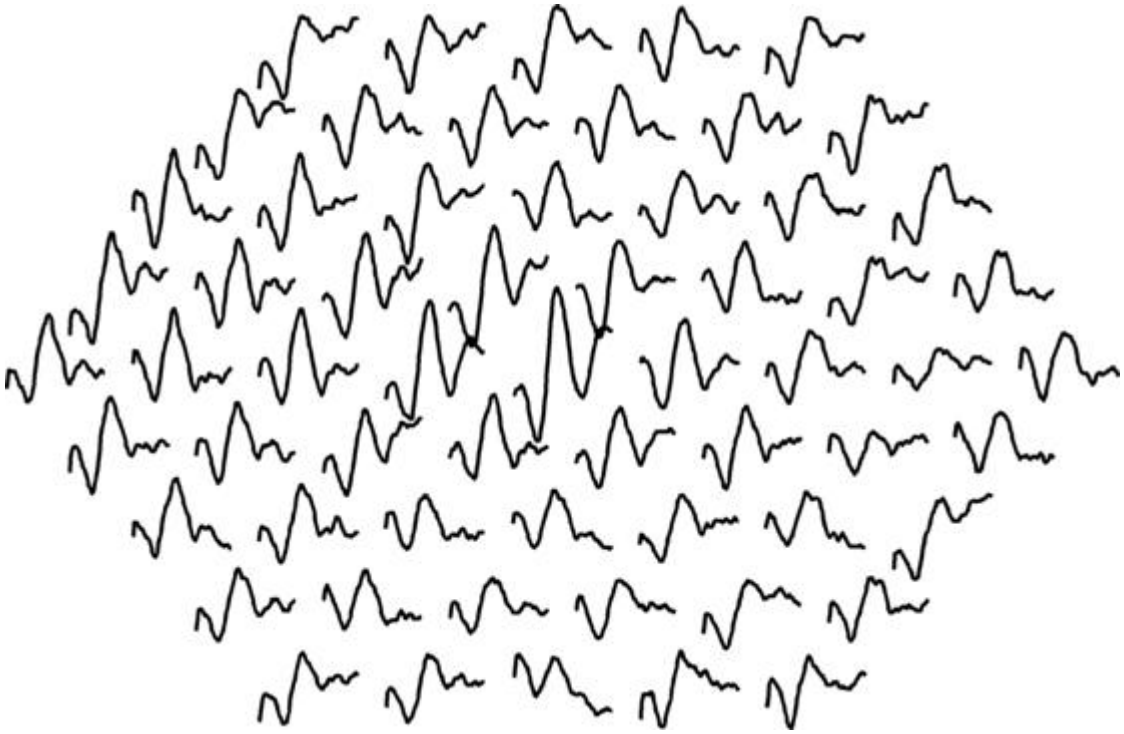
	OD (N=3)	OS (N=3)	OD-OS
Imax/Smax	1.18	1.02	0.16
Smax/Imax	0.85	0.98	-0.14
Smax/Tavg	1.98	2.91	-0.93
Imax/Tavg	2.34	2.97	-0.63
Smax/Navg	2.68	1.87	0.81
Max-Min	171.00	250.00	-79.00
Smax	192.00	314.00	-122.00
Imax	227.00	320.00	-93.00
Savg	152.00	283.00	-131.00
Iavg	147.00	278.00	-131.00
Avg.Thickness	117.12	209.47	-92.36

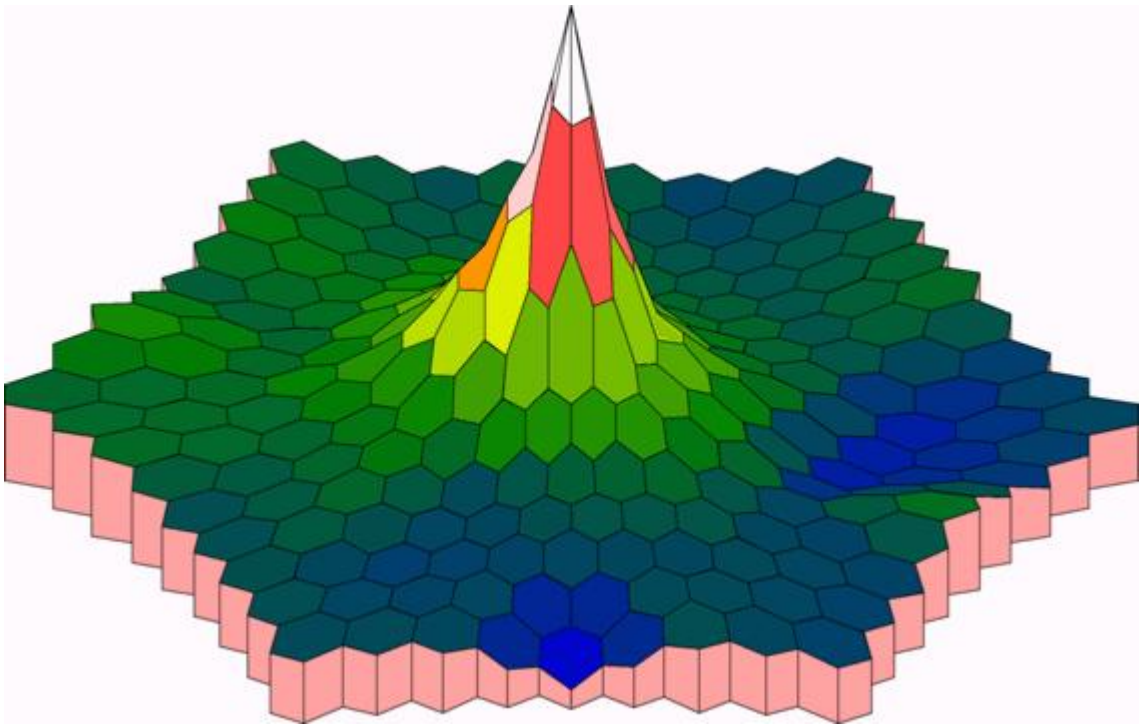
C



25 patients optic neuritis
increasing inter-eye asymmetry (*P* < .0001) in retinal nerve fiber layer (RNFL) values
eyes with optic neuritis showed progressively thinner RNFL values relative to the fellow eyes without optic neuritis over 12 months.

Multifocal ERG / VEP





What can we finally do to mirror the importance of evoked potentials in diagnosis of MS?

Diagnostic Criteria for Multiple Sclerosis: 2014 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,[1] Stephen C. Reingold, PhD,[2] Brenda Banwell, MD,[3] Michel Clanet, MD,[4] Jeffrey A. Cohen, MD,[5] Massimo Filippi, MD,[6] Kazuo Fujihara, MD,[7] Eva Havrdova, MD, PhD,[8] Michael Hutchinson, MD,[9] Ludwig Kappos, MD,[10] Fred D. Lublin, MD,[11] Xavier Montalban, MD,[12] Paul O'Connor, MD,[13] Magnhild Sandberg-Wollheim, MD, PhD,[14] Alan J. Thompson, MD,[15] Emmanuelle Waubant, MD, PhD,[16] Brian Weinshenker, MD,[17] and Mark Hallett, MD

New evidence and consensus has led to further revision of the McDonald Criteria for diagnosis of multiple sclerosis. The use of imaging for demonstration of dissemination of central nervous system lesions in space and time has been simplified, and in some circumstances dissemination in space and time can be established by a single scan. These revisions simplify the Criteria, preserve their diagnostic sensitivity and specificity, address their applicability across populations, and may allow earlier diagnosis and more uniform and widespread use.

ANN NEUROL 2011;69:292–302

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