

NEUROPHYSIOLOGICAL EVALUATION OF AXONAL DAMAGE

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Pathological substrates of functional deficit in MS

- Segmental demyelination
- Axonal degeneration

Functional effects of demyelination

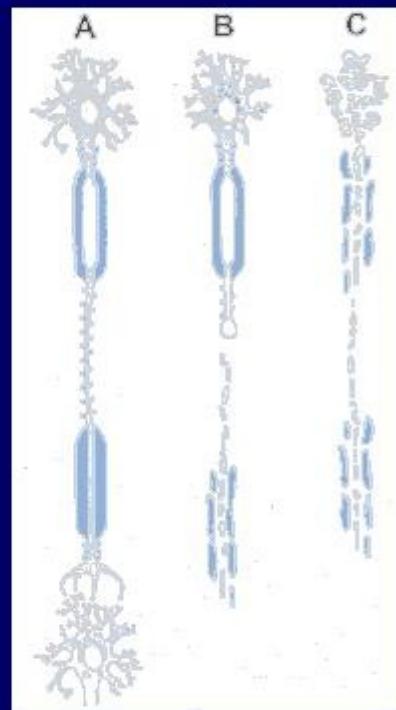
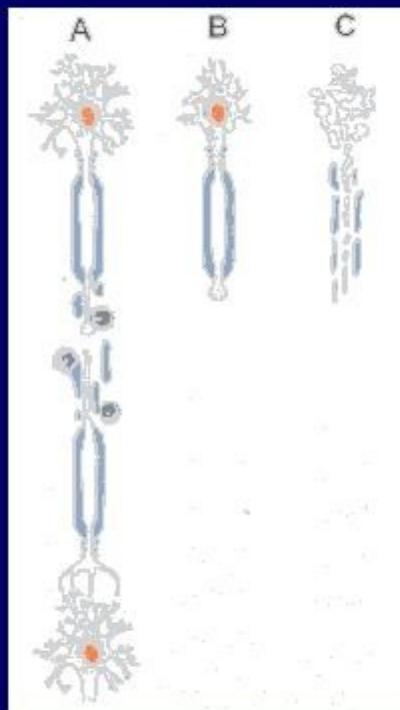
- slowing of conduction
- temporal dispersion
- increased refractory period
- conduction block
- axonal degeneration

NORMAL

ACUTE

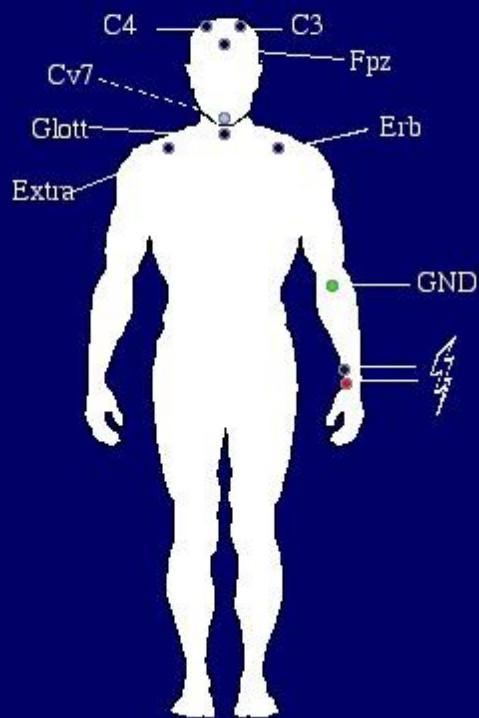
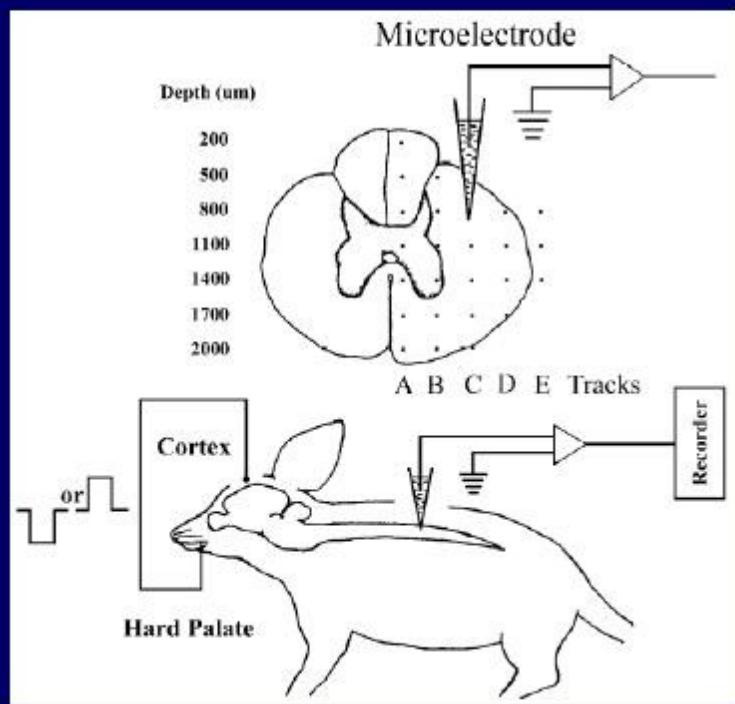
ACUTE

CHRONIC



Trapp et al. 1999

Neurophysiological evaluation of nervous conduction

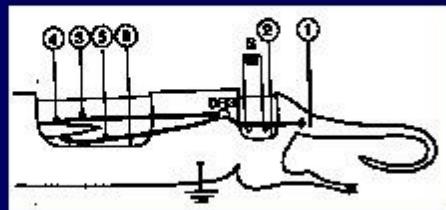


Neurophysiological abnormalities

- Delayed latency
- Abnormal morphology / reduced amplitude
- Absence

EAE - recovery

normal



Chalk et al 1995

Conduction block: pathophysiology

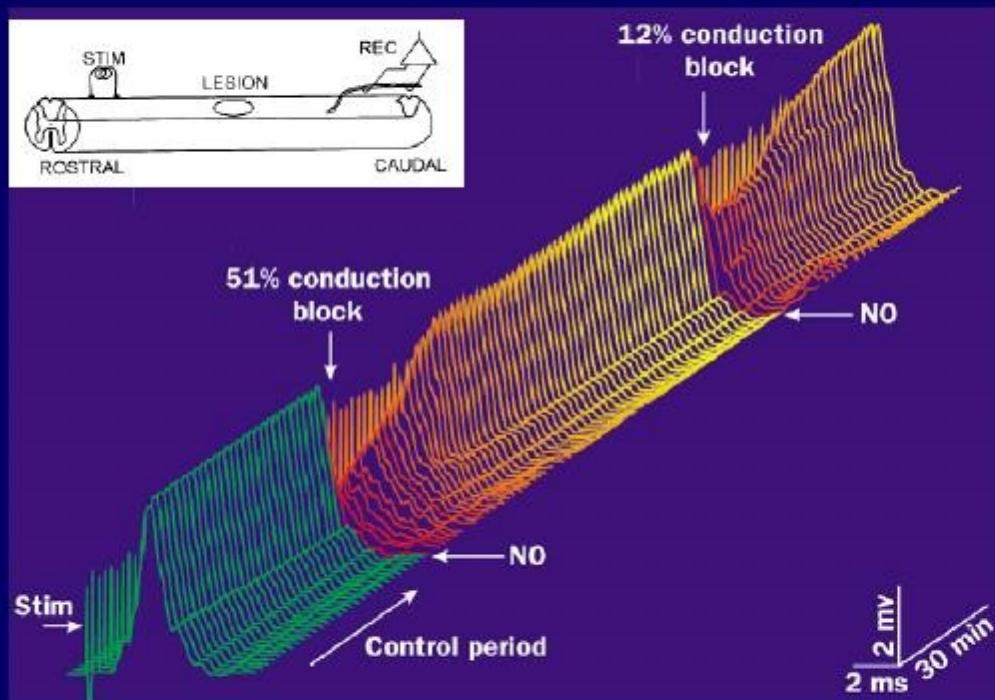
- Conduction block almost invariably occurs if the length of the demyelinated area exceeds 5 mm

McDonald and Sears 1979

- Conduction block may also be caused by soluble mediators of inflammation

Moreau et al 1996, Koller et al 1997, Redford et al 1997

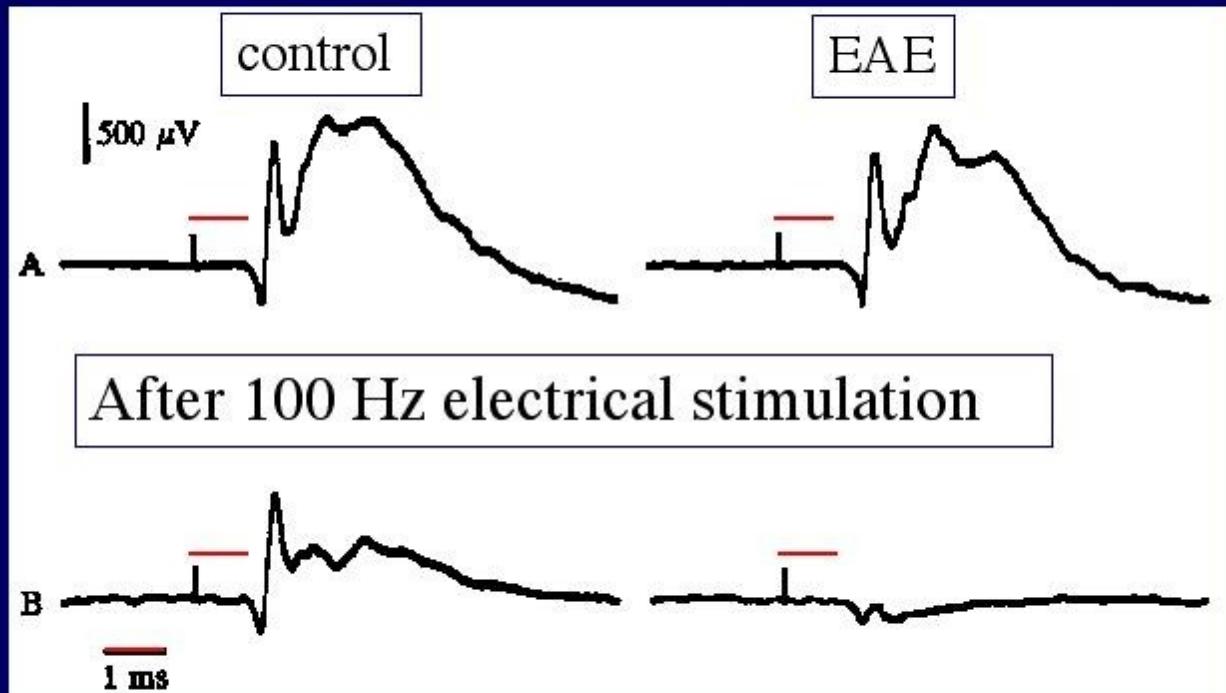
Conduction block - Effects of NO



Redford et al. 1997

EAE – Increased refractory period

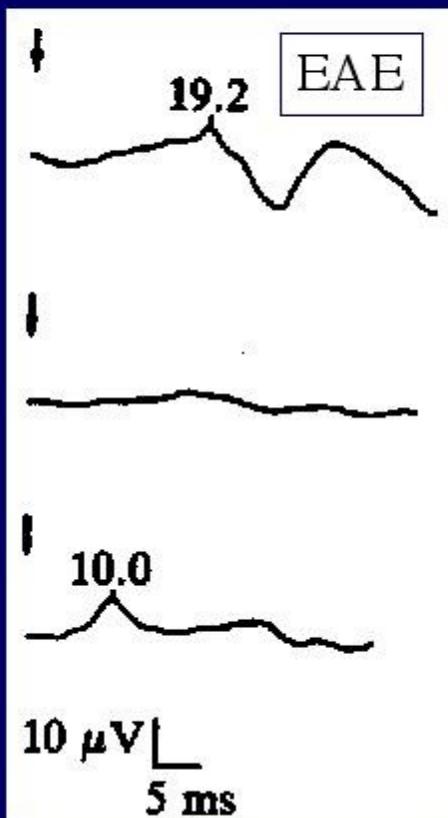
Recording: L4 dorsal root entry zone (sciatic nerve stimulation)



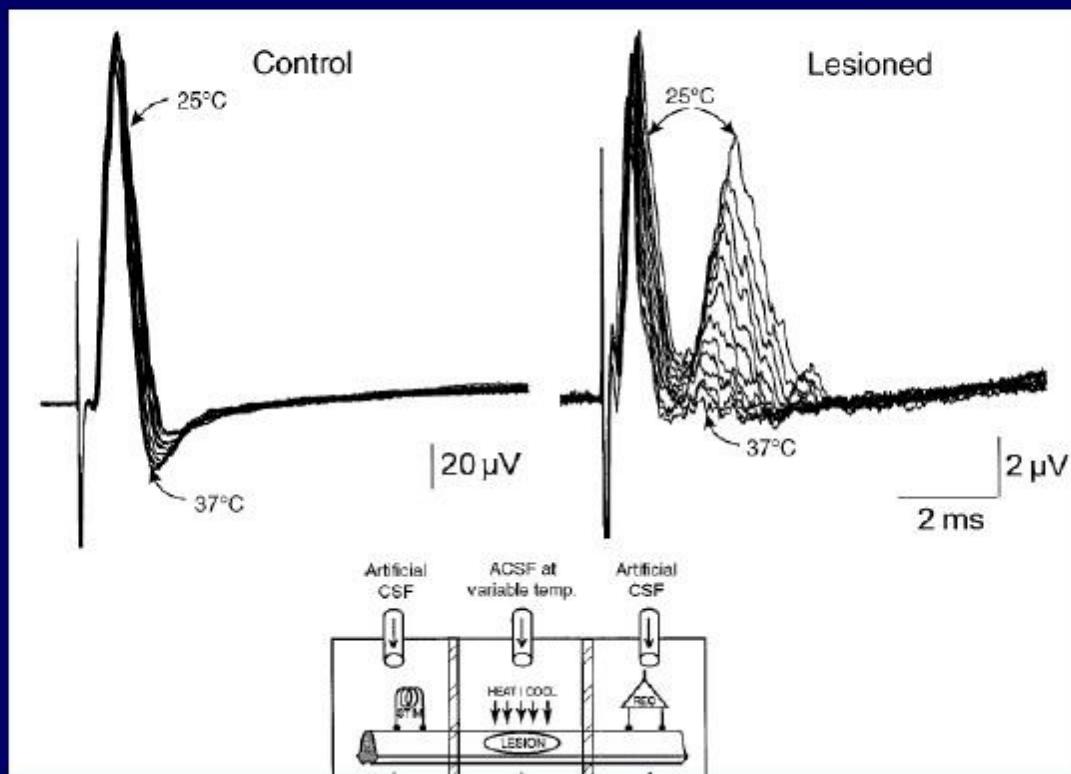
EAE – Effect of temperature

Cervical SEP - tibial n. stim.

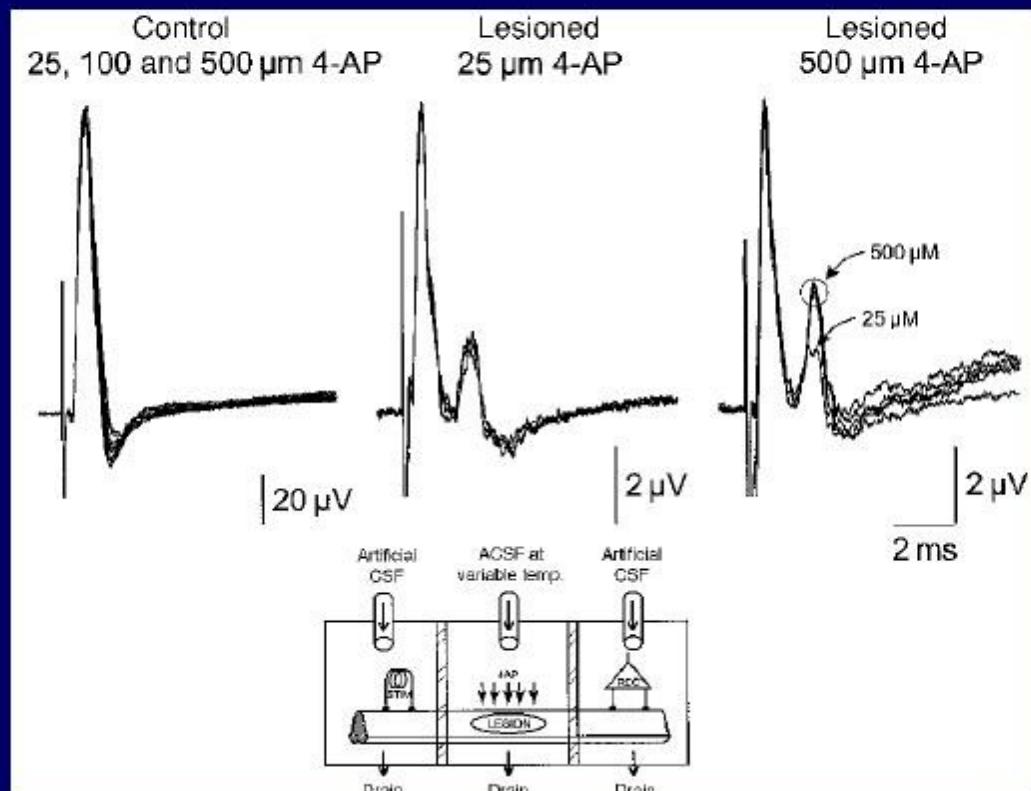
25.8°C



Conduction slowing and Conduction block Effects of temperature

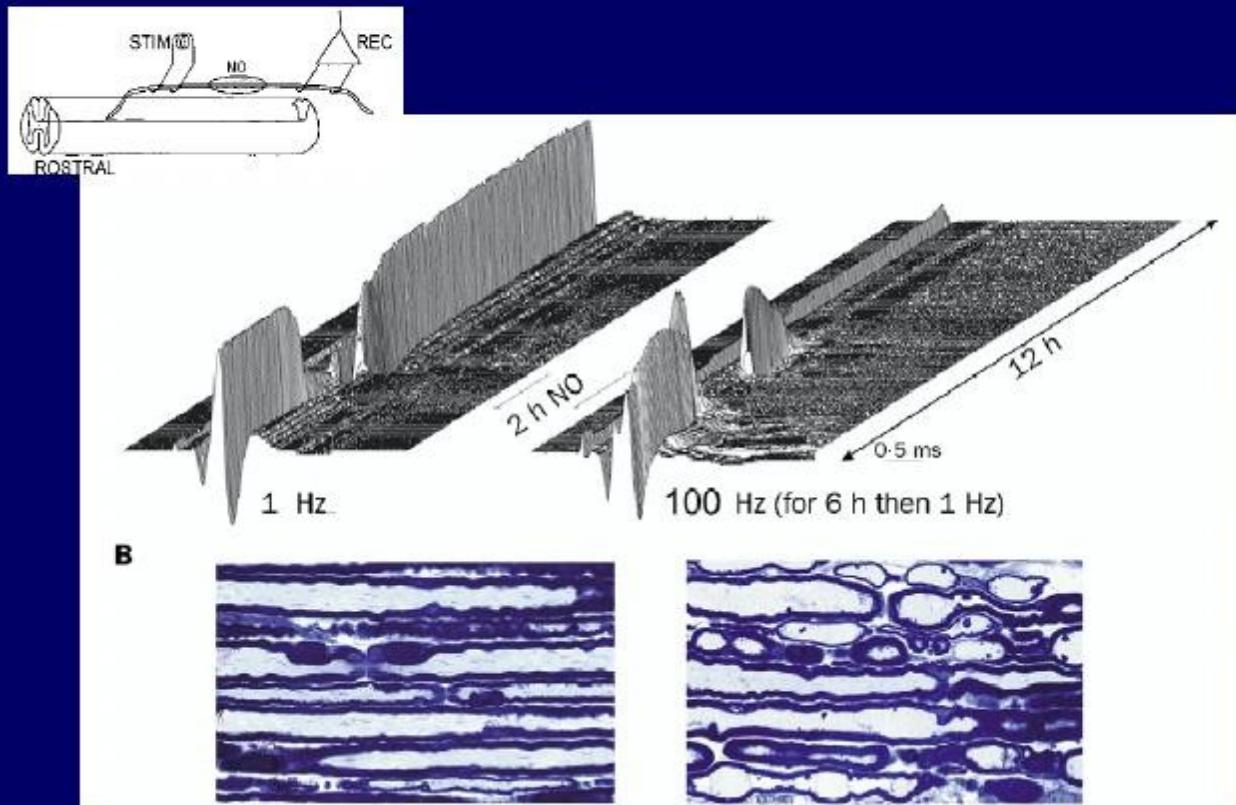


Conduction slowing and conduction block Effects of aminopyridine

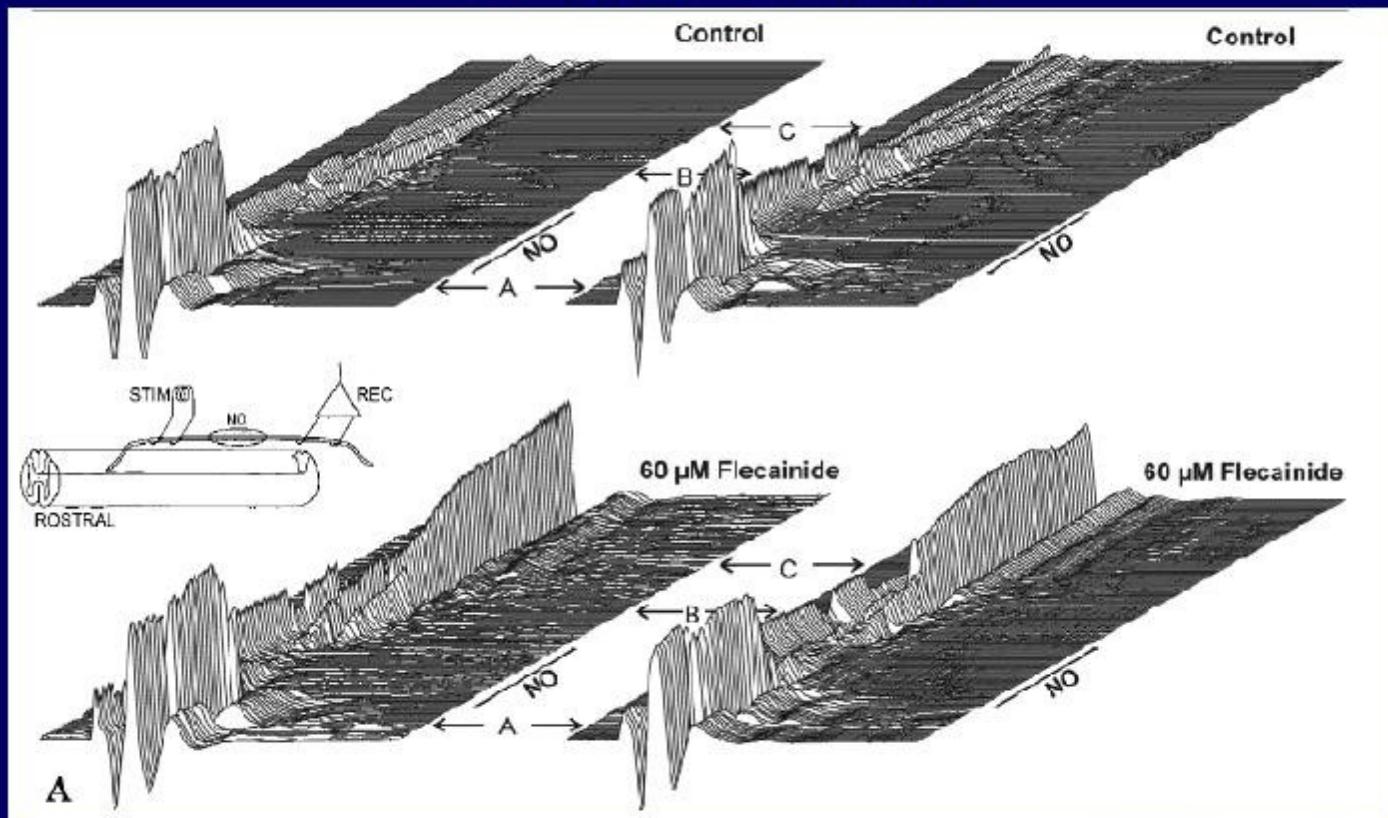


Axonal degeneration

Effects of electrical activity

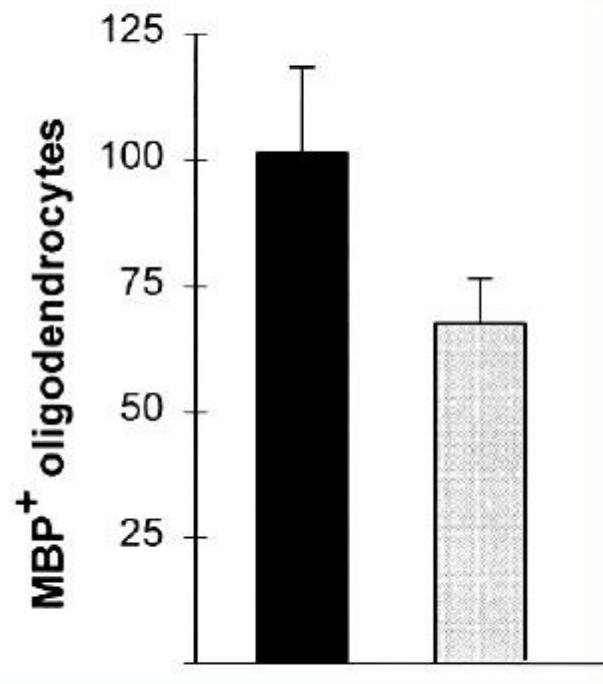
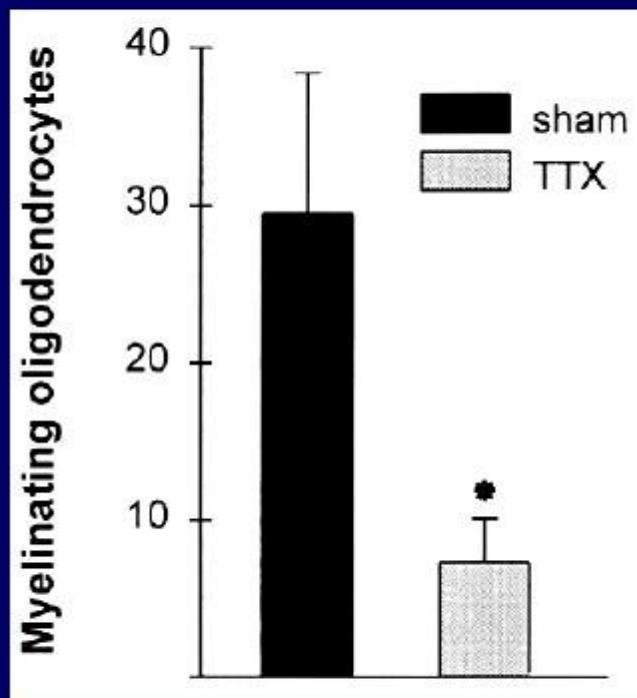


Axonal protection Effects of Na⁺ blockers



Positive effects of remyelination on electrical activity

Effects of Na⁺ block



MEP – Chronic MS animal model

- **Demyelination**

plateau at 100 days post infection (Theiler's murine encephalomyelitis virus - TMEV)

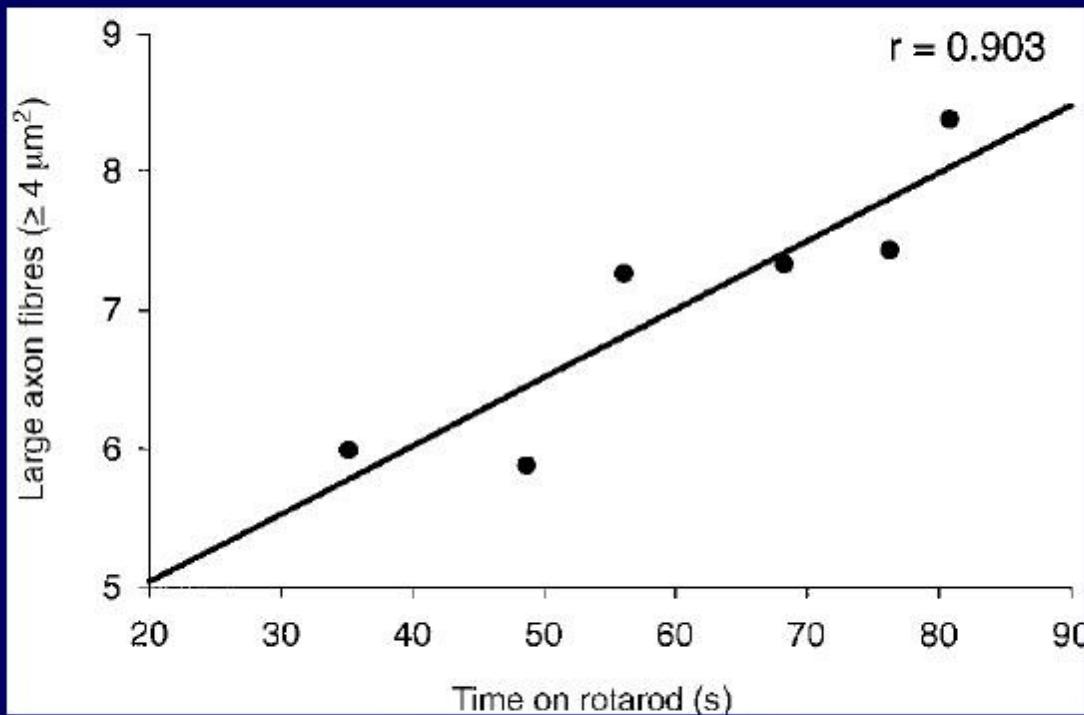
- **Axonal loss (*spinal cord atrophy*)**

prominent after the demyelinating phase

- **MEP findings**

- Demyelination – increased latency
- Axonal loss – reduced amplitude

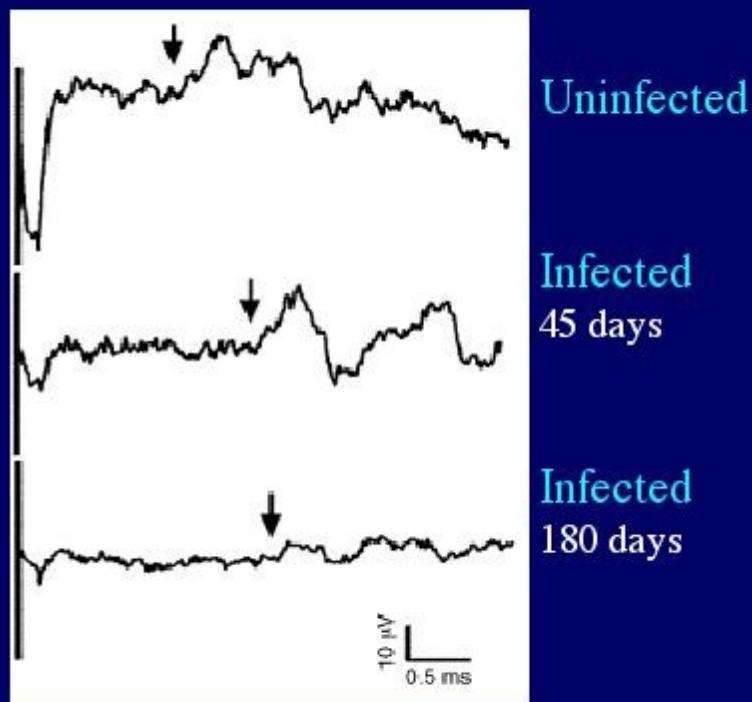
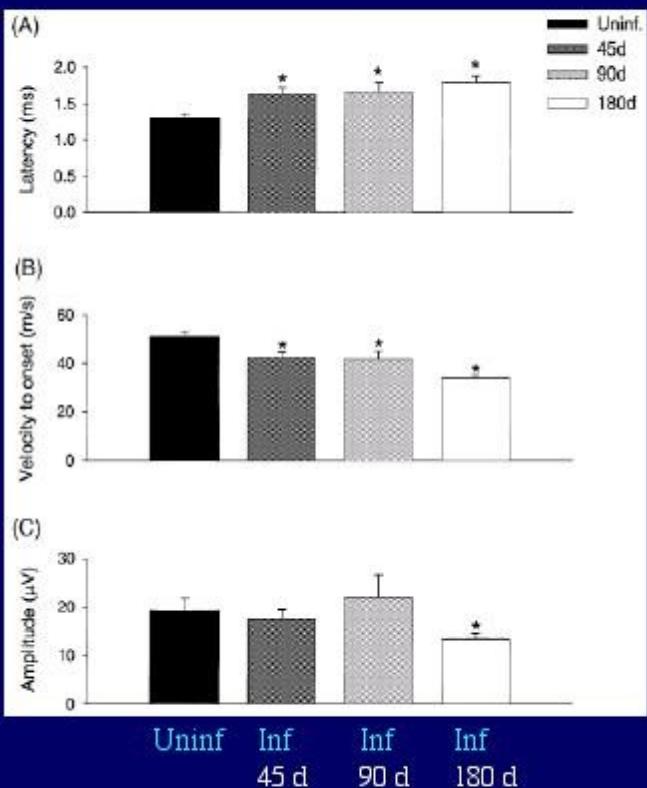
Rotarod performance – axonal loss



Time on rotarod (s)
Time on rotarod (s)

McGavern et al 2000

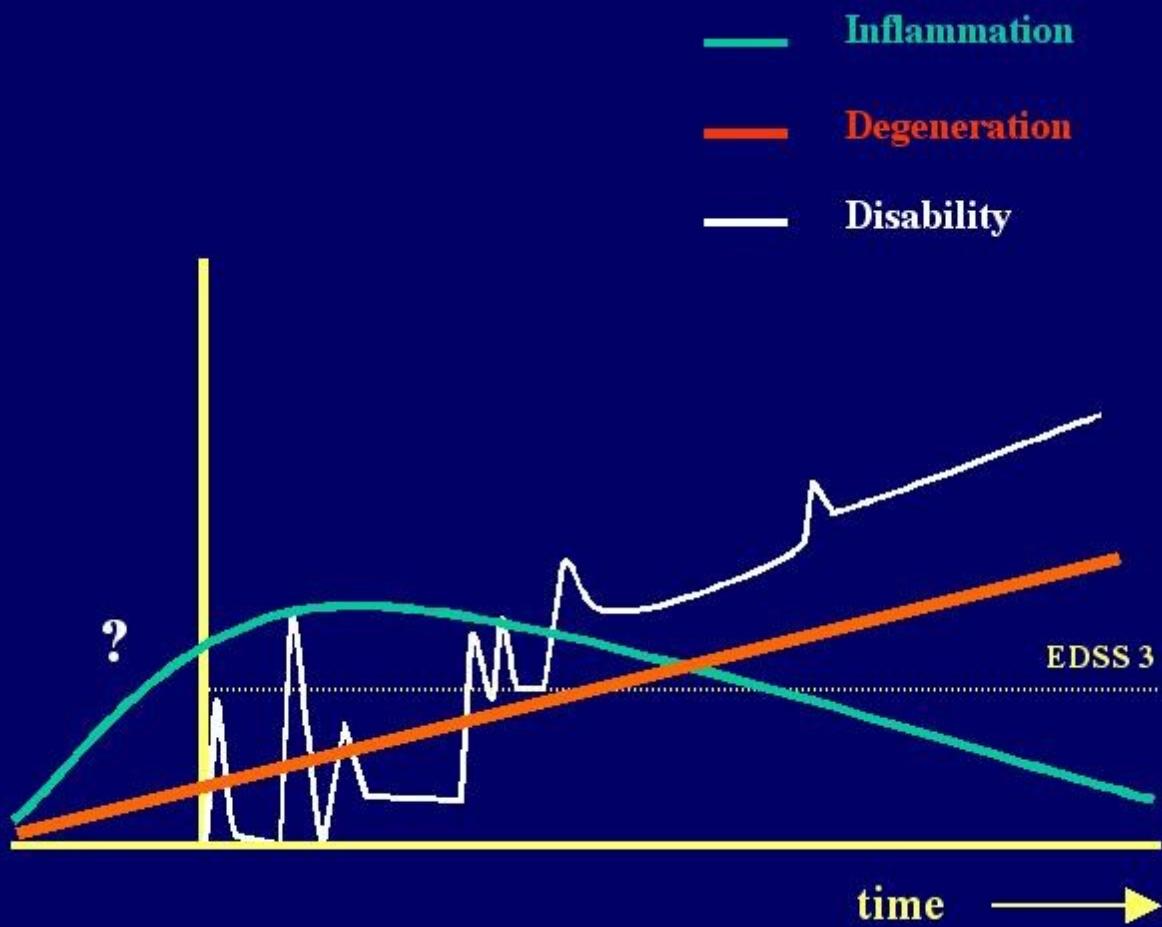
MEP – axonal loss



Neurophysiology of axonal damage in MS patients

Putative pathophysiological mechanisms of neurological dysfunction in MS

- Repeated episodes of demyelination leading to a failure of remyelination and secondary axonal degeneration
- Early axonal damage (primary or secondary to demyelination), followed by initial compensation (redundancy of CNS) and late failure
- Degenerative phase following and/or partially overlapping with the inflammatory phase



Factors influencing nerve conduction slowing in MS

- Plaque dimension (10 mm length: 15-25 ms delay)
- Plaque number
- Plaque location
- NAWM abnormalities
- Multisynaptic pathways

Functional effects of demyelination

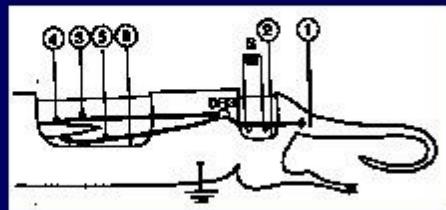
Multisynaptic pathways:

- Temporal summation of synaptic potentials to activate the next element in the pathway
- Desynchronized afferences may fail to induce post-synaptic activation

- Inflammation, demyelination, axonal degeneration, oedema, can coexist, in variable combination, in the MS plaque
- Several plaques may affect the same nervous pathway

EAE - recovery

normal



Chalk et al 1995

EAE

Cerebral Somatosensory Evoked Potentials sciatic nerve stimulation

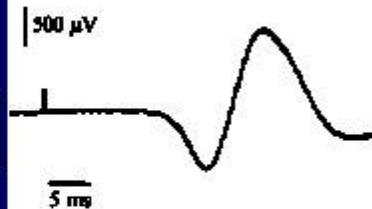
control



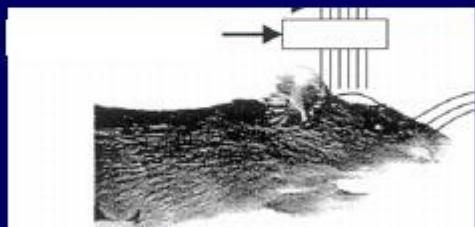
EAE 1st episode



EAE 2nd episode



← Amplitude Increase!



EAE

Cerebral Somatosensory Evoked Potentials sciatic nerve stimulation

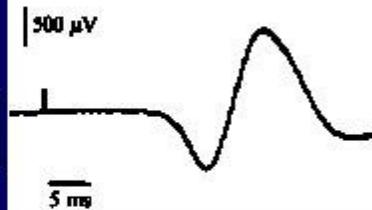
control



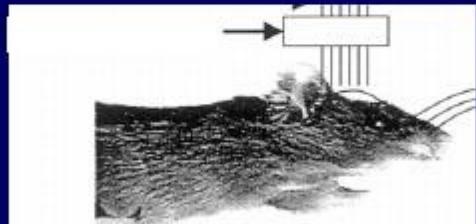
EAE 1st episode



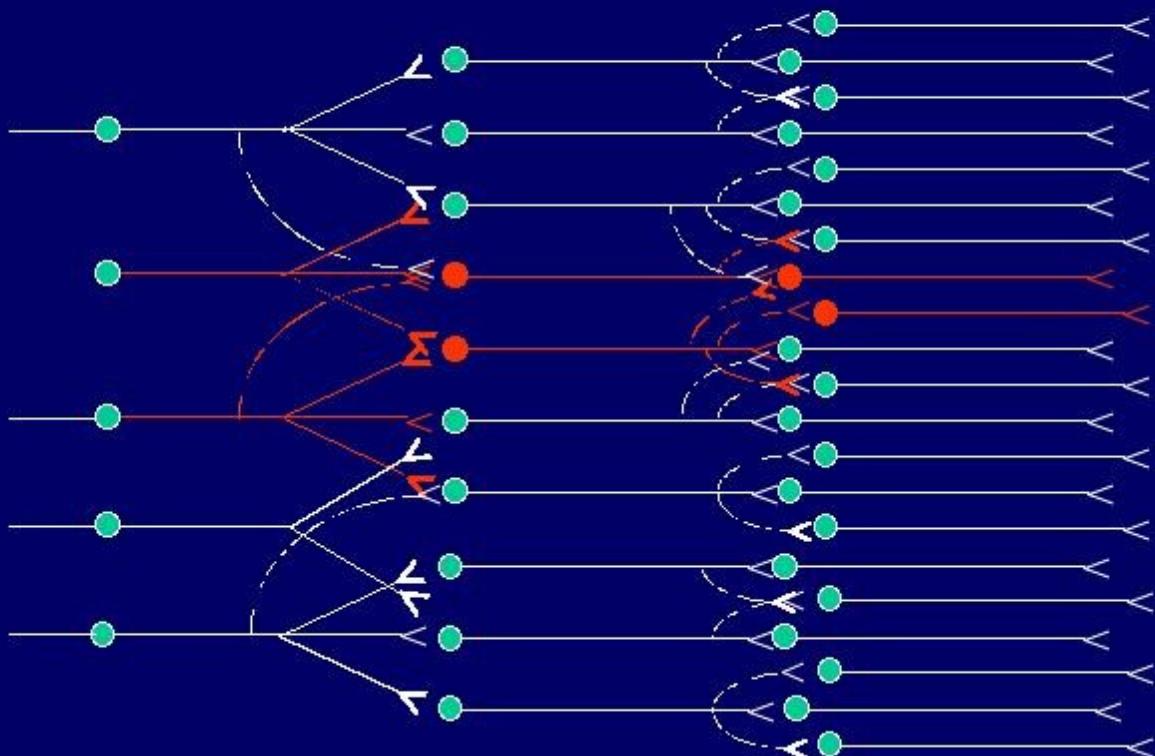
EAE 2nd episode



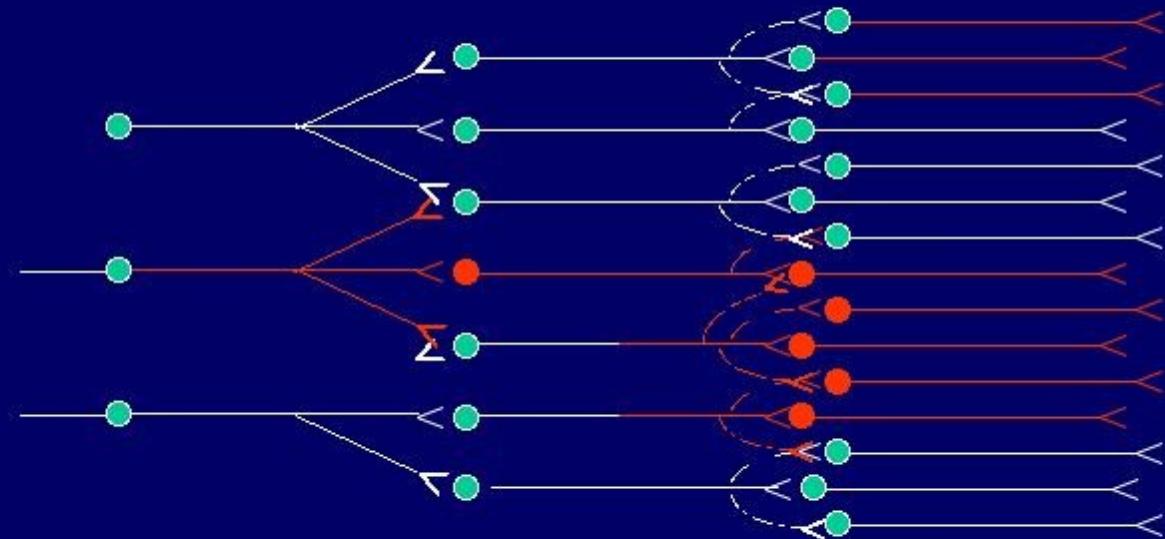
← Amplitude Increase!



Divergency/Convergency



Divergency/ConvergencY



CNS redundancy

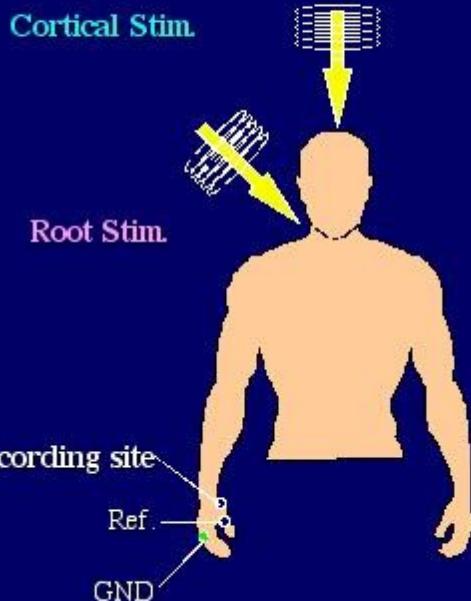
.... Examination of the retinal nerve fibre layer at the optic disc revealed that more than 50% of neural tissue must be lost before a visual defect is clinically evident

Quigley and Addicks 1982

Neurophysiological assessment of regional damage in MS: tools

- Brain
 - EEG
 - ERPs
- Brainstem
 - BAEP
 - SEPs
- Optic nerve
 - VEPs
- Spinal cord
 - SEPs
 - MEPs

Motor EPs



Cortical Stim.

Root Stim.

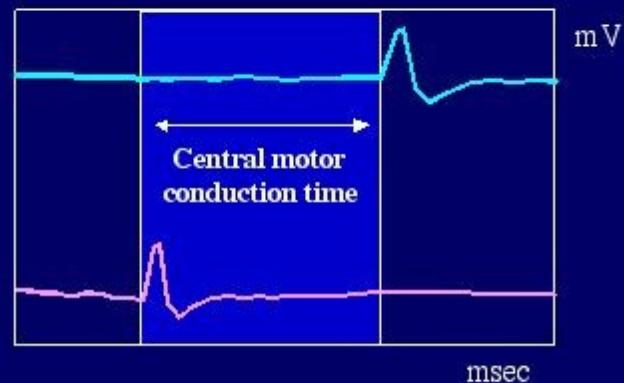
Ref.

GND

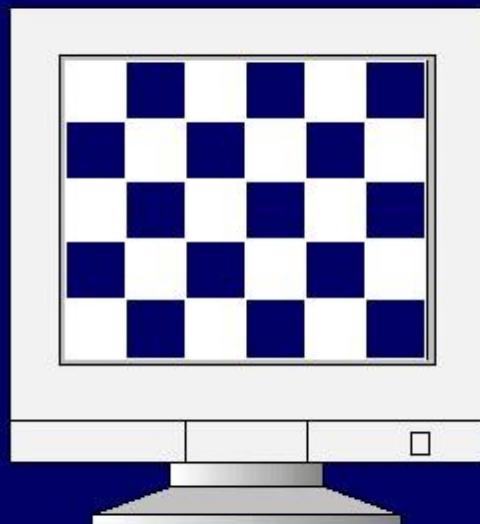
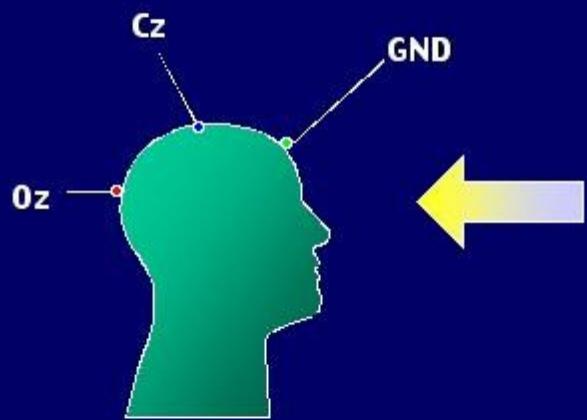
Cortical Stim.

Root Stim.

$$\text{Central MCT} = \text{Tot. MCT} - \text{Periph. MCT}$$



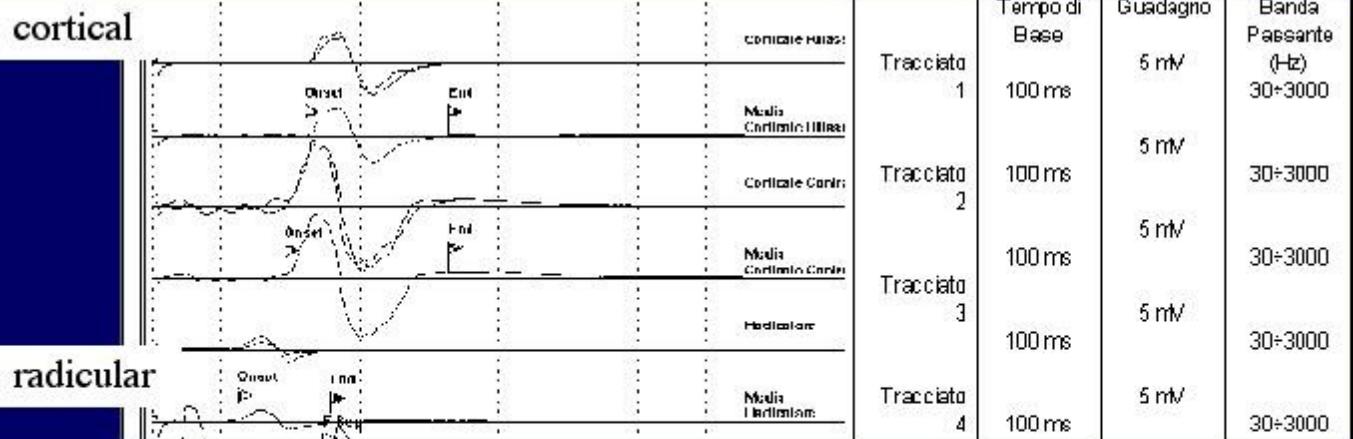
PEV



F. stim.	3 Hz
Contrasto	100%
Angolo	60' - 30' - 15'

MEP – normal subject

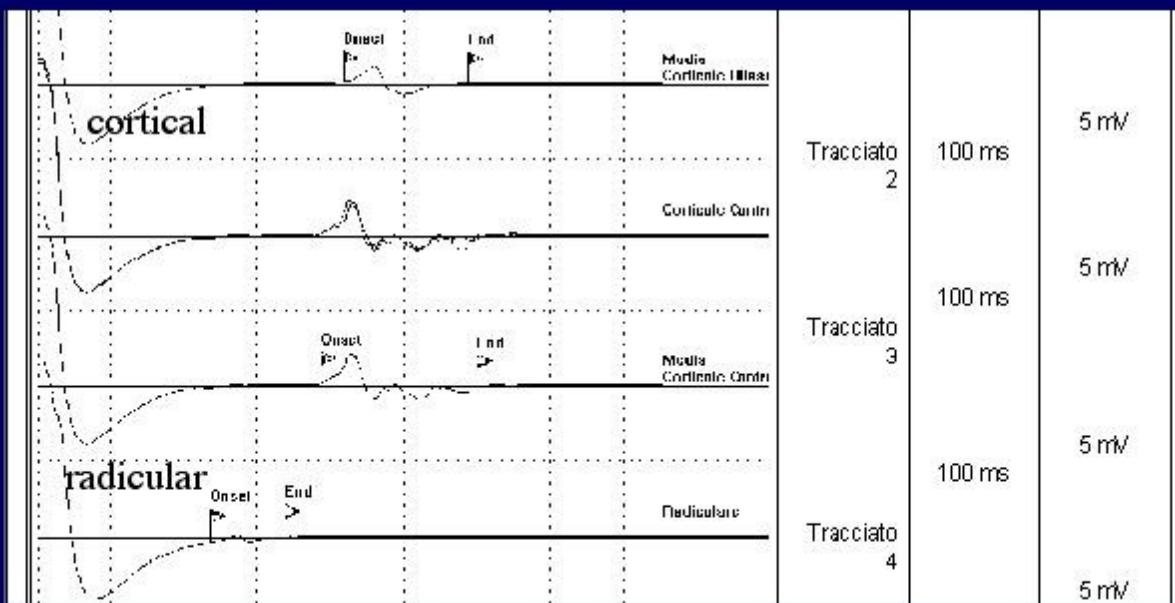
Sinistro: Opponente del pollice	Onset	Aampiezza	TCMP	TCMC
PEM Corticale (Muscolo Rilassato)	22,1ms	3,8mV		9,5ms (8,8ms*)
PEM Corticale (Muscolo Contratto)	19,0ms	8,6mV		6,5ms (5,7ms*)
PEM Radicolare	12,6ms	1,4mV		



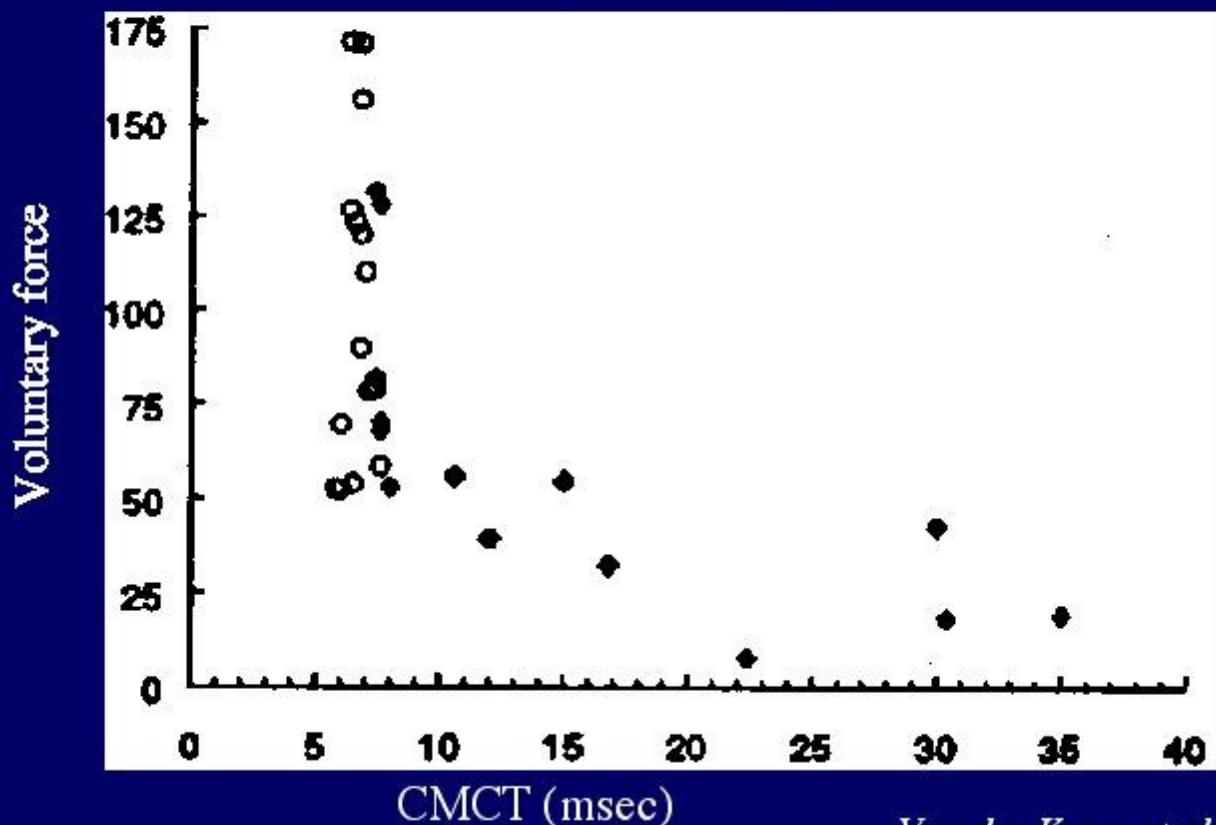
MEP – MS patient

Potenziali Evocati Motori

Sinistro: Abduttore dell'alluce	Onset	Aampiezza	TcMP	TcMC
PEM Corticale (Muscolo Rilassato)	41,6ms	1,9mV		18,1ms [14,5ms*]
PEM Corticale (Muscolo Contratto)	38,6ms	3,1mV		15,0ms [11,5ms*]
PEM Radicolare	23,6ms	450µV		

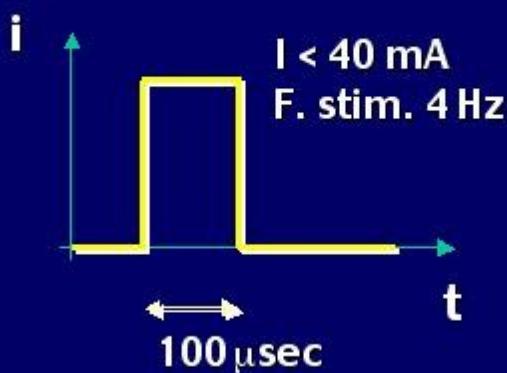
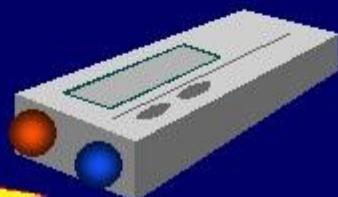
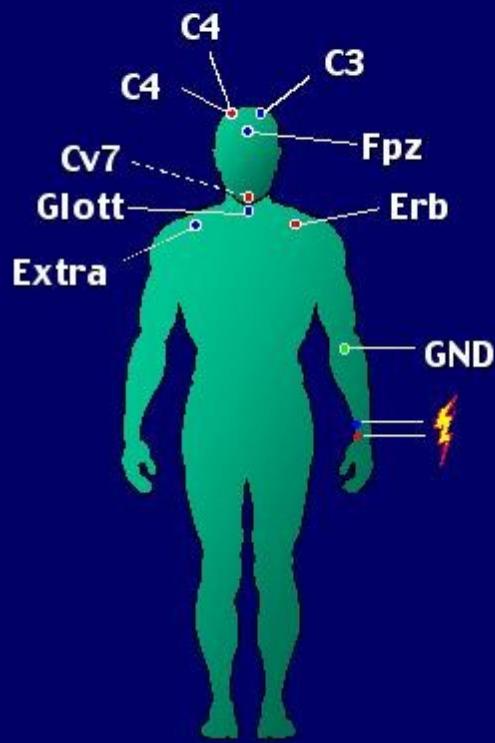


Correlation between central motor conduction time and phasic strength

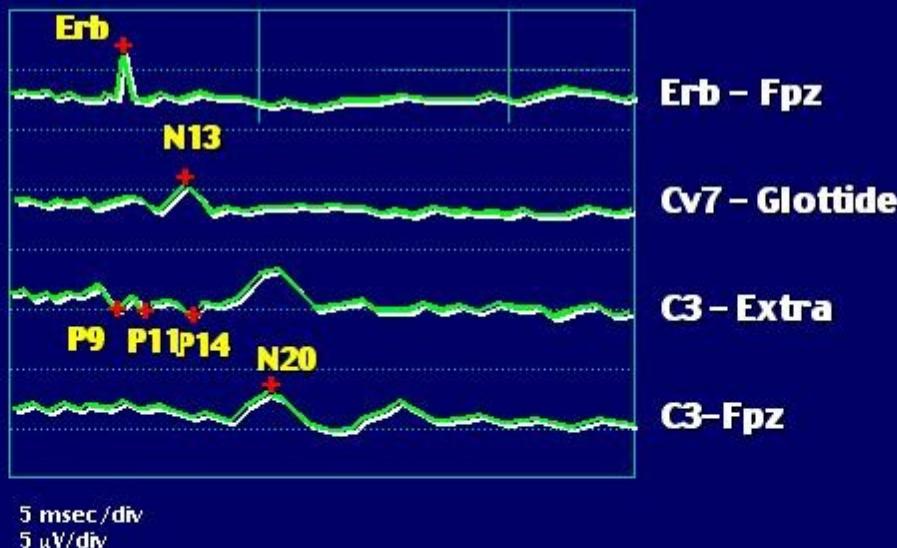


Van der Kamp et al 1991

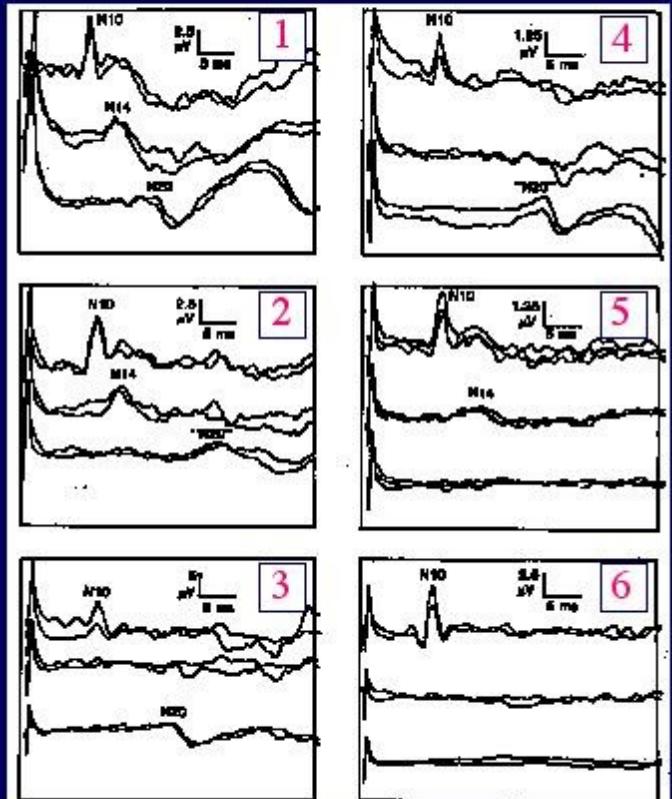
PES nervo mediano



PES nervo mediano componenti



SEPs patterns



1- Normal

2- Increased N14-N20 lat.

3- N14 absent

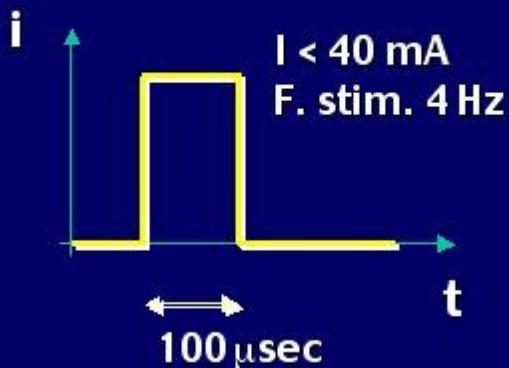
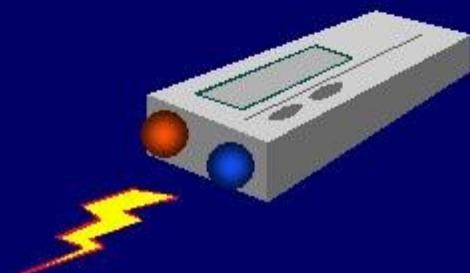
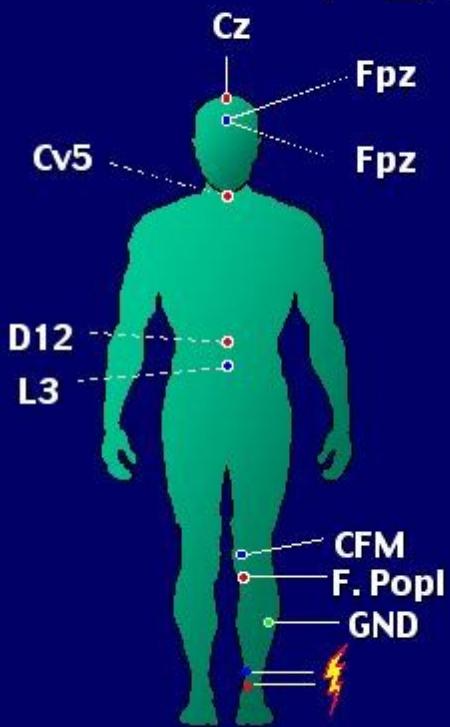
4- N14 absent, N20 delayed

5- N20 absent

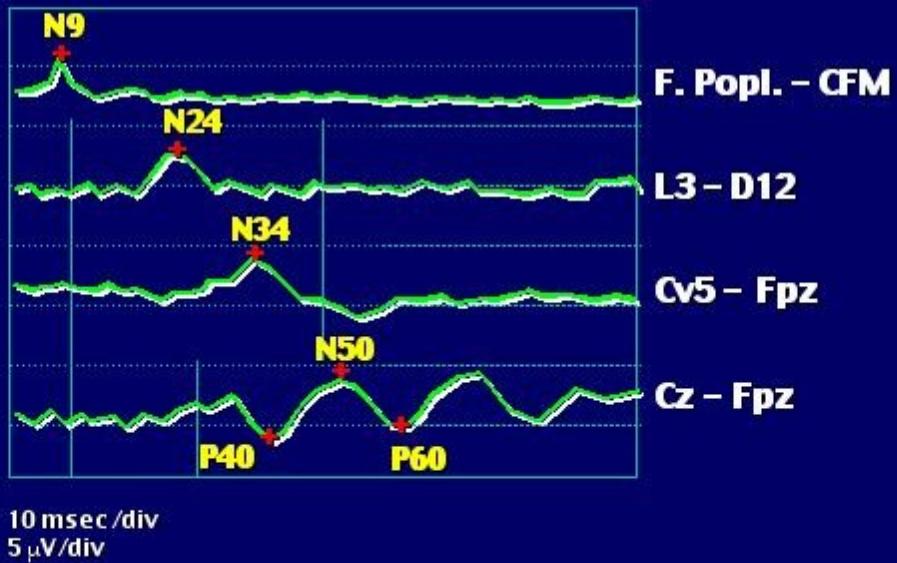
6- N14 and N20 absent

Anderson et al 1987

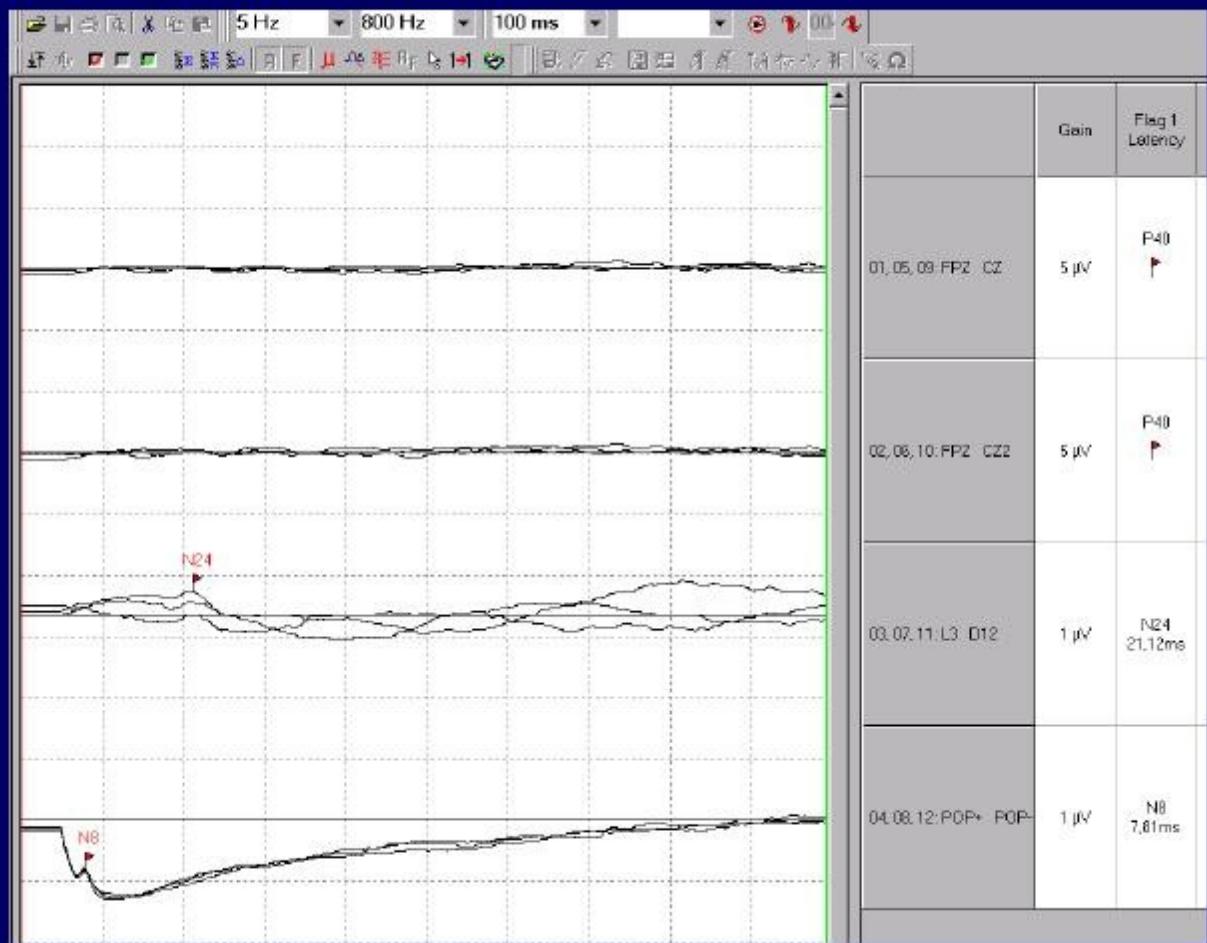
PES nervo tibiale



PES nervo tibiale



SM - Lesione midollare dorsale

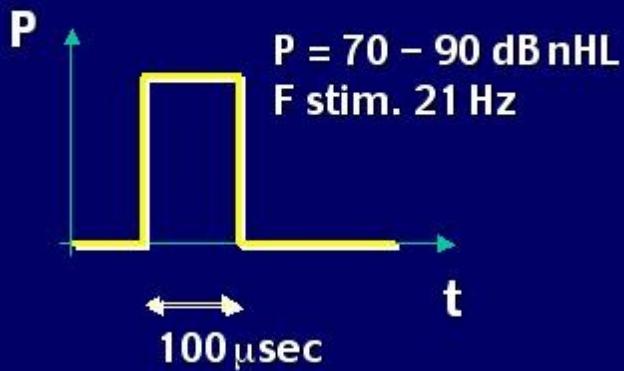
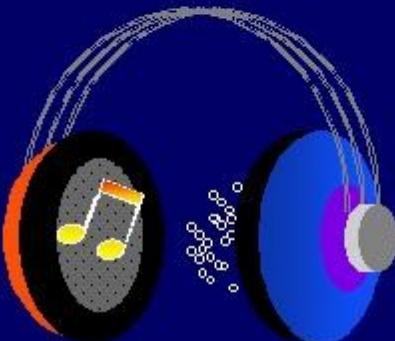
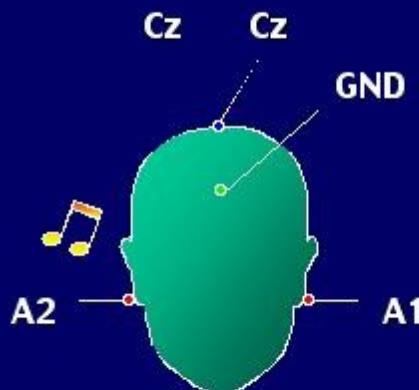


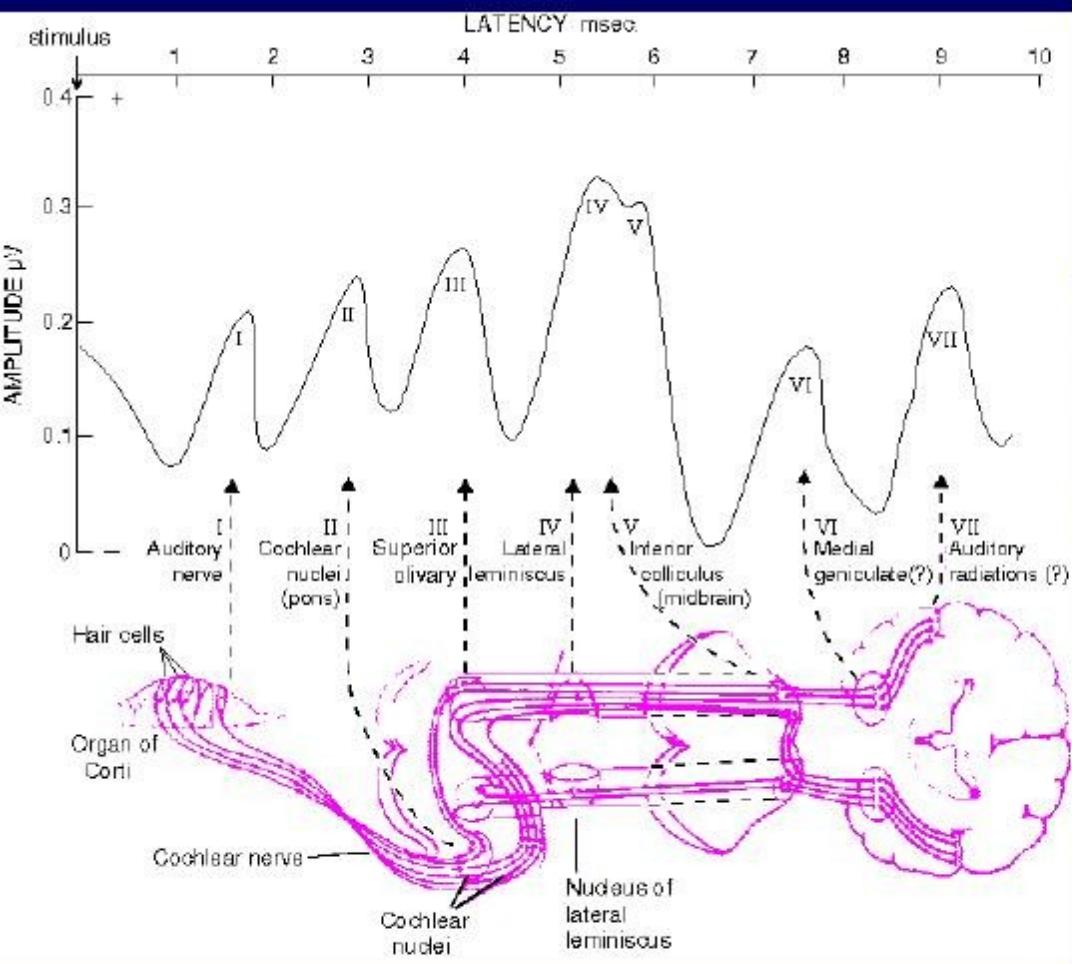
Correlations between abnormalities of vibratory threshold and of SEPs

		VPT	
		N	Abn
SEPs	N	25	9
	Abn	18	21

73 limbs examined (upper and lower limbs)

PEA





I n. acustico
ponte

II n. coclearis

III n. olivare sup.

IV lemn. lat.

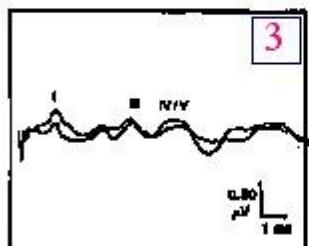
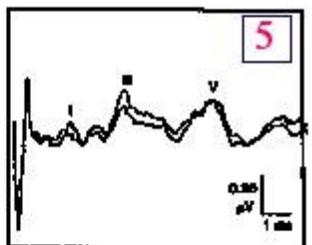
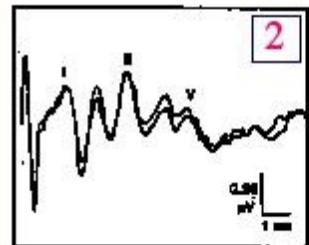
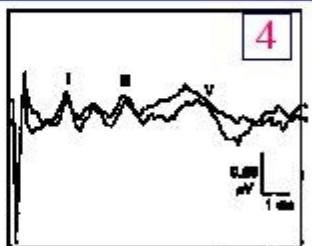
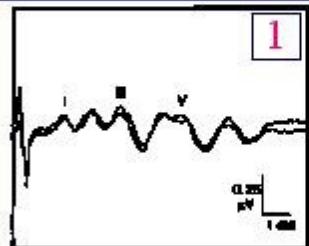
mesencefalo

V colliculo inf

VI genicol. med. (?)

VII rad. acustiche (?)

BAEPs patterns



1- Normal

2- Waveform distorsion

3- I-III prolonged

4- III-V prolonged

5- I-V prolonged

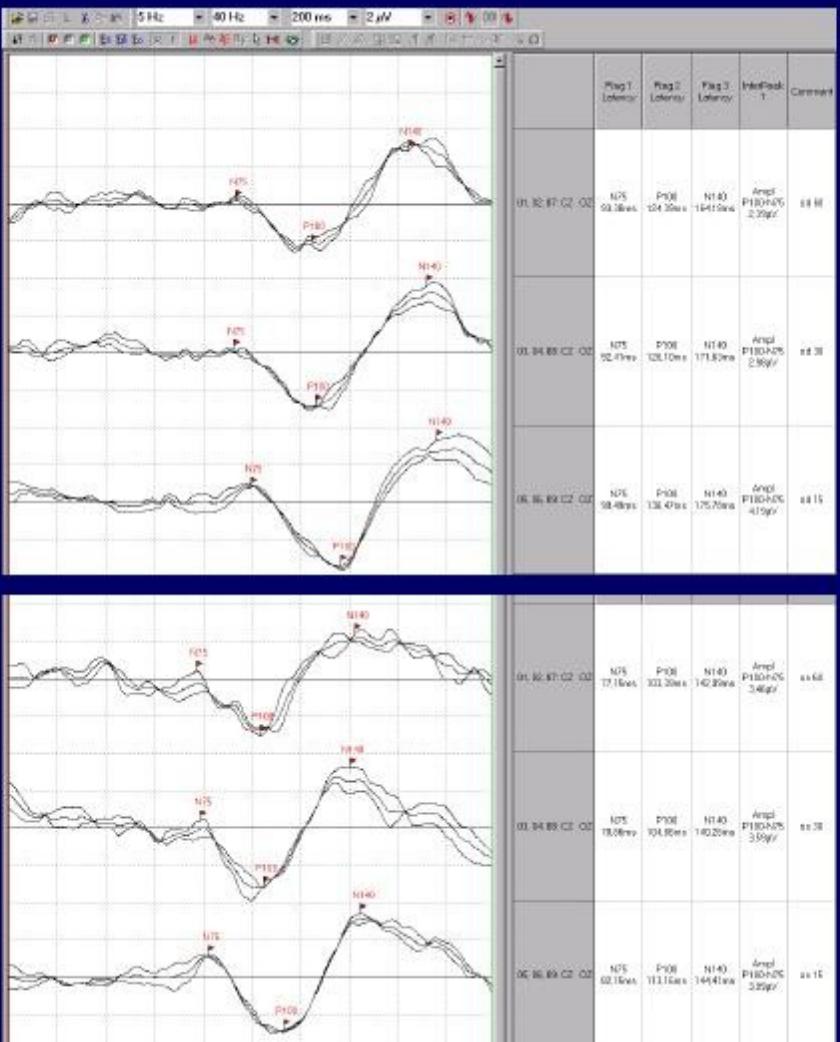
6- I-V prolonged, I/ V amplitude ratio abnormal

Anderson et al 1987

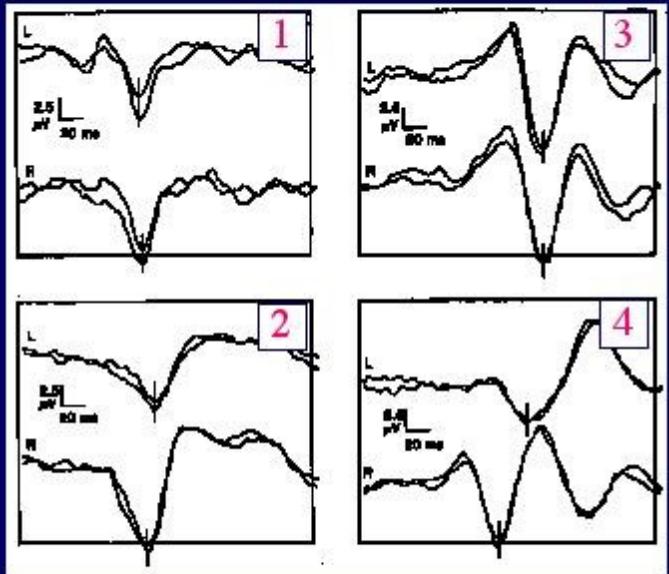
SM

OD

OS



VEPs patterns

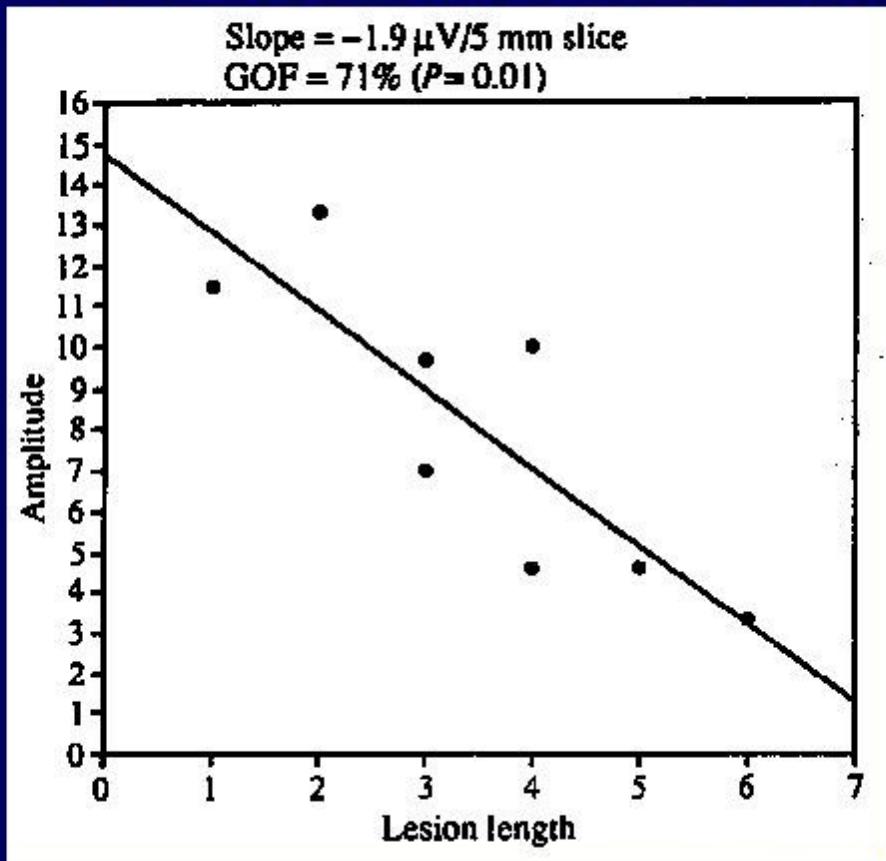


- 1- Normal
- 2- Amplitude asymmetry
- 3- Latency prolongation
- 4- Amplitude asymmetry and latency prolongation

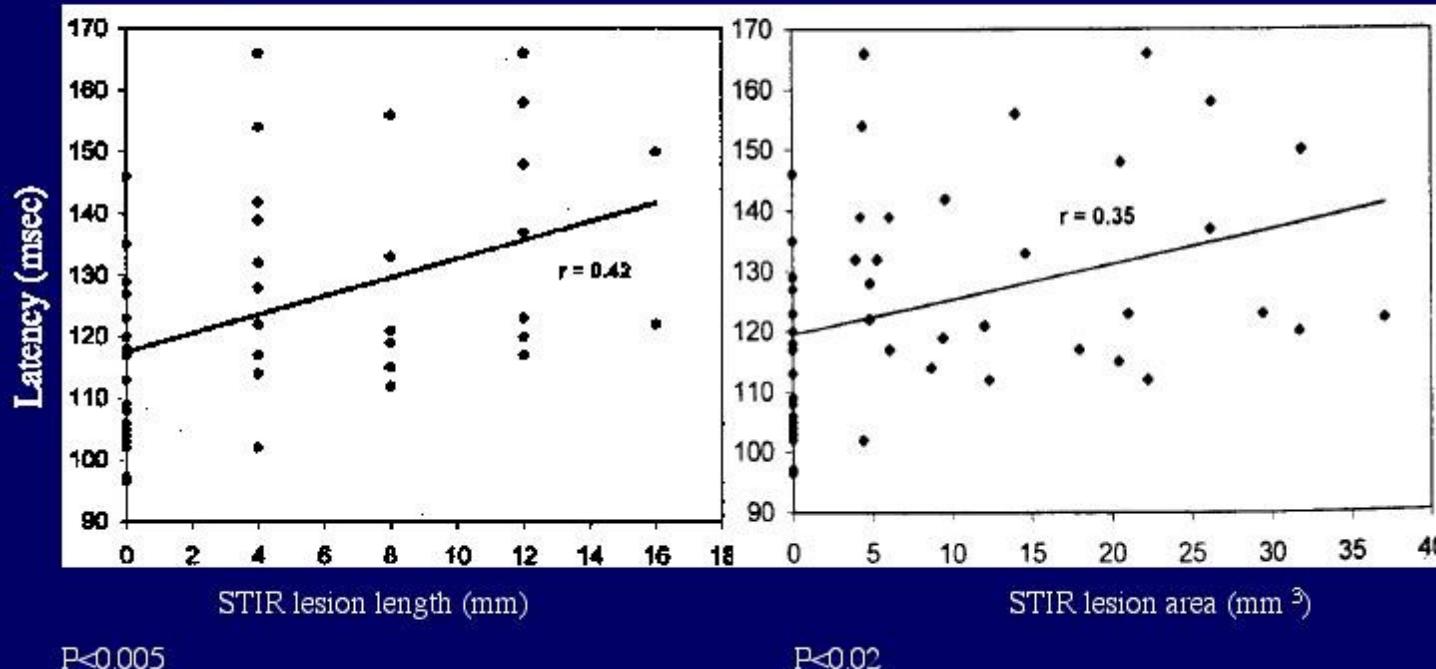
Anderson et al 1987

Acute ON

correlation between VEP amplitude and lesion length



Correlation between P100 latency and lesion length in 25 SP MS patients (4 with previous history of ON)



$P < 0.005$

$P < 0.02$

Davies et al 1998

Frequencies of optic nerve abnormalities in 25 SP MS patients (4 with previous history of ON)

VEP

Pts: 18/25 (72%)

Eyes: 25/50 (50%)

Eyes with ON: 6/6 (100%)

MRI

Pts: 19/25 (76%)

Eyes: 29/50 (58%)

Eyes with ON: 5/6 (83.3%)

VEP

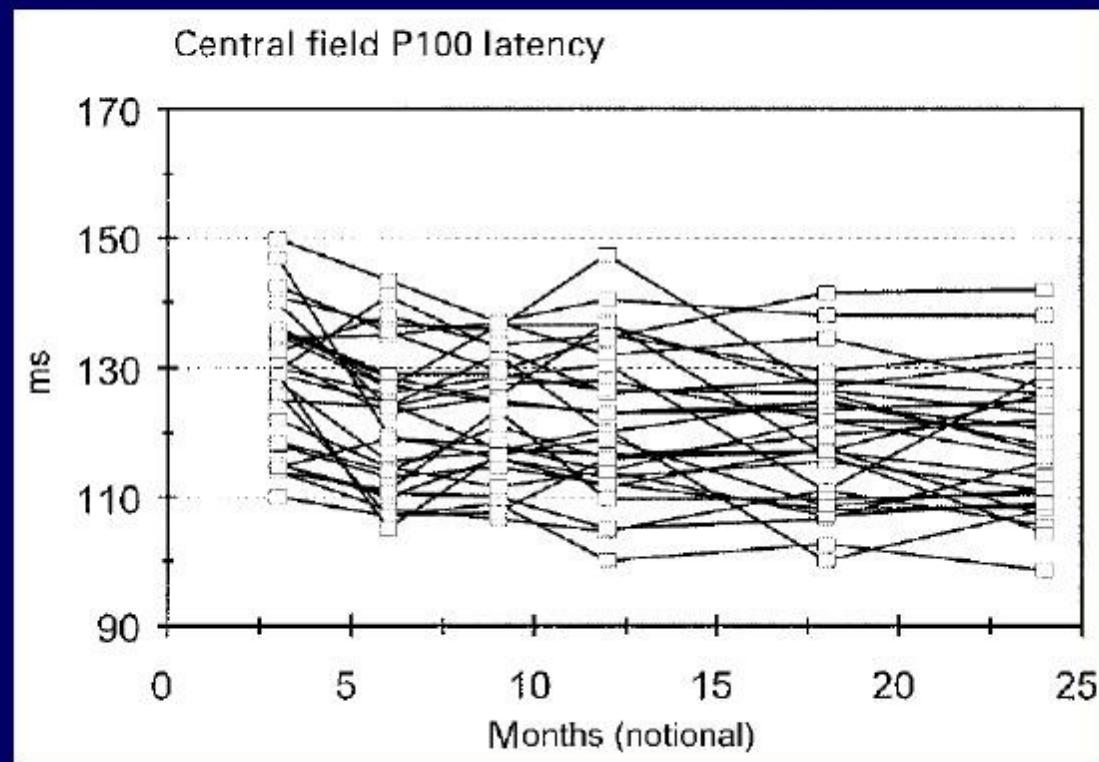
	MRI	N	P	total
		N	P	
		15	6	21
		10	19	29
		25	25	50

from Davies et al., 1998

Clinical/neurophysiological/MRI discrepancies in ON

- patients who fully recover from ON usually have persistent VEP delays
- VEP may be abnormal in asymptomatic eye
- asymptomatic MRI lesions can be detected in optic nerve which also display a normal VEP

Long-term improvement of VEP latency Remyelination? Ion channel reorganization?



EP indicators of MS progression

a) significant increase of latency

* > maximum interside difference

* > mean test/retest difference + 2SD

b) loss of a major EP component

c) new morphological abnormalities

Abnormalities must be confirmed in 2 successive tests; test interval > 3 months

Role of neurophysiology in MS

- Diagnosis
- Monitoring
- Pathophysiology

Clinical Utility of EPs in MS

- to objectivate the involvement of sensory and motor pathways in patients who complain of vague and indefinite disturbances
- to demonstrate clinically silent lesions
- to have pathological indications (demyelination, axonal degeneration)

Factors increasing EPs sensitivity in MS

- Hyperthermia (Matthews et al 1979)
- Rate of stimulation (Stockard and Rossiter 1977)
- Manipulation of stimuli (Emerson et al 1982; Maureer et al 1985; Sand 1991; Regan et al 1982; Kant et al 1988)
- Additional EPs parameters

Role of EPs in estimating disease severity

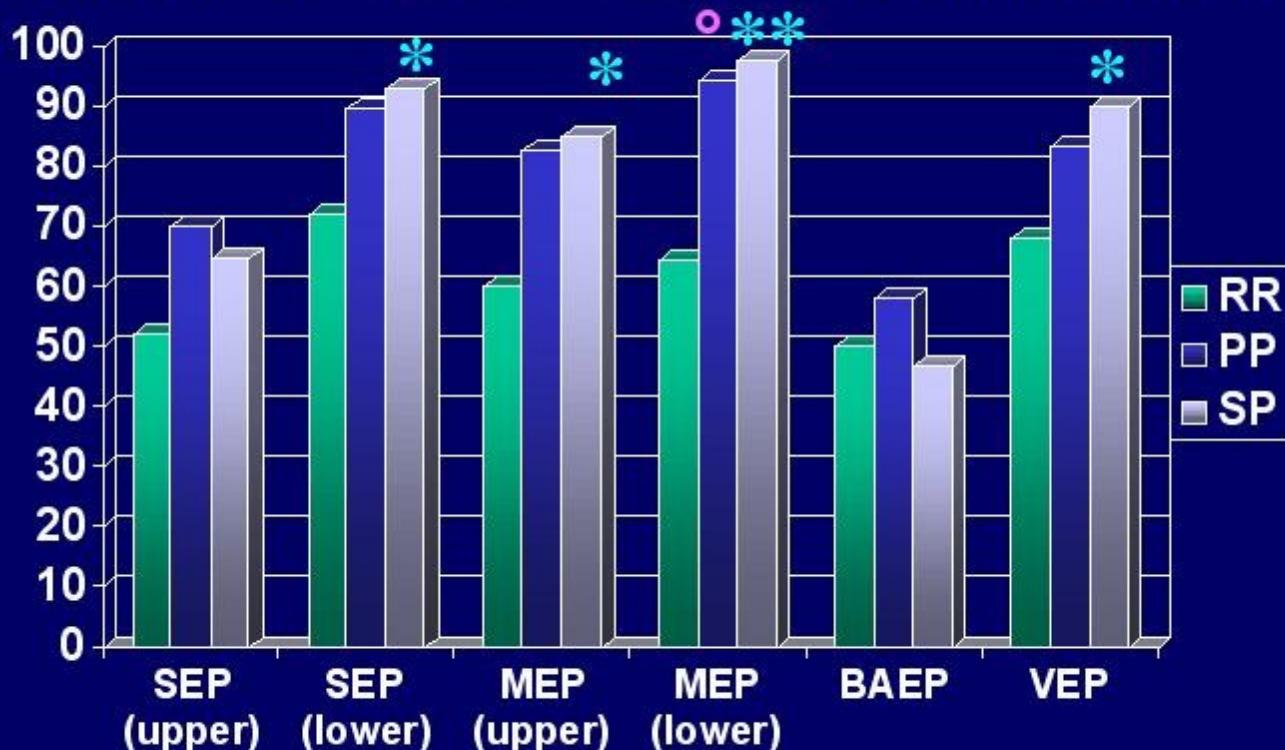
Correlations between clinical and neurophysiological findings

Frequency of abnormalities of multimodal EPs

%	Benign MS	Secondary Progressive MS	p Value*
VEP	46	83	n.s.
BAEP	15	70	0.02
MSEP	5	91	0.001
TSEP	50	100	0.01
MEP upper	17	100	0.001
MEP lower	33	100	0.004

* Chi-square

FREQUENCY OF EP ABNORMALITIES (%) in clinically definite MS (n. 116: 50 RR, 48 SP, 18 PP)



PP vs RR: \circ $p < 0.02$

SP vs RR: * $p < 0.02$; ** $p < 0.001$

Frequency of EP abnormalities in MS

related to:

- length of the explored pathways
- preferential location of MS lesions

Comparison between EPs and MRI sensitivity in Detection of MS activity

MRI > EPs in:

brain

brainstem

spinal cord

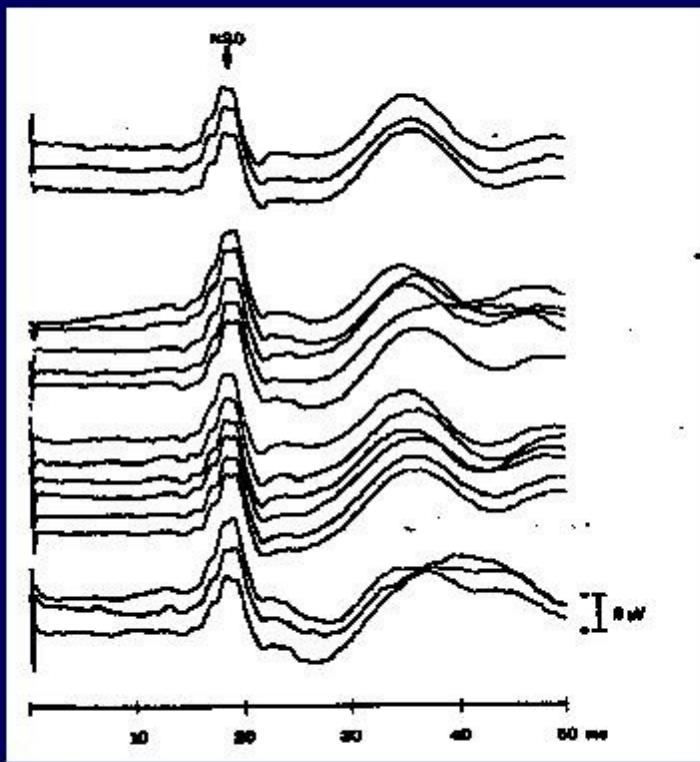
EPs \geq MRI in:

optic nerve

Requirements paraclinical tests for MS monitoring

- **Precision**
- **Accuracy**
- **Reproducibility**
- **Sensitivity to biological changes**

EP reproducibility



Andersson and Persson, 1990

Requirements for EPs utilization in MS monitoring

- **to monitor disease activity**
sensitivity to MS lesions
- **to monitor disease progression**
correlation with impairment and disability
correlation with nervous damage

Limits of EPs in detecting disease activity

- To produce electrophysiological changes the lesion
 - must affect a sensory/motor pathway
 - must involve a significant proportion of fibres in the nervous pathway
 - must produce conduction block or axonal degeneration
- It is necessary to compare the results of the actual test with the results of the previous test
- The response of the previous test must be present

Role of EPs in estimating worsening of function

PATIENTS

Clinically defined MS

N: 116 (69 F, 47 M)

Age: 38.1 ± 9.8 yrs

Clinical course: 50 Relapsing-Remitting (RR)

48 Secondary Progressive (SP)

18 Primary Progressive (PP)

EDSS (basal): 4.23 ± 1.6

Follow-up: 30.8 ± 12 months

Disease duration: 8.2 ± 6.7 yrs

EP SCORES

- 0 = normal
- 1 = abnormal latency or amplitude
- 2 = abnormal latency and amplitude of
a major component
- 3 = absence of a major component

EPs Score (116 MS pts)

	RR (n=50)	PP (n=18)	SP (n=48)
SEP	$4.3 \pm 3.8^{\circ*}$	7.3 ± 2.4	6.4 ± 3.3
MEP	$2.7 \pm 2.8^{**}$	5.3 ± 3	5.3 ± 2.3
VEP	$2.3 \pm 2.2^*$	3.2 ± 1.8	3.5 ± 1.9
BAEP	1.2 ± 1.7	1.6 ± 1.9	1.5 ± 1.8
Glob. EP	$10.4 \pm 7.8^{\circ*}$	17.2 ± 5.5	16.0 ± 6.0

SP VS RR: * $p < 0.05$

PP vs RR: $\circ p < 0.05$

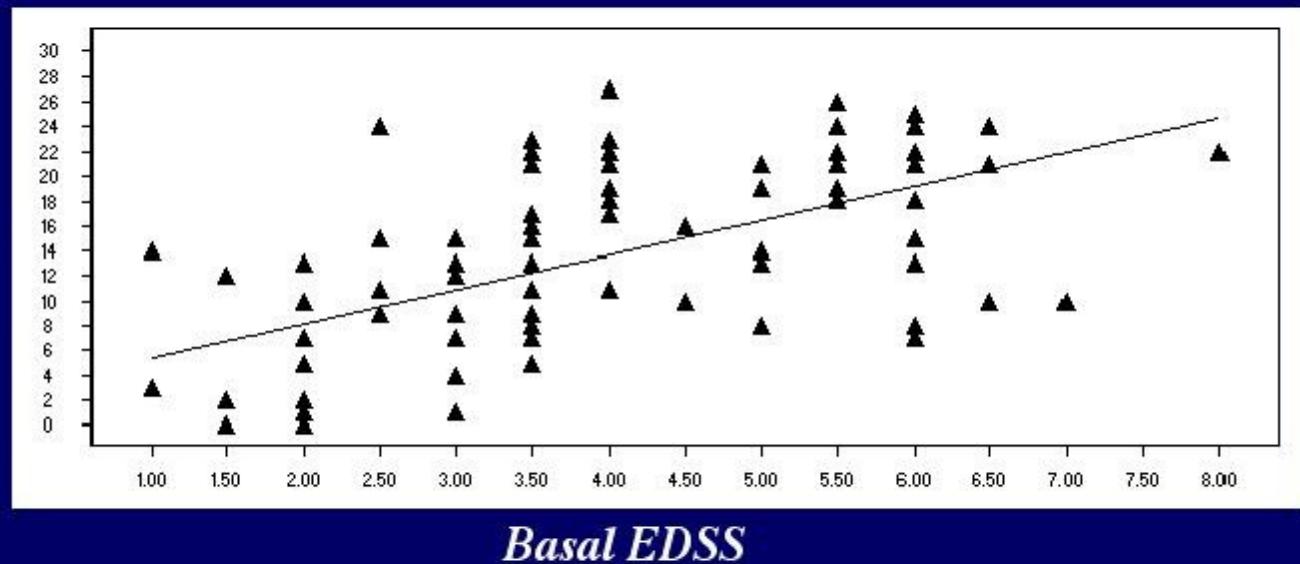
** $p < 0.01$

EPs - EDSS correlation

	EDSS basal	EDSS final	Diff.
SEP	<0.0001	<0.0001	0.048
MEP	<0.0001	<0.0001	n.s.
VEP	0.0002	0.0004	n.s.
BAEP	0.02	n.s.	n.s.
Glob. EPs	<0.0001	<0.0001	n.s.

Basal global EP score vs basal EDSS

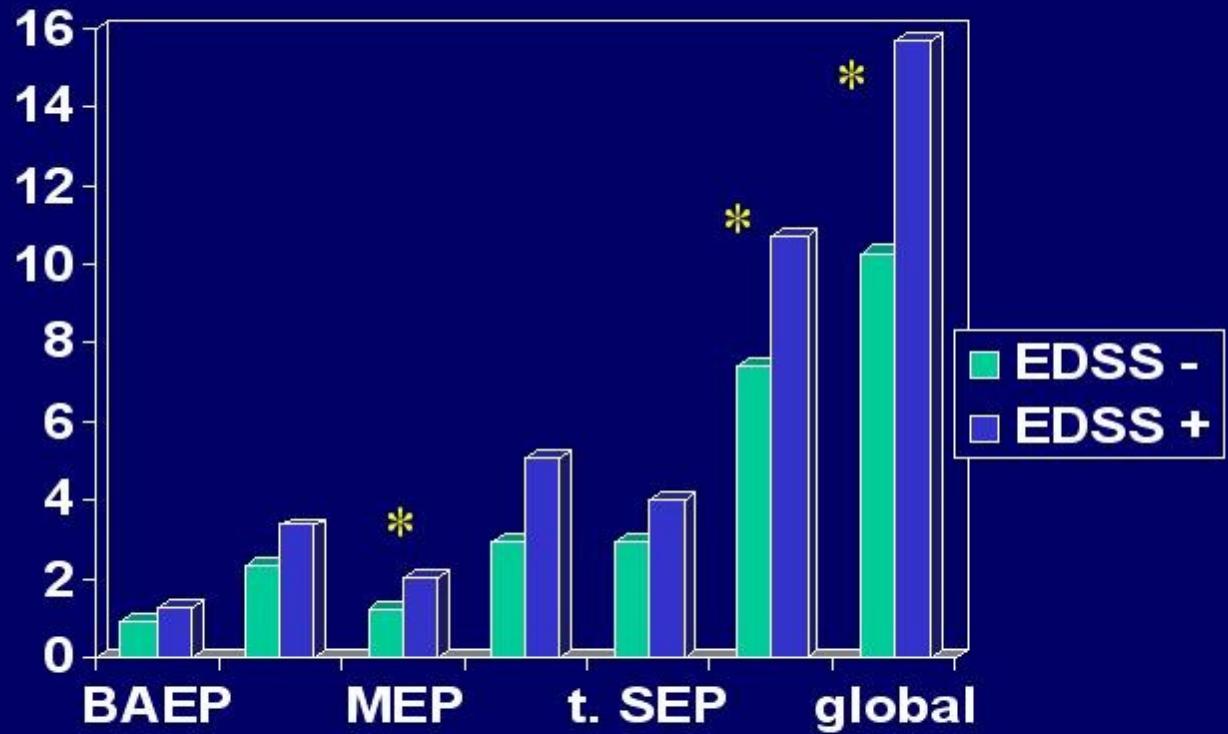
Basal global EP score



N=84

R=0.6; p<0.0001 (Spearmann rank correlation)

Basal EPs and changes in disability at follow-up



□ EDSS + ▲ 1 if basal EDSS < 5
 ▲ 0.5 if basal EDSS ≥ 5

EPs as outcome measure in MS clinical trials: PROS

- Direct measure of the function of sensory-motor pathways
- Good correlation with EDSS and related FS
- Sensitive to subclinical change
- Sensitive in spinal cord and optic nerve (\geq MRI)

EPs as outcome measure in MS clinical trials: CONS

- **High variability among labs**
- **Low sensitivity to disease activity**
- **Increased test-retest variability in MS pts**
- **No proportionality between EP changes and disease progression**

- EPs are more strictly related to function than MR measures
- “floor and ceiling” effects limit their value in the early and late phases of MS

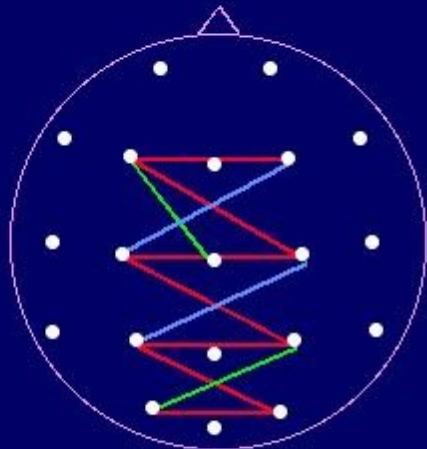
- EPs may help interpreting anatomical findings and may be used for detecting demyelination *in vivo* (delayed potentials)
 - Distinction between axonal loss (permanent) and conduction block (transient) needs repeated recording

Neurophysiological markers of
remyelination are lacking

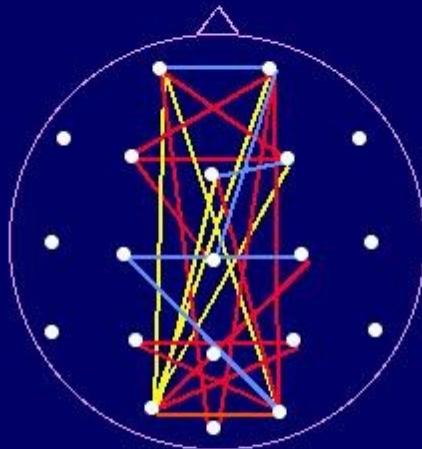
Axonal loss and cortical disconnection

COHERENCE

T-test MS (21) vs Normals (22); decrease only



Theta (4-8 Hz)



Alpha (9-12 Hz)

— $p < 0.0005$ (significant if Bonferroni corrected; temporal excluded)

— $0.0005 < p < 0.02$

— $0.02 < p < 0.03$

— $0.03 < p < 0.05$

Leocani et al 2000

MS disease unit

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