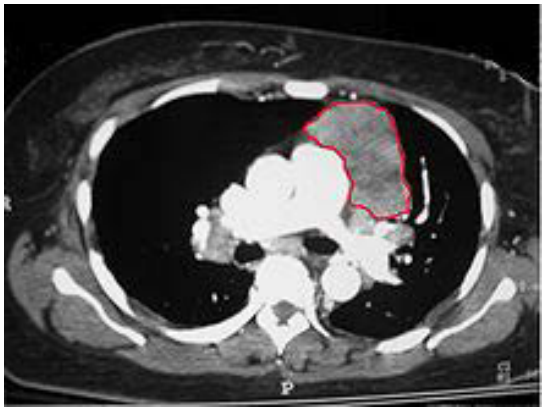
Neuromuscular Meeting

Sydney

November 15-16

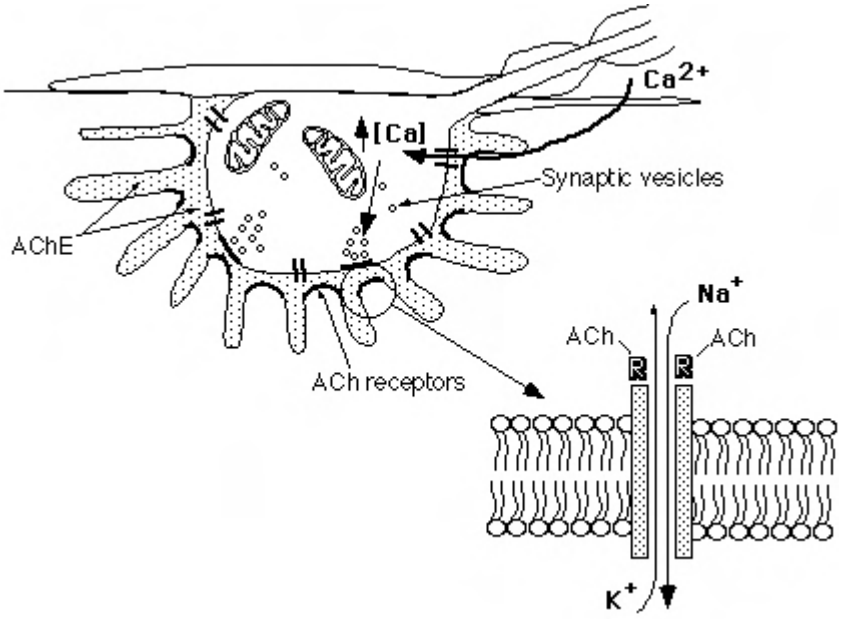
Neurophysiological assessment of neuromuscular junction disorders

- Anatomy
- Concepts of decrement
- Separation of NMJ disorders
- Practical SFEMG



Anatomy/Physiology of the NMJ

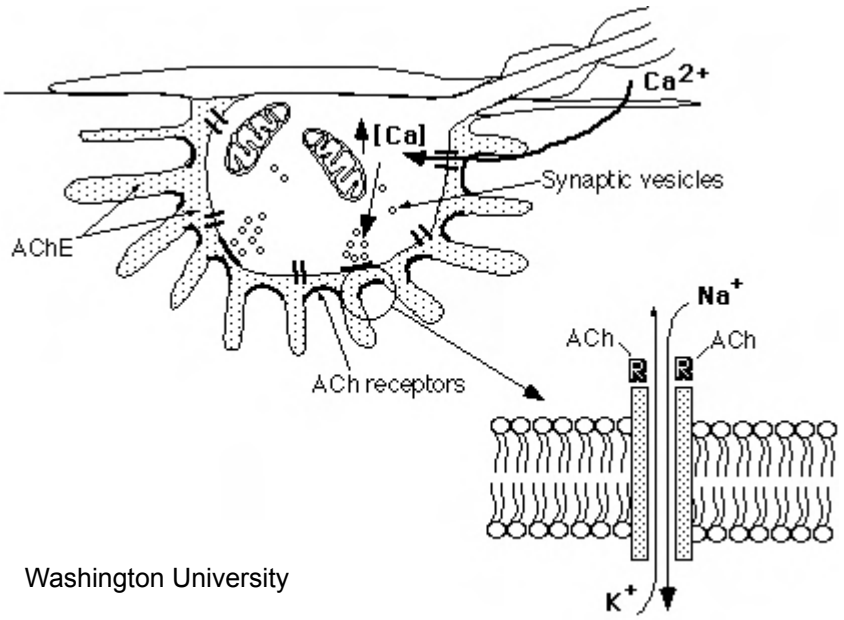
- Terminal axons with multiple branches of varying diameters in parallel
- 1,000-3,000 vesicles in active zones with each vesicle having 5,000-10,000 Ach molecules. Large store of vesicles not released
- Contents of one vesicle-quantum; synaptic vesicle release following AP – quantal content



Washington University

Anatomy/Physiology of the NMJ

- Following an action potential 50-100 synaptic vesicles released
- After binding to AchR, opening of ion channels with 1,000-5,000 channels/ quantum
- Each quantum of Ach generates an EPP
- If the combined EPP is above threshold, depolarisation occurs with muscle fibre action potential.

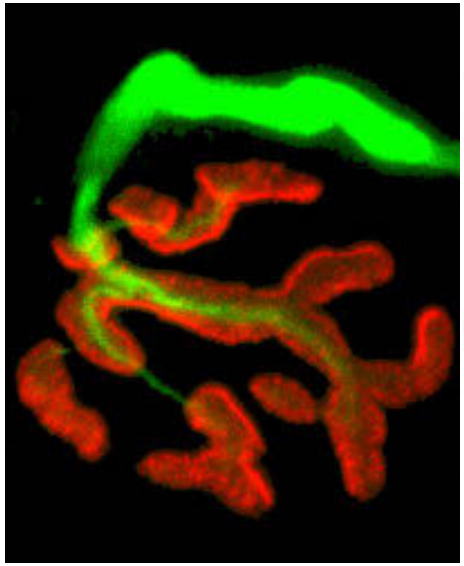


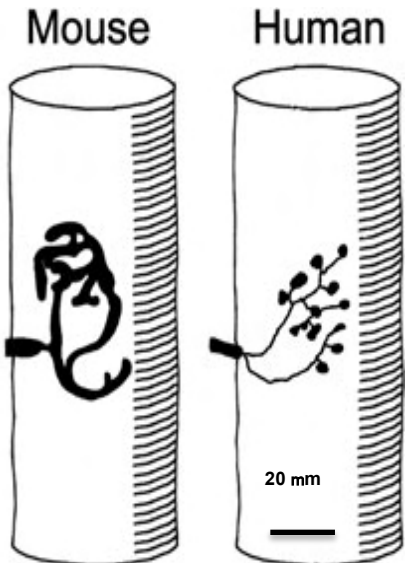
Washington University

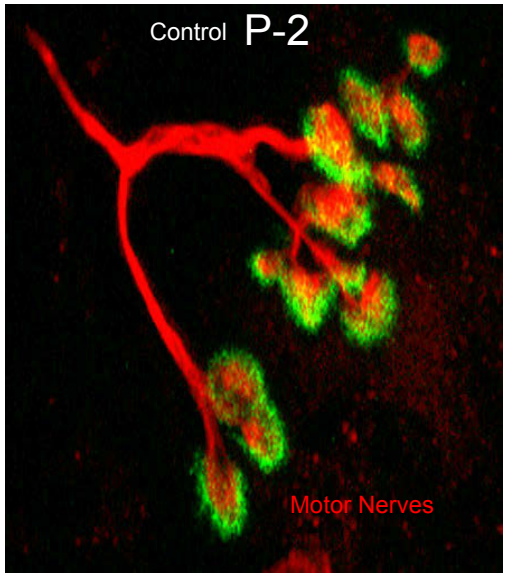
Physiology of the NMJ

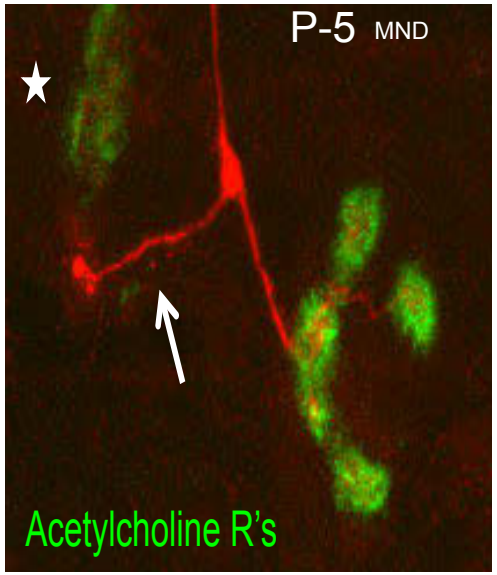
- Miniature end-plate potentials (MEPP) – end-plate noise representing spontaneous firing of one quanta of Ach at 0.2 Hz
- Corresponds to end-plate noise
- Therefore one quanta results in the activation of 1,000-2,000 AchR ~ 1 mV

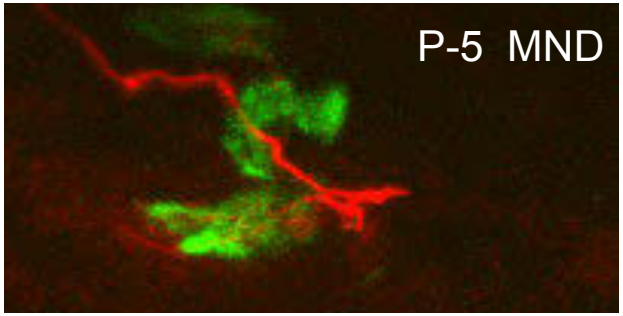
Mouse NMJs are very different in appearance to Human NMJs: implications for how we study the breakdown of pre- and post-synaptic elements of Human NMJs

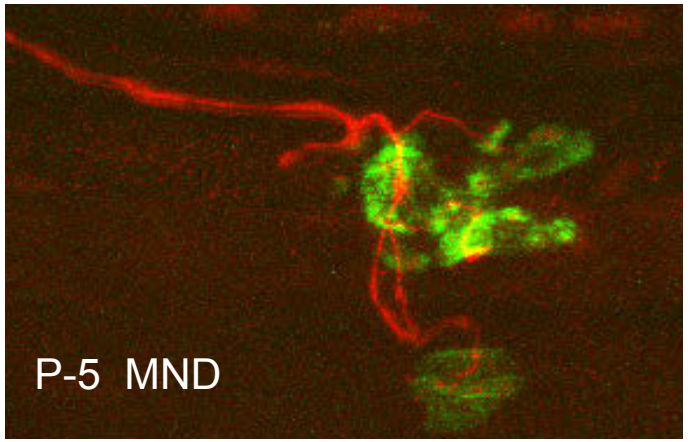












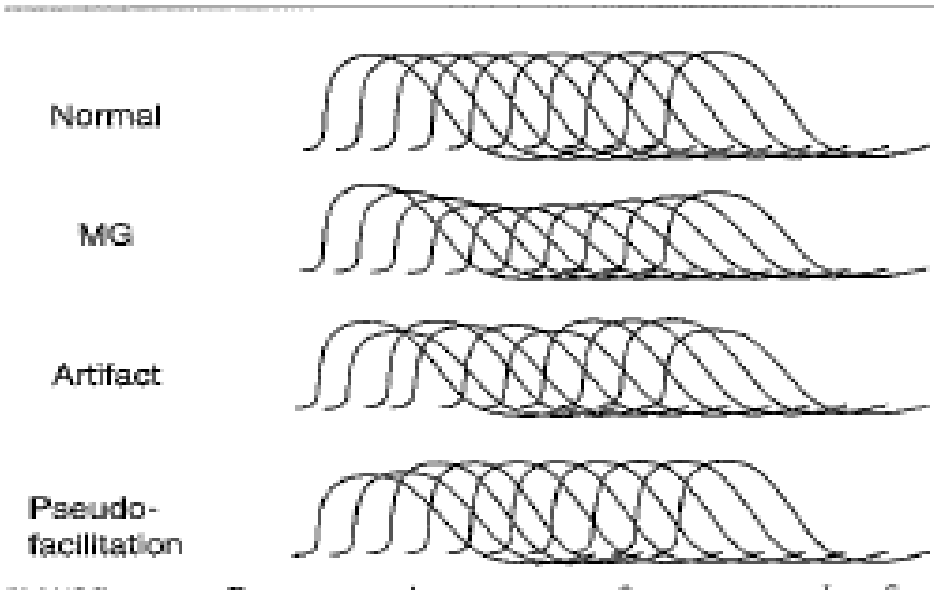
P 2– normal NMJs acetylcholine receptors in muscle.

P5 – Denervated muscle, motor axon sprouting and possible sings of acetylcholine receptor fragmentation.

Decrement

Good technique

- Avoid overstimulation
- Secure electrodes firmly
- Immobilisation of limb
- Audio on for exercise
- Recognise artefact
- Remember temperature
- Care with *baseline correct*



Decrement

NCS protocols

- **~60% of patients with MG will show a decrement (17% in ocular, up to 85% in generalised).**
- **More proximal nerves (accessory, facial, musculocutaneous, femoral) are probably more likely to show a decrement than distal (median, ulnar, peroneal) but have stabilisation difficulties.**
- **Decrement may be patchy and should preferably study more than 3 nerves.**
- **Withhold anticholinesterase for 12 hours**

AAEM practice topics in electrodiagnostic medicine (*Muscle Nerve* 2001; 24: 1239-47)

Areas of debate

- Train of 4, 5,10 stimuli?
- 2 Hz vs 3 Hz or higher?
- Exercise?
- How many nerves to study?

IS EXERCISE NECESSARY WITH REPETITIVE NERVE STIMULATION IN EVALUATING PATIENTS WITH SUSPECTED MYASTHENIA GRAVIS?

DEVON I. RUBIN, MD, and KENNETH HENTSCHEL, DO, PhD
Muscle Nerve 2007

Decrement in Normal Subjects

EFFECTS OF PROLONGED REPETITIVE STIMULATION OF MEDIAN, ULNAR AND PERONEAL NERVES

FUSUN BAUMANN, MD,[1] ROBERT D. HENDERSON, PhD,[1] FRED TREMAYNE, BSc,[1] NICOLE HUTCHINSON, BN,[1] and PAMELA A. McCOMBE, PhD[2]

[1] Department of Neurology, Royal Brisbane and Women's Hospital, Queensland, Australia
[2] Centre for Clinical Research, University of Queensland, Brisbane, Queensland. Australia

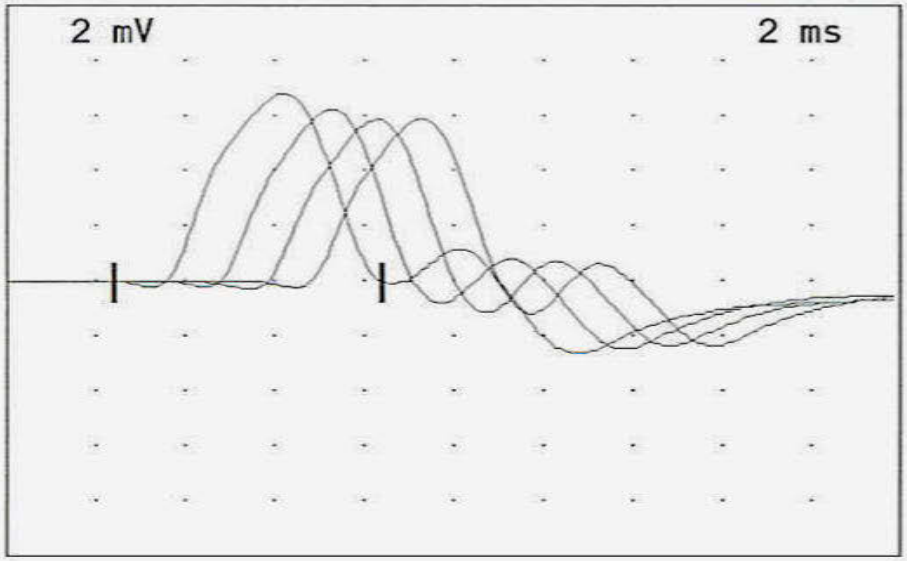
Muscle Nerve 2010

Concept of pseudofacilitation

Asawa T et al Muscle Nerve 2004

Measurement of CMAP area produces less ambiguous results than amplitude measurement in repetitive nerve stimulation studies.

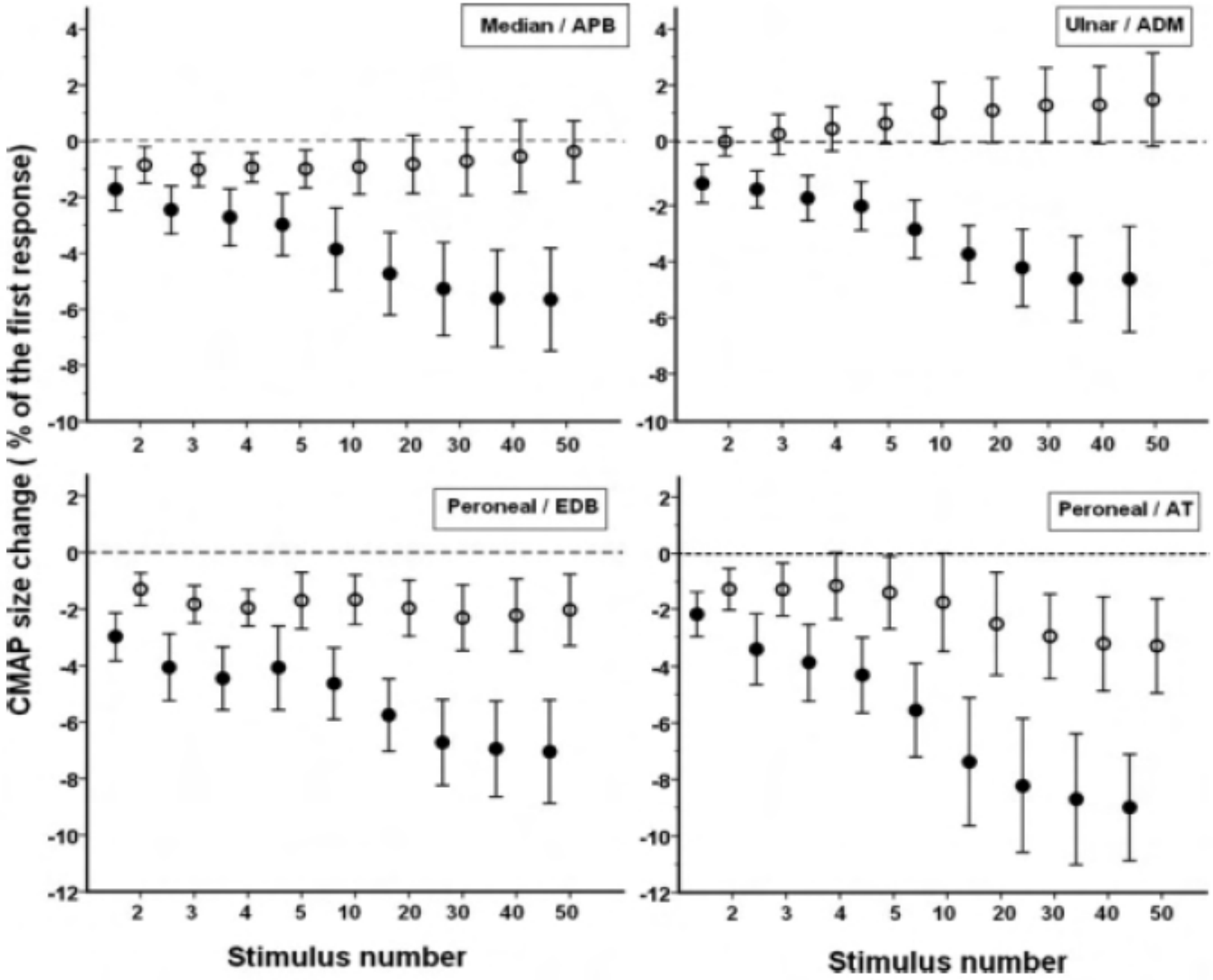
Muscle Nerve **29:** 724–728, 2004



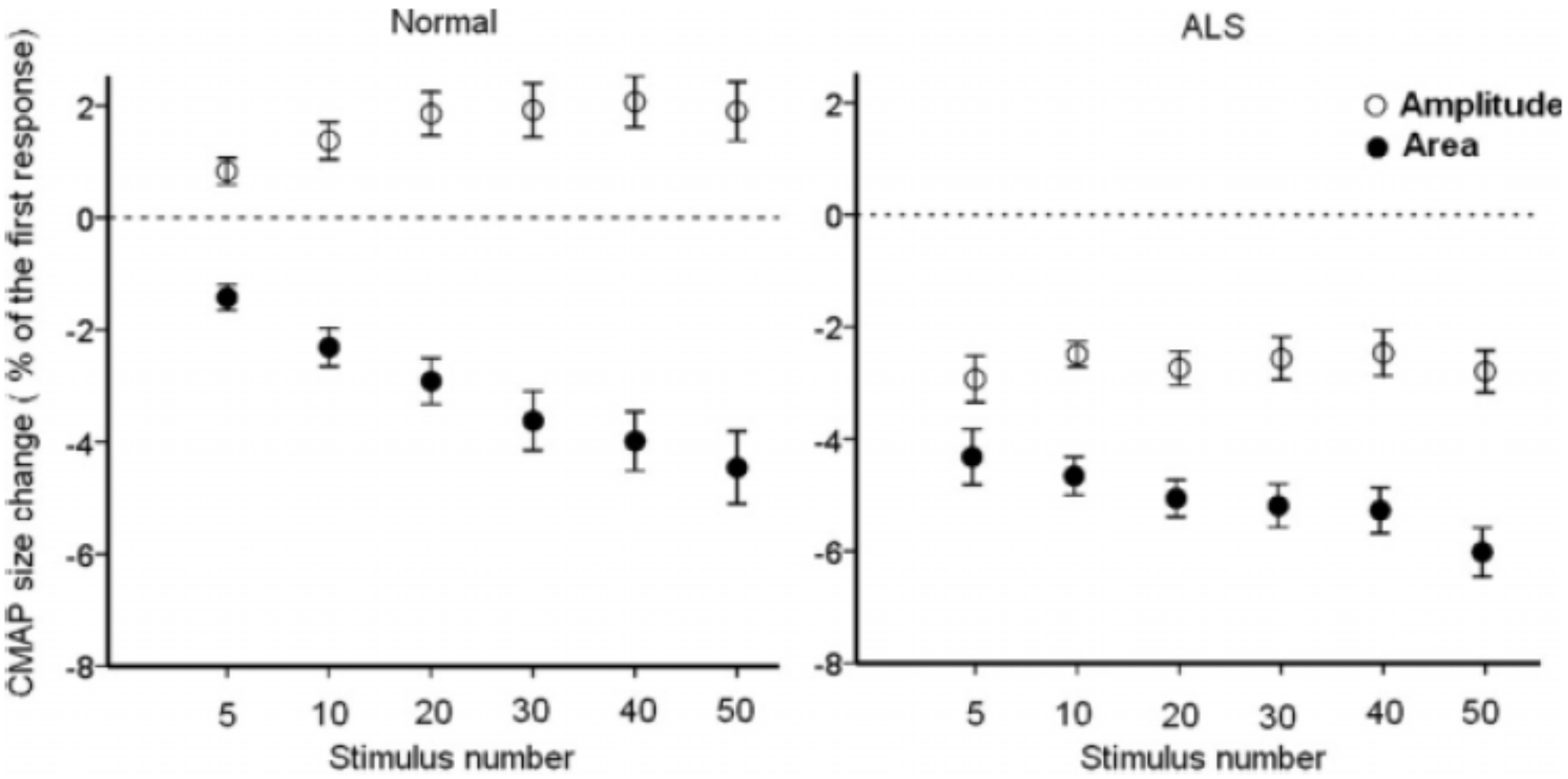
STIM.MODE: TRAIN / SINGLE

STIM FREQ: 2 Hz	NO. IN TRAIN: 10
STIM DUR: 0.1 ms	STIM RJCT: 0.5 ms
TIME: 09:53:15	
COMMENT:	

POT NO.	PEAK AMP mV	AMP. DECR %	AREA mVms	AREA DECR %	STIM. LEVEL
1	6.85	0	19.30	0	182V
2	6.27	8	16.40	15	182V
3	5.97	13	15.30	21	182V
4	5.94	13	15.30	21	182V
5					
6					
7					
8					
9					
10					


Median / APB
Ulnar / ADM
Peroneal / EDB
Peroneal / AT
CMAP size change (% of the first response)
Stimulus number
Stimulus number
4
2
0
-2
-4
-6
-8
-10
-12
2
3
4
5
10
20
30
40
50

Ulnar Nerve


Normal
ALS
CMAP size change (% of the first response)
2
0
-2
-4
-6
-8
5
10
20
30
40
50
Stimulus number
Amplitude
Area

CMAP decrement in acute denervation

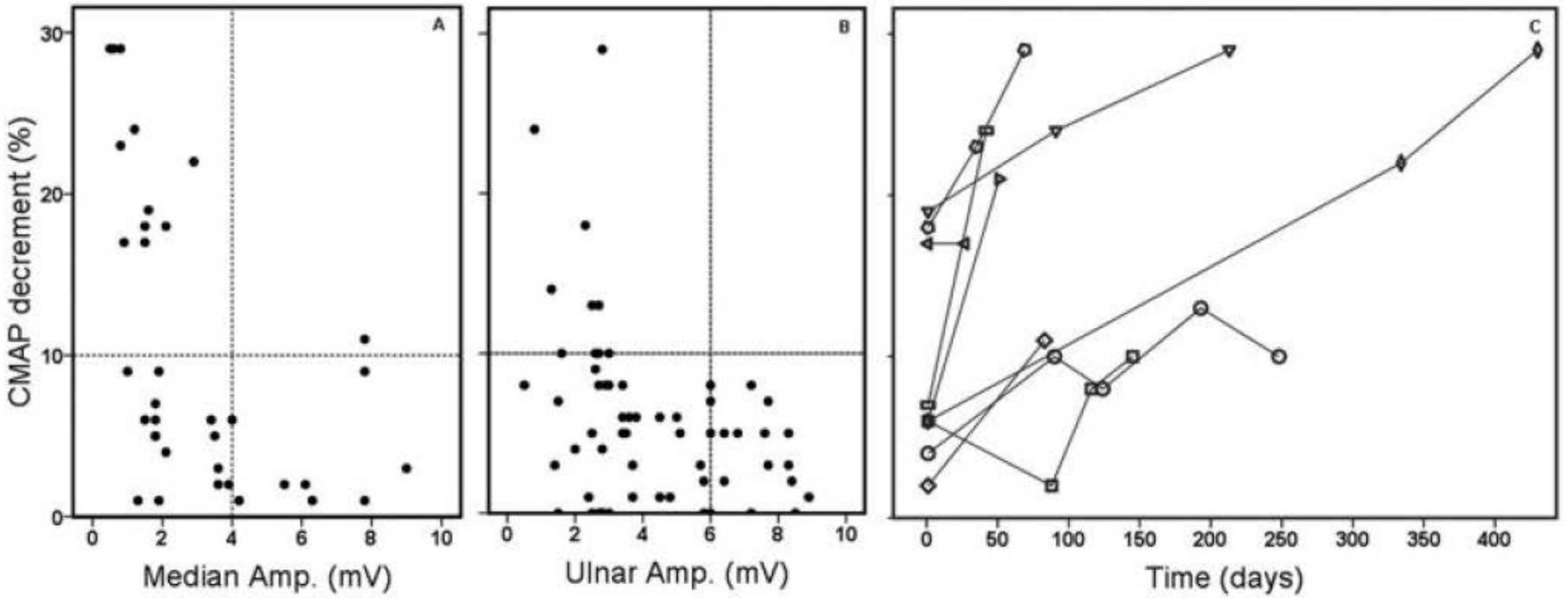
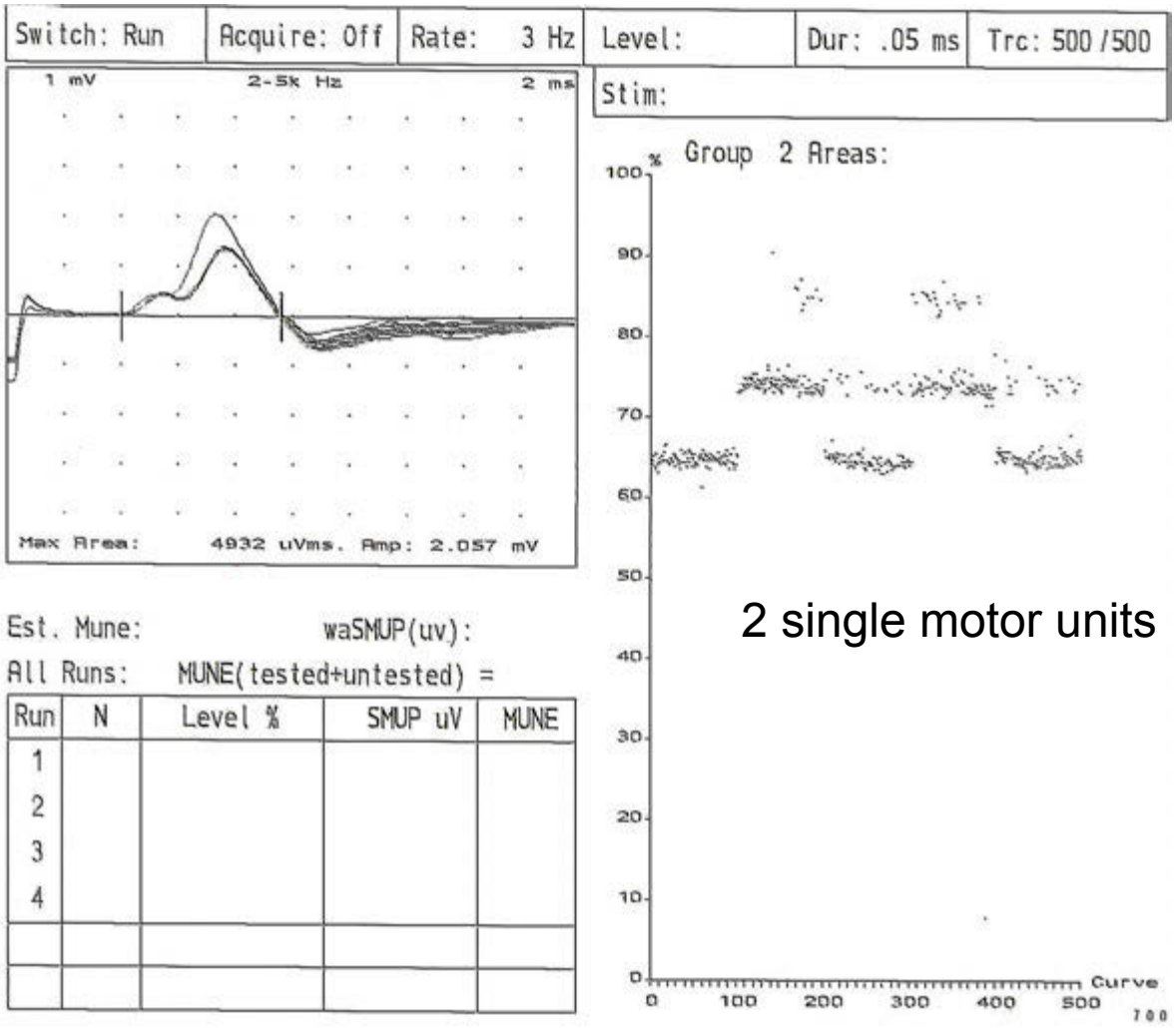


FIGURE 1. Scatterplots of the decrement and amplitude (Amp) of the compound muscle action potentials (CMAP) of the median **(A)** and ulnar **(B)** nerves; and the change in CMAP decrement over time **(C)**, where each symbol represents the value of the CMAP decrement at one timepoint and each line represents the trend in decrement for one subject.

Henderson et al; Muscle Nerve 2009

Decrement in ALS



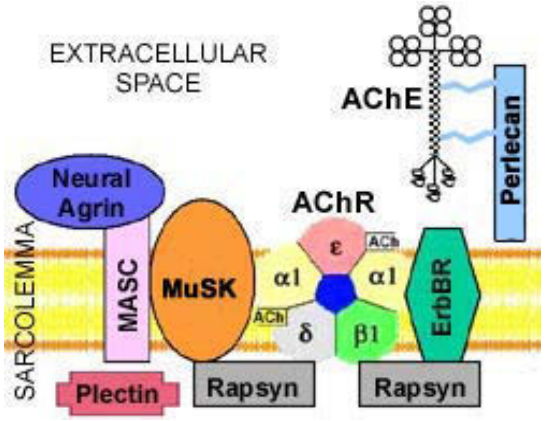
1 Hz vs 3 Hz

2 single motor units

Rate-dependent conduction block in terminal axons

Henderson, Daube Neurology 2004

Congenital myasthenia



- Many different types recognised
- Usually from birth
- Non-progressive, non- fatigable weakness
- Ptosis,ophthalmoplegia & facial weakness common
- Variable effect of Mestinon and little effect of other immune therapies
- Often familial involvement

- Abnormal RNS and SFEMG

LEMS v MG Case

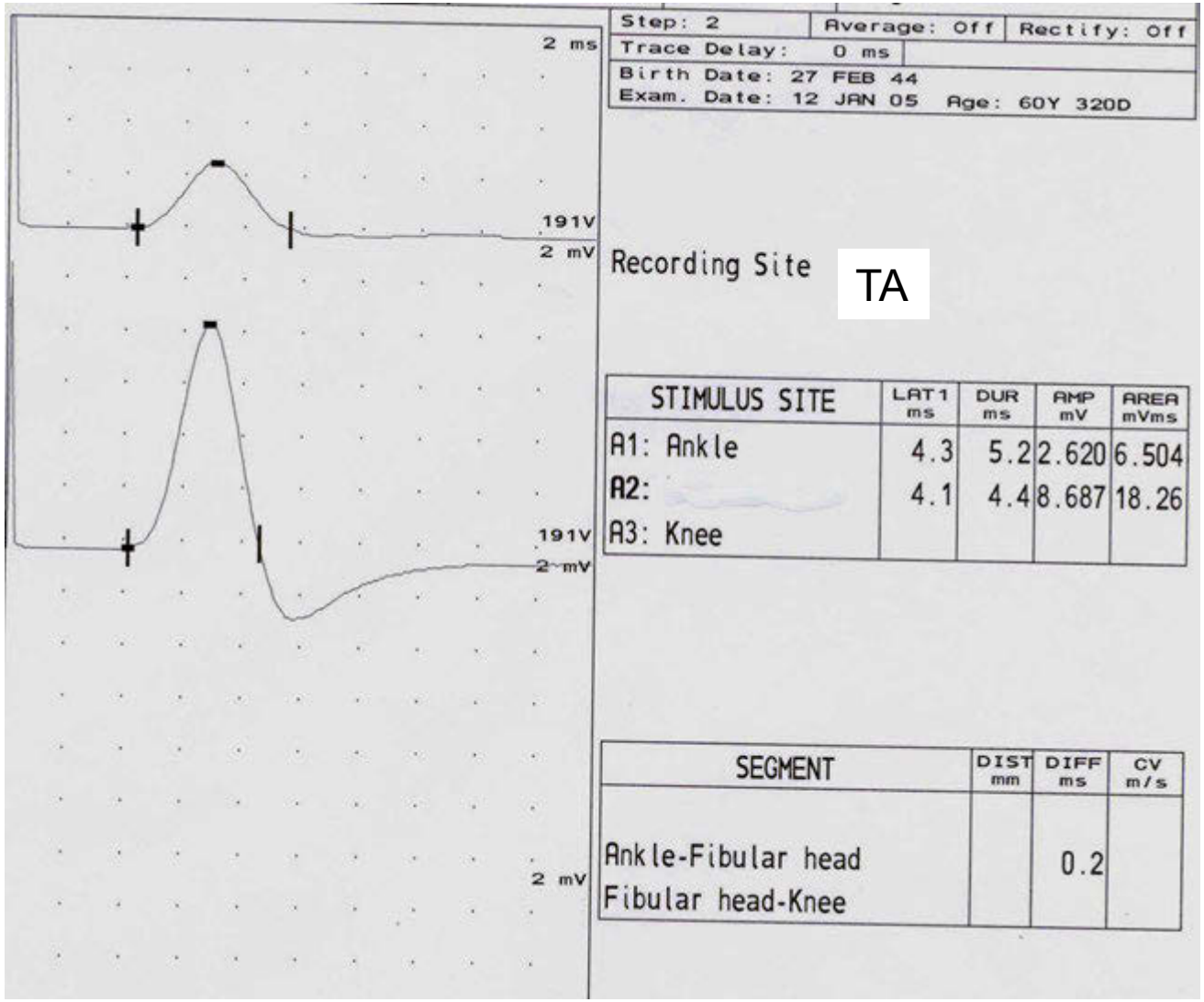
- 60 yo female
- Vague symptoms for 5 years- eg fatigable weakness in arms and legs, unusual ache/cramps in wrists/back/ thighs, mild diplopia, dry mouth.
- Past medical history of NIDDM for 7 years, pernicious anaemia.
- Medications: B12, Mestinon, Diaformin
- Ach Receptor Ab, MuSK Ab negative

LEMS v MG case

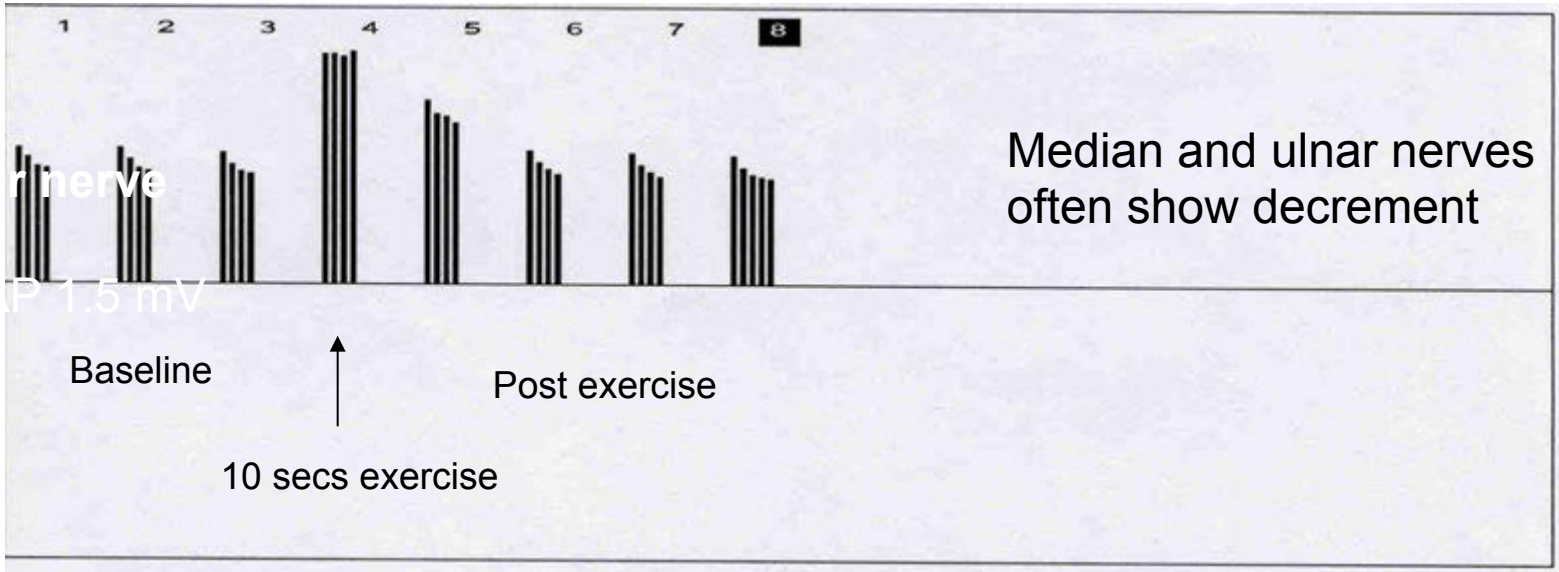
- **O/E:**
  - **No ptosis, diplopia or impairment of EOM**
  - **No definite weakness or fatigue**
  - **Reflexes difficult to elicit**

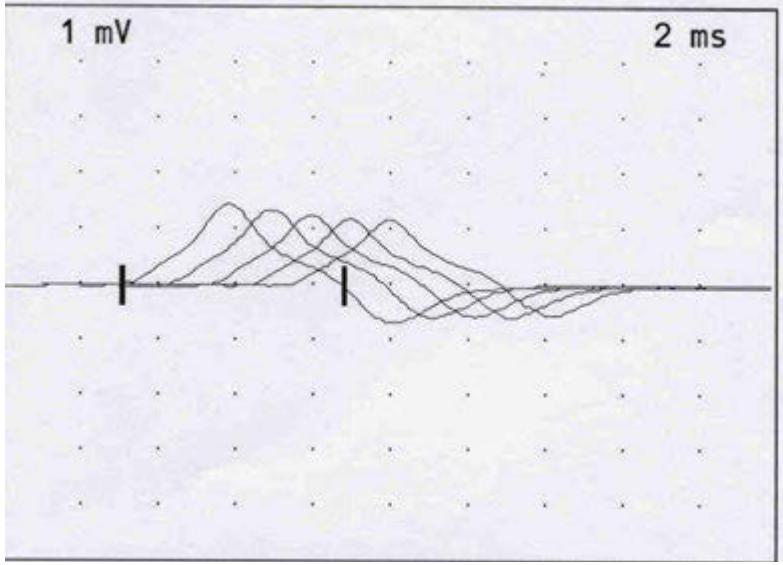
CT chest normal

Electrophysiology



Repetitive Stimulation





STIM.MODE: **TRAIN** / SINGLE

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STIM DUR: 0.1 ms	STIM RJCT: 0.5 ms
TIME: 09:23:53	
COMMENT:	

POT NO.	PEAK AMP mV	AMP. DECR %	AREA mVms	AREA DECR %	STIM. LEVEL
1	1.48	0	3.65	0	197V
2	1.36	8	3.57	2	197V
3	1.28	14	3.27	10	197V
4	1.24	16	2.99	18	197V
5	1.21	18	3.01	18	197V
6					
7					
8					
9					
10					

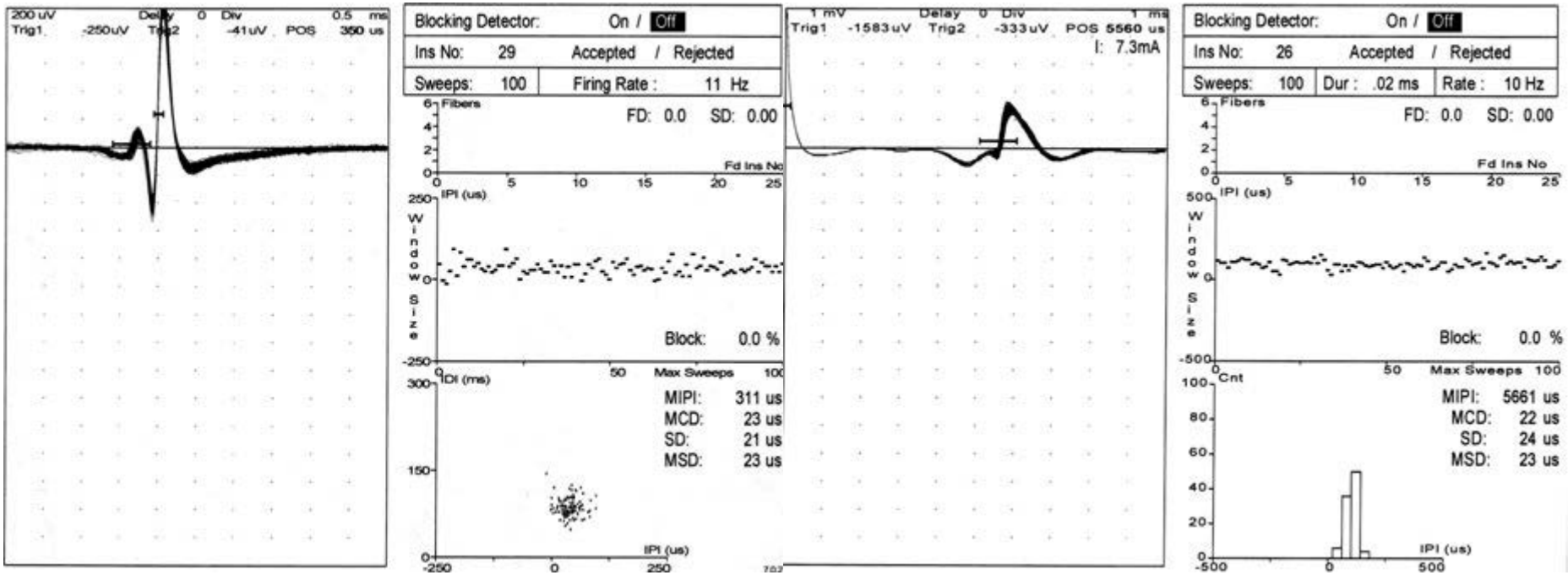
LEMS info

- **Autoimmune disease against the voltage-gated calcium channels on the pre-synaptic nerve terminal**
- **Rarely reported in children; More common in males**
- **Associated with malignancy in 50% (small cell lung), up to 3% of SCLC may have LEMS. PET scan now test of choice??**
- **VGCC antibody positive in majority**

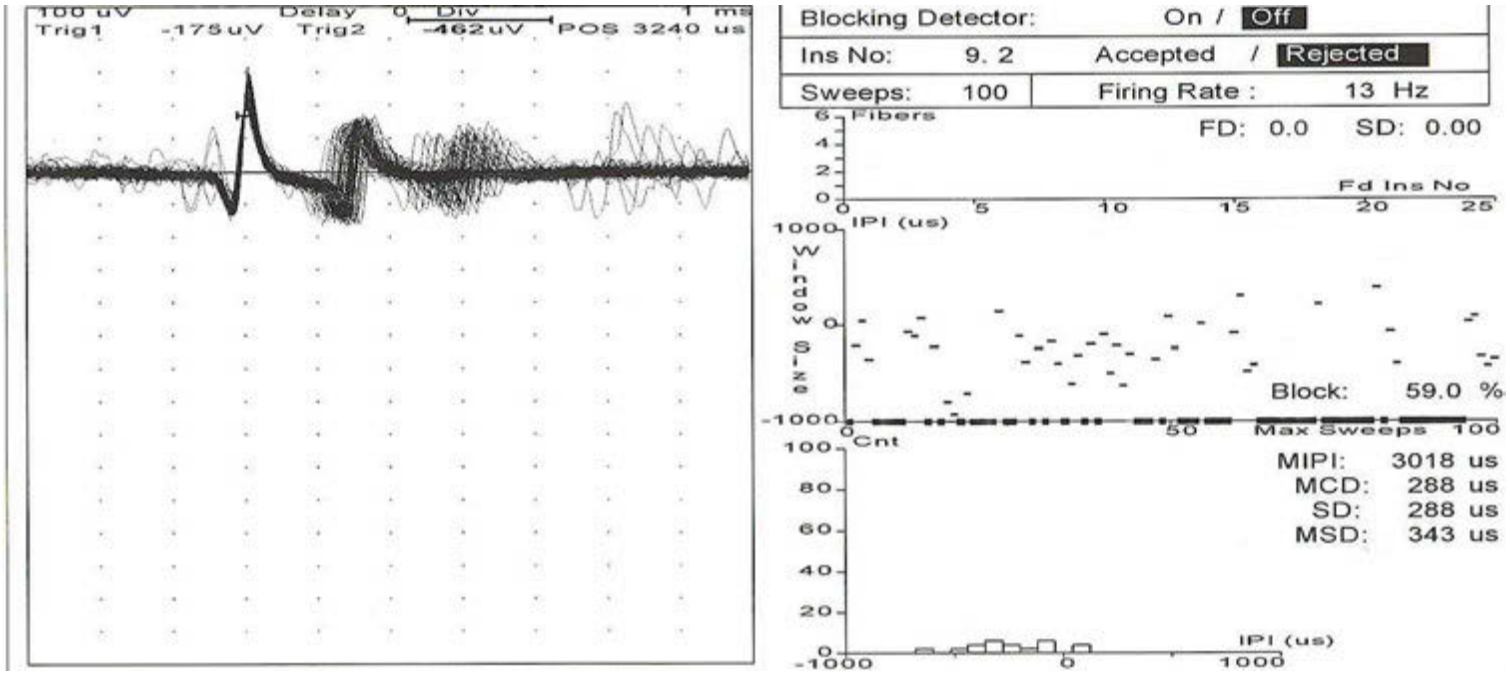
- **3,4 diaminopyridine effective**

Single fibre EMG

- Voluntary v stimulated
- Standard techniques- amplitude >200 uV, rise time less than 300 us
- Normal values dependent on muscle - 30 +/- 5 us (published values)



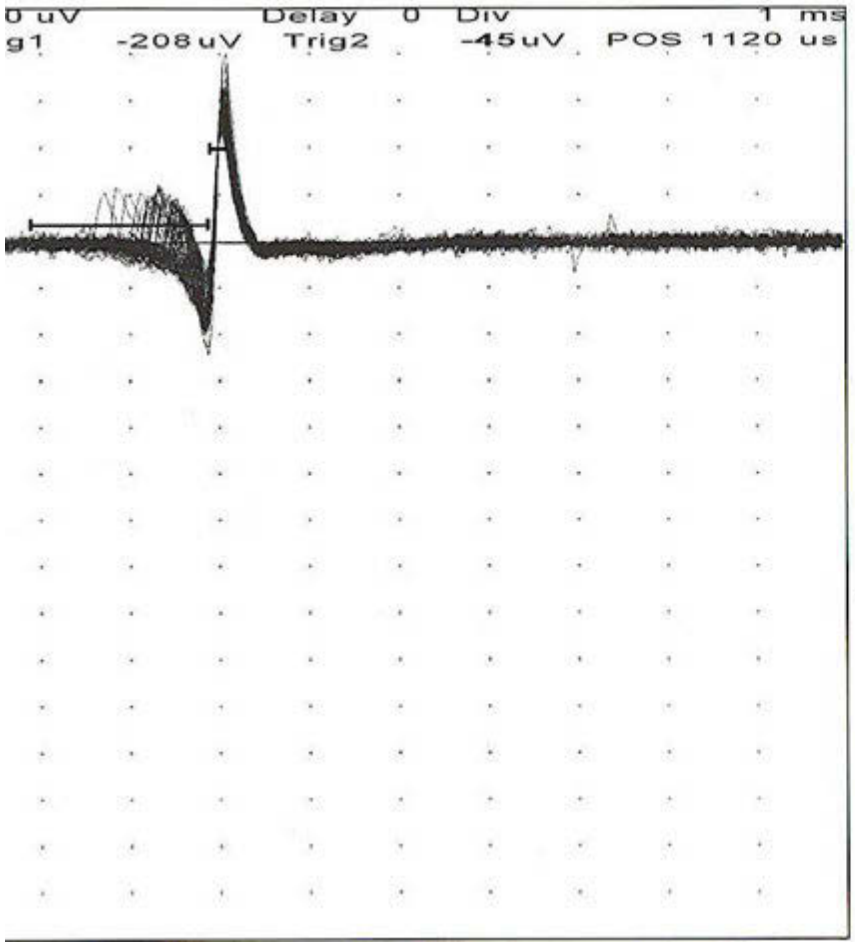
Single fibre EMG

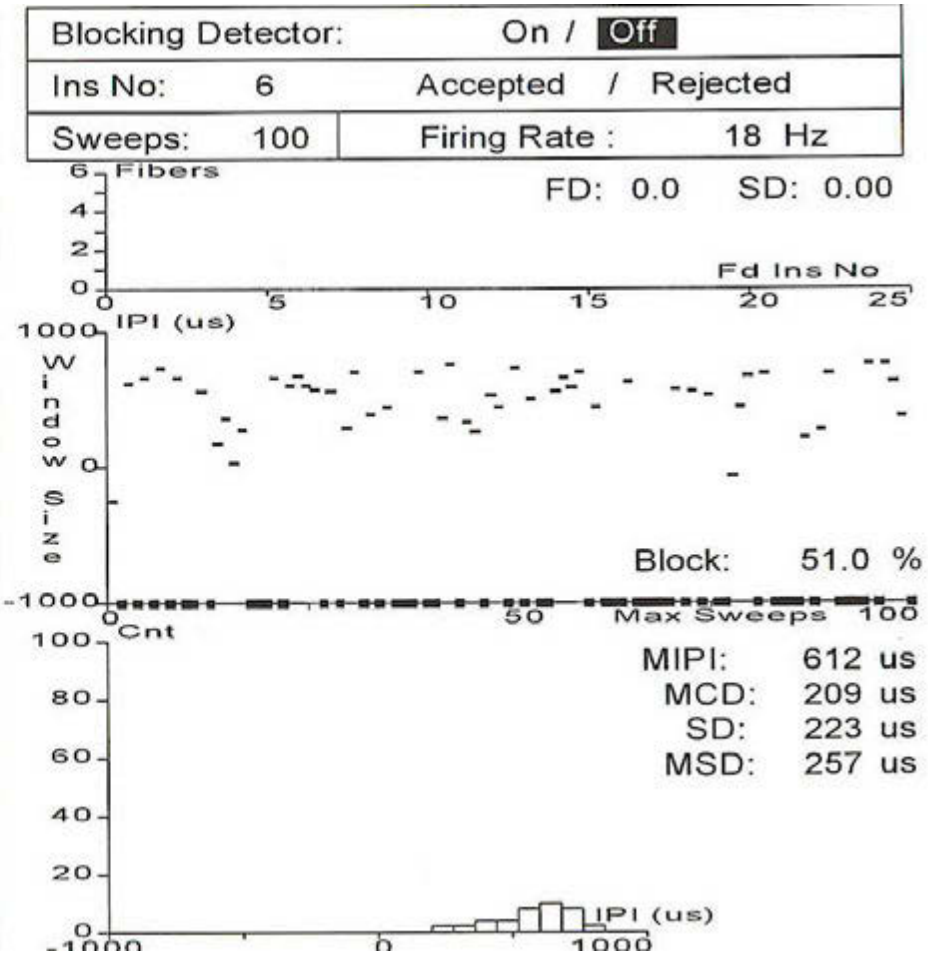


- Use MCD of interpotential interval (IPI)
- Variable firing rate falsely increases MCD
- Care with long IPI (>4ms) or very short
- If MCD/MSD >1.25, use MSD

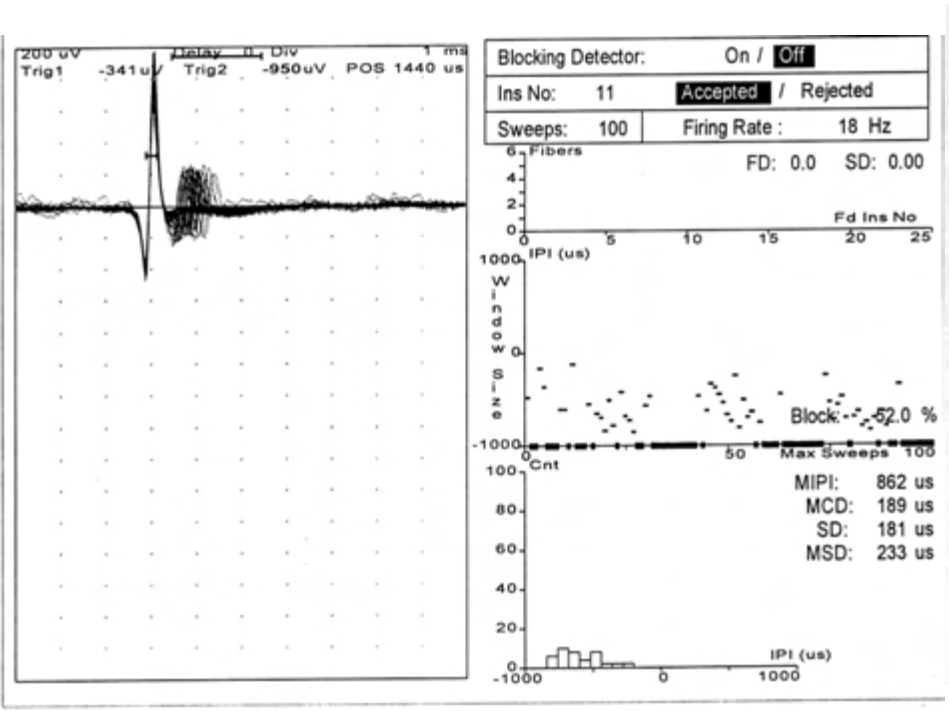
Single fibre EMG

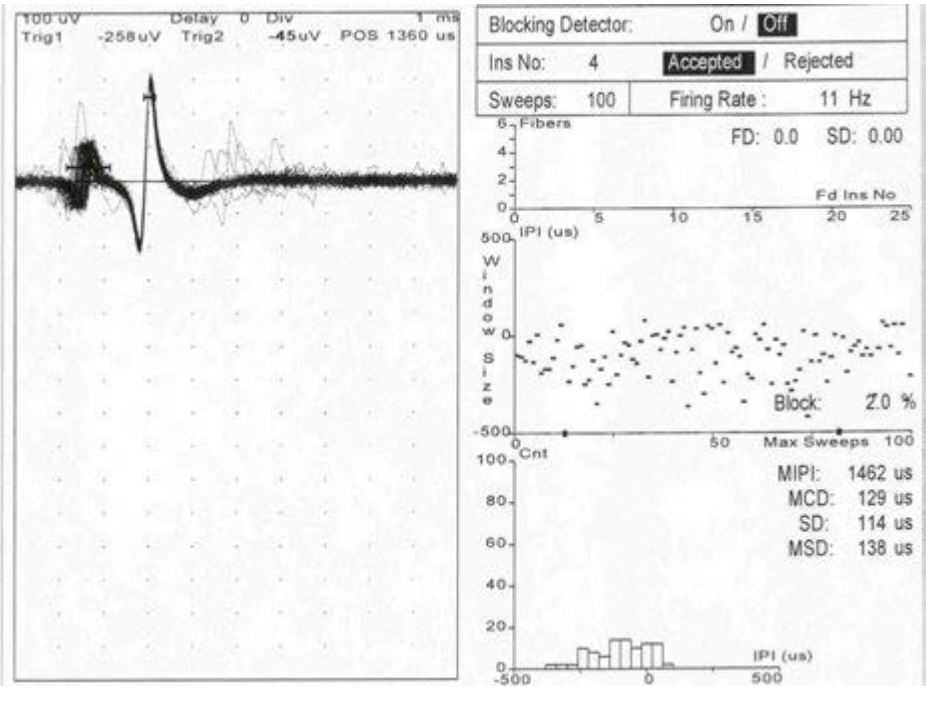
- Blocking usually associated with increased jitter of >80-100 ms





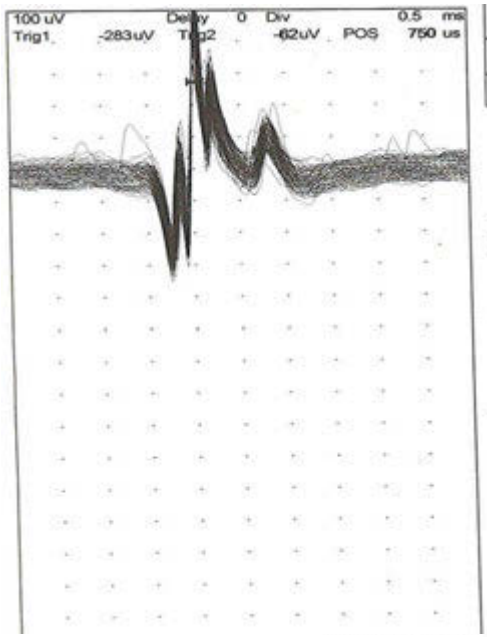
What's abnormal?

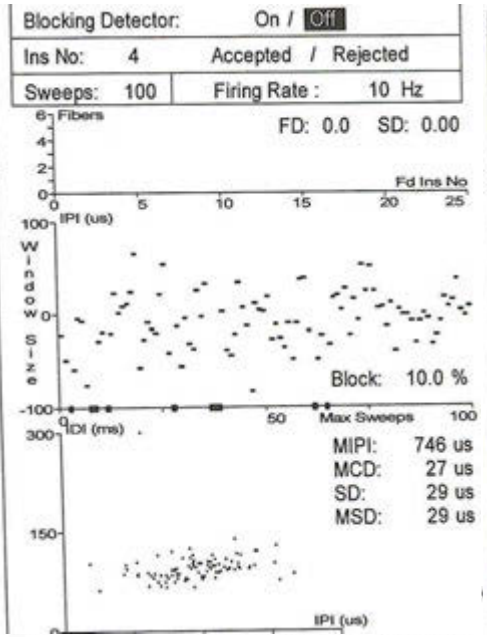


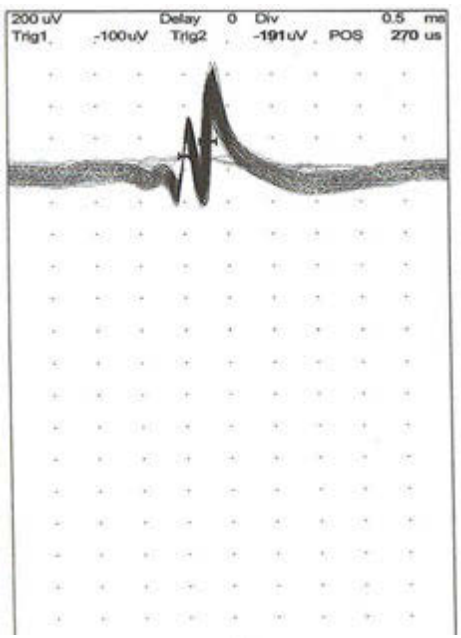


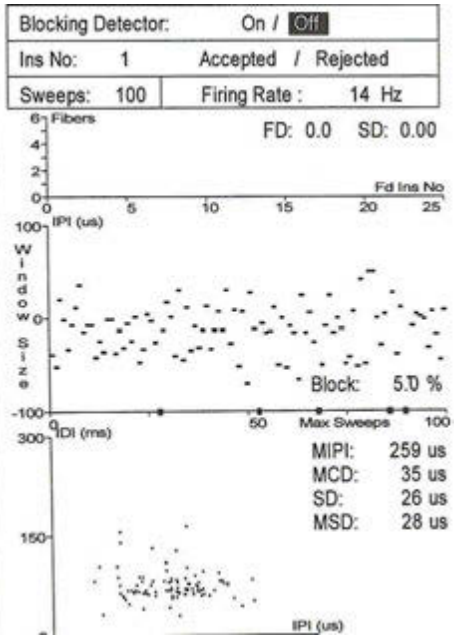
- MCD > 55 us in any fibre pair
- Greater than 10% of fibre pairs blocked
- Preferably collect 20 pairs
- Blocking (that is not technical!)

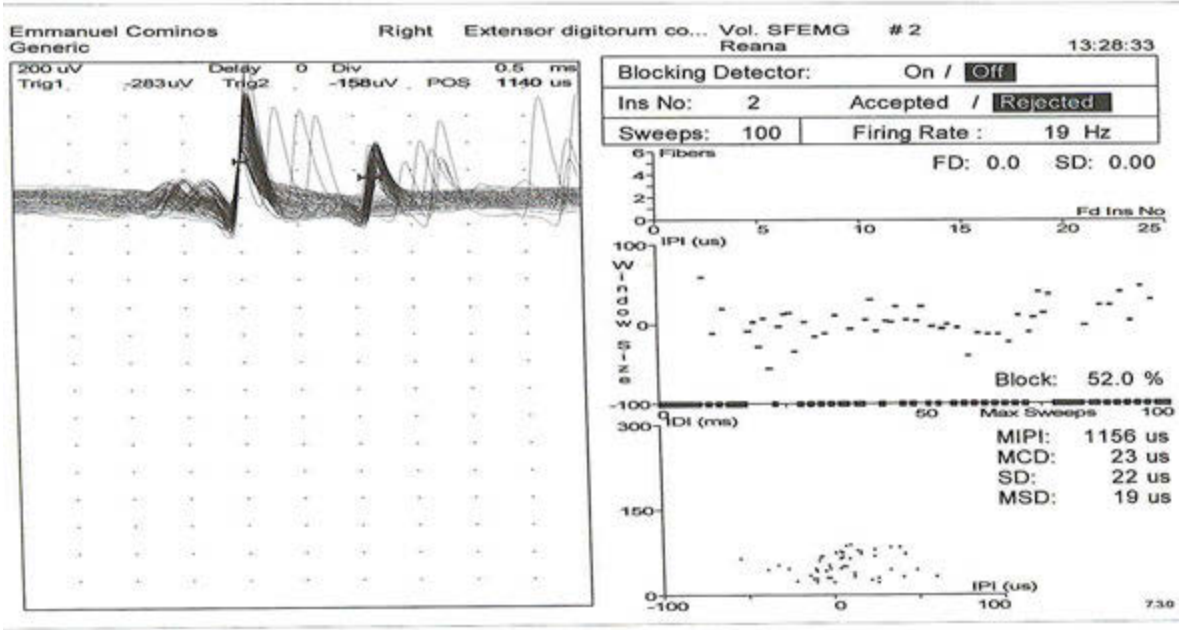
Concentric Needle – “OFEMG”









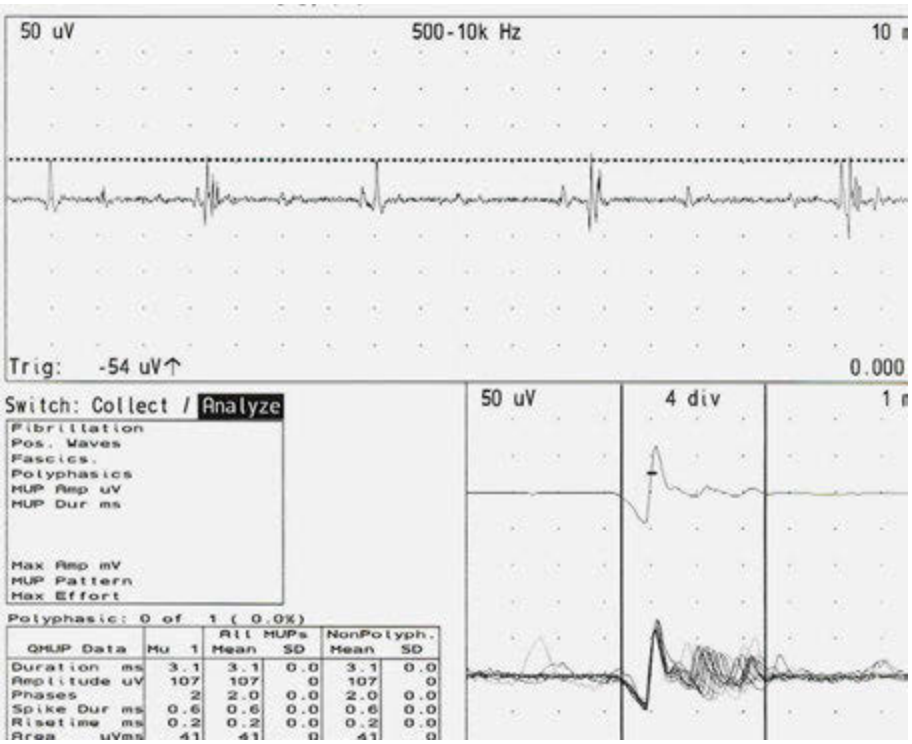


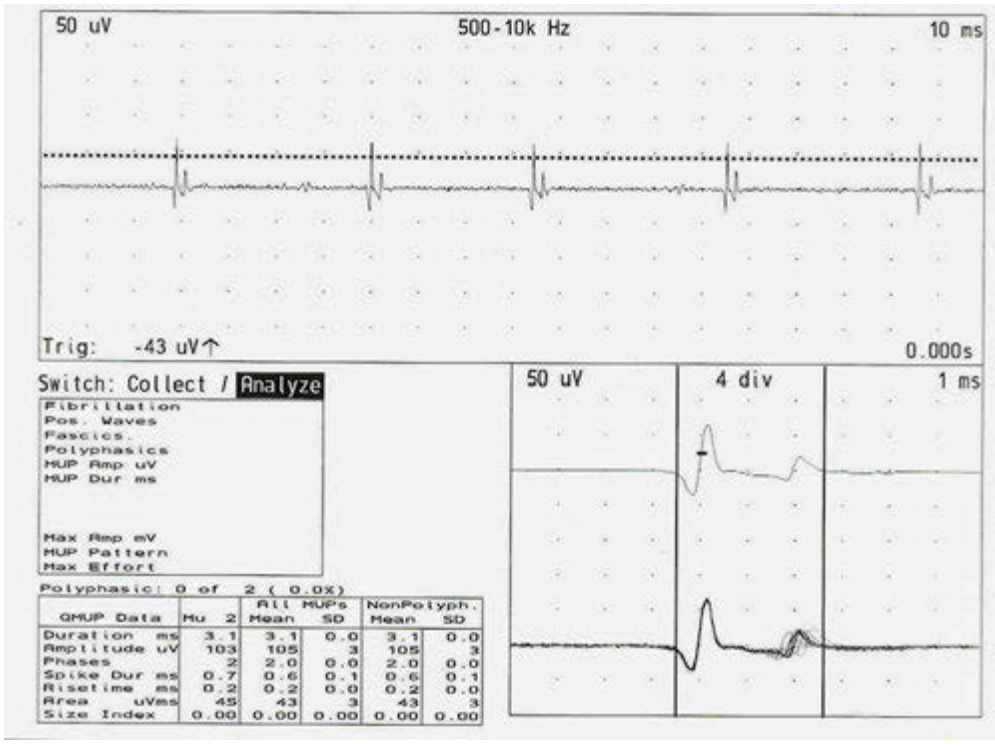
Clin Neurophysiol. 2012 Mar;123(3):613-20. doi: 10.1016/j.clinph.2011.07.044. Epub 2011 Sep 1.

Reference values for voluntary and stimulated single-fibre EMG using concentric needle electrodes: a multicentre prospective study.

Kokubun N1, Sonoo M, Abe T, Arimura K; Japanese SFEMG Study Group.

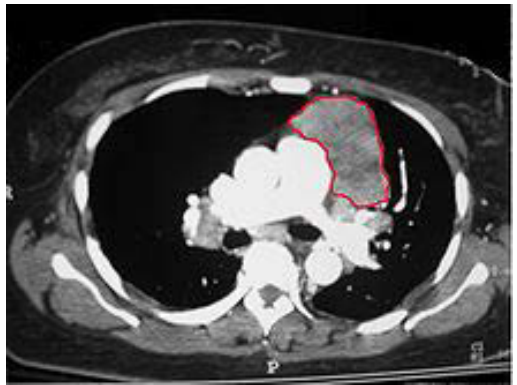
www.youtube.com/watch?v=tJYUYttERw4





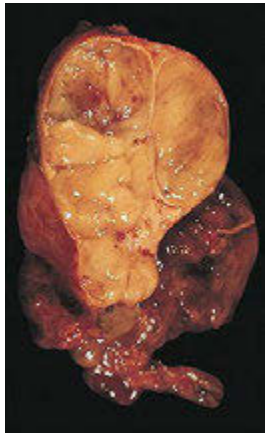
Thymic Cancer

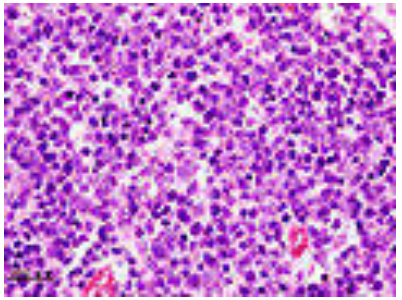
- 6 Qld cases of thymoma/thymic cancer; ages 37-54; 4 males
- Presentation:- 3 generalised, 2 bulbar, 1 ocular muscles
- CT scan chest; all diagnosed at onset of MG
- Variable resection, DXRT depending on capsule invasion



Thymic Cancer

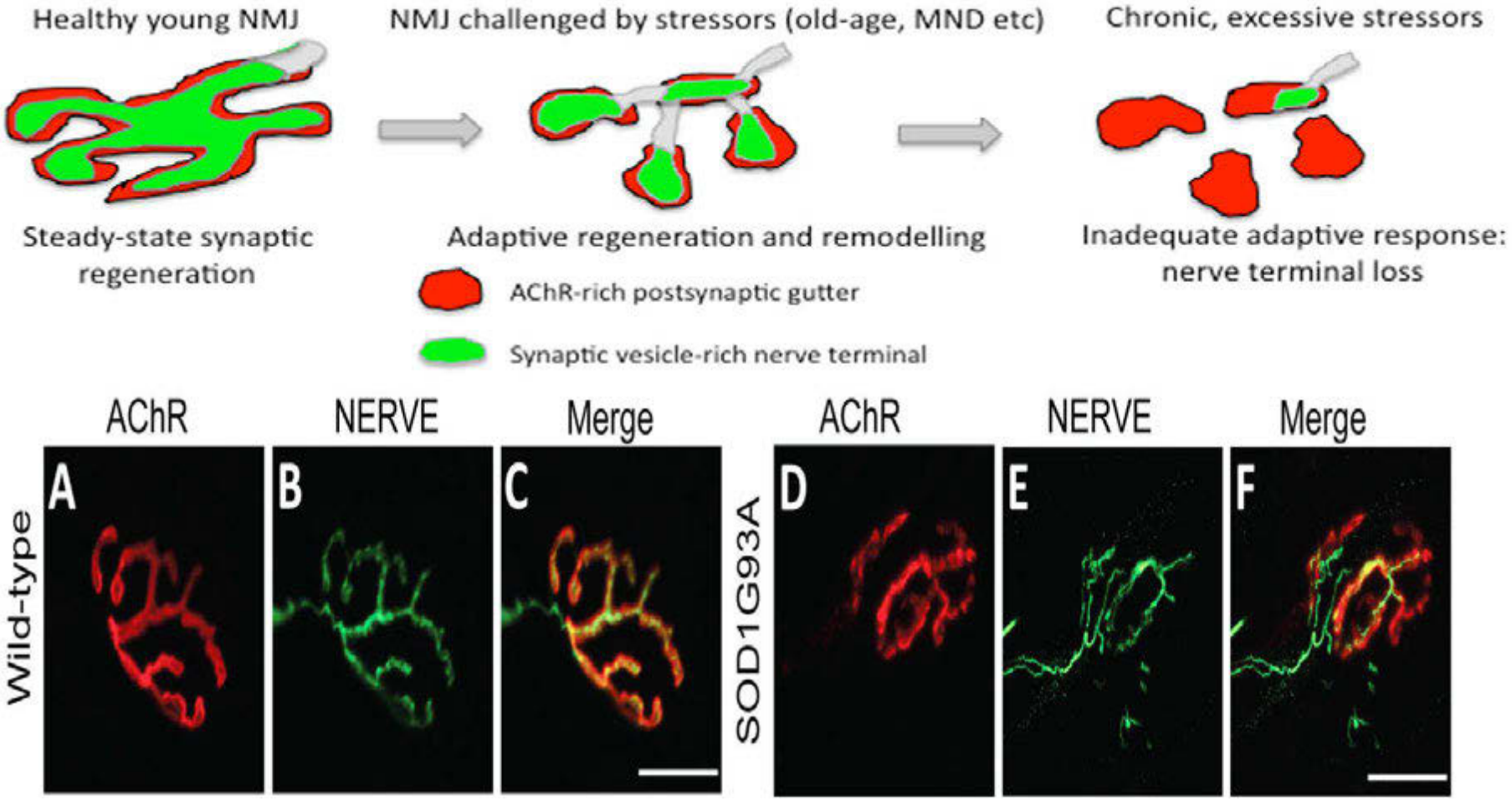
- All Ach receptor Ab positive; 4/4 had striated muscle antibody positive
- 3 have passed away with metastatic thymoma and severe MG symptoms
- Death from myasthenia rather than from metastatic cancer





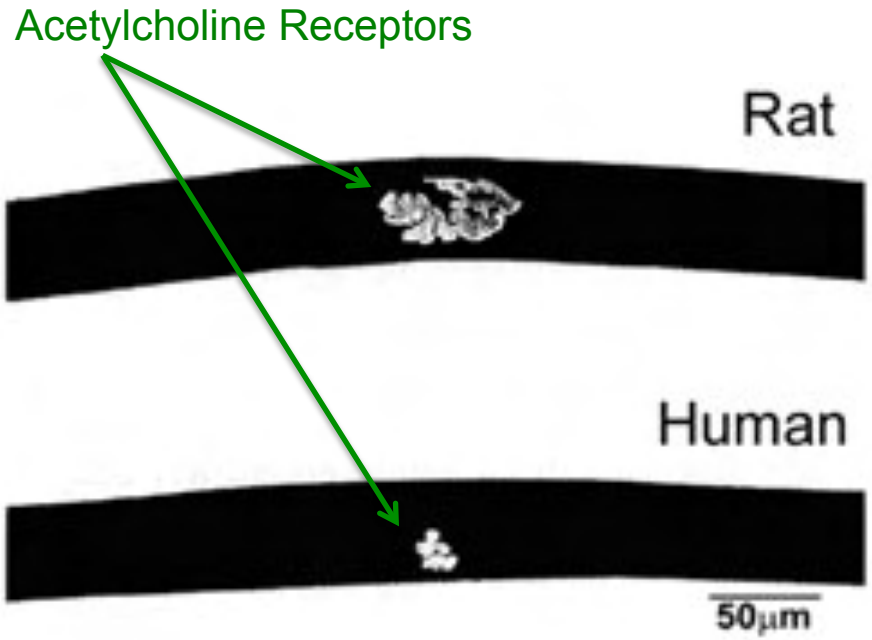
THE NMJS IN ANIMAL (Rodent) MODELS OF MND AND AGEING

Loss of the nerve terminal when the NMJs is challenged by chronic stressors such as sedentary aging and MND.

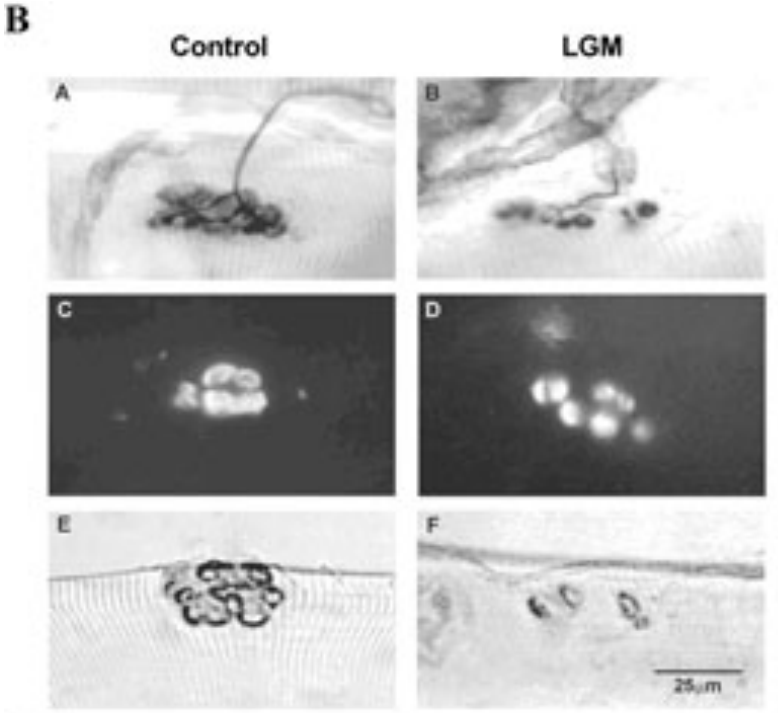


DO we see the same changes at the NMJs of early diagnosed MND patients ?

Human NMJs are smaller than our animal models



Clark Slater 1992, Ann NY Acad Sci



Loss of Synaptic a4 and b2 – Laminins from Aged ALS NMJs