http://www.dmu.ed.ac.uk/projects/NMHDhons/NMJhonsIndex.htm

**Mini Symposia:**
1. Structure and function of NMJ
2. Development and remodelling of NMJ
3. Homeostatic regulation of NMJ in health and disease
4. Cellular and molecular biology of NMJ
5. The NMJ in Motor Neurone Disease (ALS)

http://www.innerbody.com/anatomy/arm.html

The "Final Common Path" ....

...leading to the "Ultimate Synapses"

“The neuromuscular junction... is an experimentally favourable object whose study could throw considerable light on synaptic mechanisms elsewhere”

Sir Bernard Katz, Ferm Lecture, IUPS Glasgow, 1993

"Defeating Motor Neurone Diseases through Innovative Fundamental Research"
Synapses degenerate before axons in SOD1<sup>G93A</sup> mice

12 week old - asymptomatic

1. Structure and Function
Multicolour labelling of motor neurones and NMJ in 'Brainbow' mice

Four cell-types at mammalian NMJ


F. Court et al. J Cell Sci 121, 3901-3911

Desaki & Uehara, 1981

Gillingwater 0.5 µm 50 µm
Acetylcholinesterase hydrolyses ACh in the synaptic cleft

\[ \text{ACh} \rightarrow \text{CH}_3\text{COO}^- + \text{Ch} \]
**Evoked EPPs have a large safety factor**

- **Action potential**
- **Endplate potential (EPP)**
- **Threshold**

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**End-Plate Potential (EPP)**

- **2 ms**
- **200,000 channels**
- **20 mV**

**End-Plate Current (EPC)**

- **20 mV**

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**Synapses show stochastic variation in function…**

- Synaptic responses fluctuate randomly, both in response to constant excitation (EPPs) and spontaneously at rest (mEPPs)

**P(x) = \( e^{-m} \frac{m^x}{x!} \)**
Neurotransmitters are released by exocytosis from synaptic vesicles.

Measuring exocytosis with "synaptopHluorin".

Drosophila 3rd Instar Larva : Motor Unit

Segment A5: fibre 6/7 NMJs

Segment A3: fibre 7/6/7/13/12 NMJs

VNC OK6-Gal4: UAS-myr-RFP

2. Development and Remodelling
Synapse elimination occurs during postnatal development, establishing the mononeuronal innervation of motor endplates.

3. Homeostatic regulation of NMJ structure and function

The size of NMJ and the extent of junctional folding vary between species

NMJ size and muscle fibre diameter co-vary

Quantal analysis of EPPs shows a "safety factor" of 2-5

<table>
<thead>
<tr>
<th>Species</th>
<th>Quantal content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frog</td>
<td>200</td>
</tr>
<tr>
<td>Rat, mouse</td>
<td>50-75</td>
</tr>
<tr>
<td>Man</td>
<td>20-30</td>
</tr>
</tbody>
</table>
Myasthenia gravis and LEMS are autoimmune diseases.

**Myasthenia Gravis (MG):**
- AChR antibodies

**LEMS:**
- Ca channel antibodies

**Botulism:**
- Enzymatic cleavage of SNARE proteins

**MG:**
- AChR antibodies

Stimulating electrodes
Recording electrodes

**Clinical Electromyography**

**Myasthenic Syndrome (LEMS):**

**EMG**

**EPP**

EPPs have low quantal content and show facilitation

**Summary of electrophysiological changes in Myasthenia Gravis and Myasthenic Syndrome**

<table>
<thead>
<tr>
<th>Quantiy size</th>
<th>Compound Muscle Action Potential</th>
<th>Repetitive Nerve Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MES</td>
<td>Ni</td>
<td>Ni</td>
</tr>
<tr>
<td>REG</td>
<td>Ni</td>
<td>Ni</td>
</tr>
</tbody>
</table>

(NI=Normal Individual)

**4. The SOD1 mouse model of Motor Neurone Disease**
SOD1<sup>G93A</sup> mice develop progressive hindlimb paralysis

"Symptomatic"  Endstage

Motor neurone disease (eg ALS)

Synapses degenerate before axons in SOD1<sup>G93A</sup> mice

12 week old - asymptomatic

50 µm

Sympathetic system

Synapses degenerate before axons in SOD1<sup>G93A</sup> mice

Symptomatic 8 month-old mouse

30 µm
Complexity of the Motor Neurone

5. The WldS mouse model of synaptic protection

"Compartmental Neurodegeneration" Hypothesis

Augustus Waller, ca. 1860

Axons and synapses are protected from degeneration in WldS mutant mice

Synaptic degeneration precedes axonal degeneration after axotomy in WldS mice
The “Cell Vizio” confocal microendoscope

x,y resolution: ~4 µm
z resolution: ~15 µm (WD=0)

“Longitudinal” in-vivo imaging of NMJ degeneration in WldS mice

3 days axotomy 4 days axotomy