Motor Unit Number Index (MUNIX): ready for clinical ALS trials

results of a 15 months longitudinal multicentre trial

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MUNIX

- MUNIX is a novel motor unit number estimation technique
  - First reported 2004 by Sanjeev Nandedkar
  - Developed by Sanjeev Nandedkar, Paul Barkhaus and Erik Stålberg
  - > 20 publications since 2010 from different groups

- MUNIX uses a statistical approach and gives an index of the amount of functioning motor units in a given muscle
  - most MUNE techniques first calculate the size and then the amount of motor units
  - MUNIX first calculates the number of motor units (MU) and then the average size
  - MUNIX does not identify individual motor unit potential, which makes this method very fast to perform
MUNIX is a 3 step process

- Recording the compound muscle action potential (CAMP) with optimized amplitude
- Recording of surface EMGs at various voluntary isometric force levels (SIPs) (A)
- Computing MUNIX using the area and power of the CMAP und SIPs (B+C)
MUNIX vs other MUNE

**CONTRA MUNIX**
- Voluntary constant isometric muscle activation is needed; may be difficult in weak muscles
- Volume conduction from neighboured muscles may contaminate SIPs

**PRO MUNIX**
- Very fast (less than 5 min per muscle), similar results like other MUNE methods
- Can be used in every muscle where a CMAP can be elicited by supramaximal electrical nerve stimulation
- Non-invasive, few electrical stimulations needed
- Reproducible
- Tool to track motor unit loss over time, when patients serve as their own controls
- No special equipment, runs on different EMG machines (Keypoint, Synergy, Viking etc)
- Several muscles in different regions can be tracked to receive a “body-scan”
Our recent study...

- 3 centres (Lisbon, Milwaukee, St. Gallen) studied 48 ALS subjects every 3 month

  - 31 subjects were followed till month 12, 25 subjects reached month 15
  - MUNIX of 6 muscles ("body-scan")
    - abductor pollicis brevis
    - abductor dig. min.
    - biceps
    - tibial ant.
    - extensor dig. brev.
    - abductor hallucis
  
  of the initial clinically less affected side were measured

- ALSFRS-R was evaluated
- Test-retest evaluation was performed by 2 centres (intra- and inter-rater)
- Change of MUNIX was compared with ALSFRS-R
Several groups reported a good test-retest reliability, comparable to other more sophisticated MUNE methods:

- High-density motor unit number estimation (HD-MUNE)
  Boekestein, 2012, Clin Neurophysiol

- Incremental stimulation MUNE
  Furtula, 2012, Clin Neurophysiol

Variability of MUNIX is largely determined by variability of the CMAP:

- Maximum CMAP amplitude must be carefully determined
- Moving the recording electrode several times to optimize amplitude is mandatory
- Optimal location might change in the course of motor neuron diseases
# MUNIX reliability

## Intra-Class Correlation Coefficient ICC

### Intra- and inter-rater ICC at first visit

<table>
<thead>
<tr>
<th>Muscle</th>
<th>centre a</th>
<th>centre b</th>
<th>all centres</th>
<th>centre a</th>
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<tbody>
<tr>
<td></td>
<td>intra</td>
<td>intra</td>
<td>intra</td>
<td>inter</td>
</tr>
<tr>
<td>Muscle</td>
<td>n = 16</td>
<td>n = 4</td>
<td>n = 20</td>
<td>n = 15</td>
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<tr>
<td>MUNIX APB</td>
<td>0.89</td>
<td>0.93</td>
<td>0.90</td>
<td>0.86</td>
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<tr>
<td>MUNIX ADM</td>
<td>0.91</td>
<td>0.79</td>
<td>0.89</td>
<td>0.92</td>
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<tr>
<td>MUNIX BB</td>
<td>0.76</td>
<td>0.95</td>
<td>0.81</td>
<td>0.84</td>
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<tr>
<td>MUNIX TA</td>
<td>0.95</td>
<td>0.52</td>
<td>0.90</td>
<td>0.46</td>
</tr>
<tr>
<td>MUNIX AH</td>
<td>0.88</td>
<td>0.88</td>
<td>0.97</td>
<td>0.81</td>
</tr>
<tr>
<td>MUNIX EDB</td>
<td>0.92</td>
<td>0.74</td>
<td>0.88</td>
<td>0.90</td>
</tr>
<tr>
<td>CMAP APB</td>
<td>0.96</td>
<td>0.98</td>
<td>0.96</td>
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</tr>
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<tr>
<td>MUNIX mean</td>
<td>0.89</td>
<td>0.80</td>
<td>0.89</td>
<td>0.80</td>
</tr>
<tr>
<td>CMAP mean</td>
<td>0.93</td>
<td>0.91</td>
<td>0.93</td>
<td>0.86</td>
</tr>
</tbody>
</table>

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MUNIX reliability is trainable

MUNIX reliability is trainable

© Nandedkar & Stålberg
MUNIX reliability

MUNIX reliability is trainable

→ Several hands-on teaching courses in St.Gallen & Dublin

► 6 European ALS centres established MUNIX as part of the SOPHIA project
  ► Prior qualification procedure mandatory (test-retest-certification)
  ► Further centres prepare to join
MUNIX
longitudinal results in ALS patients (n=48)

Signif. codes:  * 0.01 > 0.05,  ** 0.001 > 0.01,  *** < 0.001
MUNIX sum-score
longitudinal results in ALS patients

- MUNIXscore6: all 6 muscles
- MUNIXscore4: all muscles without AH and biceps
  - Biceps: technically challenging, risk of co-stimulation of other nerves and CMAP contamination
  - AH: multiple foot muscles contribute to CMAP amplitude and pure toe abduction for recordings is rarely possible (flection)
MUNIX onset subgroups

Spinal onset (n=31)

Decline rates:
- ALSFRS-R: -2.0% / month
- MUNIXscore4: -3.7% / month

bulbar onset (n=17)

Decline rates:
- ALSFRS-R: -2.8% / month
- MUNIXscore4: -3.6% / month

Signif. codes: * 0.01 > 0.05, ** 0.001 > 0.01, *** <0.001
Subgroups: spread of disease

Upper limb onset (n=16)

- Fast decline in contralateral arm muscles

Lower limb onset (n=15)

- Fast decline in contralateral leg muscles

Signif. codes:  * 0.01 > 0.05,  ** 0.001 > 0.01,  *** <0.001
Subgroups: progress rate of disease

- Data stratified into equal groups with slower and faster decline of ALSFRS-R
  - Slow ALSFRS-R group with -1.3%/month, fast group with -3.8%
  - Corresponding MUNIX decline slow group -2.5%/month, fast group -5.7%

- Data stratified into equal groups with slower and faster decline of MUNIX
  - Slow MUNIX group with -2.6%/month, fast group with -5.7%
  - Corresponding ALSFRS-R decline slow group -1.9%/month, fast group -2.8%

→ MUNIX is able to reflect clinical disease progression

- Further data have to be collected to correlate MUNIX with clinical endpoints to evaluate its value as a biomarker in MND
MUNIX: limitations

- MUNIX needs active cooperation of the patients

- measuring multiple muscles still needs some time, depending on:
  - Experience of rater
  - Hardware/Software
  - Handicap of subjects (positioning)

- some measurements are technically challenging (e.g. biceps muscle, abductor hallucis)

- MUNIX does not reflect upper motor neuron involvement
  - usefulness in PLS or upper motor neuron predominant ALS unclear

- Comparing MUNIX with ALSFRS-R means comparing completely different parameter

MUNIX: benefits

- Independent of functional status and interventions (e.g. treating sialorrhea, immobilisation due to fracture)

- direct measure of the crucial pathological process in ALS: lower MN loss

- If hardware/software is available, low material expenses/costs
Conclusion

► MUNIX is a reliable, fast and non-invasive variant of MUNE
  ► MUNIX can be performed in a whole set of muscles longitudinally
  ► It allows an electrophysiological «body-scan» in arm- and leg-muscles

► MUNIX is able to track lower motor neuron loss in ALS
  ► significant higher decline rates than ALSFRS-R
  ► constant decline rates in different onset ALS subjects (bulbar vs. spinal)
  ► can reflect spread of disease and progression rate in the course of ALS

► Further data have to be collected to correlate MUNIX with clinical endpoints to evaluate its value as a biomarker in MND

► MUNIX has been establishes in several European centres (SOPHIA)
  ► Further centres in several countries are preparing to join
Acknowledgements

Sanjeev Nandedkar
Erik Stålberg
Paul Barkhaus
Mamede de Carvalho
José Castro
David Czell
Christian Burkhardt
Markus Weber

Neuromuscular Research Association Basel (NeRAB)

Thanks to all patients and relatives and our collaborating partners!