Structure, Plasticity & Repair of the Nervous System

Spinal Cord Injury: Assessment of SCI and approaches to Neurorehabilitation

Motor Systems II

BIO 343, 06.11.2017

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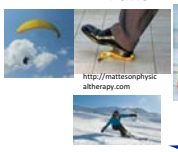
Spinal Cord Injury

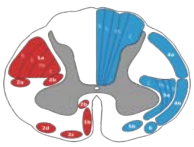
Accidents

Falls



Violent felony

Non traumatic causes



Spinal Cord Injury

Motor function:

Arm and hand function

Walking ability

Trunk stability

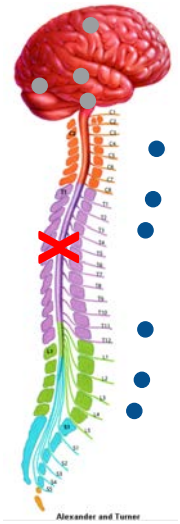
Sensory function

Pain

Bladder, bowel and sexual function

Devivo 2012, NSCISC 2011, Scivoletto 2011, Anderson 2004

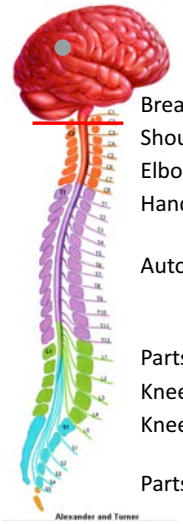
Level of lesion: impact on function



Above level of injury:
neuronal connections from and to the brain intact
FUNCTION INTACT

Below level of injury:
neuronal connections from and to the brain diminished or interrupted
FUNCTION IMPAIRED

Level of lesion: impact on function



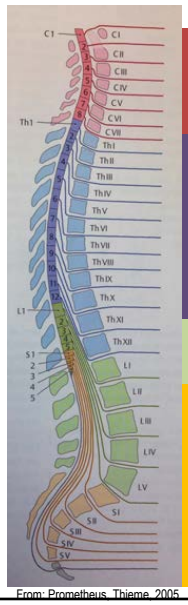
Breathing (C1-C4), Head and neck movements (C2)
Shoulder movements (C5)
Elbow and wrist movements (C6-C7)
Hand and finger movements(C7-T1)

Autonomic nervous system (Sympathikus (T1-T12) and trunk stability (T2-T12)

Parts of sexual function (T11-L2) and hip movements (L2)
Knee extension (L3)
Knee flexion (L5) and ankle movement (L4-S1)

Parts of sexual function (S2-S4) and bladder/ bowel function (S2-S3)

Lesion level – upper and lower motor neuron lesion



From: Prometheus, Thieme, 2005

Tetraplegia – Upper and lower motor neuron

arms and legs

only legs

Paraplegia – Upper and lower motor neuron

lowest part of spinal chord affected

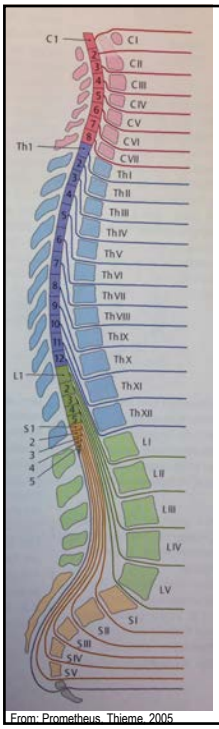
Conus medularis – Upper and lower motor neuron

nerve fibers that lie within the cord are affected

Cauda equina – Lower motor neuron

in all cases expcet the last, upper and lower motoneurons are affected

facts that i need to know



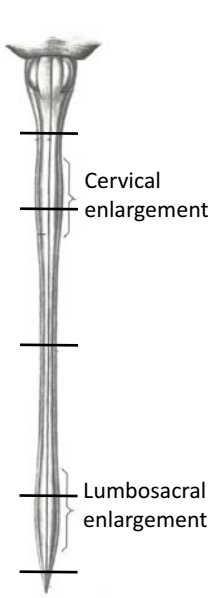
From: Prometheus, Thieme, 2005

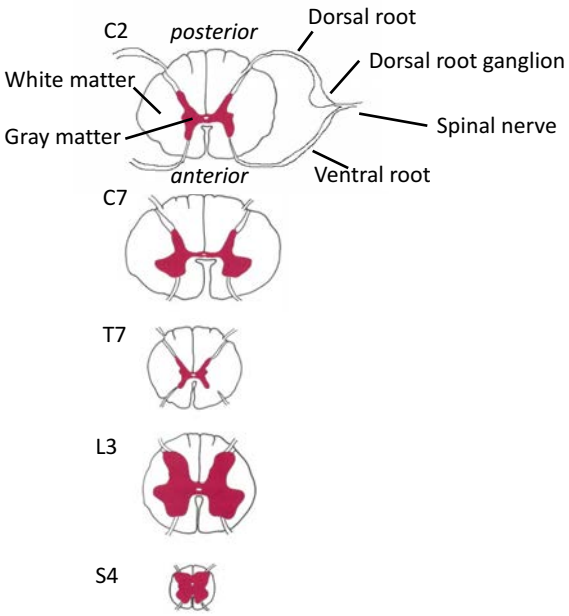
Spinal Cord

- There are 31 pairs of spinal nerves: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal
- There are enlargements in the cervical and lumbosacral regions (supplying upper and lower limbs)
- Cervical roots are named according to the vertebra **above** which they exit (exception C8: there are only 7 cervical vertebrea)
- Thoracic and lumbar nerve roots are named according to the vertebra **below** which they exit
- Spinal cord ends at approximately L1-2 vertebral level

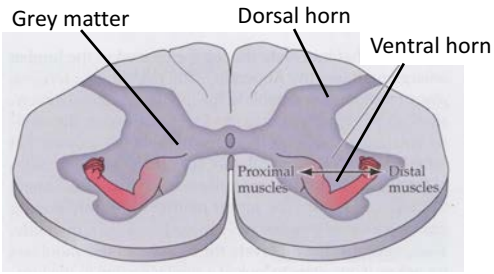
(neurological levels)

Spinal Cord





Topography across spinal cord (transverse plane)

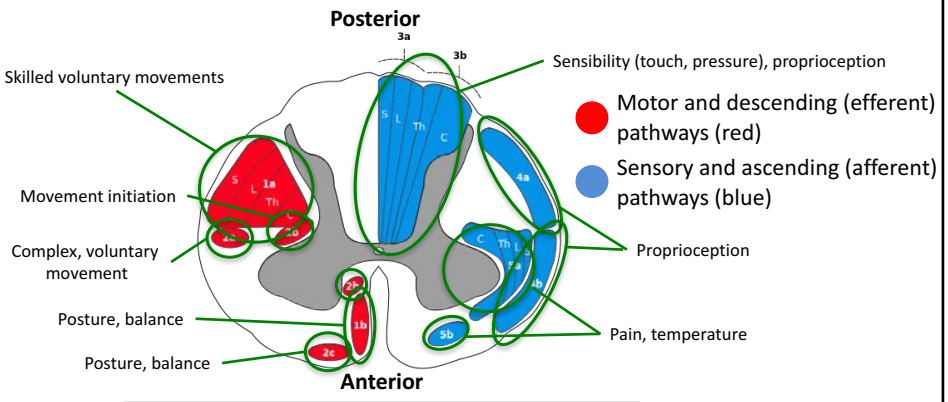


Medial motor neurons innervate axial and proximal muscles (postural control and balance). Receive input from long distance local circuits.

Lateral motor neurons innervate distale muscles (control of skilled movements). Receive input from short distance local circuits.

we have to know where the tracts are located to test the consquences of specific injuries

Topography across spinal cord (transverse plane)



Motor and descending (efferent) pathways	Sensory and ascending (afferent) pathways
1. Pyramidal Tracts	**3. Dorsal Column**
1a. Lateral corticospinal tract	3a. Gracile fasciculus
1b. Anterior corticospinal tract	3b. Cuneate fasciculus
2. Extrapyramidal Tracts	**4. Spinocerebellar Tracts**
2a. Rubrospinal tract	4a. Posterior spinocerebellar tract
2b. Reticulospinal tract	4b. Anterior spinocerebellar tract
2c. Vestibulospinal tract	**5. Anterolateral System**
	5a. Lateral spinothalamic tract
	5b. Anterior spinothalamic tract

C: Cervical, Th: Thoracic, L: Lumbar, S: Sacral

Patient examples

lesion level C2: cannot breathe, no voluntary control of arms and legs, can only control facial muscles voluntarily

lesion level C7: full paralysis of legs, can control arms, no good control of hands/finger movements, cannot really write - but is much more independent (can live alone and without help of other persons)

lesion level conus cauda: can walk with mechanical rod help, normally no control of help, bladder problems

lesion level C4 - in the cervical area: can walk naturally, has somewhat comprised fine motor skills => lesion probably in cervical area

For exam, it would be good to know these levels by heart, because there might be a description of a lesion and we need to know which level is affected

clinical facts-

Spinal Cord Injury

50% traumatic - 50% non traumatic (tendency increase of non traumatic)
50% sensorimotor complete – 50% incomplete

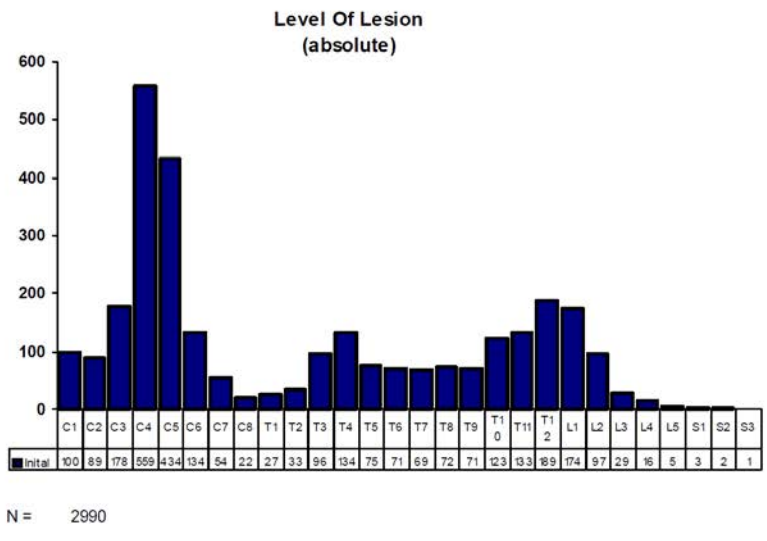
Clinical symptons
44% paraplegia
56% tetraplegia

Epidemiology
Relatively rare disease
Incident: 1.0-8.3 / 100'000 per year (Van Asbeck et al. 2000, Warren et al. 1995)
Prevelance: 4'500 (CH)

Average age 38 years (increasing)
Gender: m : f = 3.8 : 1

absolute occurrence of lesions in levels - C4 and C5 seem to be affected the most

Spinal Cord Injury



Data from European Multicenter Study about Spinal Cord Injury (EMSCI)

Consequences & Symptoms of SCI

Paresis - paralysis

Spasticity, clonus

Hyper- /hypoactive reflexes

Psychological problems or depression (30%)

Decreased bladder bowel function

Cardiovascular-blood pressure dysfunction

Restricted sexual function

Loss of sensory function (e.g. pain, allodynia,…)

Assessing Spinal Cord Injury

Standard clinical assessment

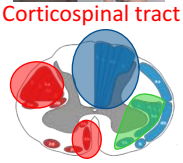
Advanced clinical assessment
E-phys

Functional assessment

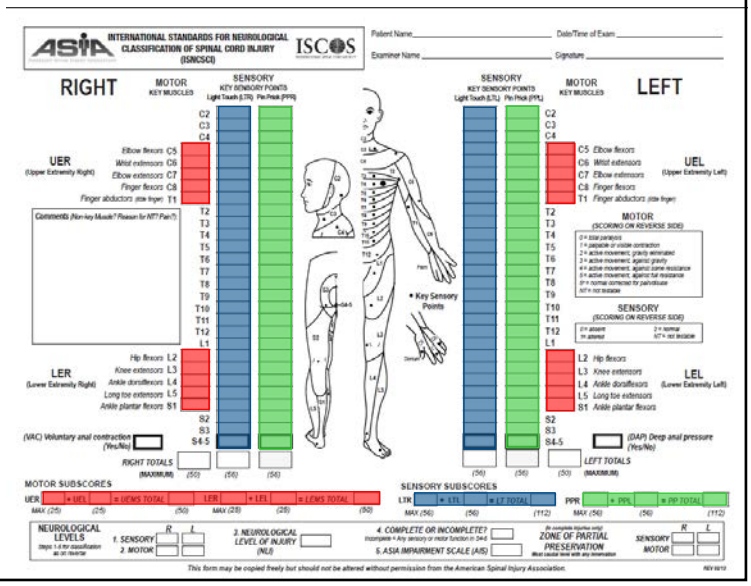
Clinical classification - ISNCSCI

Dorsal column

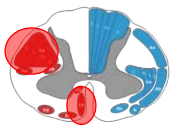
Corticospinal tract

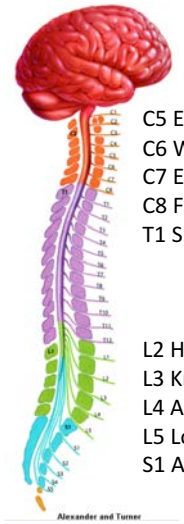


Spinathalamic tract



Clinical examination of corticospinal tract

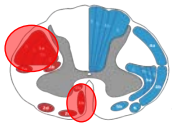




C5 Elbow flexors (biceps, brachialis)
C6 Wrist extensors (extensor carpi radialis longus and brevis)
C7 Ellbow extensors (triceps)
C8 Finger flexors (flexor digitorum profundus) to the middle finger
T1 Small finger abductors (abductor digiti minimi)

L2 Hip flexors (iliopsoas)
L3 Knee extensors (quadriceps)
L4 Ankle dorsiflexors (tibialis anterior)
L5 Long toe extensors (extensor hallucis longus)
S1 Ankle plantar flexors

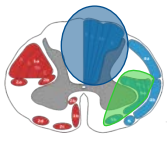
Clinical examination of corticospinal tract



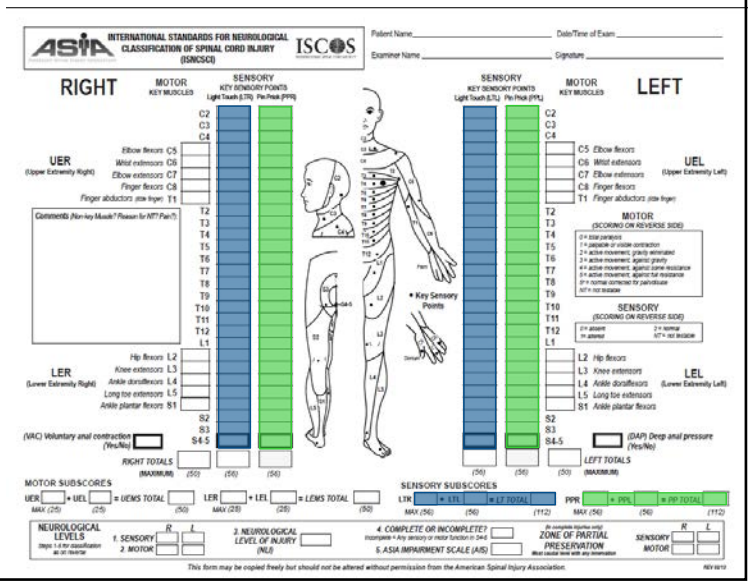
Grade	Description
0	Total paralysis
1	Palpable or visible contraction
2	Active movement, full range of motion (ROM) with gravity compensation
3	Active movement, full ROM against gravity
4	Active movement, full ROM against moderate resistance
5	(normal) active movement, full ROM against full resistance

Clinical examination - Sensory tracts

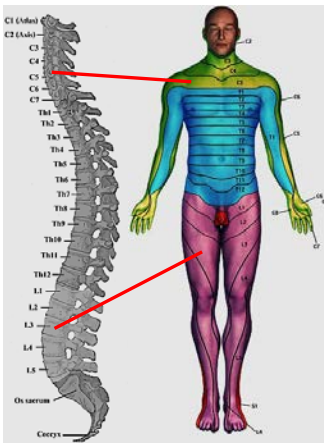
Dorsal column



Spinathalamic tract



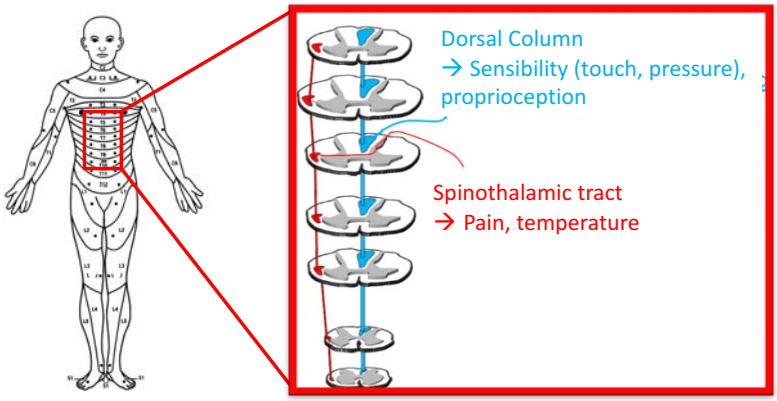
Spinal Cord and Dermatomes



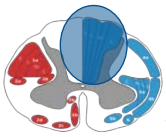
Sensory receptors of the skin travel to the brain through one spinal nerve

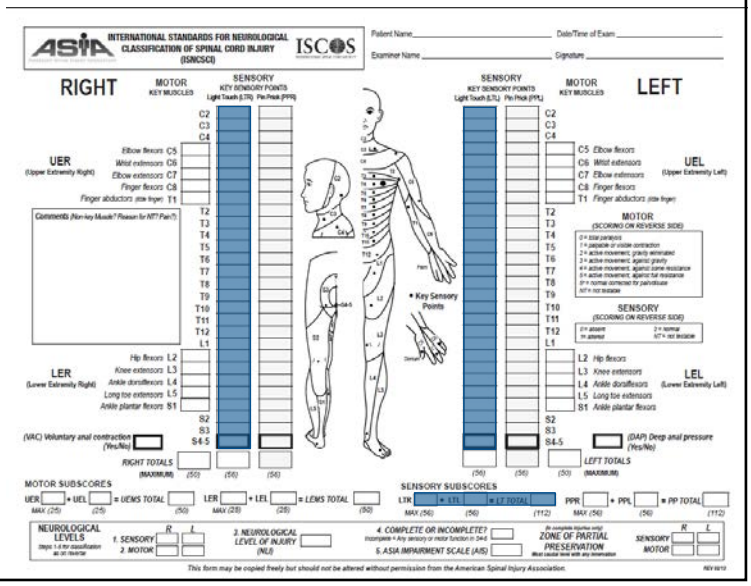
Dermatome is a segment of skin provided by one spinal nerve

Different nerve fibres conduct signals from the periphery to the brain



Clinical examination – Dorsal column

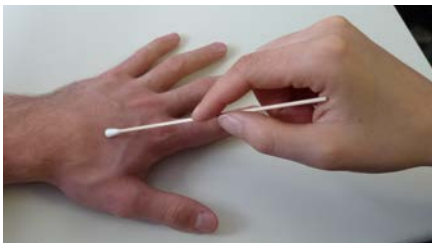




Clinical examination of dorsal column: Light touch

Principle:

Touch of different dermatomes with a cotton bud



Assessment:

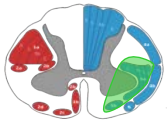
Patient reports sensation:

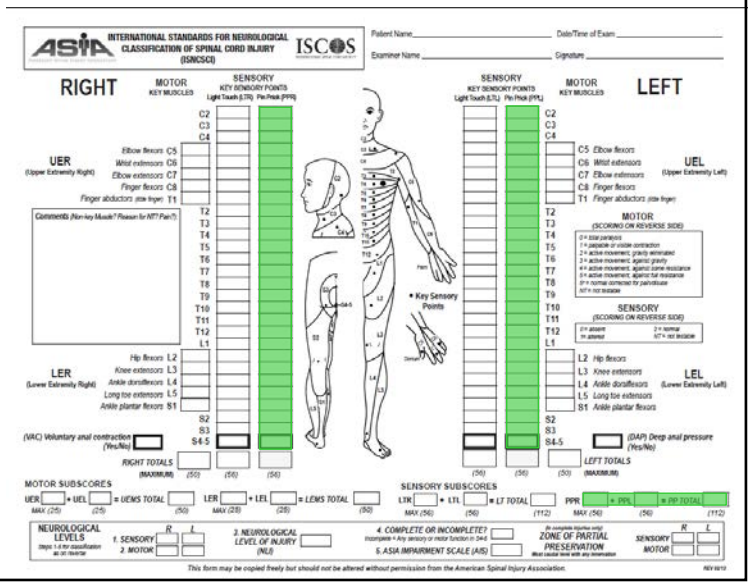
- 0 = absent
- 1 = altered (impaired)
- 2 = normal

Limitation:

Subjective assessment

Clinical examination –Spinothalamic tract





Clinical examination of spinothalamic tract: Pin Prick

<u>Principle:</u>

Touch of different dermatomes with both sides of safety pin

<u>Assessment:</u>

Patient reports sensation:

- 0 = Unable to distinguish between sharp and dull (no feeling)
- 1 = Sharp/dull sensation altered
- 2 = Sharp/dull sensation intact

<u>Limitation:</u>

Subjective assessment

Severity of lesion- ASIA Impairment Scale (AIS)

Dorsal column

Corticospinal tract

Spinathalamic tract

AIS A	**Complete.** No motor or sensory function is preserved below level of lesion (sacral segments)
AIS B	**Sensory incomplete**. Sensory but not motor function is preserved below lesion level (incl. Sacral segments)
AIS C	**Motor incomplete.** Less than half of key muscles can work against gravity.
AIS D	**Motor incomplete.** More than half of key muscles below level of lesion can work against gravity.
AIS E	**Normal.** Sensory and motor function normal.

Assessing Spinal Cord Injury

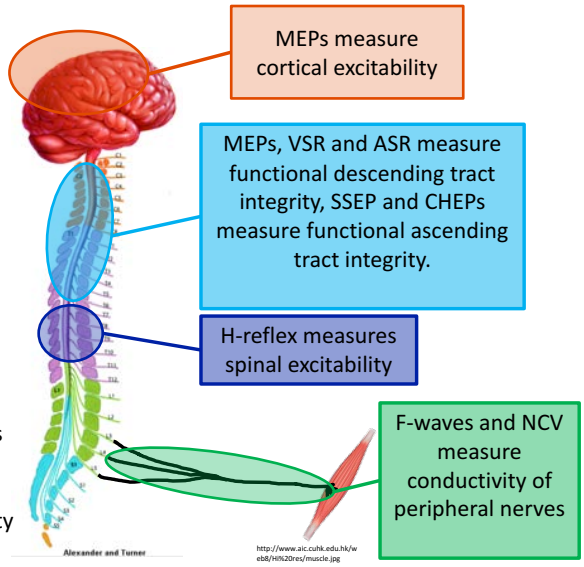
Standard clinical assessment

Advanced clinical assessment
E-phys

Functional assessment

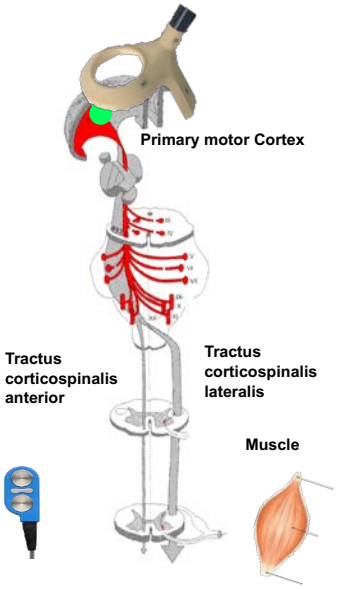
Assessing the spinal cord

Neurophysiological Assessment

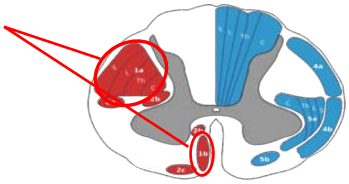


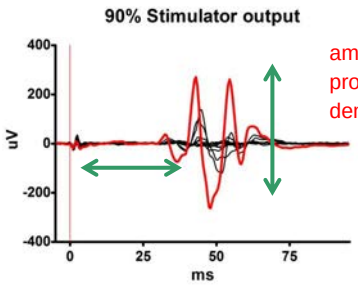
MEP: Motor evoked potentials
VSR: Vestibulospinal Reflex
ASR Acoustic startle reflex
NCV: Nerve conduction velocity

Motor evoked Potentials (MEP)



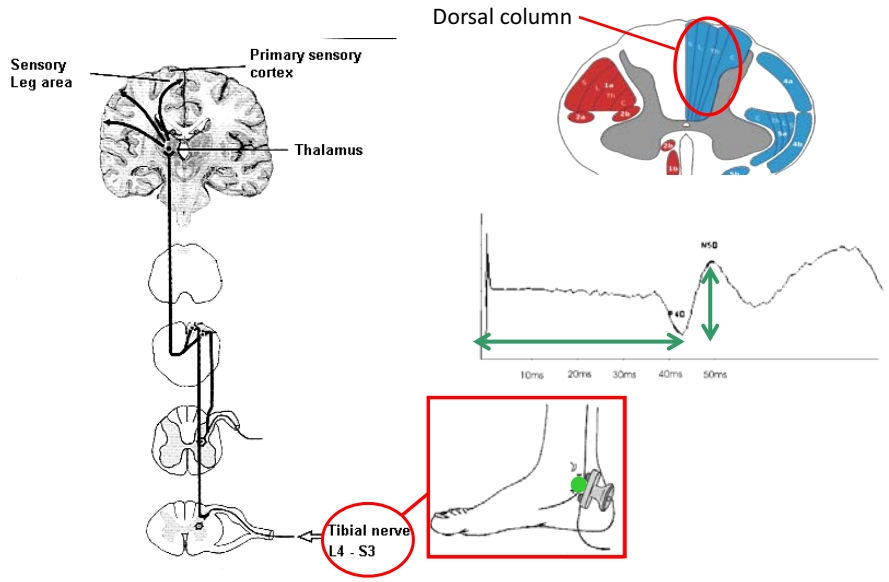
MEPs test Functional integrity of the pyramidal tract



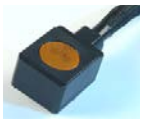


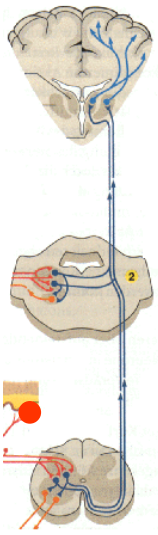
amplitude and latancies are affected in lesion - prolonged latencies are an identication for demyelination

Somatosensory evoked potentials (SSEP)

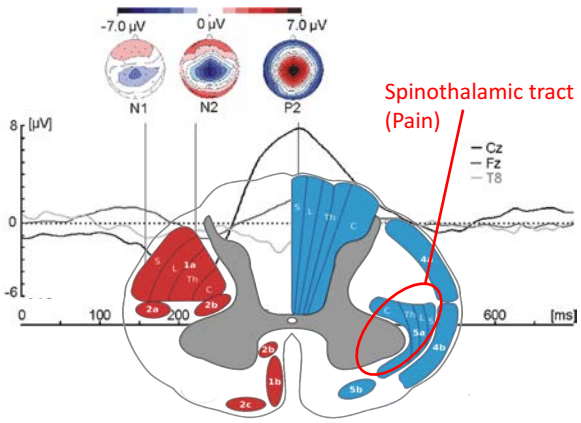


Contact Heat Evoked Potentials (CHEP)

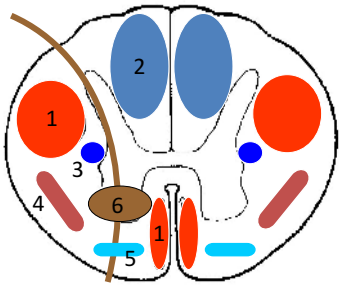




Recording over the Cortex integrity of the spino-thalamic tract



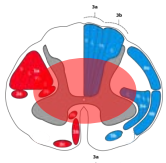
Summary: Neurophysiology in SCI



Spinal pathway	Method	Acceptance	Clinical correlate
cortico-spinal[1]	MEP	routine	central paresis
dorsal column[2]	SEP dSEP	routine	proprio-ception
sympa-thetic[3]	SSR	routine	cardio-vascular control
spino-thalamic[4]	CHEP (Contact-Heat)	routine	pain/temp perception
vestibulo-spinal[5]	GVS	investiga-tional	postural instability
peripheral system[6]	NCS / Reflex EMG	routine	peripheral paresis

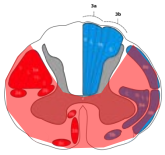
SCI Syndromes

Central Cord Syndrome: incomplete injury with greater weakness in upper limbs than in lower limbs



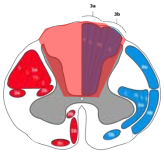
Brown-Séquard Syndrome: represents a spinal cord hemisection. Results in ipsilateral loss of proprioception and motor control below level of lesion and contralateral pain and temperature sensation.

Anterior Cord Syndrome: Mainly corticospinal and spinothalamic tracts affected. Loss of motor function, pain sensation and temperature sensation below level of lesion. touch not affected(?)



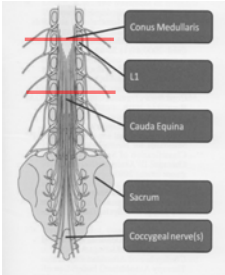
SCI Syndromes

Dorsal (Posterior) Column Syndrome: Disruption of dorsal columns. Bilateral loss of touch, vibration sense, proprioception. Intact motor function, pain and temp sensation.



Conus Medullaris Syndrome: Injury of Conus medullaris (L1-L2). Shows upper and lower motor neuron symptoms.

Cauda Equina Syndrome: Injury of lumbosacral nerve roots of cauda equina. Flaccid paralysis.



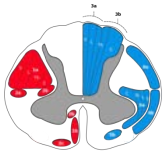
Case 1: which syndrome?

dorsal column syndrome - doesnt feel legs when eyes are closed

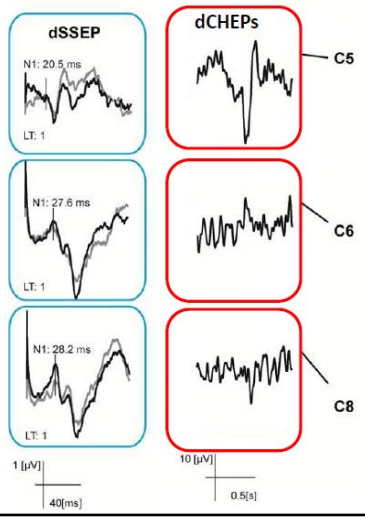
Case 2: does e-phys confirm diagnosis?

Patient

- male, 36 years
- Snowboard accident
- Central cord syndrom
- Level of injury C6



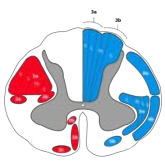
E-phys



Case 3: which syndrome?

- 38 years, male
- Below level of lesion (C6):
  - Profound left sided weakness
  - Left sided loss of touch sensation
  - Right sided loss of pain sensation

brwn-sequard syndrome



Assessing Spinal Cord Injury

Standard clinical assessment

Advanced clinical assessment
E-phys

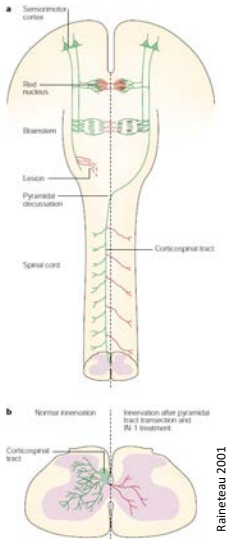
Functional assessment

Locomotion can be relearned

[Videos courtesy of UT Southwestern Medical Center, Dallas, USA]

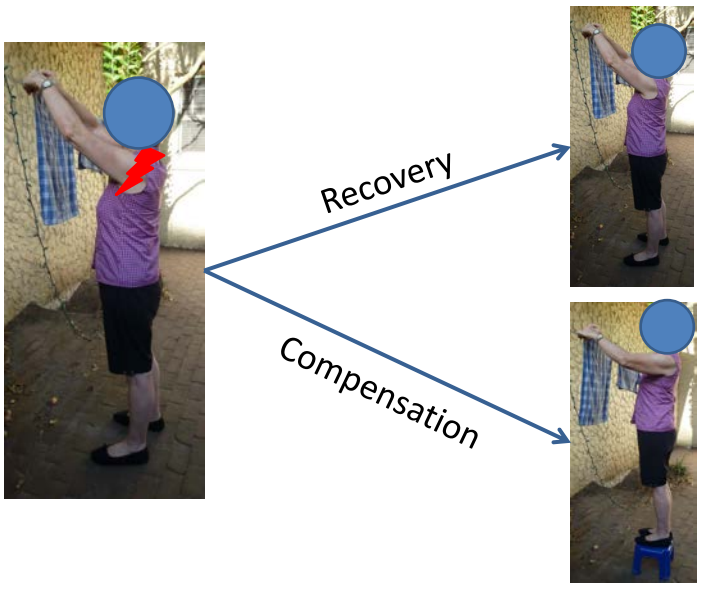
Neuroplasticity

- Any functional or cellular change in the nervous system
- Can occur in response to specific stimuli during both development and throughout life
- Injury of the nervous system itself can trigger plastic adaptations



Nudo 1996, Blesch 2009, Dunlop 2008, Wolpaw 2007, Cooke 2006, Kerchner 2008, Dobkin 1993, Chen 2007, Hagg 2009, Adkins 2006, Raineteau 2001 , Schwab 2010, Moore 2000, Rojas Vega 2008, Kafitz 1999, Lu 1997, Nathan 1994

Recovery versus Compensation

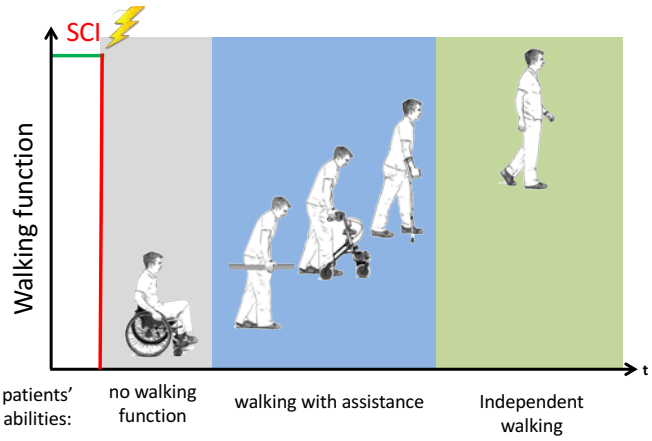


Recovery versus compensation

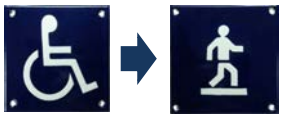
- We tend to think of recovery as:
  - Task accomplishment
  - Using limbs and end effectors typically used by nondisabled individuals
  - Performing a movement with pre-morbid movement patterns

Levin 2009

Continuum of walking function

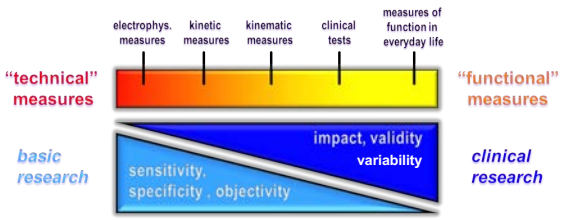


Assessment - perspective

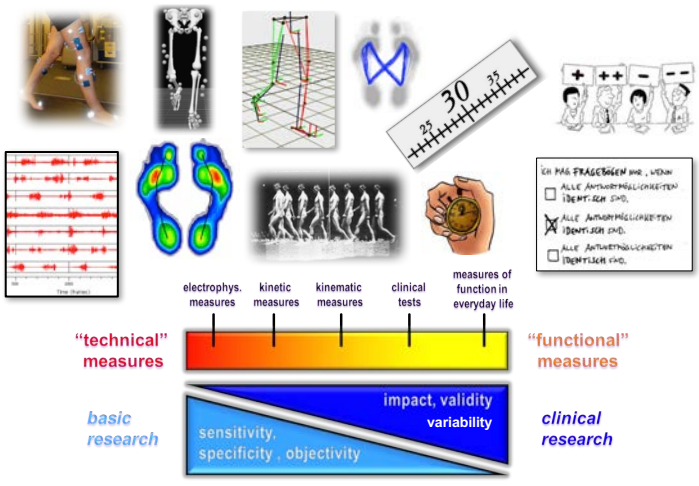


Researcher: Subclinical changes

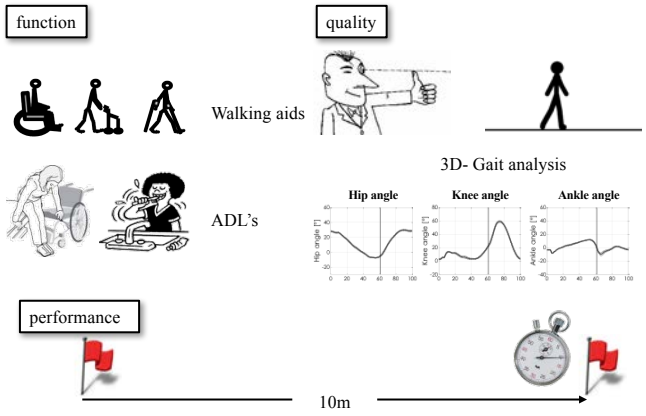
Clinician/ Patient: Clinical meaningful changes



Assessment of gait



Assessment of gait in neurology



Requirements for outcome measures

- Outcome measures must be:
  - **reliable** (Reliability: similar results under consistent conditions)
  - **valid** (Validity: the degree to which the tool measures what it claims to measure)
  - **responsive** (Responsiveness: sensitivity in detecting changes in function over time)

Assessment of gait in SCI

- Established measures:
  - **Clinical measures (ordinal score):**
    - Walking Index of Spinal Cord Injury (WISCI)
    - Spinal Cord Independence Measures (SCIM)
    - Lower extremity motor score (LEMS)
    - Spinal cord injury functional ambulation inventory (SCI-FAI)
  - **Timed measures (continuous score):**
    - 10 metre walk test (10MWT)
    - 6 minute walk test (6MWT)
    - Timed up and go (TUG)
  - **Three-dimensional gait analysis (continuous score)**

Case studies

10MWT [seconds]

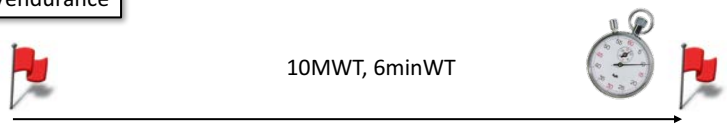
	Pre intervention	Post intervention
Subject 1	22s	14s
Subject 2	18s	18s
Subject 3	12s	5s

Which subject(s) did improve walking function?

time itself need not be an ultimate criteria - subject 2 showed regeneration, while subject 1 only showed compensation (simply walked faster so to say)

The limitation of clinical measures

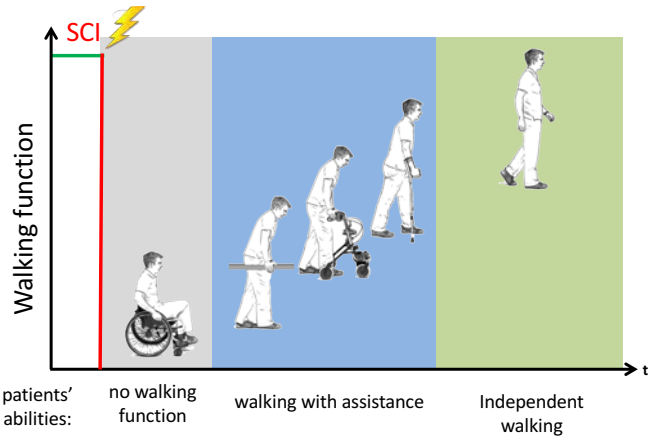
Speed/endurance



What does speed tell about gait?

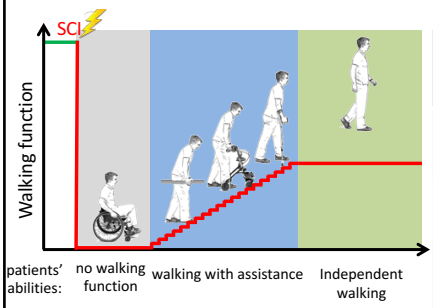
How does recovery work?

Continuum of walking function



only for severely affected pations

Standardized clinical measures: WISCI II

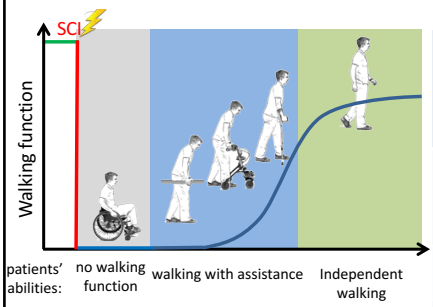


WISCI II	Walking index for spinal cord injury assesses the amount of assistance (physical, braces, devices) required to walk 10 metres.
Validity	FIM: r=0.82-0.92 SCIM mobility: r=0.81 TUG: r=-0.799
Reliability	Test-retest: ICC > 0.930 Inter-rater: ICC > 0.980
Strengths	low costs, moderate training required, little time required, valuable additional scale besides functional tests (e.g. 10mWT, 6mWT)
Limitations	ceiling effects, ordinal scale, not suitable for patients with good walking function

[Morganti et al., Spinal Cord, 2005; Burns et al., NNR, 2011; Marino et al., Am J Phys Med Rehabil, 2010; Van Hedel, Wirz & Curt, Arch Phys Med Rehabil, 2005; van Hedel et al., Spinal Cord, 2006]

ineffective for severely affected patients

Timed measures: 10mWT

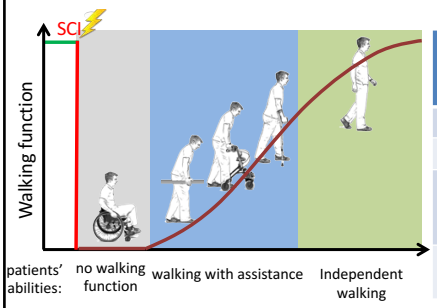


10mWT	10 metres walking test measures the time needed to walk 10 metres. Patients walk at preferred/comfortable walking speed or at fastest speed possible and are allowed to use assistive devices.
Validity	WISCI: r = 0.77-0.85 6mWT: r = -0.86 - -0.91 TUG: r = -0.646- 0.89 SCIM-mobility subscale: r = 0.89
Reliability	Test-retest: r=0.95-0.983 Inter-rater: r=0.974-0.99
Strengths	Minimal equipment needed, no advanced training needed, little time needed, use in clinical setting or at home, assesses walking function (walking speed)
Limitations	does not account the amount of assistance required, test can be performed at different speeds (comfortable vs. max speed), ceiling effects, patient must be able to walk

[Van Hedel et al., Arch Phys Med Rehabil, 2005; Scivoletto et al., Spinal Cord, 2011; Van Hedel et al., Spinal Cord, 2006; Ditunno et al., NNR, 2007; Van Hedel et al., NNR, 2009]

not used in clinical setting - is gold standard though to say how treatment works and what its effects are - is expensive

Three-dimensional gait analysis



3D-gait analysis	3-D gait analysis is the gold standard for the assessment of gait.
Validity	-
Reliability	-
Strengths	Identify mechanisms underlying gait dysfunction. Provide detailed kinematics, kinetics and spatio-temporal data
Limitations	Requires expensive equipment and skilled examiner

3-D gait analysis is the gold standard for the assessment of gait.

[Cameron & Wagner, Curr Neurol Neurosci Rep, 2011]

Summary: Assessment of locomotor function…

	Strengths	Limitations
Standardized clinical measures	• take into account the use of assistive devices • often used in clinical trials • simple and quick	• require a skilled examiner • do not identify mechanisms underlying gait dysfunction • limited precision and responsiveness • often non linear • low sensitivity
Timed measures	• simple • readily quantified • require limited training • published norms available • often used in clinical trials	• do not identify mechanisms underlying gait dysfunction • low sensitivity for compensatory strategies
3-dimensional gait analysis	• identify mechanisms underlying gait dysfunction • provide precise electrophysiological, kinematic, kinetic, and spatiotemporal data	• require expensive equipment and skilled examiner • limited to a few specialized laboratories • often low clinical impact

[modified from Cameron et al., Curr Neurol Neurosci Rep, 2011]

Rehabilitation after SCI

Key targets to restore function

in the clinic - basically physiotherapy

Goal-directed rehabilitation (e.g. locomotion)

Colombo et al. 2001, Donati et al. 2016

Reactivation (e.g.neurostimulation)

Courtine et al. 2011, Angeli et al. 2014

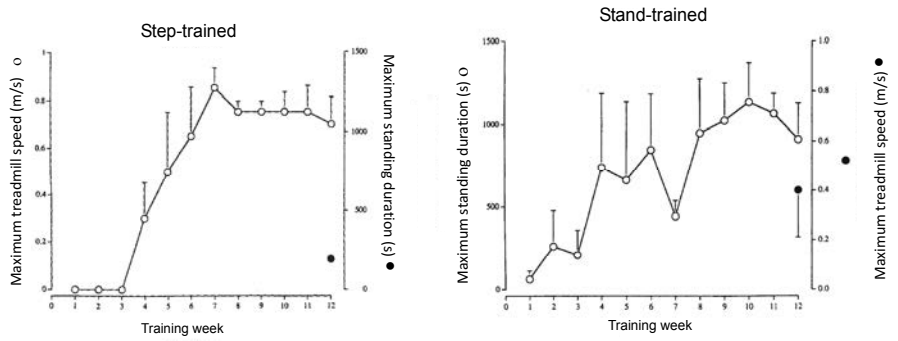
Rewiring (e.g. anti-Nogo-A, chondroitinase ABC, stem cells)

Zörner and Schwab 2010, Bradburry et al. 2002, Curt 2012

Neuroprotection (e.g. minocycline, riluzole, surgery)

Casha et al. 2012, Fehlings et al. 2016

Task specific training



[Edgerton et al., 1997]

Conventional gait training

Manual treadmill training

Manual treadmill training

- Training duration is limited by endurance of therapists, not of the patient.
- Two or more therapists needed
- Does not satisfactorily fulfil other requirements:
  - optimal control of limbs and individual joints,
  - postural control,
  - motivation of patient

- + Therapist „feels“ activity of patient!

Robotic supported gait training

Robotic supported gait training

•+ Physiological gait pattern can be ensured
+ Prolonged training duration
+ Less body weight support
+ Repeatable

- Activity of patient not apparent!

Task specific training of spinal networks

•Bodyweight supported treadmill training

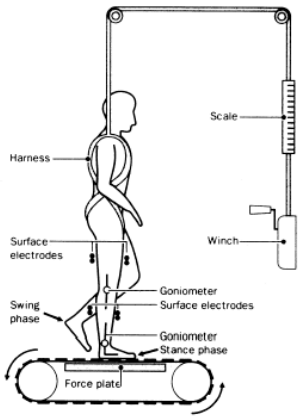


Fig. 2. The experimental set-up as used during treadmill training for humans (adapted from [66]).

rest of this was about the research

Key targets to restore function

Goal-directed rehabilitation (e.g. locomotion)
Colombo et al. 2001, Donati et al. 2016

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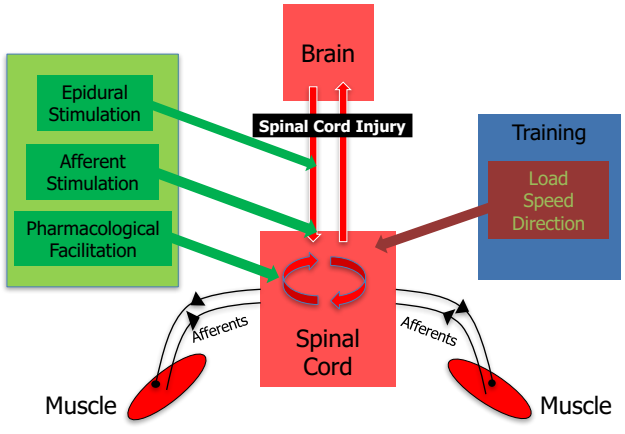
Casha et al. 2012, Fehlings et al. 2016

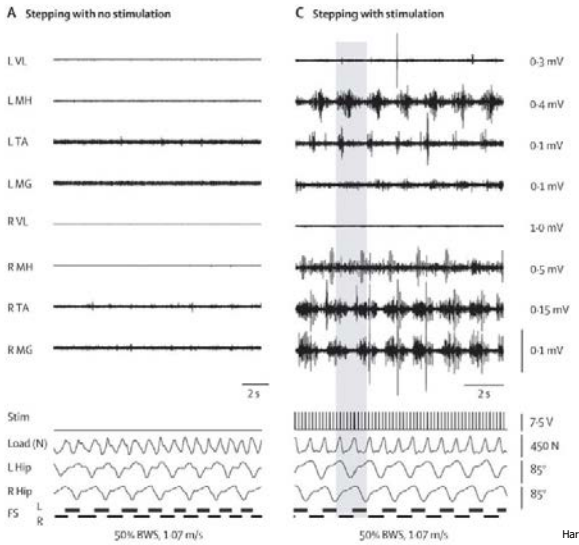
New rehabilitation & technological intervention

Epidural stimulation of the lumbosacral spinal cord



Modified from Edgerton et al., 2008

Epidural stimulation of the lumbosacral spinal cord



Harkema et al., Lancet 2011

Epidural stimulation of the lumbosacral spinal cord

Harkema et al., Lancet 2011

In witch patients could this technology be applied?

Key targets to restore function

Goal-directed rehabilitation (e.g. locomotion)
Colombo et al. 2001, Donati et al. 2016

Reactivation (e.g.neurostimulation)
Courtine et al. 2011, Angeli et al. 2014

Rewiring (e.g. anti-Nogo-A, chondroitinase ABC, stem cells)
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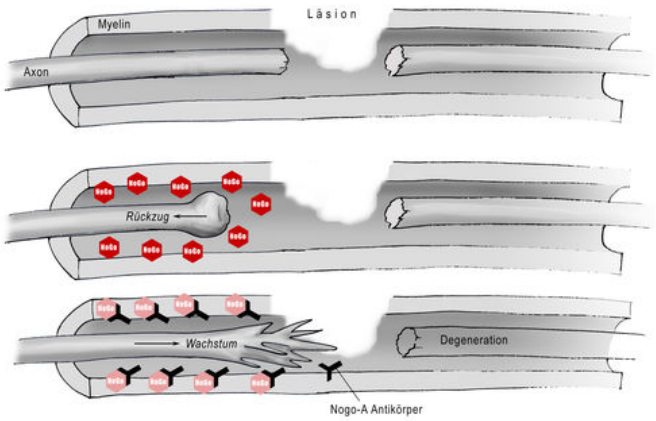
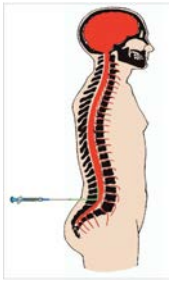
Neuroprotection (e.g. minocycline, riluzole, surgery)
Casha et al. 2012, Fehlings et al. 2016

Nogo-A



Nogo – A trial: First-in-man (phase I study)



Akute Querschnittlähmung:
- Feasibility ✔
- Safety ✔
- preliminary efficacy ✔

Cohort 1: 3 para treated

ATI355
24 hour inf
5 mg/day

Cohort 2: 3 para treated

ATI355
24 hour inf
30 mg/day

Cohort 3: 6 para treated

ATI355
14 day inf
15 mg/day
(total 210 mg)

Cohort 4a: 8 para & 3 tetra treated

ATI355
14-28 day inf
15 mg/day
(total 210 - 420 mg)

Cohort 4b: 7 para & 7 tetra treated

ATI355
6 repeated bol. injections
over 4 wks (22.5 mg/inj,
total 135 mg)

Cohort 5: 15 out of 17 tetra treated to date

ATI355
6 repeated bol. Injections
over 4 wks (45 mg/inj,
total 270 mg)

52 patients treated

Next steps….

- Phase II study in a european multicenter trail
- Started: January 2016
- First Patient in: January 2018
- Duration: 5 years
- Design: randomized double blinded
- Subjects: 158 patients with acute cervical SCI
- Involved centers: 7 hospitals

Key targets to restore function

Goal-directed rehabilitation (e.g. locomotion)
Colombo et al. 2001, Donati et al. 2016

Reactivation (e.g.neurostimulation)
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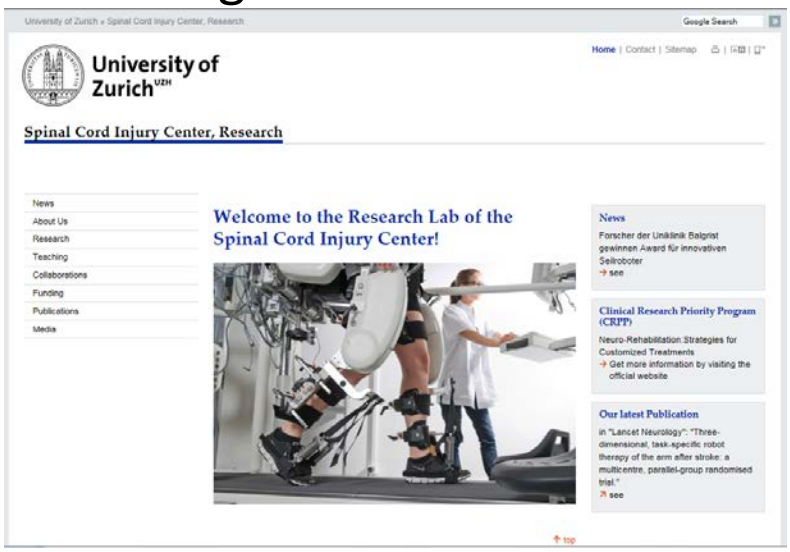
Looking for a master thesis?



http://www.sci-research.uzh.ch/teaching.html

Acknowledgement

SCI Research Lab Balgrist