Medical Grand Rounds
National Rehabilitation Hospital
Friday, 20 February, 2009

Highlights of "Summer School on Biological Treatment of Chronic Spinal Cord Injury"

at the University of Vienna (Austria) Medical School, October 2008

Arthur Sherwood, Science and Technology Advisor

National Institute on Disability and Rehabilitation Research (NIDRR)
Office of Special Education and Rehabilitative Services (OSERS)
US Department of Education

Overview

- This information is taken from the presenter's participation in the:

  Summer School[1] for Biological Control of Chronic Spinal Cord Injury, University of Vienna Medical School, Vienna, Austria, October 5-10, 2009

- Sponsored by the Foundation for Movement Recovery, Oslo, Norway and the Medical School of the University of Vienna

- Conference web site: http://movement.fesworkshop.org/Default.aspx

1-Summer School refers to the didactic nature of the meeting, not the calendar

Common goals for the Summer School:

- To advance the current clinical treatment of SCI.
- To review the potential value of experimental therapies..
- To discuss functional surgery of the human spinal cord.
- To demonstrate the significance of neurophysiological assessment in developing treatment programs for individuals with SCI.

- NOTE: The meeting was *not* intended to adjudicate which intervention was *better*; indeed realistic intervention approaches will likely require a *cocktail* approach.

Participants at the

Summer School on the Biological Treatment of Chronic SCI

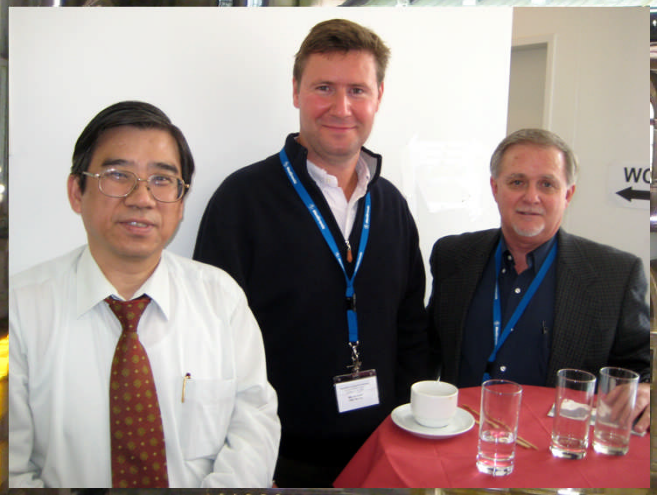
University of Vienna Medical School,

Oct. 5-10, 2008

Background: Why this meeting was important

- The natural history of SCI is complex. It:
  - Is highly variable among individuals;
  - Requires that parameters of natural recovery be carefully identified;
  - Includes neuroplastic changes in the brain as well as spinal cord; and
  - Requires objective measures for optimum treatment implementation.
- Recovery trials are underway.:
  - Preclinical experimental work must be adequate;
  - Only incremental changes are expected; and
  - The role of rehabilitation must be clarified
- Multiple challenges to recovery call for
  - Advanced treatment designs.
  - Careful monitoring

Lots of networking opportunities

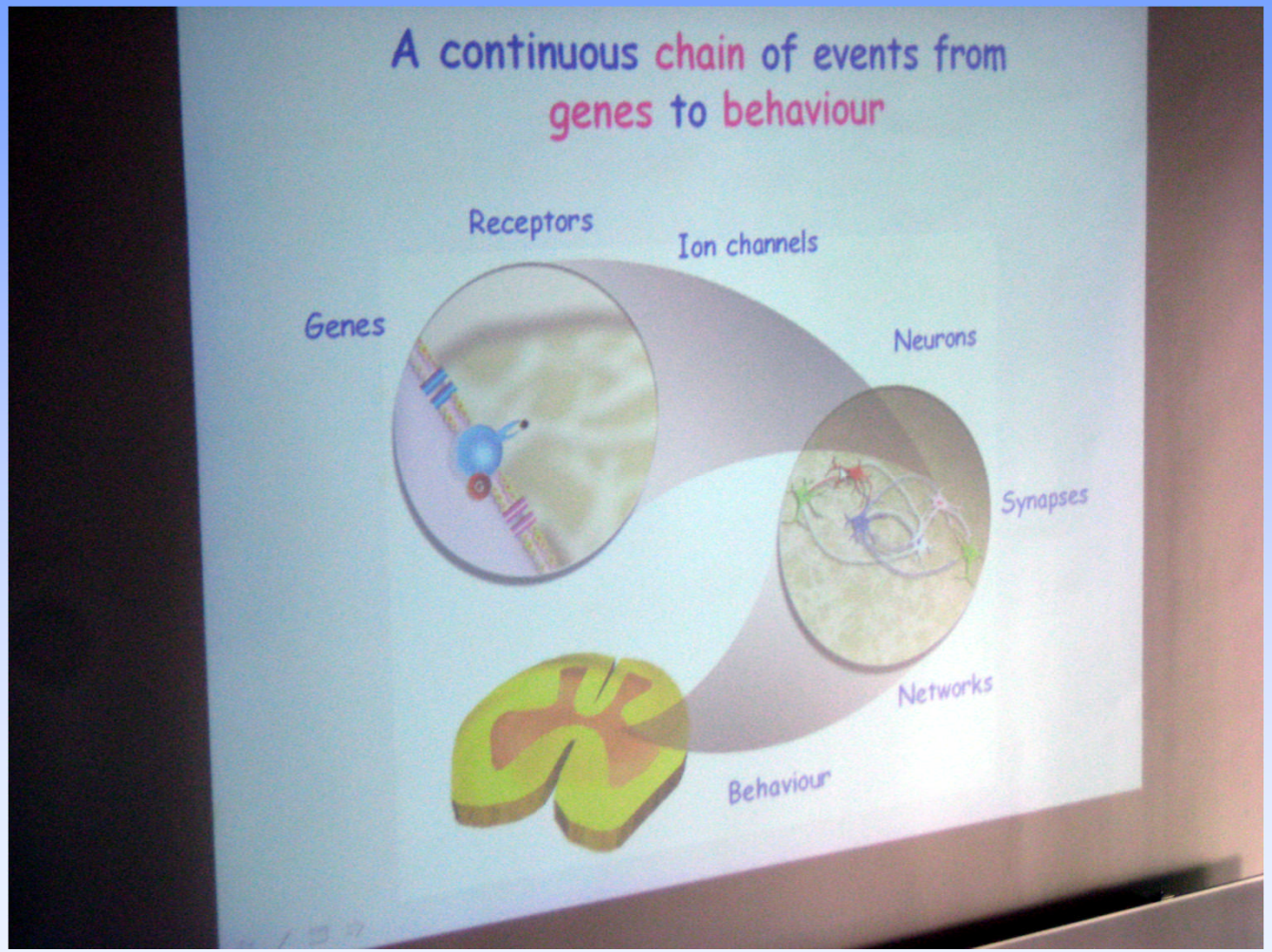


Three Types of Attendees; Three Types of Presentations – and framework for this presentation

- Neuroscientists involved in the basic science of movement (locomotion).
  - Described complex capabilities of the spinal cord (SC)
  - In both experimental and clinical models
- Human Neuroscientists & Professionals involved in assessment of motor control and monitoring spinal cord functions.
  - Demonstrated objective, neurophysiological methods of documenting functional status of the SC
  - Objectively documented changes in early recovery after SCI
  - Characterized their efforts, describing (published) results
- Surgeons and Physicians attempting experimental therapy.

Basic Science of Movement

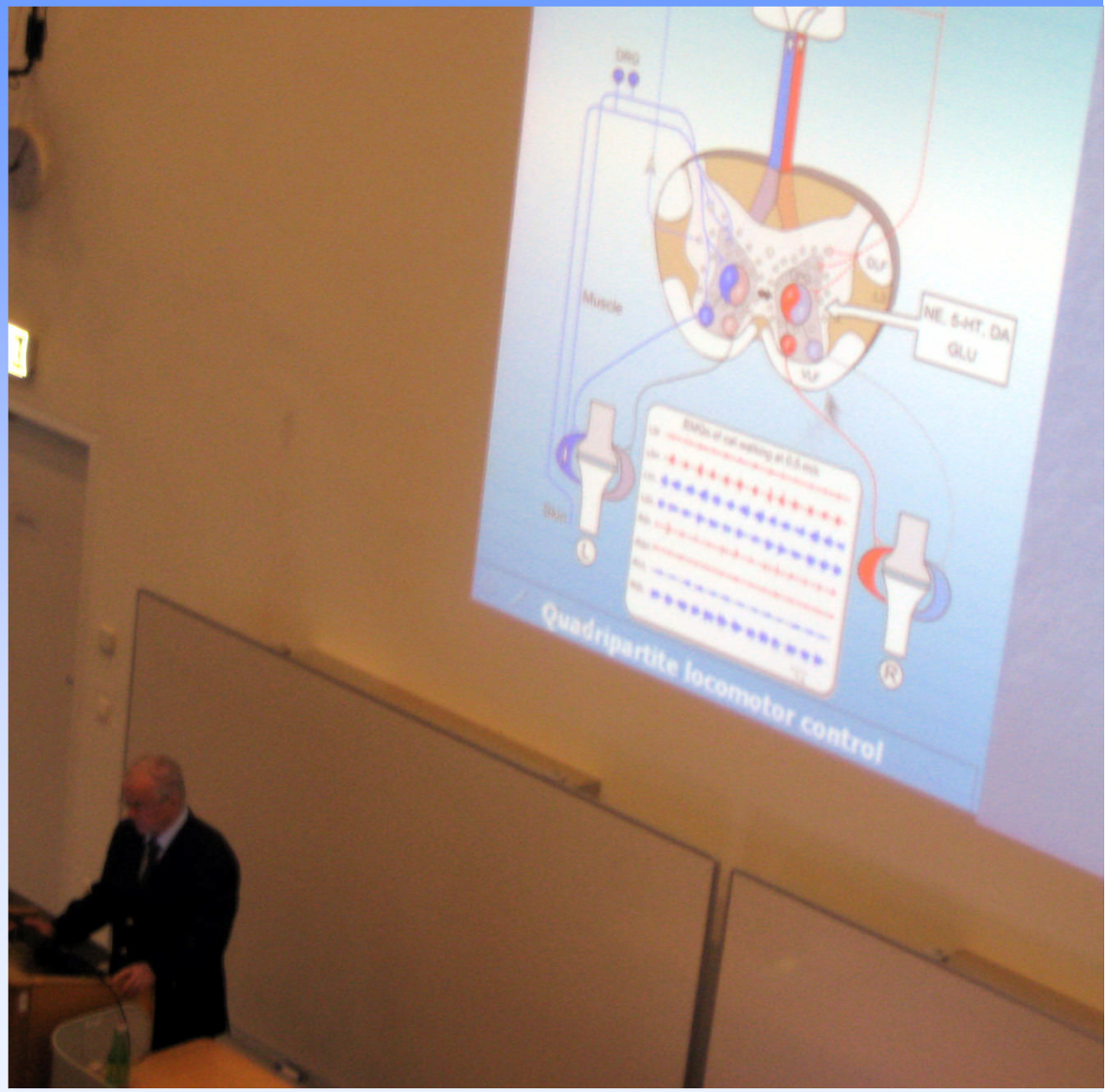
Sten Grillner: Spinal Locomotor CPG: From Ion Channels to Neuronal Networks



Presenter: Grillner

Serge Rossignol

- CPG in the recovery of locomotion after partial spinal cord lesions

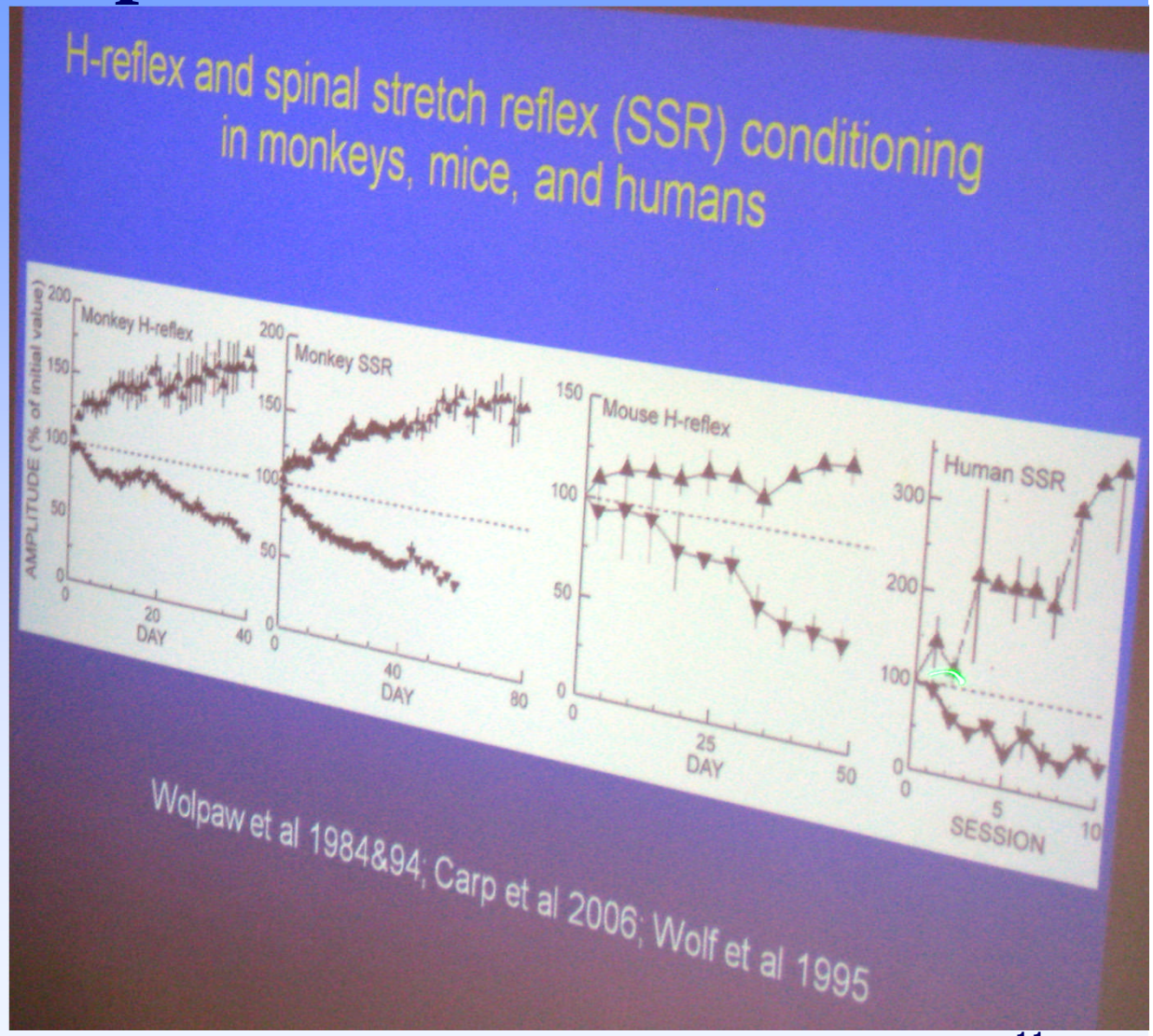


Presenter: Rossignol

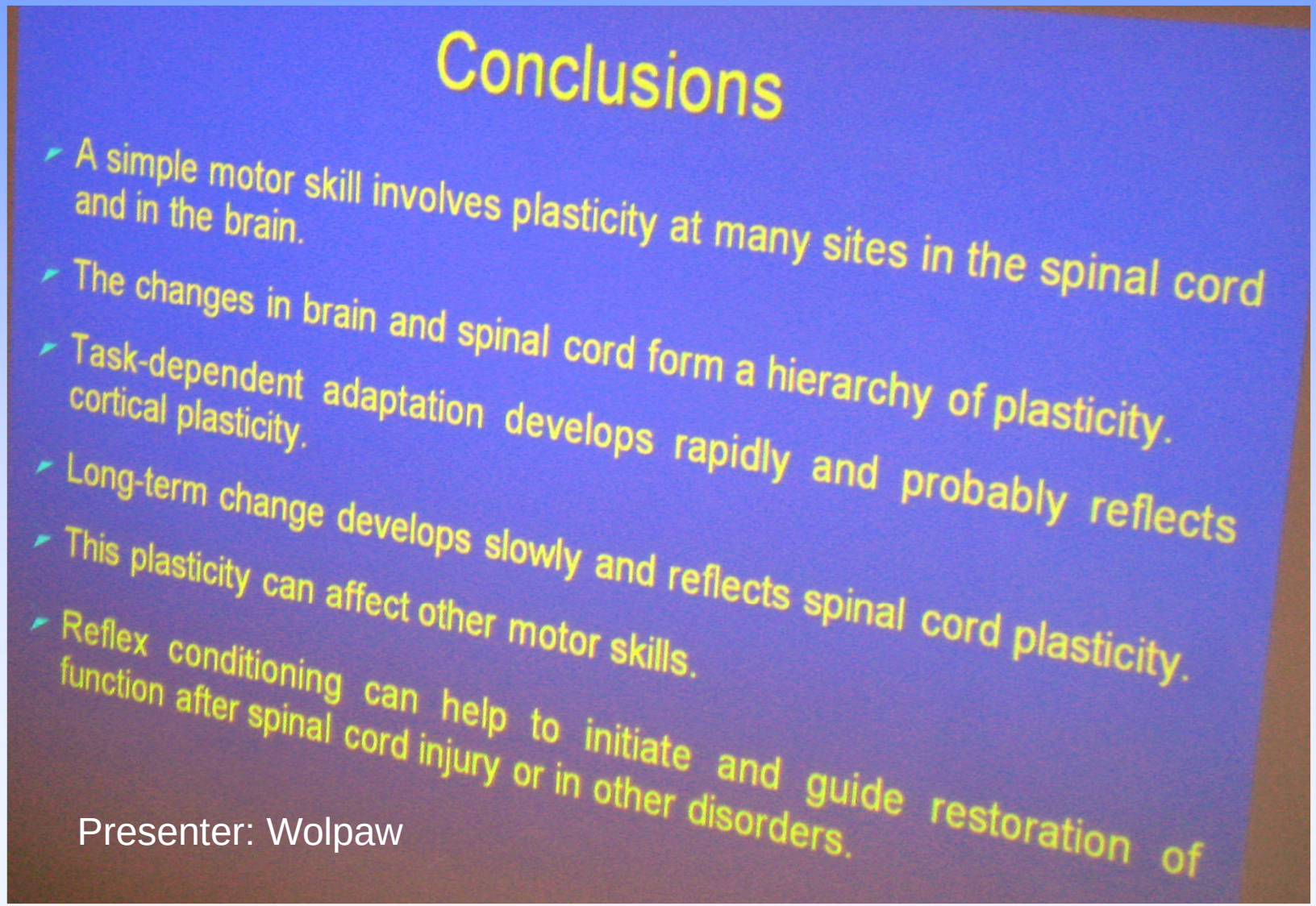
Jonathan R. Wolpaw

- Adaptive plasticity of spinal cord reflexes: CNS mechanisms and therapeutic uses

Presenter: Wolpaw

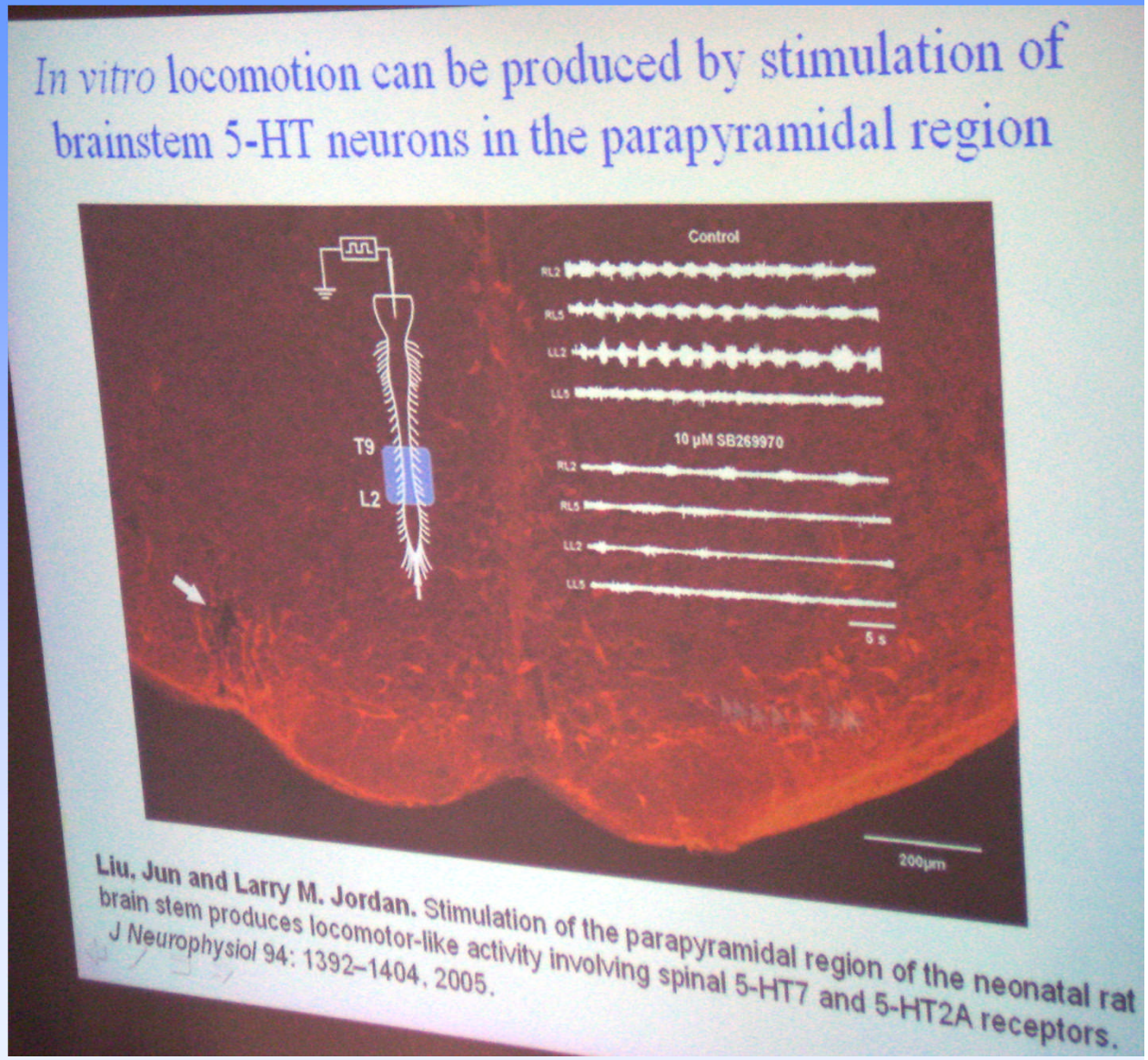


Jonathan Wolpaw: hierarchy of neuroplasticity



Larry Jordan:

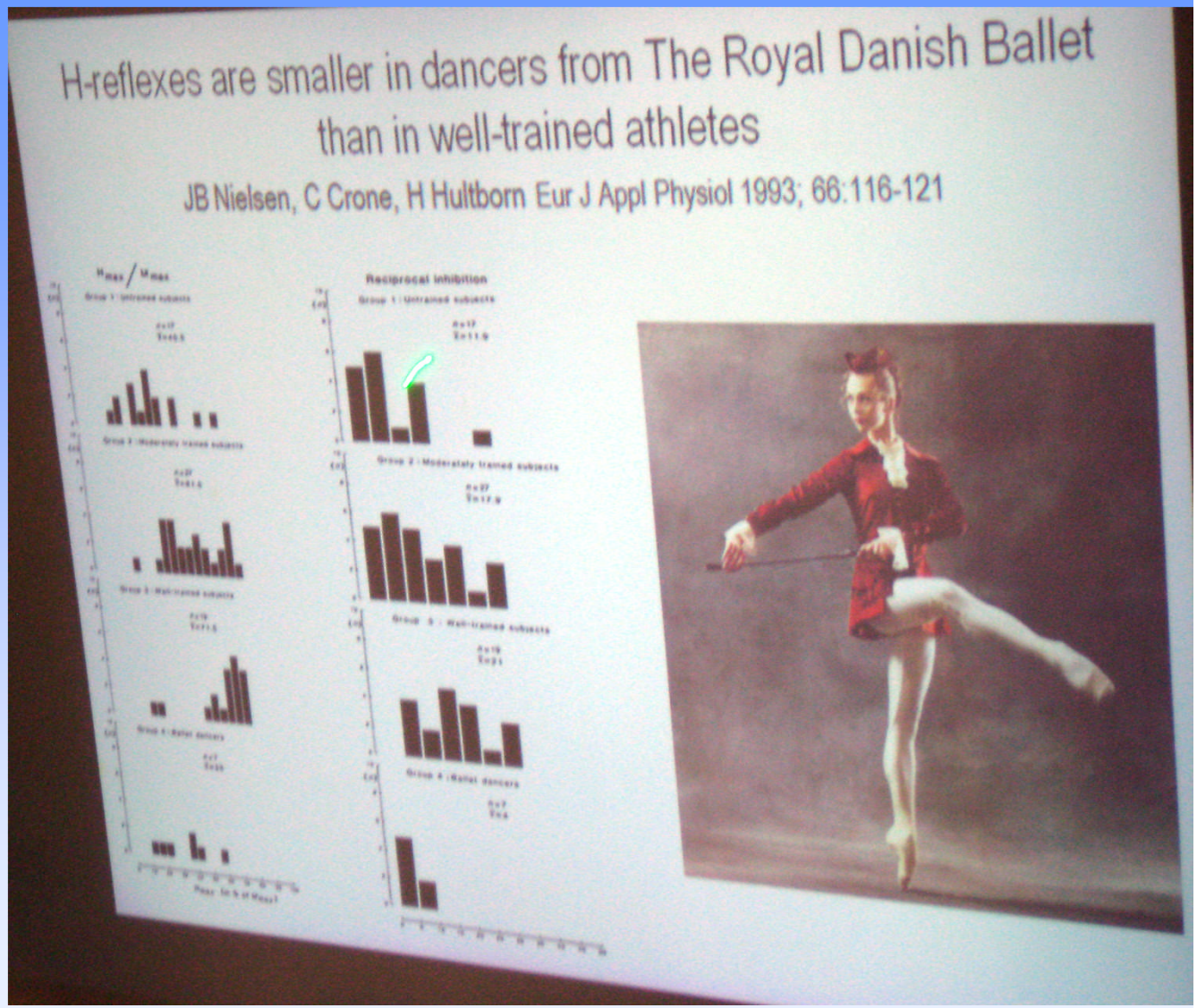
- Brainstem and spinal neural systems for the initiation of locomotion



Presenter: Jordan

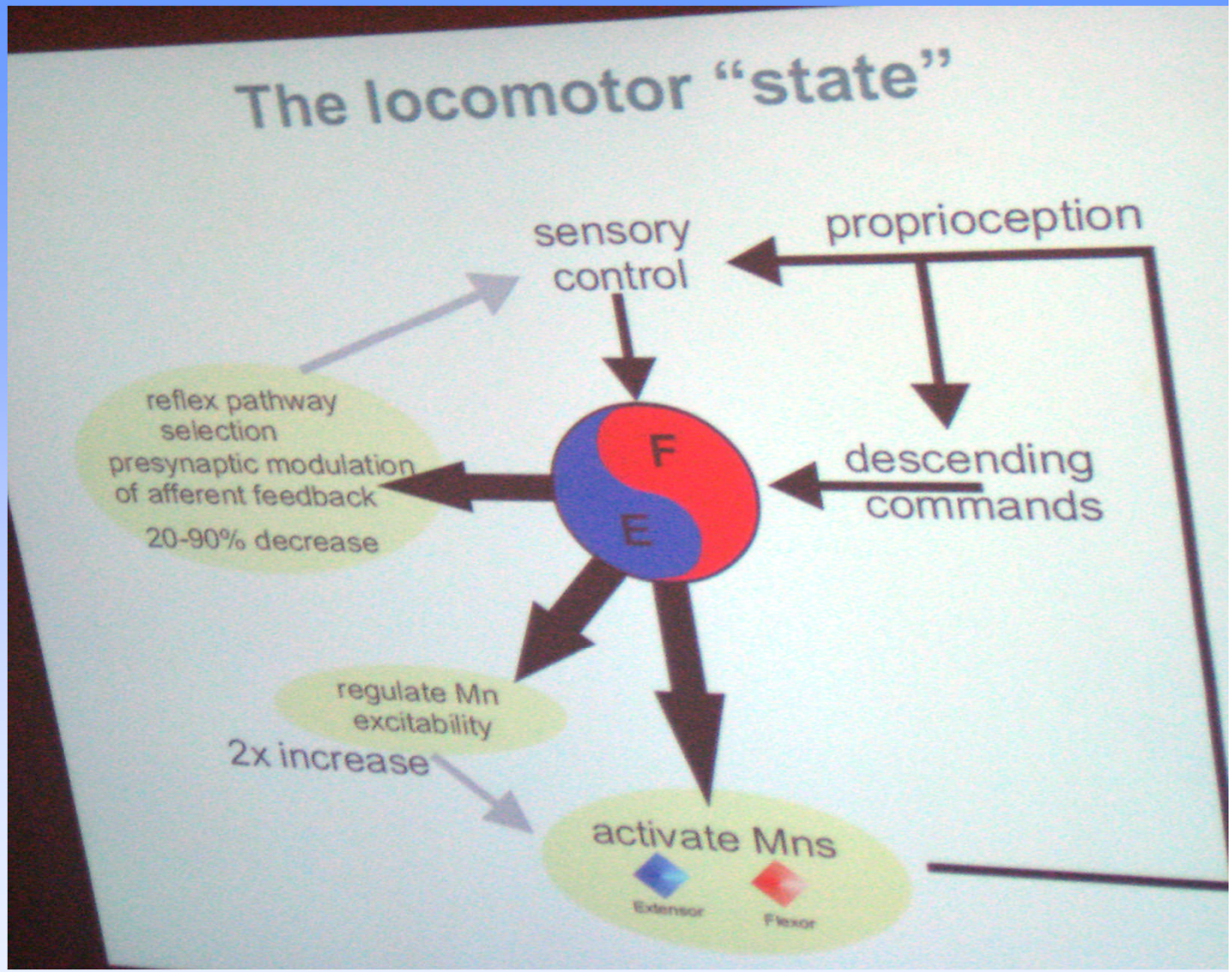
Hans Hultborn

- Plasticity at motoneuronal level following spinal cord lesions.



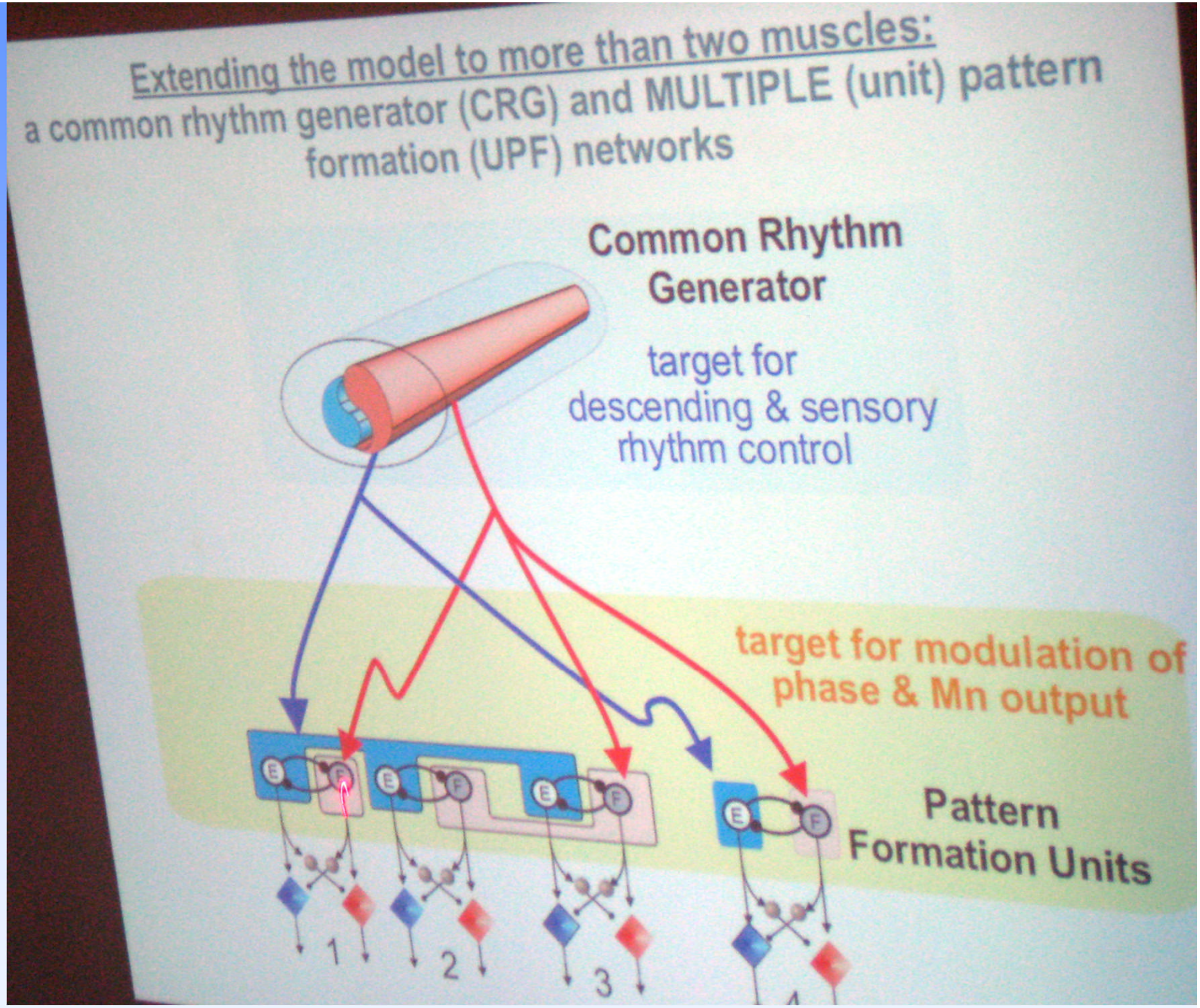
Presenter: Hultborn

Creating the Locomotor State: The Organization of the Mammalian Locomotor CPG



http://www.youtube.com/watch?v=UXPJJeISuXo

Presenter: McCrea



Presenter: McCrea

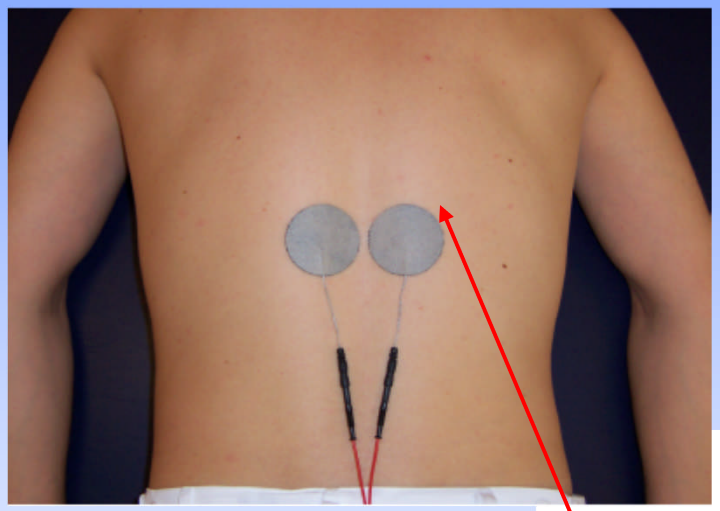
Assessment and Monitoring of Spinal Cord Functions

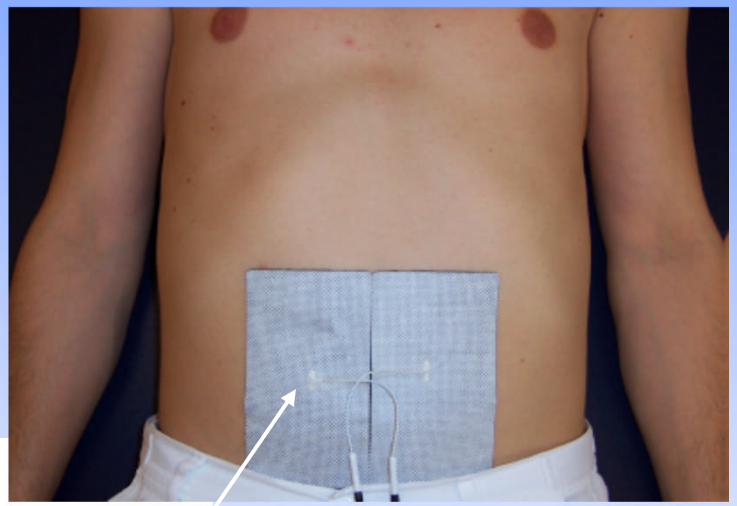
Brain Motor Control Assessment (BMCA)*, Posterior Root Muscle (PRM) Reflexes*, and Intraoperative Monitoring

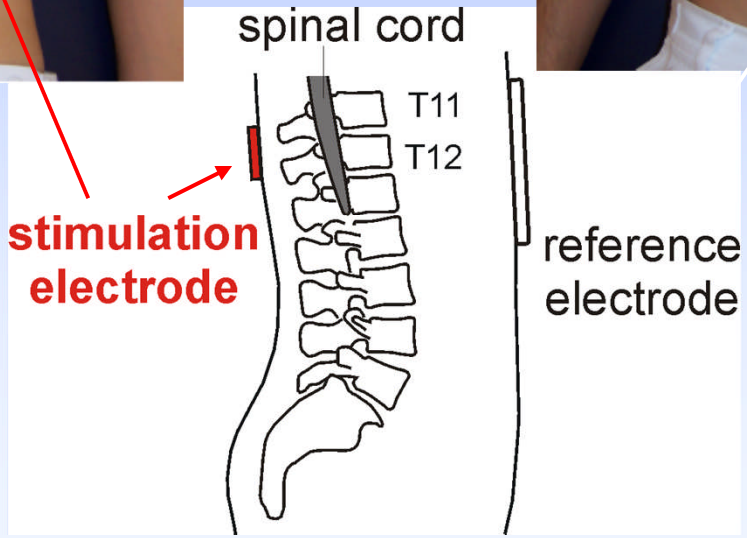
* Demonstration workshops on these topics were held each afternoon (Mon-Thur)

Assessment of Lumbar Neuronal Circuitry – Posterior Root Muscle (PRM) Reflexes

- Electrode placement

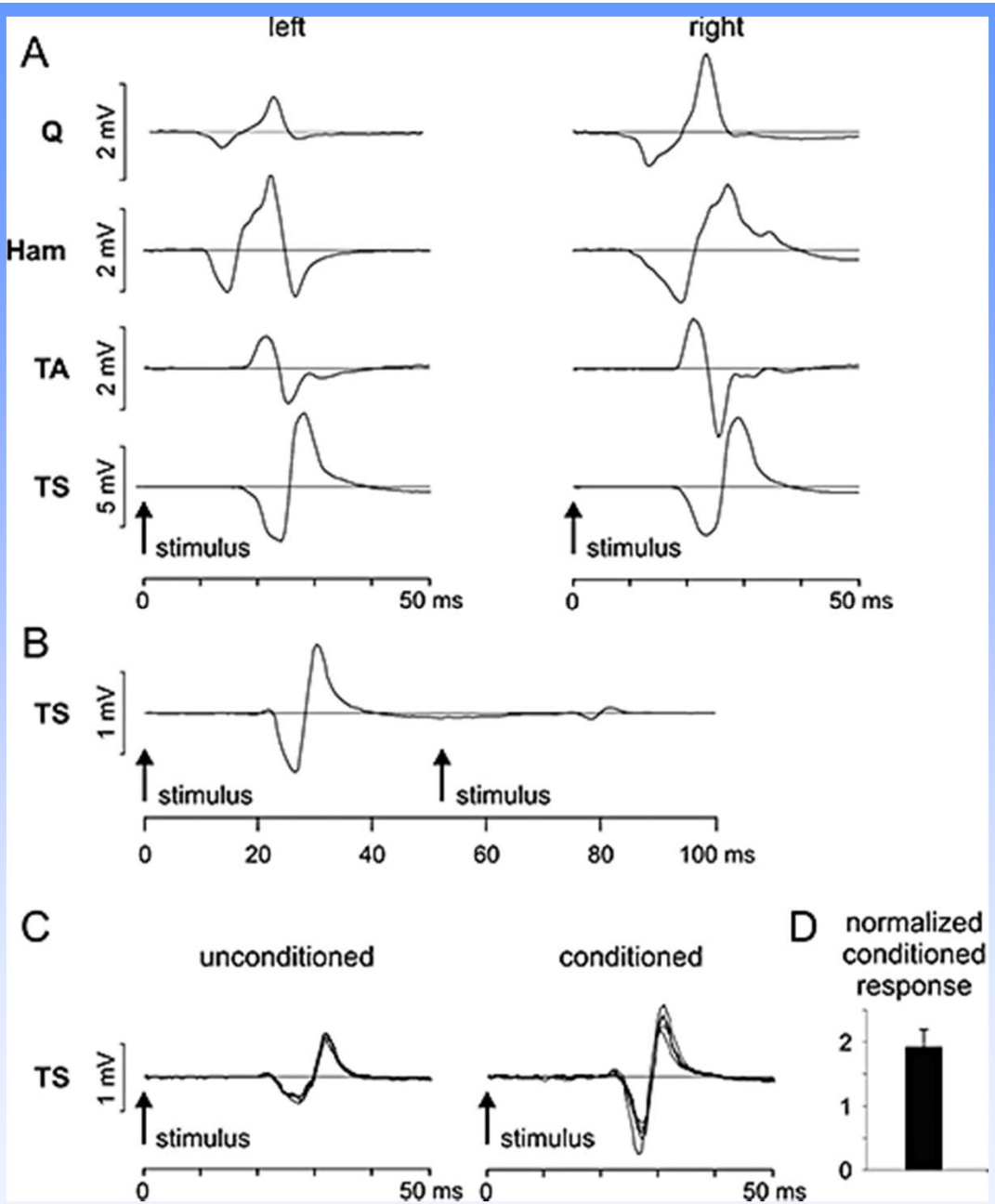






PRM Method

- A. bilateral elicitation of PRM (all sweeps 5 superimposed.
- B. Responses to paired stimuli (50 ms interval).
- C. Unconditioned and volitional conditioning.
- D. Conditioned amplitude.
- Legend
  - Q- Quadriceps
  - H- Hamstrings
  - TA- Tibialis Anterior
  - TS- Triceps Surae

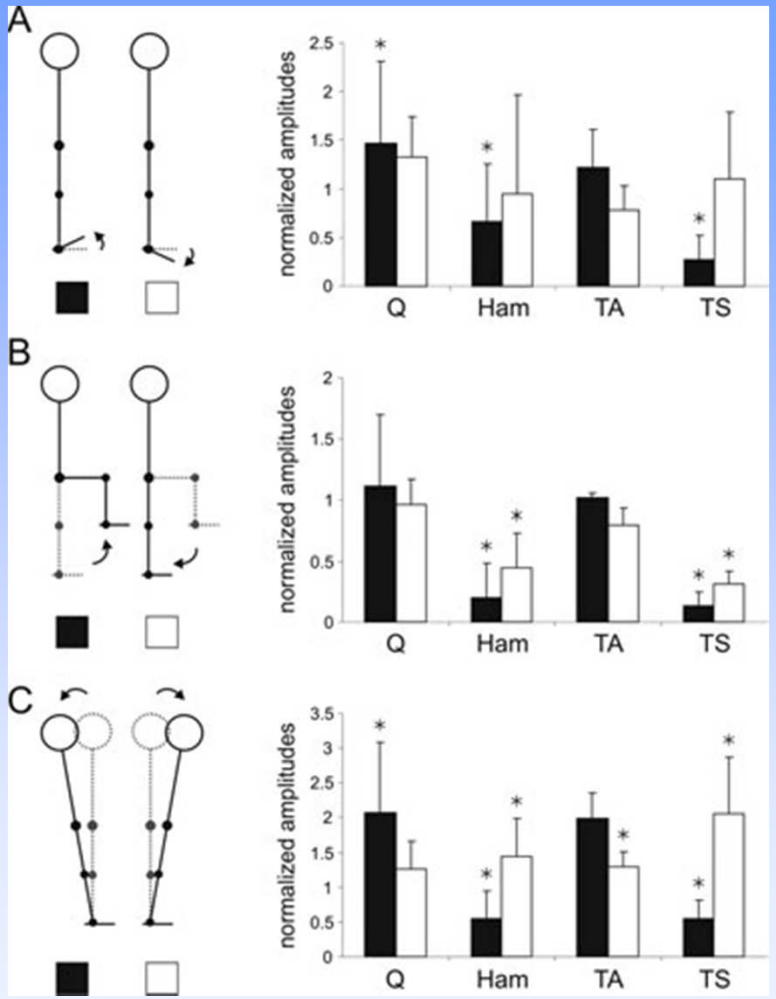


Presenter: Minassian

Hofstoetter , Artif. Organs, 2008

PRM Conditioning

- All maneuvers in standing position.
- A. Unilateral dorsal (black bars) and plantar flexion (white bars).
- B. Unilateral multijoint flexion and extension (black and white, resp.)
- C. Leaning back (black) and forward (white)
- Legend: as prev.



Presenter: Minassian

Hofstoetter , Artif. Organs, 2008

Assessment of Spinal Cord Injury Using the Brain Motor Control Assessment (BMCA) Protocol

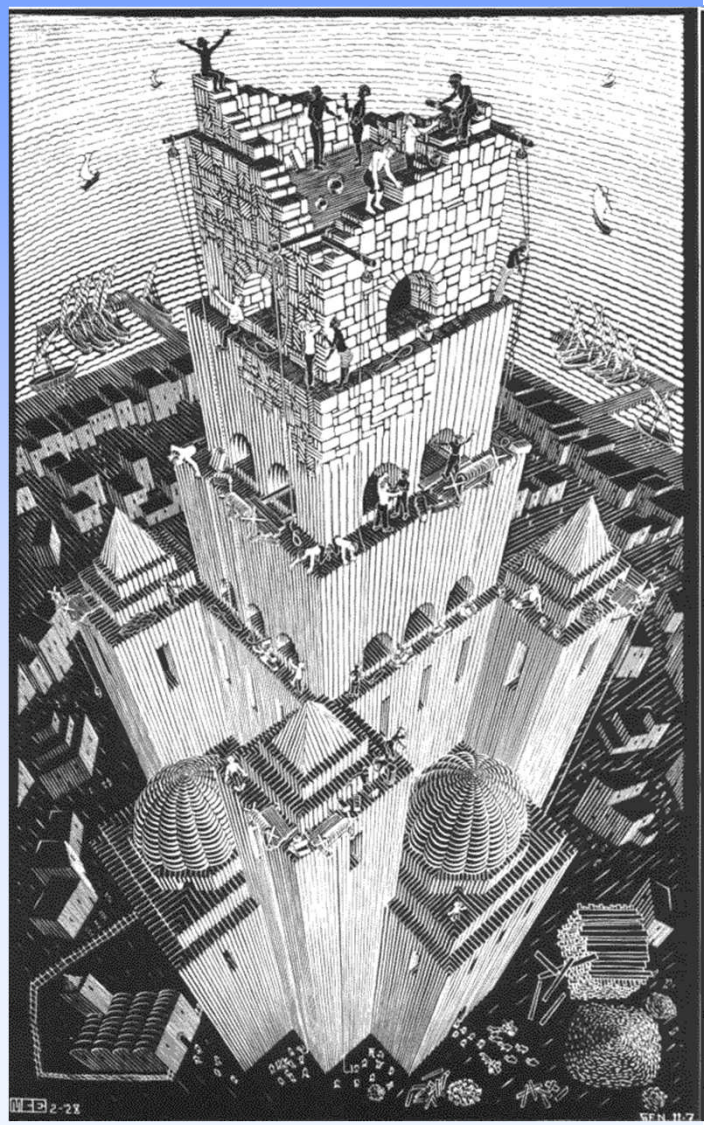
Purpose: to develop and validate a tool that will

- Uncover and characterize
  - clinically unrecognizable evidence of translesional connections between the brain and brainstem, and spinal cord motor networks
- Track
  - Recovery,
  - Progression, and
  - Intervention effect.

Presenter: Sherwood

“in other words”, the BMCA will

- Create a new language of motor control to describe the state of patient and improve ability to communicate with and about patients
- Supplement the clinical languages
  - ASIA Impairment Scale, Ashworth, FIM, SCIM, etc., i.e., inverting the tower of Babel



Presenter: Sherwood

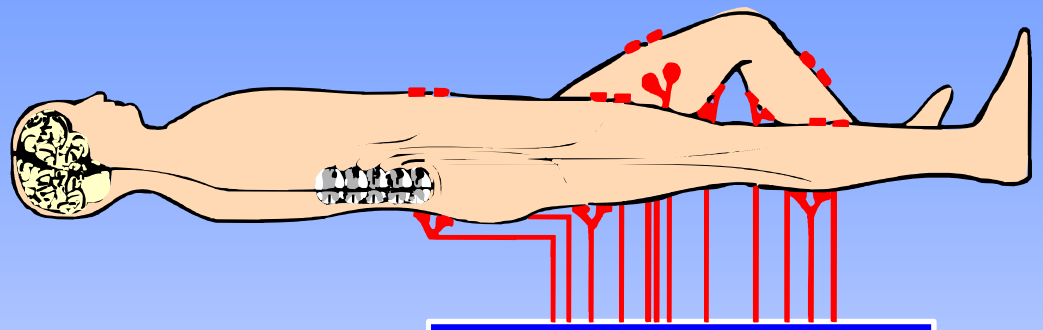
A new BMCA language that will:

- Improve *communication*
- Have its own grammar and syntax (technology)
- Have a vocabulary (phenomenology)
- Become interesting only when used to tell a story or even better, write a poem, to describe, e.g.,
  - what is a voluntarily triggered spasm?

Presenter: Sherwood

BMCA Protocol

Relaxation
Reinforcement Maneuvers
Voluntary maneuvers
Passive maneuvers
Tendon taps
Manual clonus
Vibration
Plantar stimulation
Volitional suppression of withdrawal reflex
Transcranial Magnetic Stimulation



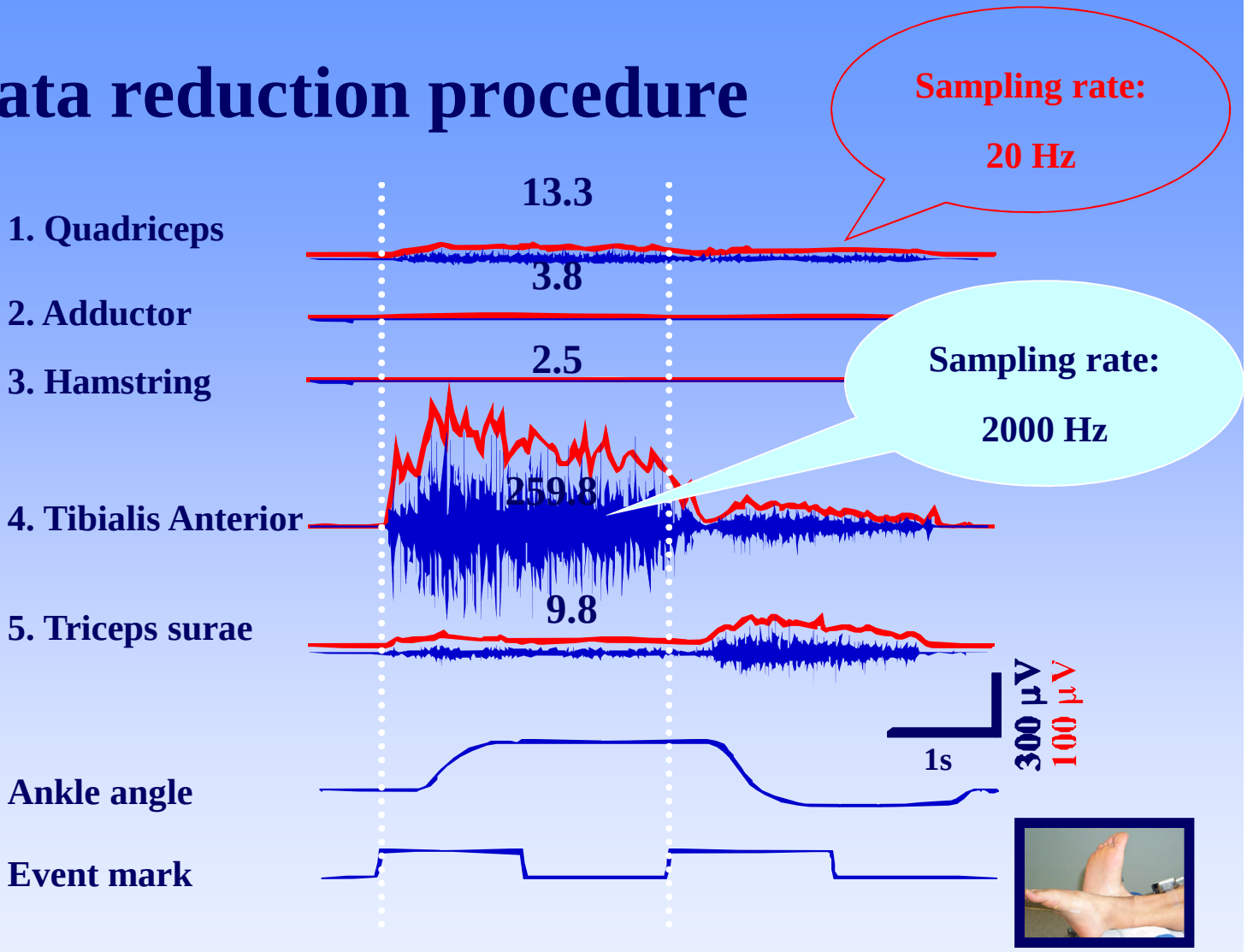
Surface EMG Right and Left

Quadriceps (Q)
Adductor (A)
Hamstrings (HS)
Tibialis Anterior (TA)
Triceps Surae (TS)
Abdominal (Abdom)
Paraspinal (Parasp)

Presenter: Sherwood

Sherwood *Muscle Nerve*, 1996

BMCA Data reduction procedure



Surface electromyographic (sEMG) activity example:
of voluntary ankle dorsiflexion and plantar flexion in a healthy subject

Presenter: Sherwood

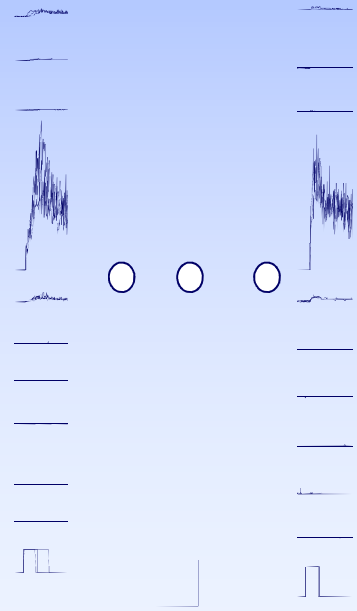
BMCA: Similarity Index (SI)

$$SI = \vec{A} \bullet \vec{B} = |A||B|\cos\theta$$

Vector (A)

Healthy Subjects

Prototype Response Vector



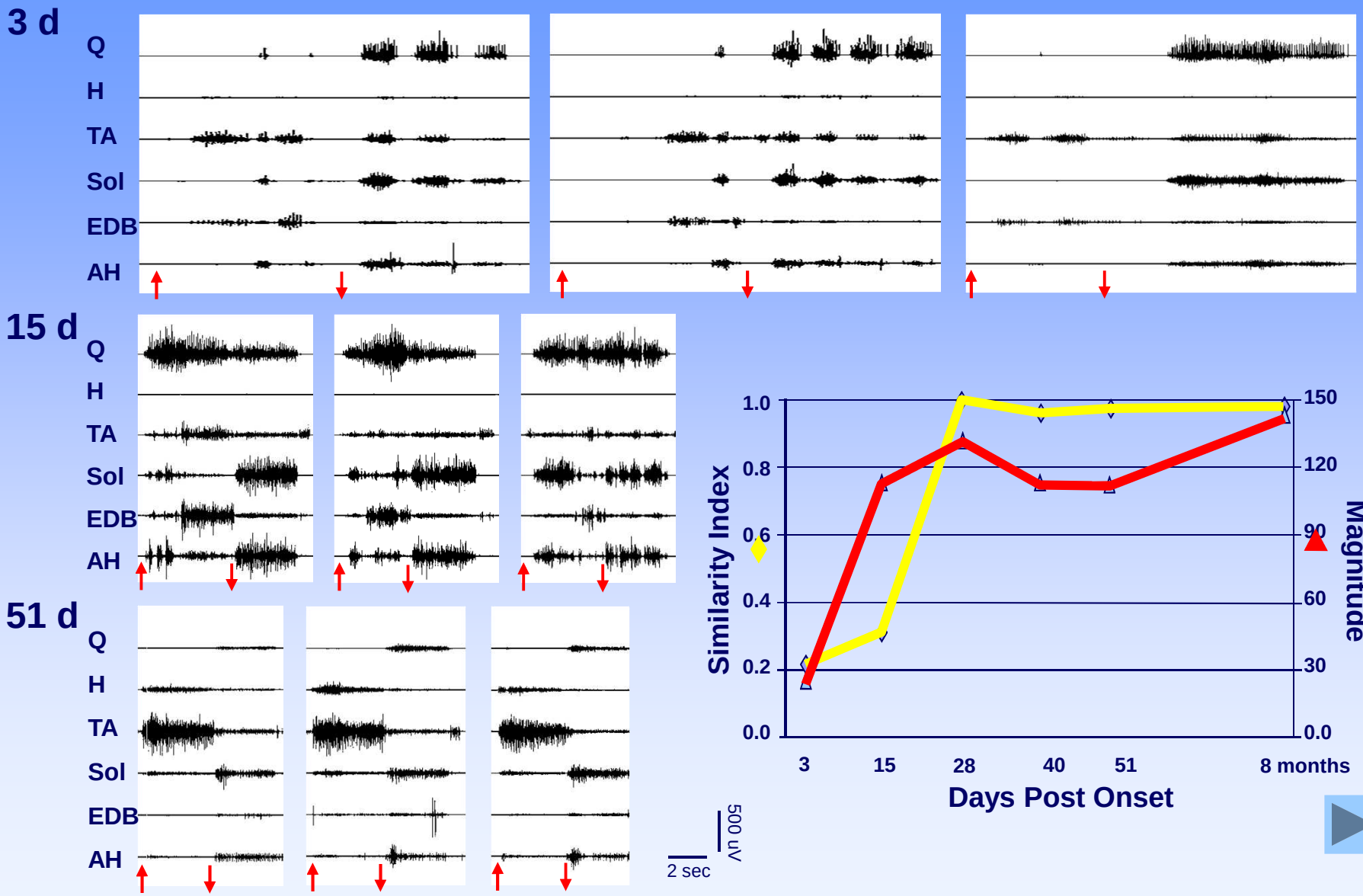
Response Vector

Vector (B)

Test Subject (w/SCI)

Presenter: Sherwood

Natural History of SCI: Early recovery of voluntary control



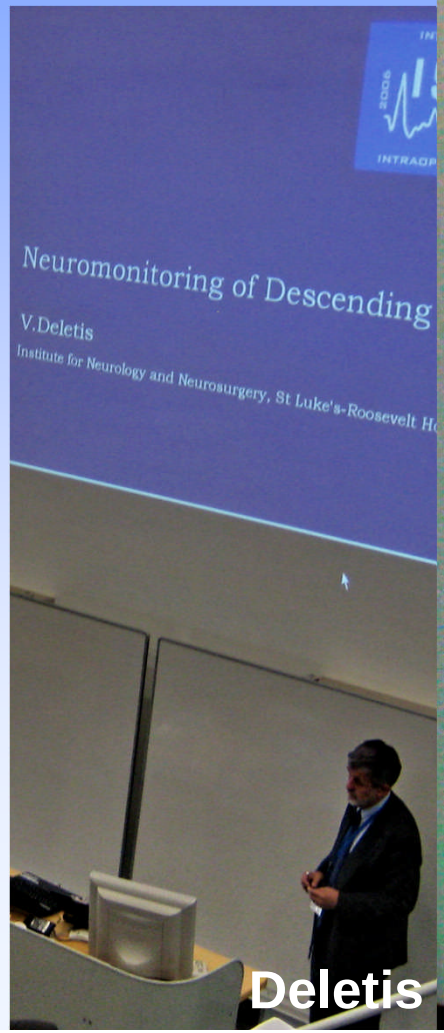
Presenter: McKay

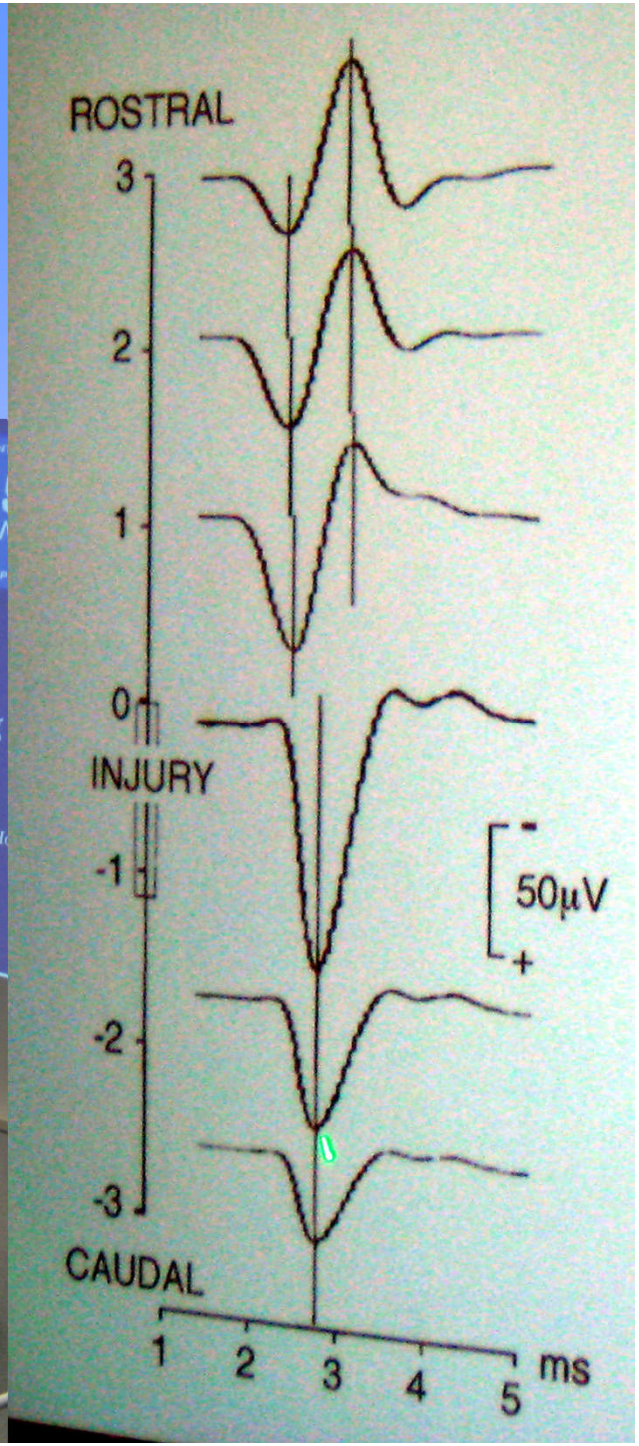
Ankle dorsal-(↑) plantar (↓) flexion

Neuromonitoring of Acute SCI

- Intraoperative monitoring in acute injury
- “killed end” injury potential after SCI (human)
- Opportunity to examine function of cord in immediate post-injury state
- Ascending, descending tracts

Presenter: Deletis





Experimental Therapies

Lammertse Zhang Dimitrijević Young Huang Sherwood

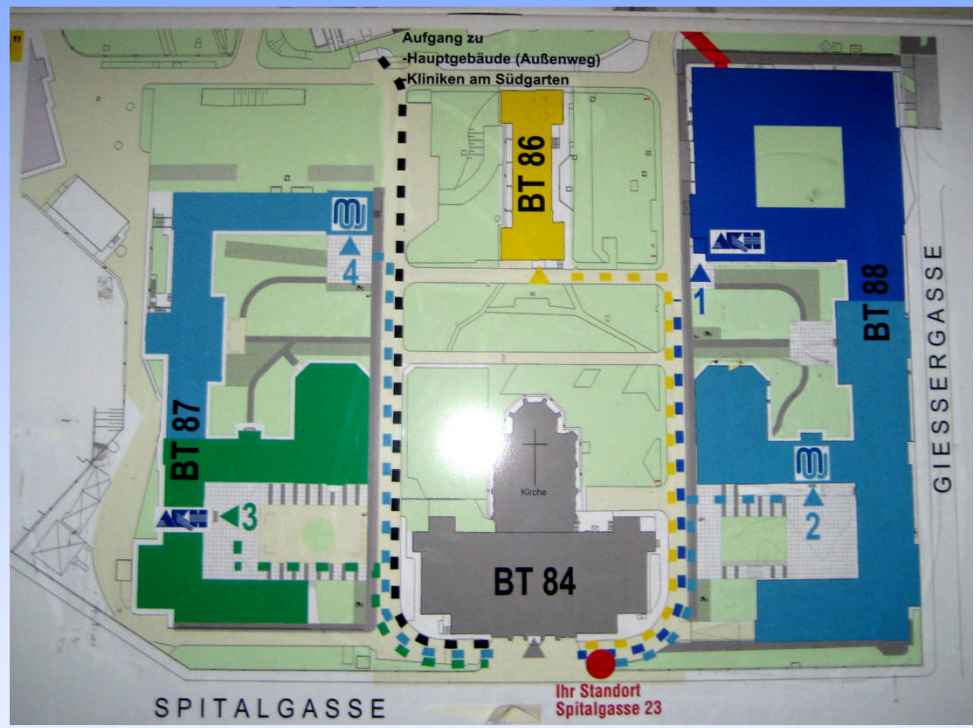
Experimental Treatments for Spinal Cord Injury

- Cellular Therapy Interventions: transplantation of:
  - olfactory ensheathing cells;
  - peripheral nerves;
  - Schwann cells,
  - embryonic CNS tissue;
  - embryonic/progenitor cells;
  - adult stem/progenitor cells;
  - engineered stem/progenitor cells;
  - activated macrophages;

Presenter: Dimitrijević

Experimental Treatments for Spinal Cord Injury (cont'd.)

- Molecular Therapeutic Intervention:
  - neuroprotective therapies;
  - enhancing conduction;
  - growth factors.
  - cAMP or small GTPases; and
  - Extracellular matrix modifiers.

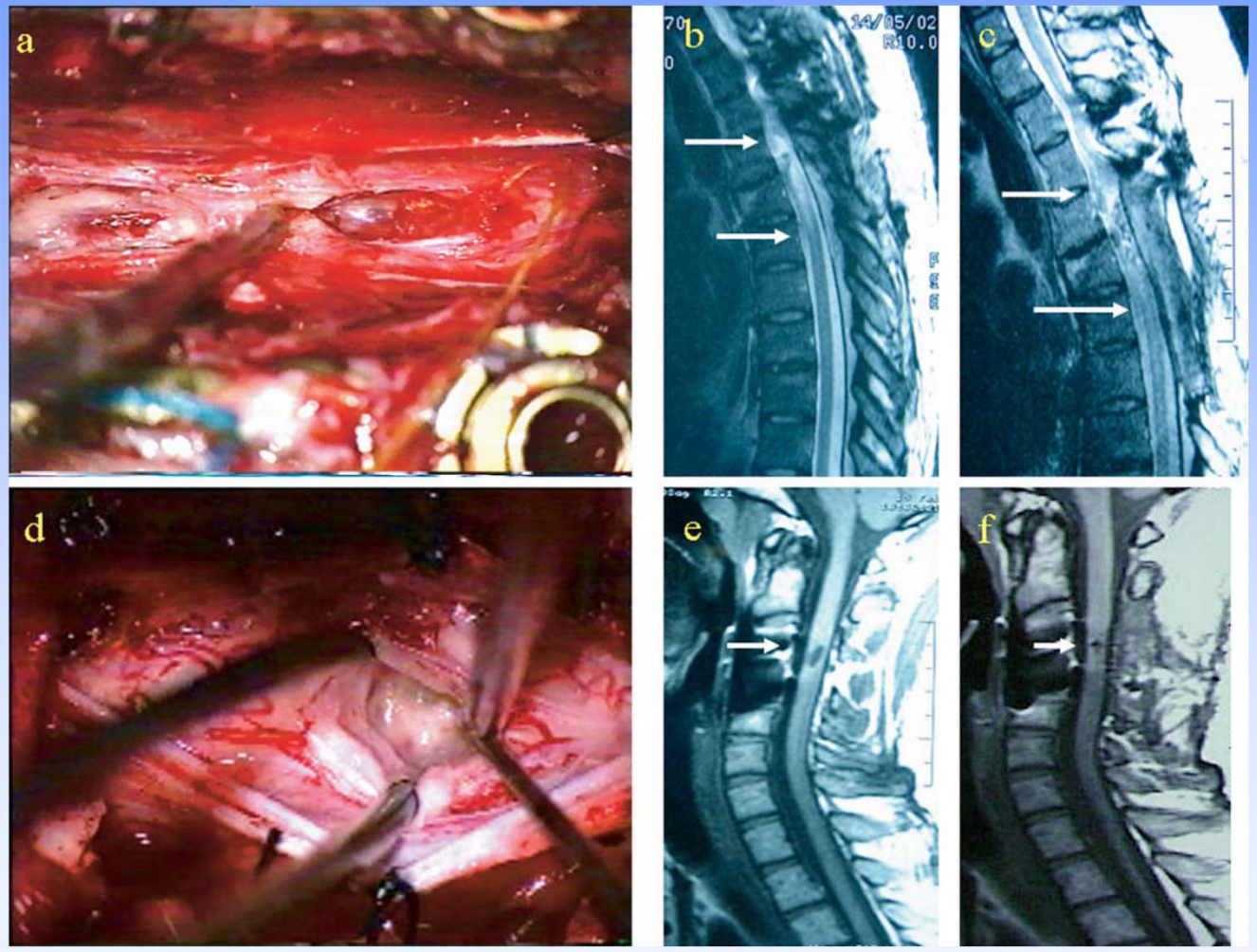


Presenter: Dimitrijević

Olfactory Mucosal Autografts and Overground Gait Training: a Combination Therapy for Human Chronic SCI Recovery

Presenter: Lima

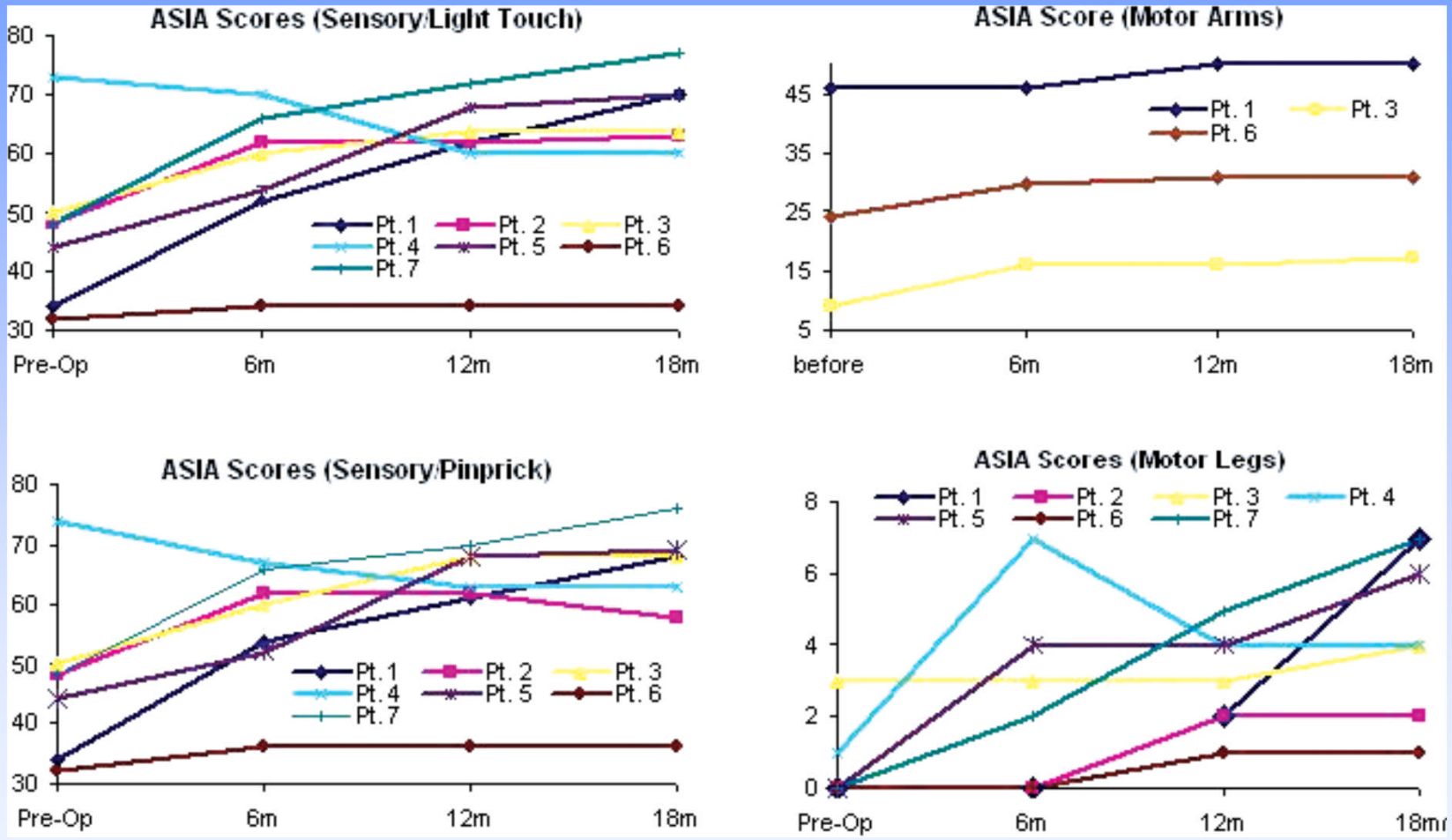
Carlos Lima: Olfactory Mucosa Autografts in Human Spinal Cord Injury: A Pilot Clinical Study



Presenter: Lima

Lima et al.: *J Spinal Cord Med*. 2006

Lima: Early results: J SC Med: 2006

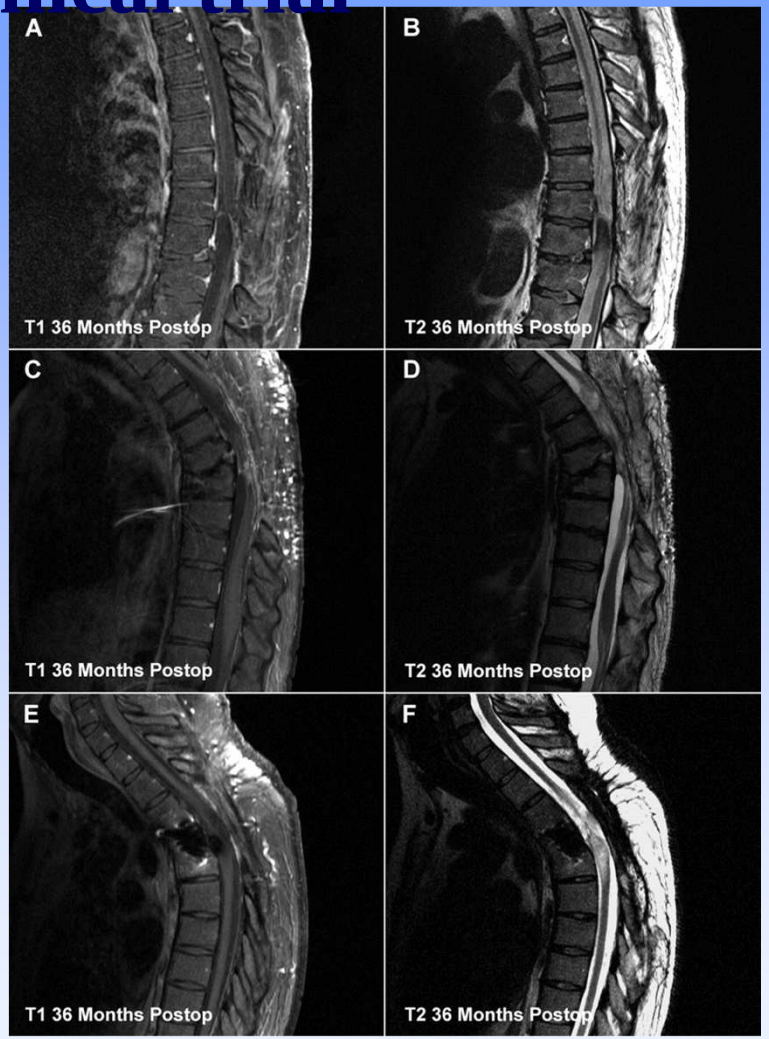


Presenter: Lima

Lima et al.: *J Spinal Cord Med*. 2006

Mackay-Sim: Autologous olfactory ensheathing cell transplantation in human paraplegia: a 3 year clinical trial

- Sagittal MR imaging of patients at 36 months after olfactory ensheathing cell transplants
- Images from the three implanted subjects are shown in pairs, T1-weighted on the left, T2-weighted on the right

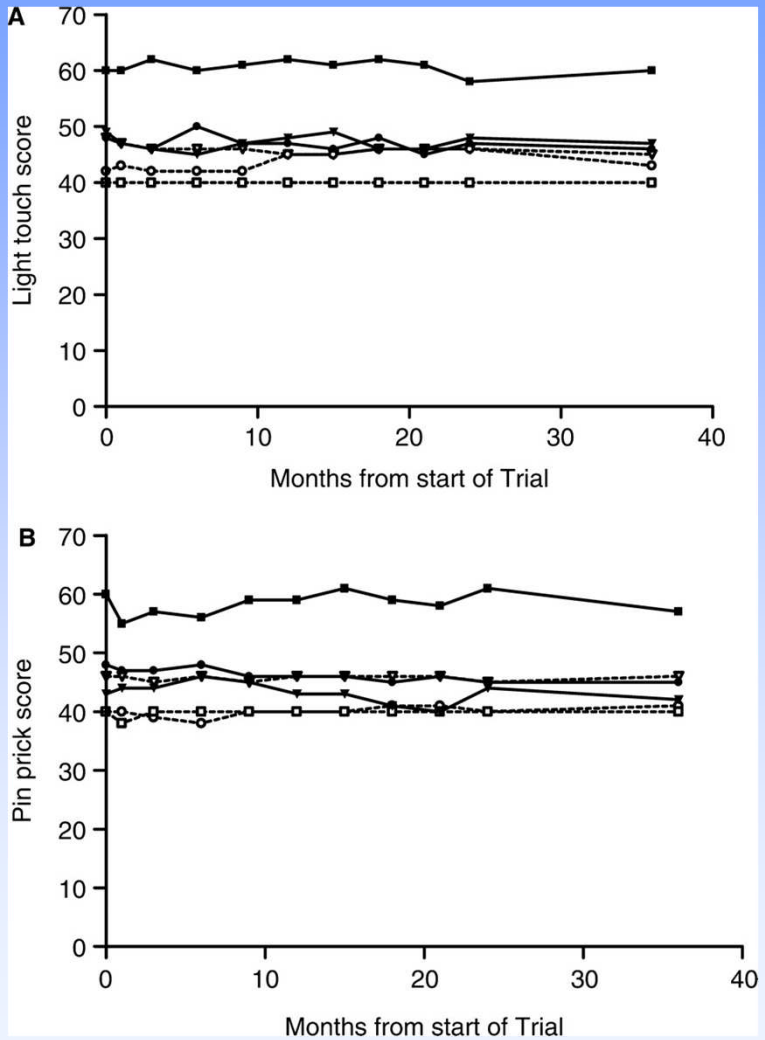


Presenter: Mackay-Sim

Mackay-Sim *Brain*, 2008

ASIA sensory scores during the period of the trial – A – light touch, B- pin prick

- Transplant recipients (closed symbols, lines), and
- Controls (open symbols, dotted lines).

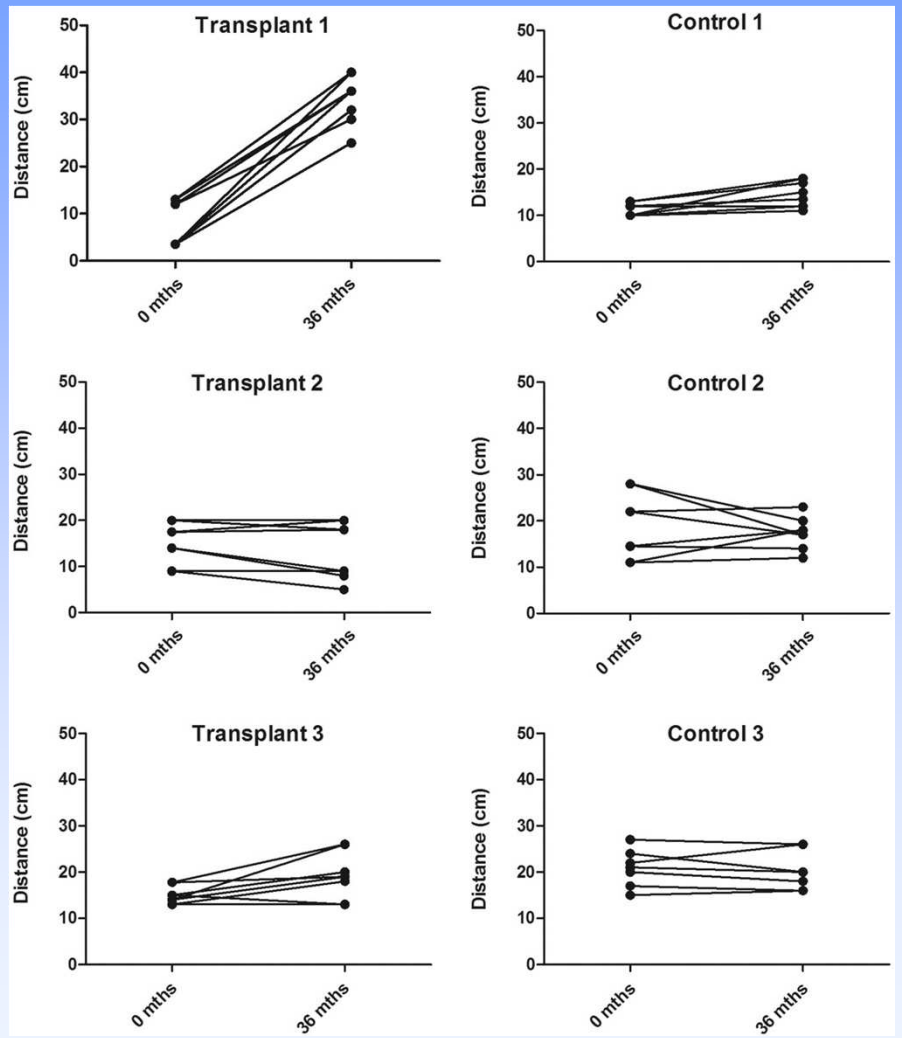


Presenter: Mackay-Sim

Mackay-Sim *Brain*, 2008

Changes in light touch and pin prick sensitivity during the period [of] the trial

- **Differences in location** of sensitivity to light touch and pin prick, anteriorly and posteriorly (8 measurements per patient)
- At baseline and 3 years post implant



Presenter: Mackay-Sim

Mackay-Sim *Brain*, 2008

Hongyun Huang

- Long term follow-up results of fetal olfactory ensheathing cell (OEC) transplants for patients with chronic spinal cord injury
- 11/2001 to 12/2003, 300 patients (222 complete, 78 incomplete, 6 months – 31 years, avg. 3.1 years) received fetal OEC transplantation
- Injections into the SC at the upper and lower ends of the injury site..

Presenter: Huang

Spinal Cord (2006) 44, 135–142

www.nature.com/sc

Case Report

Rapid recovery of segmental neurological function in a tetraplegic patient following transplantation of fetal olfactory bulb-derived cells

J Guest*[,1,2,3], LP Herrera[2] and T Qian[2,3]

[1]*The Department of Neurological Surgery, University of Miami, Lois Pope LIFE Center, Miami, FL, USA;*
[2]*The Miami P... SA;*
[3]*The Miami V...*

The first and third authors of this case report acted as observers of this transplant series[14] over a 12-day period and wrote this report. These authors systematically examined the patient prior to surgery, observed the operative procedure, and followed the patient clinically for 8 days post-operatively.

Stu... cell
Obj...
inje...
Sett...
Met... trans-
plan... been
hyp... y, or
axo... rapid
imp... plete
SCI... cells.
The... o had
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inde... s.
Spin...

Keywords: spinal cord injury; cell transplantation; olfactory ensheathing glia; stem cells

Presenter: Hwang

Huang (cont.)

Chinese Medical Journal 2003; 116(10):1488-1491

Influence of patients' age on functional recovery after transplantation of olfactory ensheathing cells into injured spinal cord injury

HUANG Hongyun 黄红云, CHEN Lin 陈 琳, WANG Hongmei 王洪美, XIU Bo 修 波, LI Bingchen 李炳辰
WANG Rui 王 锐, ZHANG Jian 张 健, ZHANG Feng 张 峰, GU Zheng 顾 征, LI Ying 李 荧
SONG Yinglun 宋英伦, HAO Wei 郝 伟, PANG Shuyi 潘树义 and SUN Junzhao 孙君昭

Keywords: *cell transplantation* · *spinal cord injury* · *function recovery*

Objective To evaluate the restoration of function after spinal cord injury (SCI) in patients of different ages who have underwent intraspinal transplantation of olfactory ensheathing cells (OECs).

Methods One hundred and seventy-one SCI patients were included in this study. Of them, 139 were male and 32 were female, with age ranging from 2 to 64 years (mean, 34.9 years). In all SCI patients the lesions were injected at the time of operation with OECs. According to their ages, the patients were divided into 5 groups: ≤20 years group (n=9), 21–30 years group (n=54), 31–40 years group (n=60), 41–50 years group (n=34) and >51 years group (n=14). The spinal cord function was assessed based on the American Spinal Injury Association (ASIA) Classification System before and 2–8 weeks after OECs transplantation. One-way ANOVA and q test were used for

Presenter: Hwang

commentary

POINT OF VIEW: DIRECTIONS FOR RESEARCH

Cellular Transplants in China: Observational Study from the Largest Human Experiment in Chronic Spinal Cord

Bruce H. Dob

Ne

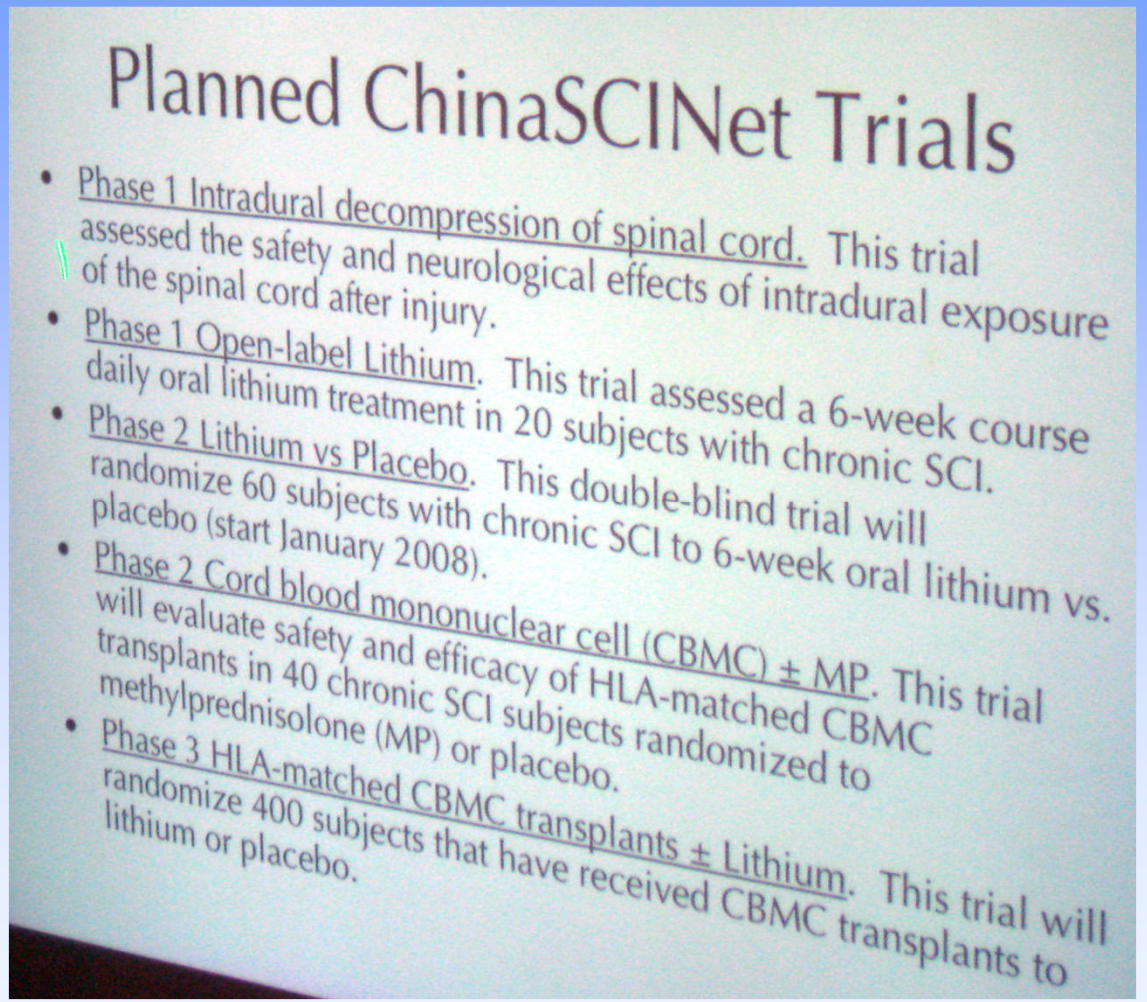
Background. In China, feta
transplanted into the lesic
patients with spinal cord i
reports have been the only
the procedure is safe and
compare available reports t

Conclusions. The phenotype and the fate of the transplanted cells, described as olfactory ensheathing cells, are unknown. Perioperative morbidity and lack of functional benefit were identified as the most serious clinical shortcomings. The procedures observed did not attempt to meet international standards for either a safety or efficacy trial. In the absence of a valid clinical trials protocol, physicians should not recommend this procedure to patients.

Presenter: Hwang

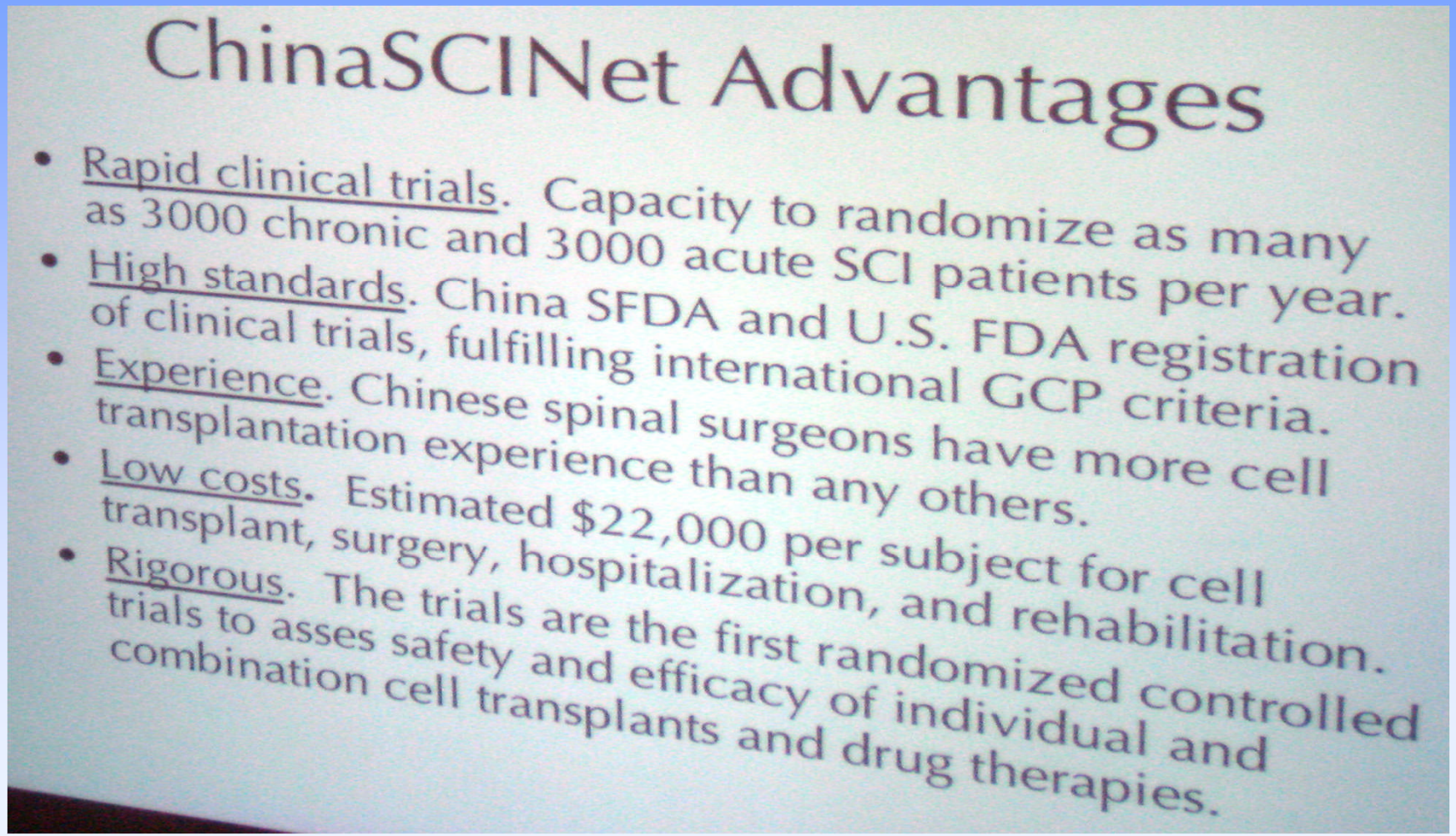
Wise Young

- Collaborative Neuosciences and Biological Therapy of Spinal Cord Injured People".



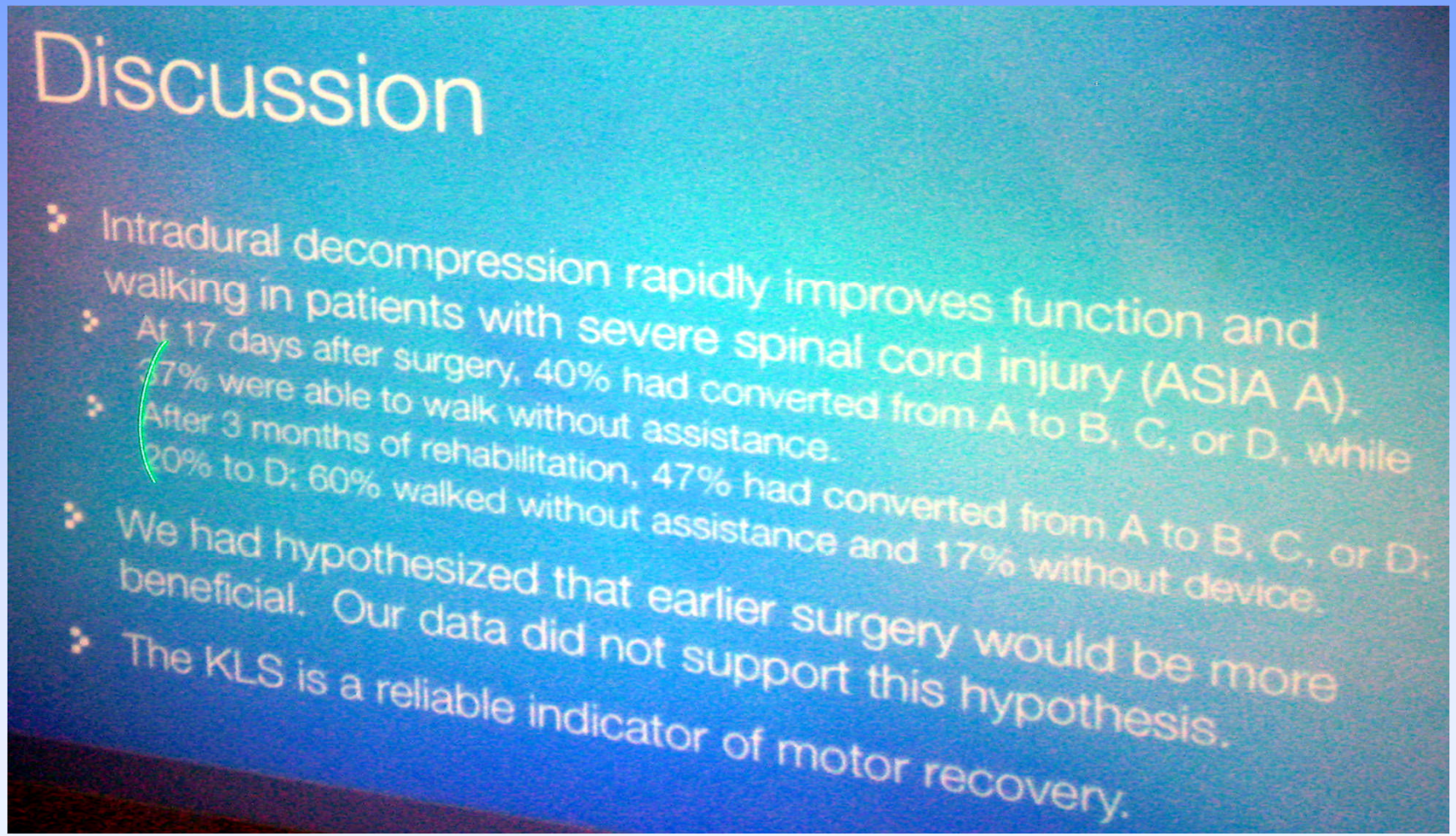
Presenter: Young

Young: ChinaSCINet



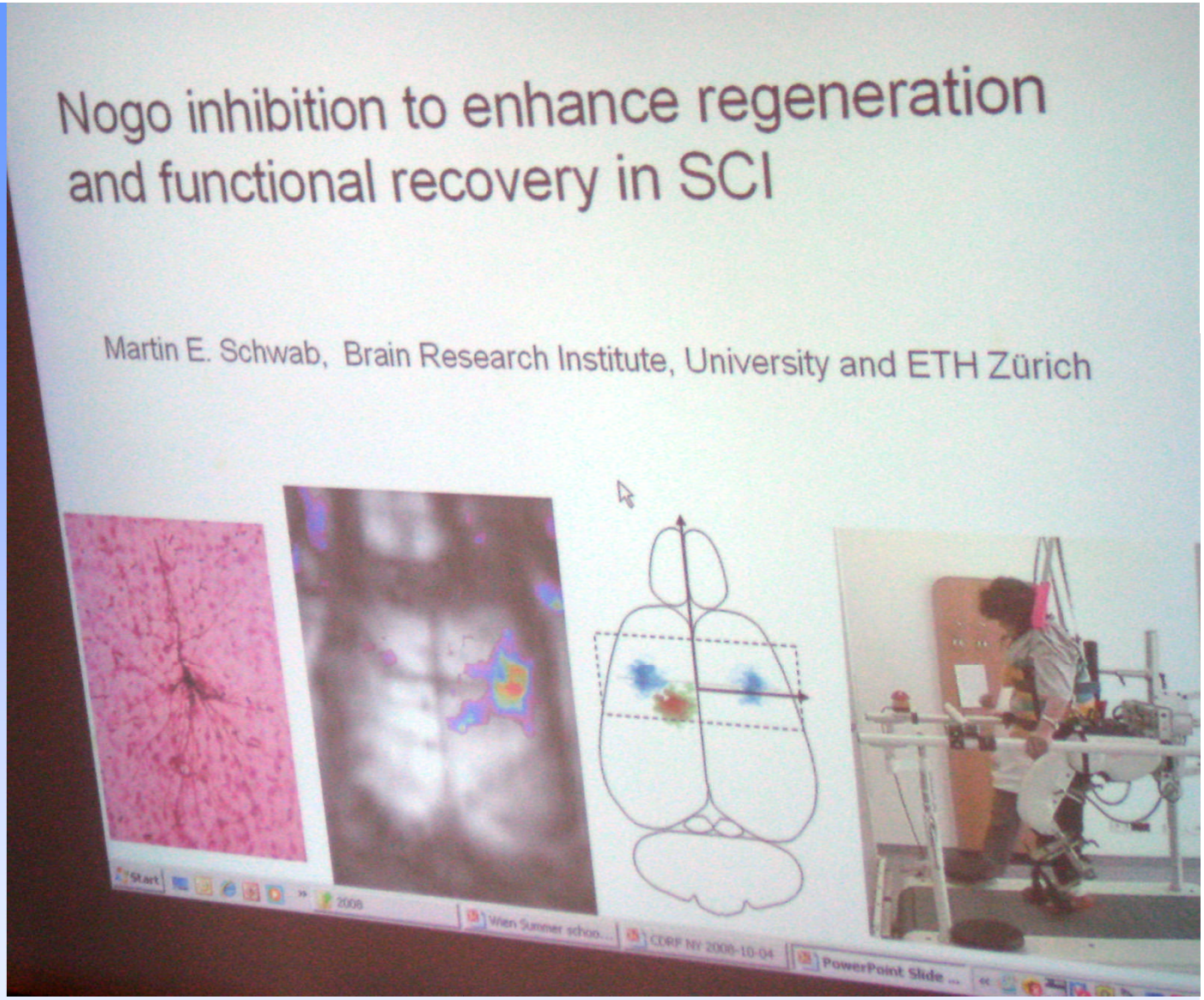
Presenter: Young

Young: Intradural decompression



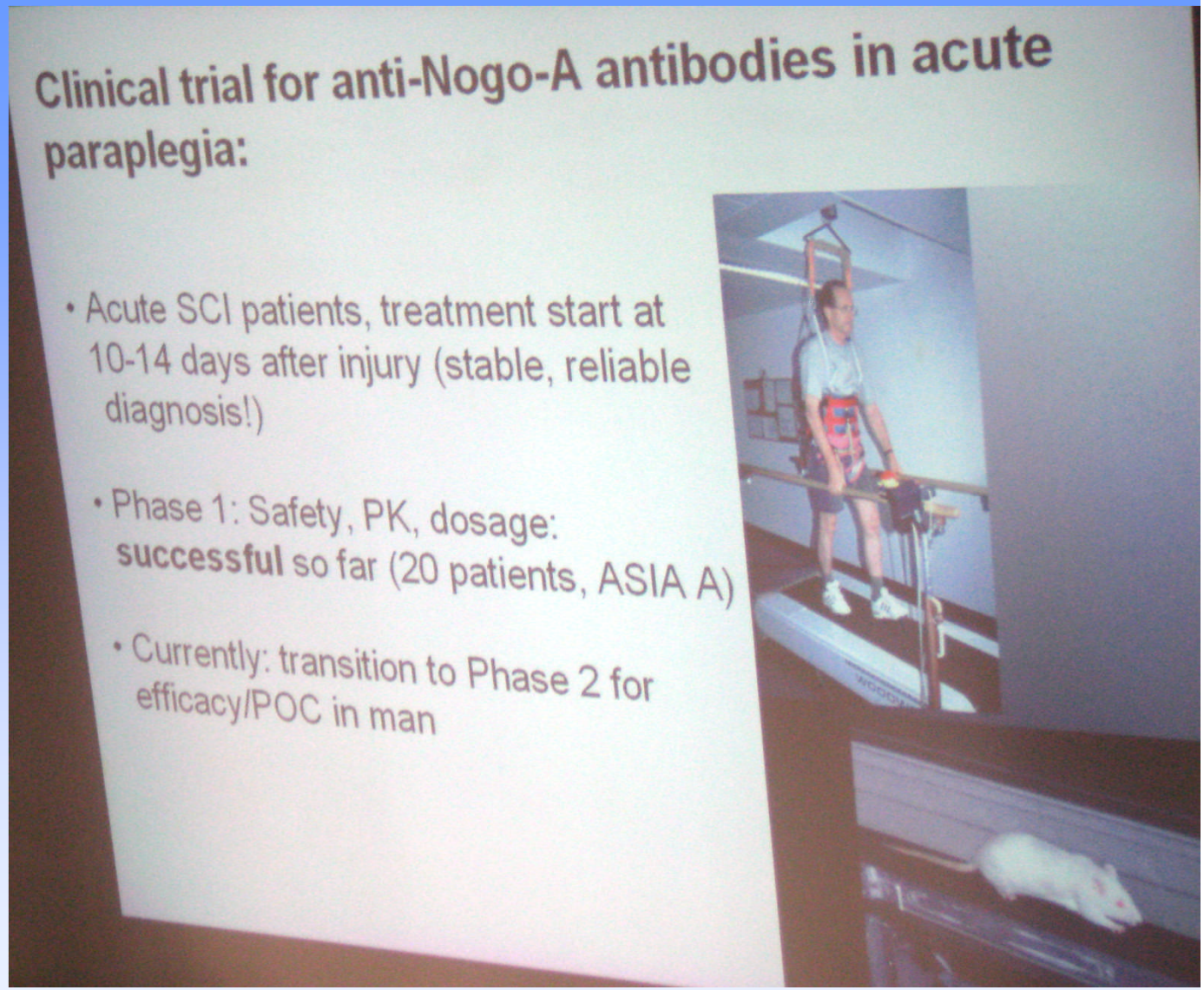
Presenter: Young

Nogo Inhibition to Enhance Regeneration and Functional Recovery in SCI



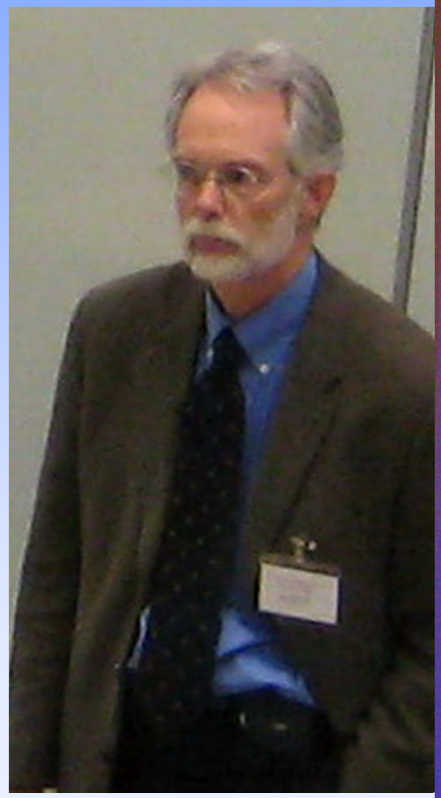
Presenter: Schwab

Novartis trial



Presenter: Schwab

Autologous cellular therapy in SCI: lessons learned from the multicenter macrophage trial



SCI Trial Pragmatics: Key Issues

- Adequacy of Pre-clinical evidence foundation
- Adequacy of prior clinical evidence foundation
- Cell Therapy: design of delivery scheme (device, dose, targeting, scale-up calculations from pre-clinical work)
- Careful choice of I/E criteria
- Careful choice of Outcome Measures
- Powering calculations—can sufficient numbers be recruited? Realistic projections of the Funnel Effect

Presenter: Lammertse

El Masri

- SCI is only catastrophic when poorly managed
- Surgical intervention not necessary
- We need more monitoring – especially first 4 hours post injury

Kakulas, El Masry, Dimitrijević

Presenter: El Masri

Algorithm for restoration of function:

- Highest quality clinical care
  - Acute - conservative/intervention?
  - Subacute - conservative/intervention?
  - Chronic - conservative/intervention?
- Interventions
  - Timing: acute/subacute/chronic
  - Target:
    - Above/at/below the lesion
    - Long tract, cell body, myelin, synapse, environment
  - Nature: biological/chemical/E.S./activity

Algorithm (cont'd.):

- Rehabilitation
  - Timing
  - Type
  - Intensity

- Assessment
  - Nature: clinical/functional/electrophysiological
  - Timing: baseline/repetitions/feasibility/cost

Thank you!