UCL

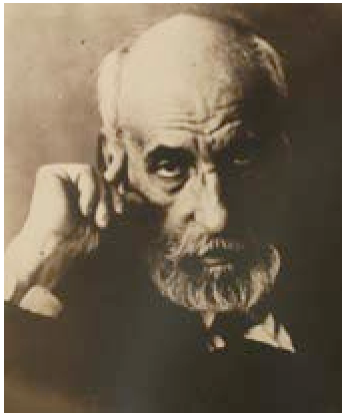
Structural changes and regeneration of the motor system

Alan J Thompson
UCL Faculty of Brain Sciences

Hamburg May 2012

Thanks to…..

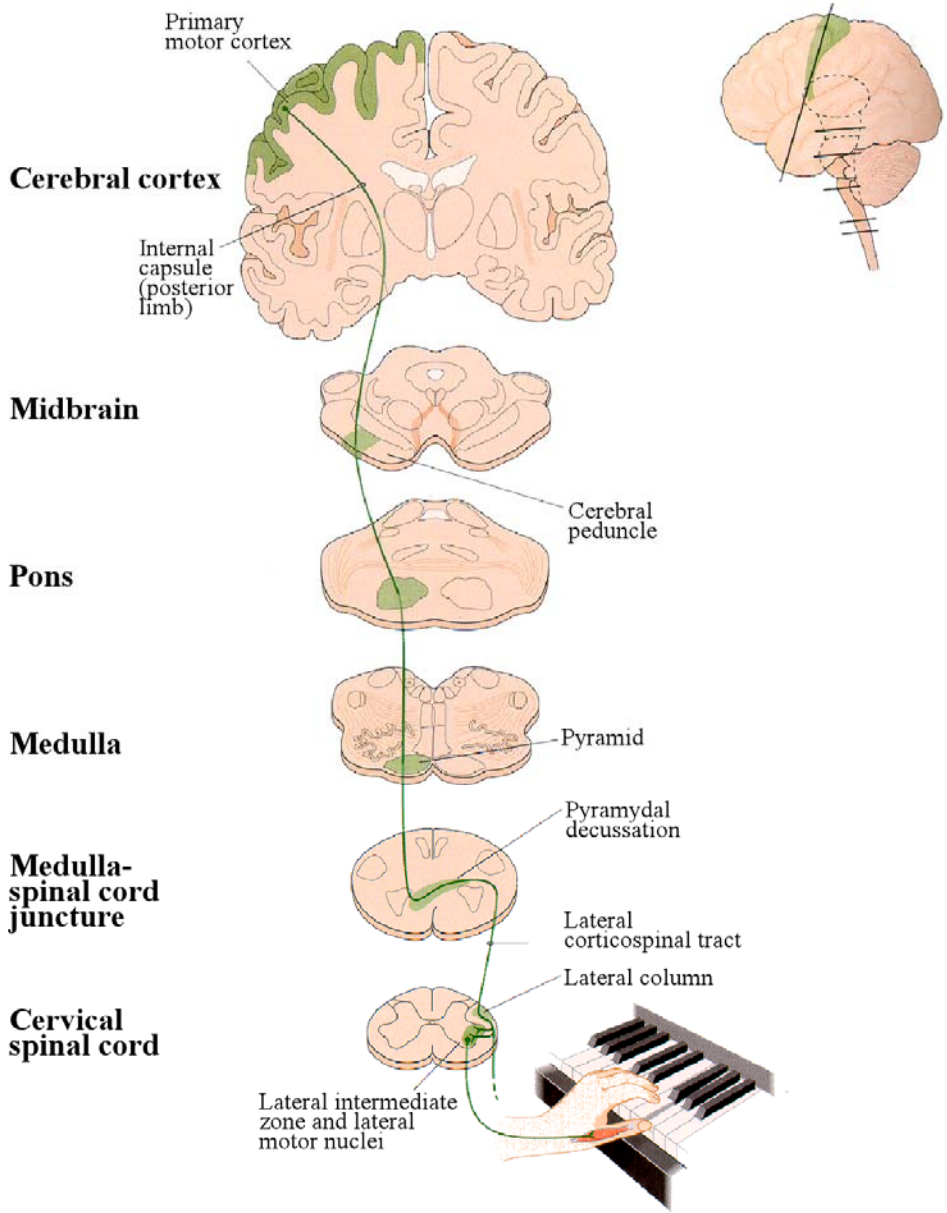
- Patrick Freund (Zurich)
- John Rothwell (London)
- Olga Ciccarelli (London)
- Heidi Johnasen-Berg (Oxford)

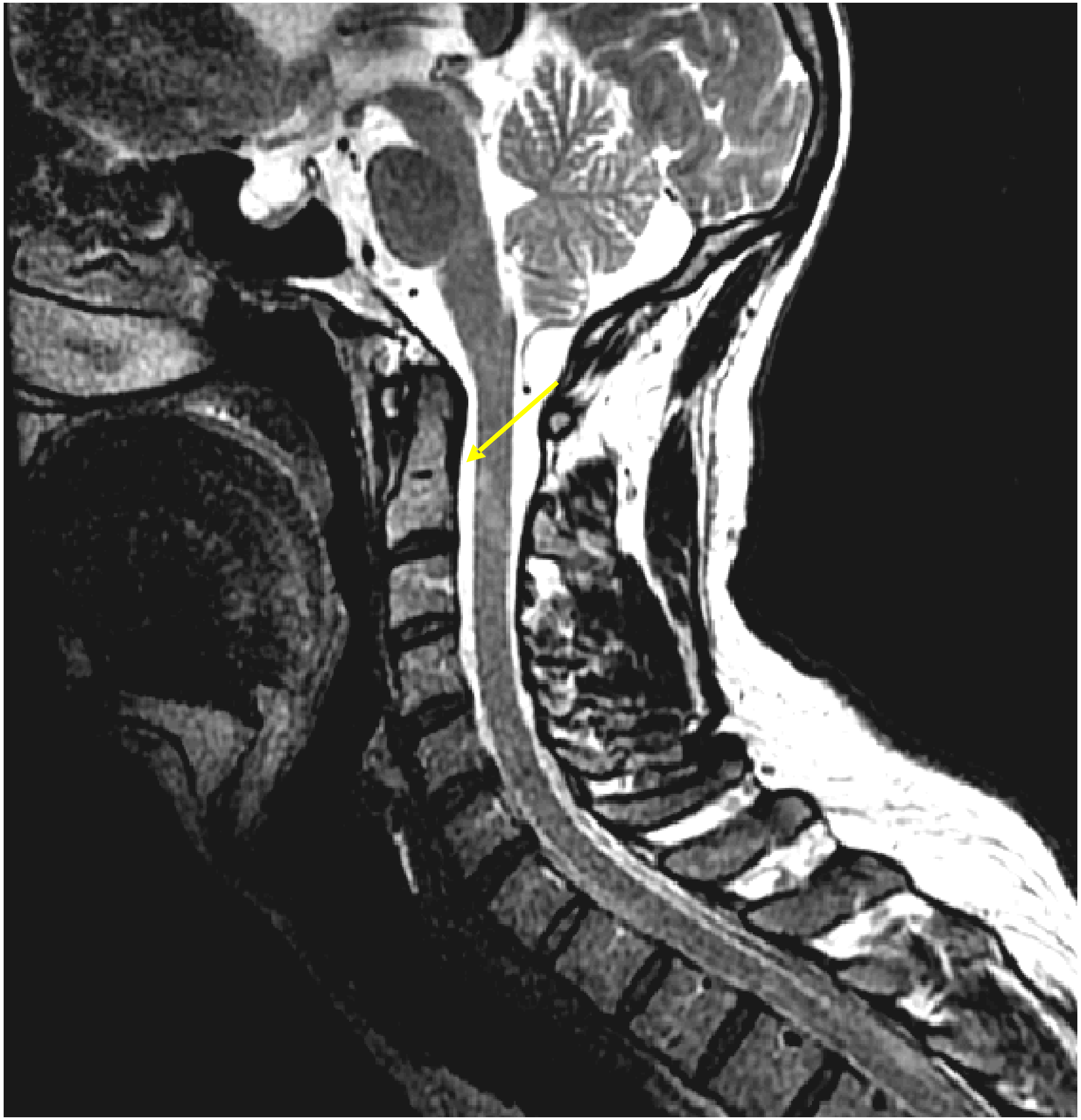


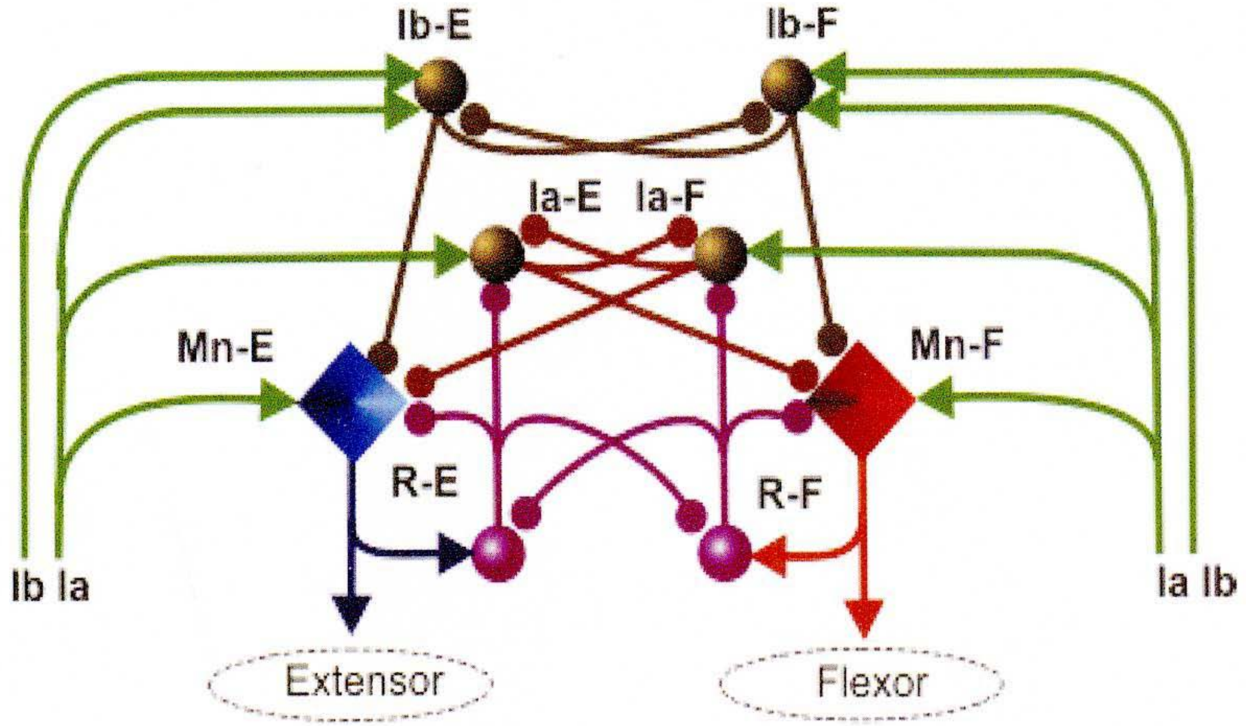
"…the acquisition of new abilities requires many years of mental and physical practice. In order to fully understand this complicated phenomenon, it is necessary to admit, in addition to the strengthening of pre-established organic pathways, the establishment of new ones, through ramification and progressive growth of dendritic arborizations and nervous terminals."

Ramon Y Cajal (1904)

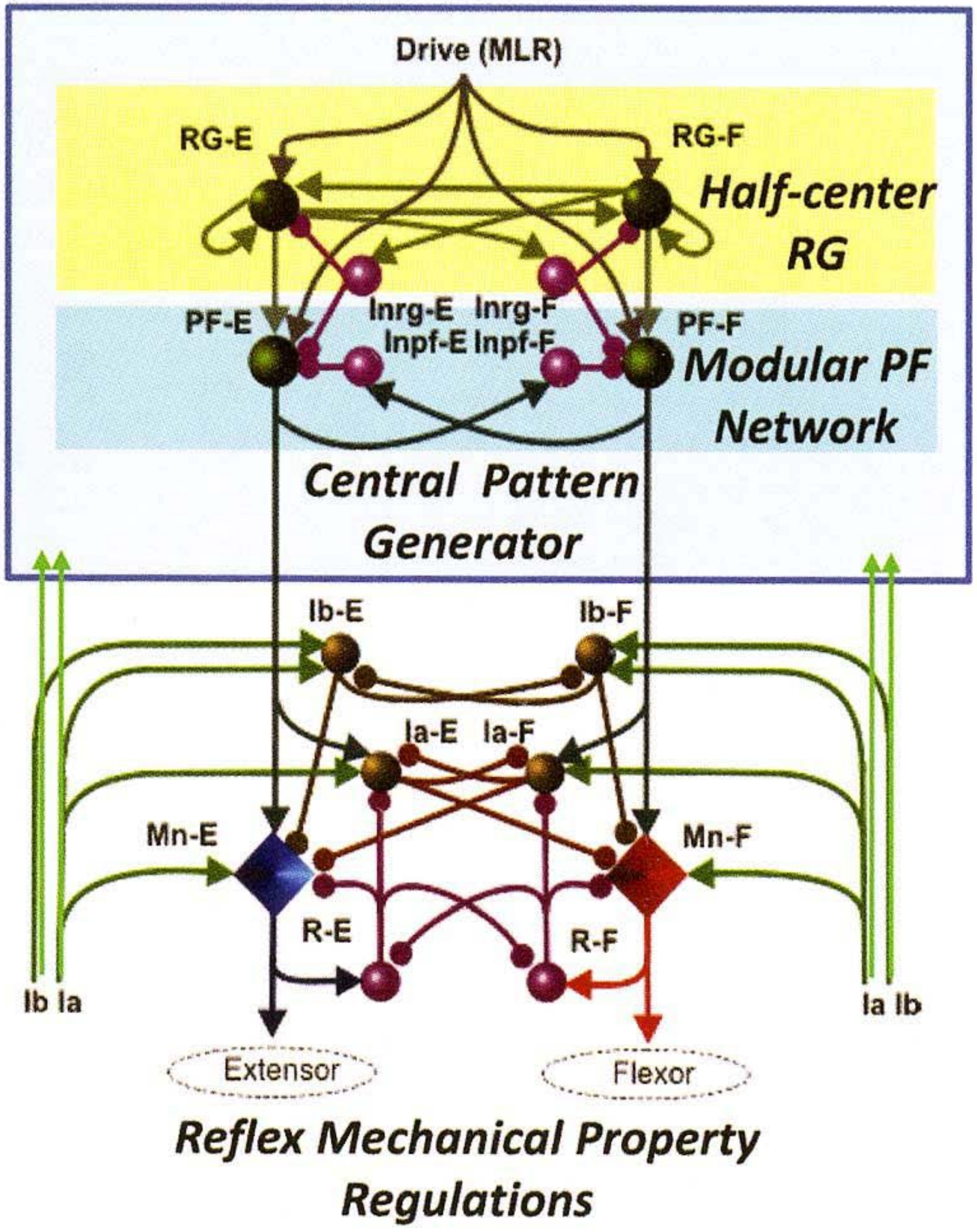
Descending lateral corticospinal pathway







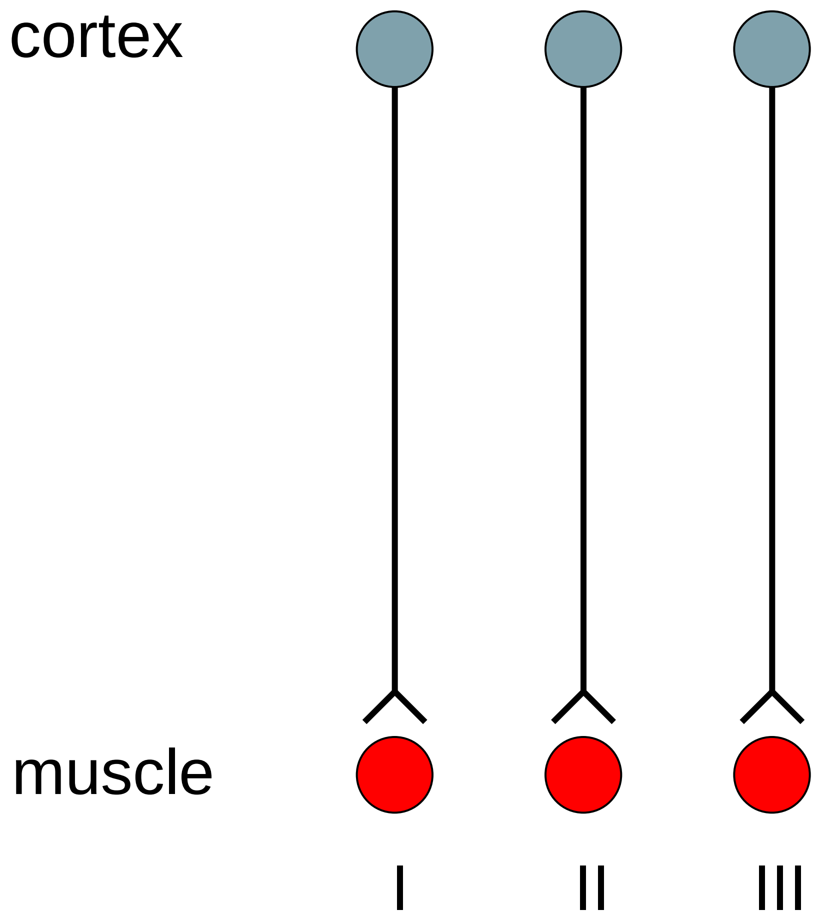
Simplified Reciprocal Reflex Circuit Organisation



Hierarchical Circuit Implementation Models

"There is very little evidence for gross structural changes in the motor system, but there is excellent evidence for reorganisation at a more localised level"

John Rothwell

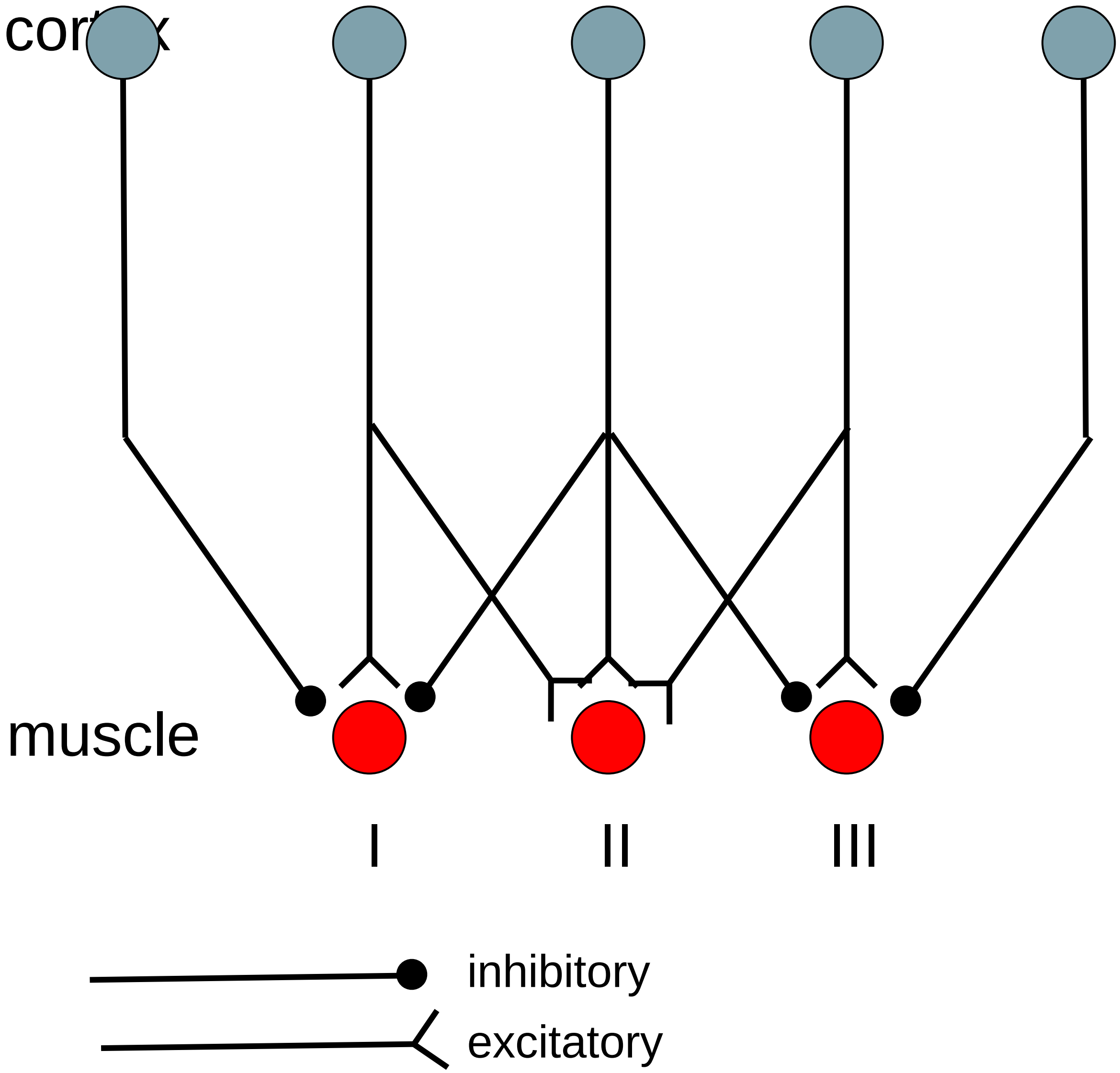


The corticospinal projection is NOT wired up like this

Remove input to muscle II and can never use it again

The real organisation is much more distributed…what are the implications?

Actual distributed organisation



Muscle II can be activated selectively by simultaneous inputs from all 3 cortical neurones.

If one is damaged, the remainder may still be able to recruit muscle II, although less selectively.

Training may induce other inputs to be unmasked or to grow that make recruitment more selective

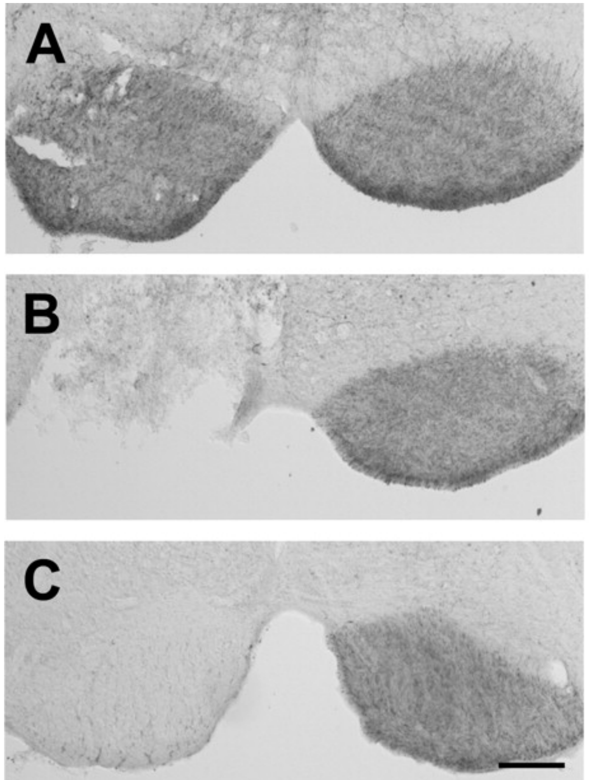
John Rothwell IoN

Constraint-induced movement therapy in the adult rat after unilateral corticiospinal tract injury

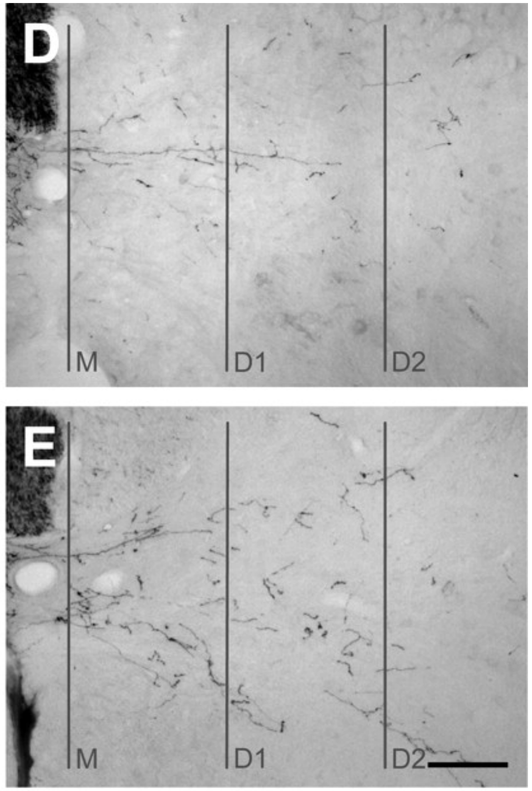
Maier I, BaumannK, Thallmair M, Weinmann O, Scholl J and Schwab M.

- Unilateral CST injury at brainstem level
- Use of impaired limb was either restricted or forced for 1-3 weeks

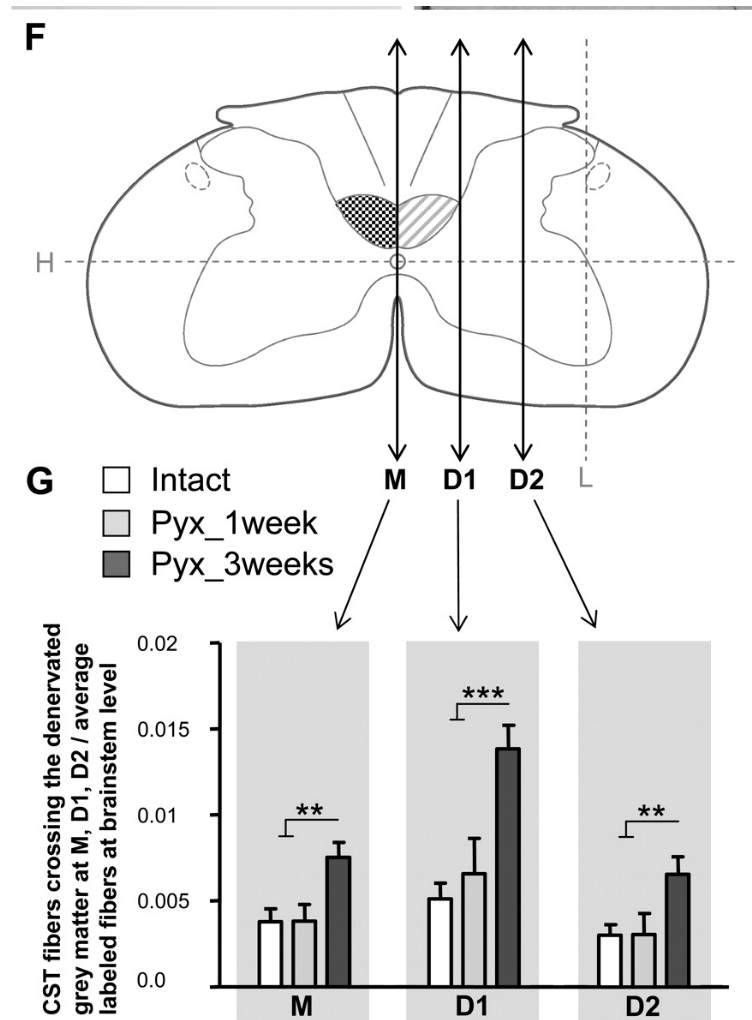
The Journal of Neuroscience 2008; 28: 9386 – 9403



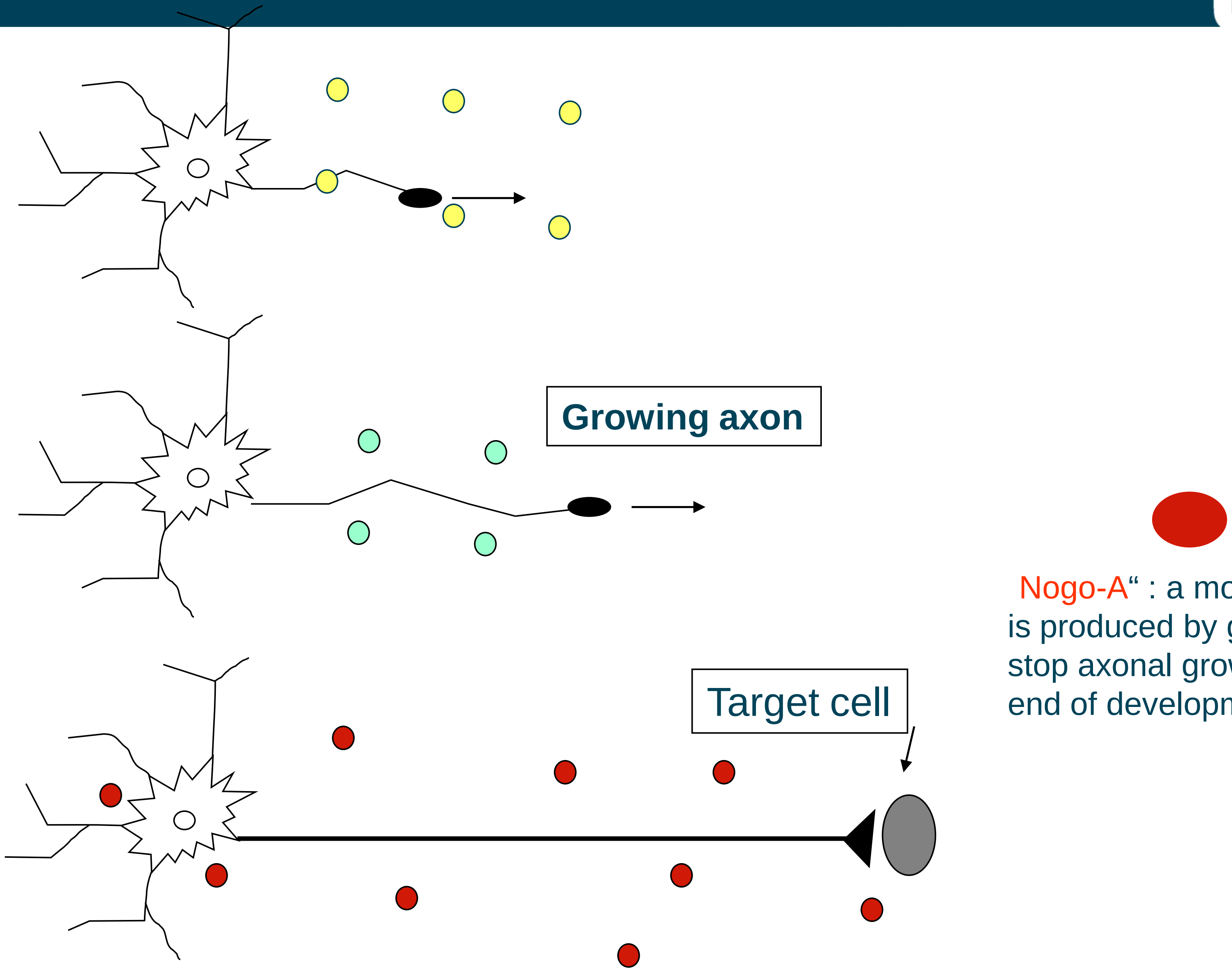
Interruption of neuronal tracer BDA



Intact (D) and injured E animals

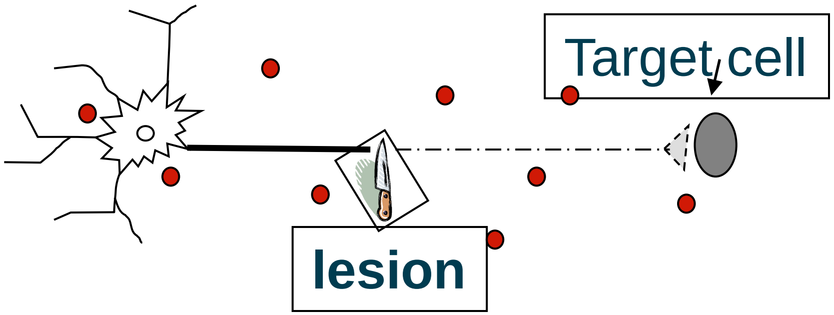


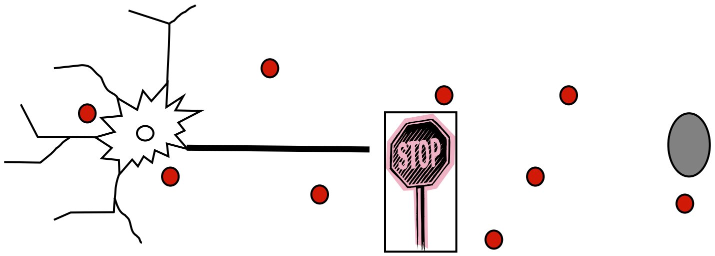
Labelling of intact CST showed lesion induced growth across midline and changes correlate with functional benefit (Maier et al, 2008)



Nogo-A“ : a molecule which is produced by glia cells to stop axonal growth at the end of development

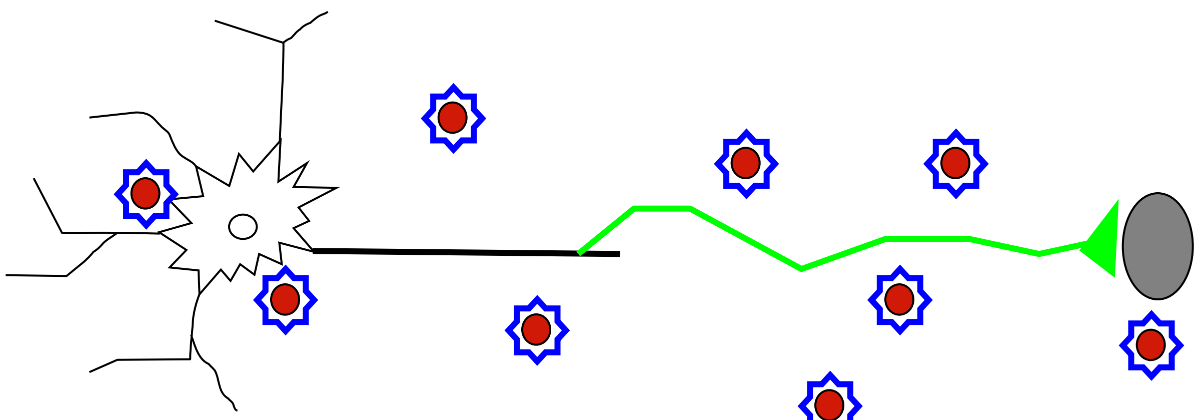
Problem: After lesion to the adult central nervous system (section of nerve fibers), the presence of Nogo-A" inhibits the regeneration of cut nerve fibers





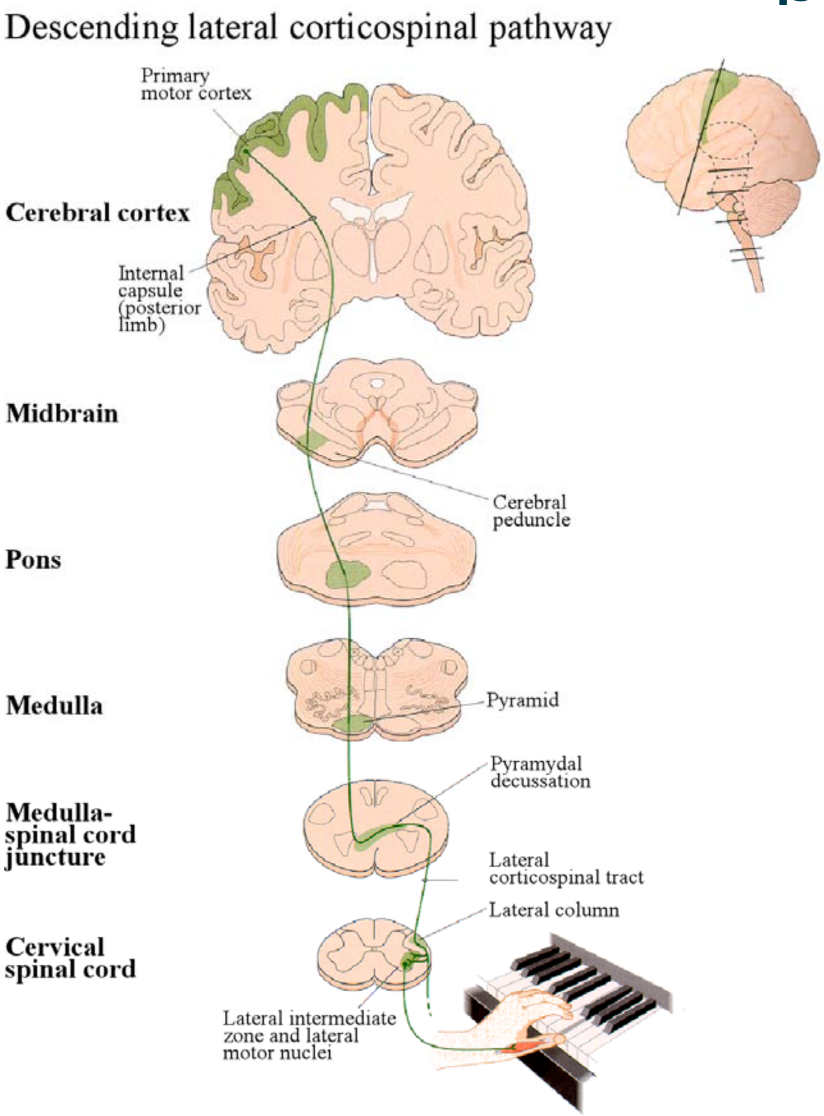
Strategy of "Anti-Nogo-A " (Martin Schwab, Unizh):

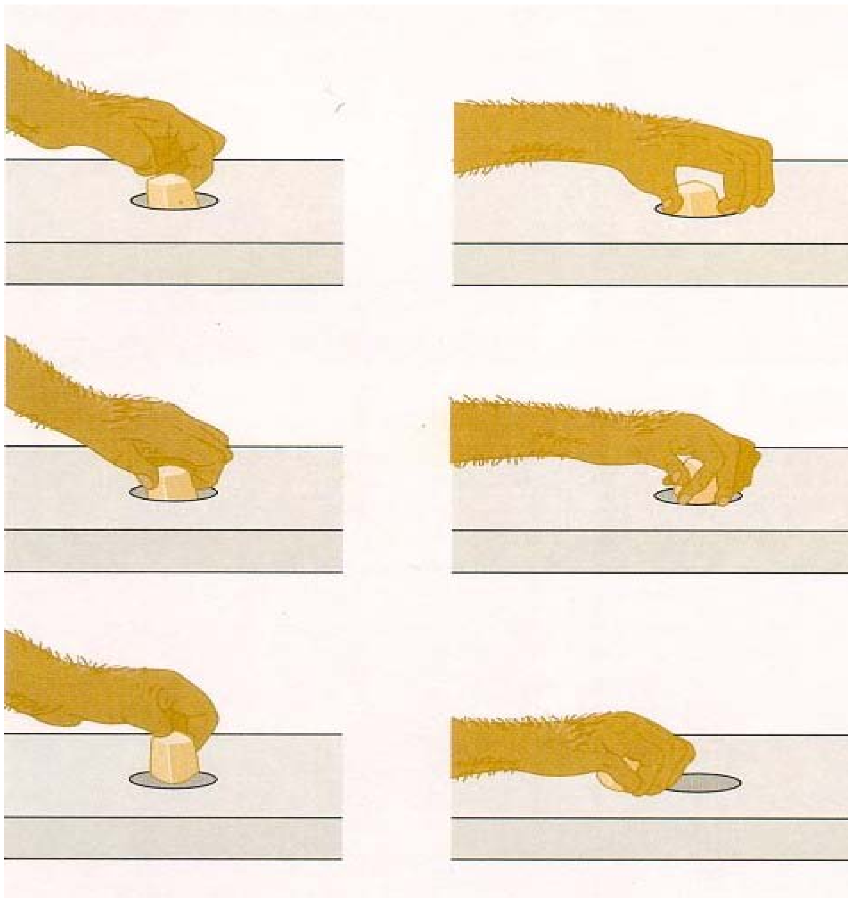
Neutralisation of "Nogo-A " using antibodies



→ **Regeneration of lesioned axons and sprouting**

Background: the corticospinal system in primates



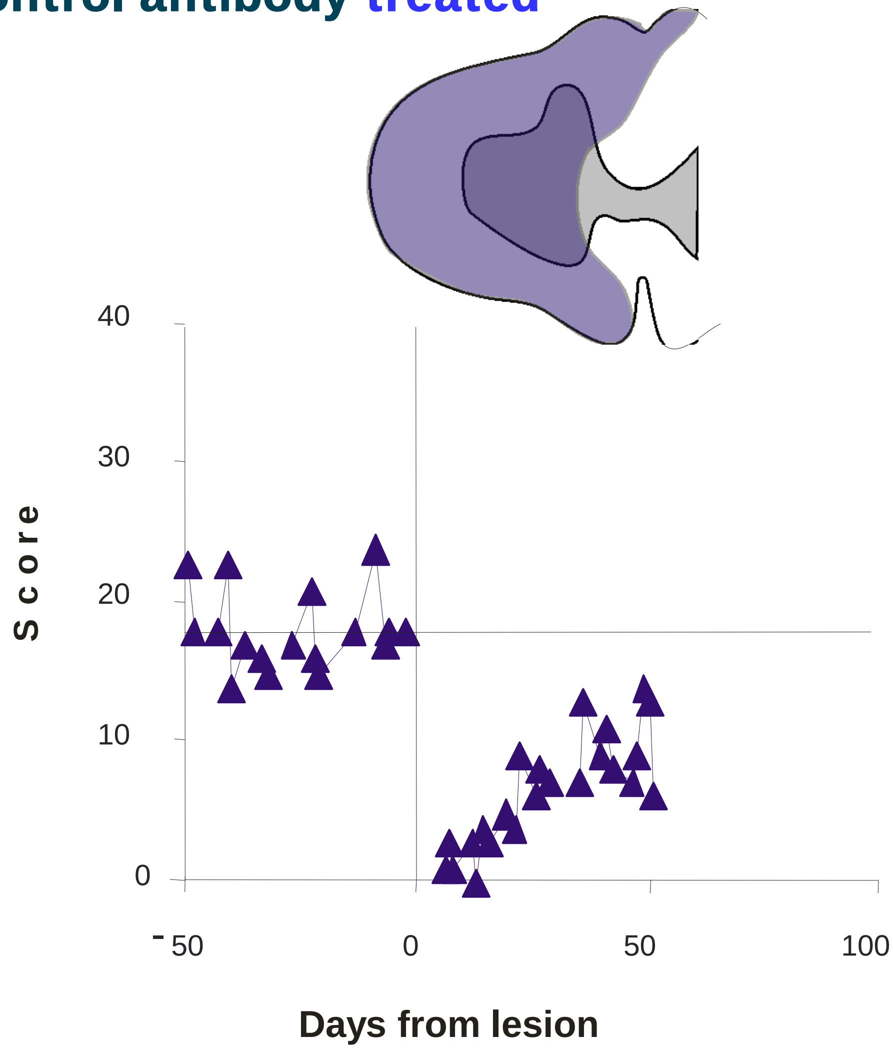


Manual dexterity test to assess CST integrity

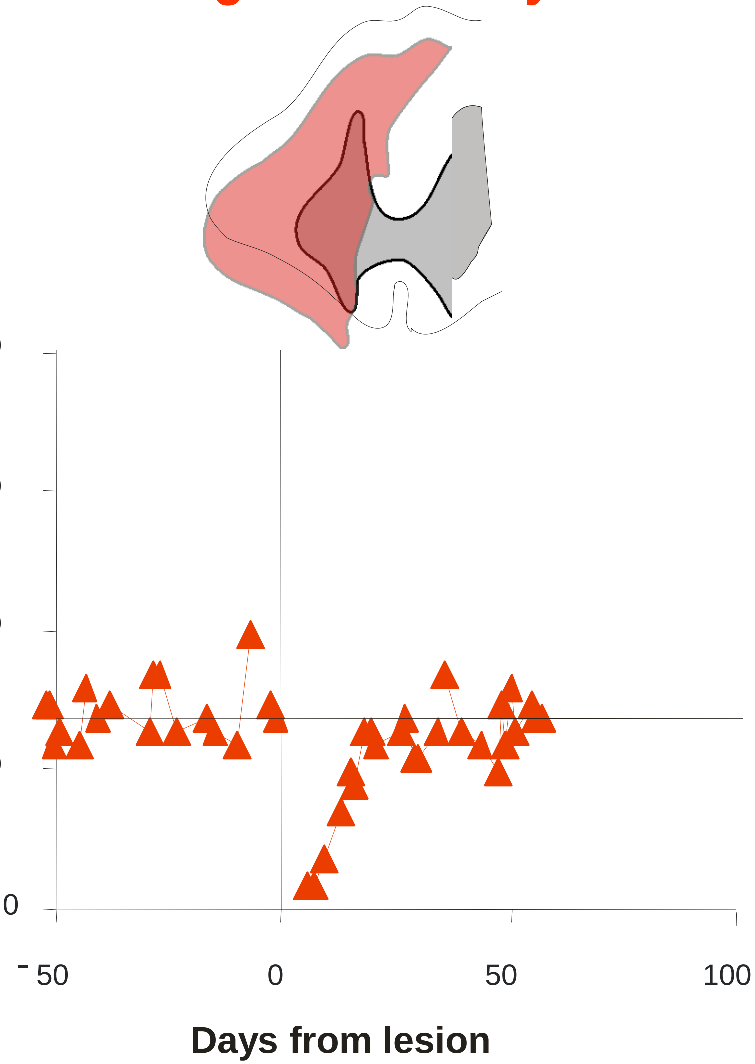
Standard (modified) Brinkman Board Task:
assessment of manual dexterity for grasping an object using the precision grip (opposition of thumb and index finger) (quantitative)

Manual dexterity score:

Control antibody treated

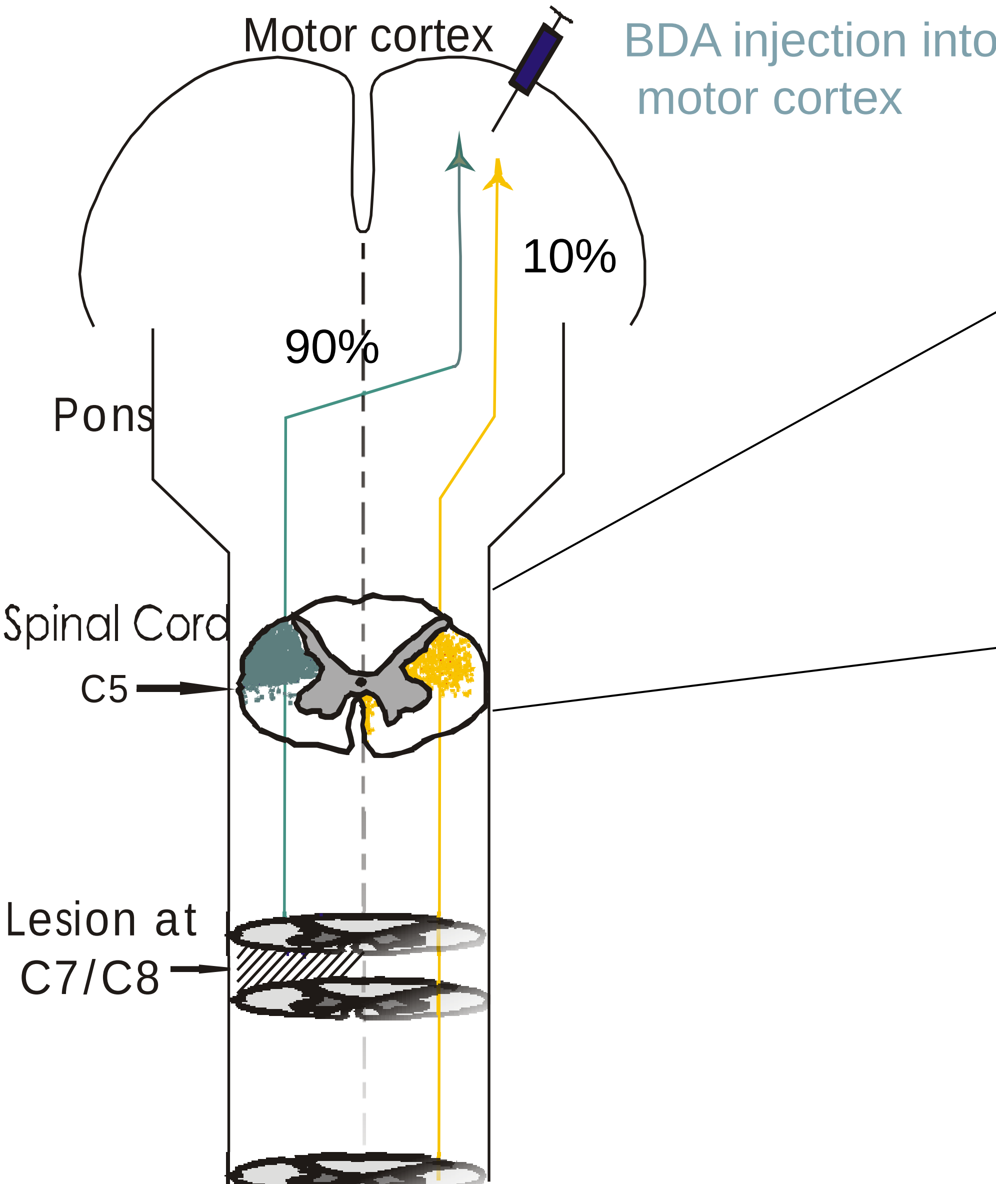


Anti-Nogo-A antibody treated

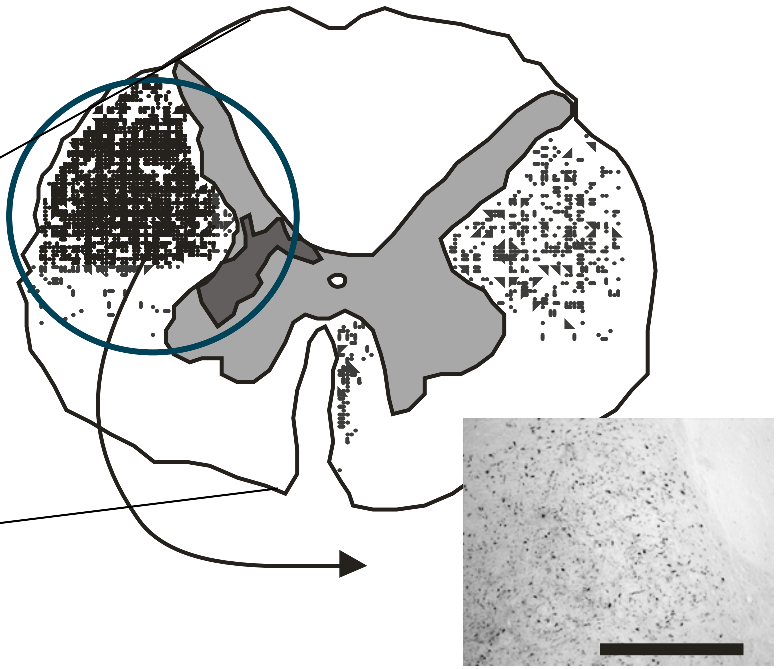


Score: Nb. of pellets retrieved in 30 sec.

Anatomical correlates ?

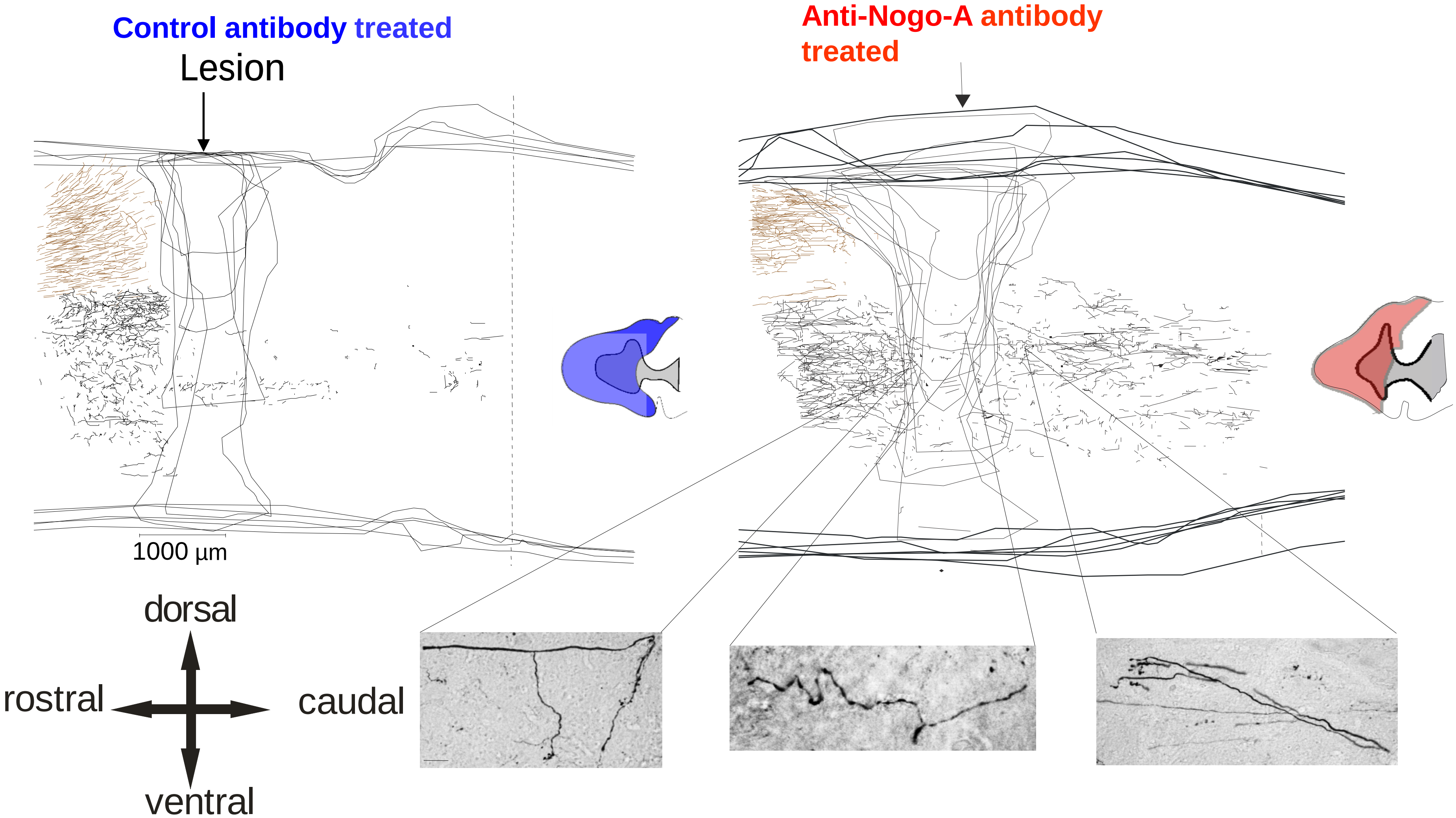


Target of cervical lesion:
Dorsolateral funiculus



Distribution of corticospinal axons at cervical level in an intact monkey following tracer injection into contralateral M1

Superimposed longitudinal reconstructions of the cervical cord showing BDA labeled fibres

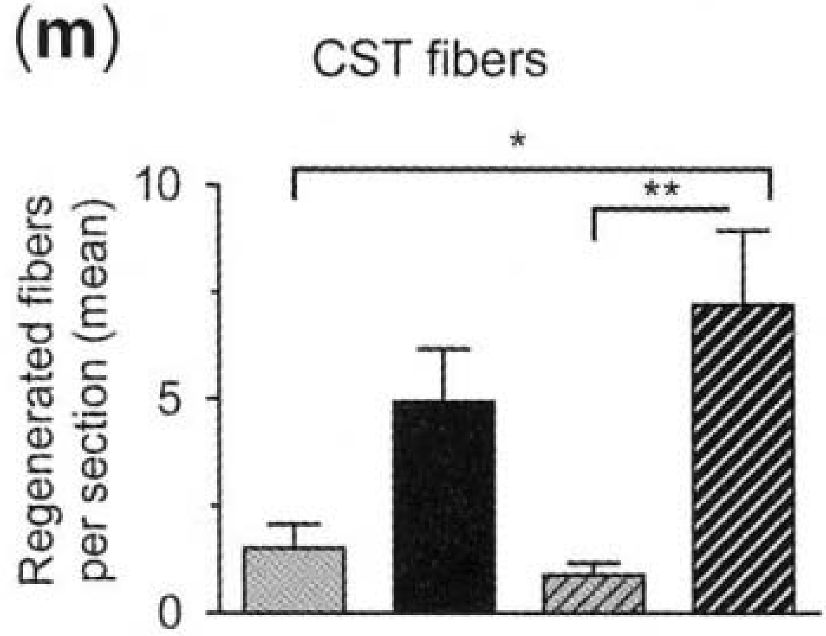


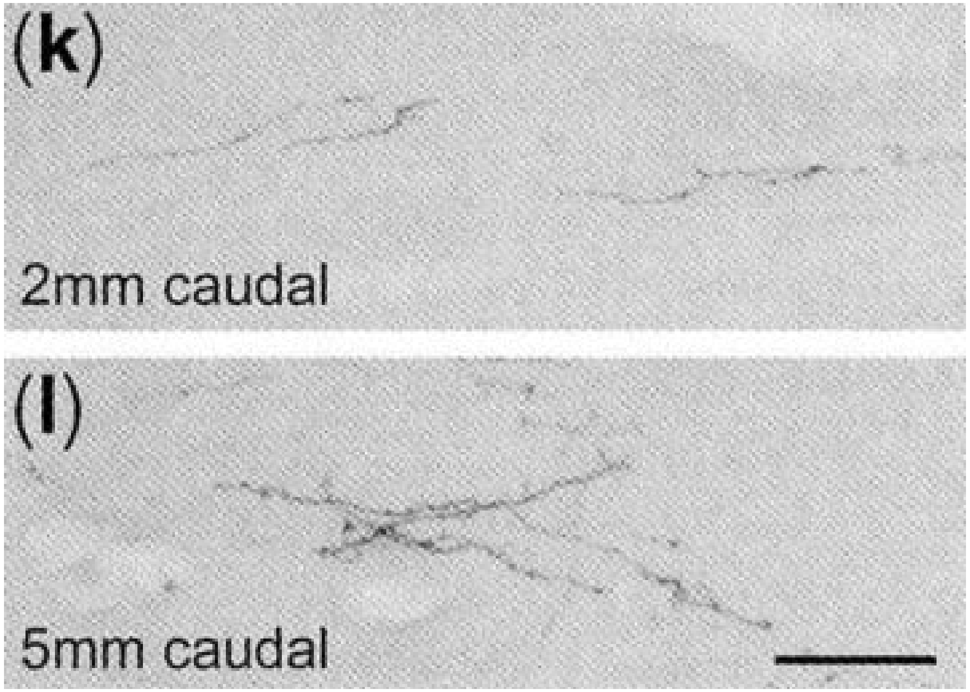
Freund et al. 2006
Nat. Med.

Differential effects of anti-Nogo-A antibody treatment and treadmill training in rats with incomplete spinal cord injury

- Locomotor training on treadmill and treatment with anti-Nogo both showed beneficial effect
- Kinematic patterns significantly different
- Synchonous combined treatment group did not show synergistic effects

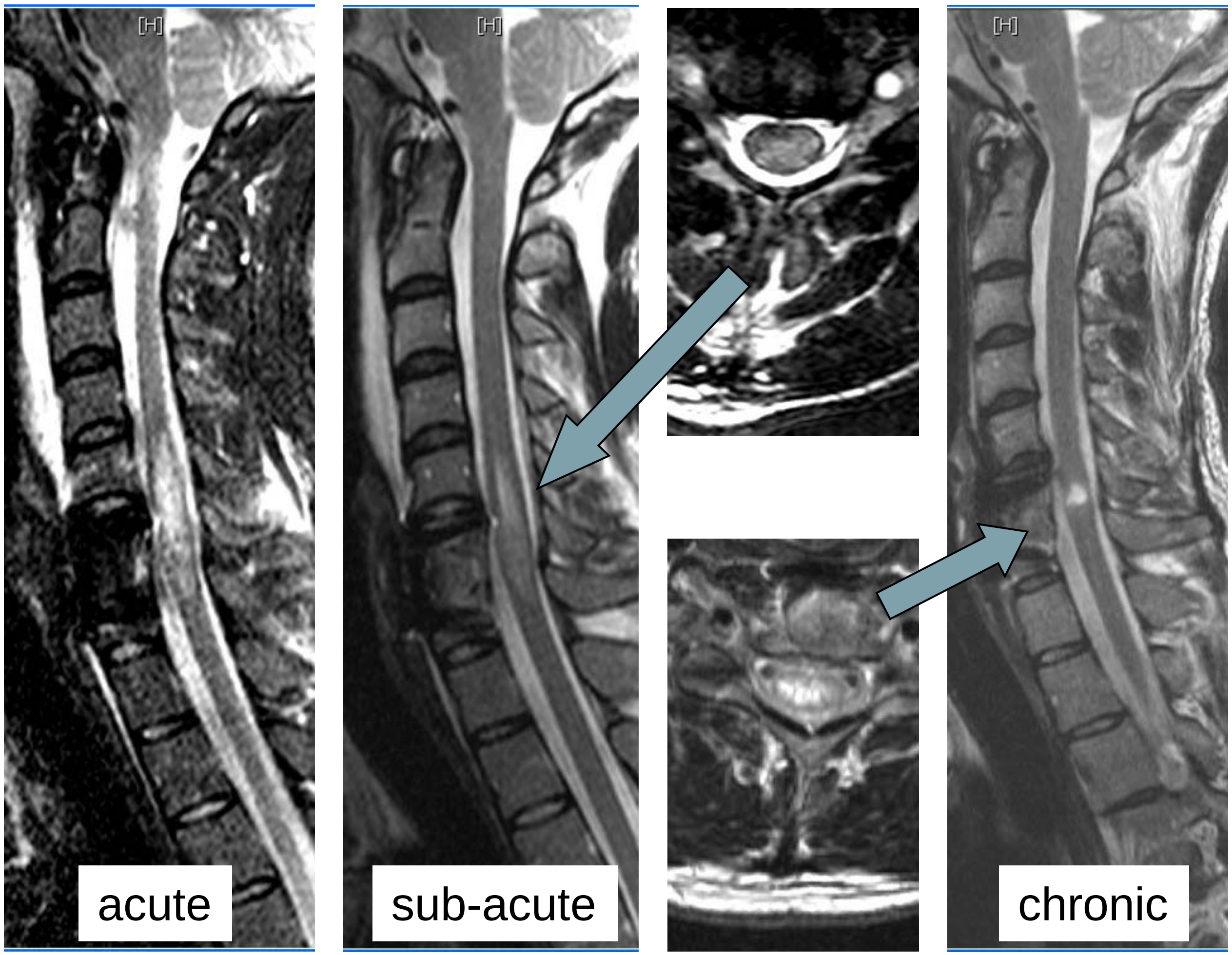
Maier et al Brain 2009;132:1426-1440





- **Fibres grow towards the caudal spine and arborise in response to Nogo-A antibody**
- **Increased regeneration in Nogo-A antibody treated was independent of locomotor training**

Neuro-imaging spinal cord



Male 36 yrs

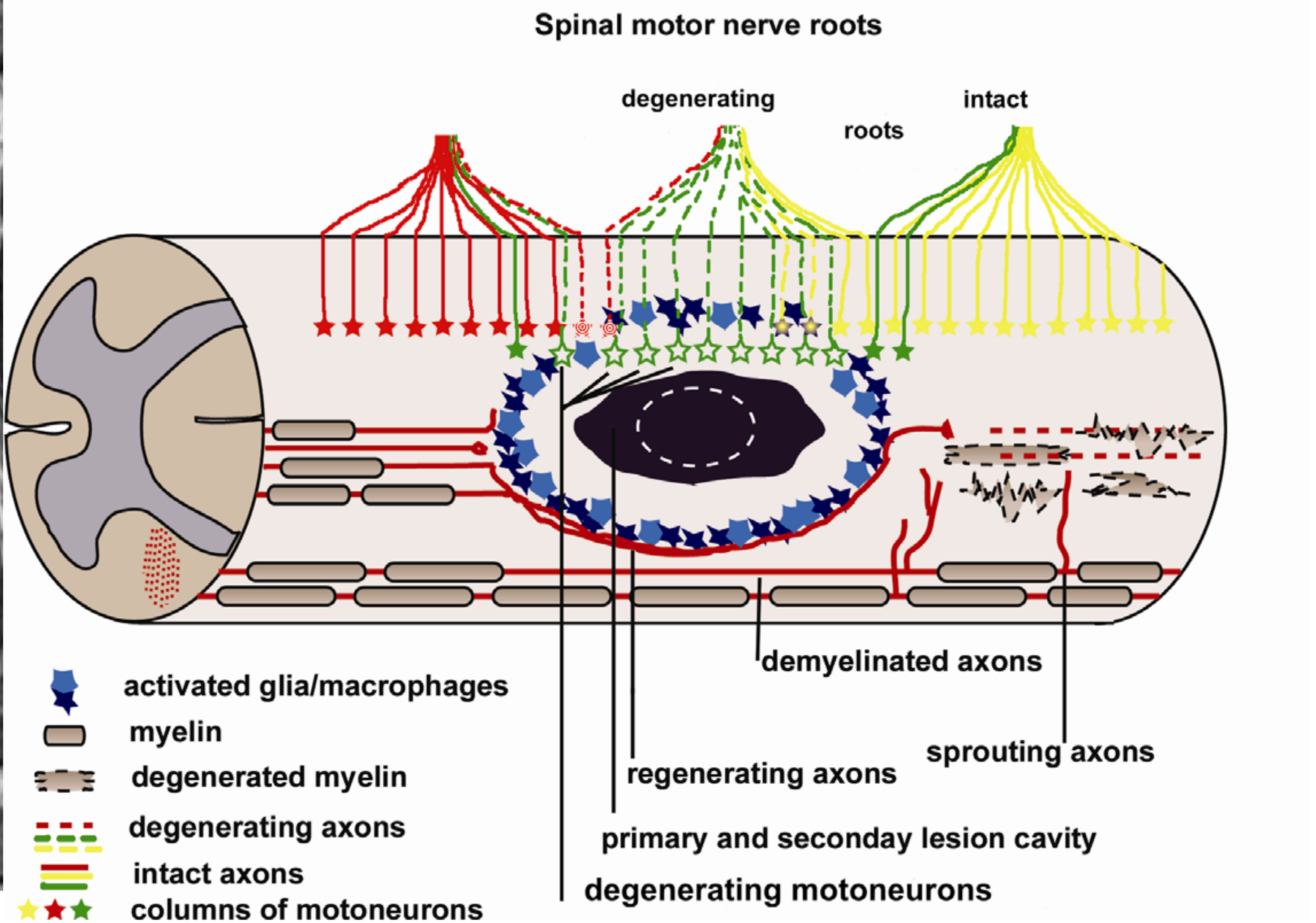
snowboard accident

mild central cord

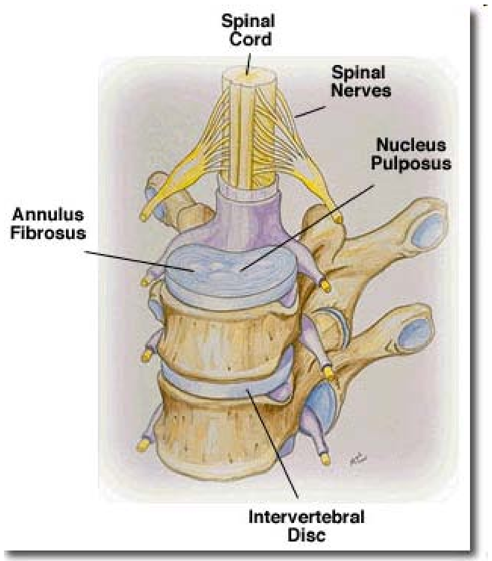
neuropathic pain

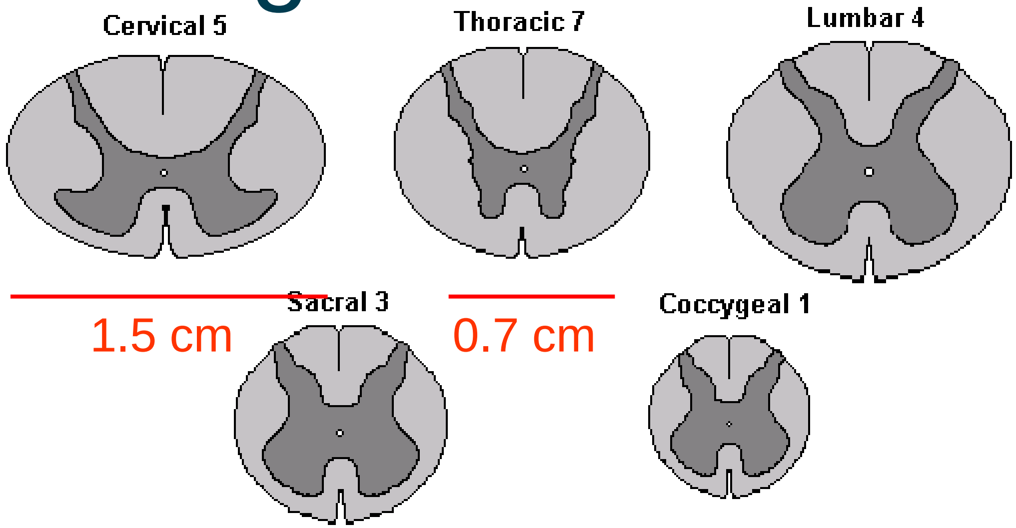
works again as a surgeon!

MRI to inform clinical trials



Challenges





- small size
- cardiac pulsation and breathing ⟶
  motion artifacts
- magnetic susceptibility at tissue/air/bone interface ⟶
  image distortions

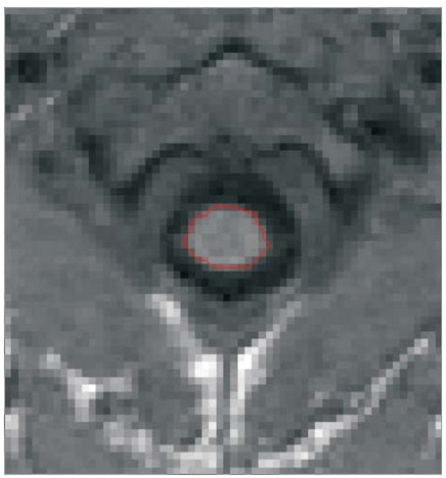
doi:10.1093/brain/awr093 Brain 2011: 134; 1610–1622 | 1610

BRAIN
A JOURNAL OF NEUROLOGY

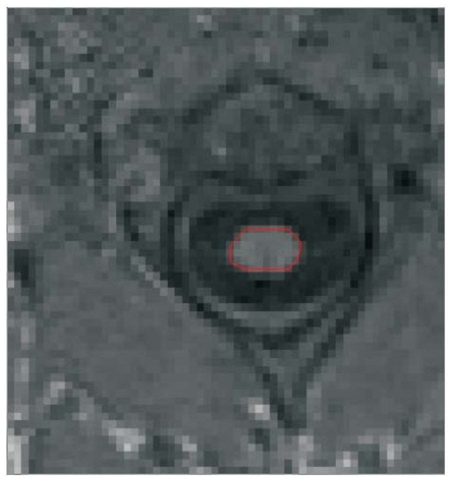
Disability, atrophy and cortical reorganization following spinal cord injury

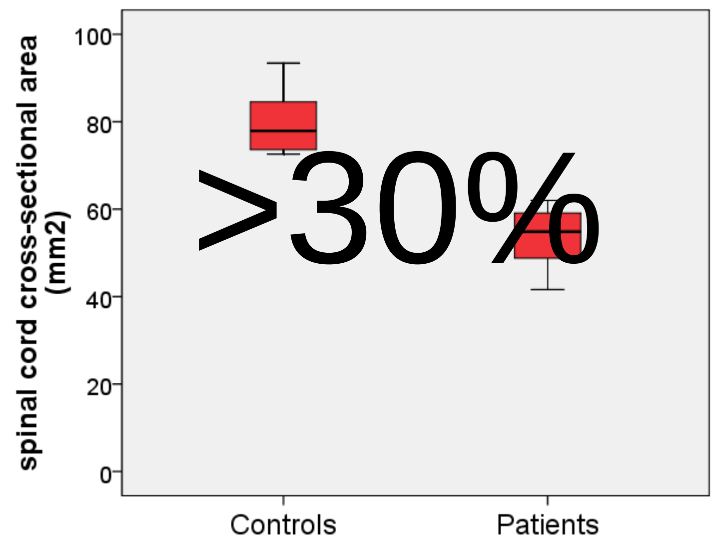
Patrick Freund,[1,2,3,4] Nikolaus Weiskopf,[2] Nick S. Ward,[5] Chloe Hutton,[2] Angela Gall,[3] Olga Ciccarelli,[1] Michael Craggs,[3] Karl Friston[2] and Alan J. Thompson[1]

Control

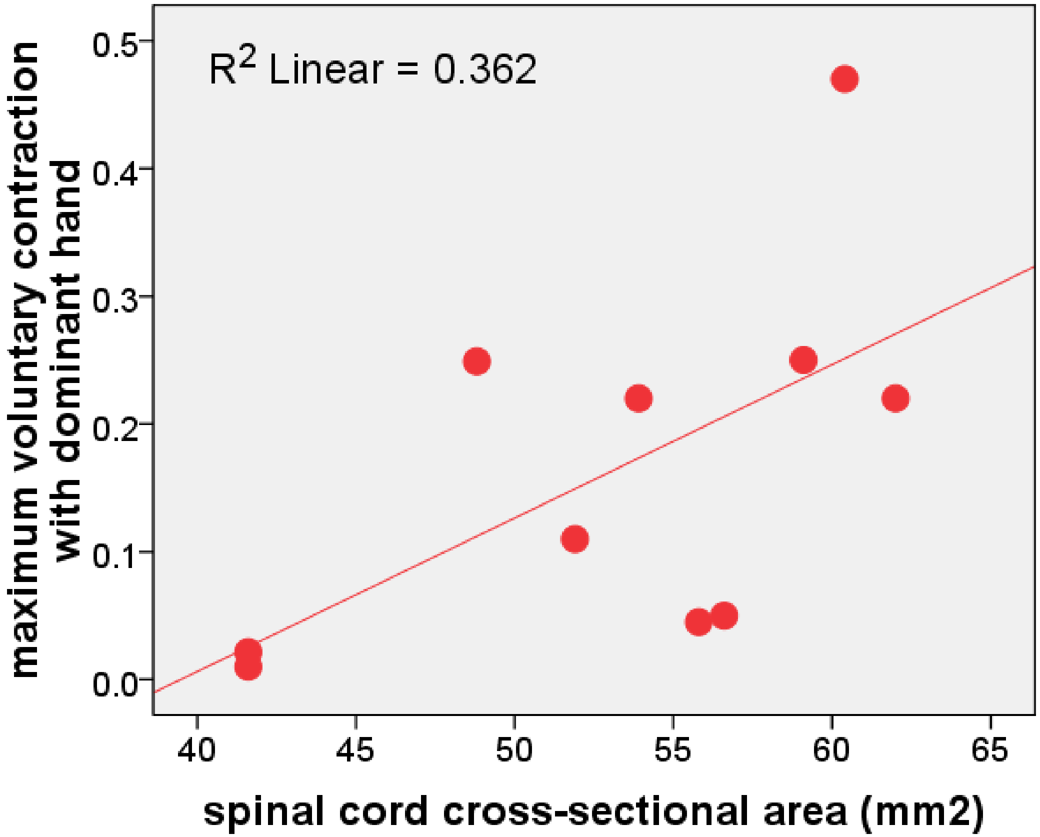


SCI





Correlates of spinal atrophy with upper limb function



p=0.01

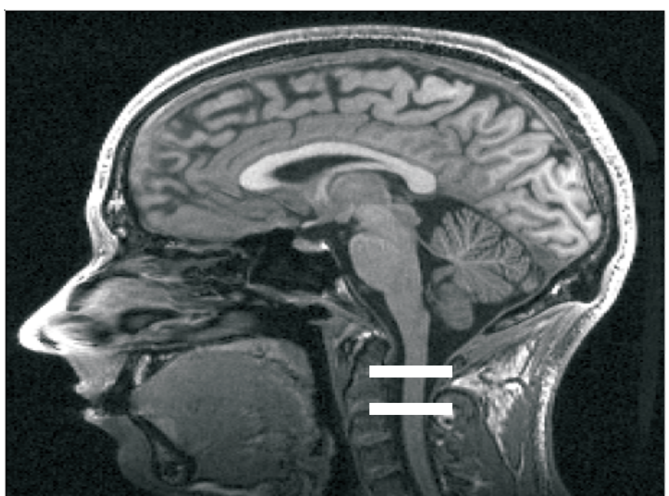
N=10

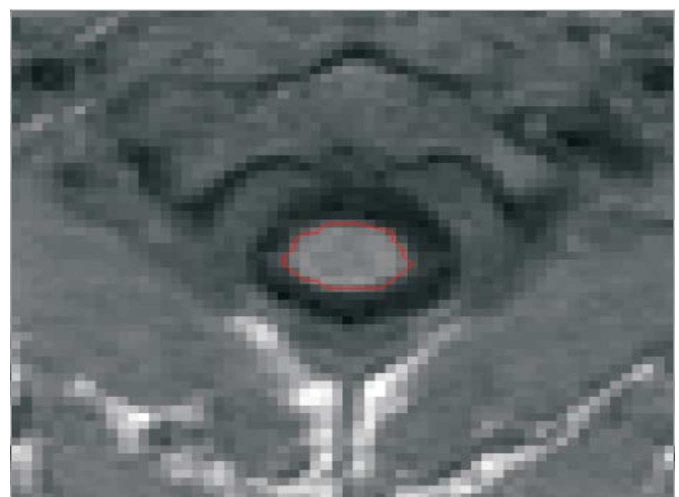
JOURNAL OF MAGNETIC RESONANCE IMAGING 32:1242–1247 (2010)

Technical Note

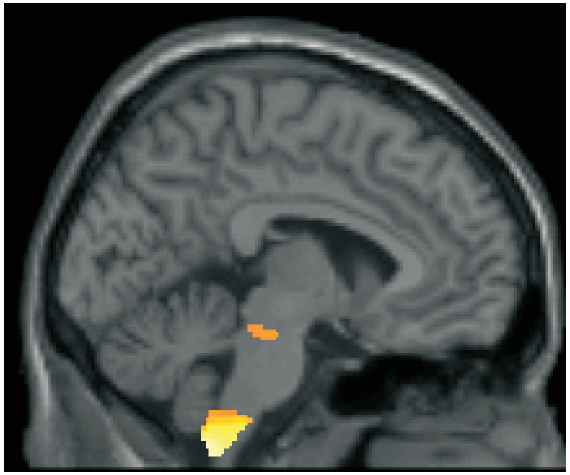
Method for Simultaneous Voxel-Based Morphometry of the Brain and Cervical Spinal Cord Area Measurements Using 3D-MDEFT

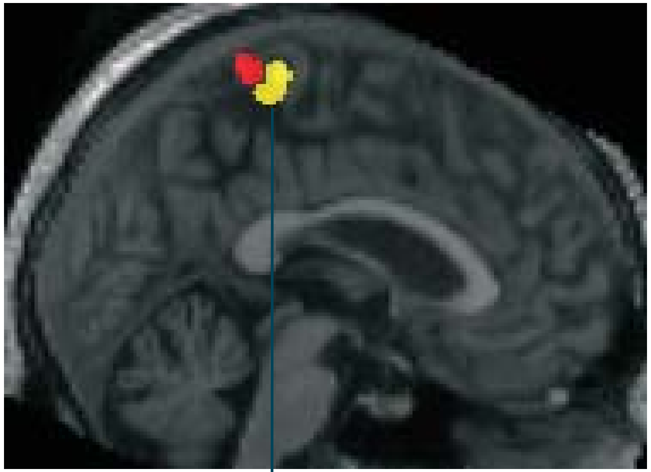
Patrick A.B. Freund, PhD,[1,2] Catherine Dalton, MD,[3] Claudia A.M. Wheeler-Kingshott, PhD,[3] Janice Glensman, DCR(R),[2] David Bradbury, BSc,[2] Alan J. Thompson, MD,[1] and Nikolaus Weiskopf, PhD[2*]

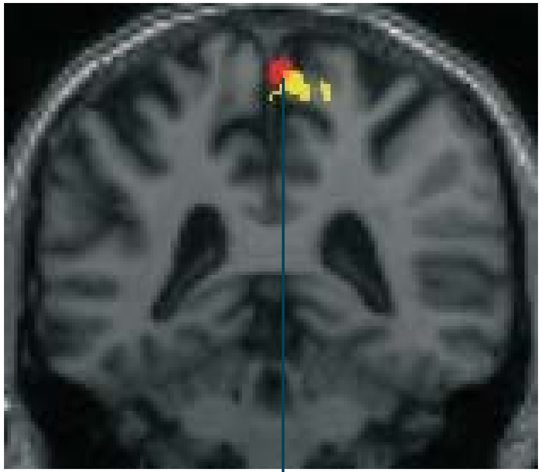




White and grey matter atrophy and cortical thinning





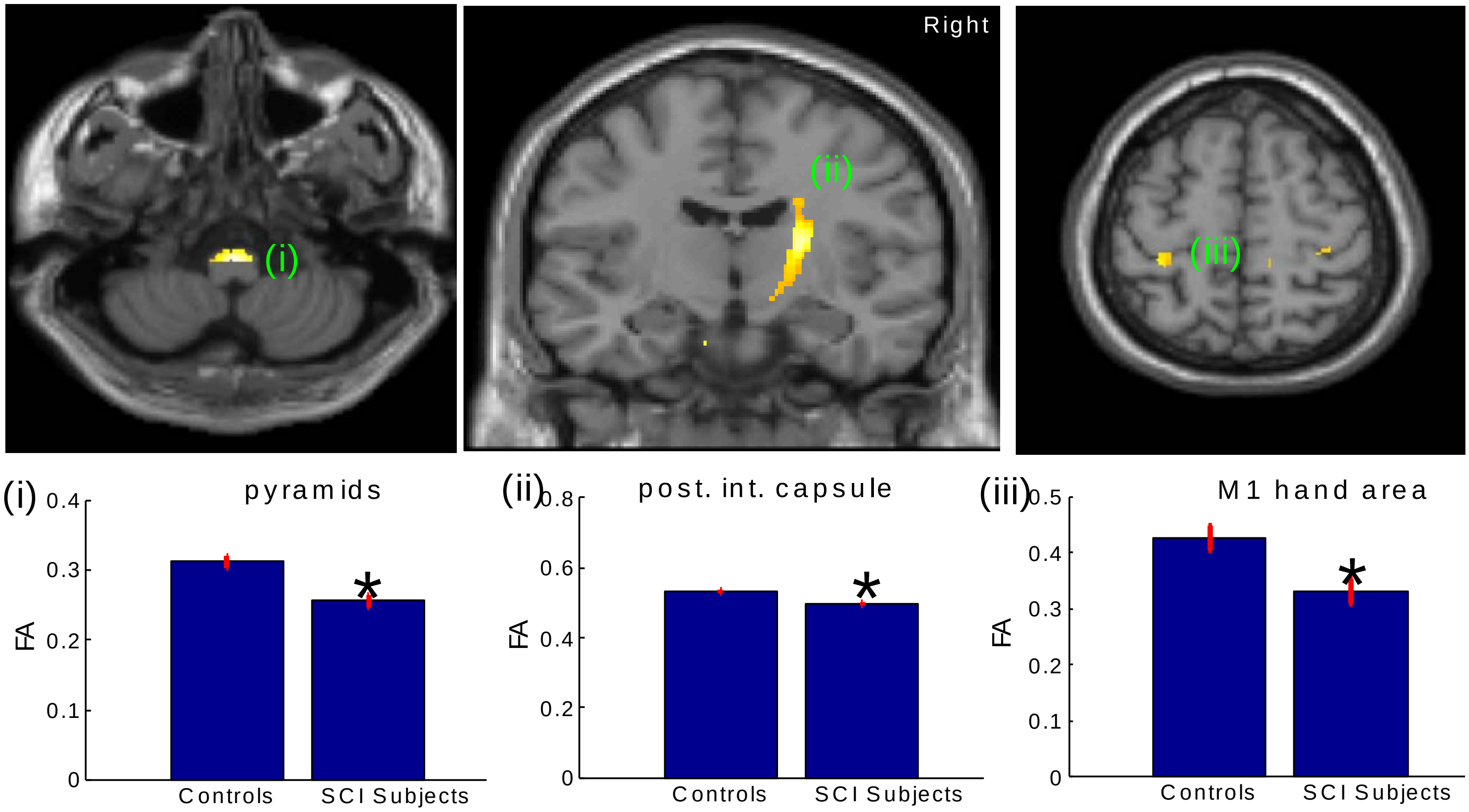


White matter atrophy in cerebellar peduncle and pyramids

Cortical thinning in leg area of S1

Grey matter atrophy in leg area of M1

Corticospinal tract integrity reduces



Freund et al 2012

doi:10.1093/brain/awr093

Brain 2011: 134; 1610–1622 | 1610

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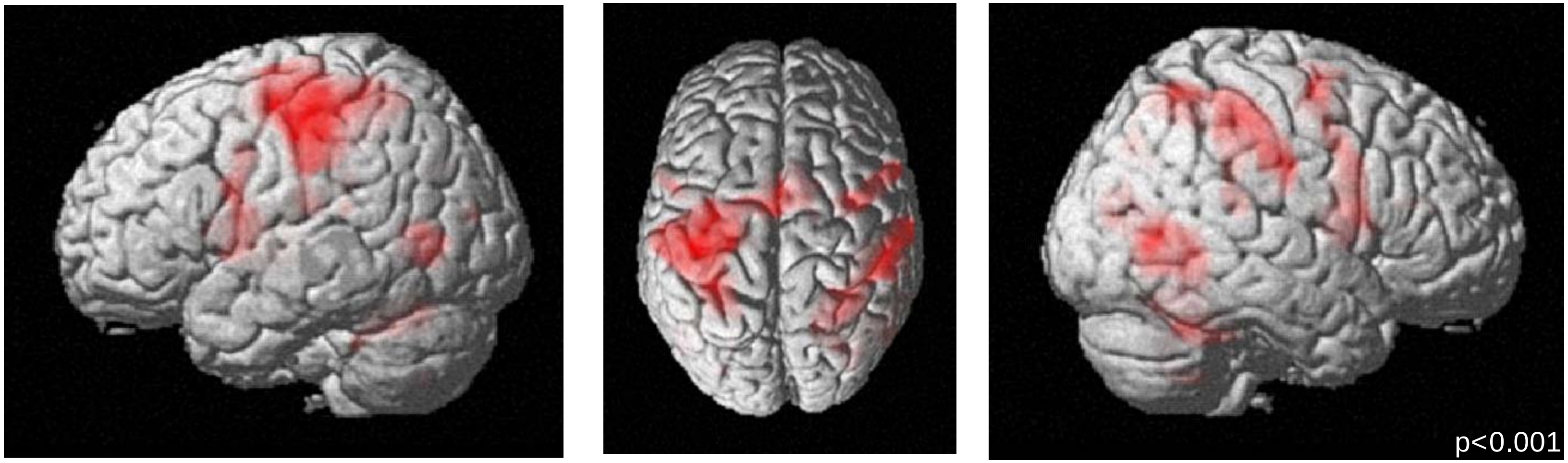
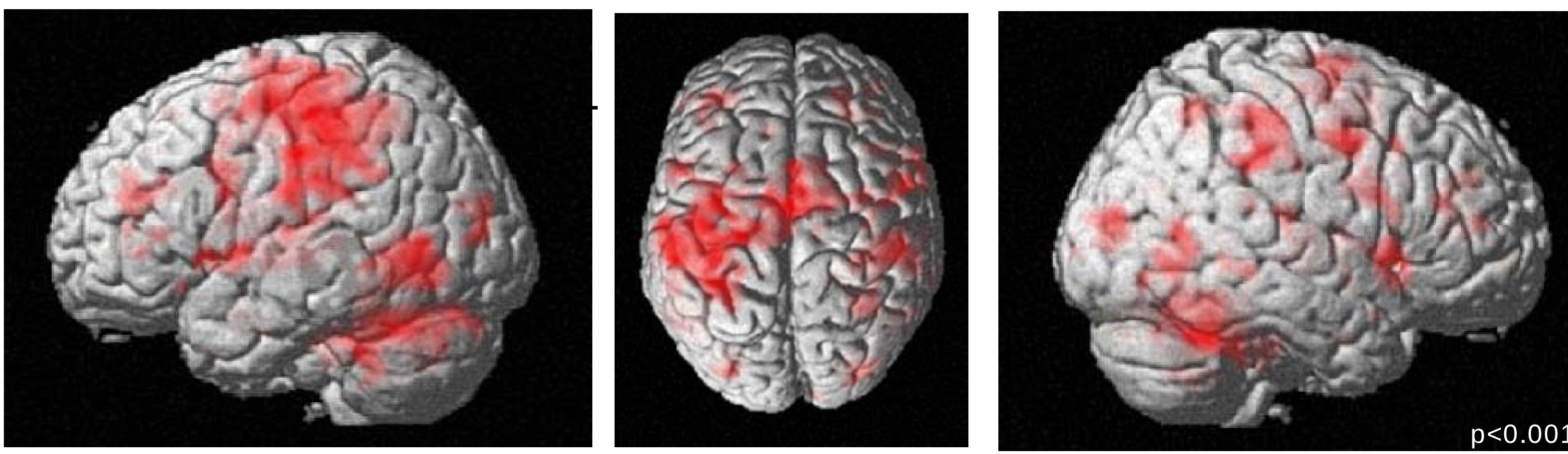
Functional changes

Stimuli➔

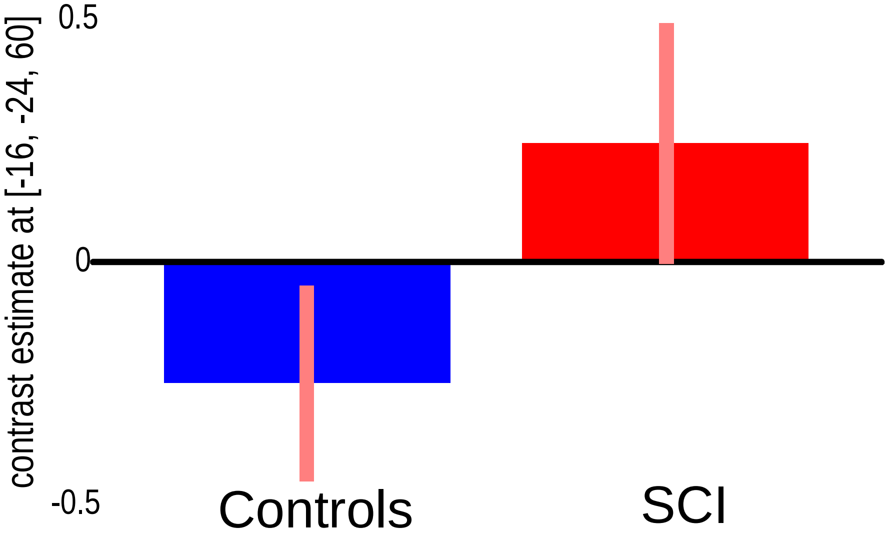
Controls

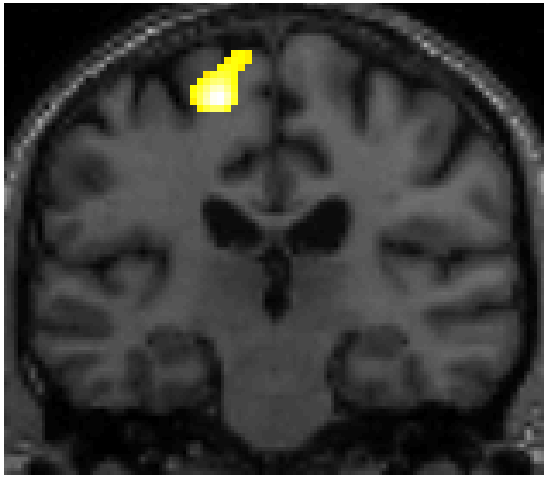


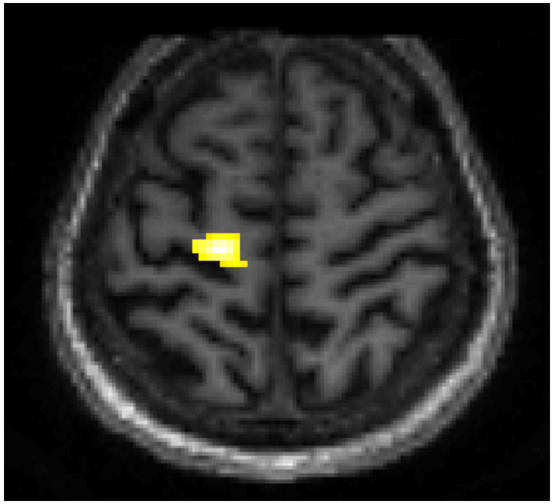
Patients



Increased BOLD signal in M1 leg area







Freund et al 2011, Brain

Multiple Sclerosis

- Mechanisms underlying motor disability
- Assessing tracts in spinal cord
- More sophisticated techniques to improve specificity

Research Paper

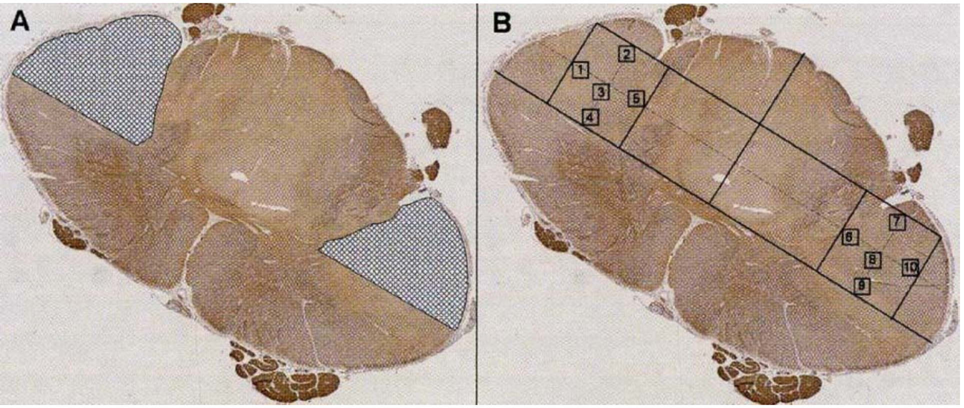
Multiple Sclerosis

Multiple Sclerosis
16(4) 406–411

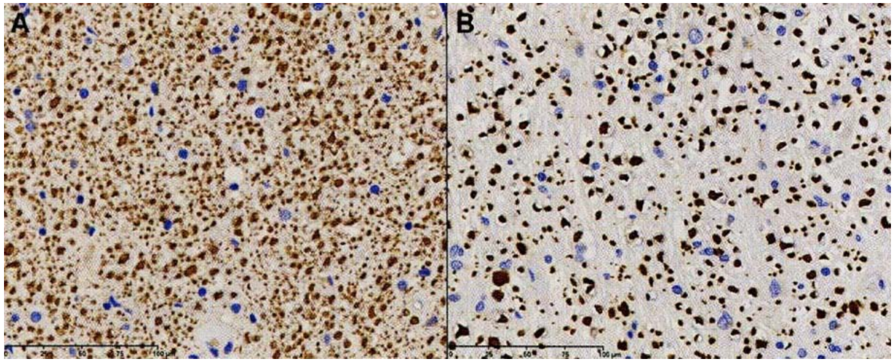
DOI: 10.1177/1352458510364992
msj.sagepub.com
SAGE

Clinico-pathological evidence that axonal loss underlies disability in progressive multiple sclerosis

Emma C Tallantyre[1], Lars Bø[2,3], Omar Al-Rawashdeh[1], Trudy Owens[4], Chris H Polman[5], James S Lowe[6] and Nikos Evangelou[7]



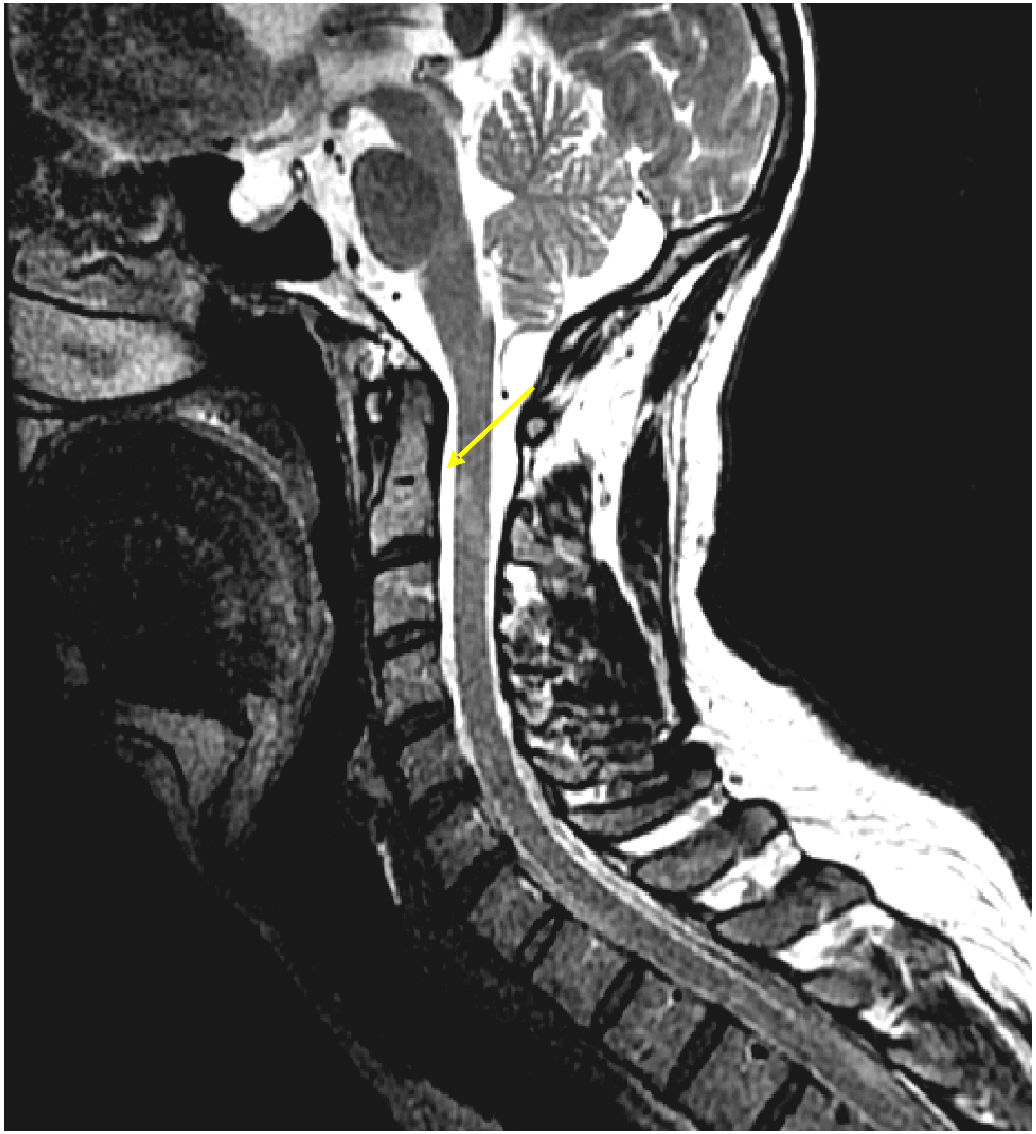
- **CST analysis at level of cervical cord**
- **SPMS patients (B) lose small axons**



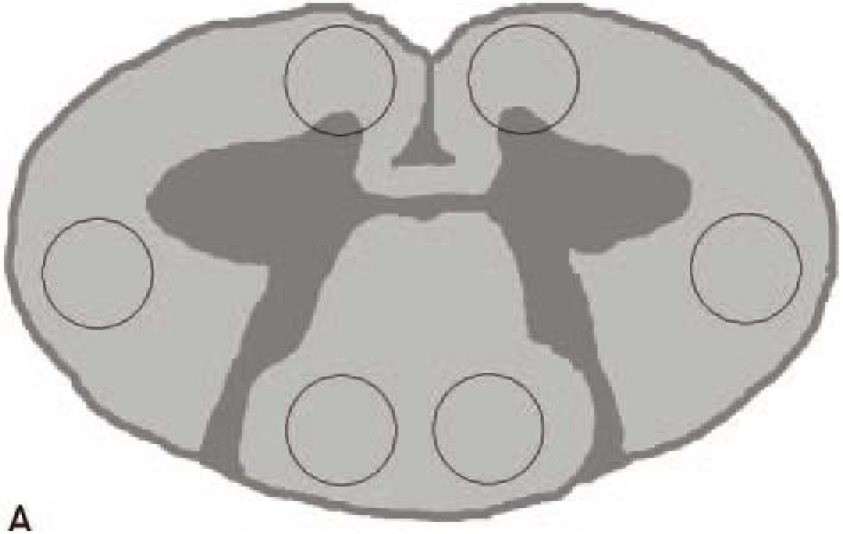
DTI and *tractography* of the major white matter tracts

MRI FEATURES

All patients had at least one lesion between C1 and C3 responsible of relapse



DTI



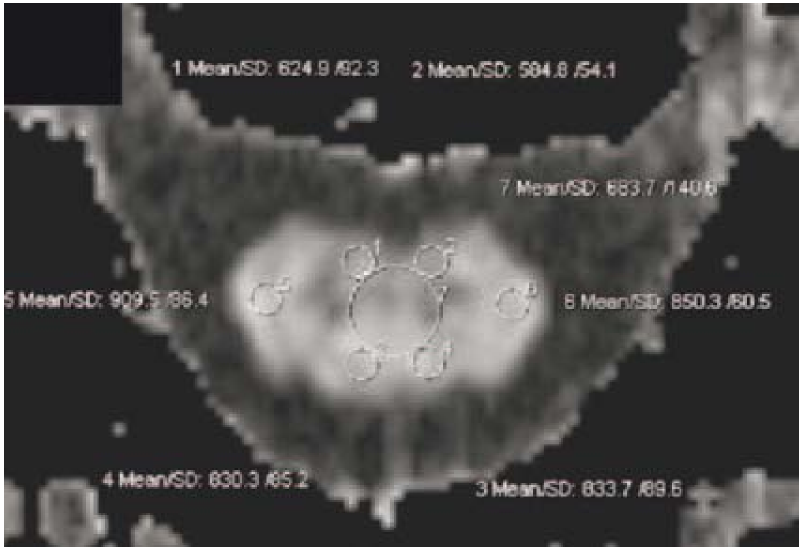
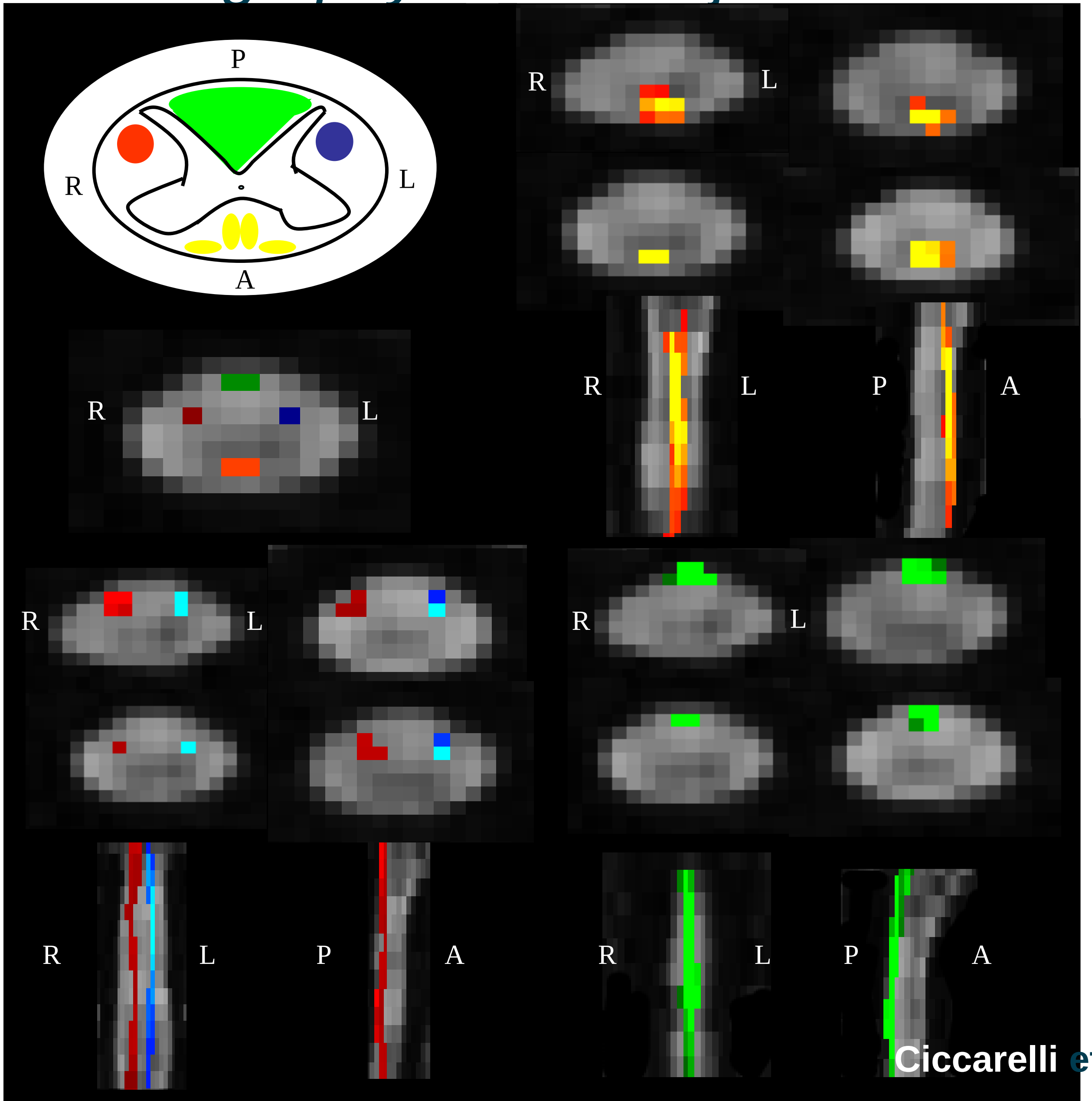


Table 1: Average fractional anisotropy and mean diffusivity in regions of interest in the anterior, lateral, posterior, and central spinal cord at the C2–C3 level, in 24 patients with multiple sclerosis and 24 age- and sex-matched normal volunteers

	Anterior		Lateral CST		Posterior		
	Left	Right	Left	Right	Left	Right	Central
Fractional anisotropy							
Cases ($n = 24$)	0.50 ± 0.12	0.50 ± 0.12	0.56 ± 0.12	0.55 ± 0.10	0.52 ± 0.11	0.52 ± 0.12	0.53 ± 0.10
Controls ($n = 24$)	0.51 ± 0.09	0.49 ± 0.10	0.69 ± 0.11	0.69 ± 0.10	0.63 ± 0.11	0.64 ± 0.11	0.58 ± 0.10
P values	.63	.67	<.0001	<.0001	.001	.001	.05
Mean diffusivity ($\times 10^{-3}$ mm^{-2}s^{-1})							
Cases	0.92 ± 0.21	0.99 ± 0.30	0.91 ± 0.29	0.92 ± 0.26	0.92 ± 0.22	0.92 ± 0.24	0.89 ± 0.18
Controls	0.86 ± 0.17	0.86 ± 0.17	0.79 ± 0.16	0.75 ± 0.25	0.80 ± 0.11	0.81 ± 0.12	0.81 ± 0.14
P values	.33	.06	.06	.02	.03	.06	.077

DTI and *tractography* of the major white matter tracts



The colour scale indicates the voxel-based connectivity value (C1 - C3)

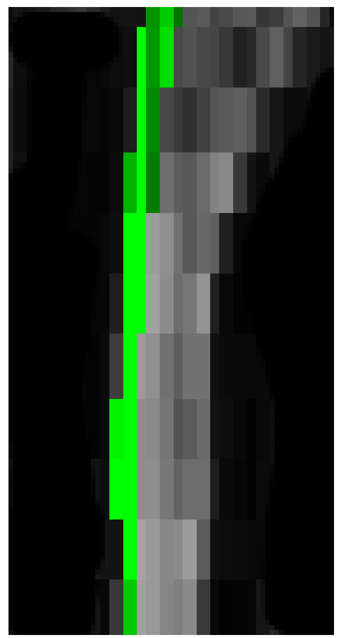
Ciccarelli et al, Brain 2007

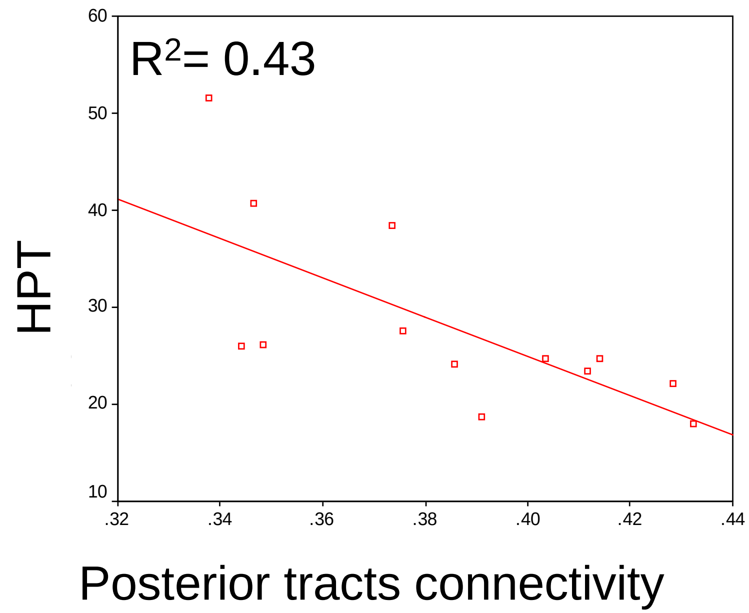
Cortico-spinal tract	Patients	Controls	
Connectivity	**0.38 (0.03)**	**0.41 (0.03)**	**0.01**
FA	**0.456 (0.06)**	**0.538 (0.05)**	**0.004**
MD ($mm^2/s \times 10^{-3}$)	0.827 (0.17)	0.811 (0.13)	n.s
Axial and radial diffusivity	1.06 (0.11) 0.52 (0.07)	1.09 (0.18) 0.46 (0.11)	n.s. 0.07
Posterior tract			
Connectivity	0.39 (0.04)	0.43 (0.05)	0.03
FA	0.394 (0.06)	0.441 (0.04)	0.02
MD	0.817 (0.17)	0.810 (0.13)	n.s.
Axial and radial diffusivity	1.15 (0.19) 0.67 (0.16)	1.17 (0.16) 0.63 (0.12)	n.s.
Anterior tract			
Connectivity	0.39 (0.06)	0.43 (0.06)	n.s.
FA	0.425 (0.06)	0.472 (0.06)	n.s. 0.07
MD	0.678 (0.10)	0.680 (0.12)	n.s.
Axial and radial diffusivity	0.99 (0.15), 0.52 (0.09)	1.05 (0.17), 0.50 (0.11)	n.s.
Spinal cord cross-sectional area	74.9 (9.1) from 14 pt. 71.9 (9.5) from 9 pt. without cord swelling	80.1(6.1)	n.s. 0.06 0.01

Clinical relevance of DTI and *tractography*

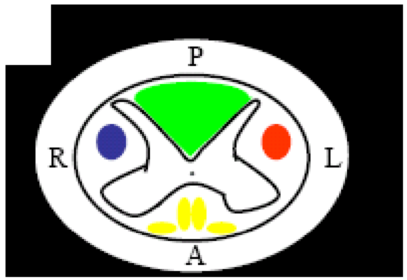
- 9HPT correlated with connectivity and FA of the posterior tracts and with connectivity of the ant. tracts

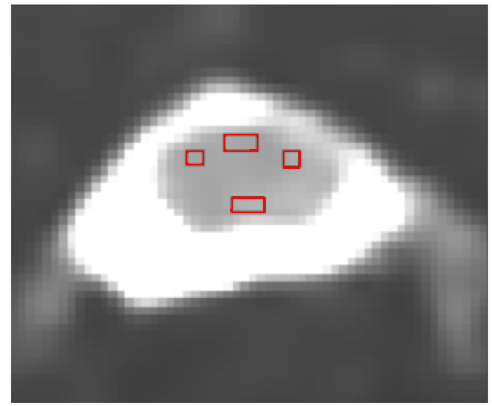
- Connectivity of the posterior tracts was associated with 9HPT independently from all other MRI variables, age and gender





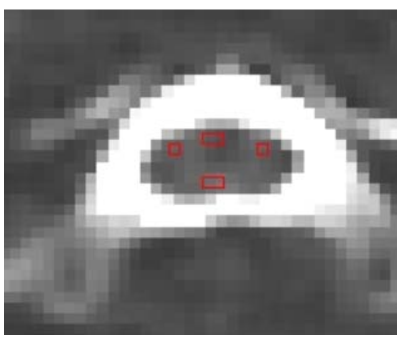
Temporal changes of FA and RD over 6 months





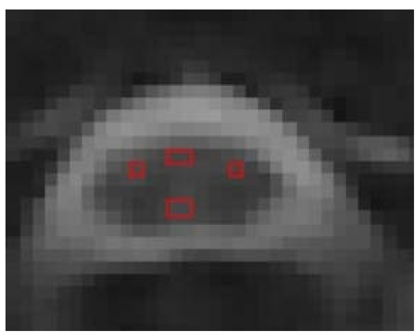
4 ROIs drawn between C1 and C3

b0



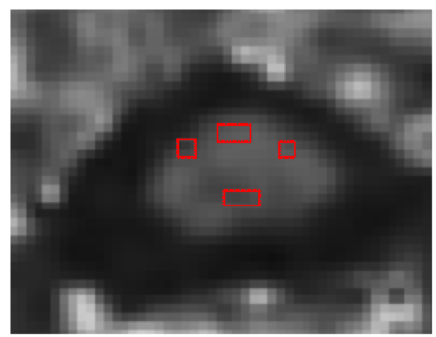
RD (radial diffusivity)

Myelin

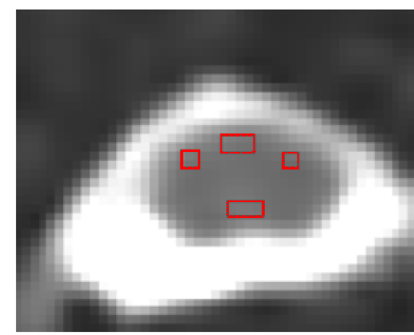


AD (axial diffusivity)

Axons

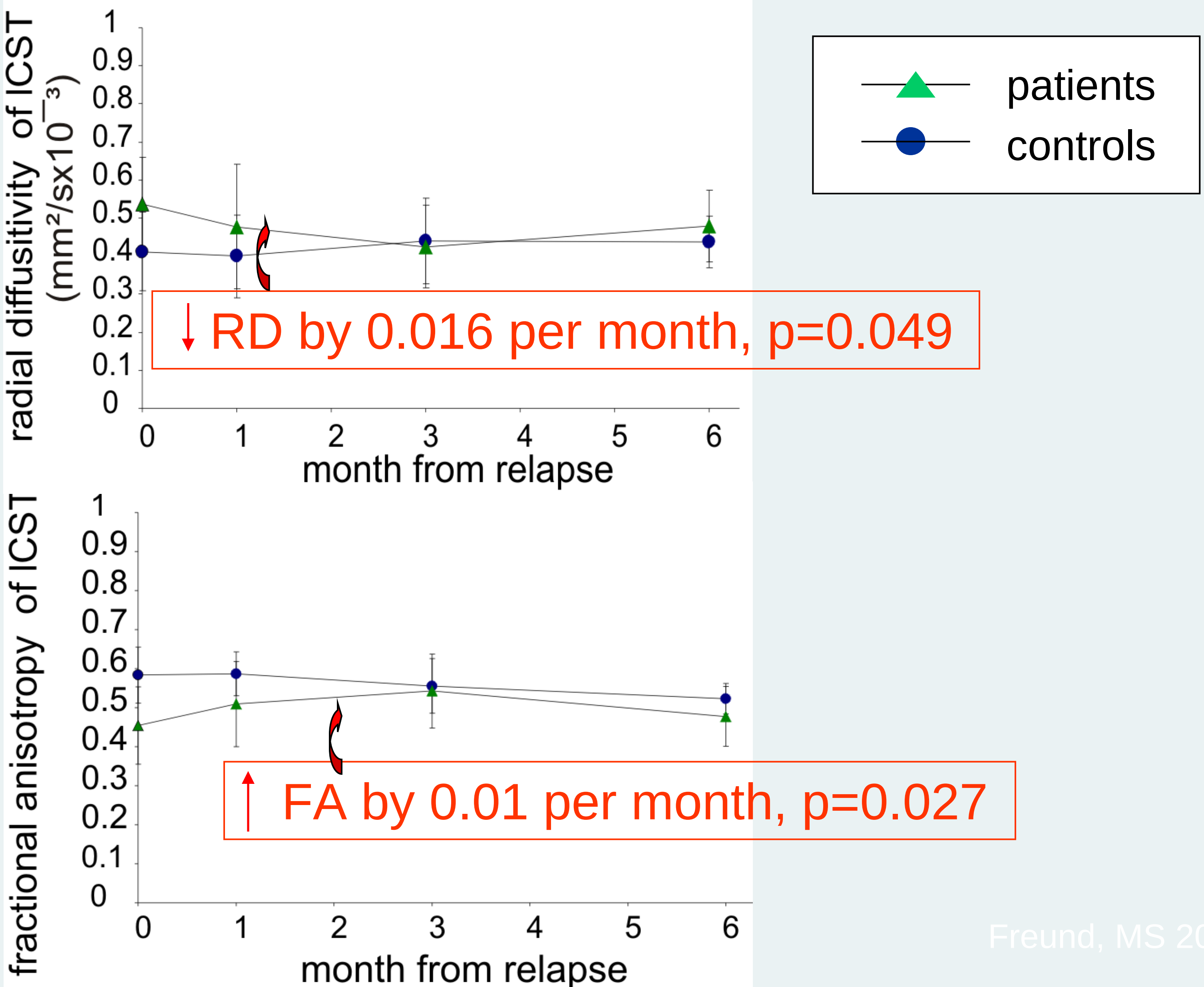


FA (fractional anisotropy)



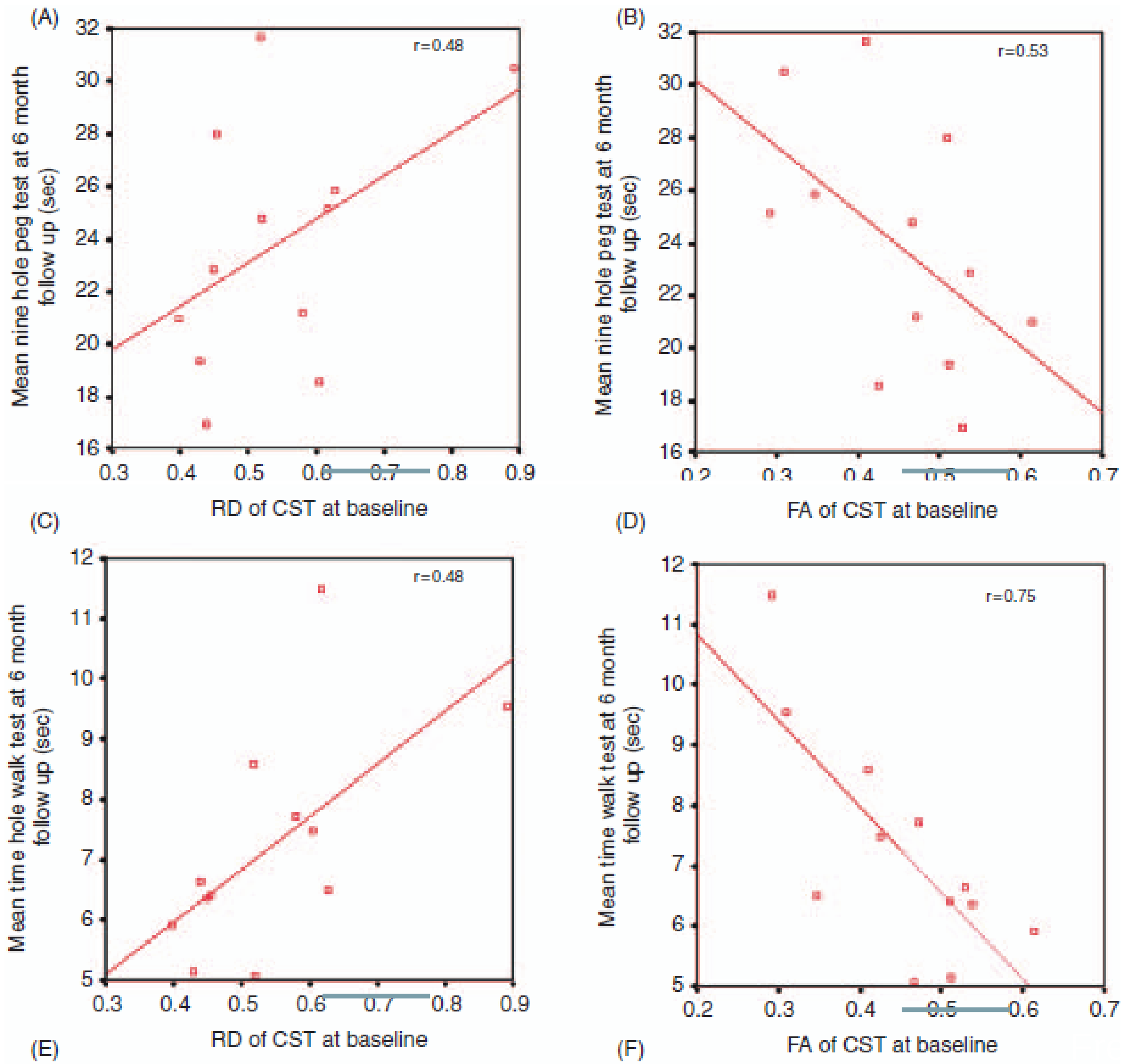
MD (mean diffusivity)

Temporal changes of FA and RD post relapse



Freund, MS 2010

Predictive role of baseline FA and RD



Combining CST connectivity and motor cortex measures to test hypothesis relevant to motor function

Patients with history of hemiparesis from a lesion in the CST

Nikos Gorgoraptis et al MSJ 2010

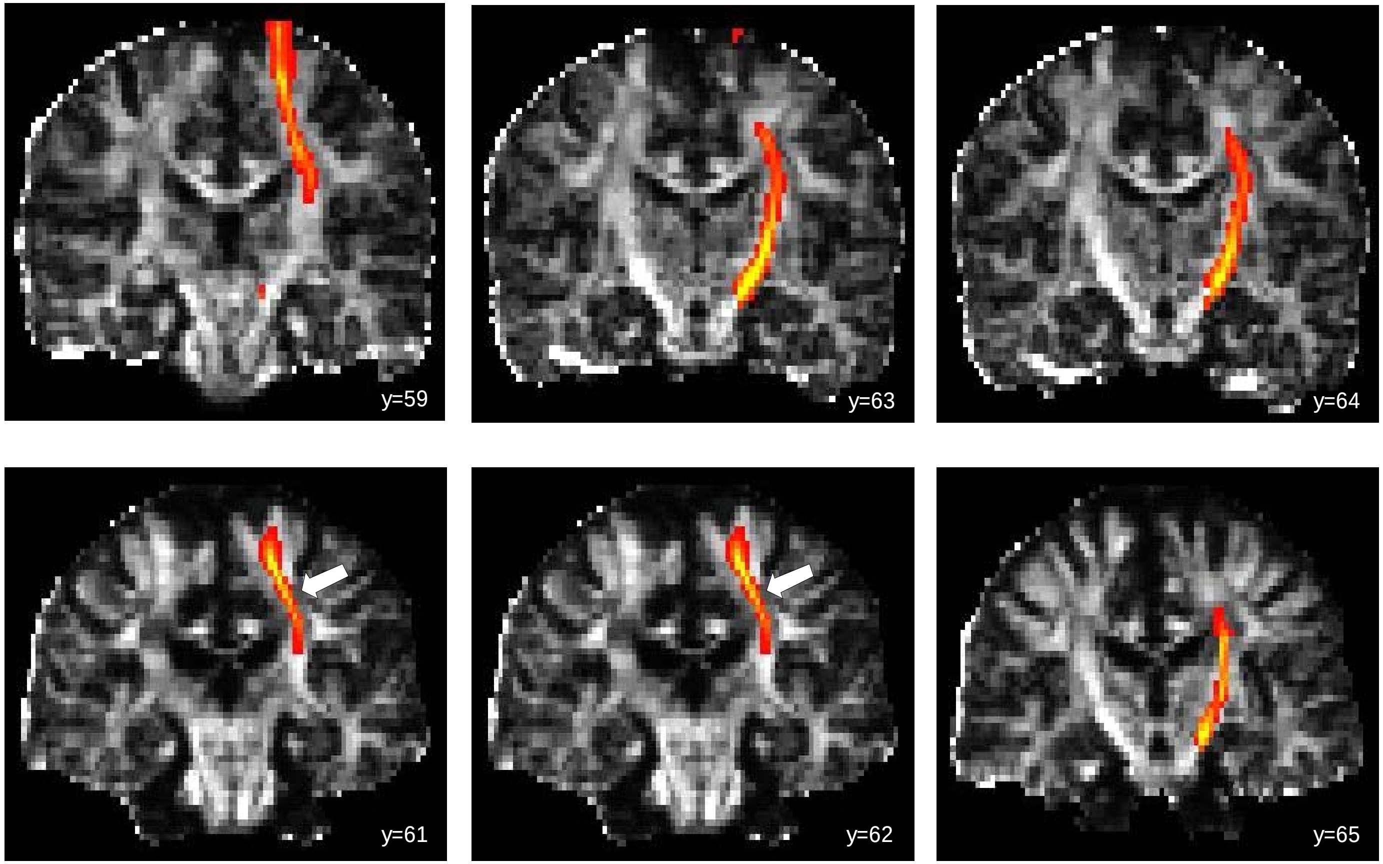
Table 1. Patients' characteristics

Age	Mean: 46 years (SD: 13.2)
Gender	5 female, 6 male
Disease type	10 relapsing–remitting MS, 1 secondary progressive MS
EDSS	Median 4.5 (range 2–6)
Pyramidal FS score	Median 3 (range 1–4)
25-foot Timed Walk Test (TWT)	Mean 8.23 s (SD: 2.15)
9-Hole Peg Test (9-HPT)	Mean 25.4 s (SD: 4.9)
Side of the lesion	7 left, 4 right
Location of the lesions	2 lesions in the WM adjacent to the precentral cortex 2 lesions in the corona radiata 2 lesions in the posterior limb of the internal capsule 2 lesions in the cerebral peduncle 2 lesions extending from the cerebral peduncle to the internal capsule 1 lesions extending from the cerebral peduncle to the corona radiata
Time from hemiparesis	Mean: 14 months (SD: 16)

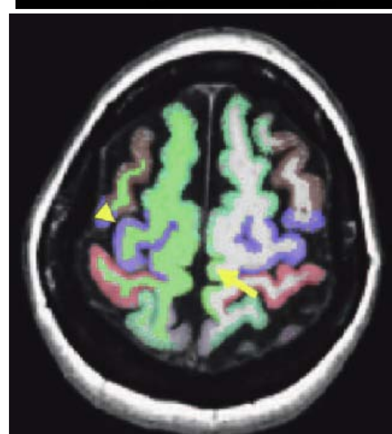
CST from probabilistic tractography

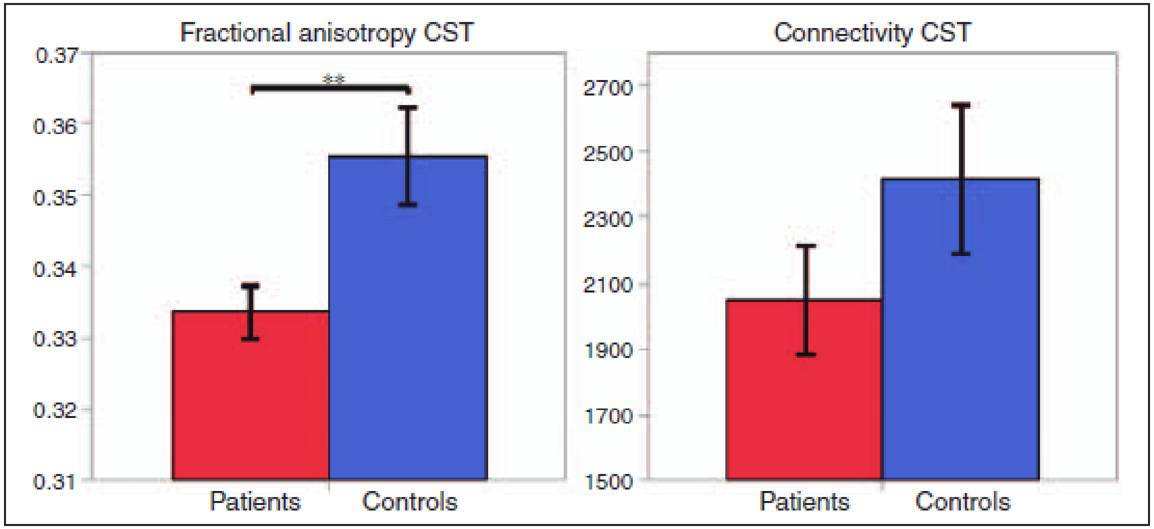
A

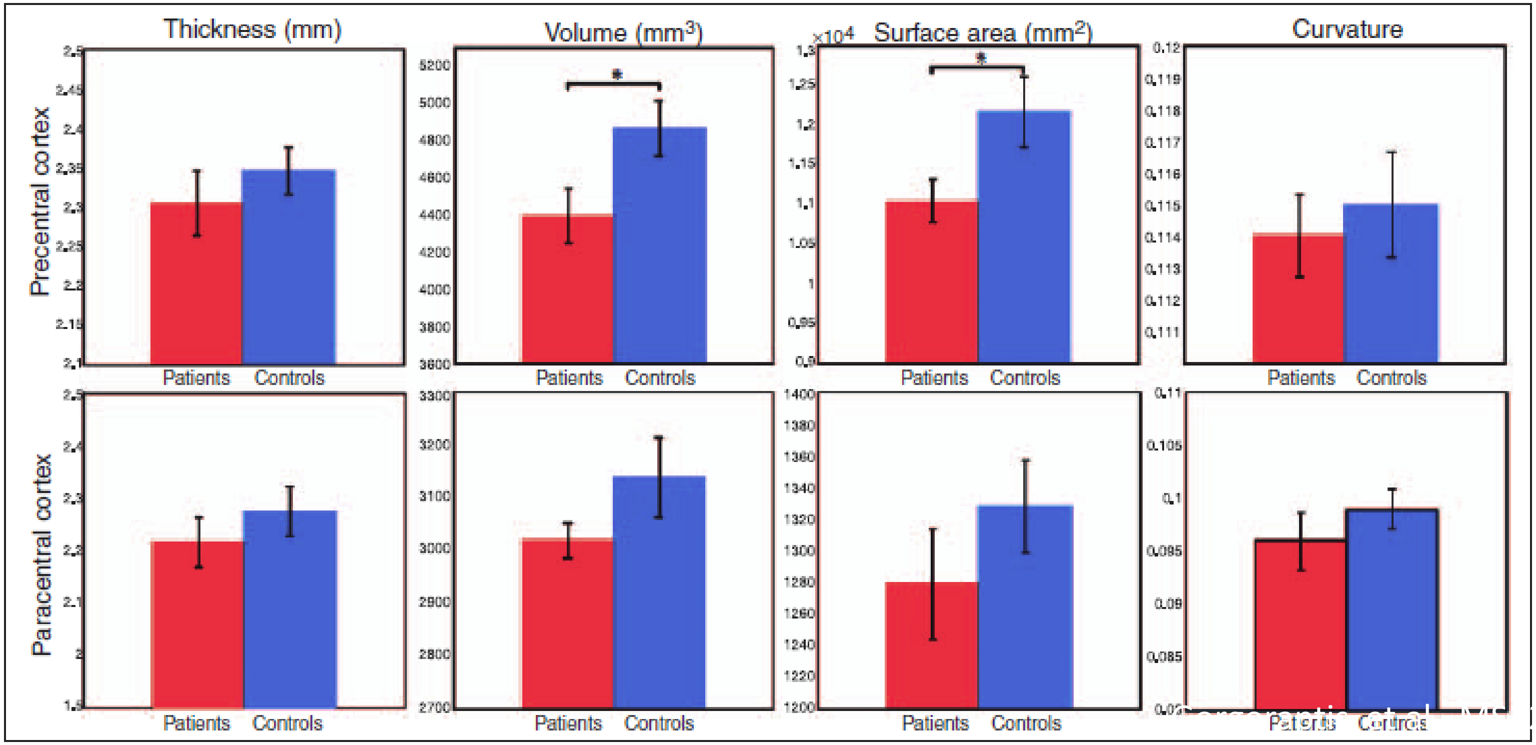
B

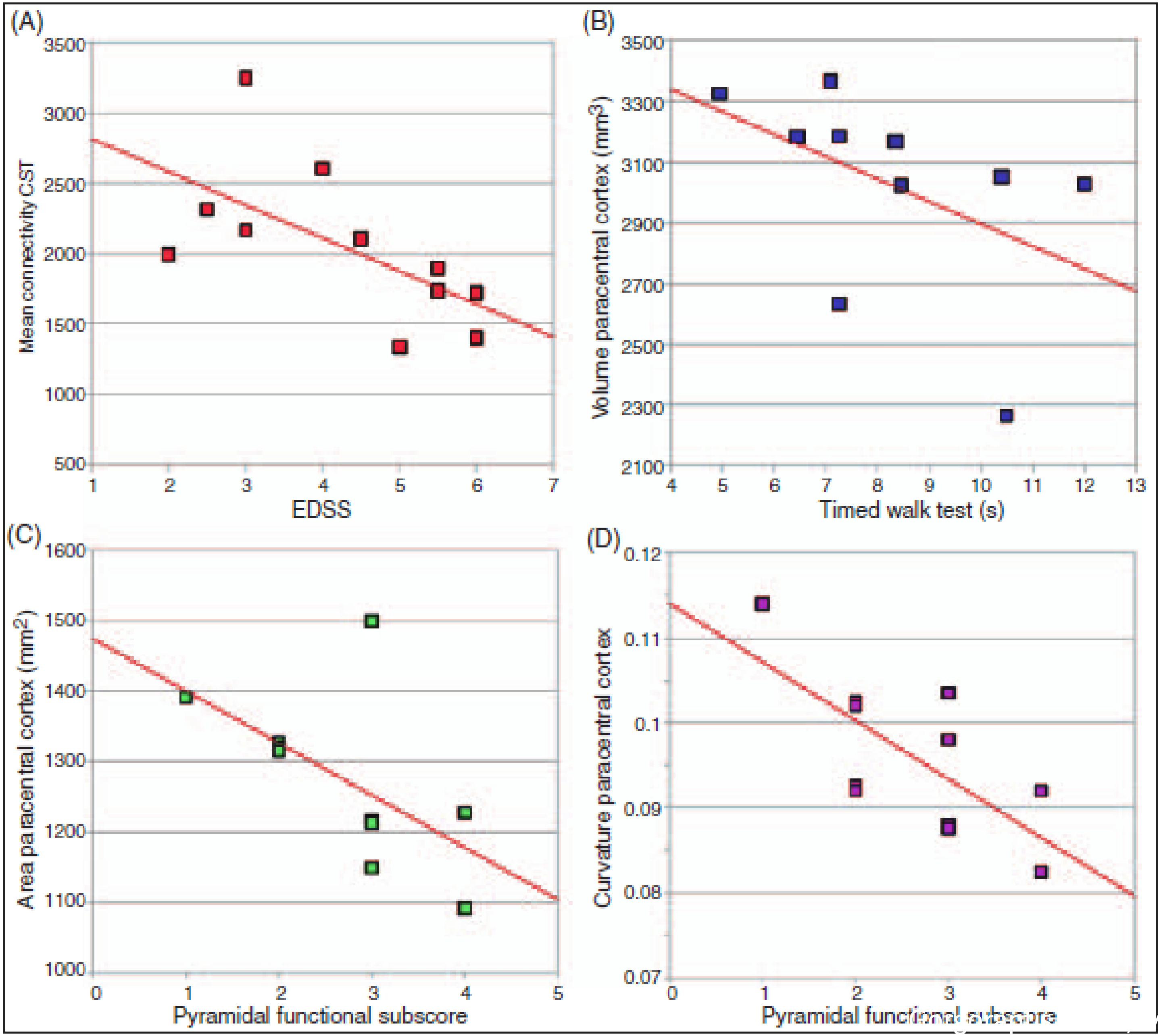


Volume, thickness, curvature and surface ares of precentral and paracentral cortex from FreeSurfer




Fractional anisotropy CST
0.37
0.36
0.35
0.34
0.33
0.32
0.31
**
Patients
Controls
Connectivity CST
2700
2500
2300
2100
1900
1700
1500
Patients
Controls


Thickness (mm)
Volume (mm³)
Surface area (mm²)
Curvature
Precentral cortex
Paracentral cortex
×10⁴
*
*
Patients
Controls


(A)
Mean connectivity CST
EDSS
(B)
Volume paracentral cortex (mm3)
Timed walk test (s)
(C)
Area paracentral cortex (mm2)
Pyramidal functional subscore
(D)
Curvature paracentral cortex
Pyramidal functional subscore

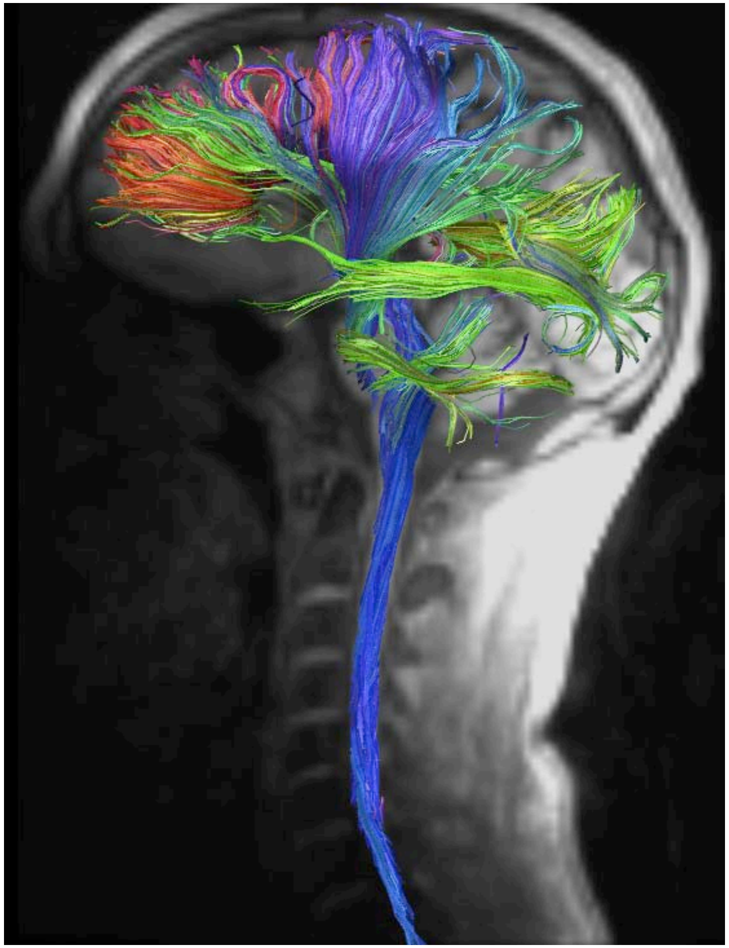
Diffusion Tensor Imaging & Tractography

- Tractography of the spinal cord is feasible
- Reduced FA and connectivity in tracts suggest reduced fibre integrity (mainly demyelination)
- Changes in RD and FA contribute to and are predictive of disability
- Reduced corticospinal tract connectivity and paracentral cortical volume are associated with increased disability

Susceptibility artifacts

Combining multi-shot with parallel imaging

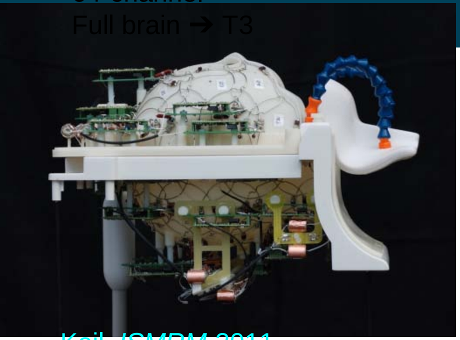
D. Porter et al. "*RESOLVE Multi-Shot Diffusion*" (Siemens WIP #544A)



2.2 mm isotropic
3 shots
R=3
echoSp.=0.38ms
b=800 s/mm^2
30 directions
cardiac gating
TA=10:45

Courtesy of Julien Cohen-Adad,
A.A. Martinos Center for Biomedical Imaging, Harvard Medical School

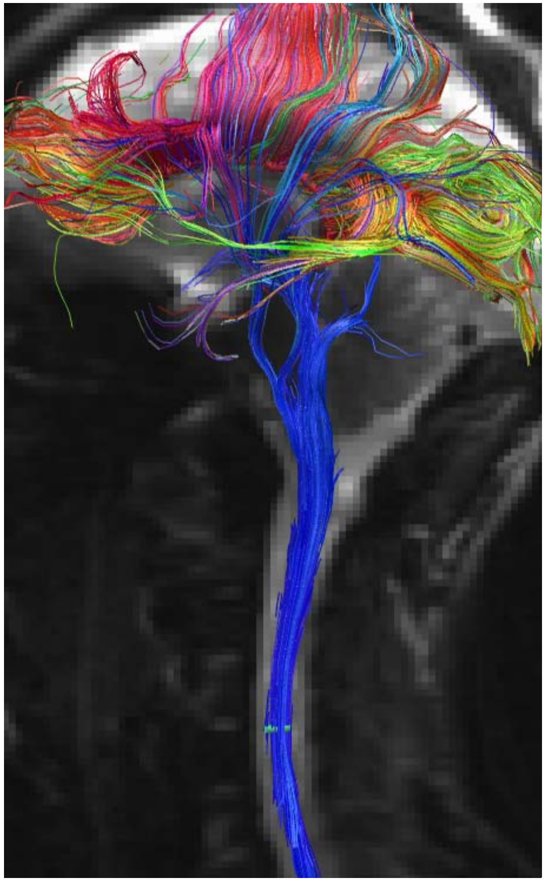
64-channel
Full brain → T3

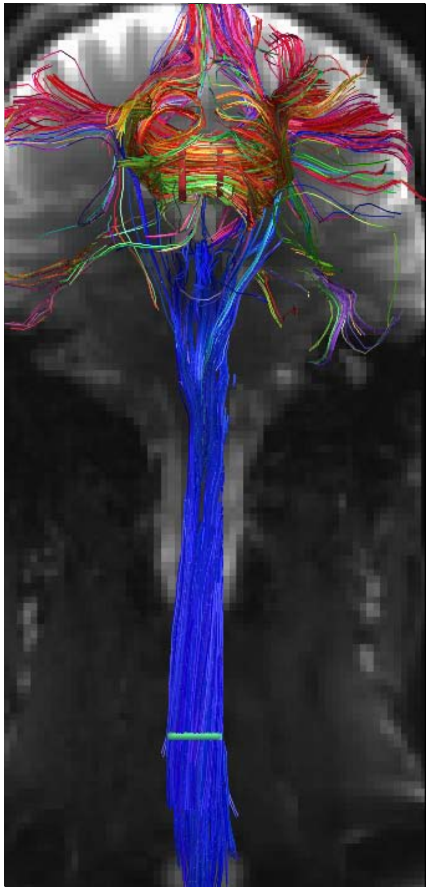


Keil, *ISMRM* 2011

Brain + Spinal Cord Tractography

- 3T Skyra with Connectome gradients (up to 300 mT/m)
- 2x2x2 mm, full brain/c-spine
- Q-Ball acquisition (64 dirs)
- Eddy-current distortion correction (FSL)
- Gradient non-linearity distortion correction
- Susceptibility distortion correction (phase field map)





Courtesy of Julien Cohen-Adad,
A.A. Martinos Center for Biomedical Imaging, Harvard Medical School