"Post-stroke brain remodeling processes in animal models and humans"

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35th CONGRESS OF THE FRENCH SOCIETY

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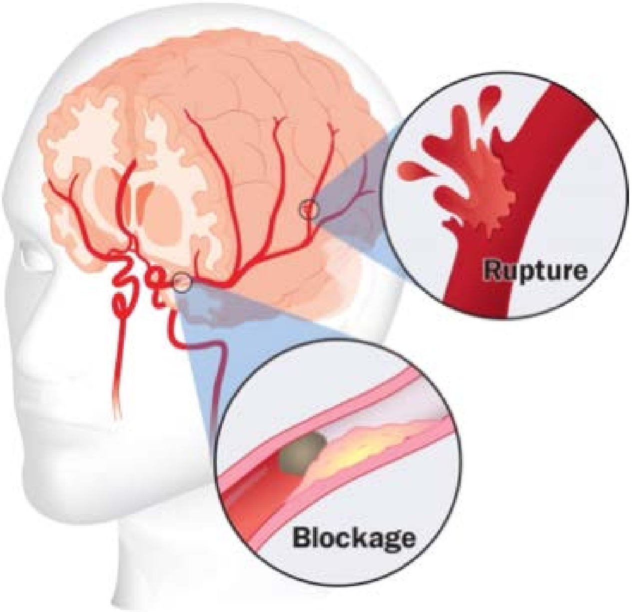
RECOVERY AFTER STROKE



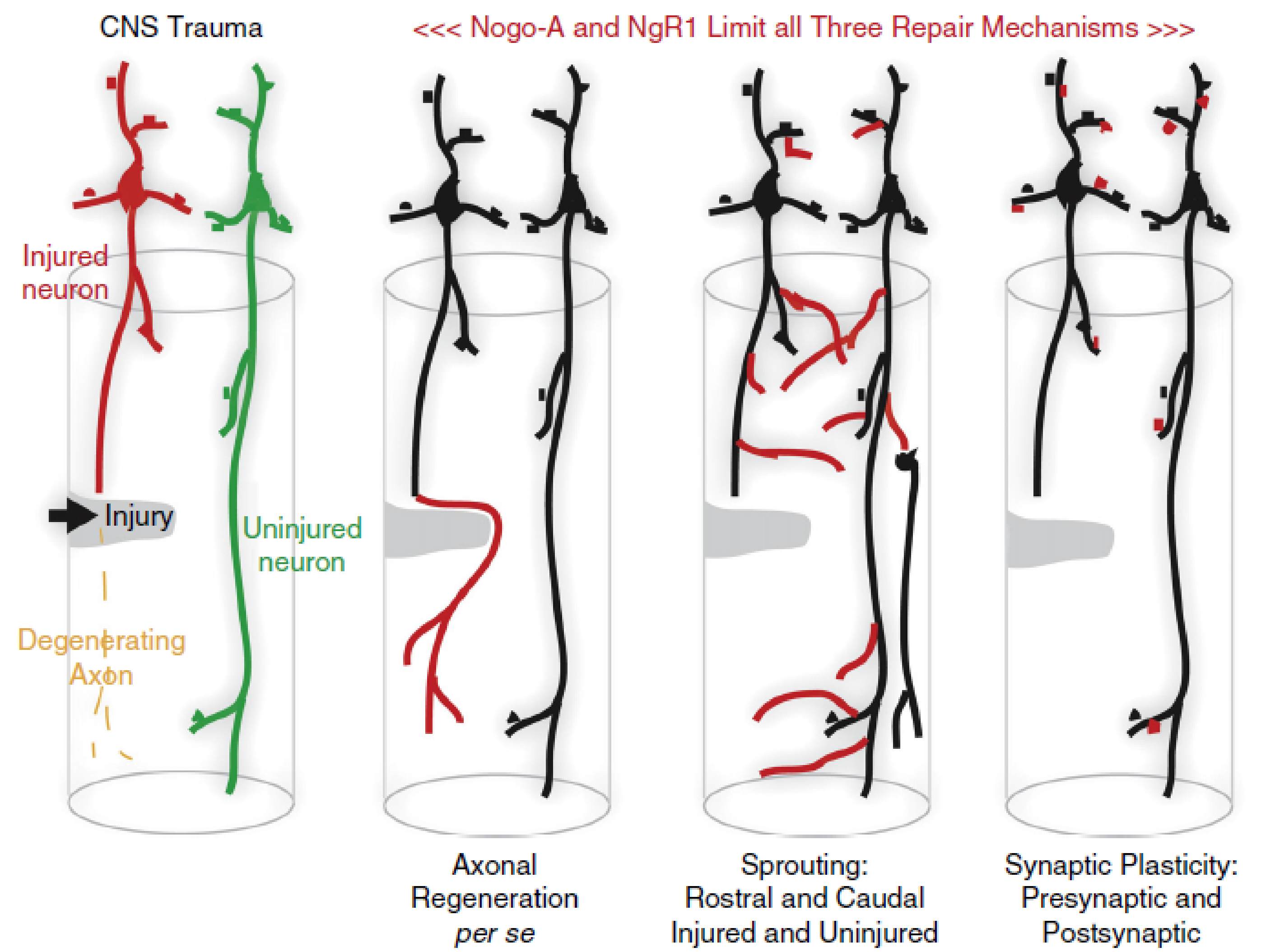
- Stroke is the first cause of handicap and long-term disability
- No recovery of upper limb motor function in 50 % patients
- No return to normal professional and personal life
- Recovery through brain and spinal plasticity
- Mechanisms not totally understood
- Main factor : Integrity of the corticospinal tract CST

MECHANISMS of BRAIN PLASTICTY

- Axon repair
- Neurogenesis
- Unmasking of perilesional neurons and redundancy
- Spinal plasticity : sprouting
- Contralesional plasticity and Transhemispheric Sprouting
- Reinforcement of direct fibers
- Alternate motor tracts
- Uni-modal and cross-modal plasticity
- Vicariance

⇨ Stratification of patients in 3 groups depending on the lesion location and level of deficit

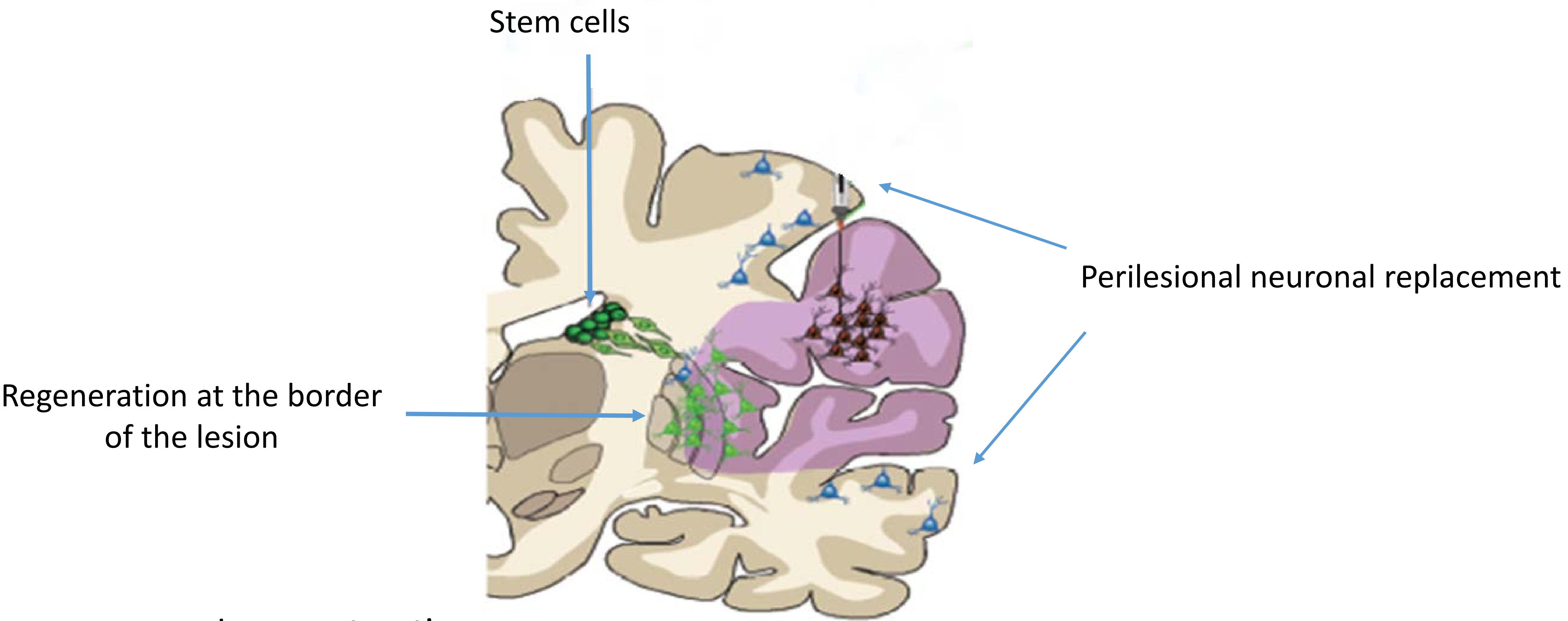
Axon repair in brain or spinal cord



Schwab & Strittmatter, 2014

No efficacious treatment in humans : *Anti-Myelin Associated Glycoprot* (Cramer, Stroke 2017)

Neurogenesis



Long maturation

Less than 1% neurons are replaced (Magavi et al, Nature, 2000; Arvidsson et al, Nature Medecine, 2002)

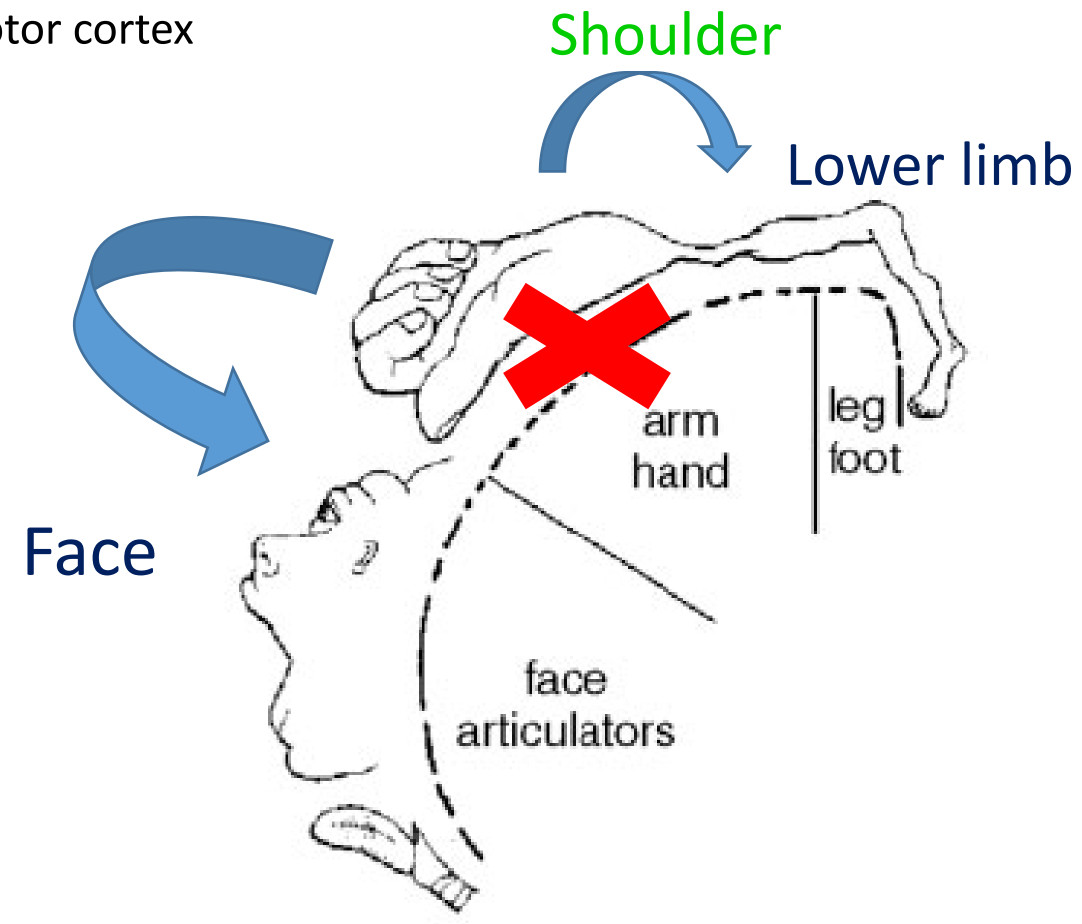
Graft of stem cells in perilesional tissue is safe in stroke patients and holds great promise

(Kalladka et al., Lancet 2016; Steinberg et al., Stroke 2016)

Unmasking of perilesional neurons

Small lesion of primary cortex or fibers, minor deficit

M1: primary motor cortex



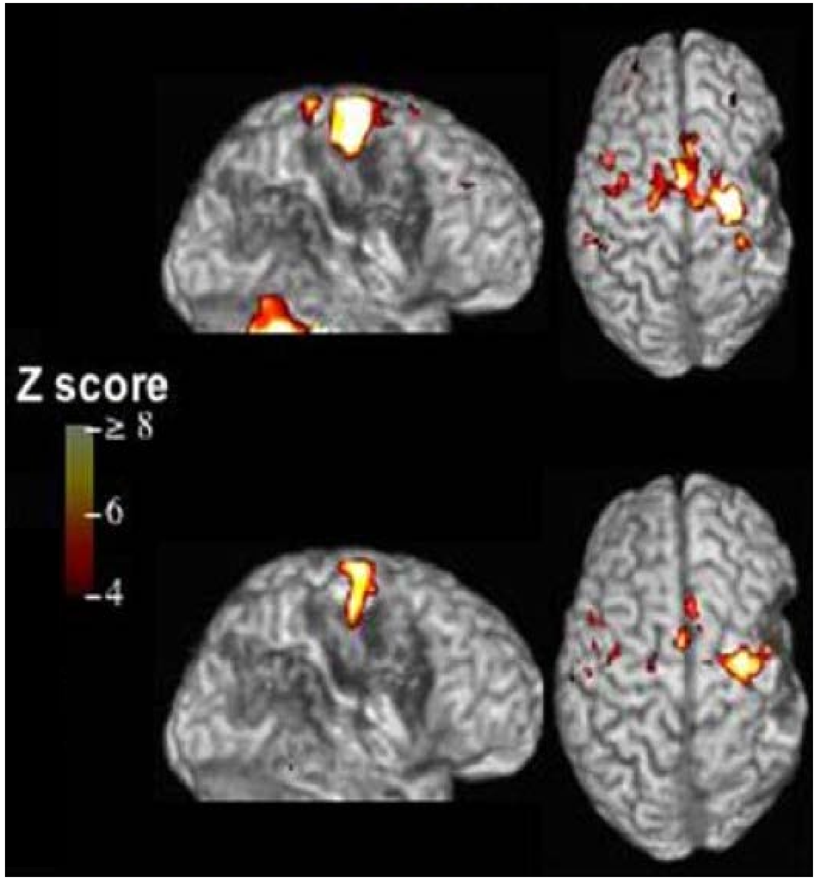
Cortical plasticity

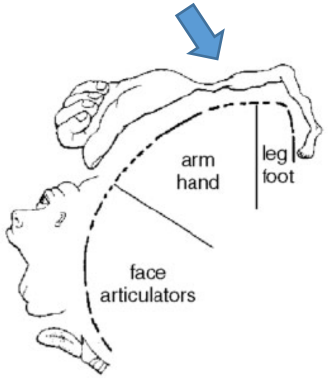
Functional Brain MR Imaging

Recruitment of an adjacent area

Shoulder

Fingers



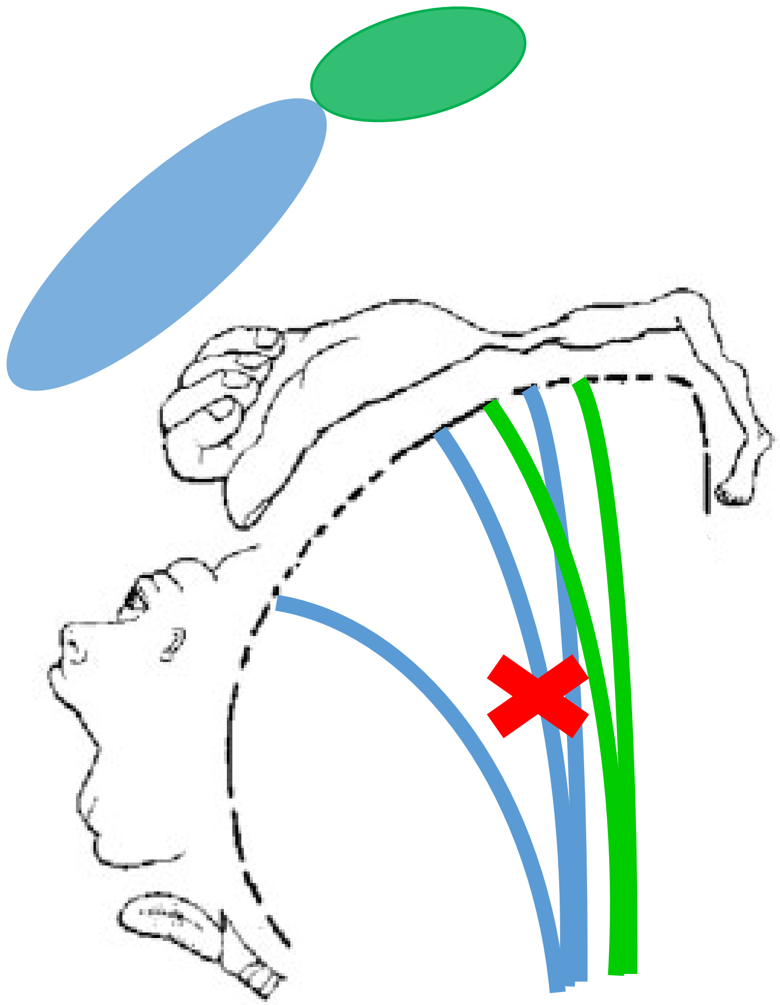


Activation for fingers in shoulder area

Cramer et al., Exp Brain Res 2006

Unmasking of perilesional neurons

M1: primary motor cortex



Overlap of digit and shoulder cortical areas

Overlap of descending corticomotor fibers

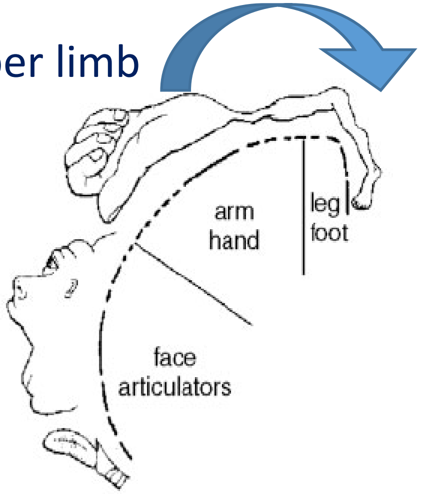
Rathelot & Strick, PNAS 2006
Rathelot & Strick, PNAS 2009

Redundancy of CST fibers

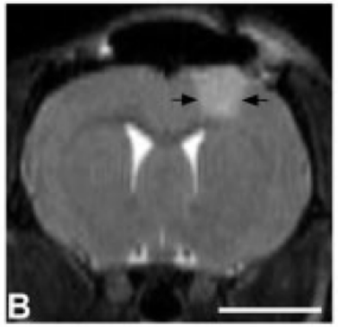
Spinal plasticity : sprouting

Upper limb

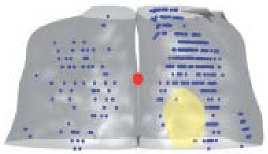
Lower limb



- ⬆ Turn-over perilesional dendritic spines
- ⬆ Synaptogenesis
- ⬆ Hyperexcitability
- ⬇ Sensitive specificity loss
- ⬆ Week 4-8, synaptic connections more specific
- ⬆ Hindlimb neurons connect forelimb

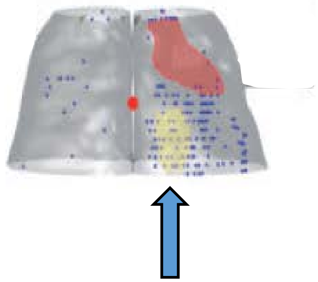


Control



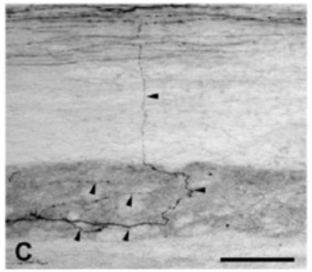
Lower limb

Lesion in upper limb area



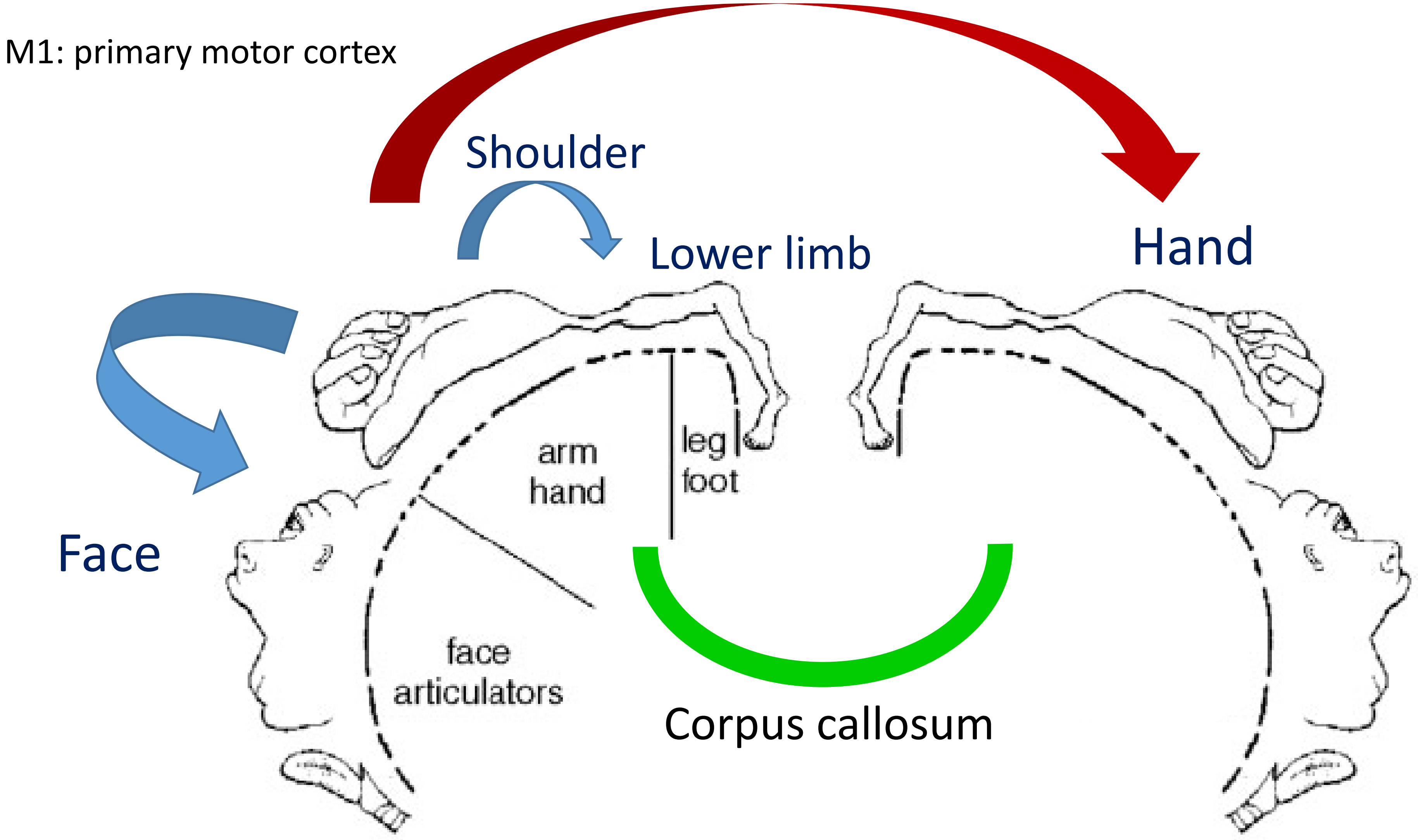
Force pinch -Dexterity

Sprouting in the spinal cord



Winship & Murphy, J Neurosci 2008; Starkey et al., Brain 2014

Contralesional plasticity



KEY MOTOR REGIONS

Voxel-based lesion-symptom mapping
VLSM

Bates et al., Nature Neurosci 2003

Regions where significant correlations with motor deficit exist

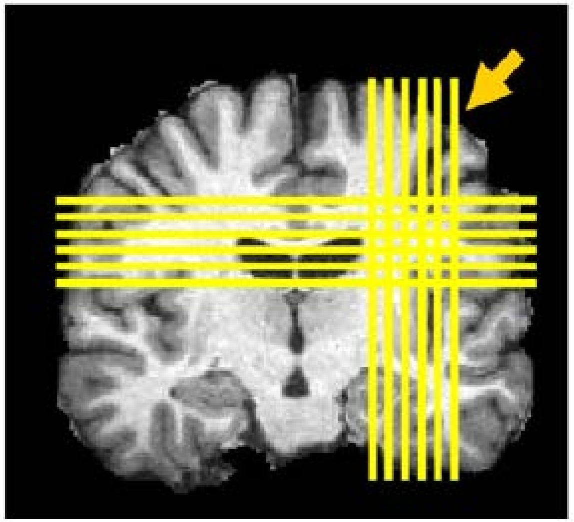
N = 41 patients
58,2 months post-stroke

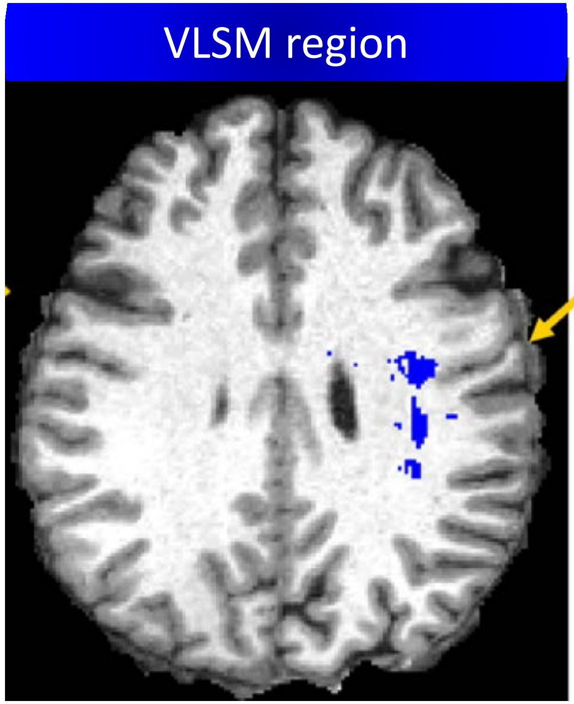
Predictor of residual motor deficit in chronic stroke :

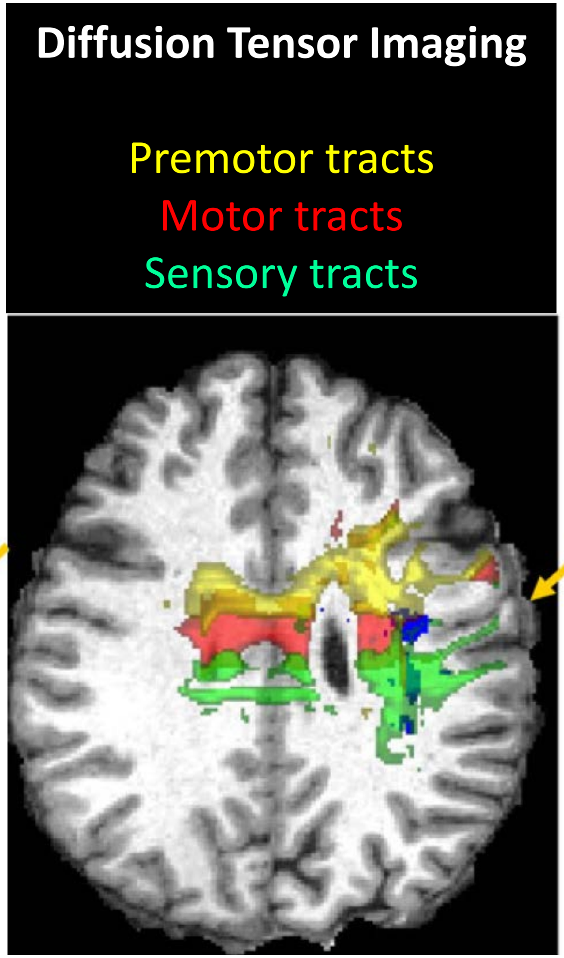
lesion location at the intersection of

- the corona radiata and
- fibers from the corpus callosum.

Lo et al., NeuroImage 2010

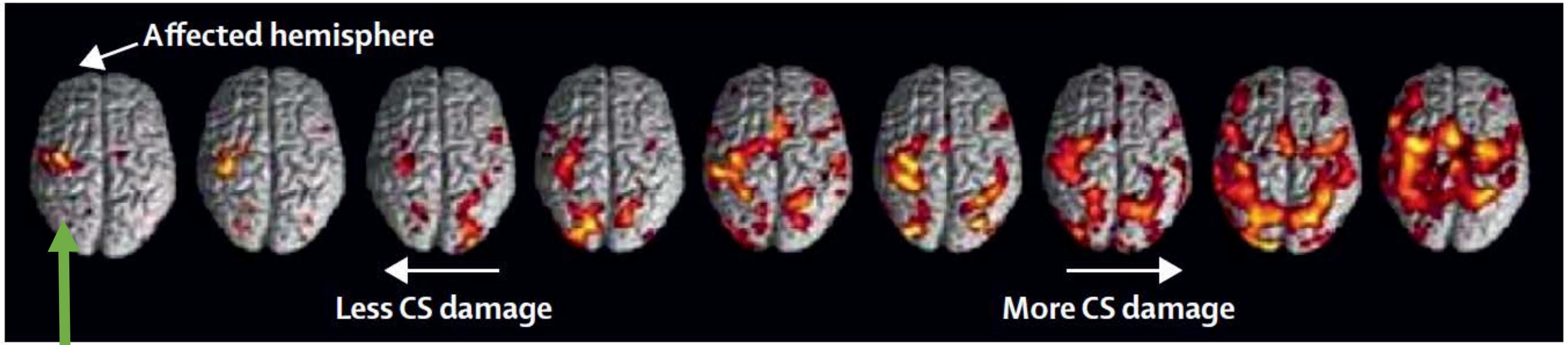






Crossroad : CST – Corpus callosum

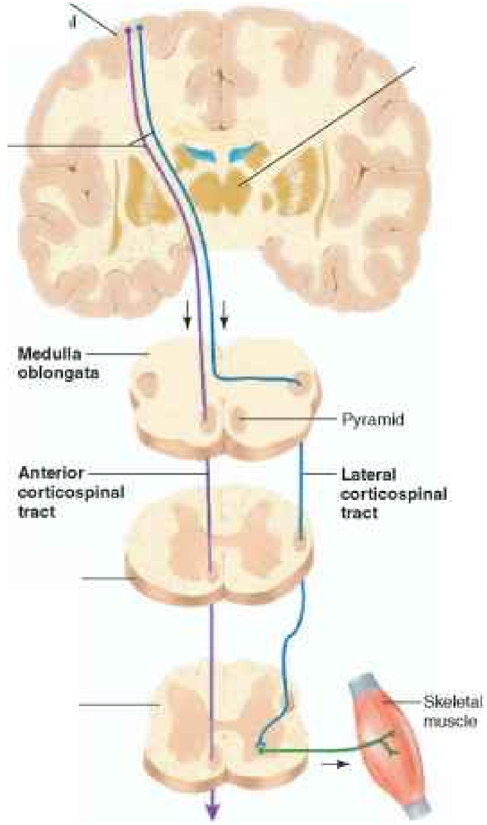
Recruitment of cortical areas

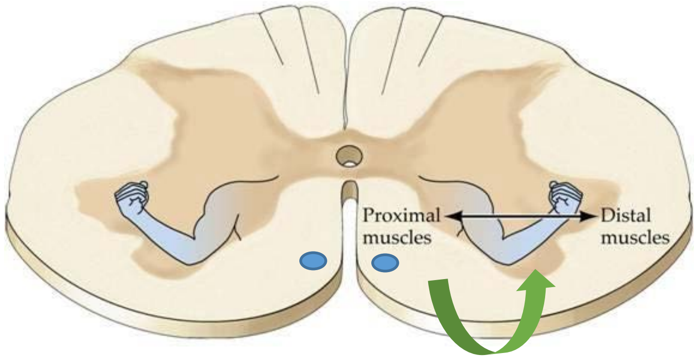


M1: primary motor cortex

Corticospinal tract integrity

Greater involvement of contralesional M1



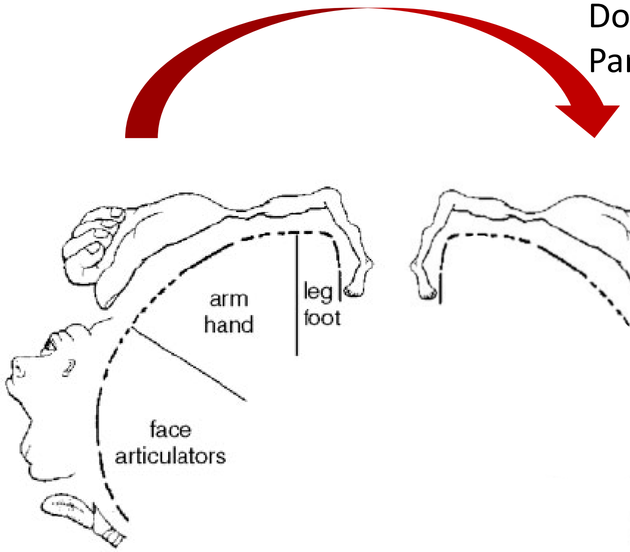


Uncrossed corticospinal tract

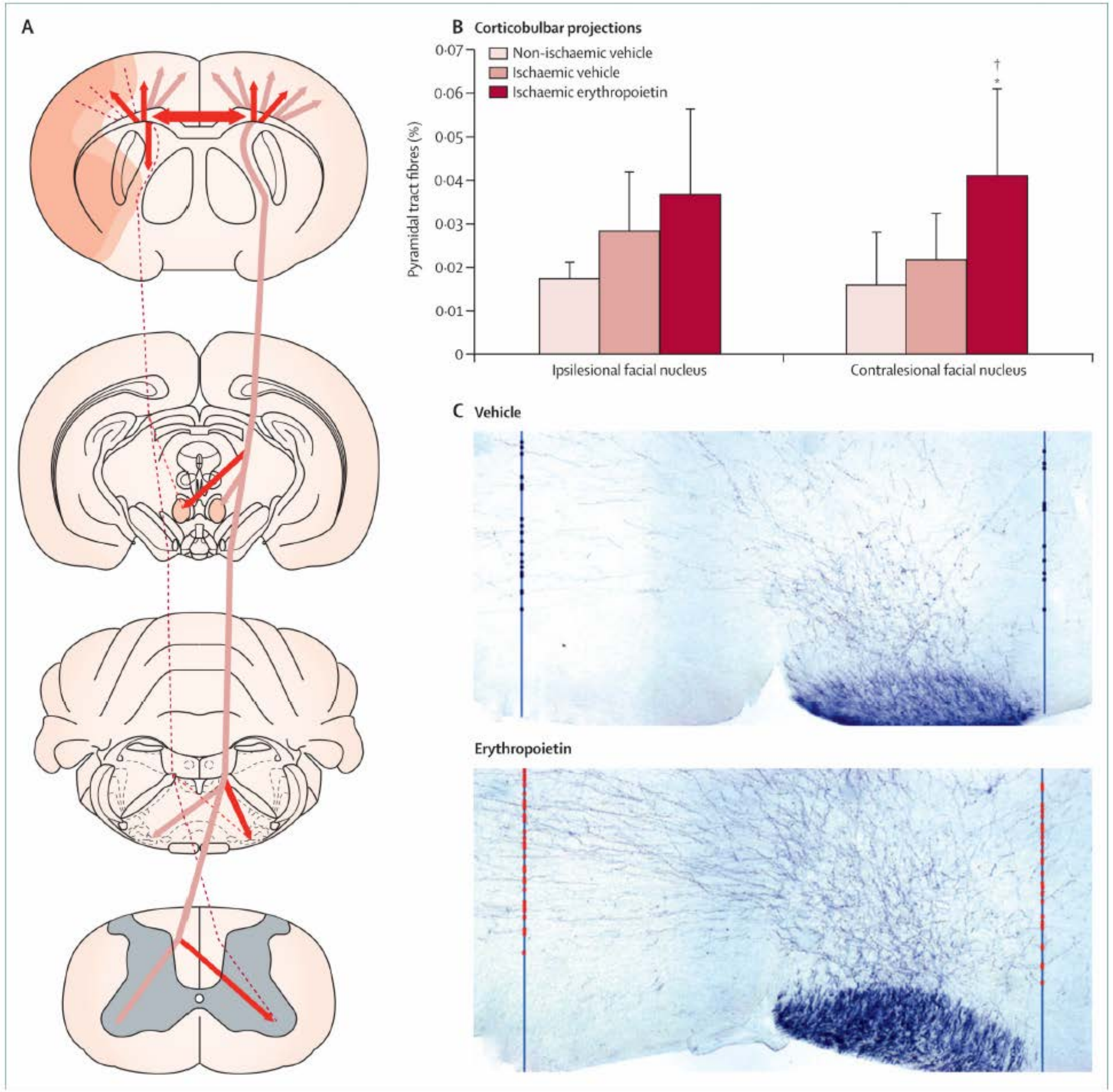
Grefkes & Fink, Lancet Neurol 2014

Transhemispheric Sprouting

in red nucleus, brain stem or spinal cord



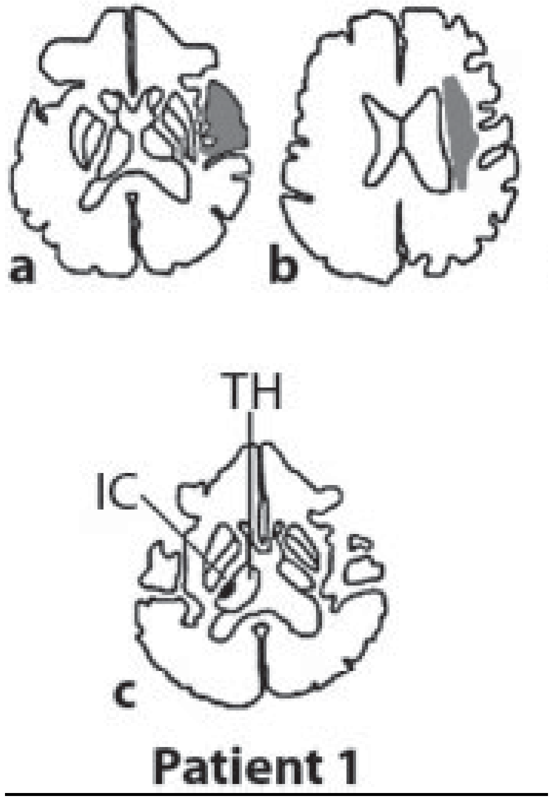
Contralesional CST
Midline crossing

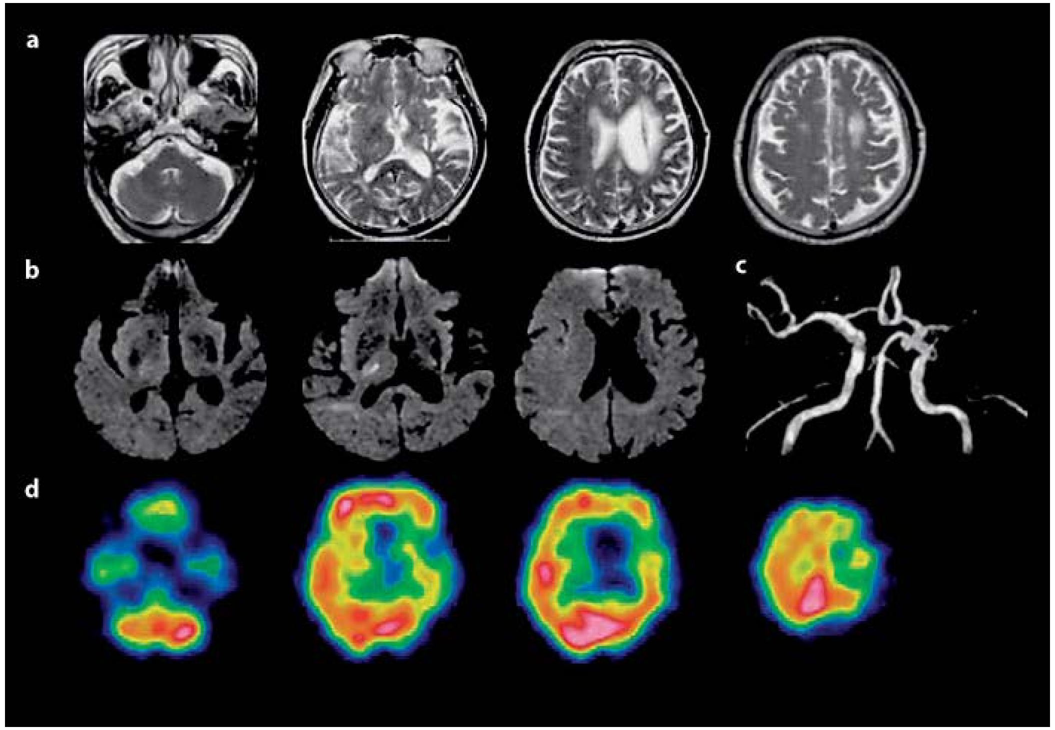


Hermann & Chopp, Lancet Neurol 2012

Evidence of contralesional hemisphere recruitement

Successful recovery after a first stroke
Paresis in both arms after a second stroke in the contralesional hemisphere

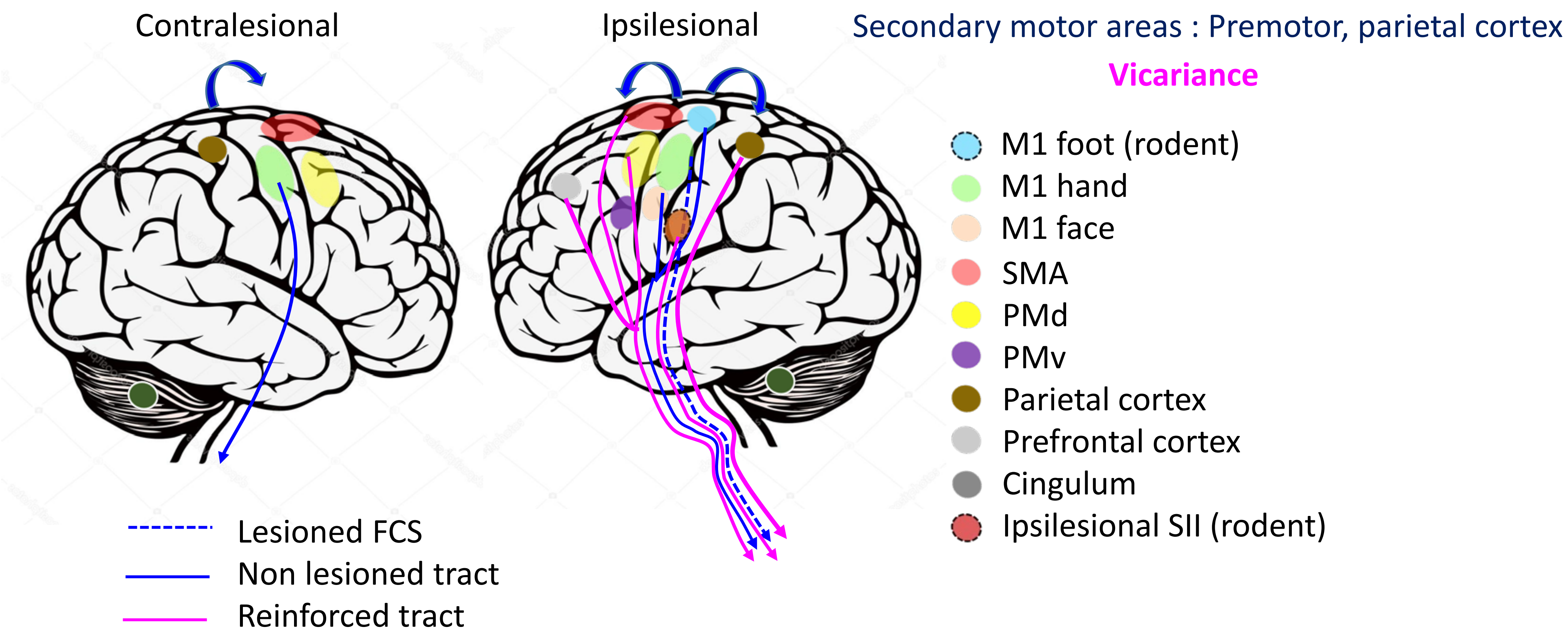




Yamamoto et al., JNNP 2006

1. Small lesion of the primary cortex or fibers, minor deficit

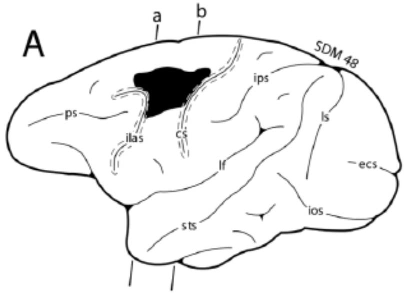
2. Medium lesion, moderate deficit, perilesional direct motor tracts



Cirillo et al., J Cereb Blood Flow 2019

Selective Long-Term Reorganization of the Corticospinal Projection From the Supplementary Motor Cortex Following Recovery From Lateral Motor Cortex Injury

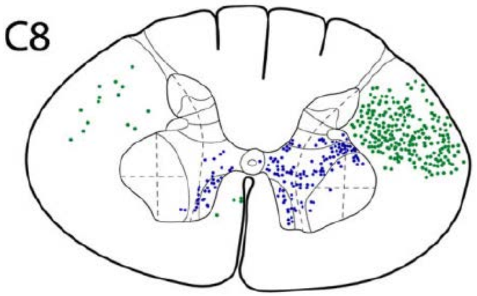
David W. McNeal,[1] Warren G. Darling,[2] Jizhi Ge,[1] Kimberly S. Stilwell-Morecraft,[1] Kathryn M. Solon,[1] Stephanie M. Hynes,[2] Marc A. Pizzimenti,[2,3] Diane L. Rotella,[2] Tyler Vanadurongvan,[1] and Robert J. Morecraft[1]*



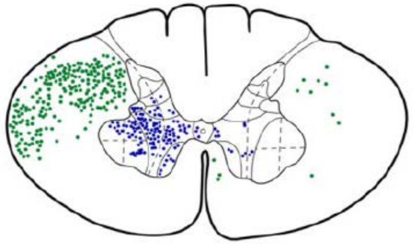
J Comp Neurol 2010

Incomplete lesion of M1/dorsolateral PMC
in the depth of the central sulcus

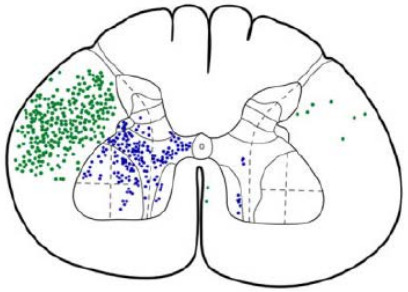
Control

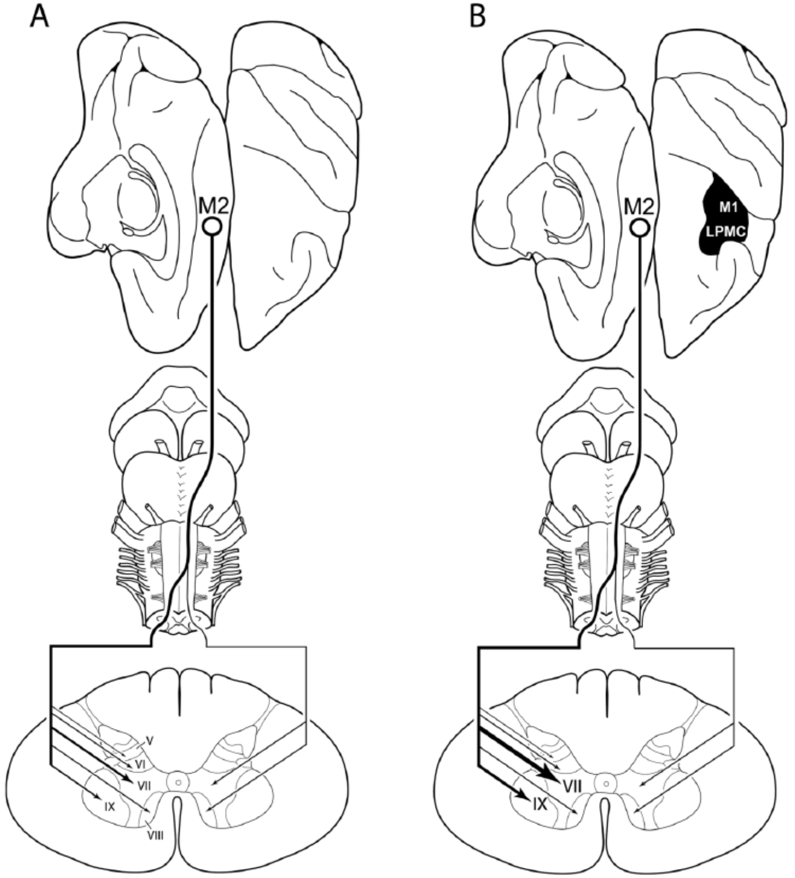


6 Month Recovery



12 Month Recovery

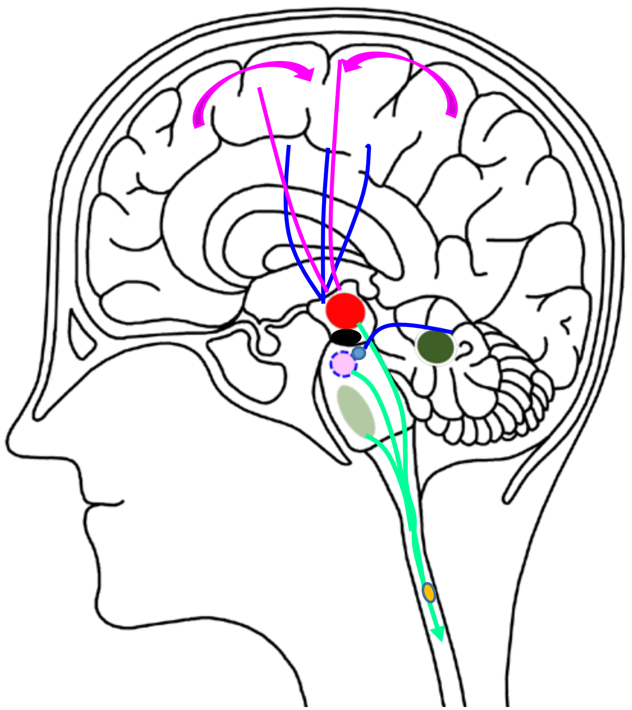




Reinforcement of direct fibers from SMC

3. Large lesion or key lesioned area, severe deficit, alternate indirect motor tracts

Disynaptic connections



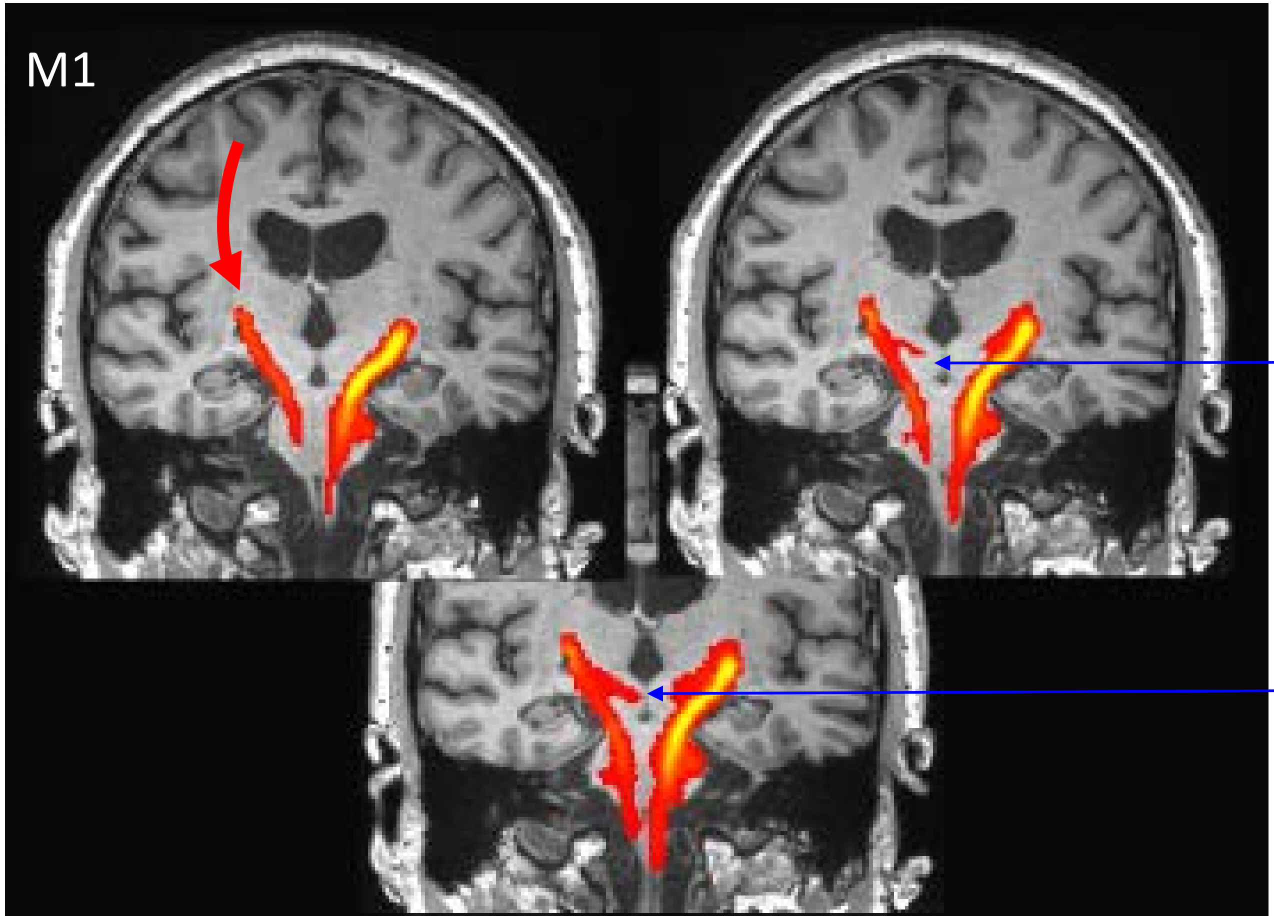
- Non lesioned tract
- Reinforced tract

- IpsiL Red Nucleus
- Substancia Nigra
- Medullary Reticular N
- Raphe N (rodent)
- Pedonculo-pontine nucleus
- Cerebellum
- Propriospinal

Cirillo et al., J Cereb Blood Flow 2019

Indirect pathway : the rubrospinal tract
from the primary motor cortex

Diffusion tensor MR imaging and tractography



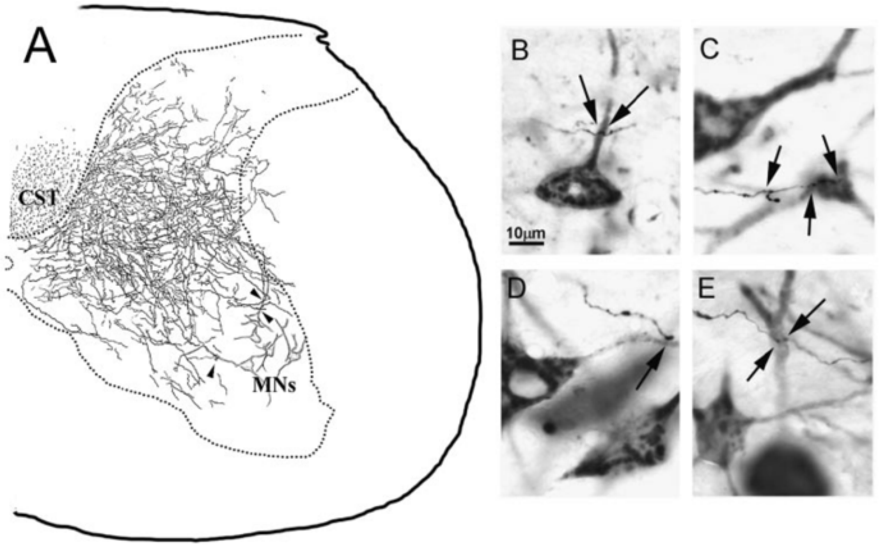
Red nucleus

Reinforcement of cortico-rubral pathway

Thiel & Vahdat, Stroke 2015

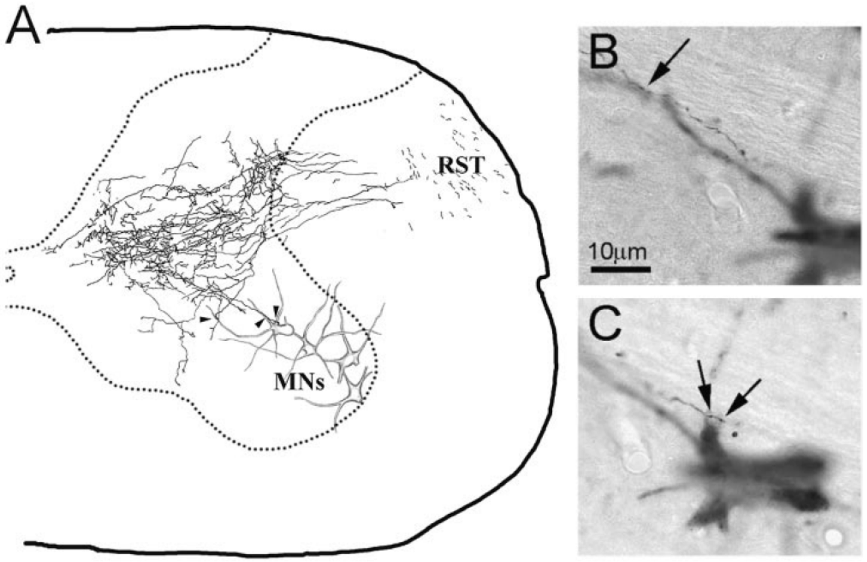
Indirect pathway : the rubrospinal tract
from the primary motor cortex

Corticospinal tract



Rubrospinal tract

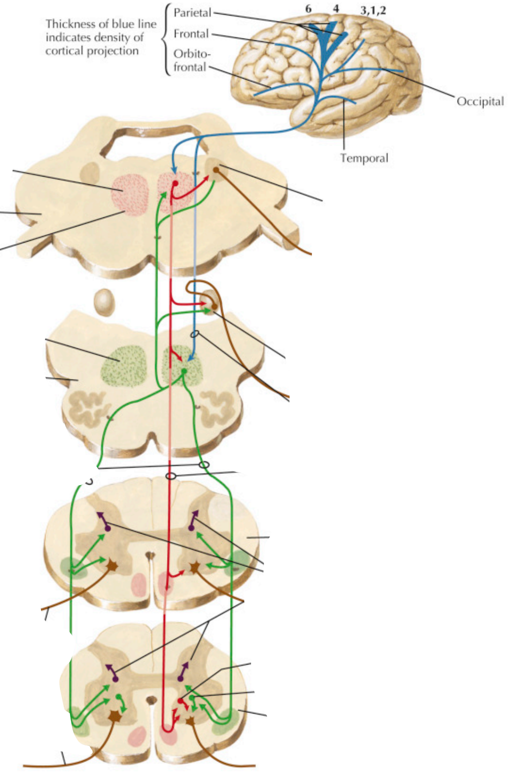
Treatment with antibody Nogo-A inhibitor

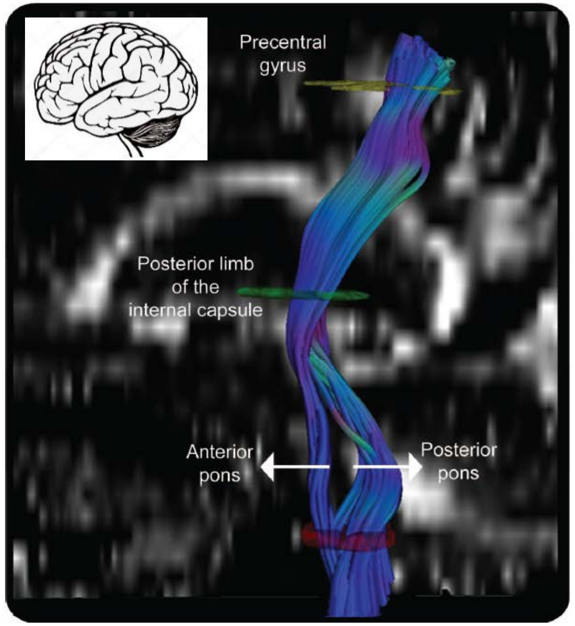


Rubrospinal fibers invade the ventral horn and synapse onto motoneurones.

Raineteau et al., Eur J Neurosci 2002

Indirect pathway : the reticulospinal tract
from the premotor and parietal cortex

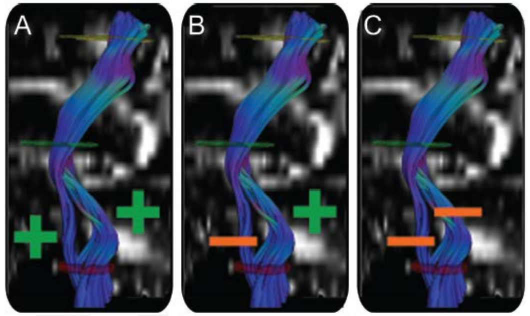




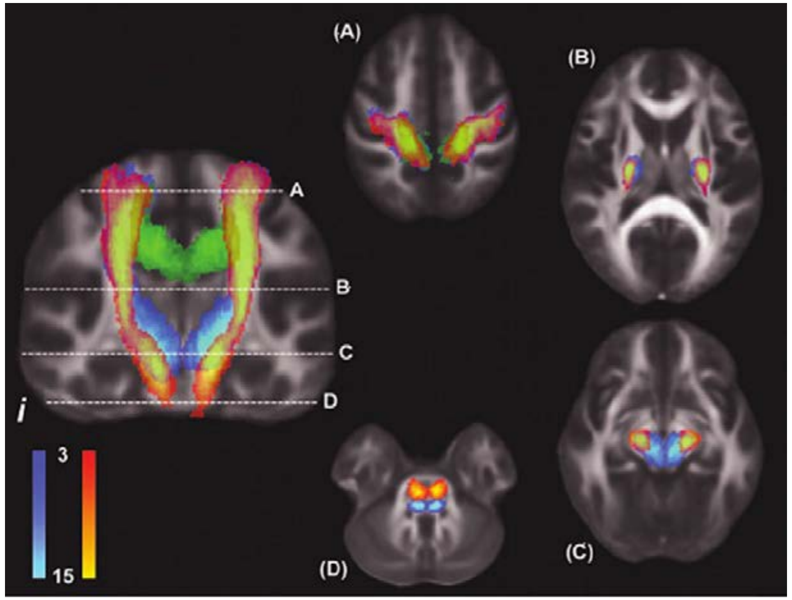
30 months post-stroke

Lindenberg et al., Neurology 2010

Diffusion Tensor Imaging and tractography



		Group 1 n = 14	Group 2 n = 8	Group 3 n = 13
Fiber number asymmetry scores	PT PT+aMF	0.4 ± 0.3 0.3 ± 0.2	1.0 ± 0.0 0.7 ± 0.2	1.0 ± 0.0 1.0 ± 0.0
Motor impairment	UE-FM	50.0 ± 10.6	33.6 ± 12.0	15.9 ± 8.8

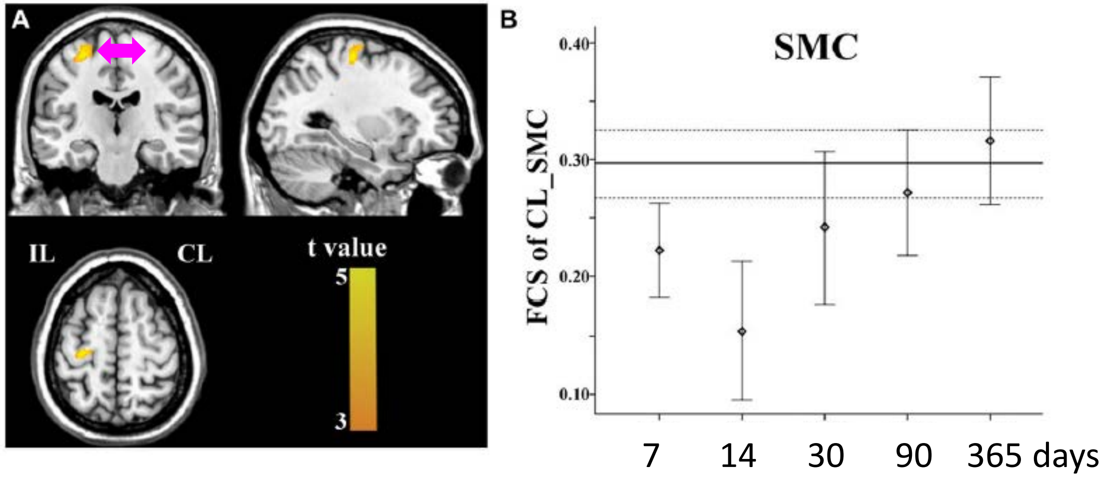


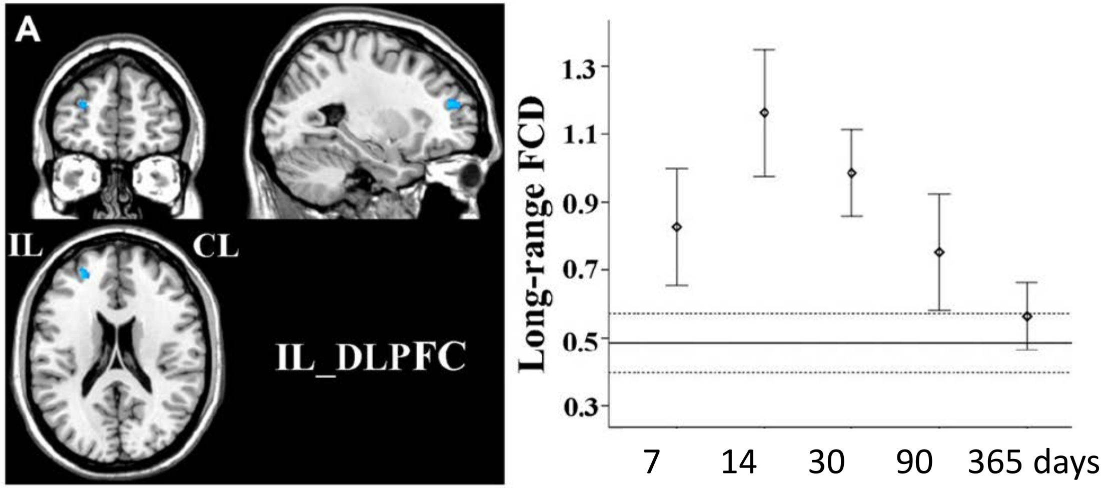
Stinear et al., A Phys Rehab M, 2004

Cross-modal plasticity

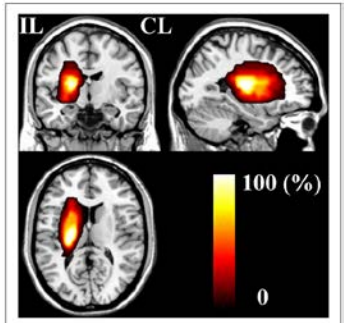
Resting state

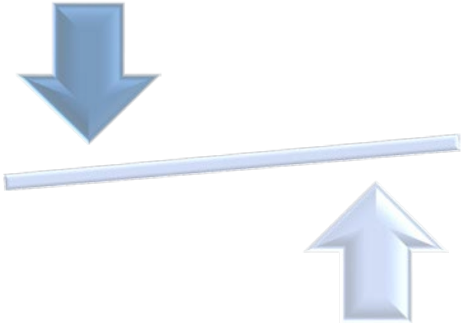
Functional connectivity
Synchronous activity





Lesions





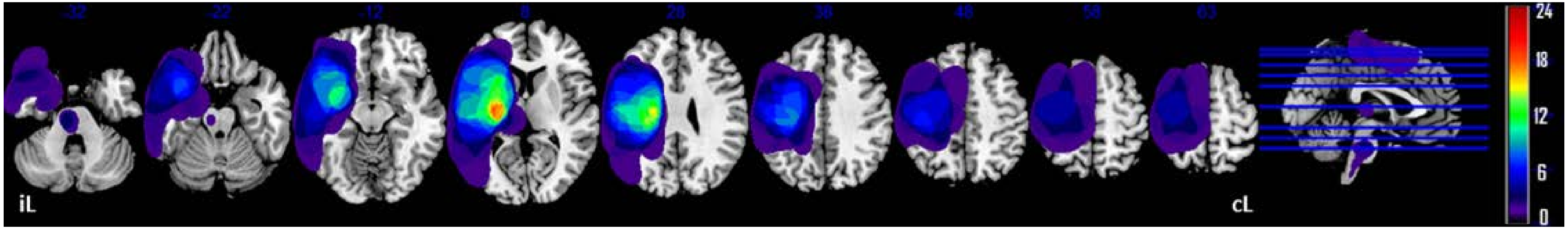
- Changes in connectivity correlate with recovery
- Normalization with recovery
- Cross-modal plasticity

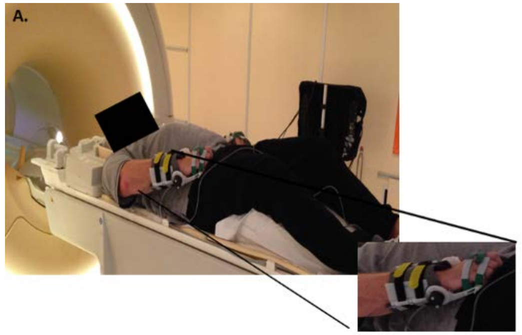
Liu et al., Frontiers Behav Neurosci 2016

Cross-modal plasticity

Sensorimotor task

Lesions





24 patients

4 months post-stroke [IQR 3 months]

Severe to moderate deficits at Fugl-Meyer scale for the upper limb : [5-50] / 66

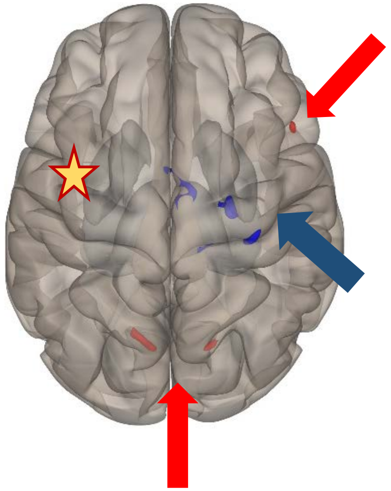
Functional connectivity during a wirst passive motor task

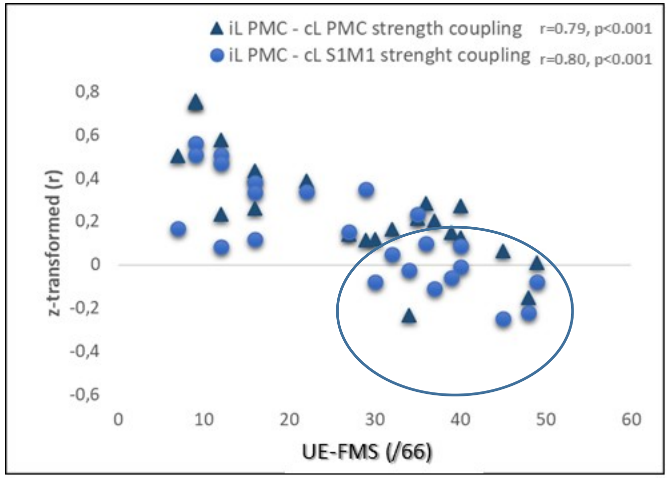
Brihmat et al., Brain Connectivity 2020

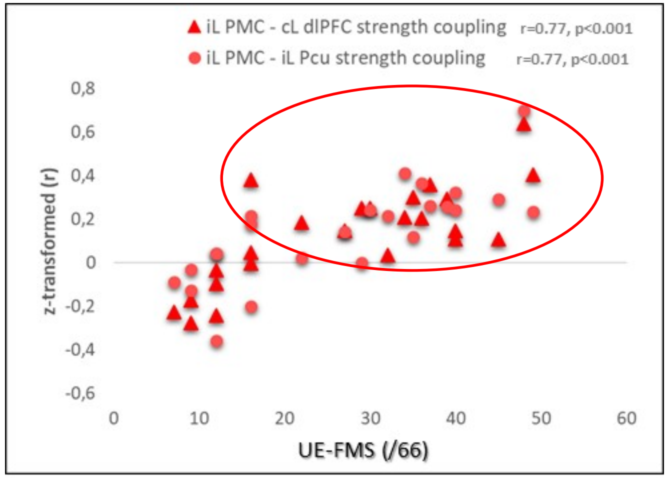
Cross-modal plasticity

Passive motor task

Seed :
ipsilesional premotor cortex







Contralesional Sensorimotor cortex : Better upper limb FMS ⇔ less coupling

DLPFC or precuneus : Better upper limb FMS ⇔ more coupling

Better recovery is associated with synchronous connectivity between the premotor cortex and the DLPFC or the precuneus

⇨ Cross-modal connectivity

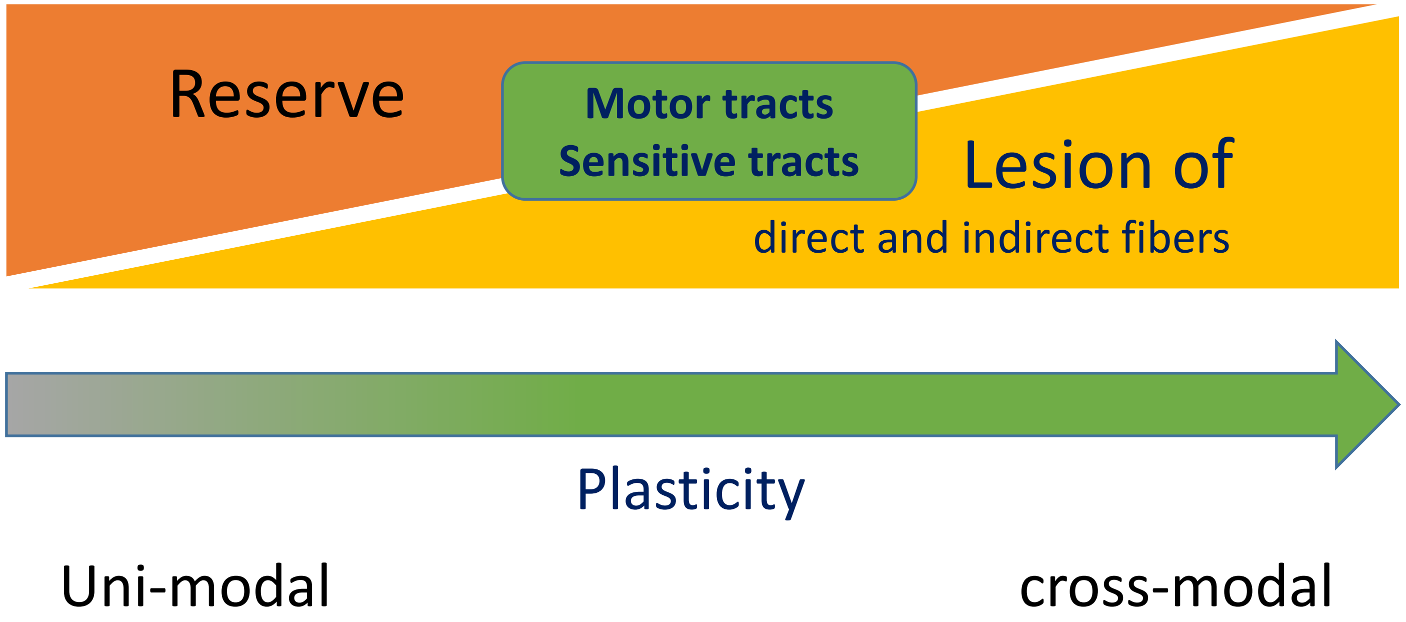
Brihmat et al., Brain Connectivity 2020

Stratification of patients

1. Small lesion of the primary cortex or fibers, minor deficit
   - Direct corticospinal fibers remaining, reorganization in M1
2. Medium lesion, moderate deficit, perilesional direct motor tracts
   - No primary motor cortex fibers remaining, but direct corticospinal fibers from secondary motor cortex spared
3. Key lesioned area, severe deficit, alternate indirect motor tracts
   - All corticospinal fibers lesioned

Cirillo et al., J Cereb Blood Flow 2019

MOTOR RECOVERY AFTER STROKE



Personalized medecine ?

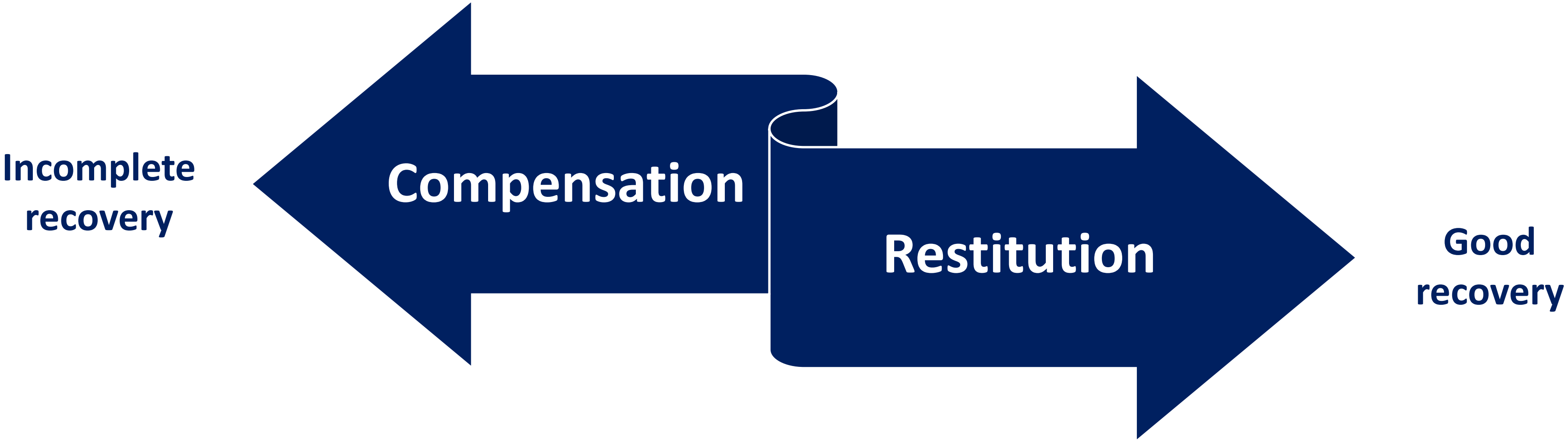
Adaptative plasticity

Maladaptative plasticity

Adverse events

- ✓ Epilepsia
- ✓ Pain
- ✓ Synkinesis
- ✓ Spasticity
- ✓ Learned non-used

RECOVERY AFTER STROKE



Plasticity

- Indirect fibers
- Vicariance
- Perilesional reorganization
- Distant reorganization

- Repair
- Redundancy
- Direct fibers
- Local reorganization