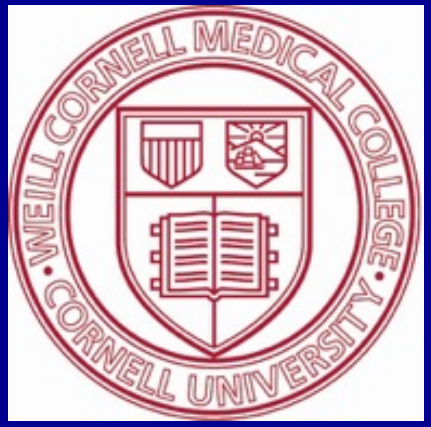
The Uninjured Hemisphere in Hemiplegia: Friend or Foe?



Jason Carmel, MD, PhD

ASNR Annual Meeting

October 15, 2015

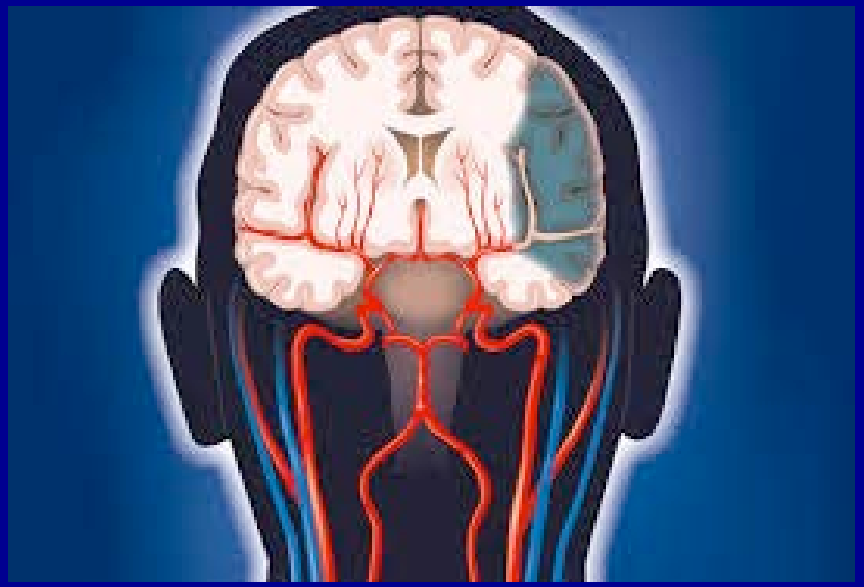
Hemiparesis is the Most Common Pattern of Motor Impairment

- 795,000 strokes/year in US
- Est. current prevalence: 7,400,000
- Est. prevalence in 2030: 11,000,000
- Direct and indirect costs total $34.3 billion/yr
- 40% of all cases of cerebral palsy; 2/1000

Go, Circulation, 2014

Knowing Role of Uninjured Hemisphere Will Change Therapy

- Friend: Some hand control in hemispherectomy
- Foe: “Inhibitory” brain stim or other interventions promote recovery



The Uninjured Hemisphere

Friend

- **Winston Byblow, PhD**

  Professor of Neuroscience, Director, Movement Neuroscience Lab, Dept of Sport & Exercise Science and Centre for Brain Research, The University of Auckland

- **Jason Carmel, MD, PhD**

  Assistant Professor, Neuroscience, Weill Cornell Medical College
  Director, Motor Recovery Lab, Burke Medical Research Institute

Foe

- **Lara Boyd, PT, Ph**

  Professor and Canada Research Chair, Department of Physical Therapy, University of British Columbia

- **Leonardo G. Cohen, MD**

  Chief, Human Cortical Physiology and Stroke Neurorehabilitation Section, National Institute of Neurological Disease and Stroke

Schedule

8:30 Intro of speakers and format

8:35 Perspective 1 present argument

9:05 Perspective 2 presents argument

9:35 Rebuttal from Perspective 1

9:45 Rebuttal from Perspective 2

9:55 Discussion and conclusion

Overview

- Role of ipsilateral hemisphere in health
- Uninjured hemisphere in hemiplegia recovery
- Promoting control from the uninjured side

Overview

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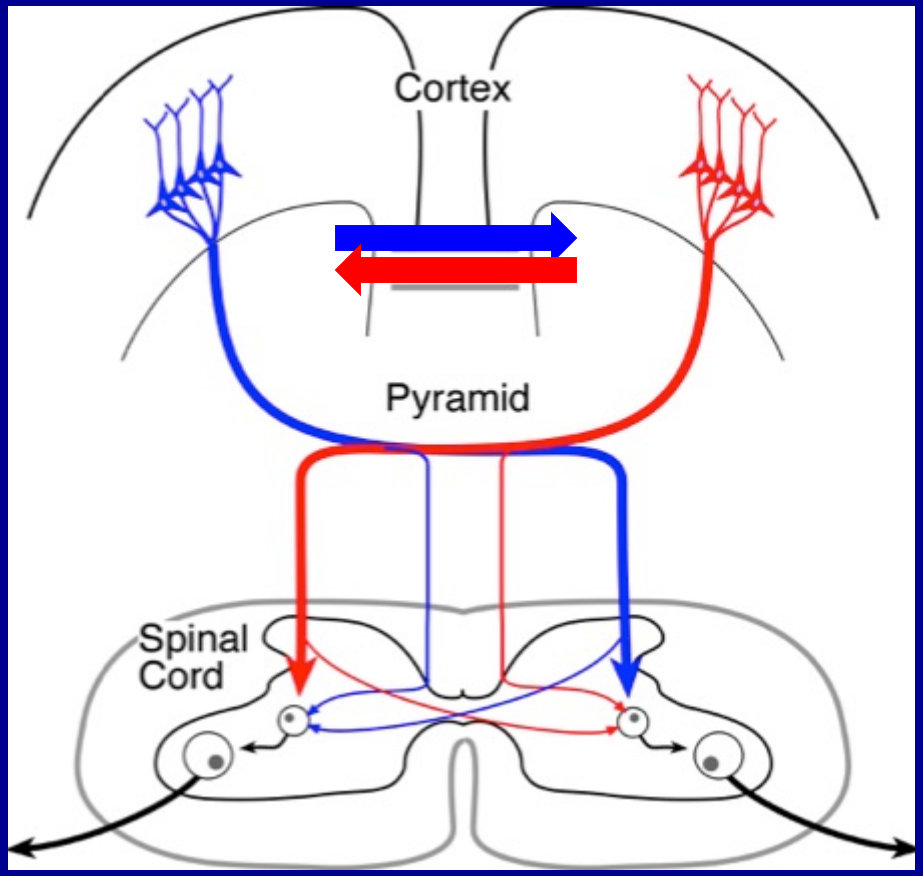
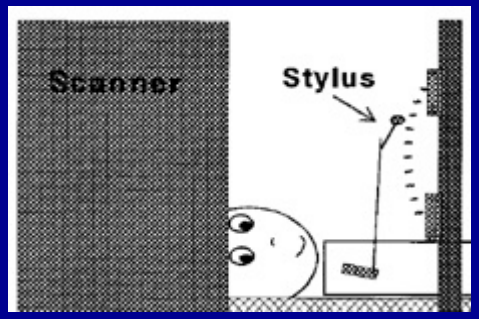
The Corticospinal System



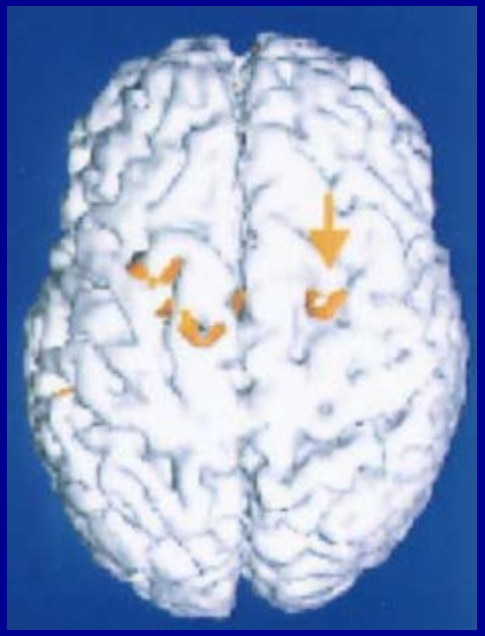
Recruitment of ipsilateral hemisphere with increased difficulty of task



Contra Ipsi

Mvmt vs No Mvmt

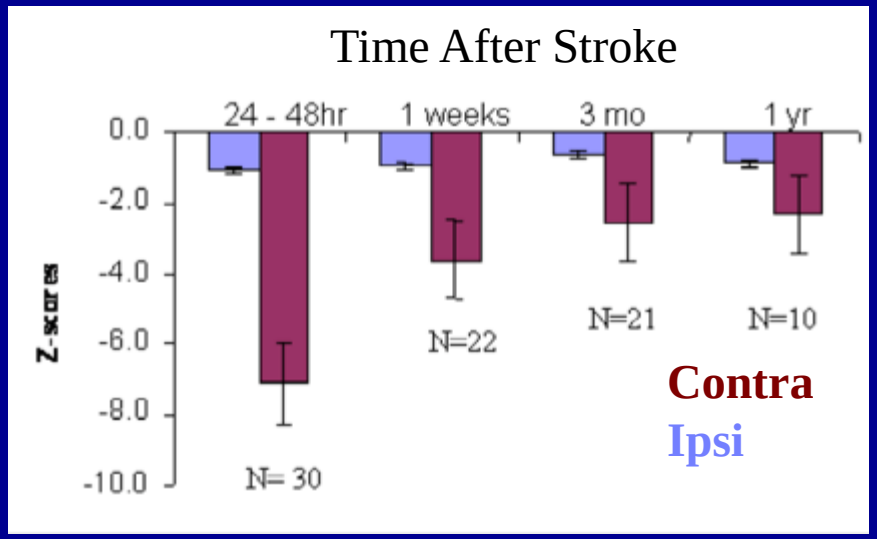
Contra Ipsi



Difficult > Easy

Winstein, J Neurophys, 1997

Stroke Impairs Ipsilateral Hand/Forelimb



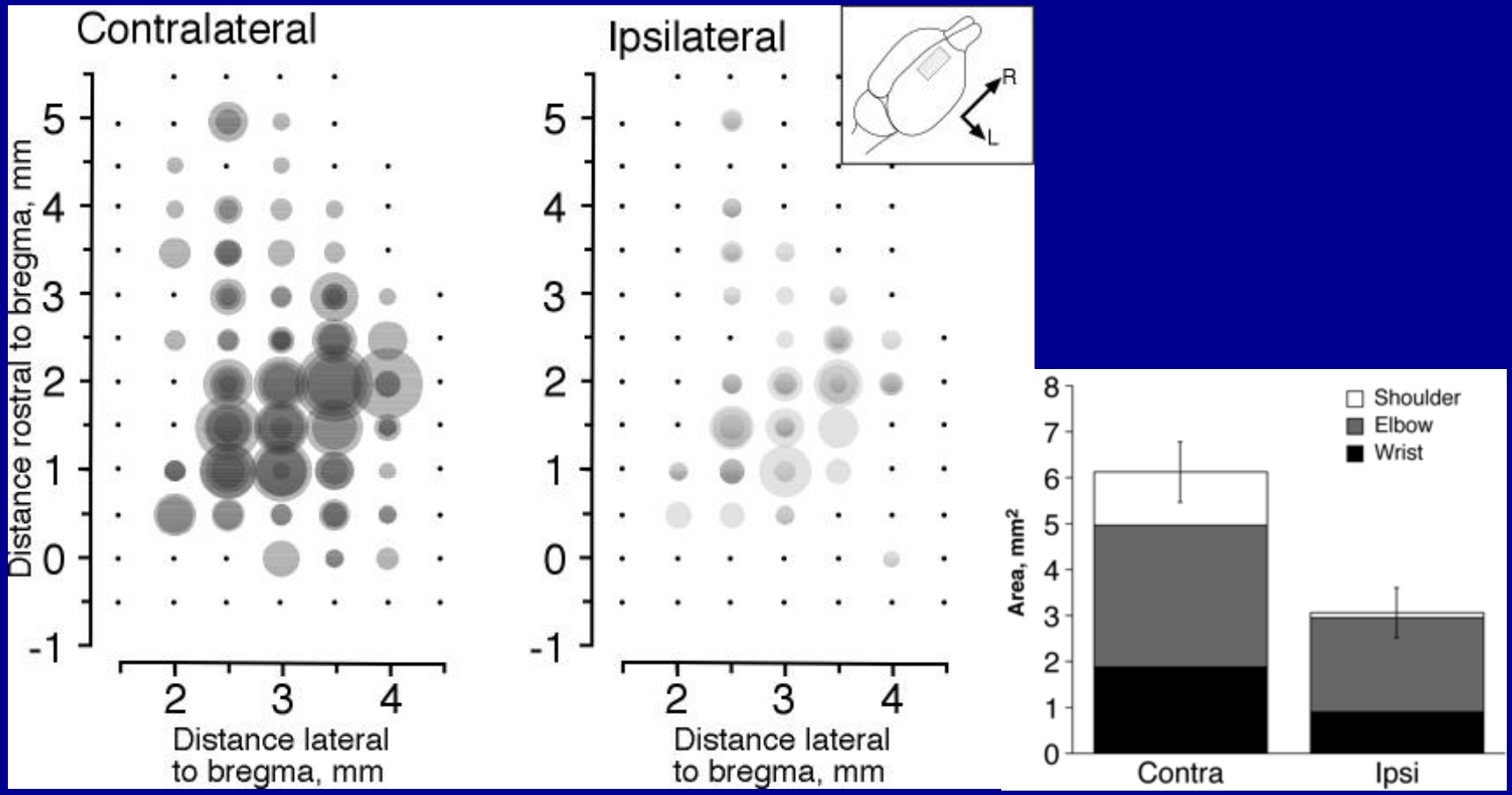
Noskin, J Neurol Neurosurg Psychiatry, 2007

Species and type of injury	Reference
Rat	
Cortex	Price & Fowler (1981) Montoya *et al.* (1991)
Basal ganglia	Dunnett *et al.* (1988) Montoya *et al.* (1990) Miklyaeva *et al.* (1994) Olsson *et al.* (1995) Fricker *et al.* (1996) Whishaw *et al.* (1997) Dobrossy *et al.* (2000) Jeyasingham *et al.* (2001)
Stroke	Grabowski *et al.* (1993) Marston *et al.* (1995) Sharkey *et al.* (1996) Cregan *et al.* (1997) Hudzik *et al.* (2000) Virley *et al.* (2000) Butovas *et al.* (2001) Moyanova *et al.* (2003)
Other	Henderson *et al.* (1999)
Human	
Stroke	Brodal (1973) Haaland & Delaney (1981) Fisk & Goodale (1988) Haaland & Harrington (1989) Jones *et al.* (1989) Dickstein *et al.* (1993) Titianova & Tarkka (1995) Winstein & Pohl (1995) Desrosiers *et al.* (1996) Baskett *et al.* (1996) Steenbergen *et al.* (1996) Yelnik *et al.* (1996) Marque *et al.* (1997) Carey *et al.* (1998) Hermsdorfer *et al.* (1999a, b) Sunderland *et al.* (1999) Winstein *et al.* (1999) Andrews & Bohannon (2000) Hermsdorfer & Goldenberg (2002) Sunderland (2000) Debaere *et al.* (2001) Laufer *et al.* (2001) Pohl *et al.* (2001) Hanna-Pladdy *et al.* (2002) Sugarman *et al.* (2002) Swinnen *et al.* (2002) Kim *et al.* (2003)

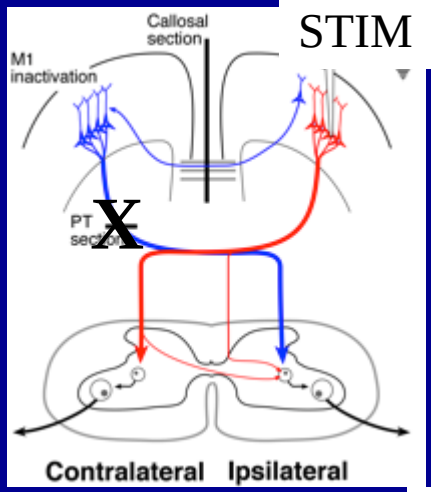
Control of Ipsilateral Movement in Motor Cortex

- Mapping of ipsilateral movements in motor cortex
- How does it relate to contralateral motor map?
- How does map change after injury to opposite side?

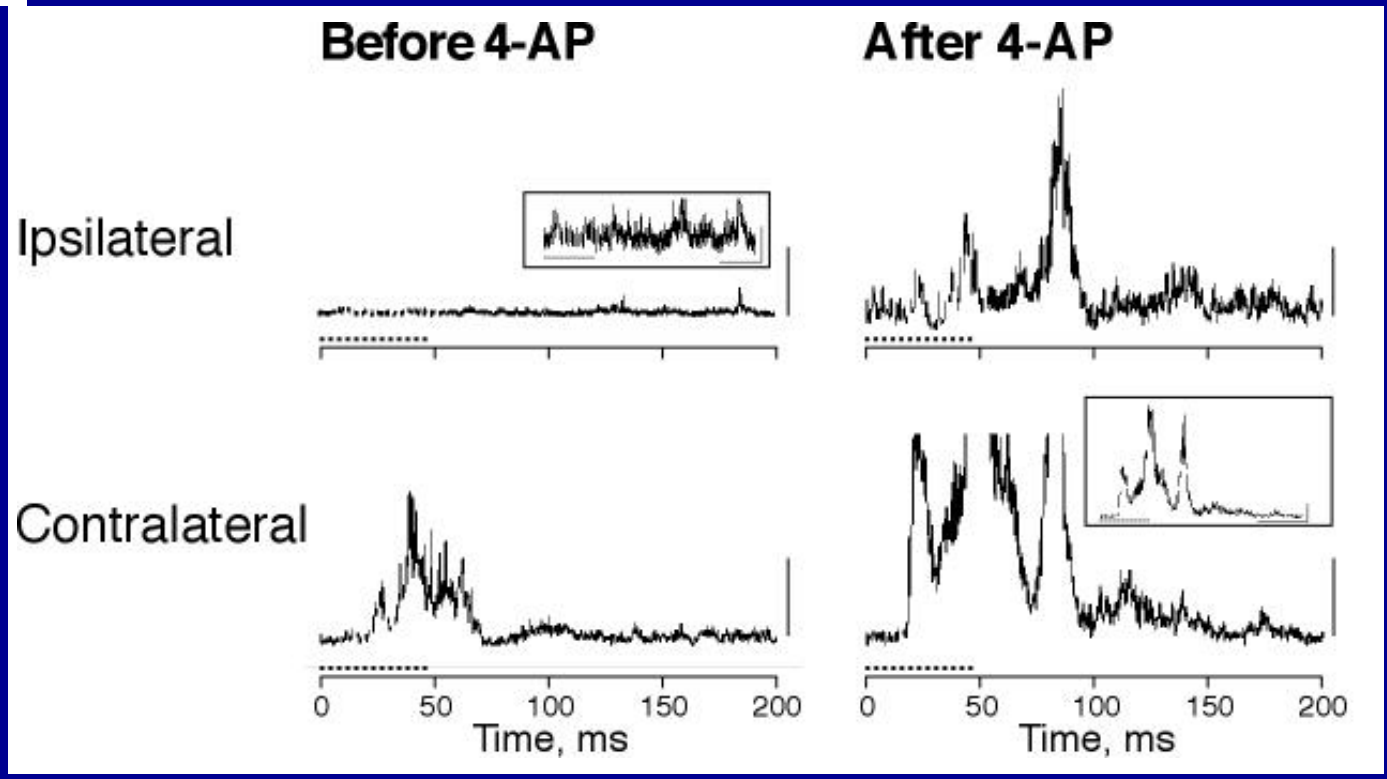
Similar Contra & Ipsi Motor Maps



J. Neurosci, 2009



4-AP Restores Ipsi Responses After CST injury



J. Neurosci, 2009

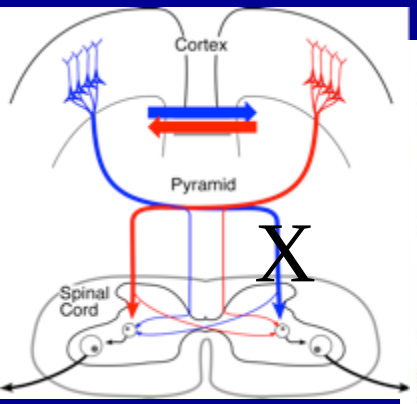
Conclusions: Ipsilateral Control

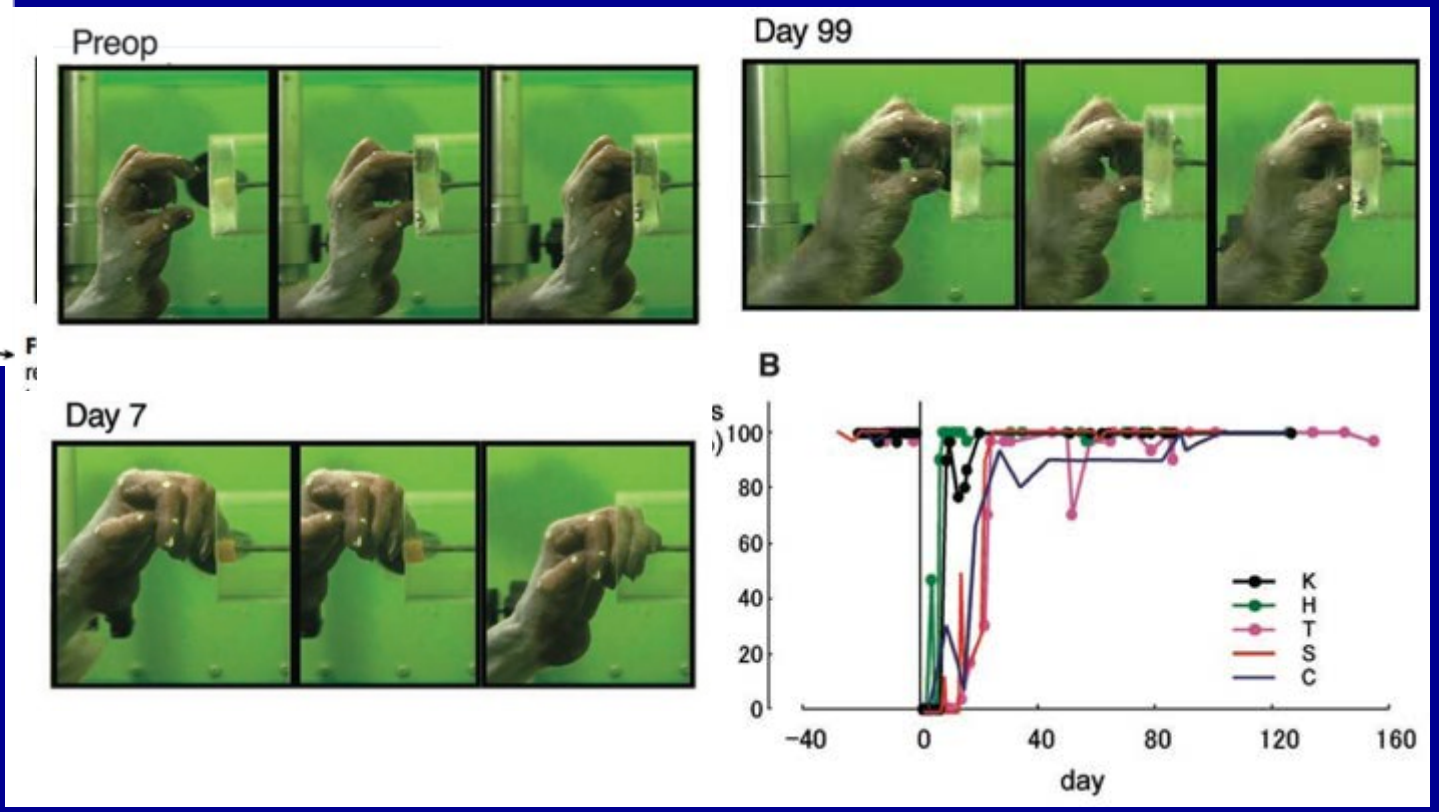
- Activation with difficult tasks
- Worse ipsi hand function with injury
- In rats, ipsi map surprisingly robust
- Ipsi responses require other hemisphere
  - Interaction in the spinal cord

Overview

- Role of ipsilateral hemisphere in health
- Uninjured hemisphere in hemiplegia recovery
- Promoting control from the uninjured side

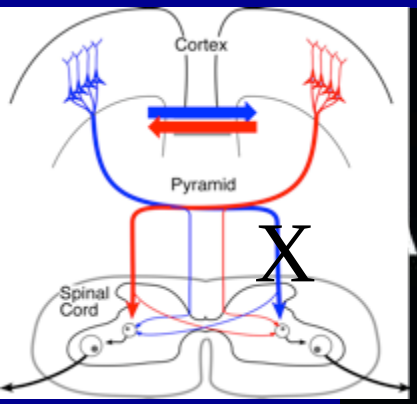
Injury and Recovery after CST Lesion in the Monkey

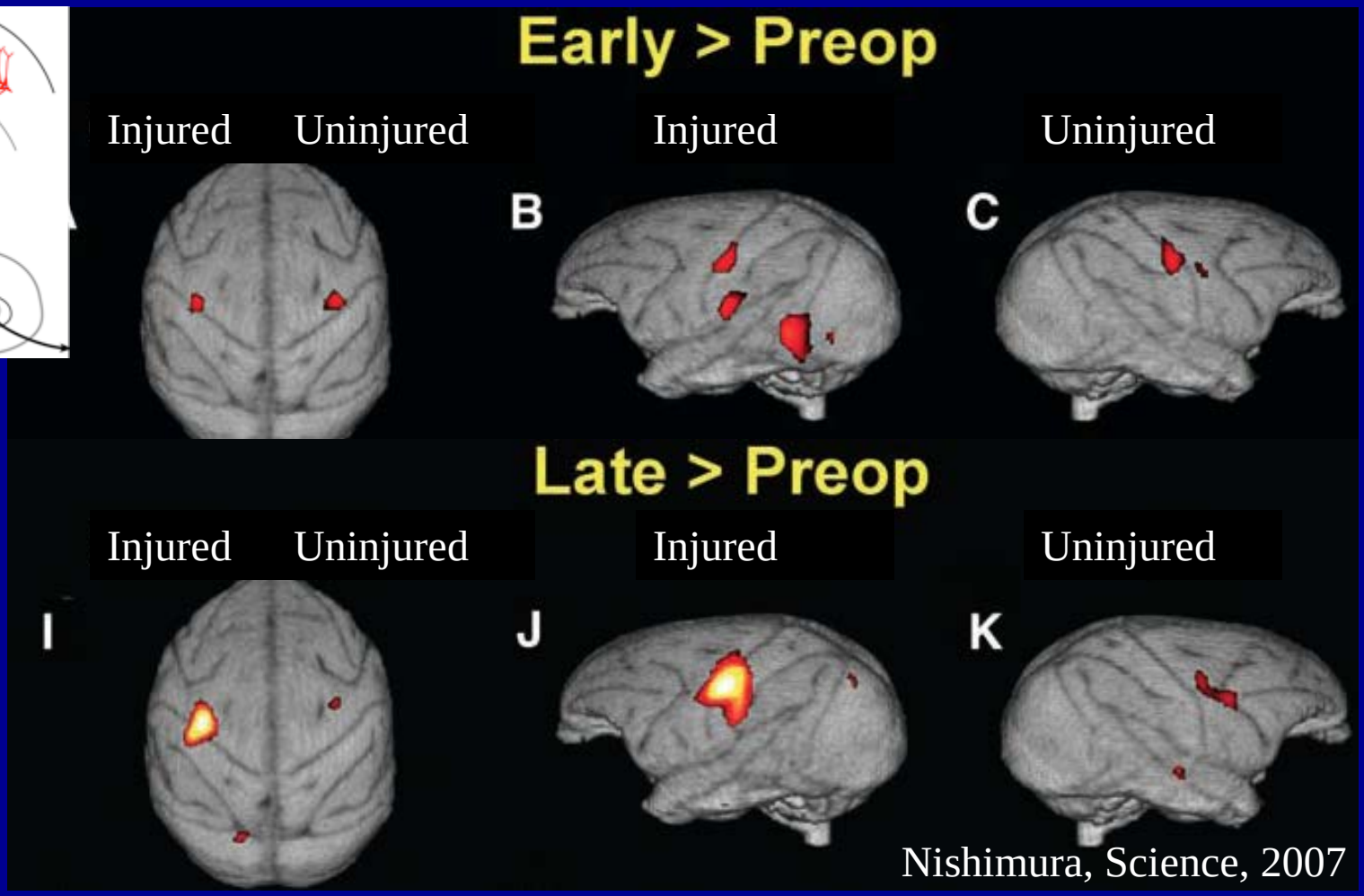




Nishimura, Science, 2007

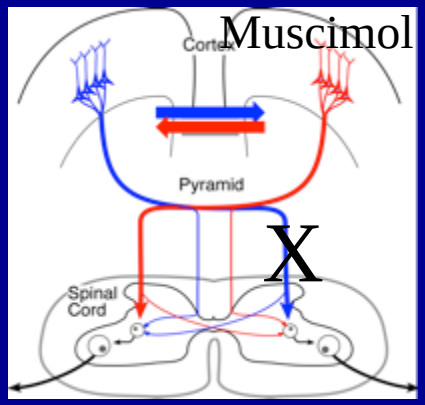
Uninjured M1 Active in Early Recovery





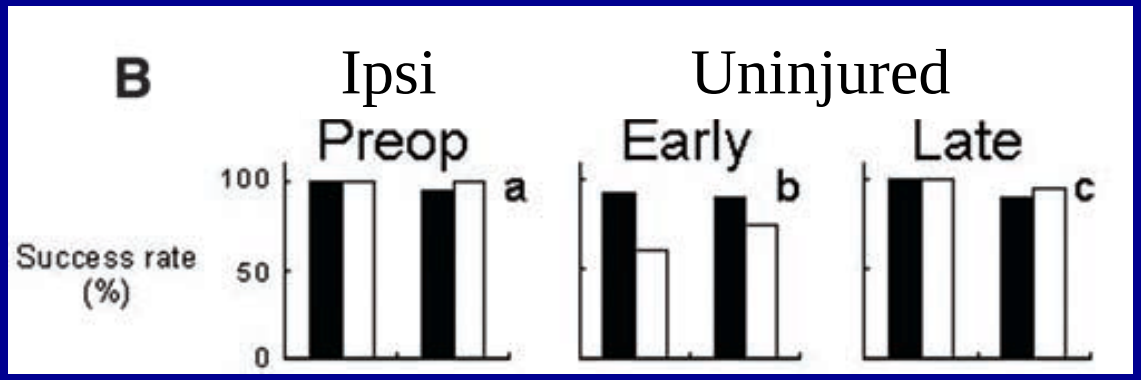
Nishimura, Science, 2007

Ipsilateral Motor Cortex Critical for Early Recovery



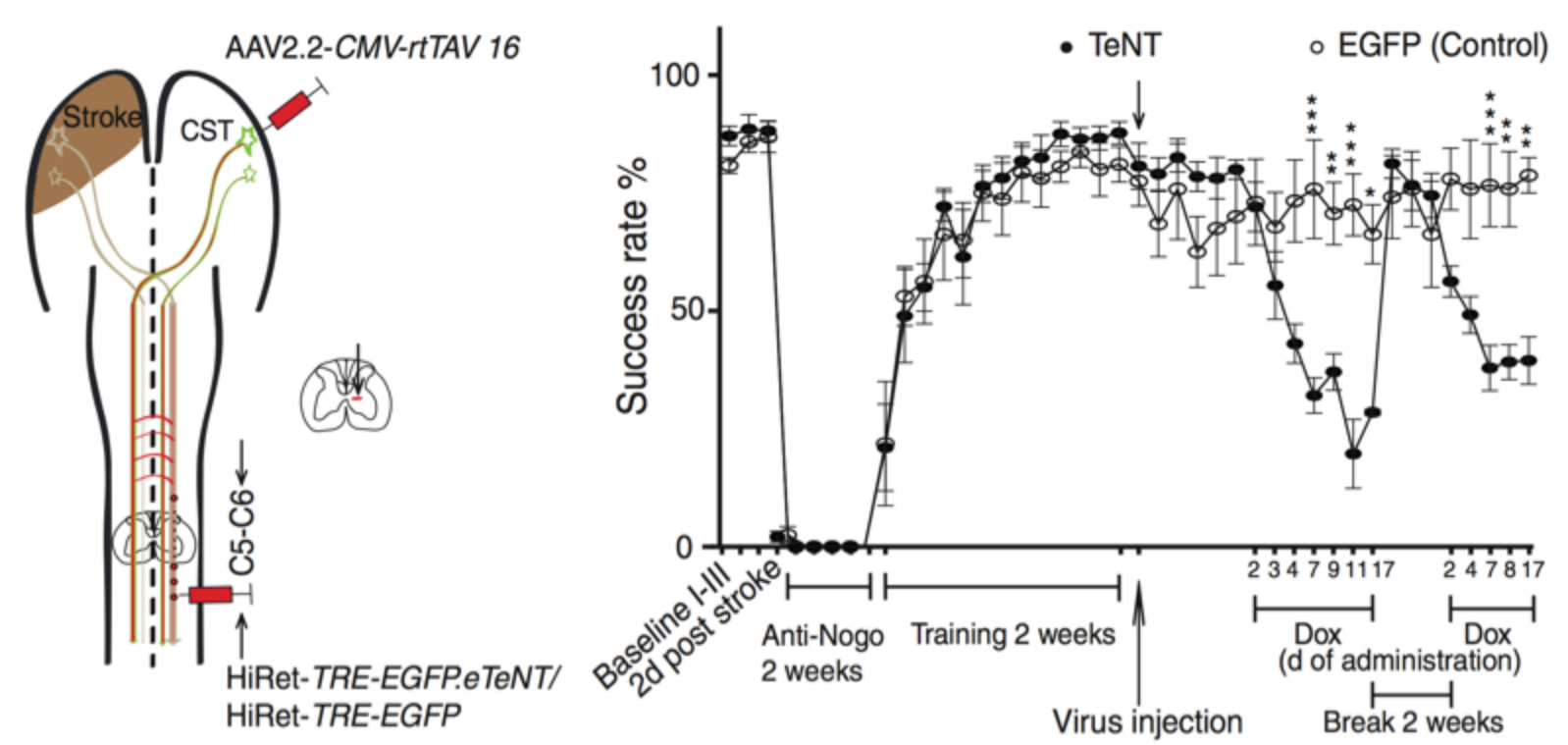
Control

Muscimol



Nishimura, Science, 2007

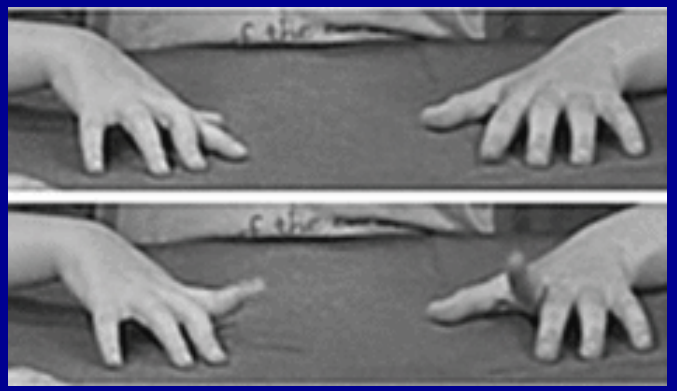
Ipsilateral Control after Stroke Therapy in Rats

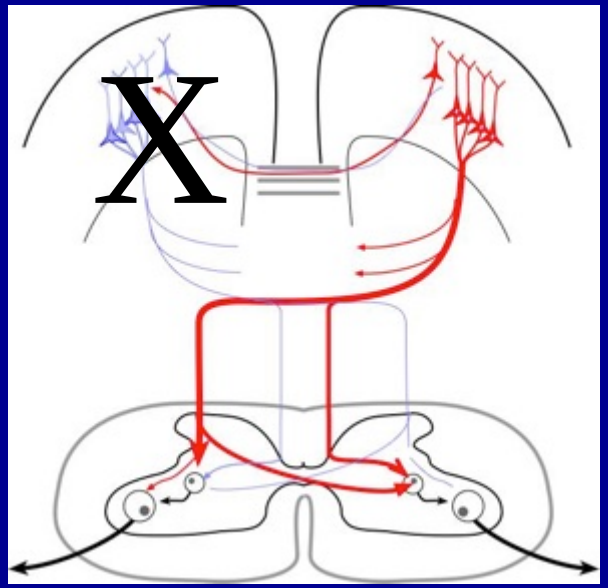


Wahl, Science, 2014

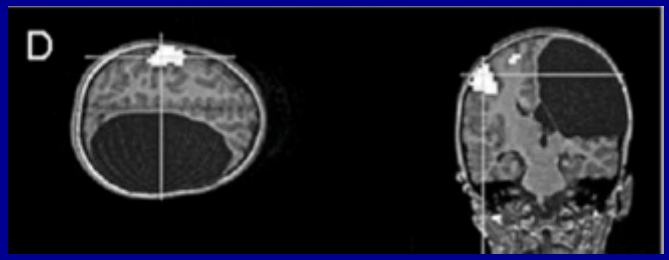
Bilateral Control From One Hemisphere

- 8 y o with left porencephaly
- Extensive physical training
- Independent finger movements

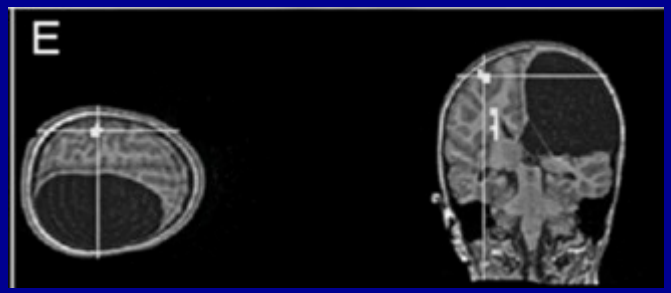




Left moves

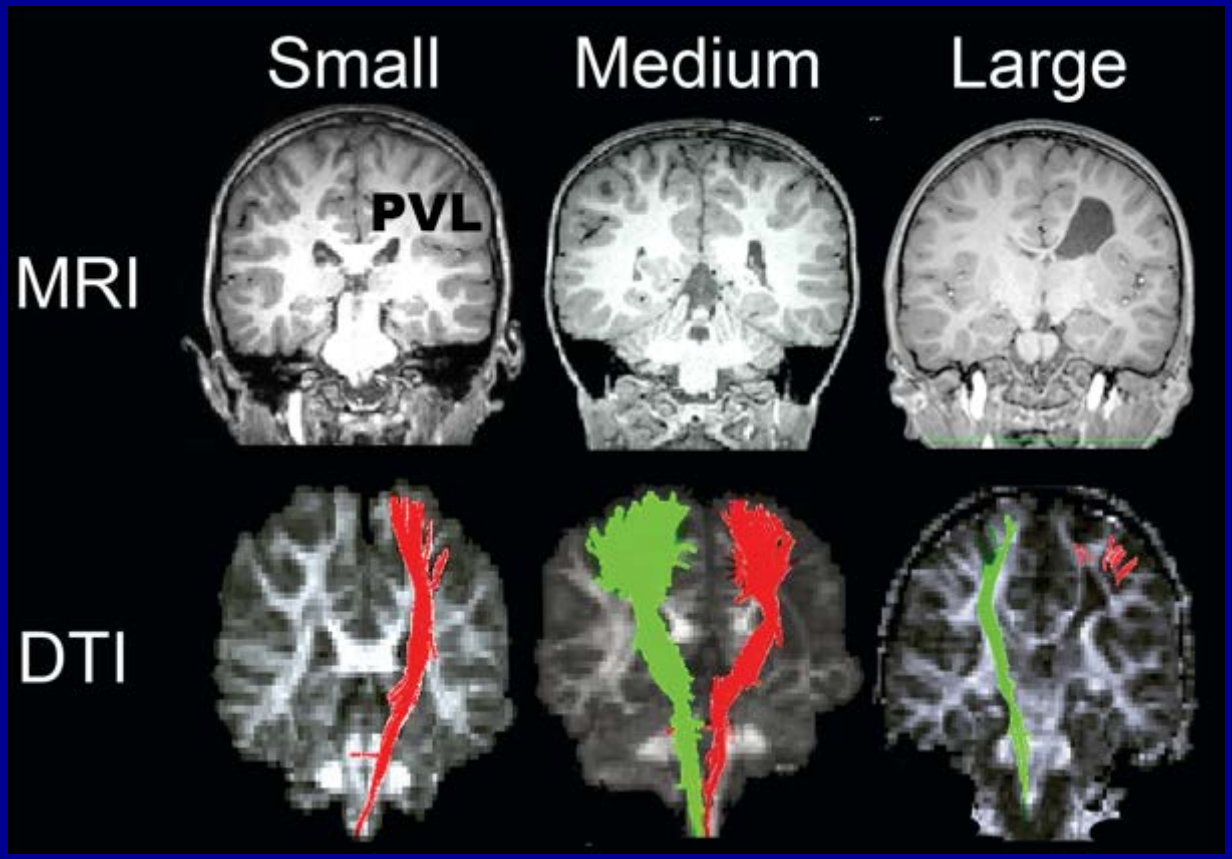


Right moves



Weber, Neurocase, 2006

Connectivity in Peds Hemiplegia



Kathleen Friel, PhD

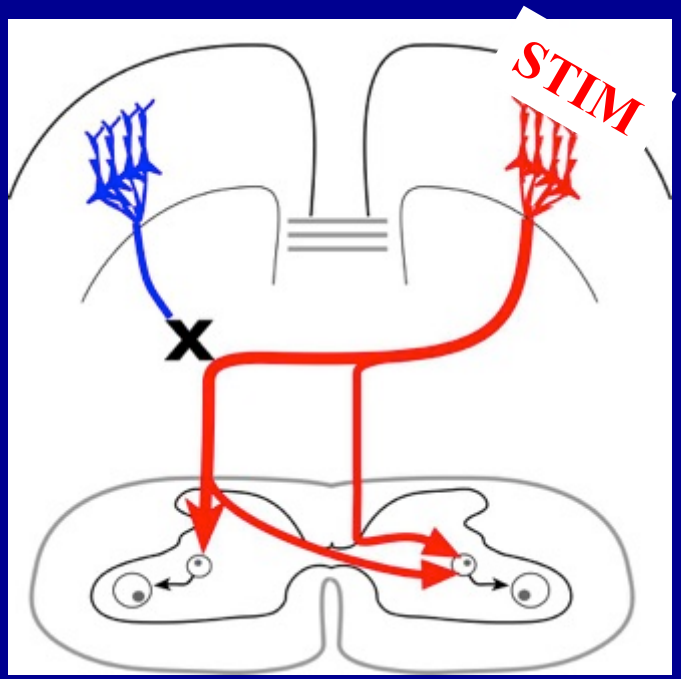
Conclusions: Hemiplegia Recovery

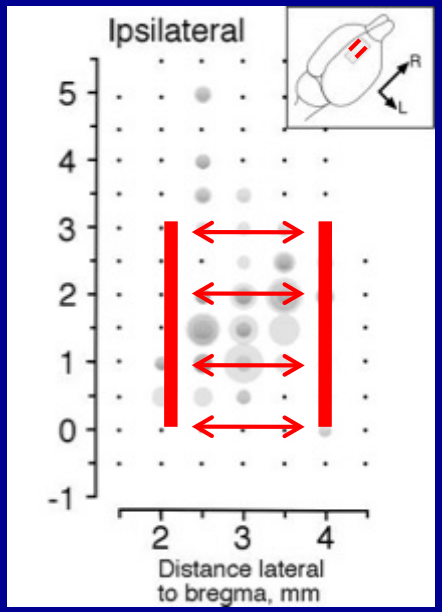
- Uninjured hemisphere critical for early recovery in monkey CST injury
- Ipsilateral CST mediates therapy-induced stroke recovery in rats
- Adaptive ipsilateral control in peds hemiplegia

Overview

- Role of ipsilateral hemisphere in health
- Uninjured hemisphere in hemiplegia recovery
- Promoting control from the uninjured side

Stimulating the uninjured hemisphere to restore limb control

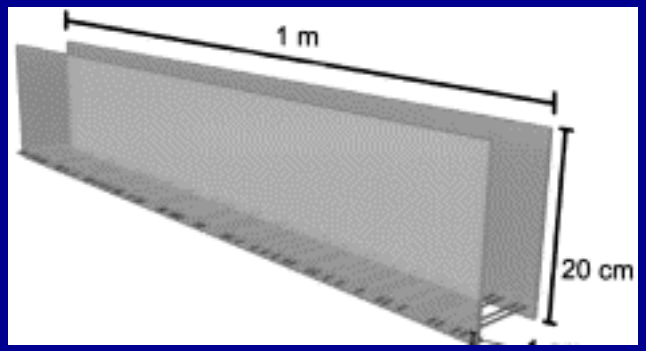




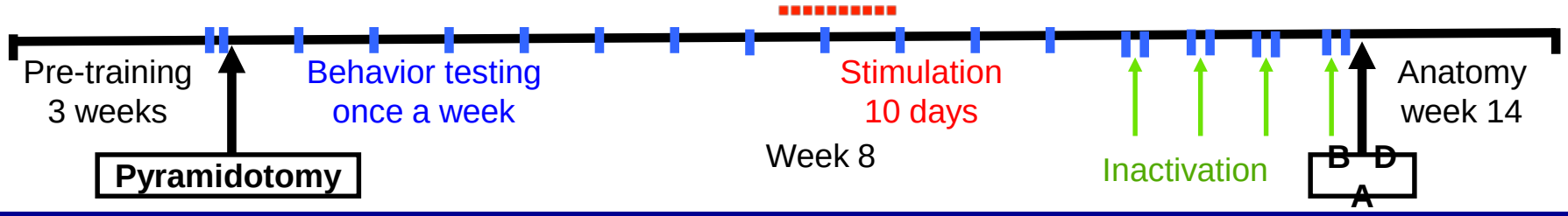
- 10 days; 6 hrs/day; 333 Hz; 0.2 ms pulses
- Threshold 1.1-1.8mA

J Neurosci, 2014

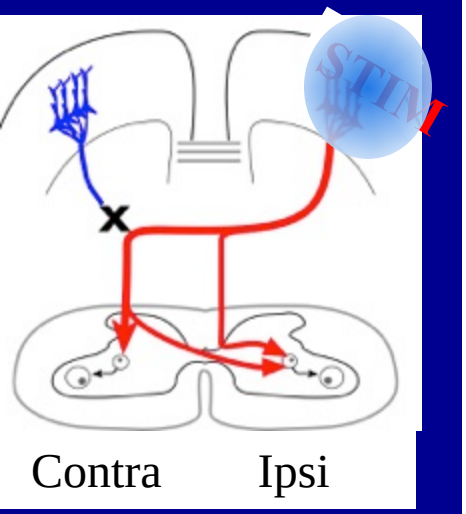
Stimulation after Chronic Injury

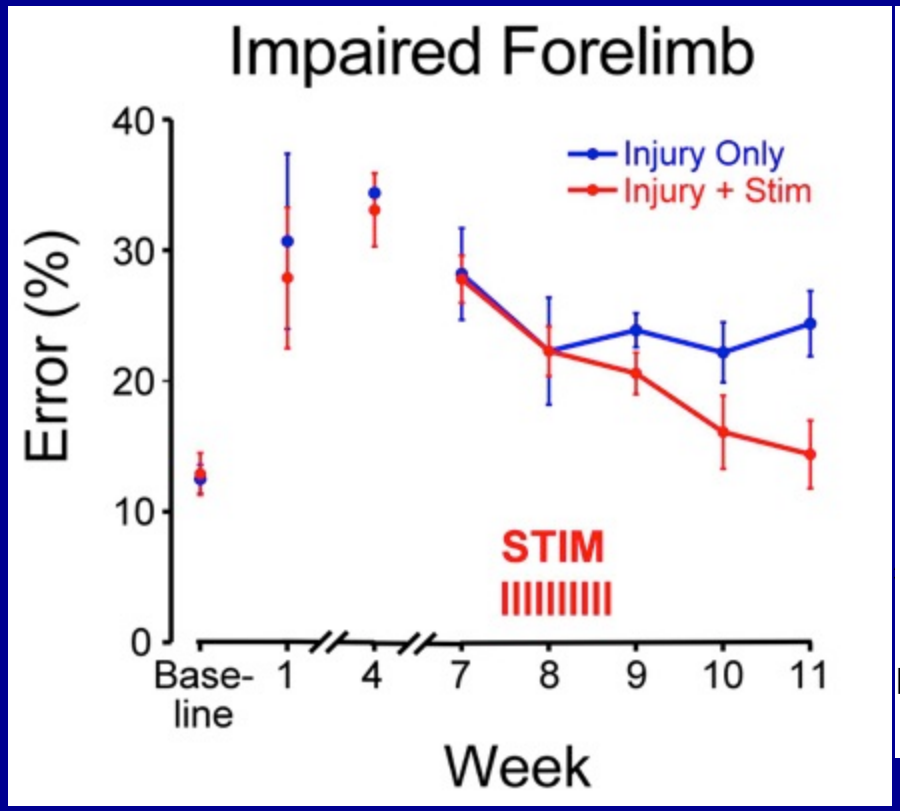


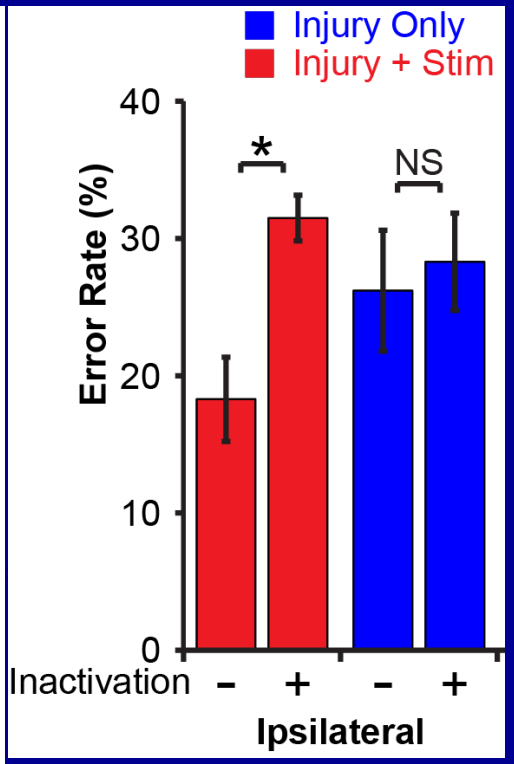
Timeline



Stimulation after Chronic Injury

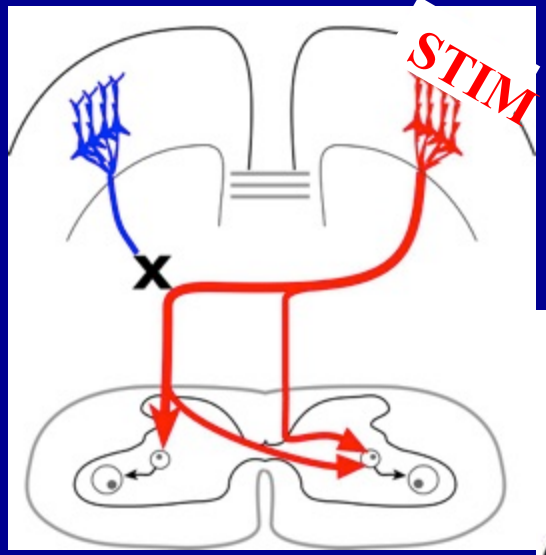


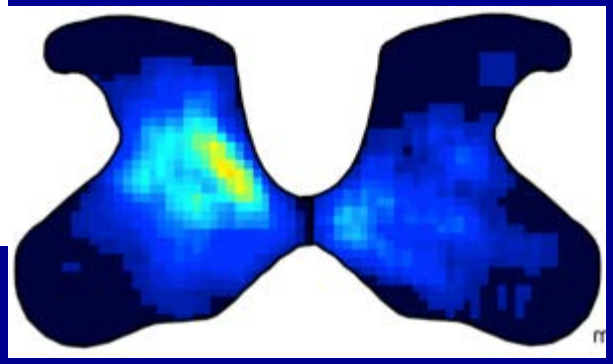


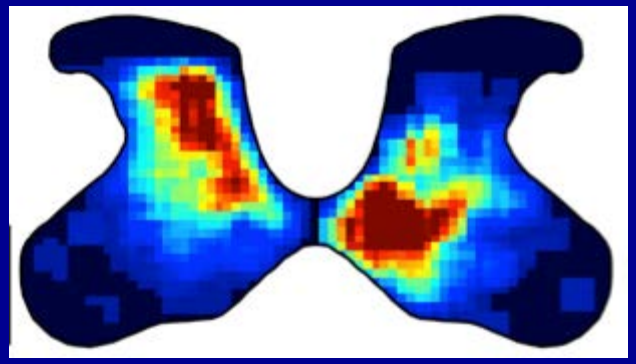


J Neurosci, 2014

Spinal Cord Axon Outgrowth







2.3x 4.6x

Eur J Neurosci, 2013

Conclusions: Stimulation Studies

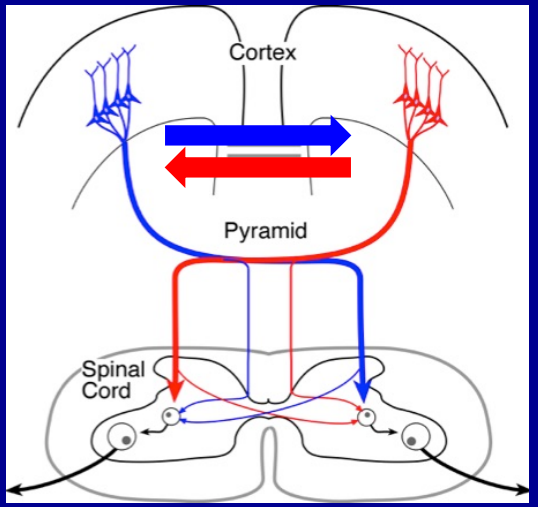
- Gain in control from uninjured hemisphere
- Effective after chronic injury
- Accompanied by axon outgrowth

Uninjured Hemisphere: Friend

- Difficult tasks require both hemispheres
- Capacity for bilateral control
- Injury causes ipsilateral deficits
- Recovery mediated by uninjured motor cortex
- Validated target for repair

How to Fill the Gap

- Understand recovery network
  - Independent tests of descending and transcallosal circuits
  - Pathway specific activation (pairing)
  - Pathway specific inactivation



Acknowledgements

Past

John H. Martin, PhD

Current

Support

National Institute of Neurological Disorders and Stroke

Travis Roy Foundation

Burke Rehabilitation & Research