Pushing Boundaries in Neuro-rehabilitation

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The Burden of Stroke

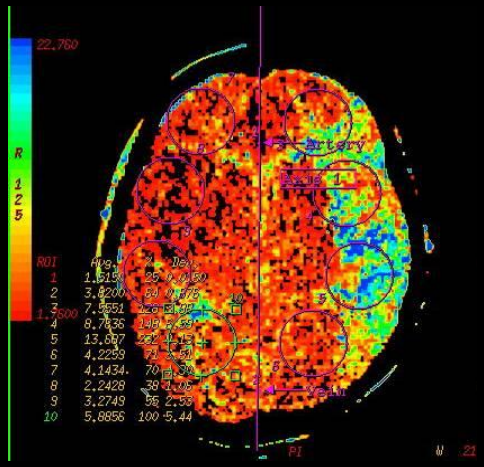
- 20% stroke patients dies within 28 days
- Only 33% of survivors make good recovery
- 15-25% survivors have severe disability
- Impact among long term survivors (> 6 months)
  - Aphasic 12-18%
  - Unable to walk 22%
  - Clinically depressed 32%
  - Hemiparesis 48%

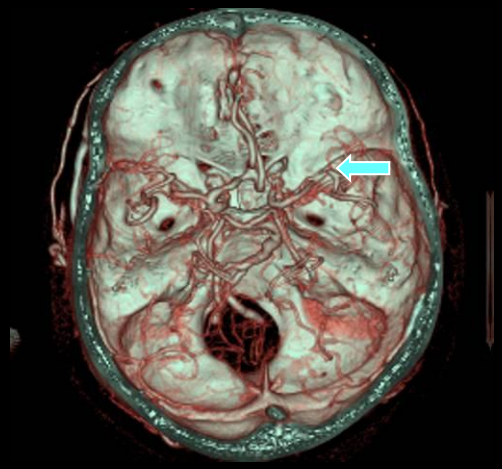
  - Dependent on carers 24-53%
  - Return to work <10%

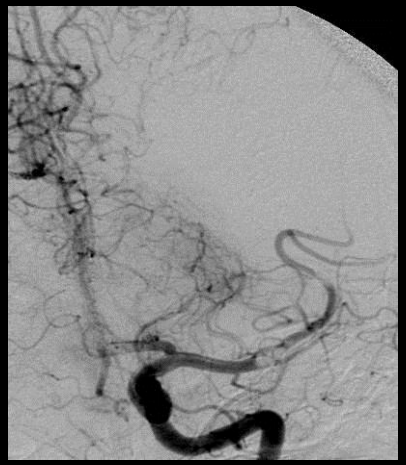
Sacco et al. Stroke 1997;28:1507-17

Acute treatments in Stroke

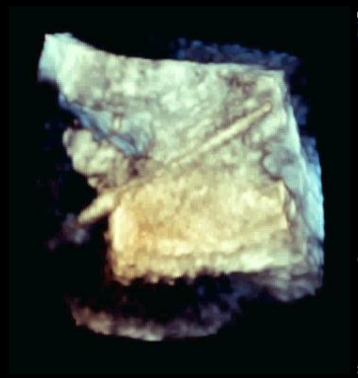
SB, 34 yrs old nurse, sudden onset right weakness and unable to speak (7:30 am)
Maidstone Hospital 8:15am, transferred KCH 11:50 pm

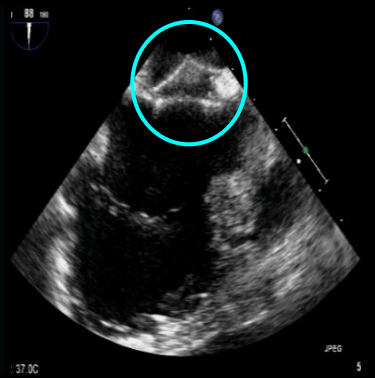






Door to treatment – 34 minutes





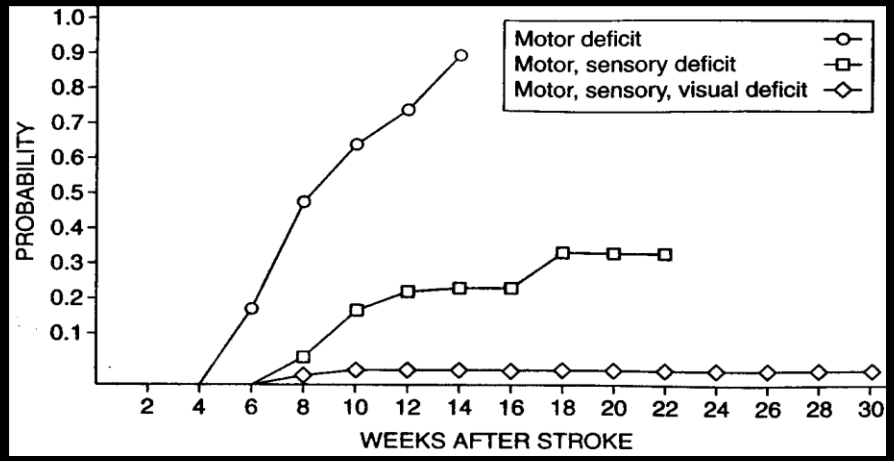
"Hole in the heart" repaired at 48 hours

Treatments in Stroke

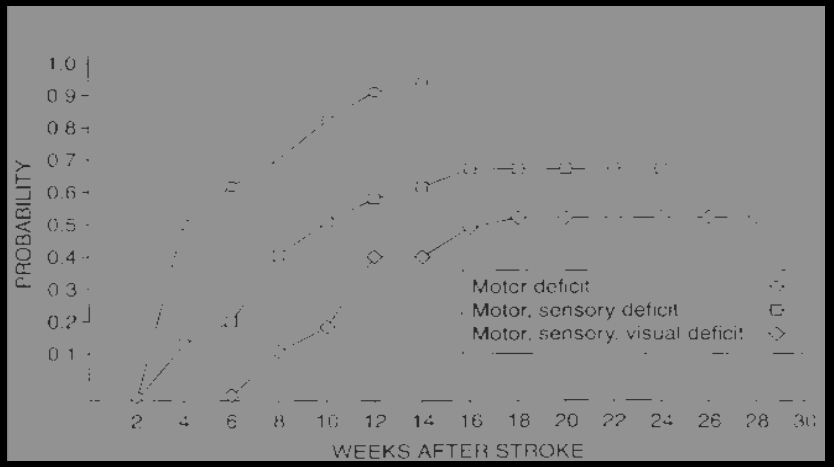
- Thrombolysis: 10% in acute patients, net impact <1%
- Endovascular interventions: specialist centres, even more limited
- Neuroprotection showed no success in human trials
- Emphasis on facilitating and expediting recovery
  - Applies to the vast majority of stroke patients
  - Interventions in non-specialist settings
  - Proven cost-effectiveness at societal level: stroke units
  - Advances in the neuroscience of recovery
  - Industry re-engagement

Natural history of recovery

- Recovery is the fastest soon after stroke
  - 30% independent in PADLs within 3 weeks
  - 50% independent in PADLs by six months
  - Further 5-10% will be independent in PADL in 6-12 months
- Later neurophysiological recovery possible for years but questionable improvement in overall function



Probability of walking ≥ 150 ft without assistance

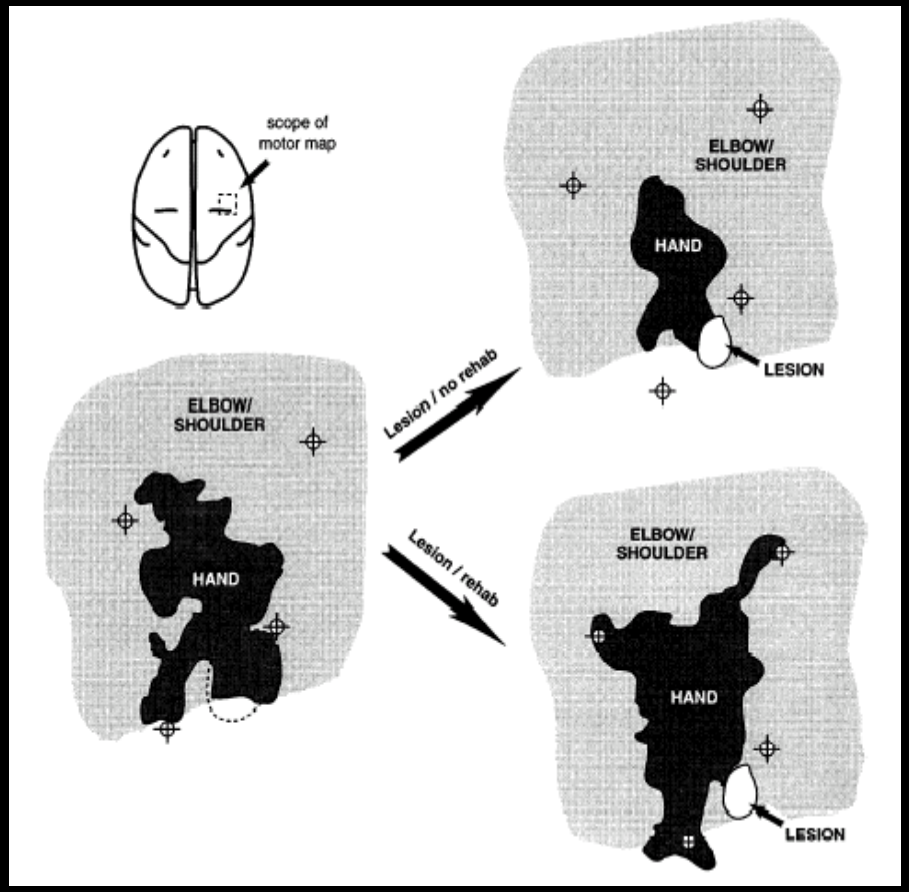


Probability of Reaching a Barthel Score ≥ 60

Reorganization Post-Stroke

- Natural ability to recover after stroke
- New and functionally related areas take over the function of damaged brain
- Other distant areas of the brain are involved in relearning and recovery
- Different strokes have different recovery patterns
- Dependent on intact cortex adjacent to infarct - importance of preserving penumbral areas
- Rehabilitation aimed at facilitating reorganisation

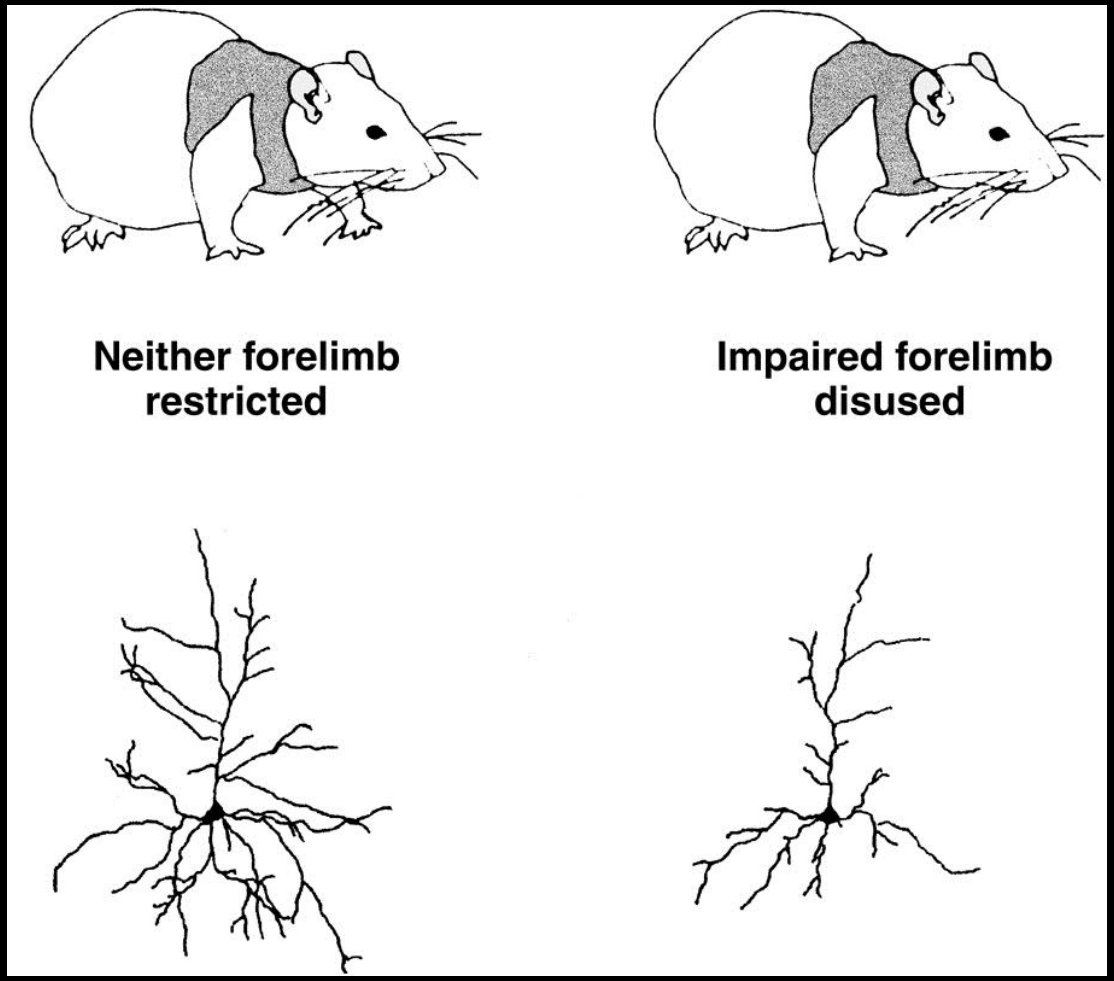
Is Modulation of Recovery Possible?



Nudo RJ 1997

Post-stroke lesion in squirrel monkey, rehabilitation results in expansion of hand representation; no rehab results in contraction

Use It or Lose It Post-Stroke *Schallert, Leasure, Kolb 2000*

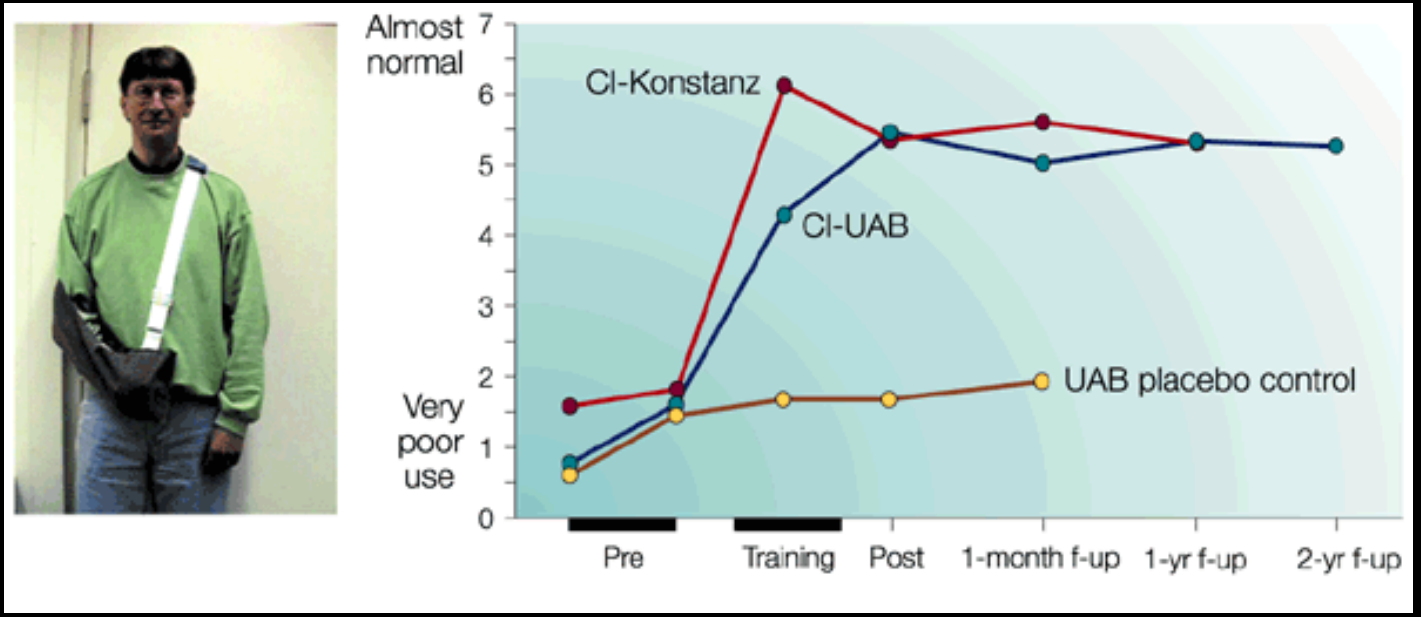


Dendritic trees of neurons in the perilesion area of rats that were not casted after injury and rats that rested the impaired forelimb because it was restrained inside a plaster cast.

Note the paucity of dendritic branches in animals that rested the impaired forelimb.

Role of Intensity of Therapy

- The greater the intensity of therapies - the better the outcomes
- Seen to be true for physiotherapy, occupational therapy, aphasia therapy, treadmill training and upper extremity function in selected patients (i.e. CIMT)

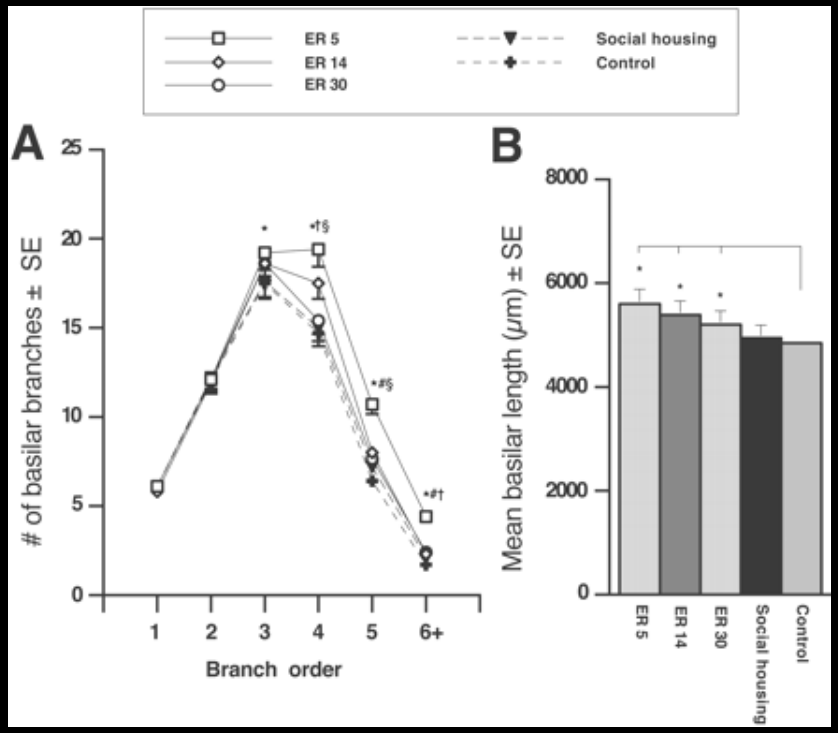


Benefit of Early Therapy

Rats rehabilitated for 5 weeks beginning at 5, 14 and 30 days post stroke v social housing

Compared with controls:

Day 5 - marked improvement
Day 14 - mod improvement
Day 30 - no improvement



Dendritic branching in undamaged motor cortex

Biernaskie et al. (2004)

Rehabilitation Techniques

- Early mobilisation
  - Key strategy associated with good functional outcomes
  - Meta-analyses over 55 years: no positive independent benefit
  - Not harmful for most stroke patients
- Restoration of motor function
  - BMT +/- sensory feedback effective for function and mobility
  - CIMT clinically relevant improvements in arm motor function
  - Robotic devices
- Neuromuscular stimulation
  - rTMS associated with function recover in motor deficit, visuospatial neglect, or aphasia
- Motor imagery
  - Positive effect arm function, promise for leg function
  - Virtual environments and tasks
  - Effects greater when combined with conventional therapy
- Spatial Neglect
  - Spatial techniques have limited success (Prism adaptation)
  - Generalised attention enhancing techniques may be better

Kalra, 2010

Evidence on Rehabilitation

Limitations

- Large number of studies but small numbers and heterogeneous samples
- Small amounts of formal therapy in any trial, more often a comparison between different intensities
- Diversity of outcome measures, limited comparability

Findings

- Intensive targeted therapy is effective
- Early therapy improves outcome
- Recovery greater if tasks are specific to functions lost
- Need for large multicentre trials with common methodology and outcome measurement

Neuroregeneration and Recovery

- Proliferation, migration and differentiation of neural stem cells are triggered in response to ischaemic damage
- This response is sustained, leads to functional improvements
- Neurogenesis can be modulated by growth factors, drugs and novel agents (cannabinoid agonists, retinoids)
- Evidence of increased and sustained endogenous neurogenesis after stroke in humans

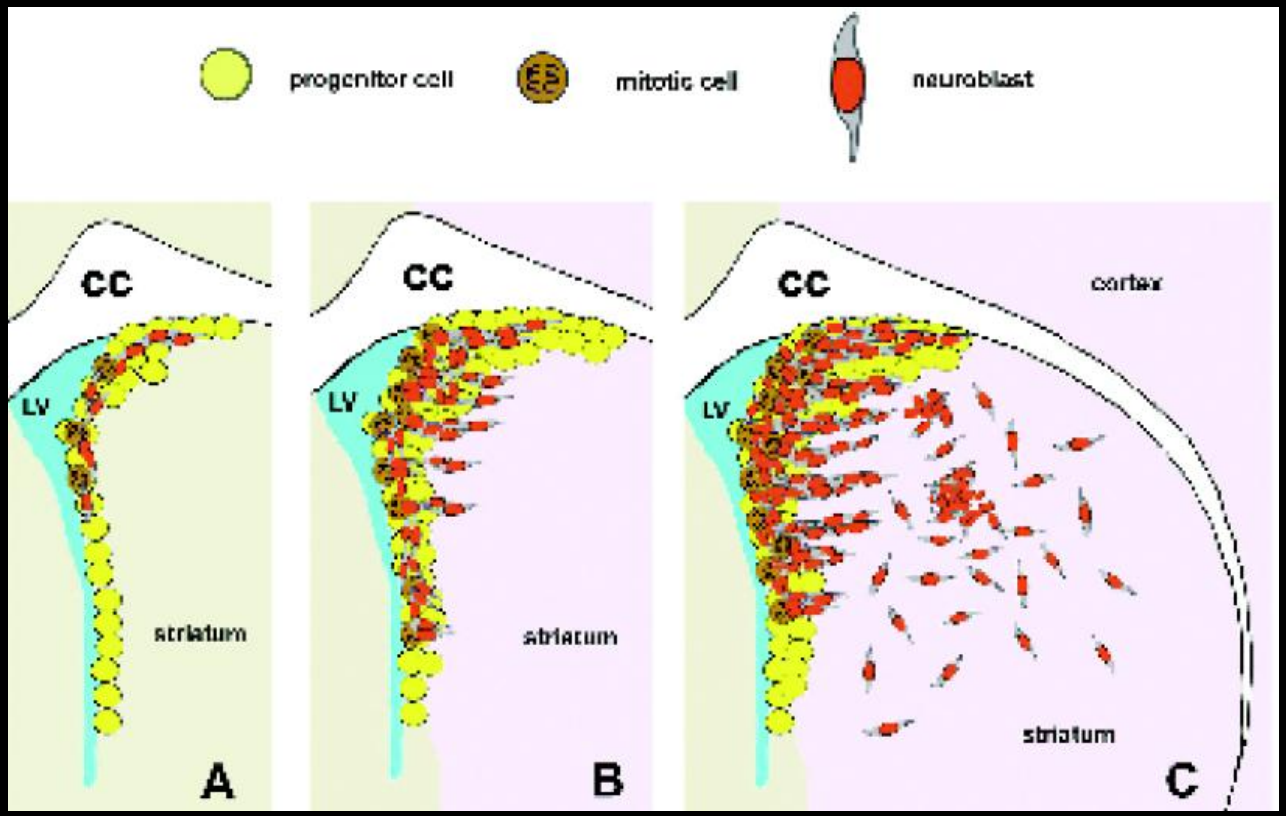
Cellular and Molecular Mechanisms

- Ischaemia activates growth-promoting genes (HIF-1, NPC in SVZ, ?Hippocampus)
- HIF-1 regulates VEGF (angiogenesis) and SDF-1 (neurogenesis)
- Angiogenesis first step – new vessels also release SDF-1
- SDF-1
  - chemotactic growth factor (survival and migration of NPC)
  - Homing of NPC to injury sites
  - Interact with astrocytes, oligodendrocytes and other GFs to promotes neurite outgrowth
  - Repair damaged connections or establish new signalling pathways

Ratan et al, 2007

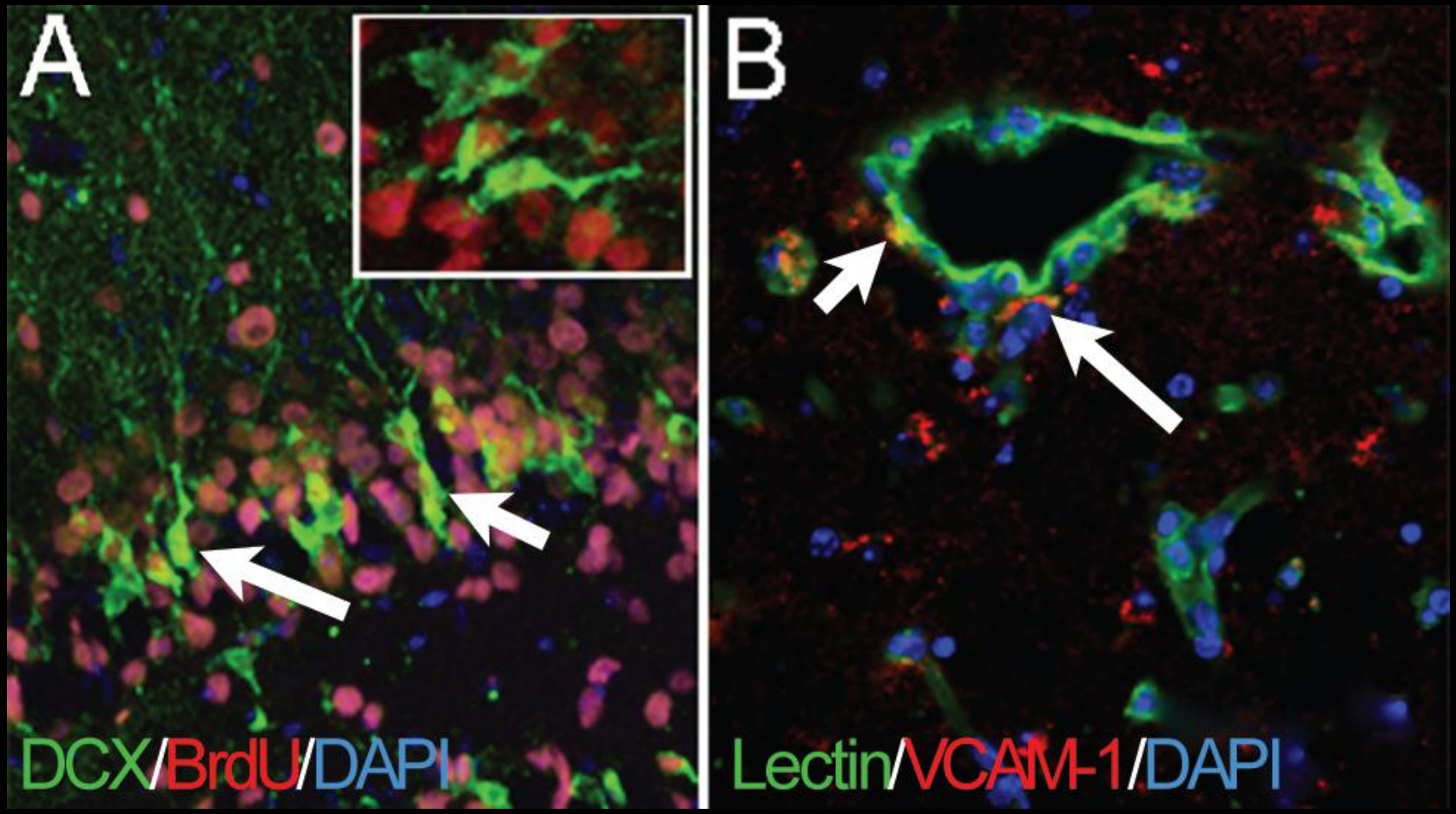
Zhang & Chopp, 2009

Neurogenesis after focal cerebral ischaemia



NPC in the subventricular zone (*A*). Ischemia increases division of NPC and neuroblasts migrate toward ischemic striatum in a chainlike structure (*B*). When migrating neuroblasts reach the ischemic boundary, they form clusters and later disperse (*C*).

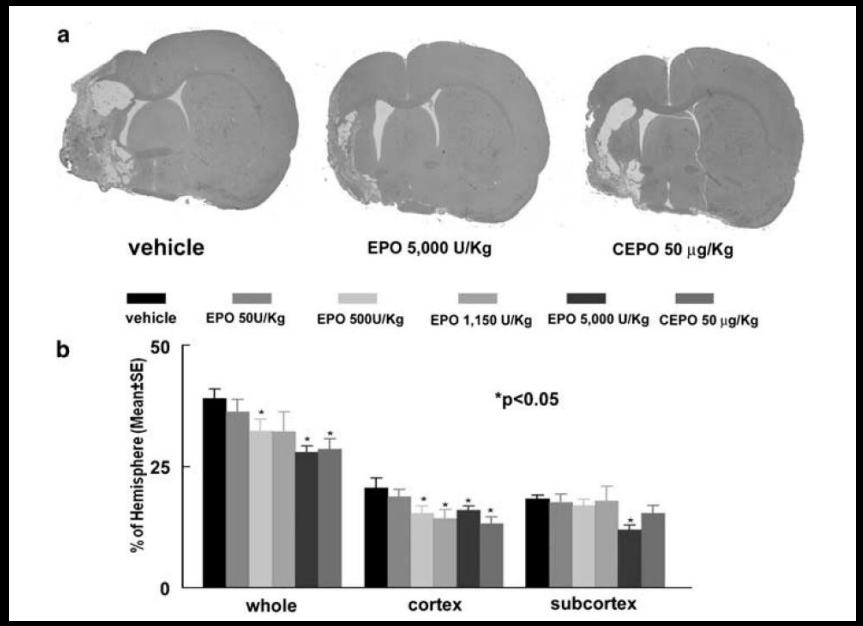
Zhang et al, 2005

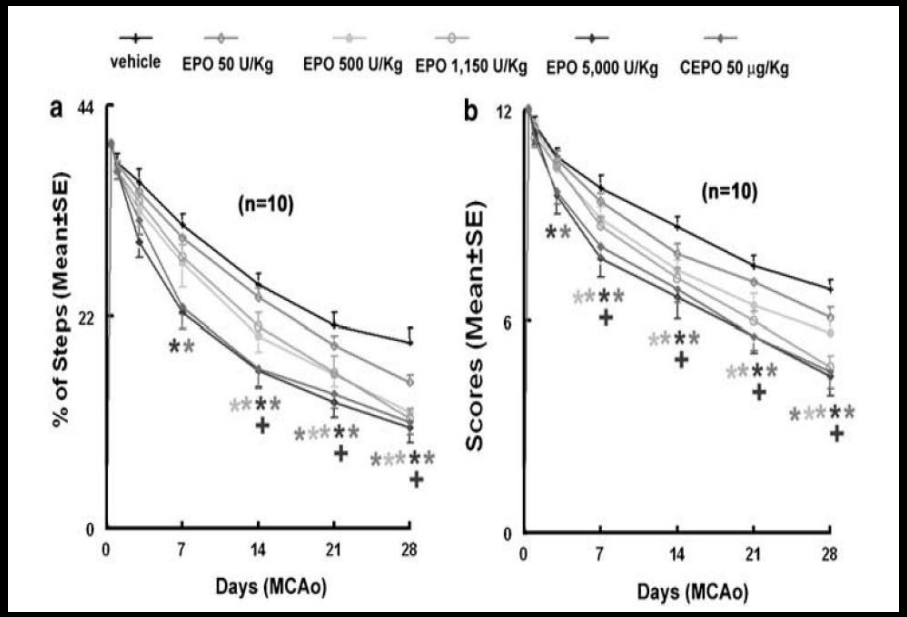


Confocal images revealing numerous cells in the stroke border zone (A). The VCAM-1 *(arrows)* is highly expressed in the stroke-affected hemisphere 48 hours after stroke (B). DCX = doublecortin; BrdU = bromodeoxyuridine; DAPI = 4'6-diamidino-2-phenylindole.

Guzman et al, 2008

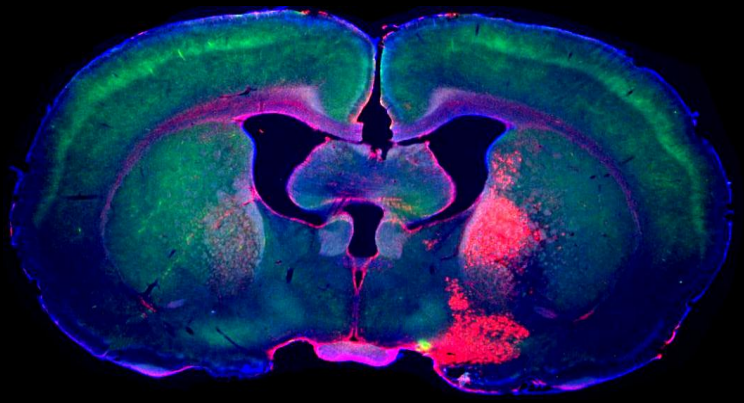
Post-ischemic treatment with erythropoietin

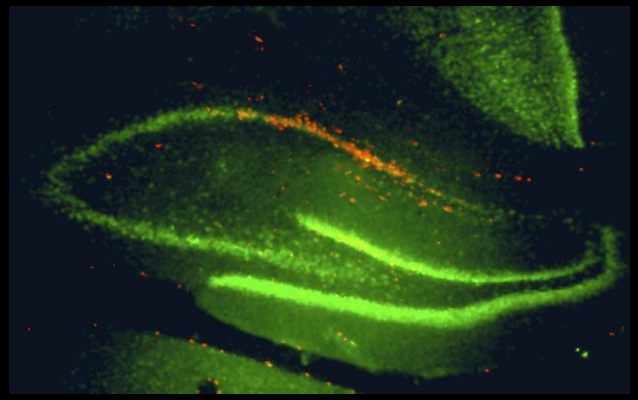




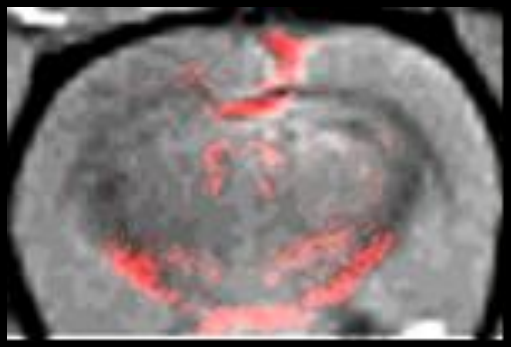
Wang, 2007

Stem Cells in Brain Repair





An ischaemia damaged hippocampus with neurons in green and transplanted neural stem cells in red



In vivo cellular MR imaging of implanted stem cells using specific MRI contrast agents to track migration and survival of transplanted cells in the brain

Courtesy Mike Modo

Stem Cells or Drugs?

- Cell replacement makes sense
- Success in other areas
- “Off the shelf” potential
- Best method for administration not known
- Rejection, infections, malignant potential
- Migration, proliferation, integration capacity unknown
- Mechanism of action unclear: cell replacement or endocrine function

- Treatments already in human use for other indications
- Safety, tolerance profile known
- No tight therapeutic window, can be given post acute
- Non-specialist settings, no special equipment
- Regeneration potential of the ageing brain
- Bioavailability, blood brain barrier, expected but unwanted affects
- Interactions may be important

Ongoing Clinical Trials in Regeneration

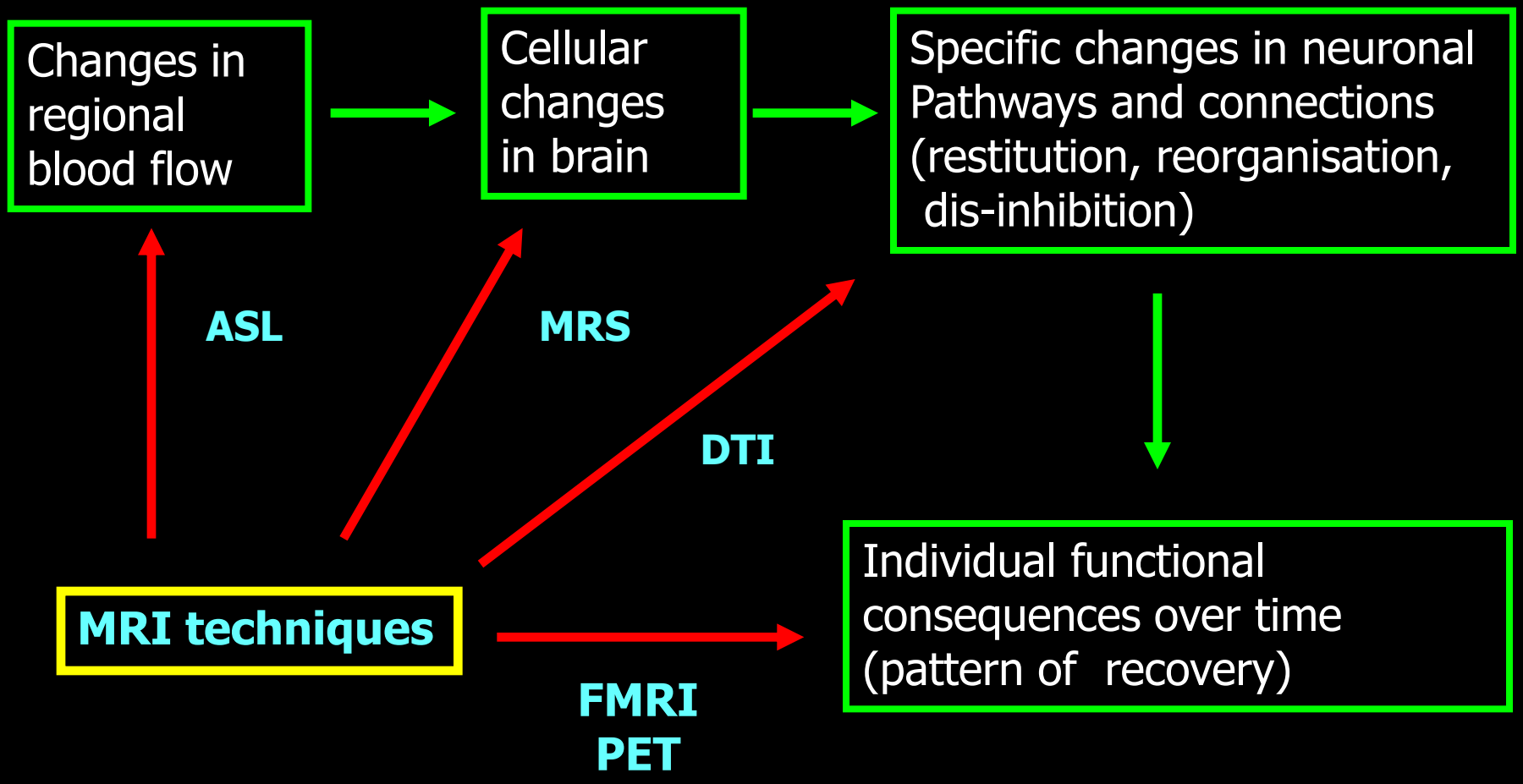
	Patients (n)	Interventions	Results
Phase I	12	NT2N cells; parenchymal implantation	No cell-associated adverse effects 12–18 months after cell transplantation[141]
Phase II	18	NT2N cells; parenchymal implantation	Safety and feasibility of neuron transplantation but no evidence of a substantial benefit on motor function[142]
Phase I/II	30	Autologous bone-marrow mesenchymal cells; intravenous injection	No adverse effects and functional improvement seen 1 year after cell transplantation[143]
Pilot	36	Granulocyte-colony stimulating factor 1–10 μg/kg for one or five doses; subcutaneous injection	Safety and feasibility 90 days after treatment[144]
Phase I	Ongoing	Sildenafil 150 mg; oral treatment	Not yet available[145]

NT2N cells=Ntera2/D1 neuron-like cells.

Table: **Clinical studies of cell-based and pharmacological restorative therapies**

Zhang & Chopp, 2009

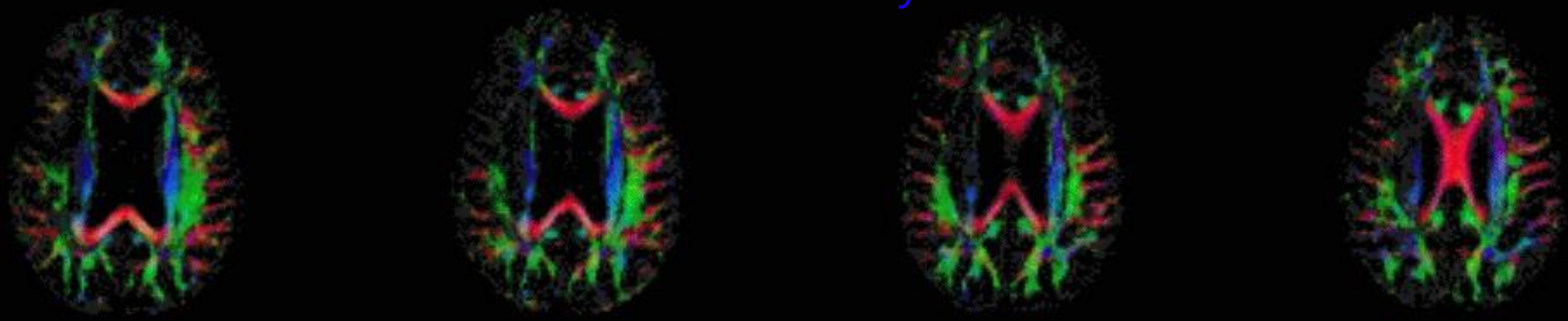
Imaging of Recovery

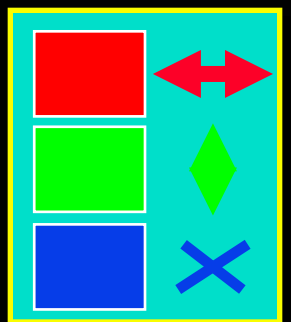


Cortical infarct - Example

T2

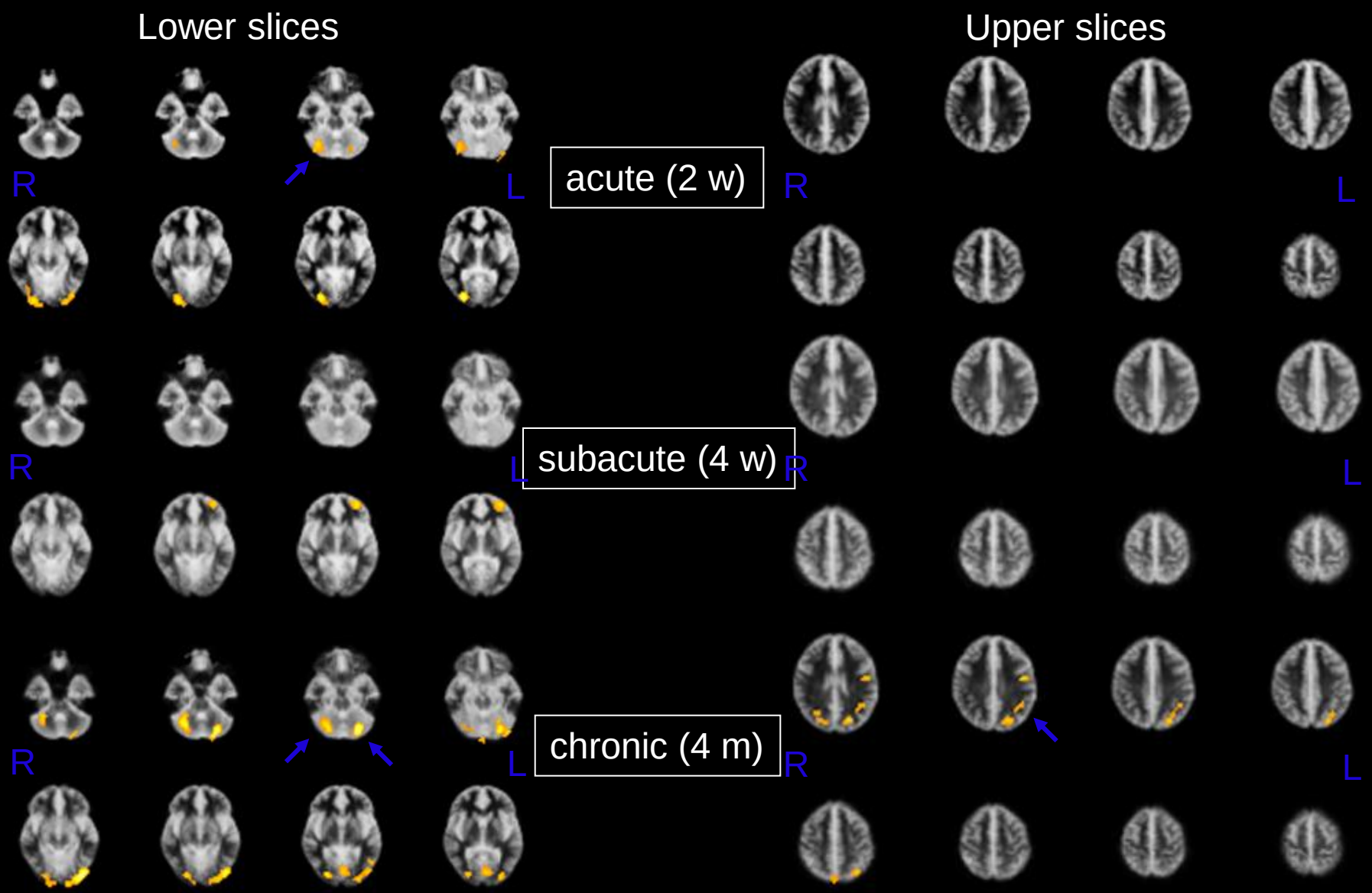
Connectivity





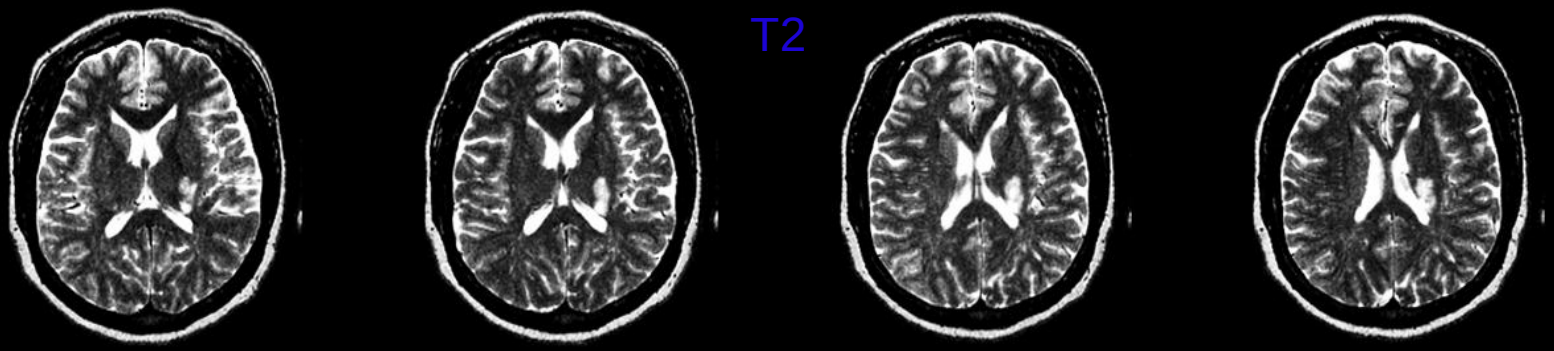
50 y male
left arm weakness

Cortical infarct – LEFT arm injured

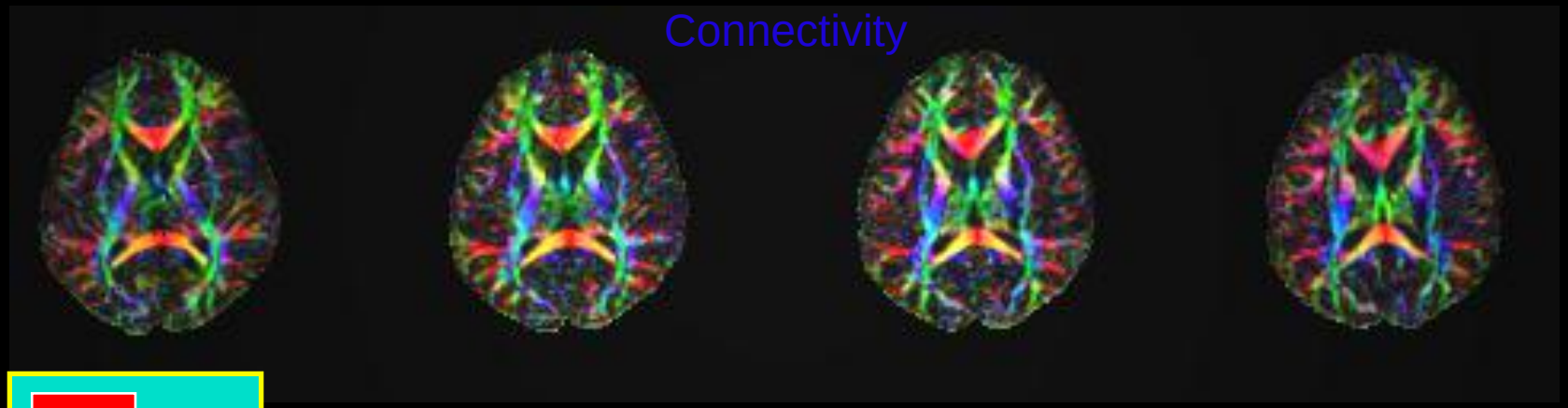


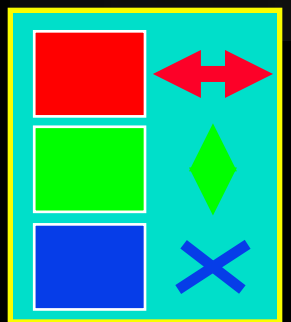
Capsular infarct - example

T2



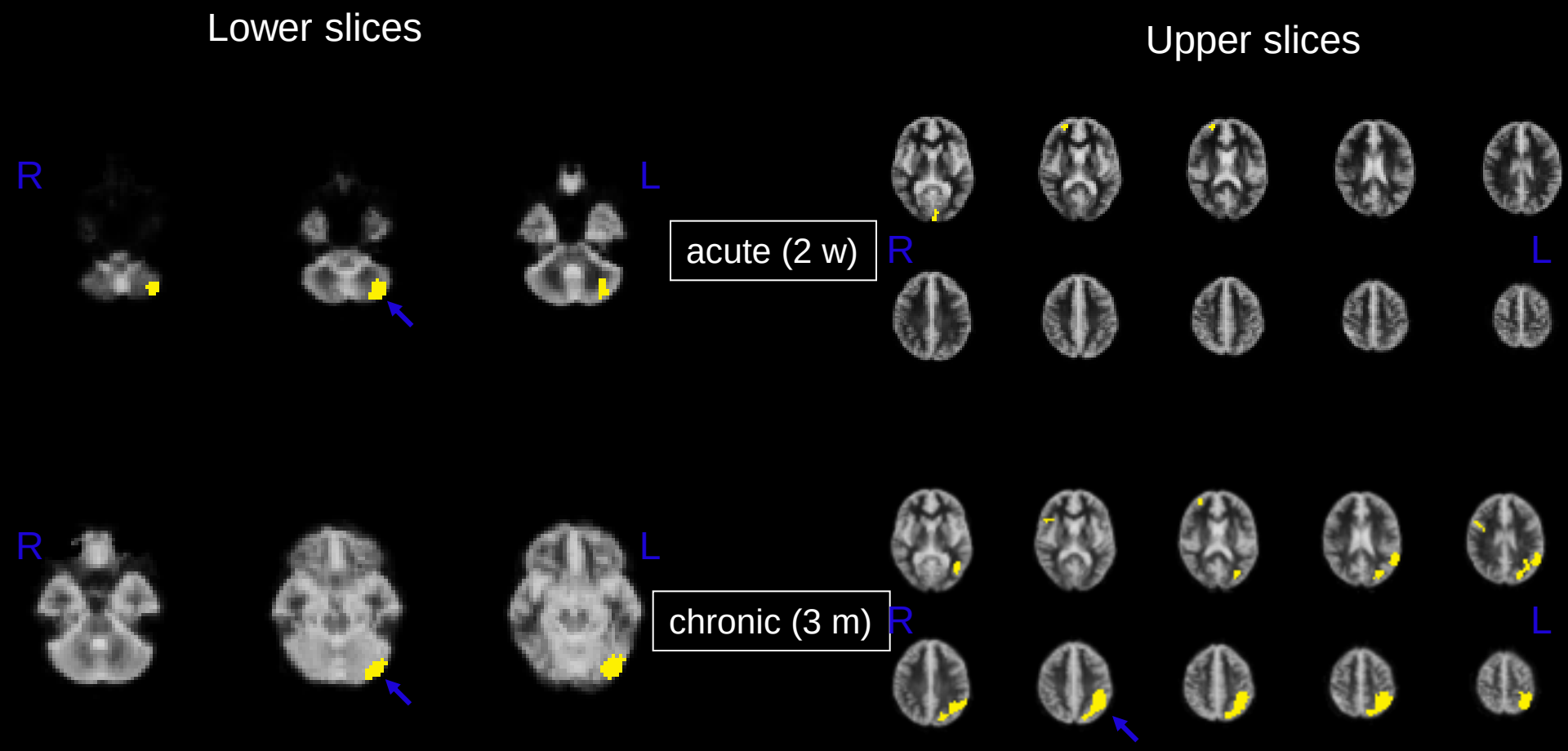
Connectivity



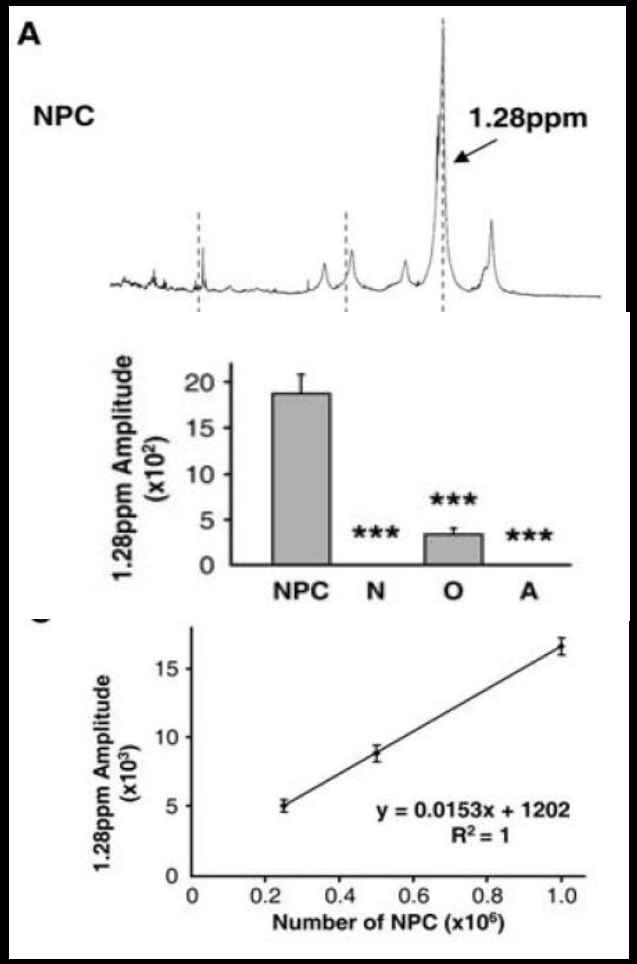


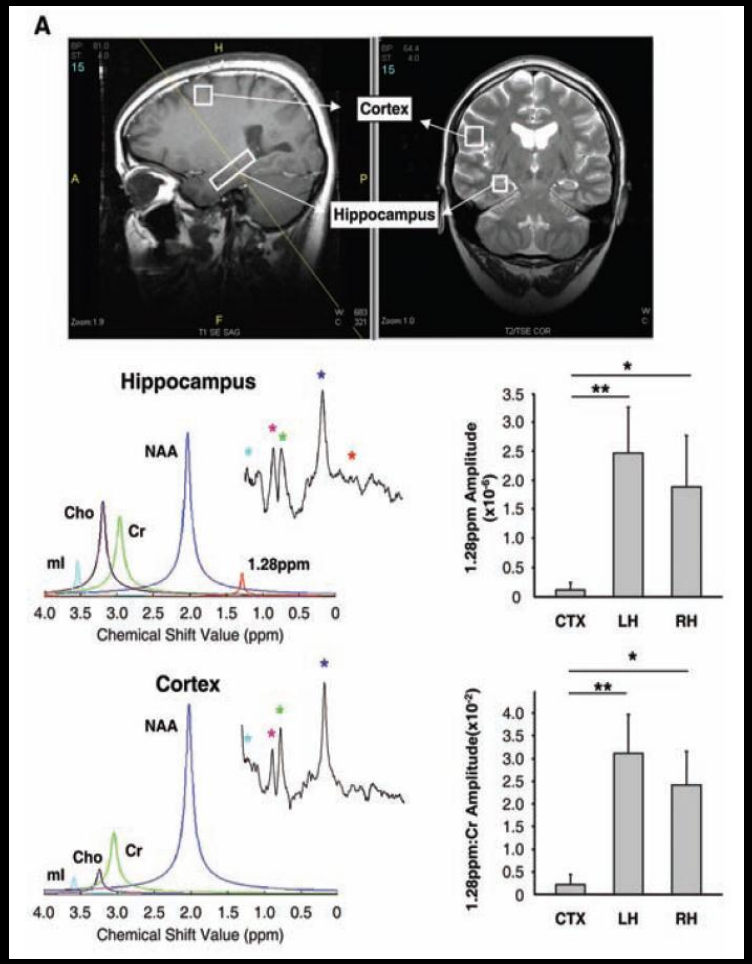
42 y female
right arm weakness

Capsular infarct – RIGHT arm injured

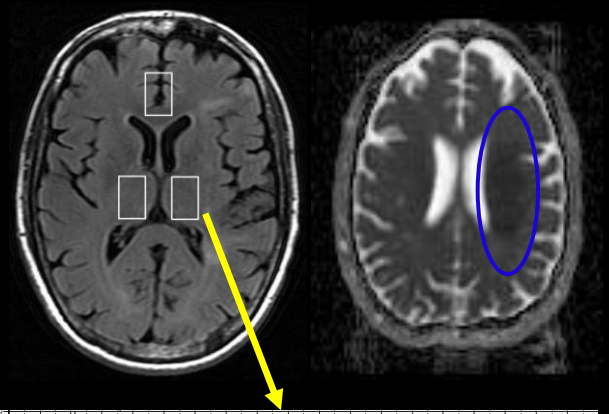


Unique MR metabolic biomarker for the detection and quantification of NPCs in the human brain in vivo identified!





(Manganas et al Science, 2007)



50 M, Baseline NIHSS: 12

2 weeks

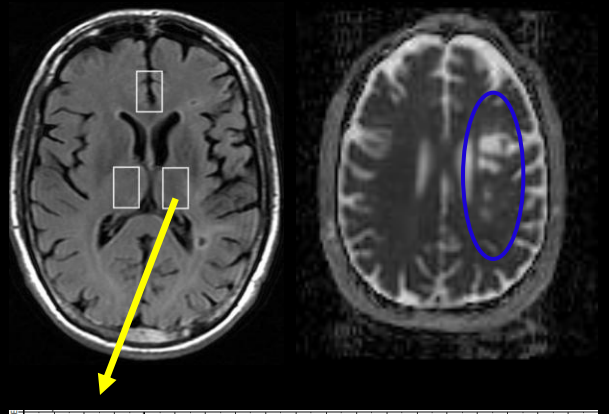
FM arm: 5

FIM motor: 65

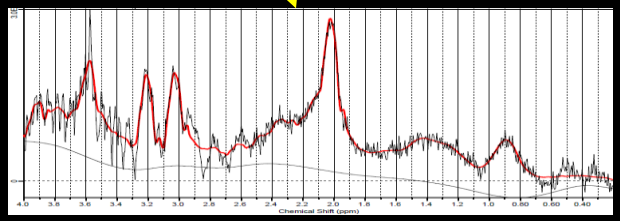
12 weeks

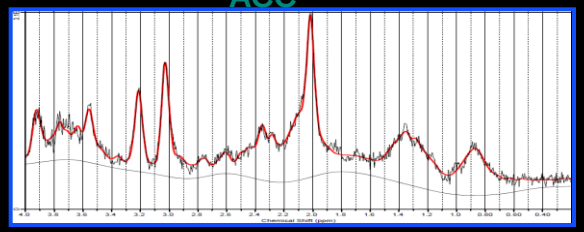
FM arm: 61

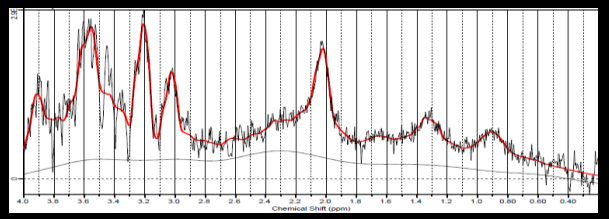
FIM motor: 83

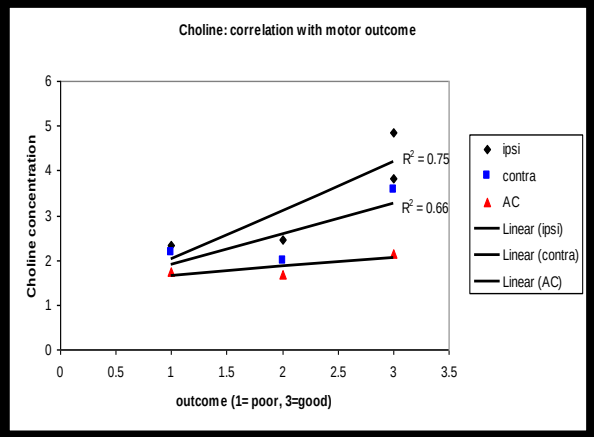


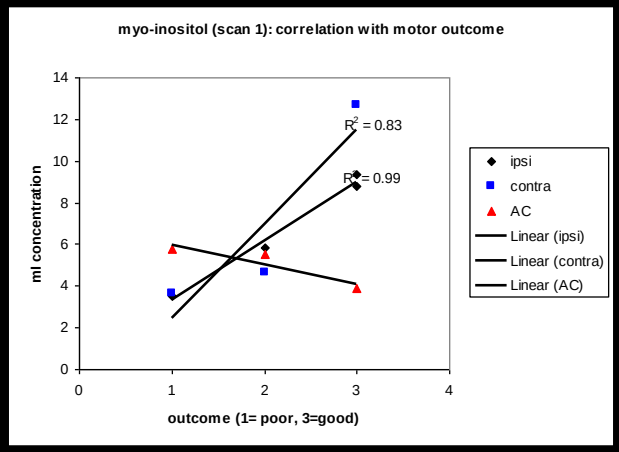
ACC

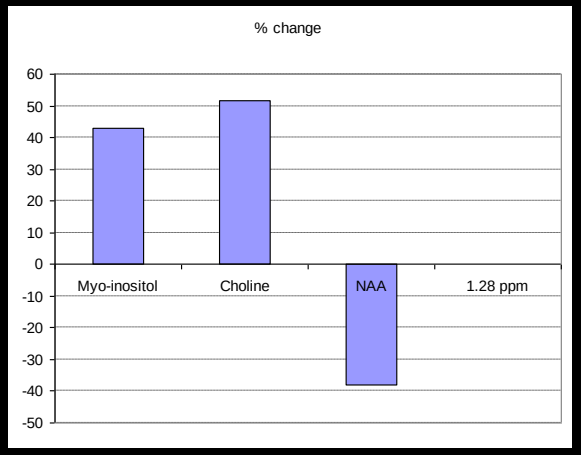












Challenges in Neurosrestoration

- Safety, especially for cell based treatments, GF
- The effect of environment, co-morbidity and other rehabilitation input
- Specific impairment based outcome measurement
- MRI techniques for in-vivo imaging of recovery
  - Restructuring of white matter
  - Angiogenesis
  - Neurogenesis
  - Synaptic activity
- STEPS guidelines but the science is still in its infancy

Key Messages

- Thrombolytic treatments have not conferred widespread benefit at population level
- Novel neurogeneisis enhancing treatments (cellular, pharmaceutical and physical) represent a major advance in stroke
- These treatments have greater promise
  - Safer than thrombolysis
  - vast majority of stroke patients
  - not time critical and do not require specialist infrastructure
- Translation into clinical practice requires partnerships between academe and industry