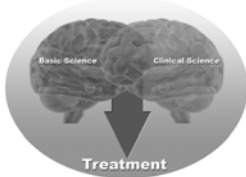
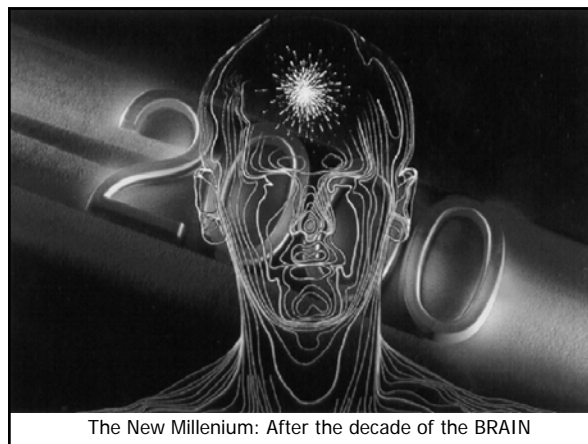


**TRAIN THE BRAIN:  
CLINICAL STRATEGIES TO PROMOTE  
NEURORECOVERY AFTER STROKE**



ALBERTA PROVINCIAL STROKE STRATEGY  
Alberta Children's Hospital  
Calgary, Alberta, Canada  
May 1, 2008

*Katherine J. Sullivan, Ph.D., P.T, FAHA  
University of Southern California*



**Messages from IIISTEP:**

- Application of principles from neuroscience such as neuroplasticity to neurorehabilitation.
- ICF classification to conceptualize PT at all levels of health-status for the individual
- Translation of science to clinical practice:
  - Theoretical Model of Neurologic Therapeutic Intervention
  - Outcome measurement
  - Defined therapy parameters
  - Selection of appropriate physical interventions

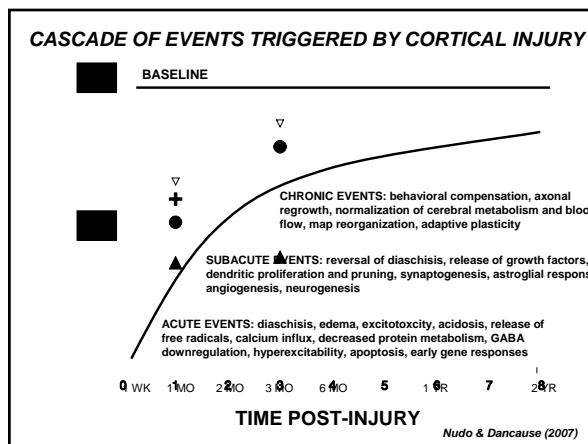
**Post-stroke recovery:**

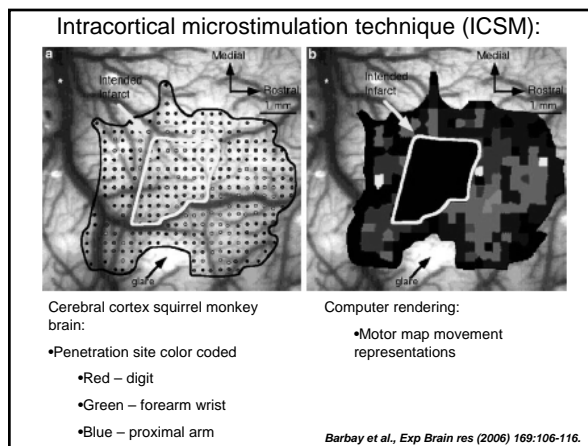
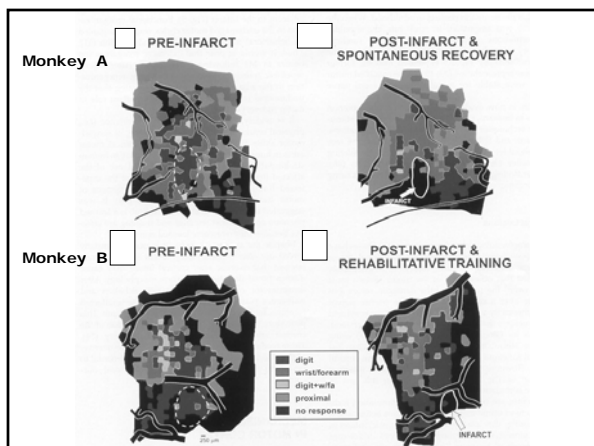
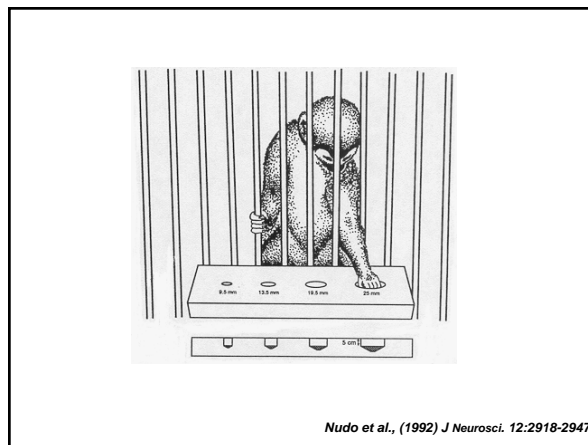
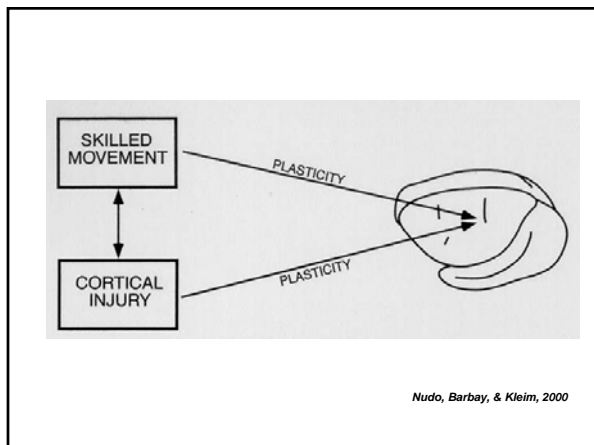
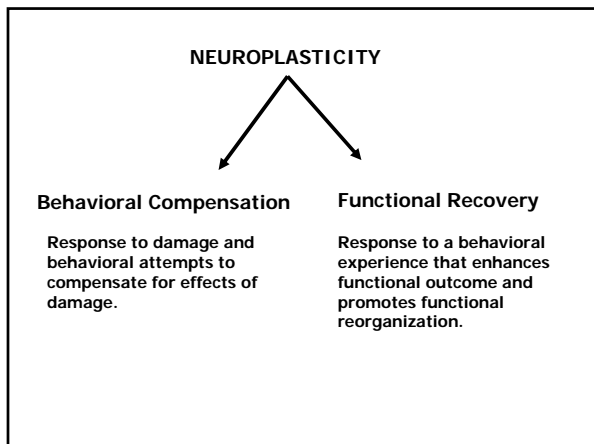
“a complex process involving spontaneous recovery and the effects of therapeutic interventions”

*Richards & Olney, 1996*

**RECOVERY:**  
Interaction of neural and behavioral events

- Spontaneous neural recovery
- Neuroplasticity
  - Behavioral compensation
  - Functional recovery





### Corticospinal neurons

- Motor map evoked movements
- CST divergence – projections to multiple motoneuron pools
- CST convergence-projections to single muscle

*Nudo & Dancause (2007)*

Manipulation of key practice variables appears to be critical for evoking neural plasticity and behavioral recovery

- *Task Complexity*
  - *Jones et al., 1998*
- *Task Difficulty*
  - *Plautz, Milliken, and Nudo, 2000*
- *Task Specificity*
  - *Nudo et al., 1997*
- *Task Intensity*
  - *Sullivan et al., 2002*

### What have we learned from basic science research?

- What drives neuroplasticity?
  - Behavioral training induces morphological and neurochemical plasticity and functional recovery.
  - Process of skill acquisition is critical.
- What drives skill acquisition?
  - Conditions of practice including: repetition, feedback.
  - Task-specificity and intensity.

### What are the exercise parameters that ensure training intensity?

- Dose-response:
  - **Frequency** – number of training sessions in a week
  - **Intensity** – within session attributes
    - time in activity
    - level of activity
      - energy expenditure
    - progression
  - **Duration of training** – total number of training sessions

### What are patient-related factors that affect responsiveness to therapeutic interventions?

- May differ based on disease process.
  - Stroke-related brain damage – acquired damage to motor neurons directly associated with skilled movements
- May differ based on disease severity and course.
  - Mild, moderate, severe damage.
  - In acquired, time post-stroke (acute, subacute, chronic)

### Experience-dependent plasticity:

- Alterations in motor cortical structural plasticity occurs with behavioral training in cortical-lesioned animal models.

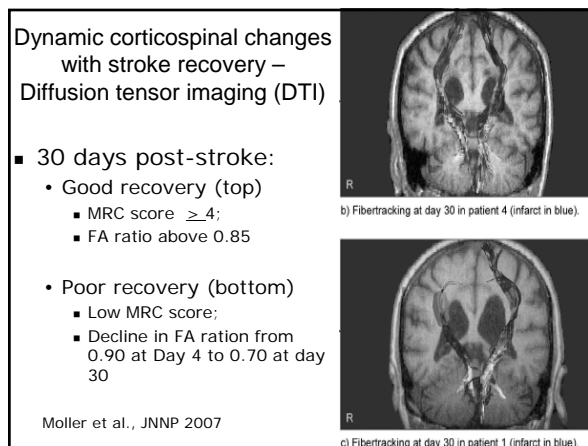
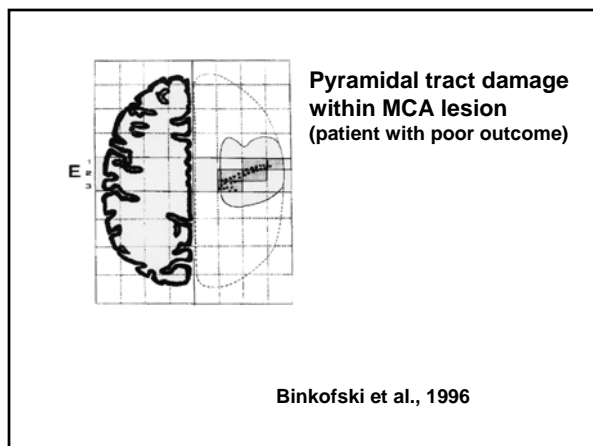
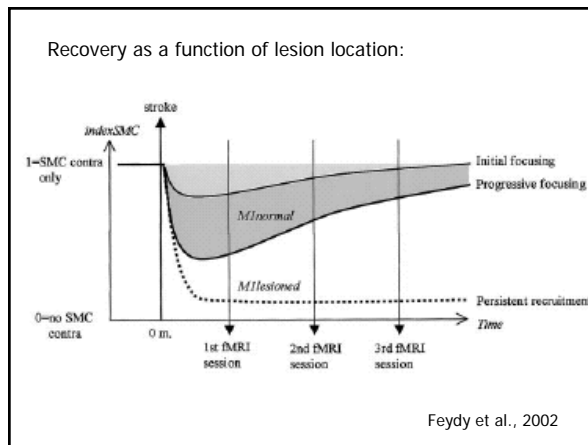
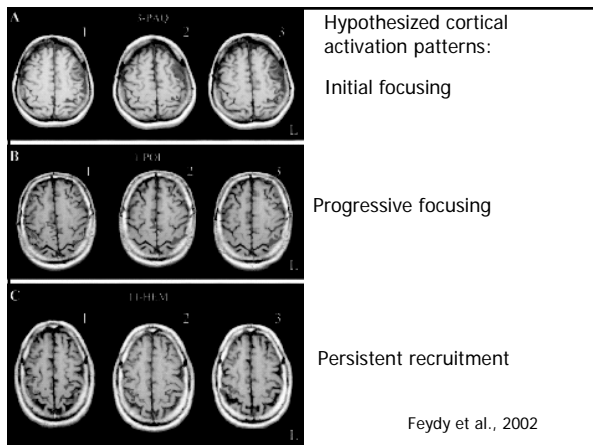
Nudo et al., 1996; Kleim et al., 1996; Jones et al., 1999

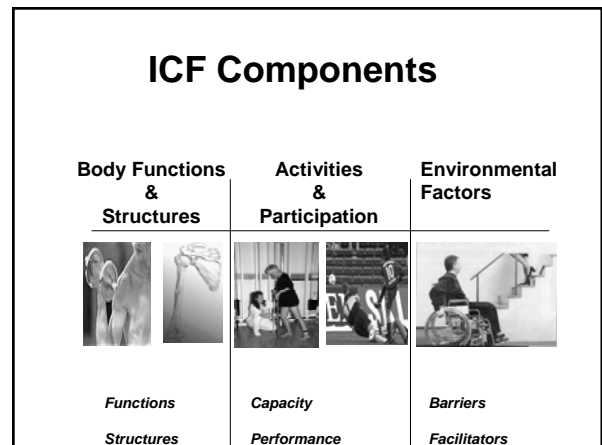
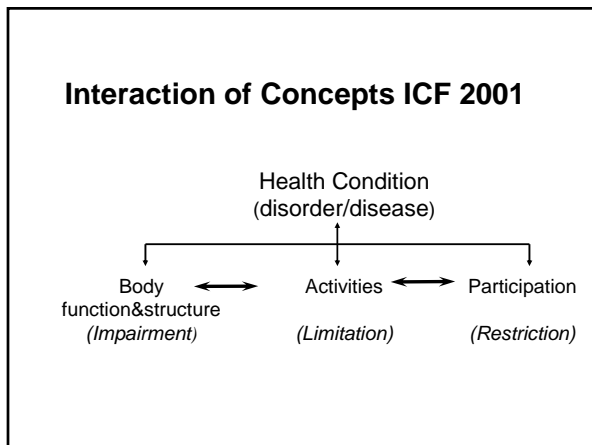
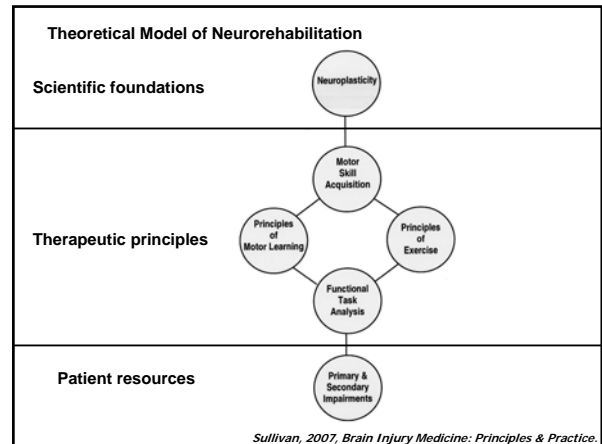
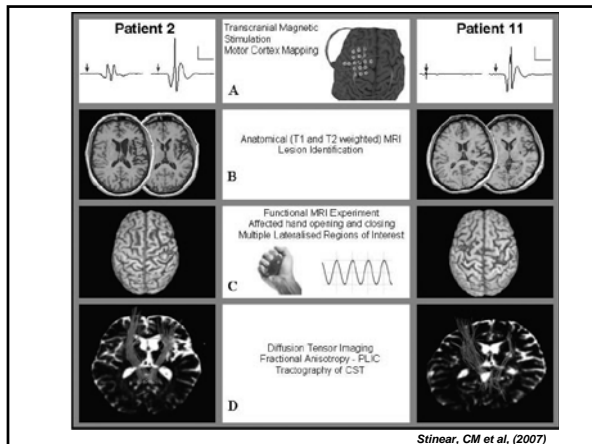
Functional reorganization of motor cortex:

- Skill dependent rather than use dependent.
- Skill acquisition is more important than movement repetition.
- Strengthening does not induce functional reorganization.
- Post-injury behavioral training can influence structural plasticity.

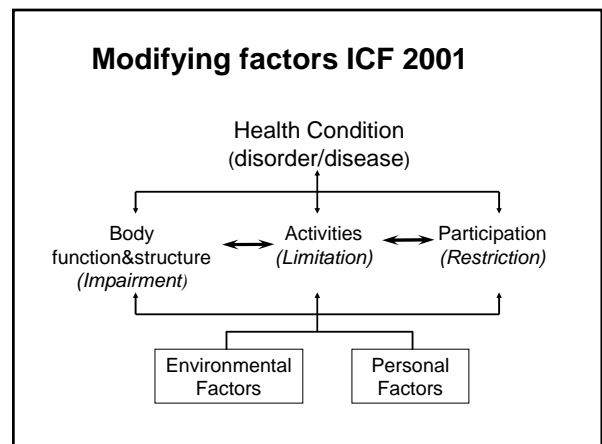
Neuroplasticity (cortical reorganization) and degree of neuronal damage:

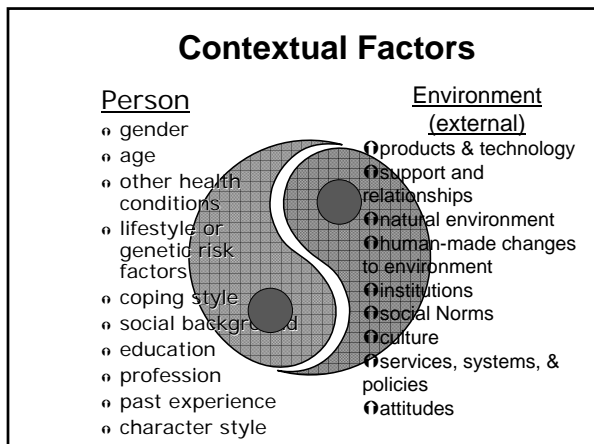
- Is there a relationship between brain damage severity and functional recovery?
- Is there a relationship between brain damage severity and cortical reorganization patterns?





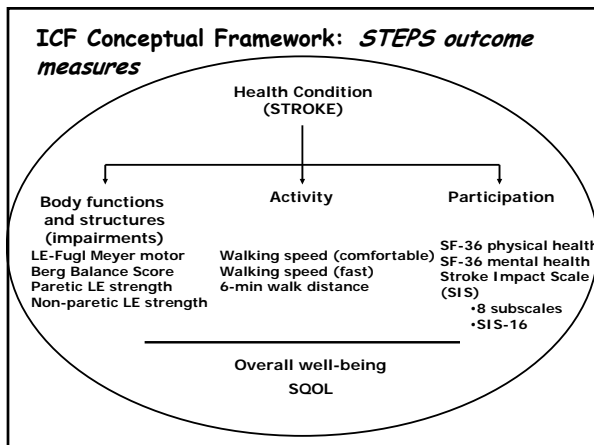
- Activities and Participation**
- 1 Learning & Applying Knowledge
  - 2 General Tasks and Demands
  - 3 Communication
  - 4 Movement
  - 5 Self Care
  - 6 Domestic Life Areas
  - 7 Interpersonal Interactions
  - 8 Major Life Areas
  - 9 Community, Social & Civic Life





### Strength Training Effectiveness Post-Stroke Study (STEPS)

- Physical Therapy Clinical Research Network (PTClinResNet – PIs: Drs. Winstein/Gordon)
- Multi-site, randomized clinical trial (USC, RLA, NWU)
  - PIs: Drs. Brown/Sullivan/Mulroy
  - Project Coordinator: Tara Klassen, MS, PT, NCS
  - Data Management/Statistical analysis team: Stan Azen, PhD, Tingting Ge, MS
- **Specific Aim:** To determine the effectiveness of specific strength training programs to promote locomotor recovery after stroke.



#### Stepwise Multiple regression analysis: Explanatory variables for SIS-16

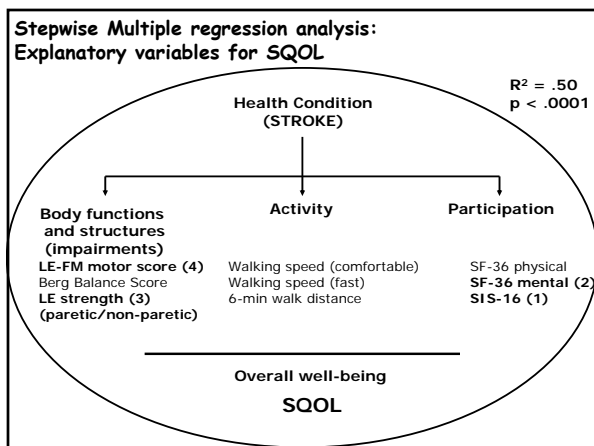
$R^2 = .43$   
 $p < .0001$

**SIS-16**

**Body functions and structures (impairments)**  
LE-Fugl Meyer motor  
Berg Balance Score  
Paretic LE strength  
Non-paretic strength

**Activity**  
Walking speed (comfortable)  
Walking speed (fast)  
6-min walk distance

STEP	VARIABLE	R	R <sup>2</sup>	p
1	FAST VELOCITY	0.316	0.316	< 0.0001
2	6-MIN WALK	0.070	0.386	0.005
3	LE-FM	0.038	0.425	0.034



### *Innovations in Neurorehabilitation*

- Constraint-Induced Therapy
- Body weight supported treadmill training
- Factors affecting treatment effectiveness.

***Essentials of CI Therapy***

- Restrain use of less affected arm for a target of 90% waking hours for two weeks
- Practice of functional task behaviors that are just beyond current capabilities (challenged) for 6 hrs/day for two weeks (10 days)

*Taub & Wolf, 1997*

***Other critical components:***

- Behavioral contract with specific home tasks that are customized to the patient's daily activities pattern.
- Caregiver contract
- Home diary (daily)
- Splint/Mitt has compliance device

■ ***Intervention:***

- two weeks; 6 hr/day in training lab
- combination mitt with task practice, and adapted task practice (shaping)
- daily diary; behavioral contract
- mitt is worn 90% of waking hours (target)

**Inclusion criteria:**

- Subjects who are between 3-9 months post-stroke
- Minimum motor criteria:
  - --high function: 20 deg active wrist extension; 10 deg of active MP and IP extension
  - --low function: 10 deg active wrist extension; 10 deg of active ext of thumb and ext of at least 2 other digits (3 x in 1 min)
- Score at least 24/30 on MMSE
- Not greater than mean of 2.5 on MAL amount
- Over age of 18

***Pre-test: Picking up a soda can***



Item on Wolf Motor Function Test

39 s pre-test

***Post-test: Picking up a soda can***



Item on the Wolf Motor Function Test

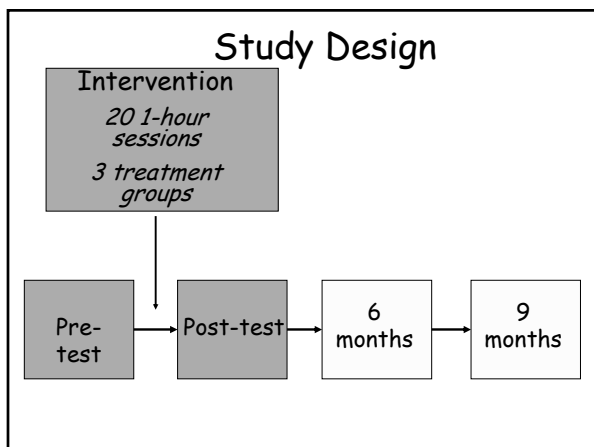
2 s post-test



### Comparison of Upper Extremity Intervention Strategies at Six and Nine Months Post-Stroke

Winstein CJ, Rose DK, et al., 2004  
Supported by NIHRO3, HD3621:

- Functional outcomes in upper extremity recovery can be modified, if we intervene during the acute post-stroke stage and with the proper therapy (task-specific) training intervention.
  - Three treatment groups:
    - Usual care (mostly compensatory training)
    - Functional task training, 20 hrs (1 hr/day; 4-6 weeks)
    - Strength training, 20 hrs (1 hr/day; 4-6 weeks)



### Orpington Prognostic Scale Range 1.6 - 6.8

- Motor deficit in upper extremity
- Proprioception in upper extremity
- Balance
- Cognition

- Study subjects stratified by baseline OPRS:
  - Less severe (LS): 1.6 - 4.1
  - More severe (MS): 4.2 - 6.8

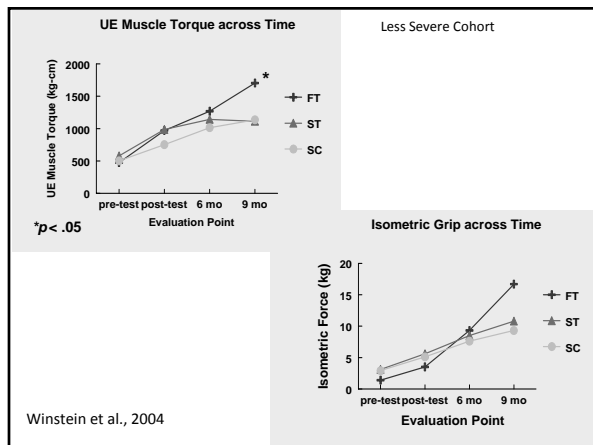
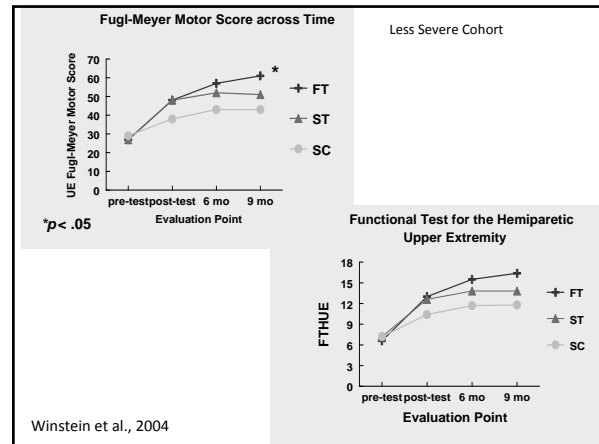
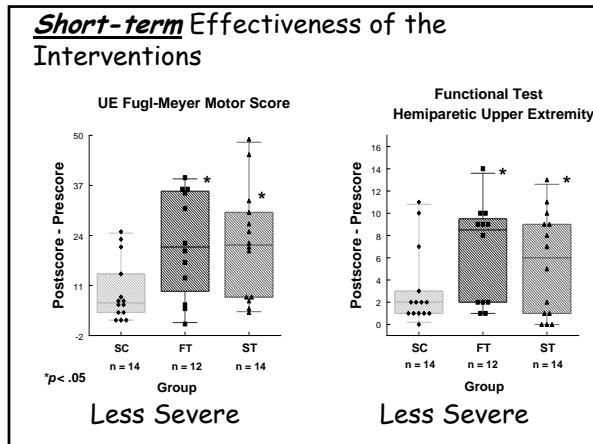
(Kalra and Crome, 1993)

### Outcome Measures

- Upper Extremity Fugl-Meyer Motor Score (Fugl-Meyer et al, 1975)
- UE Isometric Muscle Torque (UEIMT)
  - shoulder (flex/ext), elbow (flex/ext), wrist (flex/ext)
- Grip, Lateral Pinch, Palmar Pinch
- Functional Test Hemiparetic Upper Extremity (FTHUE) (Wilson et al., 1984)

### UPPER EXTREMITY INTERVENTION Groups

<b>Standard Care (SC)</b> N = 20 14 LS 6 MS	<b>Strength Training (ST) + Standard Care</b> N = 20 14 LS 6 MS	<b>Functional Task Training (FT) + Standard Care</b> N = 20 12 LS 8 MS
--	--	---



**CONCLUSIONS**

- Functional training intervention may have provided the *context* for greater gains in isolated strength and function than those who received ST or SC alone.
- In spite of similar *initial* changes for both the FT and ST groups at post-test, the ST group may have been less prepared than the FT group to carry over this benefit *long-term*.
- Long-term benefits from functional training that were *not* evident at the immediate post-test. These results are reminiscent of the well-known *performance-learning distinction*.
- Acute post-stroke intervention strategies that provide meaningful engagement in activities may be more beneficial than rote exercise. This phenomenon is well documented in the occupational therapy literature.

**Evidence for locomotor-induced plasticity:**

- Repetitive locomotor activity that optimizes the sensorimotor experience of walking resulted in changes in EMG amplitude and bursting patterns in spinalized cats and humans with SCI.

De Leon et al., 1998  
Harkema et al., 1997

**Sensorimotor experience and task-specific training effect locomotor recovery:**

- Body-weight support and repetitive treadmill stepping enhances locomotor recovery.

Sullivan et al., 2002  
Visintin et al., 1998

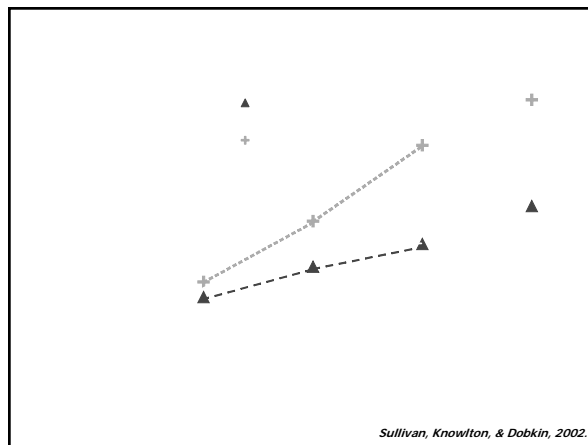
- Human spinal locomotor circuits interpret locomotor sensory inputs demonstrating activity dependent learning.

Harkema et al., 1997



**Training groups  
(stratified by initial walking speed):**

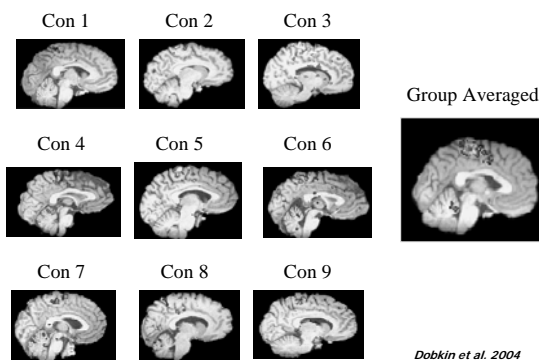
- Slow
  - Constant speed at .5 mph
- Variable
  - Variable speeds at .5, 1.0, 1.5, 2.0 mph
- Fast
  - Constant speed at 2.0 mph

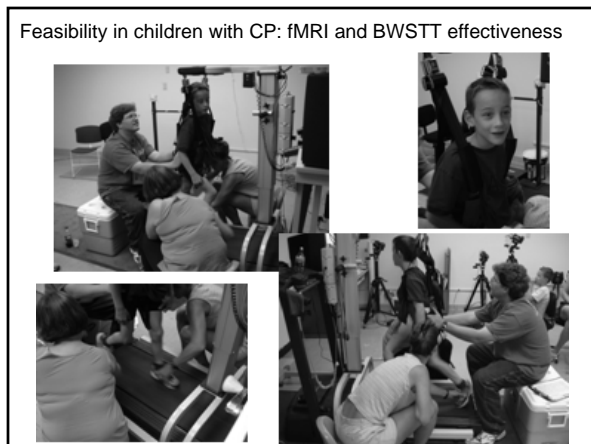
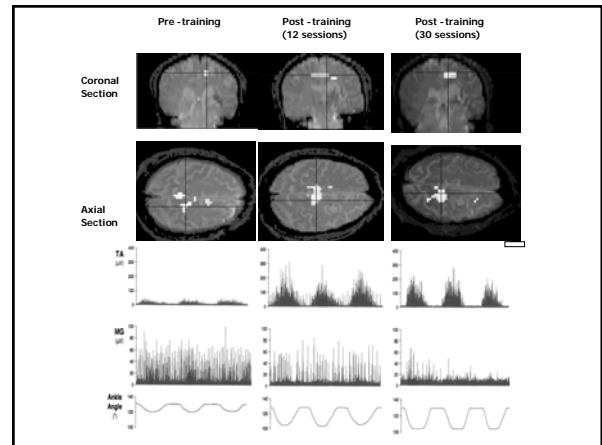
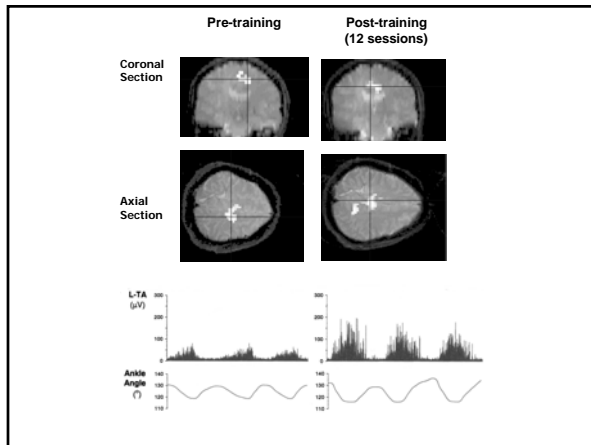
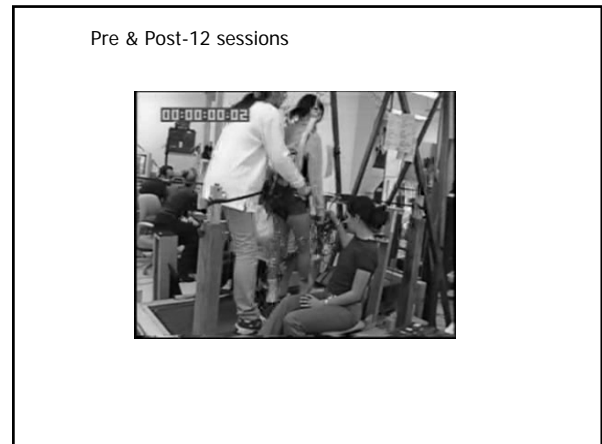


**fMRI useful tool for evaluating neuroplasticity in humans:**

- Provides a measure of training-related cortical reorganization.
- Provides a physiologic indicator of intervention dosing and effectiveness.
- In combination with structural MRI, can reveal relationships between degree of damage, potential for recovery, and responsiveness to therapy.

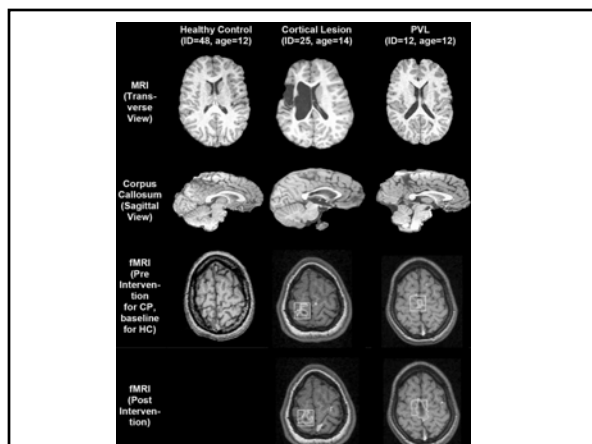
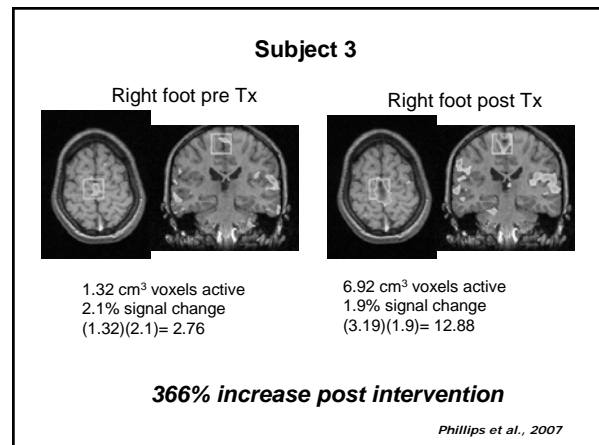
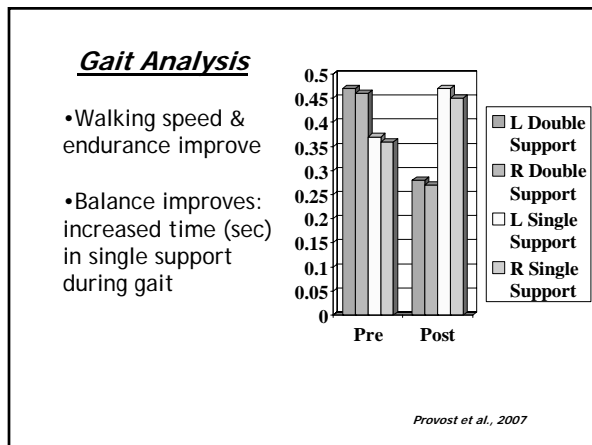
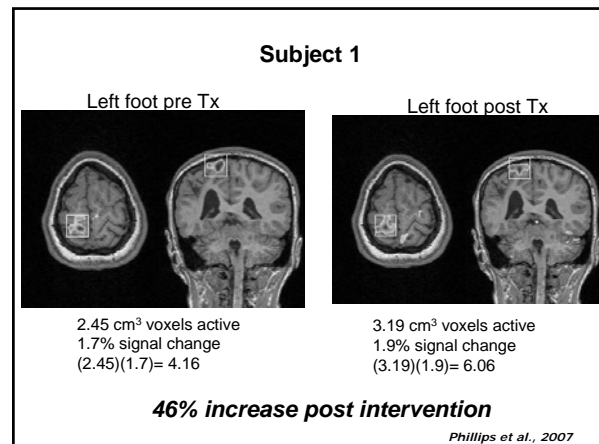
**Robust effect of fMRI foot activations in control subjects**





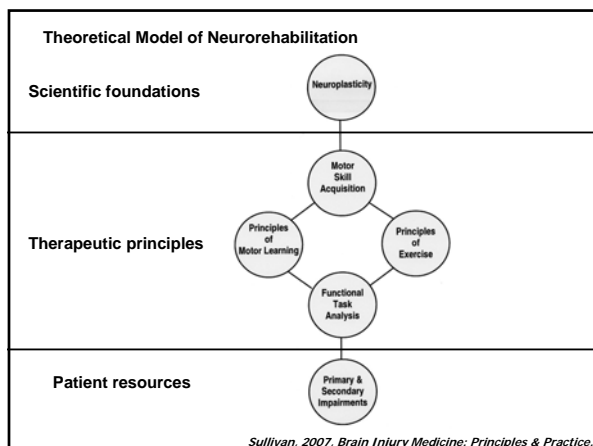
### Study Subjects

Pt #	Sex	Age (yrs)	GMFCS Level	Diagnosis	Clinical Description	Medications (current)	Prior Procedures	MRI
1	F	14	I	Left hemiplegia	Term delivery, regular classroom, language based LD	none	Left UE tendon transfers, Botox injections to UE	Right MCA stroke
3	M	12	I	Diplegia right > left	34 week twin, regular classroom, A student	none	Right LE Botox & stretch casting	PVL, left > right
4	M	8	I	Right hemiplegia	27 week delivery with IVH, regular classroom, ADHD	none	Right LE Botox & stretch casting	Left PVL



### Impact of fMRI and therapeutic intervention studies in humans:

- Understanding the effects of motor skill acquisition and exercise on neuroplasticity may provide insight to facilitate neurorecovery in stroke and developmental disorders such as cerebral palsy.
- It is likely that standardized exercise protocols will be used to optimize future experimental interventions such as pharmacologic agents, gene therapy, or tissue implants expected to promote neuroplasticity and neurorecovery after brain damage.



**Strength Training Effectiveness Post-Stroke Study (STEPS)**

- Physical Therapy Clinical Research Network (PT CLIN RES NET – PIs: Drs. Winstein/Gordon)
- Multi-site, randomized clinical trial (USC, RLA, NWU)
  - PIs: Drs. Brown/Sullivan/Mulroy
  - Project Coordinator: Tara Klassen, MS, PT, NCS
- Specific Aim:** To determine the effectiveness of specific strength training programs to promote locomotor recovery after stroke.

**Body weight supported treadmill training (BWST)**  
Task-specific, repetitive practice of walking

**Locomotor-Based Strength Training (CYCLE)**  
Limb-loaded pedaling exercise

**Muscle Specific Strength Training (LE-EX)**  
PRE for hemiparetic hip, knee, and ankle

**Upper Extremity Ergometry (SHAM)**  
Low intensity upper limb ergometry

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- Specific Aim:** To determine the effectiveness of specific strength training programs to promote locomotor recovery after stroke.

**Background and significance:**

- Post-stroke, muscular weakness contributes to decreased walking velocity and endurance, and increased disability.  
*Perry et al., 1995; Richards & Olney, 1996; Mulroy et al., 2003*
- Lower extremity strengthening exercises and task-specific training result in improved walking ability in individuals post-stroke.  
*Teixeira-Salmela et al., 1999; Sullivan et al., 2002; Patton et al., 2004*
- No studies have examined the combined effect of task-specific training with strength training, or the effect of different strengthening protocols on gait outcomes.

**Body weight supported treadmill training (BWST)**  
Task-specific, repetitive practice of walking


**Locomotor-Based Strength Training (CYCLE)**  
Limb-loaded pedaling exercise

**Muscle Specific Strength Training (LE-EX)**  
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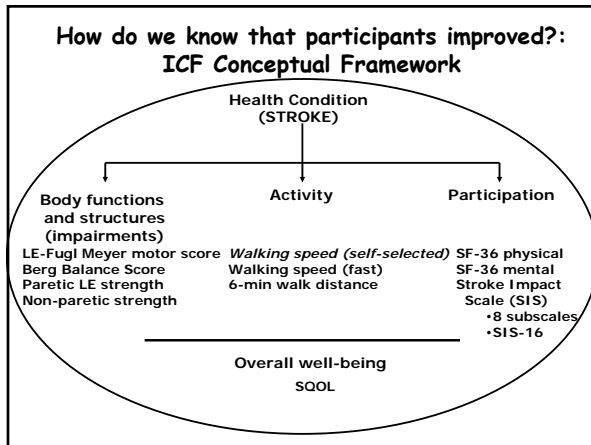
### How did we design the study?

- 80 individuals with chronic stroke, randomized to one of four exercise pairs:
  - BWST/UE-EX
  - CYCLE/UE-EX
  - BWST/CYCLE
  - BWST/LE-EX
- 4x/wk for 6 wks; 24 intervention sessions




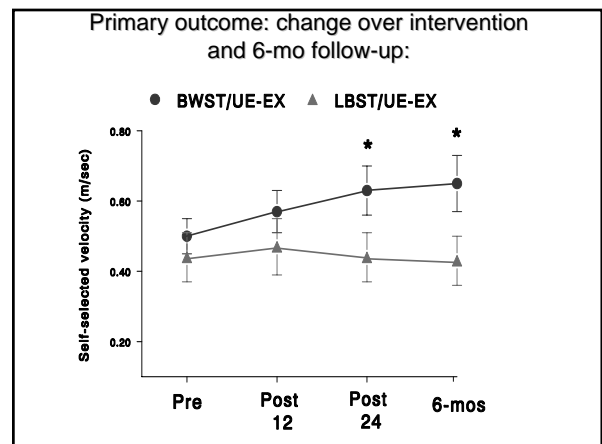
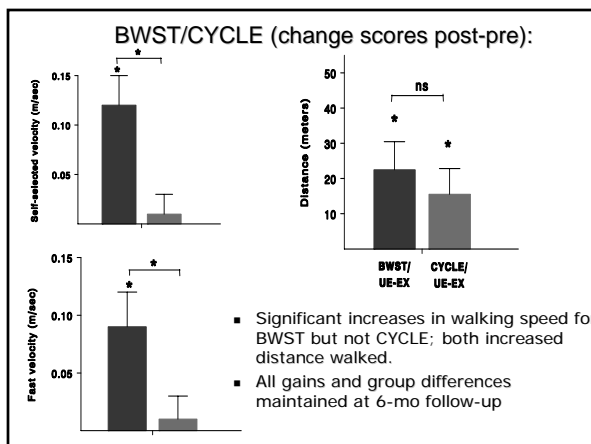
### Who participated?

- Chicago and Los Angeles
- Age: 61±12 yrs
  - Range: 32 – 83 yrs
- Gender:
  - 56% male/44% female
- Stroke onset:
  - 25.5±15 mos
  - Range: 4.1 – 58.7 mos
- Race/Ethnicity
  - Asian 15%
  - African American 22%
  - White 59% (90% white; 10% Hispanic)
  - Mixed race 4%

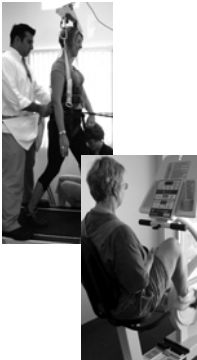
### Primary Hypotheses:

- Hypothesis 1:
  - That a resisted limb-loaded cycling task (CYCLE) that incorporated locomotor-like movements would be as effective at increasing walking speed and distance as a task-specific intervention (BWST);
- Hypothesis 2:
  - That strength training (either CYCLE or LE-EX) combined with BWST would result in increased walking speed and endurance compared with BWST training alone (UE-EX, sham).

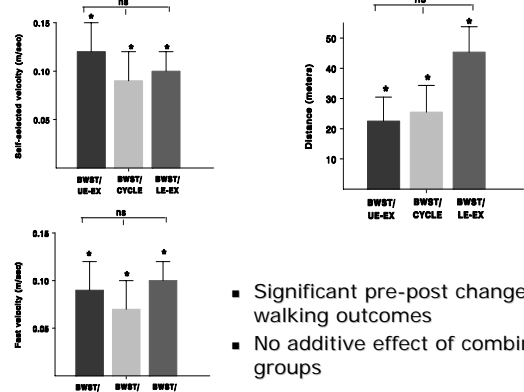



**Conclusions & clinical significance of HYPOTHESIS 1: BWST and CYCLE comparison**

- BWST training resulted in improvements in walking speed and endurance
  - Support for the benefits of task-specific training
- CYCLE resulted in similar gains in endurance but not speed
  - Support for an alternative therapy option to increase endurance
- BWST training resulted in **clinically meaningful change** with or without addition of strength program:
  - Over 50% (27 out of 53) classified at a higher functional walking level post-BWST (Perry et al., 1995)
  - Maintained at 6 mo follow-up.



**BWST combined with CYCLE or LE-EX:**




- Significant pre-post changes all walking outcomes
- No additive effect of combined groups

**How important are the results from STEPS?**

- **PRIOR STATE OF EVIDENCE:**
  - Conflicting (Level 4) evidence that BWST improves gait performance post-stroke (Moseley et al. 2005, Foley et al of Canadian Stroke Network, 2006)
- **LEVEL I EVIDENCE:**
  - STEPS provides evidence in a Phase II RCT for the efficacy of a specified protocol of BWST post-stroke for walking speed, endurance, and lower limb strength outcomes.
- **SPECIFICITY of TRAINING:**
  - Advances our understanding of the importance of task-specific training
- **DOSING OF TRAINING:**
  - STEPS provides training parameters (frequency, intensity, duration) to achieve **clinically meaningful change** (average gains 0.15 m/s > Cochrane)
  - Establishes the value of 12 sessions of high intensity BWST training for long-term walking outcomes
    - 2X/wk for 6 wks; 20-30 min TM walking at 2.0 mph

**Significant clinical findings from STEPS:**



**CLINICAL MESSAGE 1:**  
For chronic stroke survivors with hemiparesis who have decreased walking speed and endurance, BWST is more effective than CYCLE.  
However, CYCLE is an effective therapy to increase walking endurance.

**CLINICAL MESSAGE 2: More is not better.**  
BWST 2 times per week for 6 weeks was as effective at increasing walking speed and endurance; and more effective at increasing LE strength than combined programs provided 4 times per week.  
Consistent with the overtraining literature, LE strength training alternated daily with moderately high BWS treadmill walking interfered with LE strength gains.

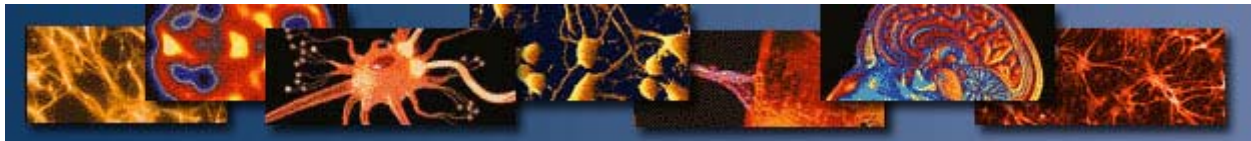
**Implications for Neurorehabilitation:**

- Neuroplasticity can be driven by high intensity, task-specific training that includes acquisition of motor skills.
- Functional recovery that results in clinically meaningful gains requires a multi-faceted rehabilitation program that includes:
  - Task-specific repetitive task of walking (BWST) or upper limb task-practice (CI therapy).
  - Exercise programs must be designed that address patient limitations and available resources.
  - Exercise specificity and intensity are critical to get a training effect and to induce changes in the nervous system.

**What are the exercise parameters that ensure training intensity?**

- Dose-response:
  - Frequency – number of training sessions in a week
  - Intensity – within session attributes
    - time in activity
    - level of activity
      - energy expenditure
    - progression
  - Duration of training – total number of training sessions

***FUTURE DIRECTIONS IN  
NEUROREHABILITATION***



**Train the Brain:  
Clinical Strategies for Post-Stroke Recovery**

**ALBERTA PROVINCIAL STROKE STRATEGY**

Alberta Children's Hospital  
Calgary, Alberta, Canada  
May 1, 2008

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