NEUROPLASTIC RESPONSES TO REHABILITATION IN CHILDREN AND INFANTS WITH CEREBRAL PALSY

Thubi H. A. Kolobe, PT, PhD, FAPTA
University of Oklahoma Health Sciences Center
Department of Rehabilitation Science
hkolobe@ouhsc.edu

Why Neuroplastic Responses?

• PT Interventions for children with an injured brain:
  – Persistent mixed results.
  – Small magnitude of change or gains
  – Sustainability
  – Outcomes and outcome measures.
  – Structure-function relationship
  – Cost
    – Huang et al., 2009; Mockford et al., 2008; Harris, 1997.

Major Contributing Factors

• Heterogeneity of diagnoses and functional levels
• Differential responses to interventions (age maturation and family attributes)
• Limited understanding of the mechanism involved
• Lack of sensitive and responsive outcome measures.
• Intervention-related dosing

Why Neuroplastic Responses?

• Relieving spasticity is not sufficient therapy to cause long term change (Hoare et al., 2010).
• Repetition not be sufficient to attain meaningful changes in motor behavior if participants are not actively engaged in an intervention (Kleim and Jones, 2010).
• Pathophysiologial evidence for decreased cortical inhibition and results of increasing inhibition (Benninger et al., 2011)
• Evidence that you gain what you train (Sakzewski et al., 2011)
• Development in brain imaging technology and capability.

Acknowledgements

• National Institute of Child and Human Development
• National Institute of Neurological Disorders and Stroke
• APTA Section on Pediatrics
• Research Summit III Participants

Structural and Behavioral changes: The disconnect

• What is motor learning without a good motor?
• Threshold for change
  – Cortical reorganization and function
  – Changes in muscle structure and gait
  – Sustainability
  – Mechanisms for adaptive learning
  – Level of influence
Institute of Medicine, 2009

“By 2020 -- 90% of clinical decisions will be supported by accurate, timely, and up to date clinical information, and will reflect the best available evidence on what works for whom, under what circumstances”

Translation

• We can pick efficacious interventions
• We know their parameters:
  - How much for whom
  - How long
  - Feasibility
  - Outcomes
  - Mediating effect
  - Cost

Translation

• The optimal dose for interventions and for clinically important change.
• The optimal dosage and interventions to improve to improve body structure and function, activity, and participation.
• How treatment outcomes are attained.
• How treatment outcomes are sustained
  - The mechanism involved (structure-to-behavior change or vice versa)

Dosing

• Frequency (how often, number of sessions for a given intervention/day/week/month)
• Intensity (how hard, such as the number of repetitions per minute, day, week, or amount of work)
• Time (onset and duration)
• Type of an intervention (includes task practice, behavioral shaping, structured vs. unstructured training, and amount of feedback or reward).

American Council on Exercise, 2003

Research Summit III (RS III)

• Goals:
  - Platform for research development
  - Method to secure position for PT in rehabilitation, prevention, health promotion, and health services research for children with or at risk for disabilities and their families
  - Opportunity for creating networks among PT researchers and other disciplines
  - Mechanism to develop multi-site research programs across multiple disciplines that is led by PT researchers
  - Catalyst to move the PT research field forward

RS III (2011) Participants

<table>
<thead>
<tr>
<th>FACULTY</th>
<th>PhD</th>
<th>PT</th>
<th>Non-PT</th>
<th>CLINICIANS</th>
</tr>
</thead>
<tbody>
<tr>
<td>24**</td>
<td>22</td>
<td>26 (56%)</td>
<td>20 (44%)</td>
<td>6**</td>
</tr>
</tbody>
</table>
Key Questions
- HOW MUCH of WHAT should be done for WHOM?
- BY WHOM? Does all need to be done in therapy?
- HOW LONG? Are we talking Antibiotics (short term) or Insulin (forever)?
- Is the optimal dose compatible with real life?
- Role of technology in providing or augmenting dose?
- HOW TO MEASURE how much is enough? Behavior vs. biomarkers.
- How to afford or fund what may be needed?

Opportunity
- Translational Research
- Knowledge Translation

Intervention-Related Dosing
- Key mediator
- Multifactorial Parameters:
  - Brain, Muscle, Bone, and Family functioning
- Interactions:
  - Active ingredients
  - Biomechanical, neuromuscular, psychological, cognitive

Research Recommendations
- A treatment must first demonstrate effectiveness before dose-related studies can be undertaken.
  - Multisite trials
  - Dosing thresholds – titration
  - Sustainability – linking structure and behavior
  - Uptake of intervention – repeated measures
  - Child and family engagement – self-efficacy

Practice Recommendations and Implications
- Systematic implementation and documentation of current treatments and treatment parameters
  - Ask a dosing question
  - Transfer from therapy sessions to life situations
  - Staging OT/PT Interventions
  - Standardizing outcomes
  - Models of care
  - Collaboration and research

“Viable Interventions”
- CIMT, mCIMT, HABIT
- Treadmill training
- Botox and exercise
- Task oriented practice/ training
  - Augmentative interventions (technology and robotics)
Can we train the brain?

- Evidence of neuroplasticity
- Cortical Reorganization

Current and novel rehabilitation protocols

- Prone locomotion
- Upper extremity
- Infant reaching
- Walking

Self-Initiated Prone Progression

- The earliest type of functional mobility available to infants -- severely compromised in children with CP.
- Develops during a period of highly active synaptic formation in the brain.
- Development during infancy linked to other systems, such as vision, arousal, vestibular function, and perceptual-cognition
- Not responsive to traditional interventions

Self-Initiated Prone Progression

Robotics and Movement Learning:

- Bypass early mobility constraints
- Early initiation of training before the age of expected emergence of or independence in skill
- Theories: Neuronal group selection, motor learning and development, and perception-action

Self-Initiated Prone Progression

Integration

- Brain imaging
- Kinematics
- Kinetics
- Performance behavior
- Skill

THANK YOU!
What is the Right Dose of Therapy?

Andrew M. Gordon, Ph.D.

TEACHERS COLLEGE
COLUMBIA UNIVERSITY

References

• Gordon, AM, Hung, YC, Brandao, M, Ferri, CL, Kuo, H-C, Frie, K, Petra, E, Chinman, A.


Motor Learning

• Children with CP have impairments in motor planning and learning above and beyond impairments in motor execution (e.g., Gordon and Duff 1999; Duff & Gordon 2003; Shelway-Cook et al. 2003; Hung et al. 2013).
• However, they do improve with practice, but only with lots of practice (Neilson et al. 1990; Valvano & Newell 1998; Gordon et al. 1999; Hung et al. 2013).
• Thus, INTENSITY MATTERS!
• How can we provide opportunities for intensive practice?
• What is the “right dose of therapy”?
• What therapies should we dose?

Successful upper extremity training protocols

How can we improve hand function?

Basic Science
• Mott-Sherrington (1895)
• Munk (1909)
• Ogden and response in small increments (successive approximations; Franz, 1917)
• Tower, German, Taub
• Merzenick, Nudo, Jones, Shallert, Kleim

Adult Stroke
• First human studies of forced use: Ostendorf and Wolf (1981), Wolf et al. (1989)
• First human studies of CIMT- Taub et. al. (1993)
• Extremity Constraint-Induced Therapy Evaluation (EXCITE) multi-site randomized clinical trial (e.g. Wolf et al. 2006 JAMA; 2007; etc)
Reviews:
• > 80 studies of peds CIMT, >30 RCT


CIMT studies in CP

• It works!
• It works in young and older children
• It works when given 24/7 or just 2 hrs/day (in young children)
• It works with casts, slings, gloves, and no restraint whatsoever
• It works one-on-one, at home, in preschool, in day camps
• No evidence that any specific model of CIMT demonstrates greater improvement than another.

International consensus meeting on pediatric CIMT, January 2012, Stockholm, Sweden

CIMT (day camp model)

• 26 CIMT/Bimanual training day camps at Columbia University since 2002
• >180 children (age 3.5 to 17yrs), with many repeating
• 6hrs/day, 10-15 days
• BE AS CHILD-FRIENDLY AS POSSIBLE
• Functional and play activities
• 1:1 interventionist/child ratio
• Repetitive (part) Practice
• Task (whole) Practice
• Feedback: Positive Reinforcement
• Home practice
• Logs

Dosing

Eliasson et al. (In Press)

Eliasson et al. (In Press)

Eliasson et al. (In Press)

Eliasson et al. (In Press)
Dosing

So CIMT is not a one-time miracle.
Intensity can be distributed over development

---

Rationale for bimanual control

- Even “less affected” hand is affected.
- Many bimanual movements may have never been practiced.
- Impaired ability to coordinate both hands together (Hung et al., 2004, 2010).
- Unlike unilateral impairments, these bimanual coordination problems may underlie some of the functional limitations these children experience.
- ~85% of parent goals found to be bimanual (Gordon et al., 2011, Brandao et al., 2012).
- During bimanual movements the non-involved hand could provide a template for the involved hand when movements are either performed sequentially (Gordon et al., 1999, 2006; Razhavan et al., 2006) or simultaneously (Utley et al., 2004, Steenbergen et al., 2008).

---

Hand-Arm Bimanual Intensive Therapy (HABIT)

- No restraint
- Same duration as CIMT (2-3 weeks)
- Bimanual activities (e.g., cards, wrapping presents, video games, ball throwing, zipping a jacket)
- Day camp (1-1 interventionist-child)

Task Designation
- Stabilizer
- Passive/active assist
- Manipulator


---

Randomized trial comparing CIMT and bimanual training (HABIT) that maintains the intensity of practice associated with CIMT

n=42, 90hrs training
Hypothesis: participants in the CIMT group will have greater improvements in unimanual dexterity whereas participants in the bimanual training group will have greater improvements in bimanual hand use—i.e., specificity of training.

Gordon et al. (2011), Neurorehab & Neural Repair
No specificity of training

![No specificity of training graph](Gordon et al. (2011), Neurorehab & Neural Repair)

Specificity of training

Movement overlap of the two hands increases after bimanual training.

![Specificity of training graph](Hung et al. (2011))

Goals

![Goals graph](Brandao et al. (2013))

Dosing

![Dosing graph](Gordon 2011 DMCN)

Cortical representations

- Single-pulse TMS mapping, Magstim 200 stimulator, figure-8 coil.
- Co-registered TMS stimulation sites to individual MRIs,Brainsight software.
- Recorded EMG in digit, wrist, and biceps muscles bilaterally during TMS.
- Mapped hand representation bilaterally, 1 cm intervals, centered around spot of greatest activation of digit muscle.
- Mapping intensity – 110% pre-training motor threshold.
- Same TMS intensity used before and after training.

![Cortical representations](Friel et al. (In Preparation))
Skill training

- Newly learned movements are represented over large cortical areas (e.g., Kleim et al. 1998, Plautz et al. 2000)
- Active training vs. “forced use” in feline model of hemiplegia (Friel et al. 2012).
- “repetitive motor activity alone does not produce functional reorganization of cortical motor maps… Instead, motor skill acquisition, or motor learning, is a prerequisite factor in driving representational plasticity in motor cortex” (Nudo 2003).

Does structured practice matter?

- RCT of 24 children, age 6-14yrs
- Structured practice group: Environmental constraints manipulated, skill progression, part-practice (shaping), goal-directed.
- Unstructured practice group: Bimanual play
- Day-camp environment, 6 hrs/day, 15 days
- AHA, Jebsen-Taylor, Abilhand-Kids, COPM
- Testing immediately before and after tx, 6-months
- Evaluator and interventionists blinded

Similar improvements regardless of practice type

Hand-Arm Bimanual Intensive Therapy Including Lower Extremity (HABIT-ILE)

- LE abilities may decrease during development in CP
- Interactions between UE and LE are rarely trained despite importance in everyday life
- We aimed to modify HABIT to include a systematic lower extremity and / or postural component
- Compare intensive HABIT-ILE with usual and customary (NDT-based) PT of equal duration.
Feasibility of a Home-based Hand-arm Bimanual Intensive Training for Young Children with Hemiplegic Cerebral Palsy

Summary

- Intensive (active) training works!
- Just increasing the dose of usual and customary (NDT-based) care does not benefit the child—ingredients matter!
- Both CIMT and bimanual training improve unimanual and bimanual function similarly in children with unilateral CP with some nuances (see also recent studies by Sakzewski, Wallen, Facchin, Hoare, Deppe).
- Not mutually exclusive of each other, and can perhaps be combined over time as seen fit.
- Skill training may enhance plasticity in motor cortex

Summary (cont.)

- Lower extremity benefits from combined UE and LE targeted intensity
- Dosing—more is better, but not more of the same, and it does not have to be delivered all at once!
- How do you get to Carnegie Hall?
  - PRACTICE!
  - Practice a lot, but practice the instrument you want to play!
**Acknowledgements**

Marina Boniface, GT, PhD, Ya-Chen Hong, PT, DPT, Chris Kae, PT, Chiradu Pappu, MS, Jobin Chinnan, PT, Joseph Chive, PT, DPT, Sashi Sundaram, Eugene Bozicikowski, PT, PhD, Vincent Hsia, PhD, PT

Kathleen Friel, PhD, Sarah O’Keefe, M.D., Juan Caravello, M.D., Marina Brandao, OT, PhD, Ya-Chen Hong, PT, DPT, Chiradu Pappu, MS, jobin Chinnan, PT, Joseph Chive, PT, DPT, Sashi Sundaram, Eugene Bozicikowski, PT, PhD, Vincent Hsia, PhD, PT

Kathleen Friel, PhD, Sarah O’Keefe, M.D., Juan Caravello, M.D., Marina Brandao, OT, PhD, Ya-Chen Hong, PT, DPT, Chiradu Pappu, MS, jobin Chinnan, PT, Joseph Chive, PT, DPT, Sashi Sundaram, Eugene Bozicikowski, PT, PhD, Vincent Hsia, PhD, PT

Volunteers

Supported by:

http://www.facebook.com/CerebralPalsyResearch

E-mail: ag275@columbia.edu

---

**Neonatal Stroke, Hemiparesis, Clinical Protocols**

Jill C. Heathcock, MPT, PhD
Assistant Professor
Division of Physical Therapy

---

**Typically Developing Infants and Young Children**

- Development of the Nervous System
- Critical Periods
  - Activity dependent myelination in first year of life
  - Activity dependent tract development and refinement in first 3 years (Martin 2005)

---

**Infants with Neonatal Stroke**

- Injury
- Risk factors
- Hemiplegia
- Reaching

---

**Neonatal Stroke**

- Brain Structure
  - Non-sedation MRI
- Reaching deficits as children with hemiparesis
- Spontaneous Arm Movements
  - Kinematics
Motor learning and the development of reaching skill

- Typically developing infants
  - Independently explore environment
- Reaching with the hands
  - 3-6 months (Gesell 1947, Thelen 1993)
- Role of spontaneous movements
- Midline behaviors
  - Precursor to reaching (Galloway, 2004)
  - March to midline

Neonatal Stroke

- Brain ischemia or hemorrhage during perinatal stage
- Focal interruption of blood supply, occurring between 20 weeks of fetal life through 28th postnatal day (Lynch 2009)

Neonatal Stroke

- Clinical presentation:
  - Seizures
  - Signs and symptoms of neonatal encephalopathy
  - Delayed milestones
- Outcomes
  - Died from the stroke: 3%
  - Neurologically normal: 40%
  - Motor and/or cognitive deficits: 57% (Lynch, 2001)

Neonatal stroke is an important contributor to the pathogenesis of cerebral palsy

Cerebral Palsy

- Hemiplegic cerebral palsy is the most common type of CP in stroke infants
- Asymmetric motor performance between both sides
  - Upper limb involved more
  - Distal part is more severe

Reaching

- Reaching is an important functional ability and may related to other motor performance (Fallang, 2003)
- To compare reaching development in infants with and without neonatal stroke.
**Reaching Experiment**

Healthy Control group (n=16)

- Main visit effect (p<0.001). Reaching number increased over time on both sides.
- There is no significant difference between right and left side on reaching number in the bilateral reaching condition (p=0.734).

**Grasping Experiment**

- Main visit effects for visit and group, p < 0.001
- p = 0.029
- Neonatal stroke demonstrated less bi-manual toy manipulation

**BSID-III**

- Fine Motor
- Raw Scores
- Gross Motor
- Raw Scores

**Target Training and Dose**

- Home Program
- Daily (5 days/week) for 10 minutes
- 20 weeks
  - 75% journal

**Training**

- Specific Movements
  - Bilateral
  - Rationale
    - Midline experience may be necessary for reaching (van Hof, 2002)
    - Children with hemiparesis have poor bilateral reaching skills (Utley, 2006)
    - Poor Midline behaviors in preliminary project
Training

- Specific Movements
  - Single joint (Bhat, 2006)
  - Rationale
    - Infants with brain injury infants show increased coupling as compared to full term infants (Heathcock, 2005, Heriza 1996, Vaal 2000, Jeng 2004)
    - Children with hemiparesis show poor dissociation (Ronnqvist, L, 2007)

Children with Hemiparesis

- Transcranial Magnetic Stimulation (TMS)
- Task-- reaching to a target
  (photo)

Effects of Training-Pilot

- Reaching
- Grasping

Kinematics of reaching

- Case series

Combination Therapies

TMS  CIMT

Feet Reaching
Lower Extremity

- **ARMS**
  - Full-term infants reach with their hands when they are three to six months of age
  - Preterm infants show delays in reaching even when age-corrected for preterm birth
    - Improved ability after several weeks of training

- **LEGGS**
  - Full-term infants display adequate control of their legs to repeatedly reach out and contact a stationary toy with their feet
    - Several weeks before they do so with their hands
    - Improve this ability after several weeks of training

Galloway et al, 2004 and Lobo et al, 2005

Purposeful Control of the Legs

- Full-term infants begin to gain purposeful control of their legs within the first months of postnatal life
  - Two most commonly studies leg behaviors
    - Spontaneous kicking
      - No external feedback
      - Developmental progression
    - Instrumented kicking
      - Significant external feedback

Type

- Social Group

Treadmill Training

- Infants
  - Novel Therapies
  - Case studies
  - Real time
    - Spina bifida
    - Full-term (healthy)
  - Sensory Input

Both groups contacted the toy multiple times in the first session. There was an increase in the number of contacts over time. Infants in the Movement group contacted the toy more frequently than the Social group.
What is the optimal dosage to improve to improve functional ambulation?

- Manuscripts
  - Protocol Ranges
    - 4 – 30 minutes
    - 2 – 5 days per week
    - 12 weeks – 30 weeks
    - Gait speed
      - Target: normal speed for age
      - Adjusted each session
    - Home vs. Clinical setting
    - Weights

- Outcomes
  - Varying Protocol
  - Limited description of Intervention
  - Locomotor Training vs. or in addition to BWSTT
  - Span ICF
    - but inconsistently
    - Limited, if any, neuroplastic changes

- Improvements
  - Independent Steps
  - Distance
  - Gait Impairments
    - Velocity, stride length,
    - Muscle activation
    - Coordination
    - Joint kinematics
  - Level of activity
  - Level of participation
  - Neuroplasticity with MRI

- High(er) Dosing Clinical Protocols
  - STRIVE
    - Skilled Therapy focused on Repetition, Intensity, Variable practice, and Education
  - Existing intensive therapy programs
    - Treadmill training for older, ambulatory children
    - CIMT for children with hemiplegia
  - Lack of an intensive therapy program for younger children and those who are non-ambulatory
    - Inspiration

- Dose
  - 2 hours per day * 5 days per week * 4 weeks
  - 40 hours total
- Patients (n=18)
  - Age
    - Mean = 26.39 months (SD = 11.75 months)
    - Range = 11.2 to 50.1 months
  - Diagnoses
    - Cerebral Palsy (n = 15)
    - Developmental Delay (n = 2)
    - Myelomeningocele (n = 1)
Results

Conclusions

- STRIVE protocol appears to improve gross motor function in young children with cerebral palsy
  - 10 of 14 had a clinically meaningful change in GMFM-66
- Younger age associated with greater changes
- May impact multiple domains of development

Acknowledgements

- Warren Lo, MD
- Nasser Kashou, PhD
- Chiao Ying Chen, MS
- Ann Cahalan
- Hanna Song
- Sara Mrowinski, SPT
- Sarah Hendershot, DPT
- Rachel Ferrante, DPT
- Kathleen Stuart, DPT
- Helen Carey, PT, MS, PCS

How do we facilitate neuroplasticity & optimize motor learning?

Laura Prosser, PT, PhD

The Children's Hospital of Philadelphia

Neuroplasticity & Infant learning

<table>
<thead>
<tr>
<th>Rehabilitation/ Learning principle</th>
<th>Integration into therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Therapy is delivered at a young age and in the beginning stages of upright mobility</td>
</tr>
<tr>
<td>Verbal</td>
<td>Many different motor activities are encouraged within each session by the therapist</td>
</tr>
<tr>
<td>Error experience</td>
<td>Frequent transitions among activities</td>
</tr>
<tr>
<td>Silent</td>
<td>Participants are not prevented from falling or losing their balance by either the therapist</td>
</tr>
<tr>
<td>Salient</td>
<td>Enencouragement of challenging tasks inherently encourages error</td>
</tr>
<tr>
<td>Immune</td>
<td>Maximum possible motor play with freedom of exploration in encourage self-</td>
</tr>
<tr>
<td>Challenging</td>
<td>Qty. of time these infant spend practicing upright activities is not independent with them</td>
</tr>
</tbody>
</table>

Motor learning during the development of walking skill

Prosser LA, Ohlrich L, Curatolo LA, Alter KA, Damiano DL
Rehabilitation Medicine Department, NIH Clinical Center, Bethesda, MD

Current strategies for gait training

- “Perfect” practice
- Regimented locomotor training programs
- Devices that compensate for poor postural control

Early Mobility Training

- 3x/week for 6 weeks
- 30 min of varied mobility training with dynamic weight support
- Mimic typical toddler motor play/exploration
- All sessions videotaped for later coding by activity

Why Dynamic Weight Support?

- Movement constrained strap length
- No postural error allowed
- Not able to mimic typical toddler walking
- Unconstrained movement
- Allows postural error and falls*
- Can closely mimic typical motor development*

Study Design

Single-subject design with repeated measures during baseline and treatment phases
<table>
<thead>
<tr>
<th>ID</th>
<th>Age (yrs)</th>
<th>Cause of CP</th>
<th>GMFCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>Preterm (30 wks)</td>
<td>III</td>
</tr>
<tr>
<td>2</td>
<td>2.3</td>
<td>Preterm (30 wks)</td>
<td>III</td>
</tr>
<tr>
<td>3</td>
<td>1.4</td>
<td>Cerebral infection at birth</td>
<td>II</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>Hypoxia at birth</td>
<td>III</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>CVA near birth</td>
<td>I</td>
</tr>
</tbody>
</table>

Introducing error and movement variability

21 month old, GMFCS II

Therapy 1

Wk 6 (Pre-tx)

Wk 8 (After 2 wks of tx)

27 month old, GMFCS III

14 month old, GMFCS III

15 month old, GMFCS I
Gross motor function

Changes attributable to treatment in 4/5

Motor development rates

Are the changes related to treatment activities?

Outcomes by GMFM sub-scale

Acknowledgements

How do we best deliver and dose rehabilitation interventions?
### Dosing Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>100s to 1000s+ repetitions&lt;br&gt;More than competing movement pattern?&lt;br&gt;(Some intermittent rest needed for consolidation)&lt;br&gt;Need to be creative to achieve high dose</td>
</tr>
<tr>
<td><strong>Intensity</strong></td>
<td>Physical challenge with mental engagement</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>Duration: Months&lt;br&gt;TIMING: Earlier vs. later?</td>
</tr>
<tr>
<td><strong>Type</strong></td>
<td>Functional context&lt;br&gt;Allows repeated practice&lt;br&gt;Encourages active engagement</td>
</tr>
</tbody>
</table>

### References