Cortical Electrical Stimulation Enhances Structural Plasticity and Functional Recovery in Rat Models of Ischemic Stroke and Traumatic Brain Injury

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Methods

Monopolar electrode

Electrode Placement

SMC Lesion

Non-Impaired

Impaired

Tray Reaching Task

Skilled Reaching Task
CS During Rehabilitative Training (RT) Improves Skilled Motor Function....Sometimes
CS+RT Improves the Quality of Reaching Movements

Combined categories: Grasp, Supination I, Supination II and Release.
CS+RT Increases Synaptic Density in Peri-lesion Cortex

CS + RT increases synaptic density in peri-lesion cortex.
Benefits of CS+RT after Ischemia

1. Improves the efficacy of rehabilitative training in rats, non-human primates and humans (in some cases).
2. In rats, improves functional recovery acutely and chronically (~40 weeks post rehab).
3. Improves quality of reaching movements.
4. Increases
   - Area of motor map representations (rat and non-human primate)
   - Synaptic density
   - Excitatory synapses
   - Dendritic processes
   - Density of peri-lesion neurons
   - Volume of motor cortical subregions

(Adkins-Muir and Jones, 2003; Adkins et al., 2004; Adkins et al., 2008; Kleim et al., 2003; Teskey et al., 2003; O’Bryant et al., 2010; see also Brown et al., 2006; Plowman et al., 2009)
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CS+RT Limitations after Ischemia

1. CS+RT induced functional improvements are not generalizable to non-rehab motor tasks.

2. Constraint Induced Movement Therapy like behavior in rats does not improve performance.

3. CS+Rehab imitated in the chronic period has reduced effects.

4. CS+Rehab in humans may not be effective if movement thresholds cannot be obtained.

5. CS+RT in severely impaired animals may not improve behavior.
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CS+RT Limitations after Ischemia

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Skilled Reaching after CCI over Motor Cortex

![Graph showing % Success over Day Post-Injury for Sham and CCI conditions.]

- **Sham Avg**
- **CCI+Yoked**

Day Post-Injury:
- 0
- 3
- 7
- 10
- 14
- 21
- 25
- 29
- 35
- 42

% Success:
- 0
- 10
- 20
- 30
- 40
- 50
- 60
- 70
- 80

Single Pellet

Sham

CCI
Skilled Reaching after CCI over Motor Cortex

![Graph showing % Success over Day Post-Injury for Sham, CCI, and CCI+RT conditions.](image-url)
EXPERIMENTAL DESIGN & METHODS

Pre-operative reach training & assessment → SMC CCI + Epidural Electrode → NoCS + Rehab Train
                           CS + Rehab Train → Weekly Reaching Assessment → ICMS

Contacts

Ground

Non-Impaired

Impaired

Electrode Placement

CCI

MI

FL

SI
Cortical Stimulation and Motor Rehabilitative Training

Performance on the Single-Pellet Reaching Task

% Successful reaches per attempt

Pre-TBI  Pre-RT  1  2  3  4  5  6  7  8  9

Assessment after week of RT

CS+RT  RT Only
CS+RT Expands Wrist Representation

Forelimb Representations in TBI–Injured Motor Cortex

Area of SMC mm²

<table>
<thead>
<tr>
<th></th>
<th>Wrist</th>
<th>Elbow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS+RT</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>RT only</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* Significant difference

Lesion

Electrode
CS+RT Following TBI

1. Significantly improves the efficacy of rehabilitative training in rats but it is not optimal.

2. Increases
   - Area of wrist representation in injured motor cortex
   - Dendrites in subregion of motor cortex

3. No Changes
   - Neurite outgrowth inhibitor (Nogo)
   - Volume of injury
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Future Studies

• Determine optimized parameters for CS+RT following TBI.

• functional changes, especially in relationship to age and injury severity.

• Investigate whether CS+neurorehabilitation in animal models of stroke and TBI-induced cognitive impairments improves episodic and working memory.

• Investigate whether CS+oral motor practice improves injury-induced deficits in vocalization.

• Investigate whether non-invasive CS chronically improves motor and cognitive function.
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Translate findings from animal models into treatments for survivors of stroke and TBI
Thank You

Dr. Theresa Jones & Lab
  Hannah Combs (undergraduate research assistant)
  Nicole Donlan (Lab Manager - Nogo & mapping)
  Dr. Stephanie Jefferson (immunohistochemistry)
  Joel McMillian (undergraduate research assistant)
  Kelly Tennate (graduate student - mapping)

Dr. Dorothy A. Kozlowski & Lab
  Lindsay Ferguson (initial TBI behavior work)
  DoD funding

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  NIH/NINDS R01 NS065866-01A1
  NIH/NINDS R21 NS064423-01
Summary & Conclusions

- TBI reduces behaviorally-linked neural plasticity in contra-cortex compared to similarly sized and placed strokes.

- Following CCI to SMC, behavioral function is most enhanced by combining tray reaching, exercise, and forelimb constraint.

- Unlike what is seen in animal models of stroke, individual therapy such as reaching, or reaching combined with exercise were not beneficial overall to the recovery of forelimb function.

- The combination of all three therapies increase motor map plasticity compared to controls.
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- This study demonstrates that neural plasticity may be limited following TBI and that the rehabilitation protocol required to produce behavioral enhancements may be more extensive than that seen in a similarly sized lesion due to stroke.
“Upper extremity” impairments

Schallert Cylinder Test

Right limb impaired
MODEL SYSTEM

Unilateral Lesion

FL - Forelimb representation area

impaired
Evidence of axonal degeneration, increased IEG expression

Structural evidence of enhanced synaptic efficacy
Motor learning and Neural Plasticity

Acrobatic training:
↑ synapse number per neuron in layers II/III and V of the motor cortex (Kleim et al., 1996; Jones et al., 1999).

Skilled reach training:
↑ length and complexity of dendrites in layer II/III & V (Greenough et al., 1985; Withers & Greenough, 1989).

Expansion of motor maps (e.g., Kleim et al., 1998).

↑ synapse number per neuron (Kleim et al., 2004).
Experience-Injury Interactions
Movement Analysis: Prior to Grasping

- Aim/Digits Semi-flexed
- Advance/Digits Open

Combined categories: Digits Semi-Flexed, Aim, Digits open and Advance
Neuronal Density in the Remaining Motor Cortex

NoCS  |  CSAnod  |  CSCath

Peri-lesion Neuron Density (10^4/mm^3)

<table>
<thead>
<tr>
<th>NoCS</th>
<th>CSAnod</th>
<th>CSCath</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
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Rehabilitation Protocol - Data from Kozlowski’s lab (i.e., Lindsay Ferguson)

<table>
<thead>
<tr>
<th>Rehabilitation Task</th>
<th>Post Injury 3-10</th>
<th>Post Injury 10-14</th>
<th>Post Injury 14-20</th>
<th>Post Injury 20-42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaching (daily)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exercise (daily)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Forelimb Constraint</td>
<td>X</td>
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CCI-FL-SMC

Reaching

Exercise

Forelimb Constraint
How do motor maps reorganize?
Neural Plasticity after Brain Damage

Behaviorally-induced

Injury-induced
Rehabilitative Training Improves Function in the Impaired Forelimb
