Neural Plasticity: Foundation For Neurorehabilitation

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“….the phenomena of habit in living beings are due to the plasticity of the organic materials of which their bodies are composed ….nervous tissue seems endowed with a very extraordinary degree of plasticity.” (William James, 1887).
The Paradigm Shift In Neurorehabilitation

The diagram shows the increase in the number of papers related to neural plasticity and neurorehabilitation over the years from 1965 to 2010. The number of papers related to neural plasticity has steadily increased, while the number of papers related to neurorehabilitation has shown a significant spike around 1980 and has continued to increase significantly since then.
Rehabilitation Is A Relearning Process

Learning

Relearning
Neurorehabilitation: *Exploiting Neural Plasticity*

Behavioral Signals

Neural Signals

Neural Plasticity

Functional Improvement

(Kleim, 2012)
Why Do Animal Studies Always Work?

Salience
Intensity
Specificity

Repetition
Difficulty
Timing
Behavioral Signals

- Salience
- Repetition
- Intensity
- Timing
- Specificity
- Difficulty

Plasticity

Kleim et al., 2012
The Inadequacy Of Existing Programs

- less than 10% of all stroke patients have access to rehabilitation programs that can induce meaningful improvements.

-of those that do receive therapy, most receive 1/6th of the therapy required to induce meaningful improvements.
Why Can’t We Achieve This In Human Patients?

Behavioral Signals

Neurorehabilitation

Neural Signals

Fatigue  Spasticity  Attention  Depression  Limited Time

Neural Plasticity

Functional Improvement
Can We Achieve This In Human Patients?

Active Movement Repetitions

![Graph showing active movement repetitions over sessions.]

ARAT

![Graph showing ARAT scores over time.]

- B1, B2, B3
- 1, 2, 3, 4, 5
- P1, P2

Time
The More Repetition The Better The Improvement

Repetition And Motor Improvement

<table>
<thead>
<tr>
<th>Change In ARAT</th>
<th>Total Number of Repetitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>8000</td>
</tr>
<tr>
<td>20</td>
<td>7000</td>
</tr>
<tr>
<td>15</td>
<td>6000</td>
</tr>
<tr>
<td>10</td>
<td>5000</td>
</tr>
<tr>
<td>5</td>
<td>4000</td>
</tr>
<tr>
<td>0</td>
<td>3000</td>
</tr>
</tbody>
</table>

The scatter plot shows a positive correlation between the total number of repetitions and the change in ARAT score.
Constrain Induced Movement Therapy

Intensity: 6 hours/day.

Repetition: 10-15 days.

Difficulty: shaping on progressively harder tasks

Salience: ADL tasks.
Gray Matter Changes With Rehabilitation

CI Therapy

Comparison
Constraint Induced Language Therapy (CILT)
Western Aphasia Battery

Repetition

Action Naming
CILT Enhances Arcuate Fasciculus Integrity

Pre-CILT

Post-CILT
15 Sessions (Repetition)
90 Repetitions/Session (Intensity)
Progressively increased range of motion (Difficulty)
Pronation/grasp movements (Timing/Specificity)
Visually Guided (Salience)

Hand Wrist Assistive Rehabilitation Device (HWARD)

Takahashi et al., 2009
Hand Wrist Assistive Rehabilitation Device (HWARD)

Takahashi et al., 2009
SMART- Arm

Timing
Specificity
Intensity
Repetition
Difficulty
Salience

Drives recovery
Motor Assessment Scale Distance Reached

<table>
<thead>
<tr>
<th>MAS (score)</th>
<th>Distance (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>20</td>
</tr>
<tr>
<td>Post</td>
<td>30</td>
</tr>
<tr>
<td>2 Months</td>
<td>40</td>
</tr>
</tbody>
</table>

SMART Control

- Baseline: 1.0
- Post: 2.0
- 2 Months: 3.0
Neurorehabilitation: *Exploiting Neural Plasticity*

- **Behavioral Signals**
  - Neurorehabilitation
- **Neural Signals**
  - Neurorehabilitation
- **Neural Plasticity**
- **Functional Improvement**
Clinically Exploiting Neural Signals

**Neurophysiological:**
- rTMS
- TDCS

**Neuropharmacological:**
- L-DOPA
- Fluoxetine
Cortical Stimulation
Transcranial Direct Cortical Stimulation (TDCS)
## Transcranial Direct Current Stimulation

<table>
<thead>
<tr>
<th>Study</th>
<th>Measure</th>
<th>Result</th>
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<tbody>
<tr>
<td>Hummel (2005)</td>
<td>Jebsen</td>
<td>✓</td>
</tr>
<tr>
<td>Hesse (2007)</td>
<td>Fugl-Meyer</td>
<td>✓</td>
</tr>
<tr>
<td>Boggio (2007)</td>
<td>Jebsen</td>
<td>✓</td>
</tr>
<tr>
<td>Klm (2010)</td>
<td>Fugl-Meyer</td>
<td>✓</td>
</tr>
<tr>
<td>Lindenberg (2010)</td>
<td>Fugl-Meyer</td>
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<tr>
<td>Geroin (2011)</td>
<td>6 Min walk</td>
<td>✓</td>
</tr>
<tr>
<td>Madhavan (2011)</td>
<td>Tracking accuracy</td>
<td>✓</td>
</tr>
<tr>
<td>Tanaka (2011)</td>
<td>Knee extension</td>
<td>✓</td>
</tr>
<tr>
<td>Bolognini (2011)</td>
<td>MAL/Fugl-Meyer</td>
<td>✓</td>
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<tr>
<td>Nair (2011)</td>
<td>Fugl-Meyer</td>
<td>✓</td>
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<tr>
<td>Rossi (2012)</td>
<td>Fugl-Meyer</td>
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<tr>
<td>Zimerman (2012)</td>
<td>Digit sequence</td>
<td>✓</td>
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</table>
Fluoxetine

Fluoxetine Score vs. Days Post-Stroke

- Fluoxetine
- Placebo

(Chollet et al., 2011)
# Drug Studies In Stroke

<table>
<thead>
<tr>
<th>Drug</th>
<th>Transmitter</th>
<th>Measure</th>
<th>Citation</th>
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</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>Serotonin</td>
<td>HSS, Barthel Index</td>
<td>Dam et al., 1996</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Serotonin</td>
<td>Fugl-Meyer</td>
<td>Chollet et al., (2011)</td>
</tr>
<tr>
<td>Escitolapram</td>
<td>Serotonin</td>
<td>RBANS, WISC-R</td>
<td>Jorge et al., (2010)</td>
</tr>
<tr>
<td>L-DOPA</td>
<td>Dopamine</td>
<td>Fugl-Meyer, Barthel</td>
<td>Sonde et al., (2007)</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Dopamine</td>
<td>Gait velocity</td>
<td>Cramer et al., (2009)</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>DA/NE</td>
<td>Fugl-Meyer</td>
<td>Cirosotomo et al., (2009)</td>
</tr>
</tbody>
</table>
Can Genotype Influence Treatment Efficacy?

Behavioral Signals

Neural Signals

Neural Plasticity

Functional Improvement

Neurorehabilitation
Pharmacogenomics

-the action of 110 FDA approved drugs are influenced by *single nucleotide polymorphisms* (SNPs).

1,5000 SNPs.

All drugs previously tested in stroke trials are affected by SNPs.
Polymorphisms In “Plasticity Genes”
Human BDNF Val/Met<sup>66</sup> Polymorphism:

- 20% population is val/met (heterozygous)
- 4% population is met/met (homozygous)
- results in aberrant BDNF transport/release
(CNN) -- The next time you see a motorist obliviously straddling two lanes, don't fault bad driving, but genetics.

In a study published recently in the journal Cerebral Cortex, researcher Steven Cramer found that people with a certain gene variant performed more than 30 percent worse on a driving test than people without it.

The study by Cramer, a neurology professor at the University of California Irvine, might also help explain why there are so many bad drivers on U.S. highways: About 30 percent of Americans have the variant.

Ordinarily, when a person performs a task, a protein called brain-derived neurotrophic factor (BDNF) is secreted to the area of the brain that is associated with that activity.

The protein helps facilitate communication among brain cells and helps retain memory.
BDNF Polymorphism and Stroke Recovery

(Kim et al., 2013)
APOE Polymorphism and Stroke Recovery

(Cramer et al., 2013)
## Polymorphisms and Traumatic Brain Injury

(Weaver et al., 2012)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Measure</th>
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<tbody>
<tr>
<td>BDNF</td>
<td>Executive function, motor performance</td>
</tr>
<tr>
<td>COMT</td>
<td>Working memory, impulsivity</td>
</tr>
<tr>
<td>DRD2</td>
<td>Working memory, impulsivity</td>
</tr>
<tr>
<td>ANKK1</td>
<td>Working memory, executive function</td>
</tr>
<tr>
<td>PPPIRIB</td>
<td>Working memory, executive function</td>
</tr>
<tr>
<td>MAO-A</td>
<td>Working memory, inhibition</td>
</tr>
<tr>
<td>SHTTLPR</td>
<td>Decision making, inhibition, impulsivity</td>
</tr>
<tr>
<td>SHT6</td>
<td>Executive function</td>
</tr>
<tr>
<td>SHT1A</td>
<td>Inhibition, impulsivity</td>
</tr>
<tr>
<td>SHT2B</td>
<td>Inhibition, impulsivity</td>
</tr>
<tr>
<td>SHT2A</td>
<td>Inhibition, impulsivity</td>
</tr>
<tr>
<td>TPH</td>
<td>Aggression</td>
</tr>
</tbody>
</table>
| TPH      | Aggression                                            @
Pharmacogenomics

- Genotype 1
- Genotype 2
- Genotype 3
“Therapogenomics?”