Neural Plasticity: Encouraging The Brain To Change After Stroke

Athol Mann Lecture, May 14th, 2015

Don Beaven Fellowship

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-3 lbs
-100 Billion Neurons.
-1 x 10^15 synapses.
-110,000 miles of axons.
The Brain Breaks Down Over Time

- we lose 1.8g of brain every year after the age of 20.
Medical Advances Are Aging Us……
Stroke

- third largest killer in NZ.

- 25 strokes/day.

- 9,000 strokes/year.

- 60,000 stroke survivors.
How Do We Treat Stroke?

Clot Busters (tPA)

Rehabilitation
I. The recognition that brain injury is not an acute medical disorder.

II. Biomedical engineering is playing a key role in optimizing treatment development and delivery.

III. Our understanding of neural plasticity is guiding the development of novel, more effective therapies.
Encouraging the nervous system to change its physiological state to re-engage neural circuits into a relearning state.

Learning

Relearning
Neural Plasticity
Why should we care about neural plasticity?
Neurorehabilitation: *Exploiting Neural Plasticity*

Neurorehabilitation

Behavioral Signals

Neural Signals

Neural Plasticity

Functional Improvement

(Kleim, 2012)
Using Animal Models To Develop Therapies
Rat Model of Upper Extremity Function
Measuring Upper Extremity Function In Rats

Gross Motor Function

Fine Motor Function
Skilled Reaching
Rat Motor Maps: Intracortical Microstimulation (ICMS)
Skill learning induces map plasticity

Kleim et al., 1998
Synaptogenesis is localized to reorganized areas.....

Kleim et al., (2002).
Using Animal Models To Develop Therapies
Rat Model of Stroke

Topical Endothelin I
Rat Motor Cortex

Laser Speckle Contrast Analysis
Topical ET-1 Rat Cortex
Rehabilitation-Dependent Motor Recovery

Stroke

Rehab

No Rehab

Day

% Success

Pre 1 7 14 21 28 35 42
Electrical Stimulation Increases Motor Map Area

Kindling

LTP

Pre-Stimulation

Post-Stimulation
Cortical Stimulation & Rehabilitative Training
Phase III CS/RT Clinical Trial (Northstar: EVEREST)

- 2.5 hrs per day, 6 weeks
- 50Hz, 50% motor threshold
- up to 13mA

(Levy et al., In press)
% Patients Reaching Clinical End Point

Follow Up

Week 4  Week 12  Week 24

% Patients

Stim  Ctrl

(Levy et al., In press)
Why Do Animal Studies “Always Work”?

Salience  Intensity  Specificity
Repetition  Difficulty  Timing
Behavioral Signals Driving Neural Plasticity

Kleim et al., 2012

Repition

Intensity

Timing

Salience

Specificity

Difficulty
Patient Vs Animal Rehabilitation

Repetitions During Therapy

- Rat
- Monkey
- Patient

Time Engaged In Movement

- Kuys et al.
- Ada et al.
- Bernhardt et al.
- Latham et al.
- Bernhardt et al.

% Total Therapy Time
Why Can’t We Achieve This In Patients?

Behavioral Signals

Fatigue  Spasticity  Attention  Depression  Limited Time

Neural Signals

Neural Plasticity

Functional Improvement
This Can Be Done Clinically

Active Movement Repetitions

Repetitions

Session

ARAT

Birkenmeyer et al., 2010
The More Repetition The Greater The Improvement

Repetition And Motor Improvement

Change in ARAT

Total Number of Repetitions

Berkenmeier et al., 2010
Constrain Induced Movement Therapy

**Intensity:** 6 hours/day.

**Repetition:** 10-15 days.

**Difficulty:** shaping on progressively harder tasks

**Salience:** ADL tasks.
The Most Powerful Driver of Plasticity Is *Experience*

“Training a stroke patient to walk again is like training you for the Olympics”.

......except we are encouraged to use performance enhancers.
Clinically Exploiting Neural Signals

Neurophysiological:
- rTMS
- TDCS
- VNS

Neuropharmacological:
- L-DOPA
- Fluoxetine
Transcranial Magnetic Stimulation
rTMS To Treat Aphasia

Inhibitory rTMS

Excitatory rTMS

Khedr et al., 2014
rTMS Enhances Language Recovery Post-Stroke

Khedr et al., 2014
Transcranial Direct Current Stimulation (TDCS)
<table>
<thead>
<tr>
<th>Study</th>
<th>Measure</th>
<th>Result</th>
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<td>Hummel (2005)</td>
<td>Jebsen</td>
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<td>Hesse (2007)</td>
<td>Fugl-Meyer</td>
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<td>Boggio (2007)</td>
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<td>Lindenberg (2010)</td>
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<td>Geroin (2011)</td>
<td>6 Min walk</td>
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<td>Madhavan (2011)</td>
<td>Tracking accuracy</td>
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<td>Knee extension</td>
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<td>Bolognini (2011)</td>
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Commercially Available TDCS
Can Genotype Influence Treatment Efficacy?

Behavioral Signals
Neurorehabilitation

Neural Signals
Neurorehabilitation

Neural Plasticity

Functional Improvement
Pharmacogenomics

- Single Nucleotide Polymorphisms (SNPs).

- Affect the action of 110 FDA approved drugs.
CYP2D6 Gene Polymorphism:

- encodes the enzyme that metabolizes codeine into morphine.
- over 100 different polymorphisms.

Ultra Metabolizers
- 75% more morphine.
- 2x more likely to overdose

Poor Metabolizers
- 0% morphine
Polymorphisms In “Plasticity Genes”
Human BDNF Val/Met^66 Polymorphism:

-20% population is val/met (heterozygous)
-4% population is met/met (homozygous)
-results in aberrant BDNF transport/release
Is The BDNF Polymorphism Associated With Abnormal Experience-Dependent Cortical Plasticity?

Map 1

30 Mins Training

Map 2

(McHughen et al, 2010)
Blame genetics for bad driving, study finds

October 29, 2009 7:41 a.m. EDT

(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

- Admission
- 1 Month
- 3 Months

Mod Rankin Scale

BDNF-SNP
Control

(Kim et al., 2013)
APOE-4 Polymorphism and Stroke Recovery

(Cramer et al., 2013)
rTMS

(Chang et al., 2014)
Pharmacogenomics

Response

Dose

Genotype 1

Genotype 2

Genotype 3
“Therapogenomics?”

- Genotype 1
- Genotype 2
- Genotype 3
\[ I = C_m \frac{dV_m}{dt} + \bar{g}_K n^4 (V_m - V_K) + \bar{g}_Na m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l), \]
“When Hodgkin and I finished writing the 1952 papers, each of us moved to other lines of work because we could not see how to make progress on the mechanism of channel action. Any idea of analyzing the channels by patch clamp or molecular biology would have seemed to us to be.....science fiction.”

“The thought of applying this to patient populations was beyond science fiction.”

Sir Andrew Huxley, 1995