Neuromodulation:
Harnessing Neuroplasticity with Brain Stimulation and Rehabilitation
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Conflicts of interest

TJK: consulting income from MicroTransponder

Others: Nothing to declare
Learning objectives

1. Be familiar with forms of brain stimulation
2. Be able to identify safety and feasibility of each technique
3. Understand the purposes of using the parameters of brain stimulation
4. Translate brain stimulation research into clinical implications
Harnessing neuroplasticity to improve motor function

1. Neuromodulation tools
2. Down-regulation
3. Up-regulation
4. Hijacking neural firing patterns
5. Where are we now, where are we going, and how do we get there?
6. Discussion
Harnessing neuroplasticity to improve motor function

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What is neuromodulation?

Publications per year

![Chart showing publications per year from 1978 to 2016 for "Neuromodulation" and "Neuromodulation & rehabilitation". Source: Pubmed]
How to neuromodulate?

Healthy state

Injury

Neuroplasticity

Neuromodulation

Medications
Rehabilitation
Neuromodulation tools
Why neuromodulate?

\[ \text{E} \quad \text{I} \]

Healthy state

\[ \Sigma: \text{greater excitability} \]

\[ \text{E} \quad \text{I} \]

\[ \Sigma: \text{greater inhibition} \]

E = excitation
I = inhibition
Tools for brain neuromodulation

- Transcranial magnetic stimulation (TMS)
- Transcranial direct current stimulation (tDCS)
- Deep brain stimulation (DBS)
- Vagus nerve stimulation (VNS)
Transcranial magnetic stimulation (TMS)

- Pulsating magnetic fields on the scalp to induce an electrical current within the brain
TMS: mechanism of action

Auriat et al., 2015
Repetitive TMS (rTMS)

• Use of repetitive pulses of TMS

• Modulation
  < 1 Hz: inhibitory
  > 5 Hz: excitatory

• Safety
  Seizures, headache

George & Aston-Jones, 2010
http://www.magstim.com/clinical-solution/0/rapid2-therapy-system
Transcranial direct current stimulation (tDCS)

- Weak direct electrical current

- Modulation
  - Anode (+): $\uparrow$ excitability
  - Cathode (-): $\downarrow$ excitability

- Safety
  - Seizures, discomfort, tingling

Paulus, 2003
George & Aston-Jones, 2010
Deep brain stimulation (DBS)

• Direct electrical stimulation through electrodes implanted into the brain

• Modulation
  Change in firing patterns

• Safety
  Surgery, exacerbation of symptoms

Lewis et al., 2016
http://academicdepartments.musc.edu/psychiatry/research/bsl/dbs.htm
Vagus nerve stimulation (VNS)

- Electrical stimulation of vagus nerve through implantable pulse generator
- Modulation
  - Norepinephrine and acetylcholine
- Safety
  - Surgery, cough, hoarseness

George & Aston-Jones, 2010
http://academicdepartments.musc.edu/psychiatry/research/bsl/vns.htm
Harnessing neuroplasticity to improve motor function

1. Neuromodulation tools
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Why down-regulate?

$E$ = excitation
$I$ = inhibition

$\Sigma$: greater excitability
Dystonia and impaired inhibition

- Excessive and involuntary contractions

Writer’s cramp

Quartarone & Hallett, 2013
Dystonia and impaired inhibition

Quartarone & Hallett, 2013
Prudente et al., 2016

Focal hand dystonia

Cervical dystonia
Cortical Silent Period (CSP)

Onset

Offset

Healthy

Time (ms)

 Kimberley et al., 2009
Cortical Silent Period (CSP)

Onset

Offset

Healthy

Dystonia

Time (ms)

Shorter CSP = decreased inhibition

Kimberley et al., 2009
rTMS in focal hand dystonia

• Groups:
  Experimental: writer’s cramp (n=9)
  Control: healthy adults (n=7)

• rTMS: 0.2 Hz, 1 session

• Targets: primary motor cortex, premotor cortex, supplementary motor area; real vs. sham
Cortical silent period

Murase et al., 2005
Cortical silent period

B: before rTMS; A: after rTMS
PMC: premotor cortex; MC: motor cortex; SMA: supplementary motor area

Murase et al., 2005
rTMS combined with rehabilitation

- Groups (n=8):
  Randomized single subject design with crossover
  Experimental: rTMS + sensorimotor training
  Control: rTMS + control therapy

- rTMS: 1 Hz, 5 sessions

- Target: premotor cortex

Kimberley et al., 2015
Sensorimotor training

Kimberley et al., 2015
Byl et al., 2002
Arm Dystonia Disability Scale

% Change from baseline

Post-test

Follow-up

Control therapy + rTMS

Sensorimotor training + rTMS

Kimberley et al., 2015
Options for down-regulation in dystonia

Down-regulation of excitatory targets

Up-regulation of inhibitory targets
Other applications for down-regulation

- Stroke
- Traumatic brain injury
- Parkinson disease
- Essential tremor
- Tourette’s syndrome
- Amyotrophic lateral sclerosis
- Tinnitus
- Neuropathic pain
Harnessing neuroplasticity to improve motor function

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Why up-regulate?

$\Sigma = \text{greater inhibition}$
Stroke

Doubly-Disabled
Corticospinal tract integrity in children with stroke

Ipsilateral Reorganization

Crossed Corticospinal Tract Integrity

Gillick and Zirpel, 2012
Ipsilateral organization
Tricky Triad in Tots

• “Doubly-Disabled”

• “Developmental Disuse”
Modulation options for goal of up regulating lesioned hemisphere
Repetitive TMS (rTMS)

- Use of repetitive pulses of TMS

- Modulation
  - $< 1 \text{ Hz}$: inhibitory
  - $> 5 \text{ Hz}$: excitatory

- Safety
  - Seizures, headache

George & Aston-Jones, 2010  
http://www.magstim.com/clinical-solution/0/rapid2-therapy-system
5 day Inhibitory rTMS to contralesional hemisphere
N=12

Kirton et al, 2008
Kirton et al, 2008
rTMS and Constraint-Induced Movement Therapy (CIMT) in Pediatric Hemiparesis

Gillick et al, 2013
rTMS in adult stroke

- rTMS positive effect
- Especially subcortical stroke
- Low frequency > high frequency
Transcranial direct current stimulation (tDCS)

- Weak direct electrical current

- Modulation
  - Anode (+): ↑ excitability
  - Cathode (-): ↓ excitability

- Safety
  - Discomfort, tingling

Paulus, 2003
George & Aston-Jones, 2010
Single Session Bihemispheric tDCS: Safe and feasible
Transcranial Direct Current Stimulation and CIMT in Children with Hemiparesis
Harnessing neuroplasticity to improve motor function

1. Neuromodulation tools
2. Down-regulation
3. Up-regulation
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Neuromodulation: Harnessing Neuroplasticity with Brain Stimulation and Rehabilitation

Invasive Neuromodulation: Hijacking neural firing patterns and harnessing neuroplasticity to improve motor function

Colum D. MacKinnon PhD
Department of Neurology
Deep Brain Stimulation (DBS)

- Direct electrical stimulation through electrodes implanted into the brain
- Goal: Modulate activity in local and distant brain circuits (ripple effect)
Deep Brain Stimulation (DBS) for Parkinson’s Disease

Amplitude:
- 1-4V (constant voltage devices)

Stimulation Rate: 130-185 Hz
Pulse Width: 60-120 us

Hickey & Stacy, Frontiers in Neurosci, 10, 2016
DBS in no longer “new”

Over 100,000+ cases worldwide

*Majority are for advanced Parkinson’s disease*

*Two FDA approved manufacturers (Medtronic, Abbott-St. Jude)*
Deep Brain Stimulation (DBS)

Clinical Indications:
- Parkinson’s disease
- Essential tremor
- Dystonia
- Obsessive-Compulsive Disorder

Future Indications
- Tourette’s
- Depression
- Pain
- Obesity
- Addiction
- Alzheimer’s disease
- Stroke? (deep cerebellar stimulation)
Why use DBS?

- Effect size and efficacy is large
- Consistent increase in quality of life
- Broad network effects (not symptom- or segment-specific)

but...

- Higher level of risk
- Higher cost
- High variability across individuals
- Some motor and non-motor symptoms can worsen
- Some symptoms do not respond to DBS
Why is DBS more efficacious than non-invasive neuromodulation?

DBS is targeted to nodes of a network (circuit-based)

- 17 million corticostriatal neurons
- 2.3 million striatal medium spiny neurons
- 46,000 GPe neurons
- 14,000 STN neurons
- 26,000 GPi/SNpc neurons
Non-invasive approaches to treating Parkinson’s disease

- rTMS sensorimotor cortex
- anodal tDCS sensorimotor cortex
- rTMS supplementary motor area
- anodal tDCS of the supplementary motor area

7T MRI, SWI
N. Harel, CMRR, U Minnesota
DBS acts on nodes of the basal ganglia-thalamocortical network
DBS is targeted to nodes of a network (circuit-based)
Understanding the effects and consequences of long-term DBS

**Goals of DBS:**
- Reduce or eliminate pathological neuronal activity
- Restore functional neuronal activity
- Promote or facilitate functional neuroplasticity

**How does DBS work?**
- *Mechanisms of action: poorly understood*
  
  **Proposed mechanisms:**
  - Inhibits the activity of target neurons
  - Activates target neurons
  - Both excites and inhibits target neurons
  - *Disrupts pathological firing patterns and generates an “informational lesion”*
Parkinson’s Disease: The Rate Hypothesis

**PRE**
- Direct
- Indirect

1. **GPi** → **VL**
2. **VL** → **Thalamus** → **Motor Cortex** → **Movement**

**POST**
- Direct
- Indirect

1. **GPi** → **VL**
2. **VL** → **Thalamus** → **Motor Cortex** → **Movement**

Lesion/Stimulation

Graphs show electrical activity and changes in response to lesion/stimulation.
THE PATTERN HYPOTHESIS OF PARKINSON’S DISEASE

Abnormal patterns at rest:
- Increased bursting
- Rhythmic activity (particularly low frequency in the theta, alpha and beta bands)
- Correlated firing both within and between nuclei

Mechanisms of action of DBS

DBS: Inactivation Hypothesis

DBS: Activation Hypothesis
DBS hijacks the abnormal firing pattern and effectively produces an informational lesion

**DBS: Inactivation Hypothesis**

- STN
- GPe
- GPI

**DBS: Activation Hypothesis**

- STN
- GPe
- GPI

Hashimoto, J Neurosci, 2008
DBS hijacks the abnormal firing pattern and effectively produces an informational lesion

**Parkinsonism**

DBS-induced neuronal activity at 130 Hz

Beneficial motor effects of the informational lesion caused by STN-DBS or GPi-DBS

- Increased velocity (decreased bradykinesia)
- Increased movement amplitude (decreased hypokinesia)
- Improved muscle activation (increased force output)
- Marked suppression of tremor
- Marked suppression of rigidity
- Marked reduction of levodopa-induced dyskinesias
- **Improved quality of life**
Effects of STN-DBS on muscle activation

Vaillancourt et al., Brain, 127, 2004
Motor features that can be worsened by the informational lesion induced by STN-DBS or GPi-DBS

- Postural stability
- Anticipatory postural adjustments
- Temporal and balance components of gait
- Speech (particularly with bilateral stimulation)
- Eye movements (saccades)

Also...
- Cognition (exacerbation of dual-task deficits)
Some motor symptoms are worsened by STN-DBS or GPi-DBS: an opportunity for PT intervention

Rocchi et al., J Neurosurg, 2014
Motor features that are *resistant* to the effects of STN-DBS or GPi-DBS

- High-rate repetitive or sequential movements
- Freezing of gait (initially effective in individuals with a good response to levodopa preoperatively)
Some motor symptoms are resistant to STN-DBS or GPi-DBS: an opportunity for PT intervention

Stegemoller et al., Neurosci Lett, 2013
Firing patterns are disordered in dystonia
DBS-evoked changes in motor function in dystonia can take weeks to months to reach maximal efficacy

Time Course of Clinical Improvement with Gpi-DBS in Primary Dystonia

Clinical Rating of Severity (BMF)

Pre  1 Month  3 Months  6 Months

OPPORTUNITY
Critical window during neuroplastic changes for therapeutic intervention to improve function

Ruge et al., Mov Disord, 26, 2011
DBS has both short latency effects (seconds to minutes) and long-latency effects (hours to weeks)

Critical window during neuroplastic changes for therapeutic intervention to improve function

The next generation of DBS

A. Adaptive stimulation

B. Coordinated reset neuromodulation

C. Temporally irregular stimulation

The Next Generation of DBS

Harness Neuroplasticity
(e.g. Coordinated Reset or CR-DBS)
Issues related to DBS therapy that the rehabilitation community needs to aware of

• Efficacy
  Positive Effects:
  o Highly effective for many of the motor symptoms of Parkinson’s disease, dystonia, essential tremor
  Null or negative effects
  o Many motor and non-motor features are either resistant or worsened by DBS
  o High variability in response across individuals

• Mechanisms of action
  o Short latency rapid response
  o Longer latency neuroplastic changes (opportunity for intervention)
Get ready

• PTs will be treating more and more individuals with DBS

• PT has the potential to be an important adjunct to DBS by:
  o Facilitating improvements in movement function mediated by DBS
  o Reducing movement impairment induced by DBS
Prime rehabilitation effects

Vagus nerve stimulation for poststroke upper extremity hemiparesis
Vagus Nerve Stimulation (VNS)

Epilepsy
Depression
Left Vagal Nerve Stimulation

- Acetylcholine + Norepinephrine
- Locus Coeruleus
- Nucleus Basalis
- Vagus Nerve
Paired rehabilitation + VNS

- VNS with sensory stimulation or motor practice
- Ischemic stroke rat model

Engineer et al., 2011, Porter et al., 2011
Ischemic stroke rat model

Paired VNS improves recovery of hit rate performance and force on compared with Rehab alone and unpaired VNS

Khodaparast et al, 2013
Upper extremity therapy

- Graded, progressive task practice
- ~300 repetitions
- Average 72 minutes
- 18 sessions (3x/week for 6 weeks)
UEFM Responder Rates (>6pt)

8.7 (5.8) VNS (n=8)
3.0 (6.1) Control (n=11)

End of Acute
+ 7 Days
+ 30 Days

ITT: P=0.064
Per protocol: P=0.038

Dawson et al 2016
Blinded, Randomized Preliminary Clinical Trial

- VNS during rehabilitation for improved upper limb motor function after stroke
- Purpose: establish safety and effect size for definitive FDA trial
- 17 people (4 sites)
Upper extremity Fugl Meyer

In-clinic Therapy

- Paired VNS
- Control

P = 0.056

Base 6 weeks Post-30 3MO

Cross-over

Kimberley et al, in progress
Upper extremity Fugl Meyer

In-clinic Therapy

![Graph showing Upper Extremity Fugl Meyer (UEFM) Change over time for Paired VNS and Control groups. The graph includes the following time points: Baseline, 6 weeks, Post-30, and 3MO. The Paired VNS group shows a significant increase in UEFM change (P=0.056) compared to the Control group. The graph also indicates a crossover point where subjects may switch between the Paired VNS and Control conditions.](image-url)

Kimberley et al, in progress
Wolf motor function test

**Graph:**
- **Y-axis:** WMFT Functional Change
- **X-axis:** Time (Base, 6 weeks, Post-30)
- **Lines:**
  - Paired VNS
  - Control

**Notes:**
- Paired VNS shows a significant improvement compared to Control.
Wolf motor function test

Kimberley et al, in progress
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5. Where are we now, where are we going, and how do we get there?

6. Discussion
Where are we now?
## FDA approved indications

<table>
<thead>
<tr>
<th>Device</th>
<th>Disease</th>
<th>FDA status</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMS</td>
<td>Treatment-resistant depression</td>
<td>General approval</td>
</tr>
<tr>
<td>tDCS</td>
<td>No indication</td>
<td></td>
</tr>
<tr>
<td>DBS</td>
<td>Parkinson disease</td>
<td>General approval</td>
</tr>
<tr>
<td></td>
<td>Dystonia</td>
<td>Humanitarian device Exemption approval</td>
</tr>
<tr>
<td></td>
<td>Obsessive-compulsive disorder</td>
<td>Humanitarian device Exemption approval</td>
</tr>
<tr>
<td>VNS</td>
<td>Epilepsy</td>
<td>General approval</td>
</tr>
<tr>
<td></td>
<td>Treatment-resistant depression</td>
<td>General approval</td>
</tr>
</tbody>
</table>
Where are we going?
Another tool: get ready
Get ready

• PTs will be delivering neuromodulation
• Adjunct to your therapy
• Consulted on ideal candidates
• Questions from your patients
• Discern the real from the hype
Caution

Headset Zaps Video Gamers' Brains For Better Reflexes

For when you just HAVE to beat everyone at Call of Duty.
By Colin Lecher May 22, 2013

Foc.us Headset

Foc.us is a company that makes headsets for gamers. Those headsets, starting to ship in July, send electricity through your brain. This is their pitch:

Overclock your brain using transcranial Direct Current Stimulation (tDCS) to increase the plasticity of your brain. Make your synapses fire faster.

Faster Processor, Faster Graphics, Faster Brain!
Need to understand these tools better

How do we get there?
Why non-invasive brain stimulation? (tDCS, rTMS)

- Evidence that patients have more capacity
- Clinical use
- Ease of use
- Low cost
- Targeted brain area
- Low risk
Why invasive brain stimulation? (DBS, VNS)

• Broad network effects
• Effect size and efficacy
• Higher level of risk
• Higher cost
Does it work?

- Case series
- Small n studies
- Large scale RCT have not yet been done
- Can they? **Should they?**
Different models

- Allow failure
- Pragmatic design and report
  - Allow clinicians to evaluate how and with whom
- Acute testing
- Models of patient selection
  - E.g. PREP algorithm (Stinear et al, 2010, 2012)
  - TMS + neuroimaging + genetics + clinical assessment
In clinic private pay

• Off label rTMS
• Post ischemic stroke
• 10 session ($2115)
• (depression: $8000-$14,000)

• Why?
  – Some efficacy
  – If we wait, it may never happen
  – Data
Vision

• PTs are **key partners** in neuromodulation therapy
• To get there we need to insert ourselves into the action
Vision: we need neuromod and neuromod needs us

• Understand the brain target and effect on circuitry
• Model of patient selection
• Dose and duration of effect
• Ideal timing/type of rehabilitation
• Multicenter studies: info from all sources
Work together
Work together