Non-invasive Brain Stimulation (NiBS) - cellular and molecular mechanisms

Insights from Animal Models
Review for Clinical Neurophysiology

Marom Bikson, Asif Rahman
Alexander Rotenberg, Flavio Frohlich, David Liebetanz, Elzbieta Janowska, Brita Fritsch, Sven Bestmann, et al...

Lucas Parra, Dennis Truong, Abhishek Datta, Davide Reato, Belen Lafon, Gregory Kronberg, Thomas Radman
Department of Biomedical Engineering, The City College of New, New York, NY
$ NIH, NSF, Epilepsy Foundation, Wallace Coulter Foundation, DoD
Goal of translational animal research on NiBS

To develop a quantitative description (model) of neuronal plasticity that supports predictions on how to optimize NiBS. Leading to more effective and specific outcomes.

• Current flow models of current flow provide the input to these models of plasticity – tissue is exposed to X current density.
• Human neurophysiology (and behavior data) retrospectively inform model validity.
• Value of model is prospective refinement in clinical/behavioral outcomes. As such, empirical model parameterization is sufficient in the absence of complete mechanistic understanding.

  Hodgkin and Huxley J Physiol. 1952

• Given diversity of brain physiology and functions: a modeling framework that can be systematically parameterized is desired.
• Biomarkers (parameters) in animal models that predict neuroplasticity (and so behavior changes). Do not presume animals are people.
The “sliding scale” explanation for NiBS (and brain function)

Brain function and disease as a change in regional “excitability”

As “explained” by:
- fMRI
- Lesion studies
- Drugs
- TMS....

Implies monolithic function of each brain region (fully) explained by “excitability”

NiBS as a universal modulator of regional brain “excitability”

“Anodal” or “High-Frequency”
- “More” function, neuronal activity
  “More” plasticity (excitatory)

“Cathodal” or “Low-frequency”
- “Less” function, less neuronal activity
  “Less” excitatory plasticity (inhibition)
What makes NiBS specific?

“Given” the diversity of NiBS application spanning neuropsychiatric treatment, rehabilitation, and learning in healthy individuals:

What makes NiBS specific?

• **Anatomical targeting (specificity)**
  The control of NiBS Dose (Peterchev Brain Stim 2013) through coil / electrode placement to produce current flow in targeted brain regions.
  Design facilitated by current flow models.

• **Functional targeting (specificity)**
  The use of NiBS *adjunct* to behavioral / cognitive training to facilitate the outcomes of training.
  Design facilitated by quantitative descriptions (cellular models) developed using animal experiments.
Potential and limits of anatomical targeting with tES

High-Definition electrodes in “4x1” configuration

Datta et. al. Brain Stim 2009

Optimized tES is a closed problem.

But “best” montage very different for:

a) Maximum intensity at target.

b) Focality (minimizing relative intensity outside of target for specificity).

Dmochowski et. al. Neural Engr. 2011
From Anatomical Targeting to Functional Targeting
From Anatomical Targeting to Functional Targeting

Network of interest (e.g. depression, math cells)

Other networks – not targets for neuromodulation

Preferential modulation of more active network (activity dependent)

Current flow across entire region

Electrode / Coil

Network of interest (e.g. depression, math cells)

Other networks – not targets for neuromodulation

Preferential modulation of more active network (activity dependent)

Current flow across entire region

Electrode / Coil
“Given” the diversity of NiBS application spanning neuropsychiatric treatment, rehabilitation, and learning in healthy individuals:

What makes NiBS specific?

- **Anatomical targeting (specificity)**
  The control of NiBS Dose (Peterchev Brain Stim 2013) through coil/electrode placement to produce current flow in targeted brain regions.
  Design facilitated by current flow models.

- **Functional targeting (specificity)**
  The use of NiBS *adjunct* to behavioral/cognitive training to facilitate the outcomes of training.
  Design facilitated by quantitative descriptions (cellular models) developed using animal experiments.
Biophysical basis of NiBS functional selectivity: tDCS
Biophysical basis of NiBS functional selectivity: tDCS

**Single Neuron Polarization**

- Weak direct current produces linear membrane polarization. At soma:
  - 0.15 - 0.3 mV polarization per V/m
  - 0.07 – 0.15 mV polarization per mA
- Field induced polarization is additive with average membrane polarization (e.g. due to synaptic inputs) Bikson JPhysiol 2004
**Biophysical basis of NiBS functional selectivity: tDCS**

**Firing Rate**

Creutzfeldt, ExpNeurol 1962  
Bindman, JPhysiol 1964  
Purpura, ElecClinNeuro 1965  
Gartside, Nature 1968  
Reato, JNeurosci 2010
Biophysical basis of NiBS functional selectivity: tDCS

Firing Rate

✓ Fundamental finding of “classic” animal studies on DCS
  ➢ Initial basis for “anodal” “cathodal”
  ➢ Initial basis for lasting changes
  ➢ Robust across systems
✓ Linear with field intensity
  ➢ 1.5 Hz change in firing rate per V/m

Reato J Neurosci 2010
Biophysical basis of NiBS functional selectivity: tDCS

**Synaptic Efficacy: evoked activity**

Direct Current stimulation + evoked response

fEPSP: metric of cellular synaptic efficacy

- **Cathodal stimulation** (soma Hyperpolarized)
- **Control**
- **Anodal stimulation** (soma Depolarized)

Sliding scale

- Synaptic efficacy

Current flow

Hyperpolarized dendrites
Depolarized soma
Layer V/VI
• Higher sustained synaptic inputs under anodal stimulation
• Substrate for plasticity + Pathway specific
Synaptic Plasticity

☑ Fritsch 2010: Activity dependent induction

Specific ongoing synaptic activity (no plasticity)

☐ tDCS induces plasticity

☑ Ranieri 2012: Additive neuromodulation
☐ Marquez-Ruiz 2012: Modulation of conditioning

Ongoing Plasticity

☐ tDCS modulates plasticity

“None-active” synapse

No tDCS synaptic plasticity

? Synaptic activity specific promotion of plasticity
The effects of low-intensity can be only be explained through a changes in the dynamics of the system.

- Both excitatory and inhibitory synaptic function can increase concurrently


Effects are (dynamical) system specific so functionally specific.
<table>
<thead>
<tr>
<th></th>
<th>Low intensity DCS + Low Level Activity (Quiescent)</th>
<th>Low intensity DCS + High Level Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Firing Rate</strong></td>
<td>↑</td>
<td>↑ + △</td>
</tr>
<tr>
<td></td>
<td>Creutzfeldt 1962, Toleikis 1974</td>
<td>Ongoing activity + DCS</td>
</tr>
<tr>
<td><strong>Δ Synaptic efficacy</strong></td>
<td>↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td></td>
<td>2013, Marquez-Ruiz 2012</td>
<td></td>
</tr>
<tr>
<td><strong>Δ Plasticity</strong></td>
<td>—</td>
<td>Activity dependent induction</td>
</tr>
<tr>
<td></td>
<td>Bikson 2004, Fritsch 2010</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ + △</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ongoing plasticity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ranieri 2012: Additive neuromodulation</td>
</tr>
<tr>
<td><strong>Functional Selectivity</strong></td>
<td>—</td>
<td>Potential for functional selectivity</td>
</tr>
</tbody>
</table>
Candidate mechanisms biomarkers of tDCS Plasticity

- Local calcium increased after DCS Islam BrainRes 1995
- NMDA-receptor dependent LTP induction & modulation Fritsch Neuron 2010, Ranieri JNeurophys 2012
- BDNF secretion modulated by DCS Fritsch Neuron 2010, Ranieri JNeurophys 2012
- c-fos and zif268 protein expression modulated by DCS Ranieri JNeurophys 2012
- Blocking A1 adenosine-receptor prevents DCS induced LTD Marquez-Ruiz 2011

The brain is complex and NiBS is complex. A systematic parameterizing of clinically relevant biomarkers supports a (unified) model of how NiBS leads to functionally specific plasticity.
Quantitative framework for NiBS (tDCS) plasticity

Plasticity = \( f(\text{activity, time, X, Y, Z}) \)

NiBS modulates \( \rightarrow \) activity

\( X, Y, Z \) are the biomarkers OR phenomenological parameters

\( X, Y, Z \) depend on the brain region and are altered NiBS

- Activity Dependent – Functional Selectivity.
- Quantitative model of role of NiBS dose for prediction.
- Framework adaptive to broad range of NiBS, brain regions, and functions.

\( \diamond \) We only need to know the effect of NiBS on activity, \( X, Y, \) and \( Z \)... parameters (which can be fitted empirical) to optimize for efficacy and specificity.
Quantitative framework for hypothesis driven NiBS

**Hypothesis:** **Functional specificity:**
Selecting for an active population → functional specificity of plasticity

**Computational neuronal model of plasticity (Rahman et al.)**

**Fast input Group:** 100 Hz
Functionally Selected Network

**Slow input Group:** 20 Hz

**Model hypothesis:** Postsynaptic depolarization preferentially amplifies synaptic strength in fast input groups

Molaee-Ardekani Brain Stim. 2013
Berker Frontiers 2013 “Computational Neurostimulation”
What makes NiBS specific?

“Given” the diversity of NiBS application spanning neuropsychiatric treatment, rehabilitation, and learning in healthy individuals:

What makes NiBS specific?

• **Anatomical targeting (specificity)**
  The control of NiBS Dose (Peterchev Brain Stim 2013) through coil / electrode placement to produce current flow in targeted brain regions.
  
  NiBS design facilitated by current flow models of targeting.

• **Functional targeting (specificity)**
  The use of NiBS adjunct to behavioral / cognitive training to facilitate the outcomes of training.
  
  NiBS design facilitated by quantitative descriptions (cellular models) of targeting.
Non-invasive Brain Stimulation (NiBS) cellular and molecular mechanisms

Insights from Animal Models
Review for Clinical Neurophysiology

Marom Bikson, Asif Rahman

Lucas Parra, Dennis Truong, Abhishek Datta, Davide Reato, Belen Lafon, Gregory Kronberg, Thomas Radman
Department of Biomedical Engineering, The City College of New, New York, NY
$ NIH, NSF, Epilepsy Foundation, Wallace Coulter Foundation, DoD