Intensive Course in TMS
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Translational value of TMS studies in healthy subjects into clinical populations

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Brain Stimulation, Elsevier: deputy editor royalties

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Repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) can modulate behaviors in healthy subjects.

- Impair (*virtual lesion*)
- Improve (*neuroenhancement*)

**Can this be a concern for our patients?**

**Can this be relevant for our patients?**
Plan

1. Noninvasive brain stimulation (NIBS) can modulate human behaviors (e.g., decision-making) in healthy subjects.

2. Translational value of NIBS studies in healthy subjects into clinical applications?
   Yes, but to some extent...
rTMS and tDCS over the DLPFC can modulate a vast variety of behaviors in healthy subjects:

- **Attention**  
  Mevorach et al. 2010 *J Neurosci*

- **Impulsivity**  
  Beeli et al. 2008a, b *Behav Brain Funct*  
  Cho et al., 2010 *Brain Stimul*

- **Planning**  
  Dockery et al. 2009 *J Cogn Neurosci*

- **Reward seeking / risk-taking**  
  Knoch et al. 2006 *J Neurosci, Science*  
  Fecteau et al. 2007a, b *J Neurosci*

- **Self-control**  
  Knoch et al. 2009 *PNAS*  
  Figner et al. 2010 *Nat Neurosci*  
  Hsu et al. 2011 *Neuroimage*

- **Emotional processing**  
  D’Alfonso et al. 2000 *Neurosci Lett*  
  Harmer et al. 2001 *Nat Neurosci*  
  van Honk et al. 2002 *Biol Psychiatry*  
  van Rijn et al. 2005 *Eur J Neurosci*

They are all involved in decision-making skills.
Decision-making appears to rely upon a distributed bi-hemispheric network including the DLPFC, the orbitofrontal cortex, the anterior cingulated cortex, and the insula.

Patients with PFC lesion

Neuroimaging studies in healthy subjects

One role of the DLPFC is to integrate cognitive and emotionally relevant information during decision-making.

**Cognitive, Reflective, Deliberative System**
- inhibitory control / executive functions

**Emotional, Reflexive, Automatic System**
- reward processing / motivation

Damasio et al. 1996; Bechara 2005; Ernst & Paulus 2005; Sanfey et al. 2003; Evans 2008
Examples of how TMS or tDCS applied over the DLPFC can modulate decision-making processes in healthy subjects.
1 Hz rTMS over the right (R) DLPFC can increase risk taking at the Risk Task in healthy subjects.

tDCS (anodal over the R DLPFC coupled with cathodal over the left (L) DLPFC) can decrease risk taking and reward seeking at the Risk Task in healthy subjects.

Fecteau, Knoch, Fregni, Sultani, Boggio, Pascual-Leone (2007a) Journal of Neuroscience
tDCS over the DLFPC can decrease risk taking at the BART task in healthy subjects.

Fecteau, Pascual-Leone, Zald, Liguori, Theoret, Boggio, Fregni (2007b) *Journal of Neuroscience*
cTBS over the R DLPFC can suppress impulsivity at the Delayed Discounting Task in healthy subjects.

Would you prefer to receive:

- $20 now
- $26 tomorrow

Cho, Pellecchia, Ko, Ray, Obeso, Houle, Strafella (2012) *Brain Stimulation*
1 Hz rTMS over the R DLPFC can modulate self-interest at the Ultimatum Game in healthy subjects.

The Ultimatum Game

The proposer has $10 and offers you $2

If you accept:
The proposer gets $8 and you get $2

If you reject:
The proposer gets $0 and you get $0

1Hz rTMS over the R DLPFC

Accepted more often unfair offers

Elicited activity in both DLPFCs when contrasting unfair > fair offers

Knoch et al. (2006) Science

Baumgartner et al. (2011) Nature Neuroscience
Plan

1. Noninvasive brain stimulation (NIBS) can modulate human behaviors (e.g., decision-making) in healthy subjects.

2. Translational value of NIBS studies in healthy subjects into clinical applications?
   Yes, but to some extent…

   Why is this relevant for patients?
Rational of targeting cognitive processes in Substance-Related and Addictive Disorders

Risky decision-making, a characteristic behavioral phenotype:
- risk taking;
- reward seeking;
- impulsivity;
- delayed gratification.

Craving, a powerful driving force balancing decisions toward maladaptive choices and a key factor associated to relapse.

Craving positively correlated with activity in DLPFC.

TDCS and rTMS can modulate cognitive functions that are clinically relevant for these patients. Can they help suppress craving and maintain abstinence?

Patients with substance use disorders take greater risk at the Risk Task.

Patients with tobacco use disorders take greater risk at the BART.

Lejuez, Aklin, Jones, Richards, Strong, Kahler, Read (2003) *Experimental and Clinical Psychopharmacology*
Patients with tobacco use disorders are more impulsive at the Delayed Discounting Task.

Would you prefer to receive:

- $20 now
- $26 tomorrow

Smokers choose more often the smaller, immediate offer of money.

Mitchell & Wilson (2012) *Psychopharmacology*
Patients with tobacco use disorders display greater self-interest at the Ultimatum Game when the reward is relevant.

The proposer has $10 and offers you $2

If you accept:
The proposer gets $8 and you get $2

If you reject:
The proposer gets $0 and you get $0

Smokers (and nonsmokers) reject most of the time unfair offers of money.

The proposer has 10 cigarettes and offers you 2 cigarettes

If you accept:
The proposer gets 8 and you get 2 cigarettes

If you reject:
The proposer gets 0 and you get 0 cigarette

Smokers accept most of the time unfair offers of cigarette.

Takahashi (2007) *NeuroEndocrinology Letters*
NIBS over the DLPFC of healthy subjects can modulate decision-making behaviors.

Impaired decision making processes seem to be linked to increased vulnerability for substance use disorders (behavioral phenotype).

What happens when we apply NIBS over the DLPFC of individuals with substance use disorders?
Proof-of concept data supporting that NIBS can reduce craving for:

- Nicotine
- Alcohol
- Food
- Marijuana
- Psychostimulant

<table>
<thead>
<tr>
<th>Study name</th>
<th>Technique</th>
<th>Stimulation site</th>
<th>Single or combined study</th>
<th>Number of sessions</th>
<th>Number of subjects</th>
<th>Hedge's g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiá et al. (2009)</td>
<td>rTMS</td>
<td>Left</td>
<td>Single Study</td>
<td>10</td>
<td>21</td>
<td>0.888</td>
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<td>Barth et al. (2011)</td>
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<td>Single Study</td>
<td>2</td>
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<td>tDCS</td>
<td>Both</td>
<td>Combined</td>
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<td>0.089</td>
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<td>Left</td>
<td>Single Study</td>
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<td>0.824</td>
</tr>
<tr>
<td>Boggio et al. (2010)</td>
<td>tDCS</td>
<td>Both</td>
<td>Combined</td>
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<td>0.587</td>
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<td>Claudino et al. (2011)</td>
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<td>Single Study</td>
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<td>Both</td>
<td>Combined</td>
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<td>0.391</td>
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<td>Fregni et al. (2008b)</td>
<td>tDCS</td>
<td>Both</td>
<td>Combined</td>
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<td>48</td>
<td>0.438</td>
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<td>Goldman et al. (2011)</td>
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<td>Right</td>
<td>Single Study</td>
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<td>19</td>
<td>0.427</td>
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<td>Herremans et al. (2011)</td>
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<td>Right</td>
<td>Single Study</td>
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<td>31</td>
<td>0.08</td>
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<tr>
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<td>Left</td>
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<td>rTMS</td>
<td>Left</td>
<td>Single Study</td>
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<td>Mishra et al. (2010)</td>
<td>rTMS</td>
<td>Right</td>
<td>Single Study</td>
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<td>45</td>
<td>1.065</td>
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<tr>
<td>Montenegro et al. (2012)</td>
<td>tDCS</td>
<td>Left</td>
<td>Single Study</td>
<td>2</td>
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<td>0.694</td>
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<tr>
<td>Nakamura-Palacios et al. (2011)</td>
<td>tDCS</td>
<td>Left</td>
<td>Single Study</td>
<td>2</td>
<td>32</td>
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<tr>
<td>Uher et al. (2005)</td>
<td>rTMS</td>
<td>Left</td>
<td>Single Study</td>
<td>1</td>
<td>28</td>
<td>0.809</td>
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<tr>
<td>Wing et al. (2012)</td>
<td>rTMS</td>
<td>Bilateral</td>
<td>Single Study</td>
<td>50</td>
<td>13</td>
<td>0.476</td>
</tr>
</tbody>
</table>

Jansen, Daams, Koeter, Veltman, van den Brink, Goudriaan (2013) *Neurosci Biobehav Rev*
Ekhtiari et al. (2019) *Neurosci Biobehav Rev*
tDSCS over the DLPFC suppressed craving in adults with tobacco use disorders.

This was a 3-arm, crossover, sham controlled, blind at 3 levels (subjects, tDSCS provider, outcome assessors) study with smokers who do not wish to quit smoking receiving 3 single tDSCS sessions.

tDCS over the DLPFC decreased the reported number of cigarettes smoked.

This was a parallel, sham controlled, blind at three levels (subjects, tDCS provider, outcome assessors) study with nicotine smokers who do not wish to quit smoking receiving a 5-day tDCS regimen (anodal over the L DLPFC coupled with cathodal over the R DLPFC).

Boggio, Liguori, Sultani, Rezender, Fecteau, Fregni (2009) *Neuroscience Letters*
tDCS over the DLPFC decreased the number of cigarettes smoked and reward seeking for cigarettes in adults with tobacco use disorders.

This was a 2-arm, crossover, sham controlled, blind at 3 levels (subjects, tDCS provider, outcome assessors) study with smokers receiving two 5-day tDCS regimens (real, sham).

Fecteau, Agosta, Hone-Blanchet, Fregni, Boggio, Ciraulo, Pascual-Leone (2014) *Drug and Alcohol Dependence*
1Hz rTMS over the L DLPFC suppressed craving and impulsivity level in adults with tobacco use disorders.

Hayashi, Ko, Strafella, Dagher (2013) PNAS
rTMS over the L lateral PFC reduced cigarette consumption and nicotine dependence in adults with tobacco use disorders.

This was a sham controlled and blind study with smokers who previously failed smoking cessation treatments receiving 13 rTMS sessions (10Hz, 1Hz, and sham).

- Reduction of self reported number of cigarettes smoked with 10Hz rTMS compared to 1Hz rTMS and sham rTMS. This was also observed at the 6-month follow-up visit.

- Reduction of urinary cotinine level with 10Hz rTMS compared to 1Hz rTMS and sham rTMS.

- Reduced FTND scores in the 10Hz rTMS group compared to the 1Hz rTMS and sham rTMS groups.

- No significant change in craving scores.

Dinur-Klein, Dannon, Hadar, Rosenberg, Roth, Kotler, Zangen (2014) *Biological Psychiatry*
rTMS over the R DLPFC combined with nicotine replacement therapy in adults with tobacco use disorders.

This was a sham controlled and blind study with smokers who previously failed smoking cessation treatments receiving 10 sessions of 1Hz rTMS with nicotine replacement therapy (NRT).

Active rTMS + NRT vs. Sham rTMS + NRT:
- Greater number of patients maintained smoking abstinence at 2-week, but not at 6- or 12-week assessments.
- Reduced craving scores.

Trojak, Meille, Achab, Lalanne, Poquet, Ponavoy, Blaise, Bonin, Chauvet-Gelinier (2015) *Brain Stimulation*
rTMS for smoking cessation (FDA)

- Each 10Hz rTMS session is preceded by a 5-min provocation procedure to induce craving (recall triggers, view images of smoking, etc.).
- Each rTMS session is followed by a 2-min motivational dialogue to encourage smoking cessation.

[Graph showing CQR and Craving VAS scores over weeks, with statistical significance indicated by asterisks.

Other addictive behaviors?

So can NIBS treat substance use disorders?

Meta-analyses (positive or negative): great, but what do individual studies tell us?
<table>
<thead>
<tr>
<th>NIBS in patients with tobacco use disorders.</th>
<th>Craving</th>
<th>Use</th>
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</thead>
<tbody>
<tr>
<td>1 x 20Hz L DLPFC (Johann et al. 2003)</td>
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<td>1 x 20Hz L DLPFC (Eichhammer et al. 2003)</td>
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<td>10 x 10Hz L DLPFC (Amiaz et al. 2009)</td>
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<td>1 x 1Hz L SFG (Rose et al. 2011)</td>
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<td>1 x 10Hz SFG (Rose et al. 2011)</td>
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<td>1 x 10Hz L DLPFC (Li et al. 2013)</td>
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<td>1 x 10Hz L DLPFC (Pripft et al. 2013)</td>
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<td>4 x 1Hz L DLPFC (Hayashi et al. 2013)</td>
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<td>13 x HF lateral PFC (Dinur-Klein et al. 2014)</td>
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<tr>
<td>10 x 1Hz R DLPFC (Trojak et al. 2015)</td>
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<tr>
<td>1 x 10Hz L DLPFC (Li et al. 2017)</td>
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<tr>
<td>10 x 20Hz L DLPFC + superior medial frontal cortex (Chang et al. 2018)</td>
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<tr>
<td>10 x 10Hz L DLPFC (Li et al. 2020)</td>
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<tr>
<td>10 x 20Hz L DLPFC (Abdelrahim et al. 2021)</td>
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<td>1 x i/cTBS R IFG (Upton et al. 2023)</td>
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<td>1 x 2mA R/L DLPFC (Fregni et al. 2008)</td>
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<td>5 x 2mA R/L DLPFC (Boggio et al. 2009)</td>
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<tr>
<td>1 x 2mA L DLPFC / R supraorbital area (Xu et al. 2013)</td>
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<tr>
<td>5 x 2mA R/L DLPFC (Fecteau et al. 2014)</td>
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<tr>
<td>1 x 1mA occipital / FPT (Meng et al. 2014)</td>
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<tr>
<td>1 x 1mA L DLPFC / R supraorbital area (Faclone et al. 2015)</td>
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<tr>
<td>1 x 1mA L/R DLPFC (Yang et al. 2017)</td>
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<tr>
<td>5 x 1mA L DLPFC / R supraorbital area (Vitor de Souza et al. 2018)</td>
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<tr>
<td>10 x 2mA R DLPFC / L occipital (Mondino et al. 2018)</td>
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<tr>
<td>3 x 1.5mA L/R DLPFC (Alghamdi et al. 2019)</td>
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<td>3 x 1.2mA L DLPFC / R supraorbital (Faclone et al. 2019)</td>
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<td>6 x 2mA R/L DLPFC (Verveer et al. 2020)</td>
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<td>20 x 2mA L/R DLPFC (Behnam et al. 2020)</td>
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<tr>
<td>5 x 2mA R/L DLPFC (Perri &amp; Perrotta 2021)</td>
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<tr>
<td>5 x 2mA L/R DLPFC / OFC (Lin et al. 2021)</td>
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<tr>
<td>30 x 1mA L/R FPT (Meng et al. 2022)</td>
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</tbody>
</table>
Plan

1. Noninvasive brain stimulation (NIBS) can modulate human behaviors (e.g., decision-making) in healthy subjects.

2. Translational value of NIBS studies in healthy subjects into clinical applications?
   Yes, but to some extent:
   - brain morphometry can impact the effects of NIBS;
   - brain activity can impact the effects of NIBS;
   - behaviors can impact the effects of NIBS.

   Are they different between healthy subjects and patients?

   Are they different within a clinical population (and within a patient)?
### Meta-analyses (positive or negative): great, but what about individual studies?

<table>
<thead>
<tr>
<th>In alcohol use disorders:</th>
<th>Craving</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 x 10Hz R DLPFC (Mishra et al. 2010)</td>
<td>≈</td>
<td>≈</td>
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<tr>
<td>10 x 20Hz L DLPFC (Hopnner et al. 2011)</td>
<td>=</td>
<td>=</td>
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<tr>
<td>15 x 1Hz dorsal ACC, case study (De Ridder et al. 2011)</td>
<td>≈</td>
<td>≈</td>
</tr>
<tr>
<td>1 x 20Hz R DLPFC (Herremans et al. 2012)</td>
<td>=</td>
<td>=</td>
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<tr>
<td>1 x 10Hz SFG (Herremans et al. 2013)</td>
<td>=</td>
<td>=</td>
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<tr>
<td>4 x 10Hz L DLPFC (Del Felice et al. 2016)</td>
<td>=</td>
<td>=</td>
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<tr>
<td>4 x 10Hz R / L DLPFC (Addolorato et al. 2017)</td>
<td>=</td>
<td>=</td>
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<tr>
<td>10 x 10Hz frontal (Perinin et al. 2020)</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>1 x 2mA L / R DLPFC (Boggio et al. 2008)</td>
<td>≈</td>
<td>≈</td>
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<tr>
<td>5 x 2mA L DLPFC / R supradeltoid area (Nakamura-Palacios et al. 2012)</td>
<td>=</td>
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<tr>
<td>5 x 2mA L DLPFC / R supraorbital area (da Silva et al. 2013)</td>
<td>≈</td>
<td>≈</td>
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<tr>
<td>1 x 1mA L DLPFC / R supraorbital area (den Uyl et al. 2015)</td>
<td>≈</td>
<td>≈</td>
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<tr>
<td>1 x 1mA L / R DLPFC (Wietschorke et al. 2016)</td>
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<tr>
<td>3 x 1mA L DLPFC / R supraorbital area + CBM (den Uyl et al. 2016)</td>
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<td>4 x 2mA L / R DLPFC + CBM (den Uyl et al. 2017)</td>
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<td>10 x 2mA R / L DLPFC (Klauss et al. 2018)</td>
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<td>4 x 2mA L / R DLPFC + ABM (den Uyl et al. 2018)</td>
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<td>4 x 2mA R IFG / L arm + CBM (Claus et al. 2019)</td>
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<td>4 x 2mA R IFG / L arm + mindfulness-based relapse prevention (Witikiewitz et al. 2019)</td>
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<td>5 x 2mA R / L DLPFC (Holla et al. 2020)</td>
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<td>5 x 2mA R / L DLPFC (Dubuson et al. 2021)</td>
<td>=</td>
<td>≈</td>
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<tr>
<td>10 x 2mA L / R DLPFC + cognitive flexibility (Camchong et al. 2023)</td>
<td>=</td>
<td>≈</td>
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</table>

**Did NIBS reach the cortex?**
## Meta-analyses (positive or negative): great, but what do individual studies tell us?

<table>
<thead>
<tr>
<th>The use of NIBS to decrease craving for psychostimulant</th>
<th>Craving</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 10Hz R DLPFC (Camprodon et al. 2007)</td>
<td>↓</td>
<td>=</td>
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<tr>
<td>1 x 10Hz L DLPFC (Camprodon et al. 2007)</td>
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<tr>
<td>10 x 15Hz L DLPFC (Politi et al. 2008)</td>
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<td>1 x 1Hz L DLPFC (Li et al. 2013)</td>
<td>↑</td>
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<tr>
<td>8 x 15Hz L DLPFC (Terraneo et al. 2016)</td>
<td>↓</td>
<td>=</td>
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<tr>
<td>5 x 1 or 10Hz R or L DLPFC (Liu et al. 2017)</td>
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<td>=</td>
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<tr>
<td>5 x 10Hz L DLPFC (Su et al. 2017)</td>
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<td>15 x 10Hz or 1 Hz mPFC (Martinez et al. 2018)</td>
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<td>15 x 15Hz L DLPFC (Lolli et al. 2021)</td>
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<td>2 x 15Hz L DLPFC (Martiotti et al. 2022)</td>
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<td>1 x 2mA R DLPFC / L supraorbital area (Shahbabaie et al. 2014)</td>
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<tr>
<td>5 x 2mA R DLPFC / L DLPFC (Conti et al. 2014)</td>
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<td>5 x 2mA R / L DLPFC (Nakamura-Palacios et al. 2016)</td>
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<td>10 x 2mA R / L DLPFC (Verveer et al. 2022)</td>
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<tr>
<td>15 x 2mA R / L DLPFC (Gaudreault et al. 2022)</td>
<td>=</td>
<td>=</td>
</tr>
</tbody>
</table>

### Did NIBS reach the cortex?
A lesson from history?

- More than a century ago... There were some behavioral changes, but the effects were unreliable.
- The current was presumably not going through the brain.

- If applied to the brain, current can modulate brain activity (Purpura & McMurtry, 1964).
- Thus, with appropriate stimulation parameters, behavioral changes should be due to brain modulation and should be replicable.

- Negative findings: a lesson from history?
  tDCS:
  - Tremblay et al. 2014 The uncertain outcome of prefrontal tDCS. *Brain Stimul*
  - Horvath et al. 2015 Quantitative review finds no evidence of cognitive effects in healthy populations from single-session tDCS. *Brain Stimul*
  - Horvath et al. 2016 No significant effects in tDCS found on simple motor reaction time comparing 15 different stimulation protocols. *Neuropsychologia*

  rTMS:
  - Novak et al. 2006 The double-blind sham-controlled study of high-frequency rTMS (20 Hz) for negative symptoms in schizophrenia: negative results. *Neuro Endocrinol Lett*
  - Slotema et al. 2011 Can rTMS really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial. *Biol Psychiatry*
  - Paz et al. 2018 Randomised sham-controlled study of high-frequency bilateral dTMS to treat adult ADHD: negative results. *World J Biol Psychiatry*
  ... and this is considering publication bias.

- In order to move forward, we need to deepen mechanistic knowledge of NIBS to induce reliable and replicable effects.

- Our goal: to identify the neural effects of NIBS, which may consequently modulate behaviors, by combining NIBS with neuroimaging

Fecteau (2023) *The Neuroscientist*
Dosing dogma of NIBS

Purpura & McMurtry (1964) J Neurophysiol

The Pitfalls

- Optimal dosing unknown, infinite parameter space
  - Conventional “Dosing dogma” is misleading

<table>
<thead>
<tr>
<th>rTMS</th>
<th>High freq</th>
<th>Low freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBS</td>
<td>Intermittent</td>
<td>Continuous</td>
</tr>
<tr>
<td>tDCS</td>
<td>Anodal</td>
<td>Cathodal</td>
</tr>
</tbody>
</table>

Excitatory

Inhibitory

Motor-evoked potential increase/decrease

Cognition/personal change

Populaion activity

Inference

Increase/TP
decrease/LTD

Network activity

Neuromodulation

Motor-evoked potential

Neuromodulation

Membrane excitability

Increase (anodal)

Decrease (cathodal)

Contribution to

Microscopic

Macroscopic

rTMS did not modulate functional connectivity between the regions under the anode and cathode electrodes, during or after stimulation in any tDSC-fMRI studies targeting the PFC.

Lisanby (2016) Transcranial Electric Stimulation Workshop. NIH

Bestmann, de Berker, Bonaituo (2016) Trends Cogn Sci

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Neuromodulation

Motor-evoked potential

Neuromodulation

Variability

Abstract

The ability of repetitive transcranial magnetic stimulation (rTMS) to improve long-term plasticity in the human cortex has opened exciting possibilities for its use in both basic and clinical research. Changes in the amplitude of motor-evoked potentials (MEPs) elicited by single-pulse transcranial magnetic stimulation have been used to predict the effects of rTMS. However, a growing number of studies have reported large inter-individual variability in the mean motor evoked response to rTMS, raising important questions about the reliability of this measure for guiding therapy. Although the increasing application of different analagous approaches allows for transfer rTMS-induced somatosensory evoked potentials to occur as changes in sensory activity that impact other aspects of human behavior, the high variability of rTMS effects in these measures remains an important issue for the field to address. In this review, we turn to recent advances in conventional transcranial magnetic stimulation that promise the results of rTMS findings, presenting a unified framework for measuring rTMS-induced neuroplasticity. We consider the evidence that rTMS is able to modulate an individual's moment-to-moment variability in neural activity, and whether this could have implications for guiding the therapeutic application of rTMS.
**rTMS in a severe case of treatment refractory of substance use disorder**

<table>
<thead>
<tr>
<th>Day</th>
<th>MRS</th>
<th>OCDUS: Compulsion</th>
<th>Obsession</th>
<th>DASS: Stress</th>
<th>Depression</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>21</td>
<td>16</td>
<td>19</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>6</td>
<td>5</td>
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<tr>
<td>3</td>
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<td>4</td>
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<td>5</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>MRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-mo follow up</td>
<td>MRS</td>
<td>20</td>
<td>14</td>
<td>16</td>
<td>18</td>
<td>10</td>
</tr>
</tbody>
</table>

**5-day 1Hz rTMS over the right dIPFC**

<table>
<thead>
<tr>
<th>DDQ</th>
<th>Desire &amp; Intention</th>
<th>Negative Reinforcement</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDQ</td>
<td>-12</td>
<td>-2</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>5</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>-1</td>
<td>0</td>
</tr>
</tbody>
</table>

**1Hz rTMS: elevated NAA (excitatory effects?)**

Hone-Blanchet, Mondino, Fecteau (2017) *Brain Stimul*
Let’s start with the “simplest” question:

What are the neural effects of tDCS in a resting healthy brain?

A concurrent tDCS - Magnetic Resonance Spectroscopy (MRS) study
Concurrent NIBS and neuroimaging: to identify the neural effects of NIBS applied over the DLPFC.

This was a 2-arm, crossover, sham controlled, blind at 3 levels (subjects, tDCS provider, outcome assessor) study with subjects receiving 2 single tDCS-MRS sessions.

**Healthy adults**

<table>
<thead>
<tr>
<th>T1 MRI (6 min)</th>
<th>tDCS (30 min of real or sham)</th>
<th>MRS dlPFC (11 min)</th>
<th>MRS striatum (11 min)</th>
<th>MRS dlPFC (11 min)</th>
</tr>
</thead>
</table>

- Local and distal tDCS effects.

- Effects during tDCS, but not long lasting.

- Effects with repeated tDCS sessions?

- Effects in patients?

Hone-Blanchet, Edden, Fecteau (2016) *Biological Psychiatry*

**Patients with gambling disorder**

- Potential intervention targeting the GABAergic system? Medications targeting the GABAergic system can reduce craving and impulsivity level in gambling disorder.

Dickler, Lenglos, Renauld, Ferland, Edden, Leblond, Fecteau (2018) *Neuropharmacology*
Plan

1. Noninvasive brain stimulation (NIBS) can modulate human behaviors (e.g., decision-making) in healthy subjects.

2. Translational value of NIBS studies in healthy subjects into clinical applications?
   Yes, but to some extent:
   - brain morphometry can impact the effects of NIBS;
   - brain activity can impact the effects of NIBS;
   - behaviors can impact the effects of NIBS.
The impact of brain morphometry on NIBS effects

**Connectivity strength**

**Neurotransmitter levels**

Greater dIPFC volume

= Greater tDCS impact on neural substrates

*Bouchard, *Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau (2021) *Brain Connect*

Bouchard, Dickler, Renauld, Lenglos, Ferland, Edden, Rouillard, Leblond, Fecteau (2020) *Brain Stimul*
The impact of brain morphometry on NIBS effects

Patients with gambling disorders as compared to healthy controls displayed smaller left dIPFC volume.

Should we adjust the stimulation parameters according to patient’s individual dIPFC morphometry?

The impact of brain morphometry on NIBS effects

- Impact of coil-to-scalp distance, grey matter volume of the area under the coil, white matter tract integrity from the coil location to the striatum.

- cTBS effects applied over the left frontal pole on functional connectivity during cue-reactivity in AUD.

Treating a patient with MDD, who also drinks too much alcohol?

The impact of functional connectivity on NIBS effects

Instantaneous and subsequent tDCS effects in a sham controlled, blind at 3 levels study with healthy subjects receiving concurrent tDCS-fMRI.

A. Impact of baseline rs-fMRI on changes in rs-fMRI after active and during sham stimulation in the fronto-parieto-occipital circuit

B. Impact of baseline rs-fMRI on changes in rs-fMRI during active and sham stimulation in the fronto-parietal circuit

C. Impact of baseline rs-fMRI on changes in rs-fMRI during and after active stimulation, and during sham stimulation in the fronto-parieto-occipitotemporal circuit

D. Impact of baseline rs-fMRI on changes in rs-fMRI during and after active stimulation, and during sham stimulation in the frontal circuit

**Stronger baseline functional connectivity = stronger tDCS impact on functional connectivity**

**Stronger fronto-parietal connectivity = stronger tDCS impact during stimulation**

**Stronger fronto-parietooccipital connectivity = stronger tDCS impact after stimulation**

Bouchard, Renauld, Fecteau (2023) *Front Hum Neurosci*
The impact of functional connectivity on NIBS effects

Efficiency of the right frontal cortex correlated with risk taking level in patients with gambling disorders

If we want to reduce risk taking, should we adjust the stimulation parameters according to patient’s individual frontal connectivity?

Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau (2023) *Eur Neuropsychopharmacol*
The impact of behaviors on NIBS effects

Greater risk taking, impulsivity, craving levels
Greater tDCS impact on neurotransmitter levels in the DLPFC and striatum

The importance of brain state on effects of NIBS

Do these effects differ based on brain state?

<table>
<thead>
<tr>
<th>rTMS</th>
<th>Craving</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 x 20Hz L DLPFC (Amiaz et al. 2009)</td>
<td>with smoking-related pictures</td>
</tr>
<tr>
<td>1 x 1Hz L SFG (Rose et al. 2011)</td>
<td>with neutral pictures</td>
</tr>
<tr>
<td>1 x 10Hz L SFG (Rose et al. 2011)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>tDCS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 2mA R DLPFC / L supraorbital area</td>
<td>when assessed with a cue-induced paradigm</td>
</tr>
<tr>
<td>(Shahbabaie et al. 2014)</td>
<td>when assessed at rest</td>
</tr>
</tbody>
</table>

Neuroimaging indicate differential patterns of activation between groups and processing stimuli:

- Smokers vs non-smokers
- Within a group of smokers, depending on their clinical characteristics
The importance of *brain state* on clinical responses to NIBS

rTMS for smoking cessation:
Each rTMS session is preceded by a 5-min provocation procedure to induce craving and followed by a 2-min motivational dialogue to promote smoking cessation.

rTMS to treat Obsessive-Compulsive Disorder:
Each rTMS session is combined by a 3-5 min individualize symptom provocation:
1. A hierarchically order list of personalized OCD symptom provocation before the rTMS regimen
2. At each rTMS session, the item that triggers the highest distress score is used
3. The patient is asked to think about this item before and during rTMS
Roth et al. *J Psychiatr Res* 2021
In which brain state should we stimulate?

Lack of effect of transcranial direct current stimulation (tDCS) on short-term smoking cessation: Results of a randomized, sham-controlled clinical trial

Mary Falcone, Leah Bernardo, E. Paul Wileyto, Cheyenne Allenby, Anne Marie Burke, Roy Hamilton, Mario Cristancho, Rebecca L. Ashare, James Loughead, Caryn Lerman

![Graph showing number of days abstinent with different levels of tDCS current and monetary rewards]
In which brain state we should stimulate?

Nicotine intake can cancel the effects of iTBS on motor function.

↑ thumb acceleration with iTBS over the contralateral M1.

Nondominant thumb abduction

Teo et al. (2011) *Cerebral Cortex*
When to prime the brain?  
(the impact of study design on NIBS effects)

Effects of NIBS on an orientation discrimination task testing 6 groups (N=14/group):  
online tDCS, offline tDCS,  
online tRNS, offline tRNS,  
online sham, offline sham.

Online protocol

~ 4 min
Block 1 Block 2 Block 3 Block 4 Block 5  
hf-tRNS, a-tDCS, or sham

~ 30 min

Offline protocol

~ 4 min
Block 1 Block 2 Block 3 Block 4 Block 5  
hf-tRNS, a-tDCS, or sham

~ 60 min

- Improvement with offline, but not with online tDCS.

- Improvement with online, but not with offline tRNS.

When to measure the outcome?

Pirrulli, Fertonani, Miniussi (2013) *Brain Stimul*
When to prime the brain?
(the impact of study design on NIBS effects)

Instantaneous and subsequent tDCS effects in a sham controlled, blind at 3 levels study with healthy subjects receiving concurrent tDCS-fMRI.

The effects are not always the same during vs after NIBS.

What if we measure symptom or prime the brain during or after NIBS?

Bouchard, Renauld, Fecteau (2023) Front Hum Neurosci
Value of cognition in understanding NIBS effects

tDCS can decrease level of food craving and intake.

This was a 3-arm, crossover, sham controlled, blind at 3 levels (subjects, tDCS provider, outcome assessors) study with adults with abnormal food craving receiving 3 single tDCS sessions.

Fregni, Orsati, Pedrosa, Fecteau, Tome, Nitsche, Mecca, Macedo, Pascual-Leone, Boggio (2008) *Appetite*
Value of cognition in understanding NIBS effects

tDCS induced an attentional shift from food to non-food related items.


tACS induced an attentional shift from smoking to non-smoking related items.
- tACS also reduced impulsive decision-making to smoke cigarettes.
- tACS did not diminish craving level.
Mondino, Lenglos, Cinti, Renauld, Fecteau (2020) Drug Alcohol Depend

Instantaneous and subsequent tDCS and tACS effects in healthy adults.

Mondino, Ghumman, Gane, Renauld, Whittingstall, Fecteau (2020) Front Hum Neurosci

Potential intervention targeting the fronto-parietal network to modulate attentional processing?
It works

rTMS to treat depression in military veterans:

![Graph showing remission rates for MDD without PTSD and with PTSD](Image)

**Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans**

A Randomized Clinical Trial

Jerome A. Yesavage, MD; J. Kaci Emslie, PhD; Zhilei Mi, PhD; Kousick Biswas, PhD; Anne Davis Karim, PharmD; Ciaran S. Phibbs, PhD; Steven D. Forman, MD, PhD; Michael Thase, MD; Leanne M. Williams, PhD; Amit Etkin, MD, PhD; Ruth O'Hara, PhD; Gerald Geriguette, RN; Tamara Beale, MA; Grant D. Huang, MPH, PhD; Art Noda, MD; Mark S. George, MD, for the VA Cooperative Studies Program Study Team
Does it work? Neuroimaging: please help!

rTMS to treat depression in military veterans:

Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans: A Randomized Clinical Trial

Jerome A. Yesavage, MD, J. Kaci Fajerchild, PhD, Zhida Li, PhD, Kousick Biswas, PhD, Anne Davis Karim, PharmD; Ciaran S. Phibbs, PhD; Steven D. Forman, MD, PhD; Michael Thase, MD; Leanne M. Williams, PhD; Amrit Etkin, MD, PhD; Ruth Offord, PhD; Gerald Geriggette, RN; Tamara Beale, MA; Grant D. Huang, MPH, PhD; Art Noda, MD; Mark S. George, MD, for the VA Cooperative Studies Program Study Team
Value of neuroimaging and cognition in understanding NIBS effects and the translational value from healthy to clinical populations

Cascade of neuro-cognitive impact of NIBS over the DLPFC

Koob & Volkow (2010) Neuropsychopharmacology

What we want is to reach and stimulate a receptive network

Fecteau, Camprodon, Boggio, Fregni, Pascual-Leone (2010) Subst Use & Misuse

Changing social norm compliance with noninvasive brain stimulation.
Ruff CC, Ugazio G, Fehr E.


The truth about lying: inhibition of the anterior prefrontal cortex improves deceptive behavior.


Disrupting the prefrontal cortex diminishes the human ability to build a good reputation.
Knoch D, Schneider F, Schunk D, Hohmann M, Fehr E.


Disrupting the right prefrontal cortex alters moral judgement.


Enhancing social ability by stimulating right temporoparietal junction.
Santiesteban I, Banissy MJ, Catmur C, Bird G.


The world can look better: enhancing beauty experience with brain stimulation.
Take Home Message

NIBS can modulate behaviors in healthy individuals

Impair (*virtual lesion*)

Improves (*neuroenhancement*)

*Can this be a concern for my patients?*

*Can this be relevant for my patients?*

---

Translational value of NIBS studies in healthy subjects into clinical applications?

Yes, but to some extent:
- brain morphometry can impact the effects of NIBS
- brain activity can impact the effects of NIBS
- behaviors can impact the effects of NIBS
- Are they different between healthy subjects and patients?
- Are they different within a clinical population (and within a patient)?
Thank you!

Questions?