Intensive Course in TMS - June 2025

Translational value of TMS studies in healthy subjects into clinical populations

Shirley Fecteau, PhD

Professor of Psychiatry and Neurosciences, Medical School, Université Laval

Deputy Editor, *Brain Stimulation*, Elsevier
Deputy Editor, *Transcranial Magnetic Stimulation*, Elsevier

Fellow at BIDMC 2005 - 2010
TMS Course lecturer 2005 - …

Deputy editor royalties from Elsevier

Fundings: CIHR, NSERC, NFRF, CFI, CPCoE, Canadian National Defence

Plan

Translational value of noninvasive brain stimulation (NIBS) studies in healthy subjects into clinical applications: Yes, but to some extent.

Example with substance-related and addictive disorders.

Repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS) over the dorsolateral Prefrontal Cortex (dlPFC) can modulate behaviours in healthy subjects.

↓

Impair
(virtual lesion)

↓

Can this be a concern for our patients?

↓

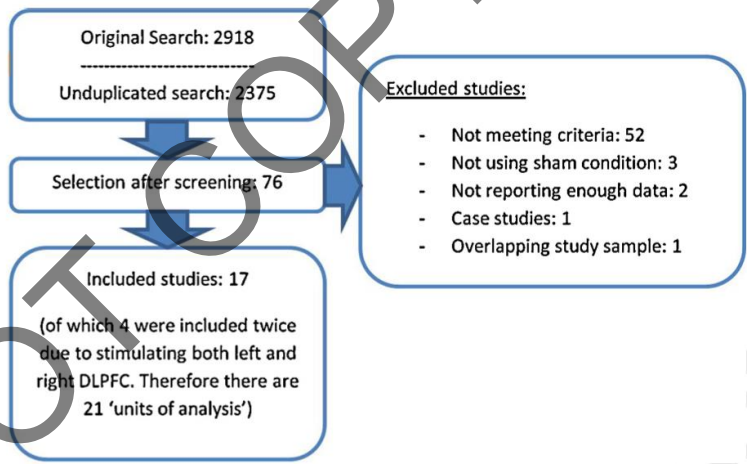
Improve
(neuroenhancement)

↓

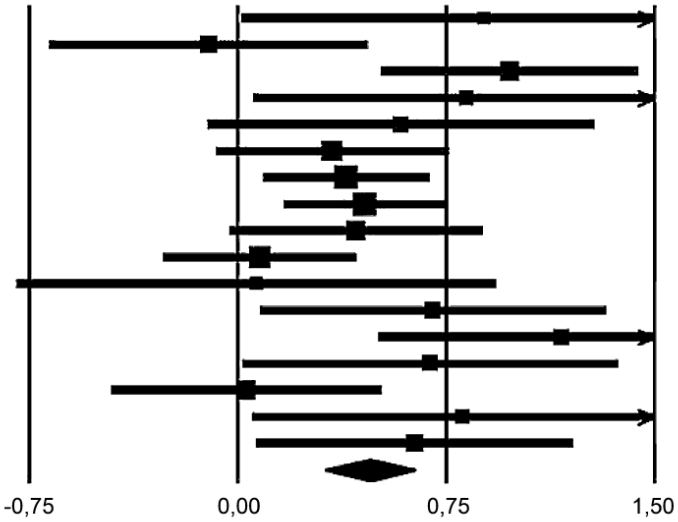
Can this be beneficial for our patients?

NIBS can reduce craving for:

- Nicotine
- Alcohol
- Food
- Marijuana
- Psychostimulant



Study name	Technique	Stimulation site	Single or combined study	Number of sessions	Number of subjects	Hedge's *g*
Amiaz et al. (2009)	rTMS	Left	Single Study	10	21	0.888
Barth et al. (2011)	rTMS	Left	Single Study	2	10	−0.104
Boggio et al. (2008)	tDCS	Both	Combined	2	26	0.98
Boggio et al. (2009)	tDCS	Left	Single Study	5	27	0.824
Boggio et al. (2010)	tDCS	Both	Combined	1	33	0.587
Claudino et al. (2011)	rTMS	Left	Single Study	1	22	0.341
Fregni et al. (2008a) (food)	tDCS	Both	Combined	2	46	0.391
Fregni et al. (2008b) (smoking)	tDCS	Both	Combined	2	48	0.458
Goldman et al. (2011)	tDCS	Right	Single Study	2	19	0.427
Herremans et al. (2011)	rTMS	Right	Single Study	1	31	0.08
Hoppner et al. (2011)	rTMS	Left	Single Study	10	19	0.069
Johann et al. (2003)	rTMS	Left	Single Study	2	11	0.703
Mishra et al. (2010)	rTMS	Right	Single Study	10	45	1.165
Montenegro et al. (2012)	tDCS	Left	Single Study	2	9	0.694
Nakamura-Palacios et al. (2011)	tDCS	Left	Single Study	2	32	0.031
Uher et al. (2005)	rTMS	Left	Single Study	1	28	0.809
Wing et al. (2012)	rTMS	Bilateral	Single Study	50	13	0.699
						0.476



Jansen, Daams, Koeter, Veltman, van den Brink, Goudriaan, *Neurosci Biobehav Rev* 2013.

Sham-controlled rTMS and tDCS trials on use and craving

Alcohol use disorder (AUD)

rTMS	Drinking	Craving
Addolorato et al. 2017	↓	n.s.
Perini et al. 2020	n.s.	n.s.
Harel et al. 2022	↓	↓
McCalley et al. 2022	n.s.	↓
Zhang et al. 2022	↓	↓
Hoven et al. 2023	n.s.	n.s.
Selim et al. 2024	↓	↓

tDCS	Drinking	Craving
Claus et al. 2019	n.s.	n.s.
Witikiewitz et al. 2019	n.s.	n.s.
Holla et al. 2020	↓	n.s.
Dubuson et al. 2021	↓	n.s.
Camchong et al. 2023	↓	n.s.
Dayal et al. 2024	n.s.	n.s.

Cocaine use disorder (CUD)

rTMS	Use	Craving
Bolloni et al. 2016	n.s.	
Martinez et al. 2018	↓	n.s.
Lolli et al. 2021	n.s.	↓
Garza-Villarreal et al. 2021	n.s.	↓
Martinotti et al. 2022	n.s.	n.s.
McCalley et al. 2024	n.s.	↓

tDCS	Use	Craving
Verveer et al. 2020	n.s.	n.s.
Gaudreault et al. 2022	n.s.	n.s.
Verveer et al. 2022	n.s.	n.s.

What do we know about brain morphometry of these patients?

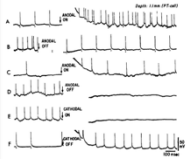
Reduced gray matter volume in the frontal cortex (including the prefrontal cortex) and insula in AUD[1] and CUD.[2]

[1] Spindler, Trautmann, Alexander, Broning, Bartscher, Stuppe, Muellhan, Sci Rep 2021; Yang, Tian, Zhang, Zeng, Chen, Wang, Jia, Gong, *Neurosci Biobehav Rev* 2016.

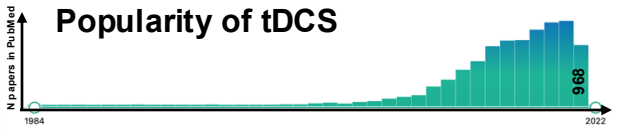
[2] Poireau, Segobin, Maillard, Clergue-Duval, Icick, Azuar, Volle, Delmaire, Bloch, Pitel, Vorspan, *Psychiatry Res Neuroimaging* 2024.

A lesson from history? Do we reach the cortex?

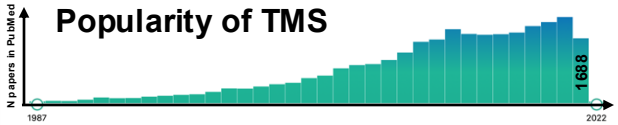
- More than a century ago… There were some behavioral changes, but the effects were unreliable.
- The current was presumably <u>not going through the brain</u>.



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



- Ruff et al. 2013 Changing social norm compliance with noninvasive brain stimulation. *Science*
- Brunoni et al. 2017 Trial of electrical direct-current therapy versus escitalopram for depression. *N Engl J Med*



- Yesavage et al. 2018 Effect of rTMS on treatment-resistant major depression in US veterans: a randomized clinical trial. *JAMA Psychiatry*
- Romero et al. 2019 Neural effect of TMS at the single-cell level. *Nat Commun*

- 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 of positive findings.

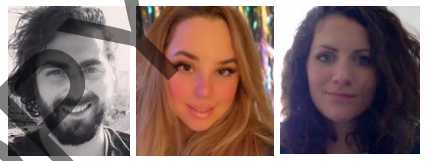
- In order to move forward, we need to deepen mechanistic knowledge to induce reliable and replicable effects.

Fecteau, *The Neuroscientist* 2023.

Let's start with the "simplest" question…:

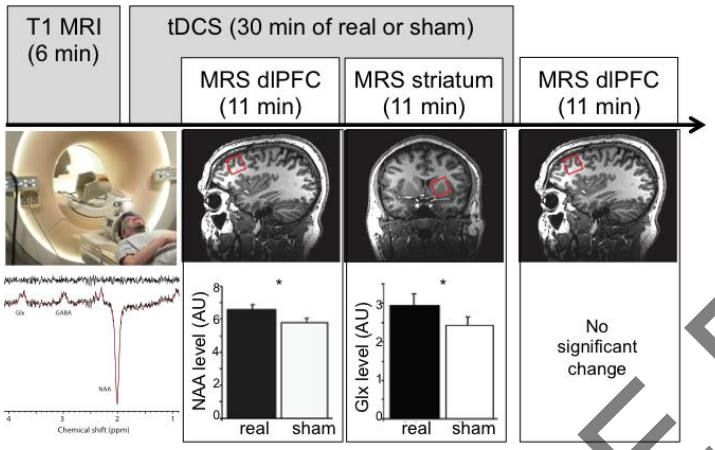
Do we reach the cortex?

Did NIBS reach the cortex?

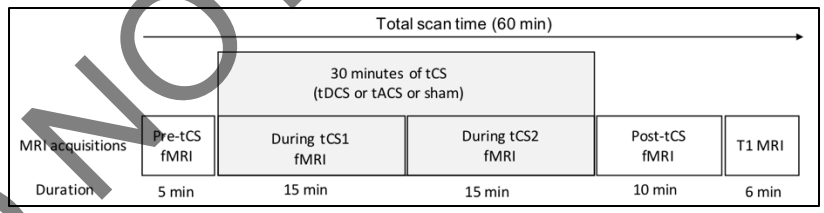


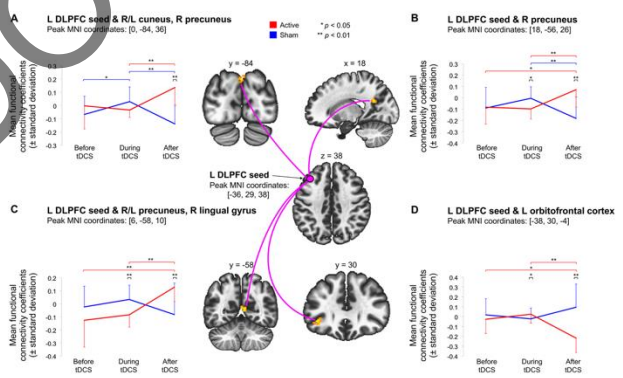
Concurrent tDCS-MRI, sham controlled, blind at 3 levels studies to identify the neural effects of tDCS in healthy adults.

Concurrent tDCS-MRSI[1]

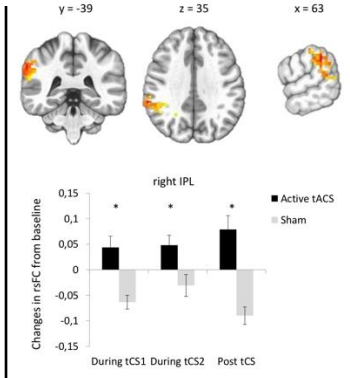


Concurrent tCS-fMRI





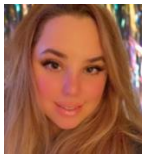
tDCS[2]



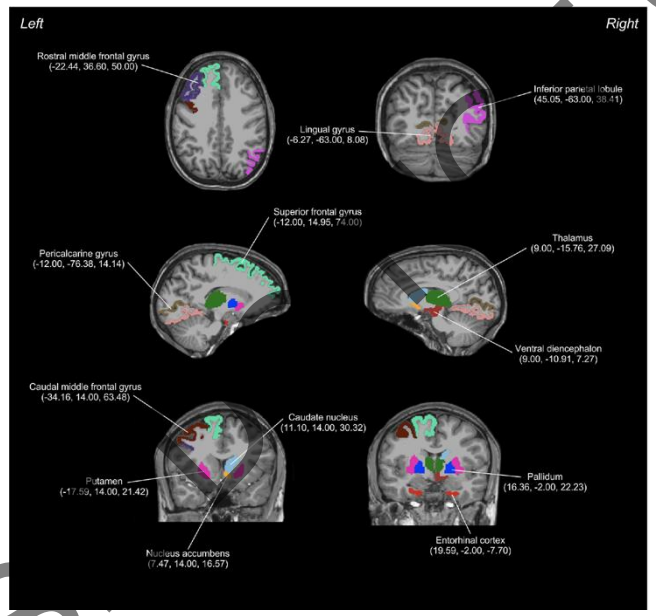
tACS[3]

[1]Hone-Blanchet, Edden, Fecteau, *Biol Psychiatry* 2016.
[2]Bouchard, Renauld, Fecteau, *Front Hum Neurosci* 2023.
[3]Mondino, Ghumman, Gane, Renauld, Whittingstall, Fecteau, *Front Hum Neurosci* 2020.

Can NIBS reach the cortex of adults with gambling disorder?

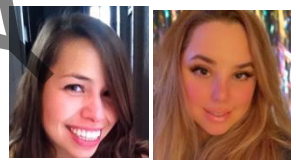


Adults with gambling disorders compared to healthy controls displayed smaller volume of the left dlPFC.



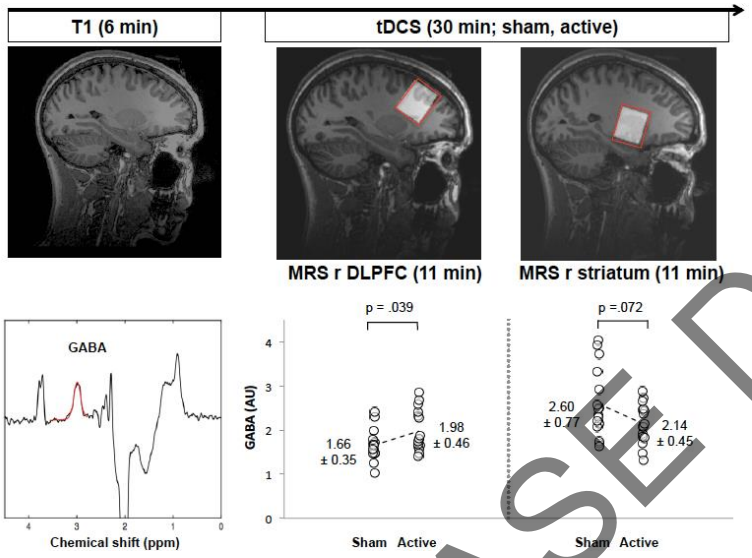
Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau. *J Psychiatr Res* 2021.

Did NIBS reach the cortex of adults with gambling disorder?



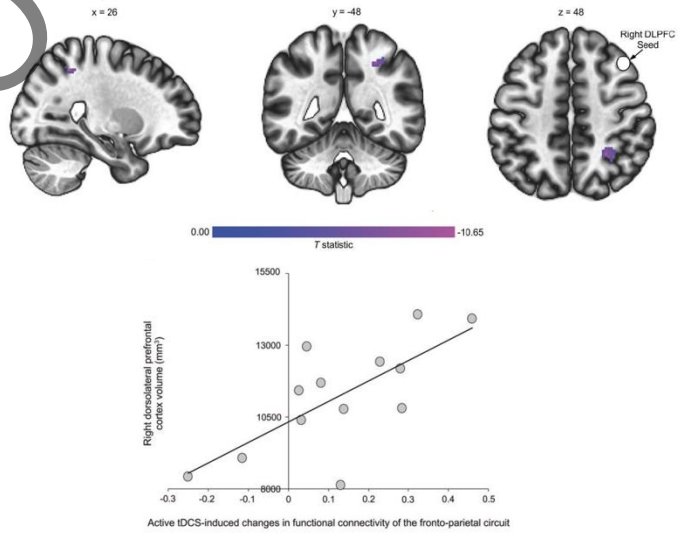
Concurrent tDCS-MRI, sham controlled, blind at 3 levels studies to identify the neural effects of tDCS applied over the dlPFC.

Concurrent tDCS-MRSI[1]



Potential intervention targeting the GABAergic system?

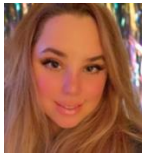
Concurrent tDCS-fMRI[2]



Potential intervention targeting the fronto-parietal circuit, known to be involved in attentional processes?

[1]Dickler, Lenglos, Renauld, Ferland, Edden, Leblond, Fecteau, *Neuropharmacology* 2018.
[2]Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau, *Brain Connect* 2021.

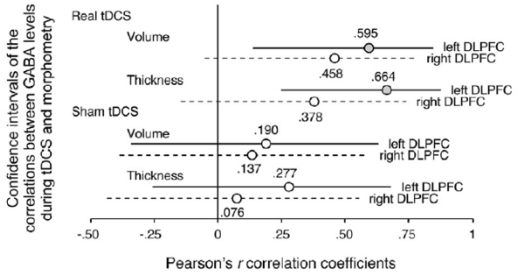
The impact of brain morphometry on the neural effects of tDCS.

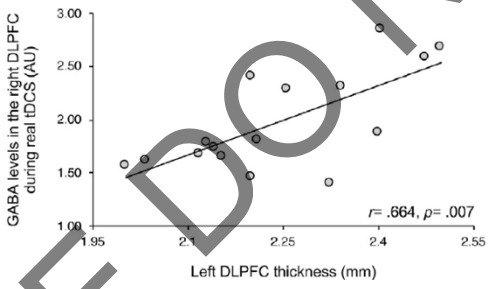


tDCS applied over the dlPFC in adults with gambling disorder.

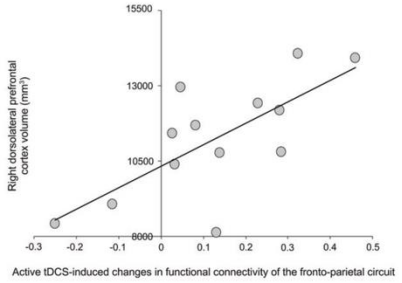
Greater dlPFC volume and thickness
=
Greater tDCS related changes in neurotransmitter levels and functional connectivity strength.

Concurrent tDCS-MRSI[1]





Concurrent tDCS-fMRI[2]



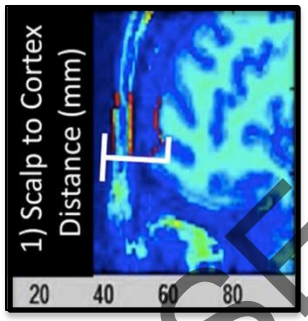
Should we adjust the stimulation parameters based on patient's morphometry of the stimulation site (dlPFC morphometry)?

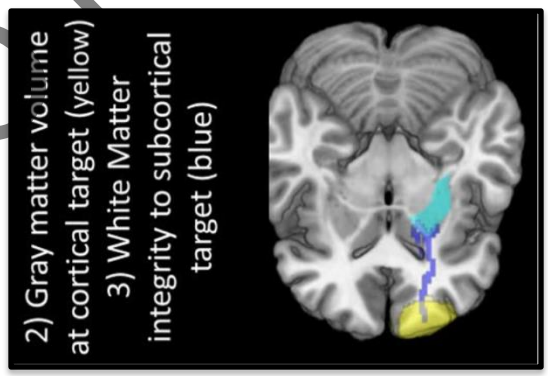
[1]Bouchard, Dickler, Renauld, Lenglos, Ferland, Edden, Rouillard, Leblond, Fecteau, *Brain Stimul* 2020.
[2]Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau, *Brain Connect* 2021.

The impact of scalp-to-cortex distance on the neural effects of rTMS.

cTBS applied over the left frontal pole on functional connectivity fMRI in adults with Alcohol Use Disorder.

cTBS related change in fronto-striatal connectivity was influenced by the scalp-to-cortex distance (strongest predictor).





Hanlon, Lench, Dowdle, Ramos. *Clin Pharmacol Ther* 2019.

Plan

Translational value of noninvasive brain stimulation (NIBS) studies in healthy subjects into clinical applications: Yes, but to some extent.

The effects of NIBS can be impacted by brain morphometry.

Brain morphometry can be different:
- between groups (e.g., healthy subjects and patients)
- within a group (e.g., patients with or without comorbid depression and Alcohol Use Disorder.)
- within an individual (e.g., sobriety).

Next, what does NIBS modulate when it induces clinical benefits?

rTMS on smoking in Tobacco Use Disorder.

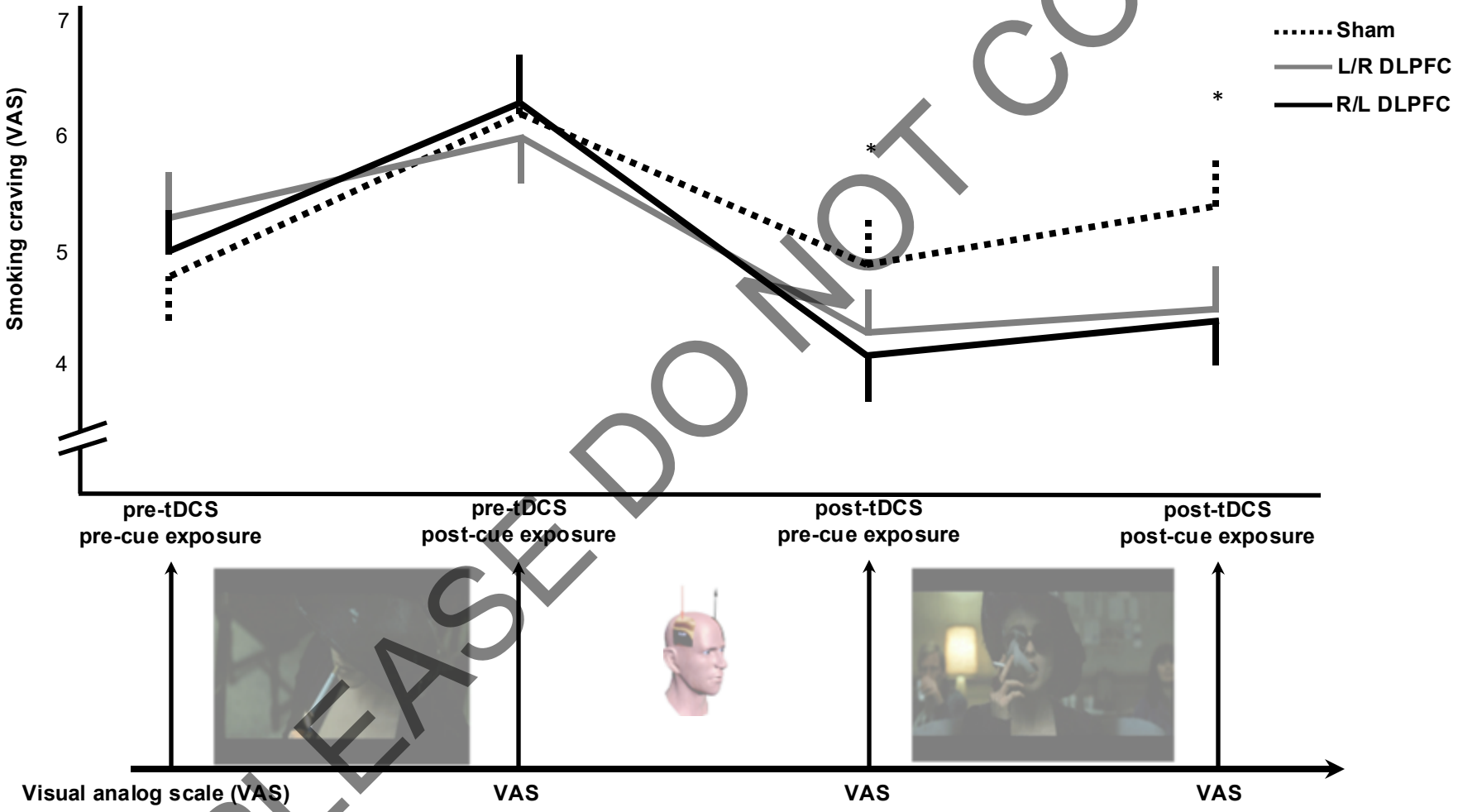
The US FDA cleared protocol of rTMS as an aid in short-term smoking cessation in adults

- **Daily rTMS, 5 days/week, for 3 weeks, followed by 1 weekly rTMS session for 3 weeks.**
- **Each 10Hz rTMS session is preceded by a 5-min provocation procedure to induce craving.**
- **Each rTMS session is followed by a 2-min motivational language to encourage smoking cessation.**

Young, Galla, Appelbaum. *Am J Prev Med* 2021.

tDCS over the dlPFC on craving in adults with Tobacco Use Disorder.

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



Fregni, Liguori, Fecteau, Nitsche, Pascual-Leone, Boggio. *J Clin Psychiatry* 2008.

What do we modulate when NIBS induces lasting clinical benefits?

	smoking	craving	rTMS protocol		
			N sessions	Hz	coil site
Li et al. 2020	↓	↓	10	10	l dlPFC

10 sessions of 10Hz rTMS over the left dlPFC of adults with tobacco use disorder:

- **Quitting smoking:**

  lower connectivity between the dorsal anterior cingulate cortex (dACC) and medial orbitofrontal cortex

- **Reduced cigarette consumption:**

  increased activity in the dACC

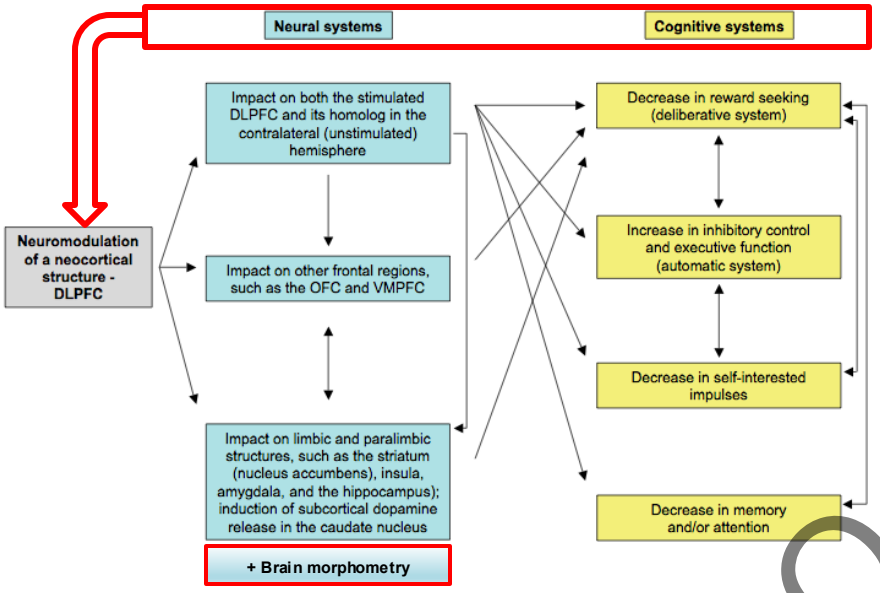
- **Craving:**

  no changes in functional connectivity

- **Impact of rTMS on the balance between drive-reward and executive control?**

Li, Caulfield, Hartwell, Henderson, Brady, George, *Brain Imaging Behav* 2024.

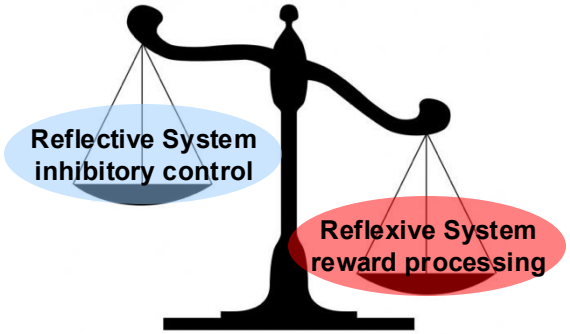
What do we modulate when we apply NIBS over the dlPFC?



There are several ways to induce clinical benefits, and they are not mutually exclusive.

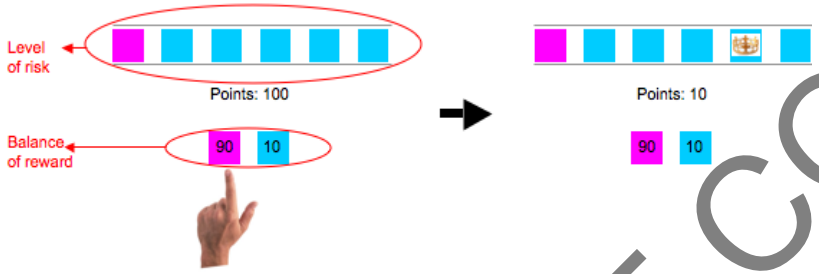
Risky decision-making, a characteristic behavioural phenotype in addictions:

- risk taking;
- reward seeking;
- impulsivity;
- delayed gratification;
- attention.

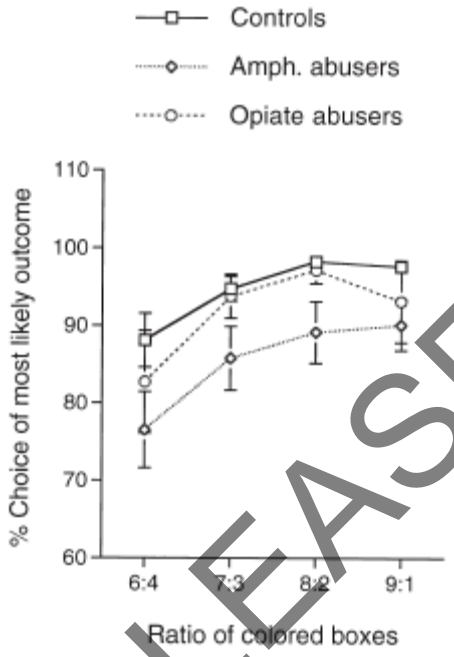


Fecteau, Camprodon, Boggio, Fregni, Pascual-Leone, *Subst Use Misuse* 2010.

Risk taking, reward seeking

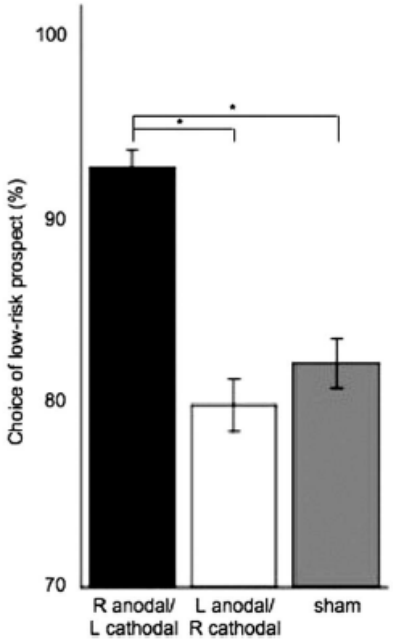


Patients with substance use disorders take greater risk at the Risk Task.



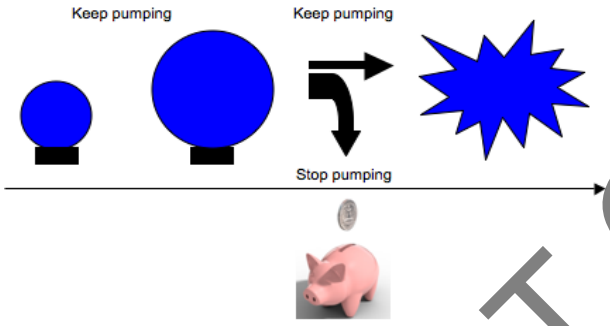
Rogers, Everitt, Baldacchino, et al. *Neuropsychopharmacology* 1999.

tDCS over the dlPFC can decrease risk taking and reward seeking at the Risk Task.

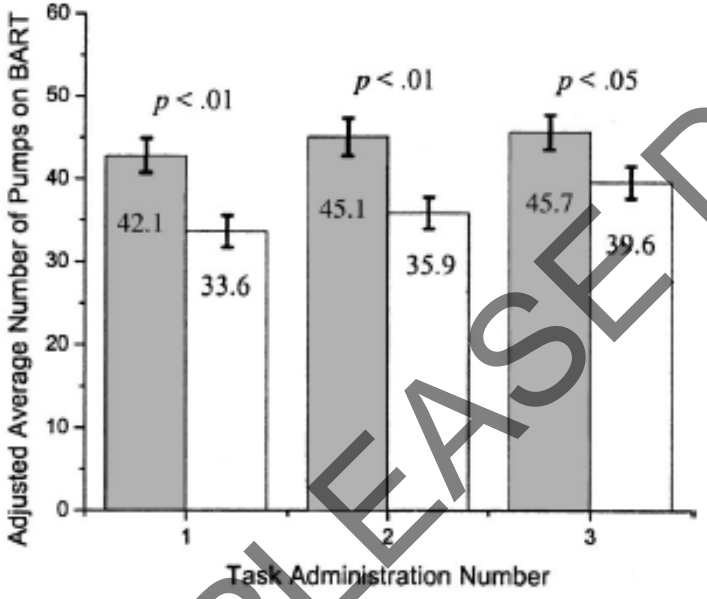


Fecteau, Knoch, Fregni, Sultani, Boggio, Pascual-Leone, *J Neurosci* 2007a.

Risk taking, reward seeking

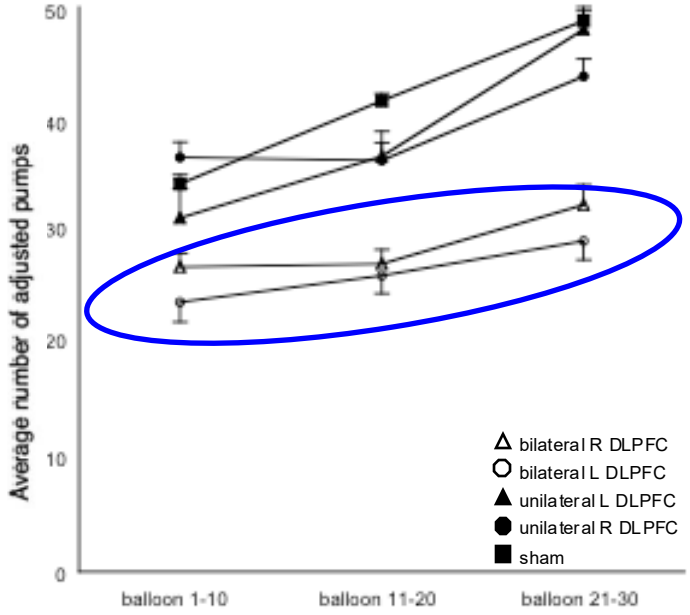


Patients with tobacco use disorders take greater risk at the BART.



Lejuez, Aklin, Jones, Richards, Strong, Kahler, Read, *Exp Clin Psychopharmacol* 2003.

tDCS over the dlPFC can decrease risk taking at the BART task.



Fecteau, Pascual-Leone, Zald, Liguori, Theoret, Boggio, Fregni, *J Neurosci* 2007b.

Self-interest

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

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

Ultimatum Game

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. *Neuro Endocrinol Lett* 2007.

Self-interest

The Ultimatum Game

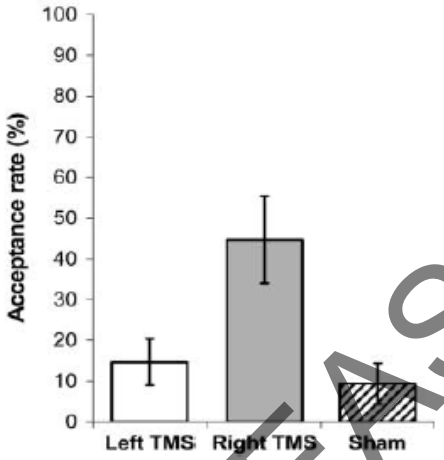
The proposer has $10 and offers you $2

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

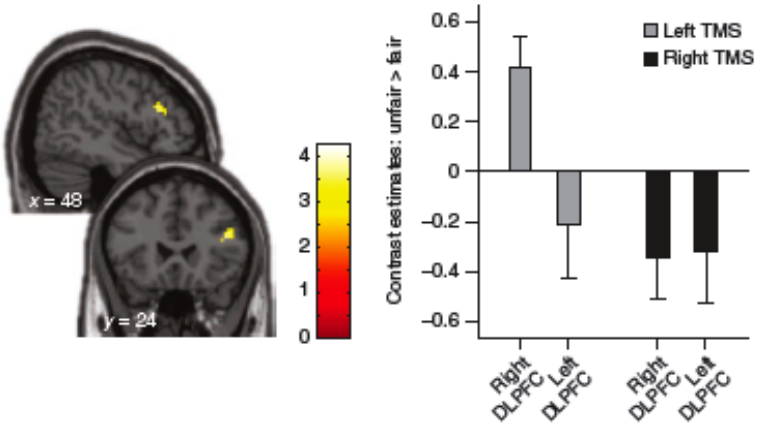
If you reject :
The proposer gets $0 and you get $0

1Hz rTMS over the R dlPFC

Accepted more often unfair offers



Elicited activity in both dlPFCs when contrasting unfair > fair offers



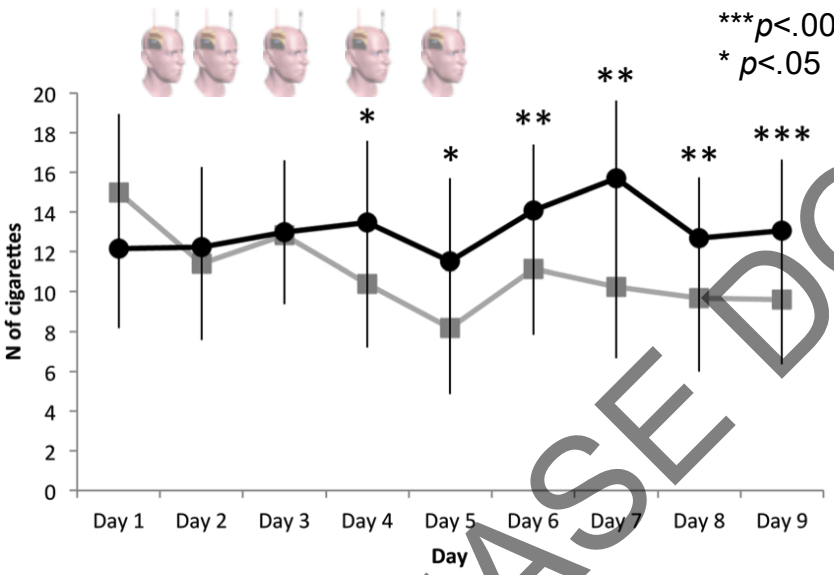
Knoch, Pascual-Leone, Meyer, Treyer, Fehr. *Science* 2006.

Baumgartner, Knoch, Hotz, Eisenegger, Fehr. *Nat Neurosci* 2011.

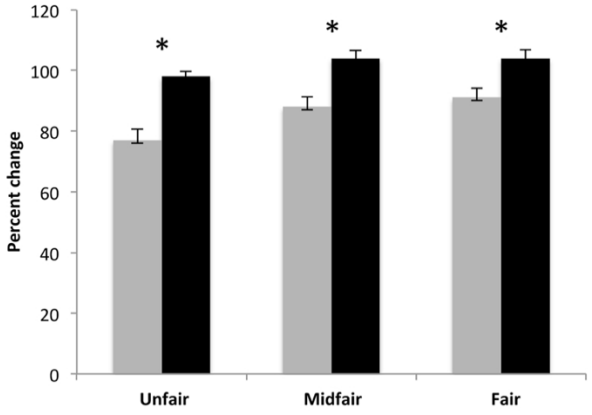
Self-interest, smoking

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).

N of reported cigarettes smoked



Ultimatum Game



Real tDCS (anode and cathode over the R and L DLFPC)
Sham tDCS (anode and cathode over the R and L DLFPC)

Fecteau, Agosta, Hone-Blanchet, Fregni, Boggio, Ciraulo, Pascual-Leone. *Drug Alcohol Depend* 2014.

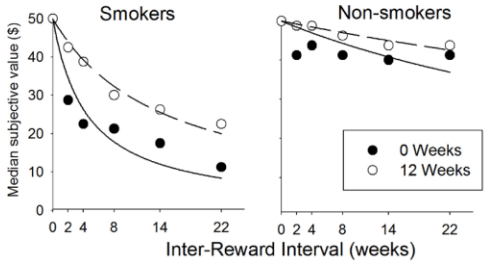
Impulsivity, delayed gratification, craving

Would you prefer to receive:

$20 now

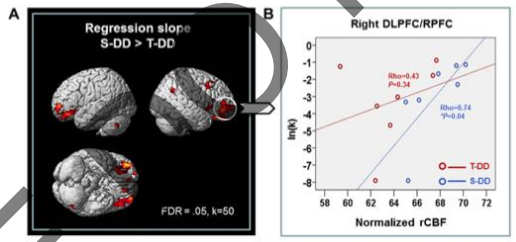
$26 tomorrow

Smokers choose more often the smaller, immediate offer of money



Mitchell & Wilson, *Psychopharmacology* 2012.

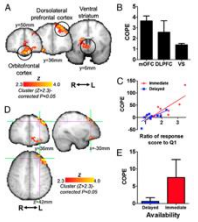
cTBS over the R dlPFC in healthy subjects



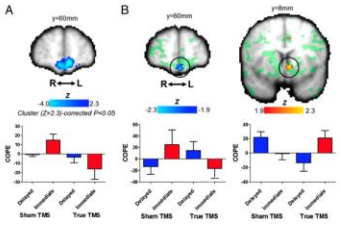
Cho, Pellecchia, Ko, Ray, Obeso, Houle, Strafella. *Brain Stimul* 2012.

1Hz rTMS over the l dlPFC in smokers

Delayed gratification



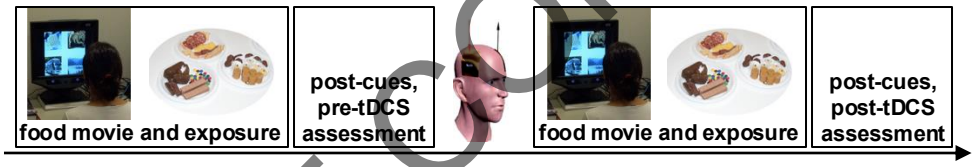
Decreased craving

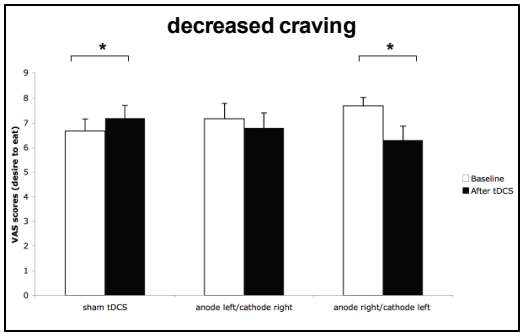


Hayashi, Ko, Strafella, Dagher, *PNAS* 2013.

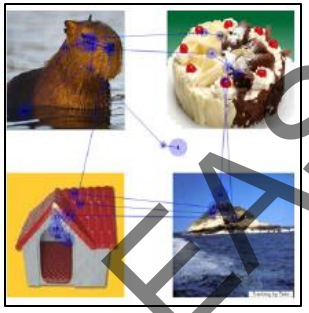
Craving, consumption, attentional processes

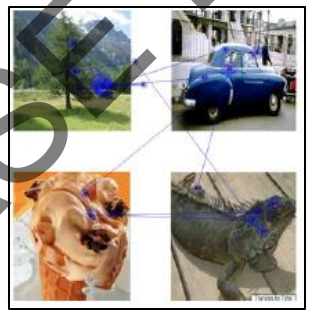
This was a 3-arm, crossover, sham controlled, blind at 3 levels study with adults with abnormal food craving receiving single tDCS sessions.

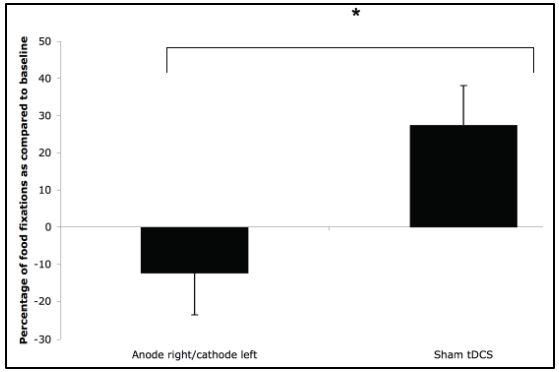




tDCS induced an attentional shift from food to non-food related items.



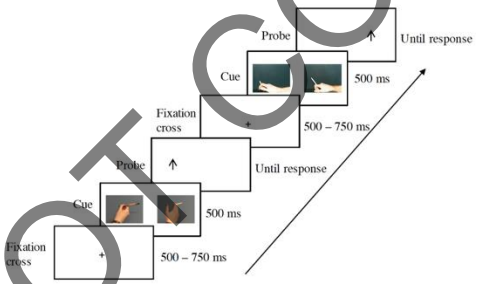




Fregni, Orsati, Pedrosa, Fecteau, Tome, Nitsche, Mecca, Macedo, Pascual-Leone, Boggio. *Appetite* 2008.

Craving, attentional processes

This was a crossover, sham controlled, blind at 3 levels study with adults with tobacco use disorder receiving tACS over the dlPFC.



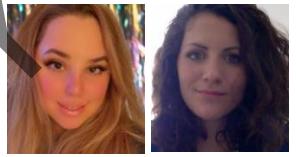
- tACS induced an attentional shift from smoking to non-smoking related items.

- tACS reduced impulsive decision-making to smoke cigarettes.

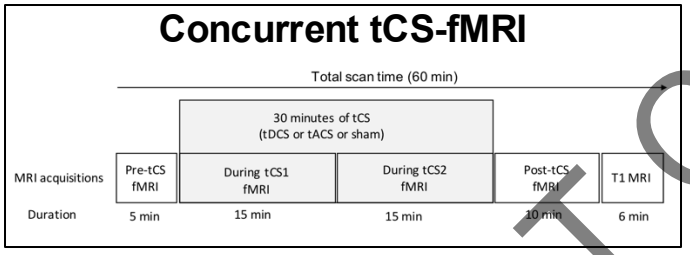
- tACS did not change craving level.

Mondino, Lenglos, Cinti, Renaud, Fecteau, *Drug Alcohol Depend* 2020.

NIBS applied over the dlPFC modulates fronto-parietal networks, known to be involved in attentional processes

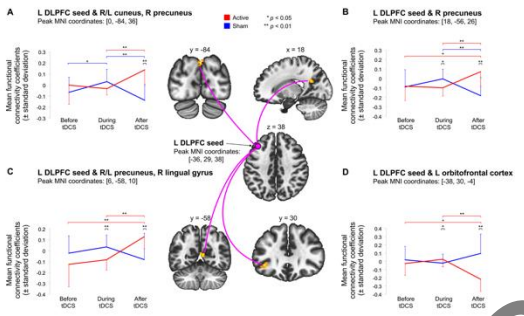


Concurrent tCS-fMRI

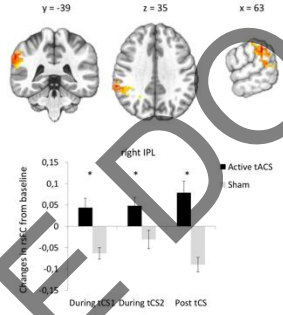


Healthy adults

tDCS-fMRI[1]

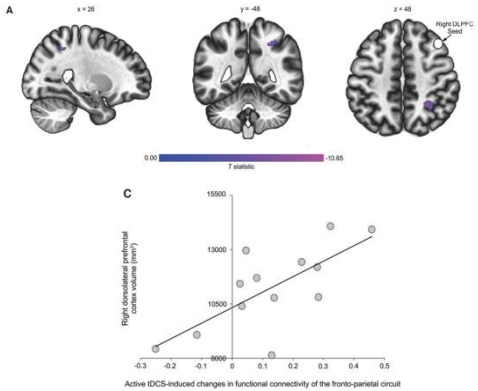


tACS-fMRI[2]



Adults with gambling disorder

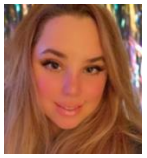
tDCS-fMRI[3]



Potential intervention targeting the fronto-parietal circuit, known to be involved in attentional processes?

[1]Bouchard, Renauld, Fecteau, *Front Hum Neurosci* 2023.
[2]Mondino, Ghumman, Gane, Renauld, Whittingstall, Fecteau, *Front Hum Neurosci* 2020.
[3]Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau, *Brain Connect* 2021.

The impact of functional connectivity on the neural effects of NIBS

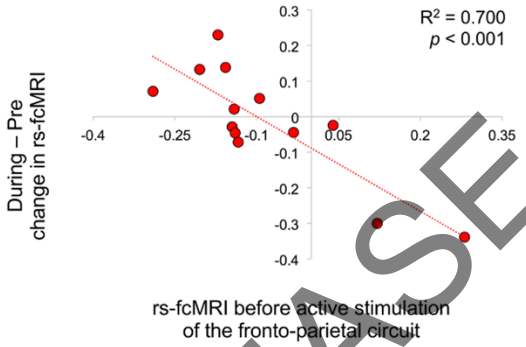


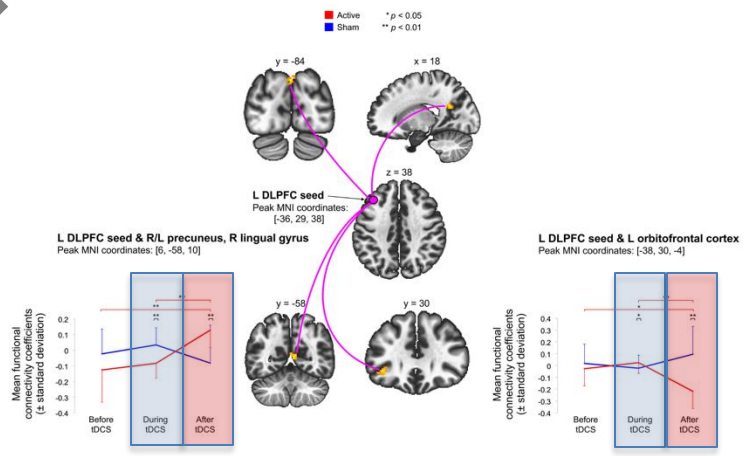
Concurrent tDCS-fMRI : instantaneous and subsequent tDCS effects in a sham controlled, blind at 3 levels study with healthy adults.

Stronger baseline functional connectivity
=
stronger tDCS impact on functional connectivity

tDCS induced changes in functional connectivity

during ≠ after tDCS



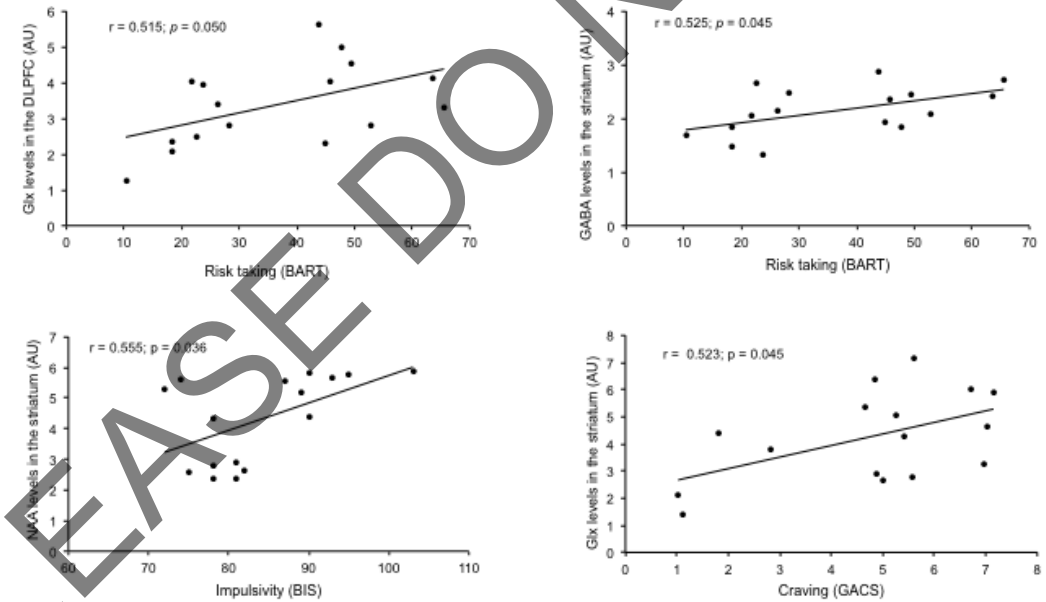


Bouchard, Renauld, Fecteau, *Front Hum Neurosci* 2023.

The impact of behavioural <u>trait</u> on the neural effects of NIBS

Concurrent tDCS-MRI, sham controlled, blind at 3 levels design to identify the neural effects of tDCS in adults with gambling disorder.

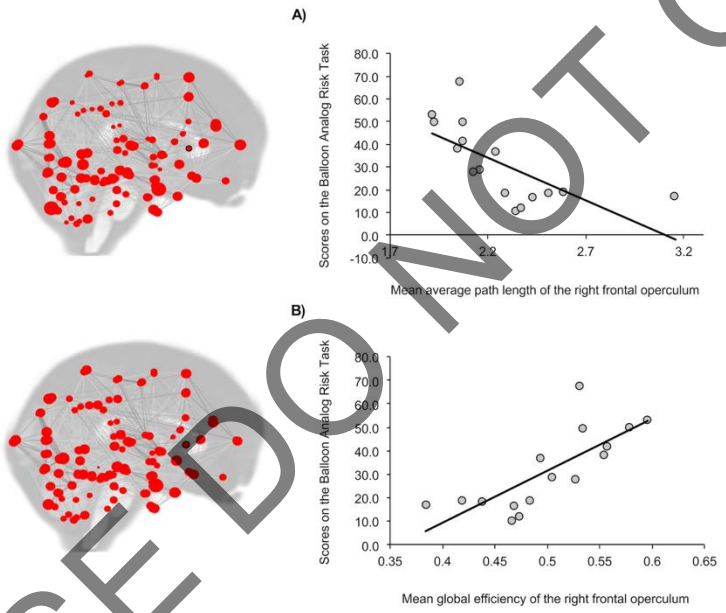
Greater risk taking, impulsivity, craving levels
=
Greater tDCS impact on neurotransmitter levels in the dlPFC and striatum



Dickler, Lenglos, Renauld, Ferland, Edden, Leblond, Fecteau, *Neuropharmacology* 2018.

The relevance of resting state functional connectivity for behavioral trait.

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. *Eur Neuropsychoparmacol* 2023.

Plan

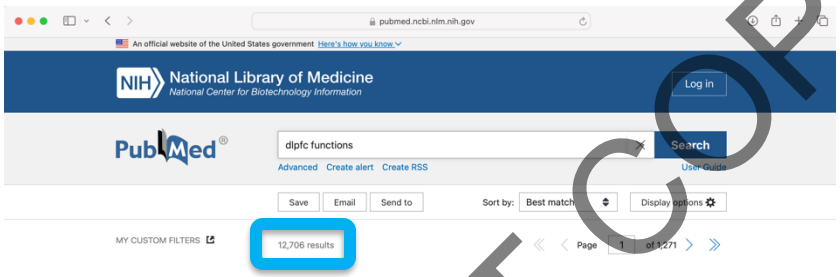
Translational value of NIBS studies in healthy subjects into clinical applications? Yes, but to some extent.

The effects of NIBS can be impacted by:
- brain morphometry
- brain activity
- behavioural trait and state.

Brain morphometry, activity and behaviours can be different:
- between groups (e.g., healthy subjects and patients)
- within a clinical population (e.g., patients with comorbid MDD and AUD)
- within an individual (e.g., sobriety).

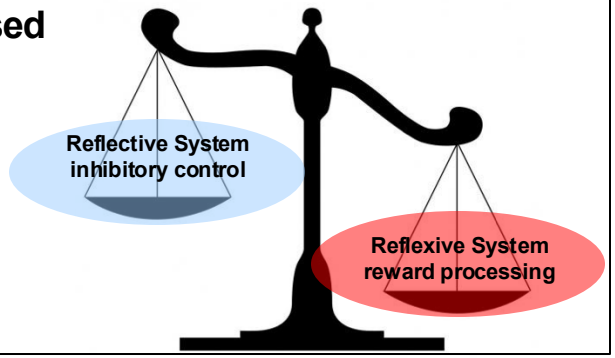
NIBS over the dlPFC can modulate decision-making processes and…?

Functions related to the dlPFC



Impaired decision making processes seem to be linked to increased vulnerability for substance-related and addictive disorders (behavioural phenotype)[1].

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



The US FDA cleared protocol of rTMS as an aid in short-term smoking cessation in adults

- **Each 10Hz rTMS session is preceded by a 5-min provocation procedure to induce craving.**

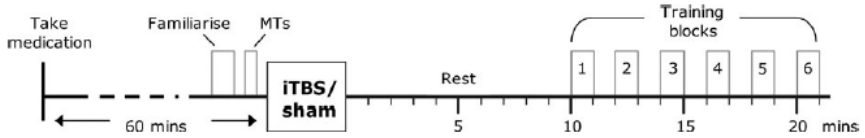
Is craving the best option to prime the brain for all?

[1] Goldstein & Volkow. *Am J Psychiatry* 2002; Wilson, Sayette, Fiez. *Nat Neurosci* 2004; Epstein, Bang, Botvin. *Addict Behav* 2007.

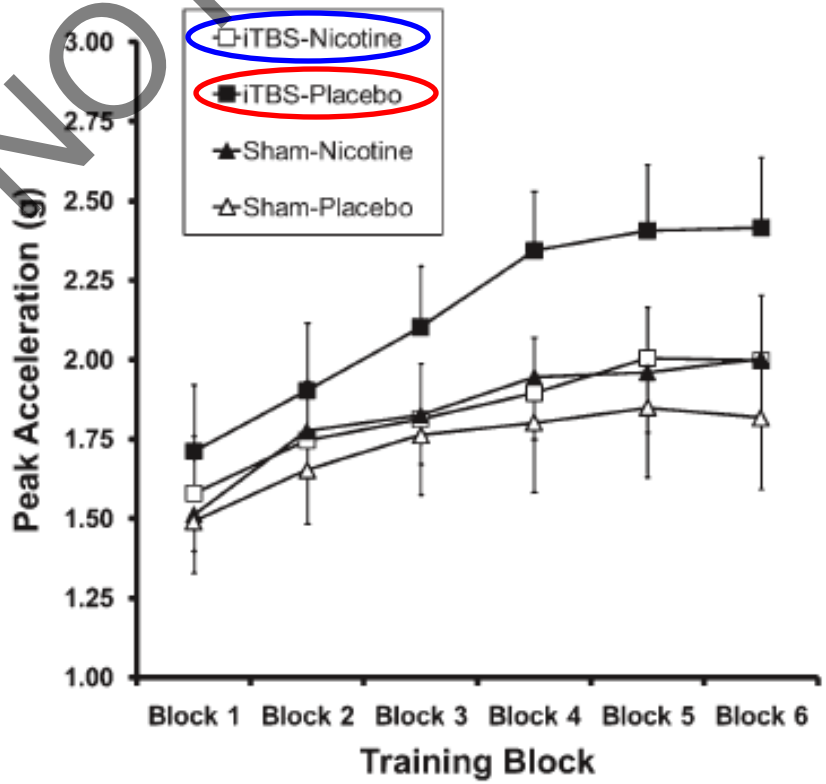
In which brain state we should stimulate?

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

↑ **thumb acceleration with iTBS over the contralateral M1.**



Nondominant thumb abduction

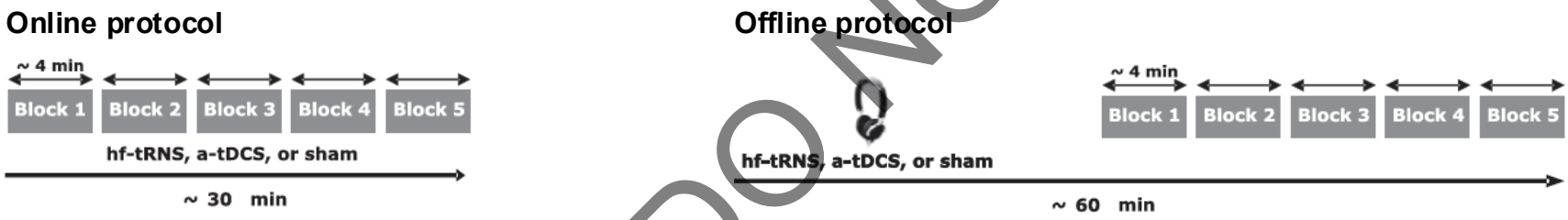


Teo, Swayne, Cheeran, Greenwood, Rothwell. *Cereb Cortex* 2011.

When to prime the brain?

Effects of NIBS on an orientation discrimination task testing:

- **online tDCS, offline tDCS,**
- **online tRNS, offline tRNS,**
- **online sham, offline sham.**



- Improvement with offline, but not with online tDCS.

- Improvement with online, but not with offline tRNS.

Pirrulli, Fertonani, Miniussi. *Brain Stimul* 2013.

Plan

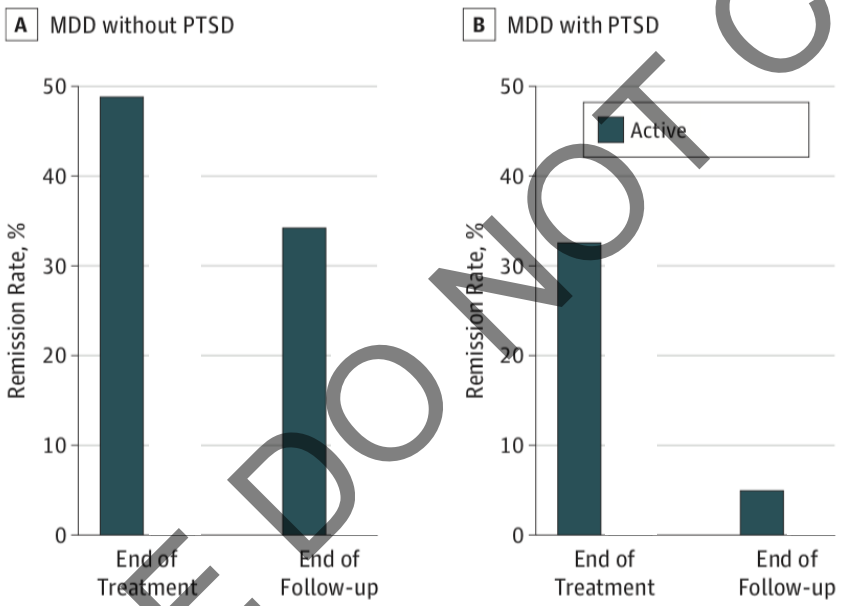
Translational value of NIBS studies in healthy subjects into clinical applications? Yes, but to some extent.

The effects of NIBS can be impacted by:
- brain morphometry
- brain activity
- behavioural trait and state.

Value of neuroimaging and cognition in understanding the clinical benefits of NIBS.

The value of neuroimaging in NIBS treatment.

rTMS to treat depression in military veterans



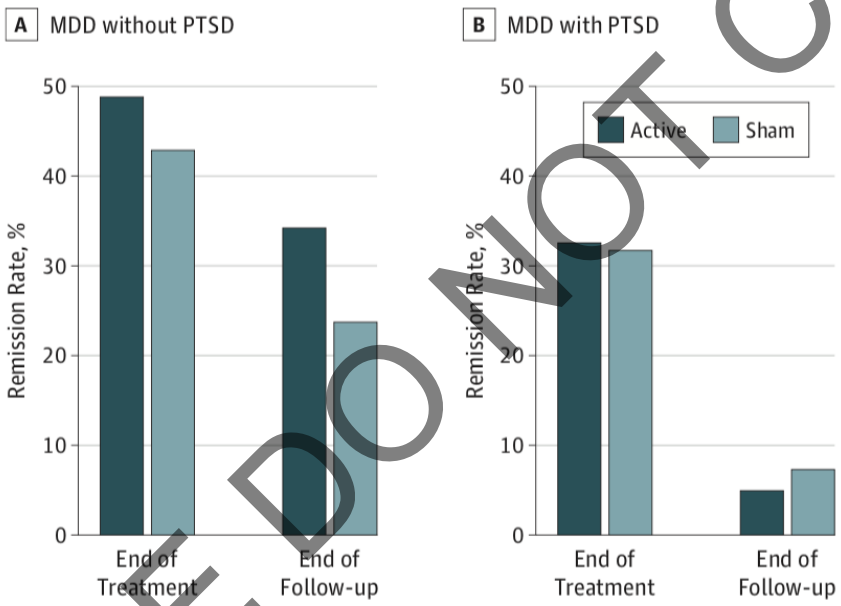
JAMA Psychiatry | Original Investigation

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

Jerome A. Yesavage, MD; J. Kaci Fairchild, PhD; Zhibao 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 Georgette, RN; Tamara Beale, MA; Grant D. Huang, MPH, PhD; Art Noda, MS; Mark S. George, MD; for the VA Cooperative Studies Program Study Team

The value of neuroimaging in NIBS treatment.

rTMS to treat depression in military veterans



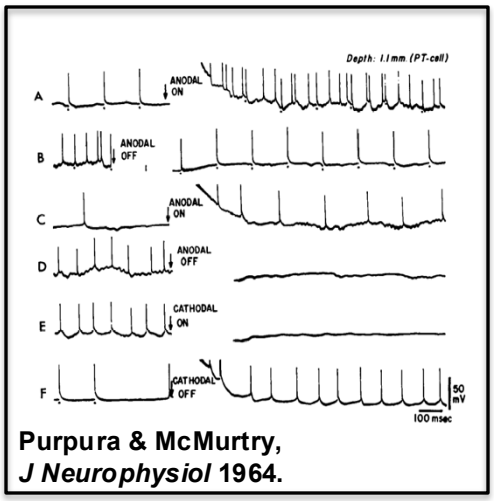
The importance of sham-controlled trial

JAMA Psychiatry | Original Investigation

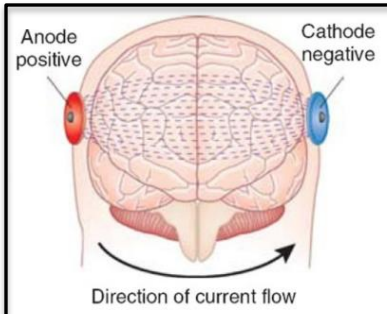
Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans
A Randomized Clinical Trial

Jerome A. Yesavage, MD; J. Kaci Fairchild, PhD; Zhibao 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 Georgette, RN; Tamara Beale, MA; Grant D. Huang, MPH, PhD; Art Noda, MS; Mark S. George, MD; for the VA Cooperative Studies Program Study Team

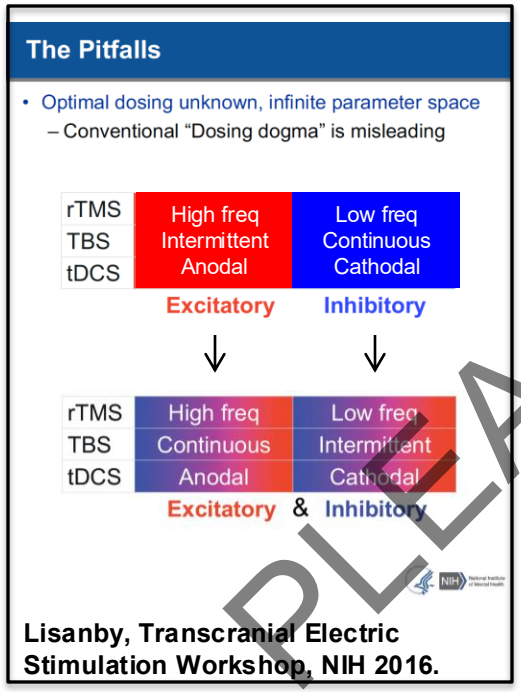
Dosing dogma of NIBS



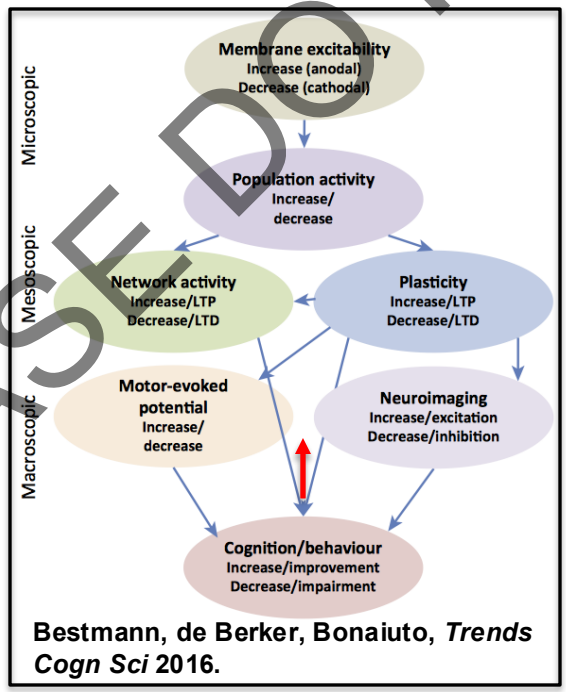
Purpura & McMurtry, *J Neurophysiol* 1964.



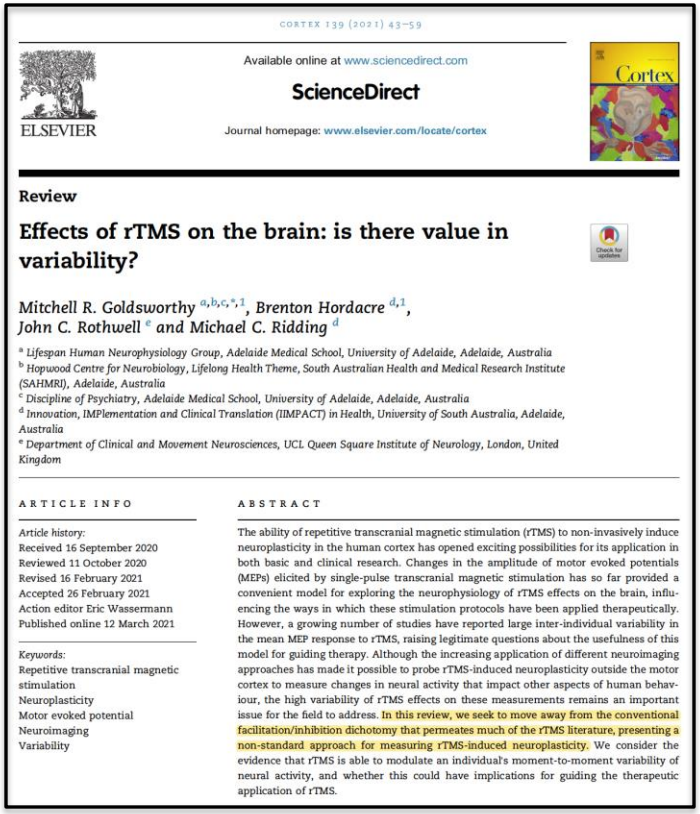
tDCS did not modulate functional connectivity between the regions under the anode and cathode electrodes, during or after stimulation in any tDCS-fMRI studies targeting the PFC.



Lisanby, Transcranial Electric Stimulation Workshop, NIH 2016.



Bestmann, de Berker, Bonaiuto, *Trends Cogn Sci* 2016.



CORTEX 139 (2021) 43–59

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

ELSEVIER

Cortex

Review

Effects of rTMS on the brain: is there value in variability?

Mitchell R. Goldsworthy [a,b,c,*,1], Brenton Hordacre [d,1], John C. Rothwell [e] and Michael C. Ridding [d]

[a] Lifespan Human Neurophysiology Group, Adelaide Medical School, University of Adelaide, Adelaide, Australia
[b] Hopwood Centre for Neurobiology, Lifelong Health Theme, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, Australia
[c] Discipline of Psychiatry, Adelaide Medical School, University of Adelaide, Adelaide, Australia
[d] Innovation, IMPlementation and Clinical Translation (IIMPACT) in Health, University of South Australia, Adelaide, Australia
[e] Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, United Kingdom

ARTICLE INFO

Article history:
Received 16 September 2020
Reviewed 11 October 2020
Revised 16 February 2021
Accepted 26 February 2021
Action editor Eric Wassermann
Published online 12 March 2021

Keywords:
Repetitive transcranial magnetic stimulation
Neuroplasticity
Motor evoked potential
Neuroimaging
Variability

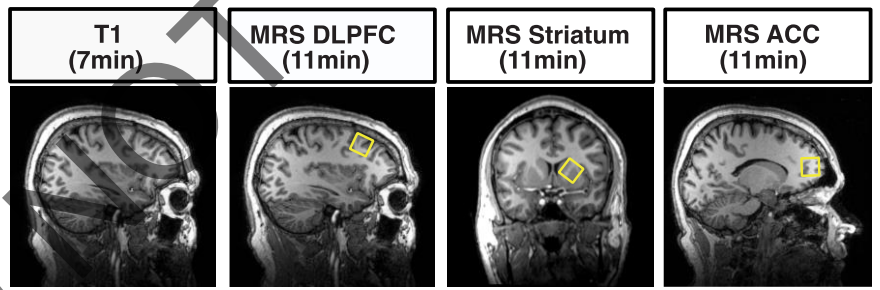
ABSTRACT

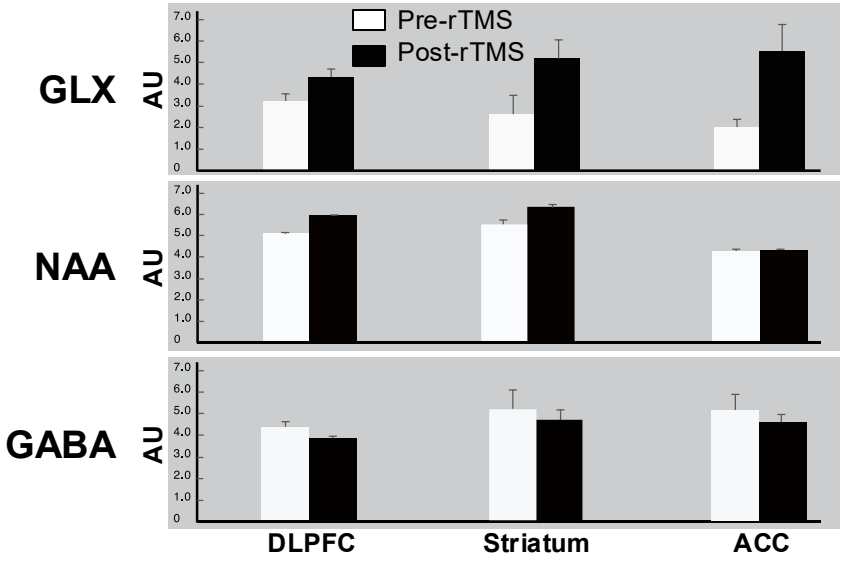
The ability of repetitive transcranial magnetic stimulation (rTMS) to non-invasively induce neuroplasticity in the human cortex has opened exciting possibilities for its application in both basic and clinical research. Changes in the amplitude of motor evoked potentials (MEPs) elicited by single-pulse transcranial magnetic stimulation has so far provided a convenient model for exploring the neurophysiology of rTMS effects on the brain, influencing the ways in which these stimulation protocols have been applied therapeutically. However, a growing number of studies have reported large inter-individual variability in the mean MEP response to rTMS, raising legitimate questions about the usefulness of this model for guiding therapy. Although the increasing application of different neuroimaging approaches has made it possible to probe rTMS-induced neuroplasticity outside the motor cortex to measure changes in neural activity that impact other aspects of human behaviour, the high variability of rTMS effects on these measurements remains an important issue for the field to address. In this review, we seek to move away from the conventional facilitation/inhibition dichotomy that permeates much of the rTMS literature, presenting a non-standard approach for measuring rTMS-induced neuroplasticity. We consider the evidence that rTMS is able to modulate an individual's moment-to-moment variability of neural activity, and whether this could have implications for guiding the therapeutic application of rTMS.

The value of neuroimaging in NIBS treatment.

Case study of a patient with severe polysubstance use and treatment refractoriness

		Pre-rTMS	Post-rTMS	3-mo follow up
OCDUS:	Compulsion:	21	20	14
	Obsession:	16	12	5
DASS:	Stress:	19	16	18
	Depression:	16	6	5
	Anxiety:	14	10	2
DDQ:	Desire & Intention:	-12	10	
	Negative Reinforcement:	-2	-1	
	Control:	15	0	





1Hz rTMS: elevated NAA (excitatory effects?)

Hone-Blanchet, Mondino, Fecteau. *Brain Stimul* 2017.

Science. 2013 Oct 25;342(6157):482-4. doi: 10.1126/science.1241399. Epub 2013 Oct 3.

Changing social norm compliance with noninvasive brain stimulation.

Ruff CC, Ugazio G, Fehr E.

Cereb Cortex. 2010 Jan;20(1):205-13. doi: 10.1093/cercor/bhp090.

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

Karim AA, Schneider M, Lotze M, Veit R, Sauseng P, Braun C, Birbaumer N.

Proc Natl Acad Sci U S A. 2009 Dec 8;106(49):20895-9. doi: 10.1073/pnas.0911619106. Epub 2009 Nov 30.

Disrupting the prefrontal cortex diminishes the human ability to build a good reputation.

Knoch D, Schneider F, Schunk D, Hohmann M, Fehr E.

Soc Cogn Affect Neurosci. 2012 Mar;7(3):282-8. doi: 10.1093/scan/nsr008. Epub 2011 Apr 22.

Disrupting the right prefrontal cortex alters moral judgement.

Tassy S, Oullier O, Duclos Y, Coulon O, Mancini J, Deruelle C, Attarian S, Felician O, Wicker B.

Curr Biol. 2012 Dec 4;22(23):2274-7. doi: 10.1016/j.cub.2012.10.018. Epub 2012 Nov 1.

Enhancing social ability by stimulating right temporoparietal junction.

Santiesteban I, Banissy MJ, Catmur C, Bird G.

Soc Cogn Affect Neurosci. 2013 Oct 15. [Epub ahead of print]

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

Cattaneo Z, Lega C, Flexas A, Nadal M, Munar E, Cela-Conde CJ.

How may NIBS induce enhancement?

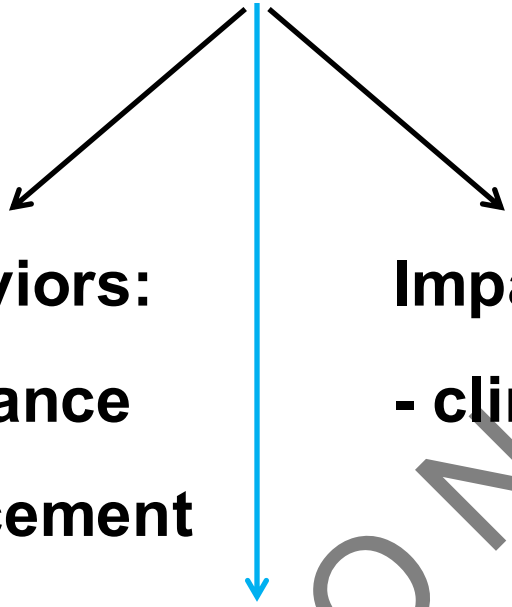
Conceptual framework of neuroenhancement

Three potential mechanisms :

1. **Zero-sum**
2. **Stochastic resonance**
3. **Entrainment enhancement**

Brem, Fried, Horvath, Robertson, Pascual-Leone. *Neuroimage* 2014.
Miniussi, Harris, Ruzzoli. *Neurosci Biobehav Rev* 2013.

NIBS can modulate behaviors in healthy subjects.



Improve behaviors:

- clinical relevance

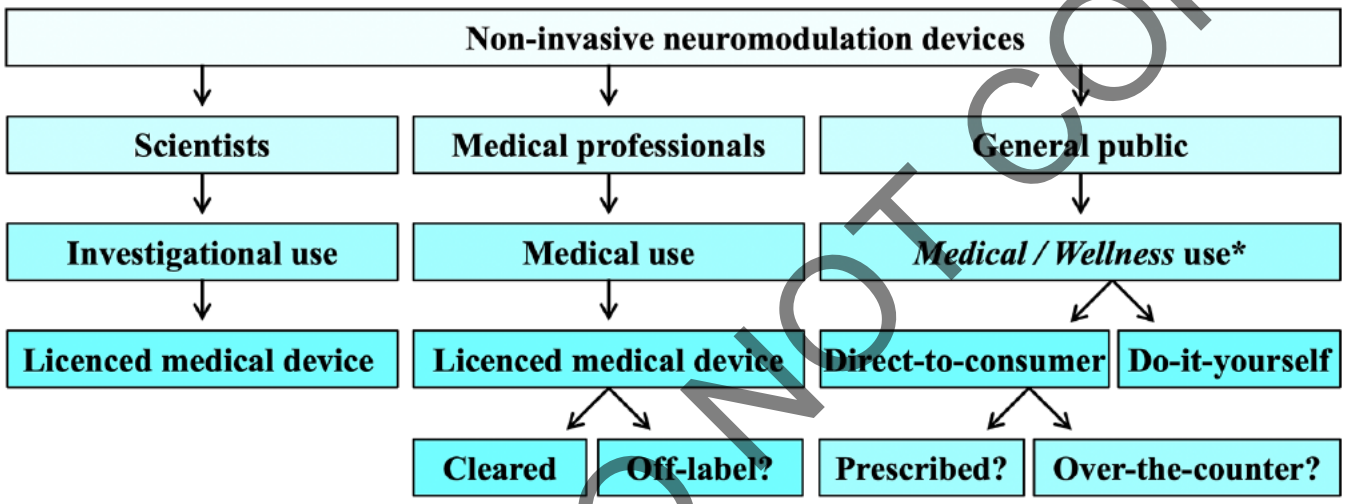
- neuroenhancement

Impair behaviors:

- clinical relevance

Ethical considerations

Ethical considerations



Fecteau (2023) *The Neuroscientist*

Vulnerable populations: children, etc.

Special issue "Ethico-Legal Issues in Brain Stimulation" *Brain Stimulation*

Take Home Message

NIBS over the dlPFC can modulate various behaviors

Impair (virtual lesion) → ***Can this be a concern for my patients?***

Improve (neuroenhancement) → ***Can this be beneficial for my patients?***

Translational value of studies in healthy subjects into clinical applications?

Yes, but the effects of NIBS can be influenced by:

- **brain morphometry**
- **brain activity**
- **behavioral state**

- **Are they different between healthy subjects and patients?**
- **Are they different within a clinical population and within a patient?**

The value of neuroimaging and cognition to understand the clinical benefits of NIBS.

Thank you!

Questions?