Intensive Course in TMS - November 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 - ...

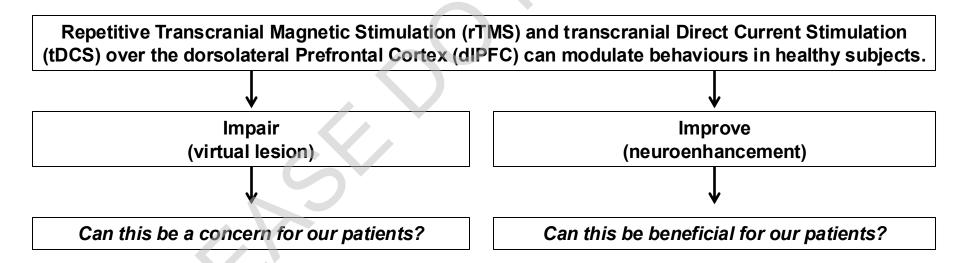
Deputy editor royalties from Elsevier

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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.

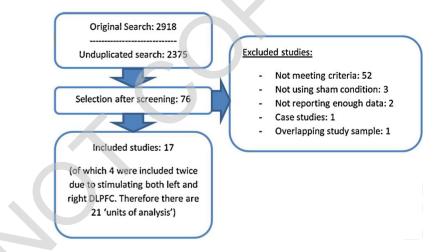


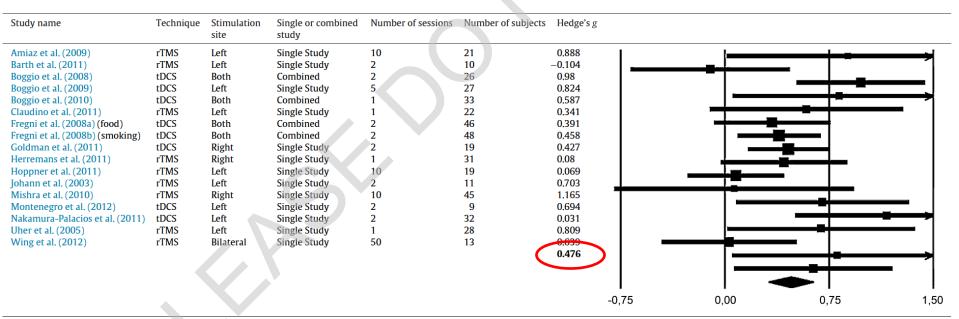
1. Noninvasive brain stimulation (NIBS) to treat substance-related and addictive disorders (SRAD)

- a. Does it work?
- b. How does it work?

NIBS can reduce craving for:

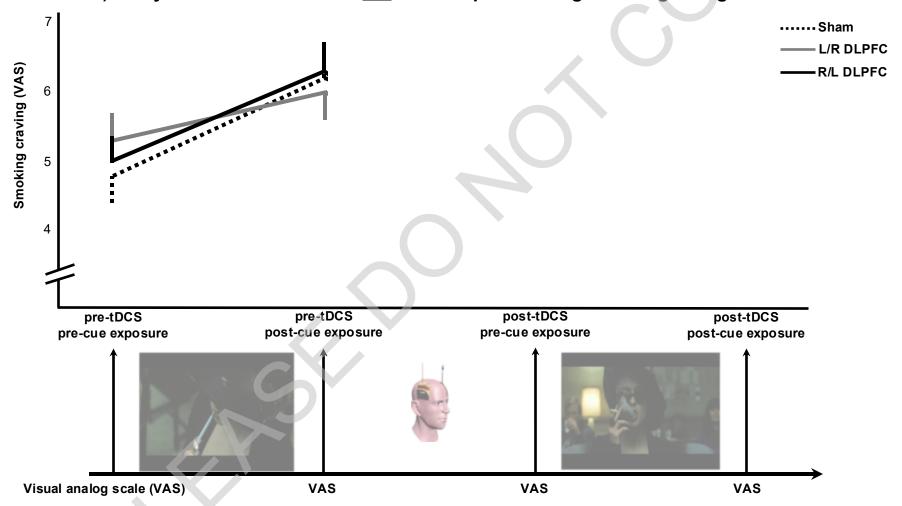
- Nicotine
- Alcohol
- Food
- Marijuana
- Psychostimulant





tDCS over the dIPFC 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 <u>not</u> wish to quit smoking receiving 3 single tDCS sessions.



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

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.

Sham-controlled rTMS trials in Tobacco Use Disorders on smoking

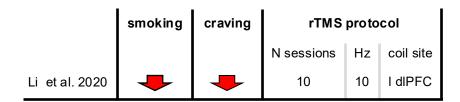
	Primary outcomes of smoking
Amiaz et al. 2009	reduction cig/d
Dinur-Klein et al. 2014	reduction cig/d, cotinine
Li et al. 2020	2-d abstinence cig/d, CO, cotinine
Zangen et al. 2021	4-wk abstinence cig/d, cotinine
Abdelraham et al. 2021	reduction cig/d
Eichhammer et al. 2003	reduction cig ad libitum
Sheffer et al. 2019	continuous abstinence cig/d, CO
Ibrahim et al. 2023	7-d abstinence cig/d, cotinine
Trojak et al. 2015	continuous abstinence cig/d, CO
Dieler et al. 2014	continuous abstinence
Lechner et al. 2022	n.s. delay to smoking analog task
Addicott et al. 2024	n.s. 7-d abstinence cotinine
Bellini et al. 2024	n.s. 2-wk abstinence cig/d, CO, cotinine

Sham-controlled rTMS trials in Tobacco Use Disorders on smoking and craving

	Primary outcomes of smoking	Craving
Amiaz et al. 2009	reduction cig/d	-
Dinur-Klein et al. 2014	reduction cig/d, cotinine	•
Li et al. 2020	2-d abstinence cig/d, CO, cotinine	•
Zangen et al. 2021	4-wk abstinence cig/d, cotinine	+
Abdelraham et al. 2021	reduction cia/d	*
Eichhammer et al. 2003	reduction cig ad libitum	n.s.
Sheffer et al. 2019	continuous abstinence cig/d, CO	n.s.
Ibrahim et al. 2023	7-d abstinence cig/d, cotinine	n.s.
Trojak et al. 2015	continuous abstinence cig/d, CO	n.s.
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Bellini et al. 2024	n.s. 2-wk abstinence cig/d, CO, cotinine	n.s.

If NIBS does not reduce craving, what does it modulate to promote smoking abstinence?

What do we modulate when NIBS induces lasting clinical benefits?

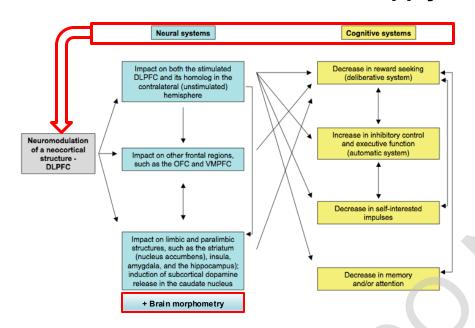


10 sessions of 10Hz rTMS over the left dIPFC of adults with tobacco use disorder:

- 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?

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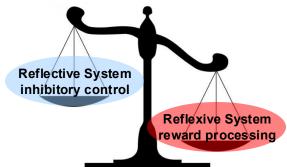
What do we modulate when we apply NIBS over the dIPFC?



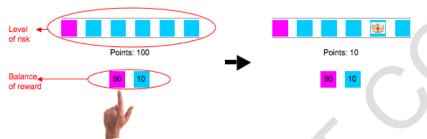
There are several ways to induce cognitive and clinical benefits, and they are not mutually exclusive.

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

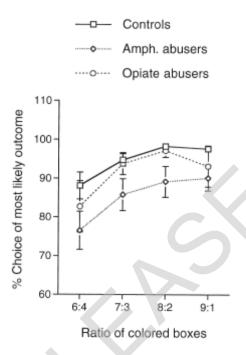
- risk taking;
- reward seeking;
- impulsivity;
- delayed gratification;
- attention.



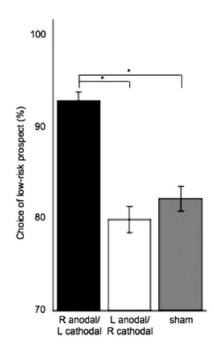
Risk taking, reward seeking



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



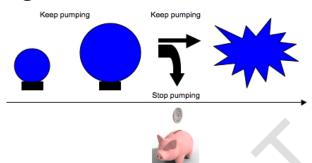
tDCS over the dIPFC can decrease risk taking and reward seeking at the Risk Task.



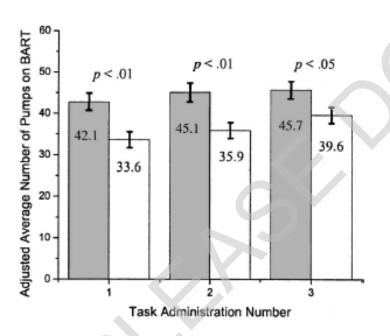
Rogers, Everitt, Baldacchino, et al. *Neuropsychopharmacology* 1999.

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

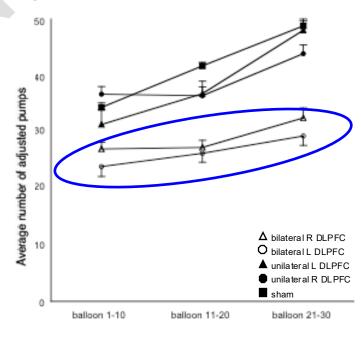
Risk taking, reward seeking



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



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



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

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

Self-interest



The proposer has \$10 and offers you \$2

Ultimatum Game 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.

Self-interest

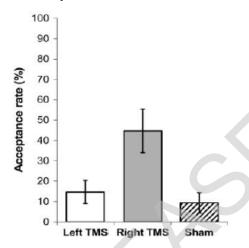


The Ultimatum Game The proposer has \$10 and offers you \$2 If you accept: The proposer gets \$8 and you get \$2 The proposer gets \$0 and you get \$0

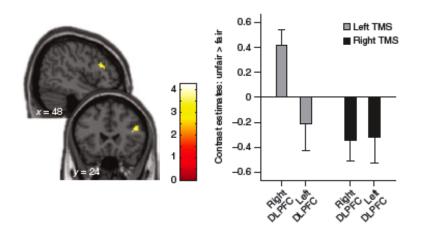


1Hz rTMS over the R dIPFC

Accepted more often unfair offers

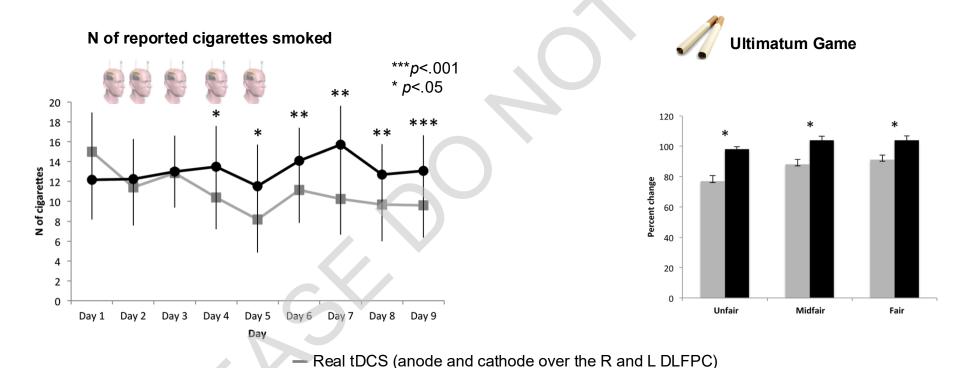


Elicited activity in both dIPFCs when contrasting unfair > fair offers



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).



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

Impulsivity, delayed gratification, craving

Would you prefer to receive:



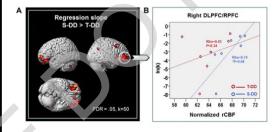
Smokers choose more often the smaller, immediate offer of money

Smokers Non-smokers of deal and the smokers Non-smokers of deal and the smokers of deal and

Inter-Reward Interval (weeks)

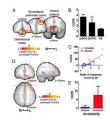
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cTBS over the R dIPFC in healthy subjects

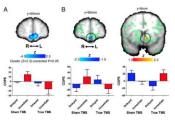


1Hz rTMS over the L dIPFC in smokers

Delayed gratification



Decreased craving



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

 $Hayashi,\,Ko,\,Strafella,\,Dagher,\,\textit{PNAS}\,\,2013.$

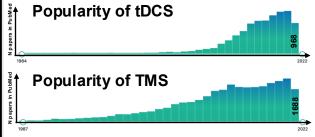
Mitchell & Wilson, *Psychopharmacology* 2012.

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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.

Sham-controlled rTMS and tDCS trials on use and craving

Alcohol use disorder (AUD)

Drinking rTMS Addolorato n.s. et al. 2017 Perini et n.s. n.s. al. 2020 Harel et al. 2022 McCalley et al. 2022 Zhang et al. 2022 Hoven et al. 2023 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.	•
	,	

Use	Craving
n.s.	n.s.
n.s.	n.s.
n.s.	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 AUD¹ 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.

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

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

Do we reach the cortex?

Did NIBS reach the cortex?







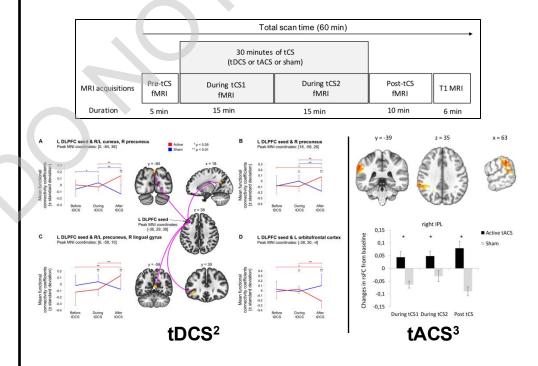
Concurrent tDCS-MRI, sham controlled, blind at 3 levels studies to identify the neural effects of tDCS in healthy adults.

T1 MRI (6 min) tDCS (30 min of real or sham) MRS dIPFC (11 min) MRS striatum (11 min) MRS dIPFC (11 min) No significant change

sham

real sham

Concurrent tCS-fMRI



¹Hone-Blanchet, Edden, Fecteau, Biol Psychiatry 2016.

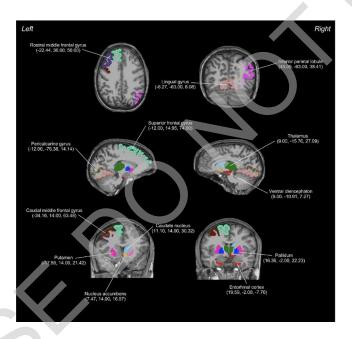
²Bouchard, Renauld, Fecteau, Front Hum Neurosci 2023.

³Mondino, 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 dIPFC.



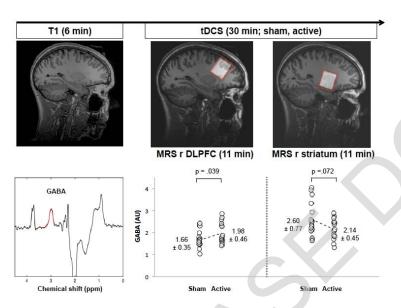
Did NIBS reach the cortex of adults with gambling disorder?





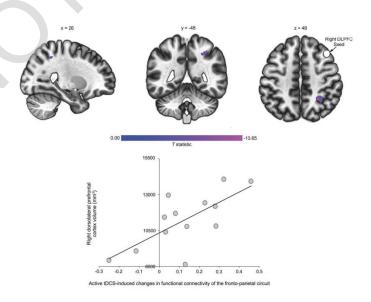
Concurrent tDCS-MRI, sham controlled, blind at 3 levels studies to identify the neural effects of tDCS applied over the dIPFC.

Concurrent tDCS-MRSI¹



Potential intervention targeting the GABAergic system?

Concurrent tDCS-fMRI²



Potential intervention targeting the frontoparietal circuit, known to be involved in attentional processes?

¹Dickler, Lenglos, Renauld, Ferland, Edden, Leblond, Fecteau, Neuropharmacology 2018.

²Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau, *Brain Connect* 2021.

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 - a. Impact of brain morphometry
 - b. Impact of functional connectivity
 - c. Impact of behavioural trait and state

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



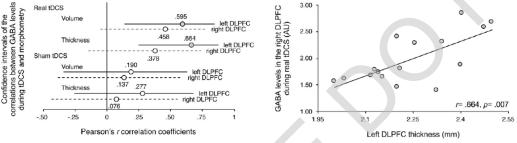
tDCS applied over the dIPFC in adults with gambling disorder.

Greater dIPFC volume and thickness

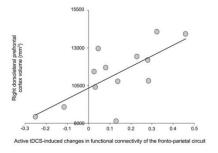
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Greater tDCS related changes in neurotransmitter levels and functional connectivity strength.

Concurrent tDCS-MRSI¹



Concurrent tDCS-fMRI²



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

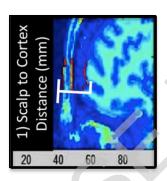
¹Bouchard, Dickler, Renauld, Lenglos, Ferland, Edden, Rouillard, Leblond, Fecteau, *Brain Stimul* 2020.

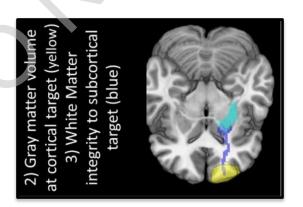
²Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau, *Brain Connect* 2021.

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).





The impact of <u>functional connectivity</u> on the neural effects of NIBS

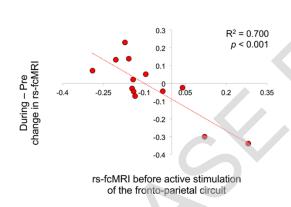


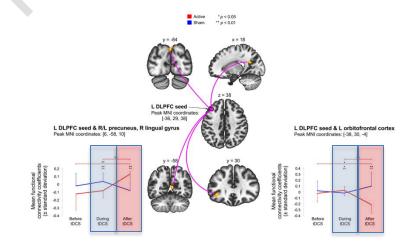
Concurrent tDCS-fMRI: instantaneous and subsequent tDCS effects in a sham controlled, blind at 3 levels study with healthy adults.

Stronger baseline functional connectivity = stronger tDCS impact on functional connectivity

tDCS induced changes in functional connectivity

during ≠ after tDCS



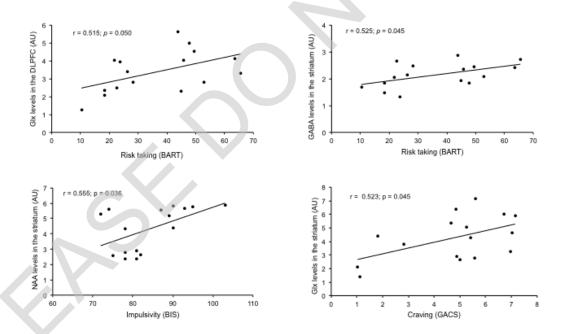


The impact of behavioural trait and state on the neural effects of NIBS



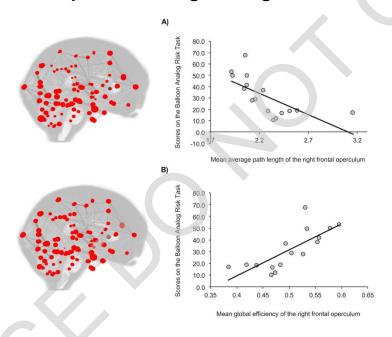
Concurrent tDCS-MRI, sham controlled, blind at 3 levels design to identify the neural effects of tDCS in adults with gambling disorder.

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



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?

NIBS over the dIPFC can modulate decision-making processes and...?



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 <u>craving</u>.

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

rTMS applied over the dIPFC for... depression, anxiety, chronic pain, etc.

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.

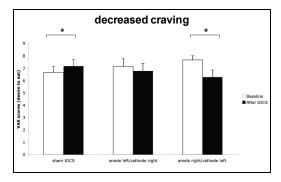


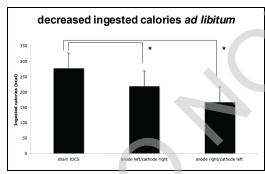
post-cues, pre-tDCS assessment

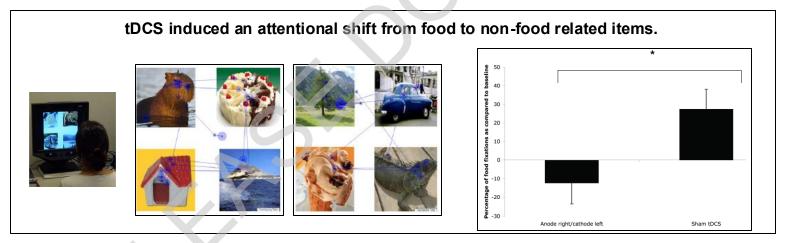




post-cues, post-tDCS assessment



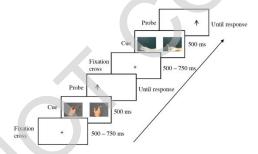




Craving, attentional processes



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



- 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.

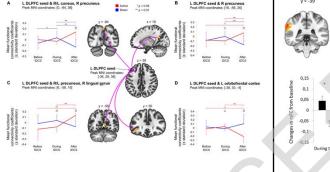
NIBS applied over the dIPFC modulates fronto-parietal networks, known to be involved in attentional processes



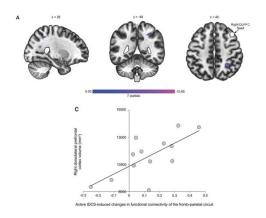


	C	oncurrer	nt tCS-fN	IRI	
		Tota	al scan time (60 min)		
		30 minutes of tCS (tDCS or tACS or sham)			
MRI acquisitions	Pre-tCS fMRI	During tCS1 fMRI	During tCS2 fMRI	Post-tCS fMRI	T1 MRI
Duration	5 min	15 min	15 min	10 min	6 min

Healthy adults tDCS-fMRI¹ tACS-fMRI²



Adults with gambling disorder tDCS-fMRI³



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

¹Bouchard, Renauld, Fecteau, Front Hum Neurosci 2023.

²Mondino, Ghumman, Gane, Renauld, Whittingstall, Fecteau, Front Hum Neurosci 2020.

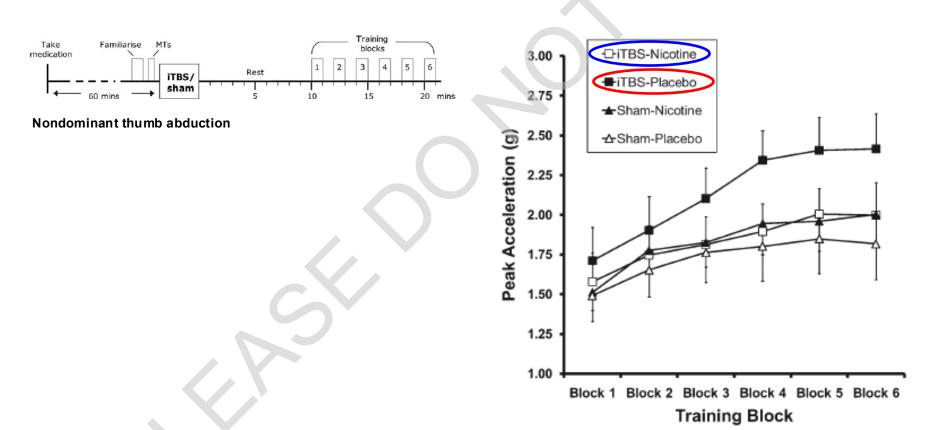
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 - a. Impact of brain morphometry
 - b. Impact of functional connectivity
 - c. Impact of behavioural trait and state
- 5. What's next?

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.

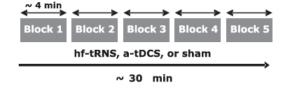


When to prime the brain?

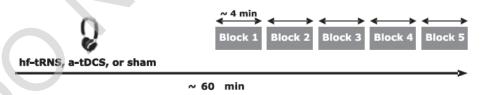
Effects of NIBS on an orientation discrimination task testing:

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

Online protocol



Offline protocol



- Improvement with offline, but not with online tDCS.
- Improvement with online, but not with offline tRNS.

What's next?

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

The effects of NIBS can be impacted by:

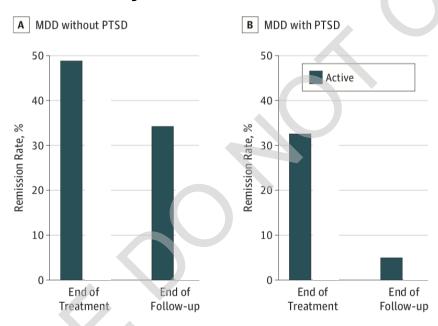
- brain morphometry
- brain activity
- behavioural trait and state.

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).

Next, what does NIBS modulate when it induces cognitive and clinical benefits? Value of neuroimaging and cognition in understanding the cognitive and clinical benefits of NIBS.

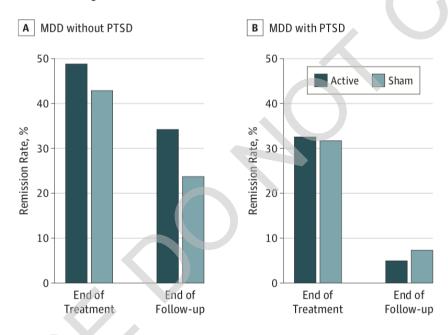
rTMS to treat depression in military veterans



JAMA Psychiatry | Original Investigation

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

rTMS to treat depression in military veterans



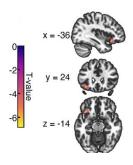
The importance of sham-controlled trial

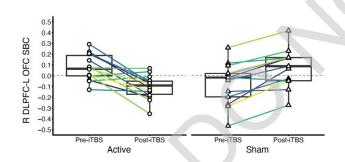
JAMA Psychiatry | Original Investigation

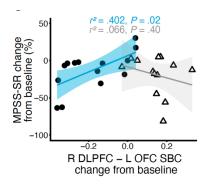
Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans A Randomized Clinical Trial

iTBS to treat posttraumatic stress disorder in military personnel

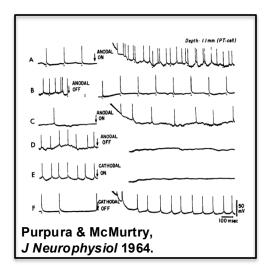
- 32% of remission in the active and sham iTBS groups
- Different patterns of functional connectivity between groups

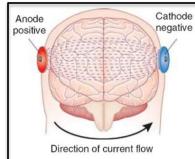






Dosing dogma of NIBS





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.

Article history:

Neuroplasticity

Variability

Motor evoked potential

Received 16 September 2020

Reviewed 11 October 2020

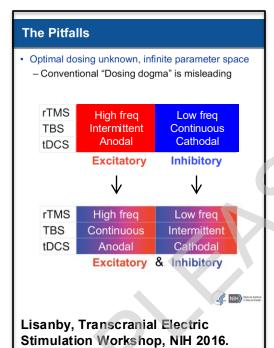
Revised 16 February 2021

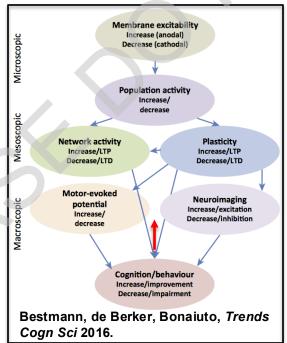
Accepted 26 February 2021

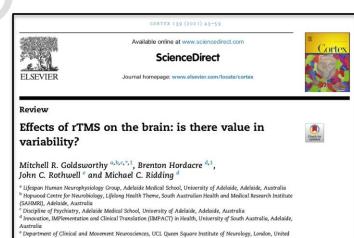
Action editor Eric Wassermann

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Repetitive transcranial magnetic







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, influ-

encing 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 behav-

iour, the high variability of rTMS effects on these measurements remains an important

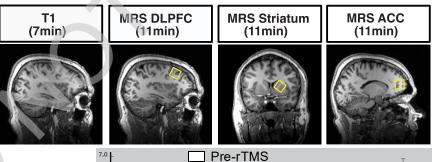
issue for the field to address. In this review, we seek to move away from the conventional

facilitation/inhibition dichotomy that permeates much of the rTMS literature, presenting a

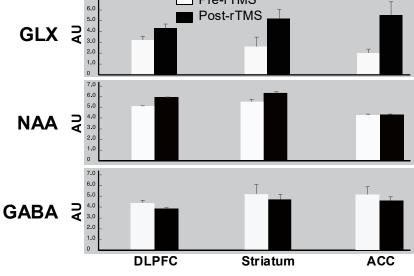
non-standard approach for measuring 1TMS-induced neuroplasticity. We consider the evidence that rTMS is able to modulate an individual's moment-to-moment variability of neural activity, and whether this could have implications for guiding the therapeutic

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: Negative Reinforcemer Control:	-12 nt: -2 15	10 -1 0	



1Hz rTMS: elevated NAA (excitatory effects?)



How may NIBS induce enhancement?

Conceptual framework of neuroenhancement

Three potential mechanisms:

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

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.

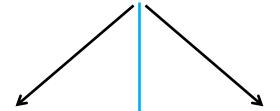
Santiesteban I, Banissy MJ, Catmur C, Bird G.

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.

NIBS can modulate behaviors in healthy subjects.



Improve behaviors:

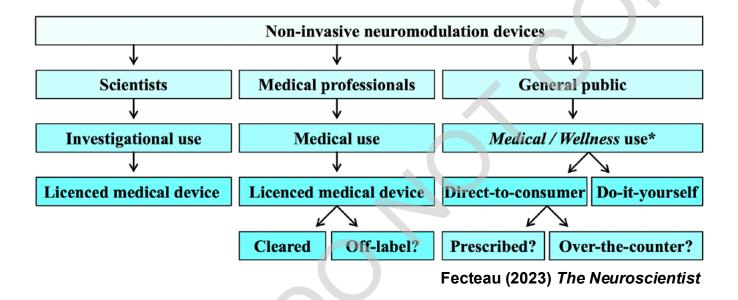
- clinical relevance
- neuroenhancement

Impair behaviors:

- clinical relevance

Ethical considerations

Ethical considerations



Vulnerable populations: children, etc.

Take Home Message

NIBS over the dIPFC can modulate various behaviors

Impair (virtual lesion) Improve (neuroenhancement)

Can this be a concern for my patients? 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?