Translational value of TMS studies in healthy adults into clinical populations

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TMS Course lecturer 2005 - …

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What is the main target (TMS coil site) to treat these populations?

- **Depression**
- **Anxiety**
- **Chronic pain**
- **Posttraumatic stress disorder**
- **Substance related and addictive disorders**
- **etc.**

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An example

Main goal: to treat depression.

Primary hypothesis: rTMS will modulate dlPFC activity and its connected networks which will, consequently, alleviate depression.

Intervention: 10 Hz rTMS over the left dlPFC.

Primary outcome: depression measured with a standardized questionnaire (BDI, HAMD, etc.).

Are the effects of rTMS over the dlPFC only on depression?

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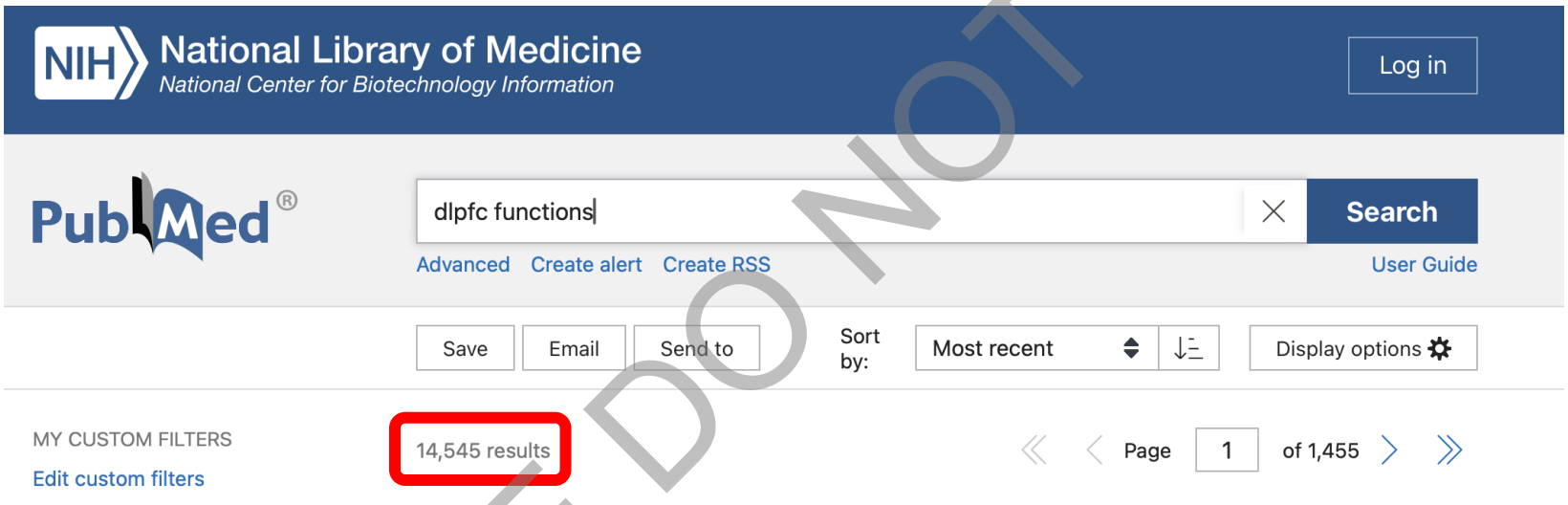
What are the functions known to be related to the dlPFC?



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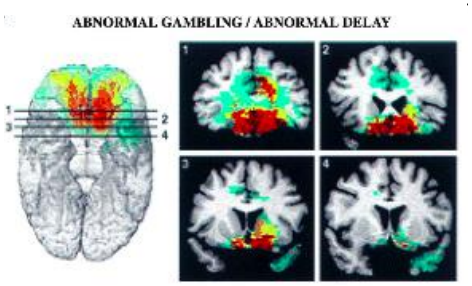
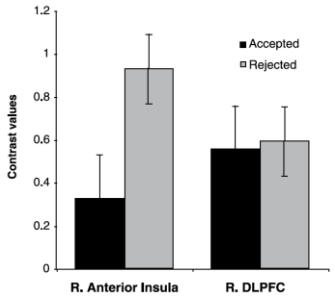
One role of the dlPFC is to integrate cognitive and emotionally relevant information during decision-making.

Patients with PFC lesion



Neuroimaging studies in healthy adults





A distributed bi-hemispheric network including the dlPFC, the orbitofrontal cortex, the anterior cingulated cortex, and the insula is known to be involved 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

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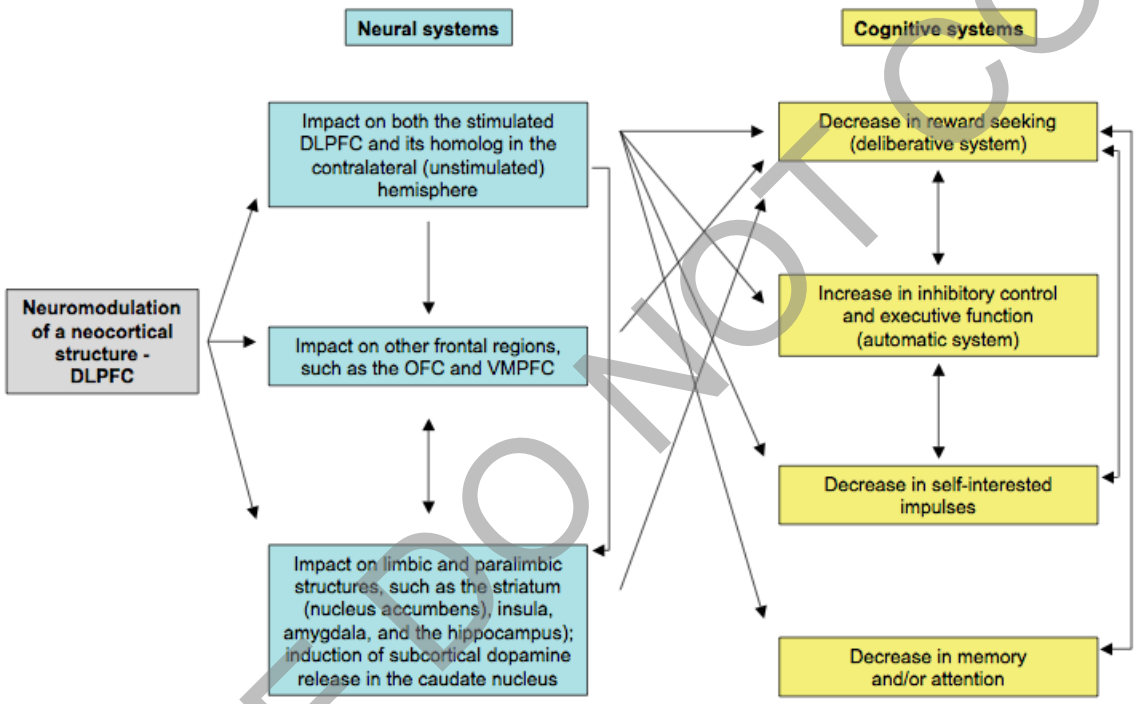
Non-invasive brain stimulation (NIBS) over the dlPFC



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

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

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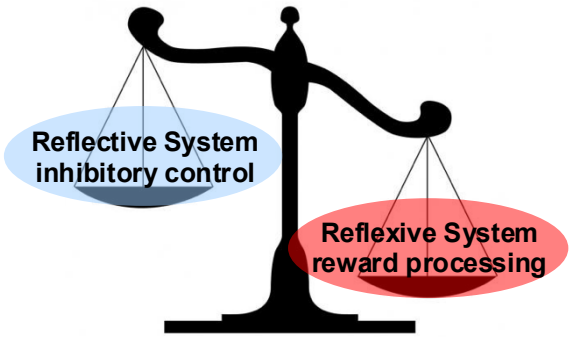
Relevance of the dlPFC for substance related and addictive disorders (SRAD)

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

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



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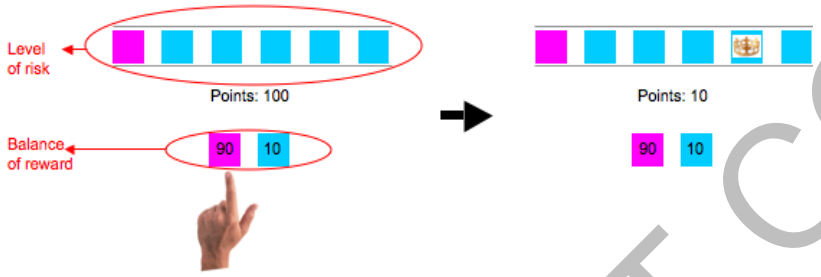
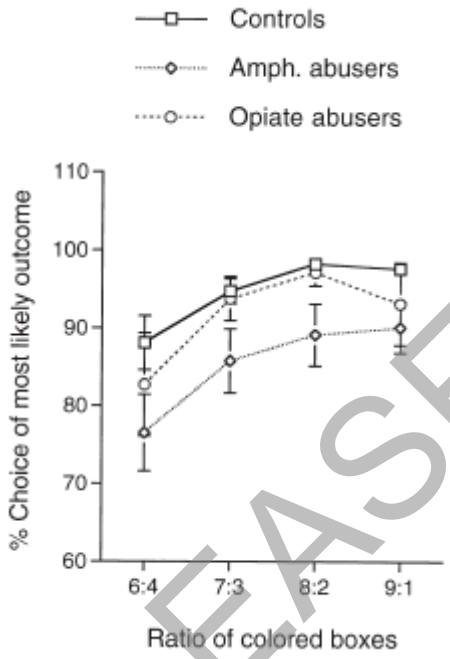
Koob & Volkow, *Neuropsychopharmacology* 2010.

Risk taking, reward seeking

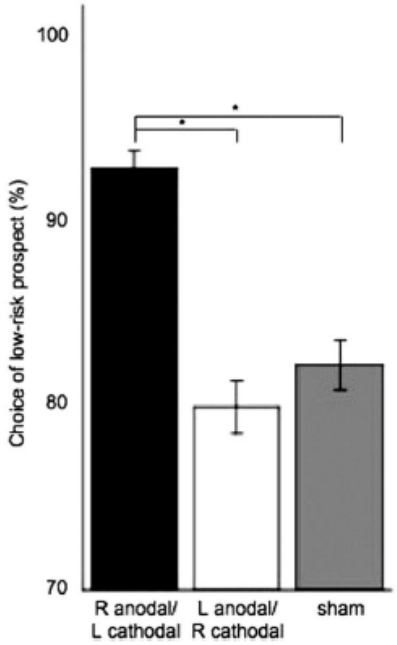


Patients with substance use disorders take greater risk at the Risk Task.



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.

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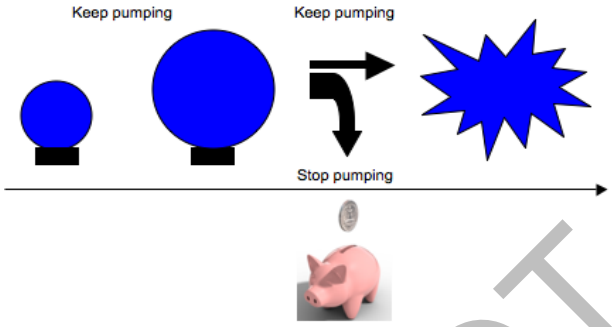
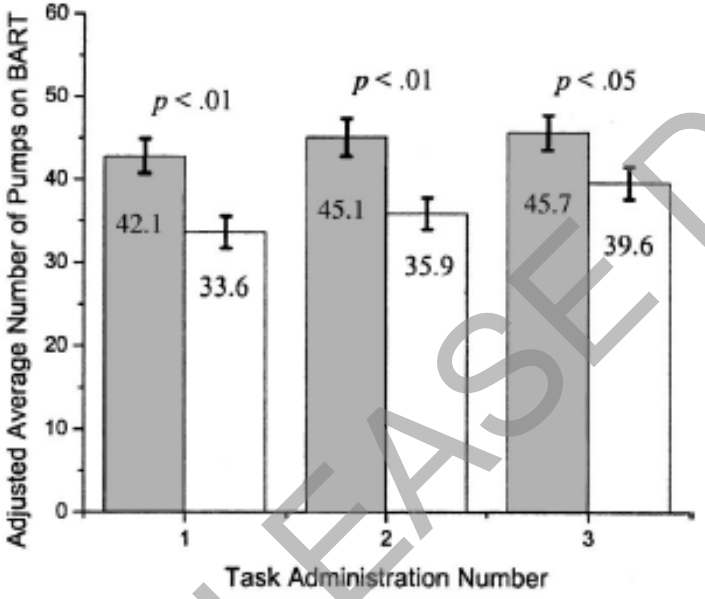
Risk taking, reward seeking

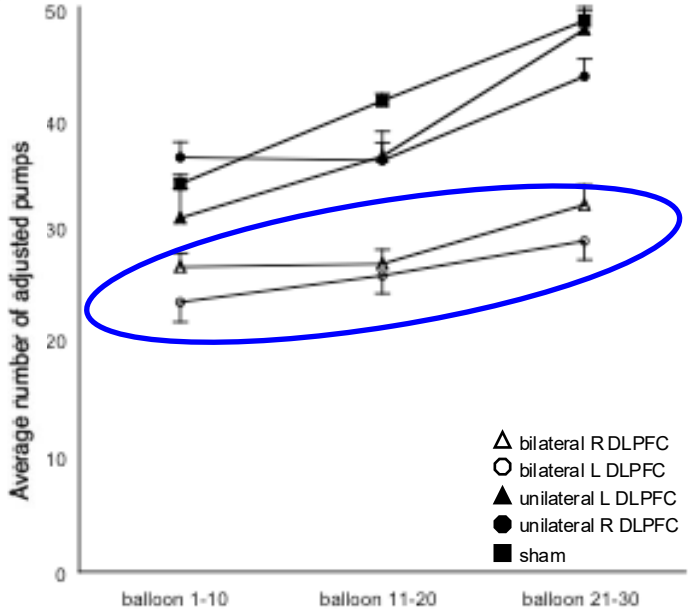


Patients with tobacco use disorder take greater risk at the BART.



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.

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Self-interest



Ultimatum Game

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 at the Ultimatum Game.



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.

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Self-interest



The Ultimatum Game

The proposer has $10 and offers you $2

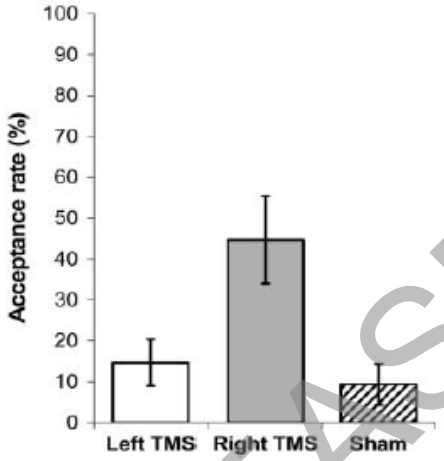
If you accept :
The proposer gets $8 and you get $2

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

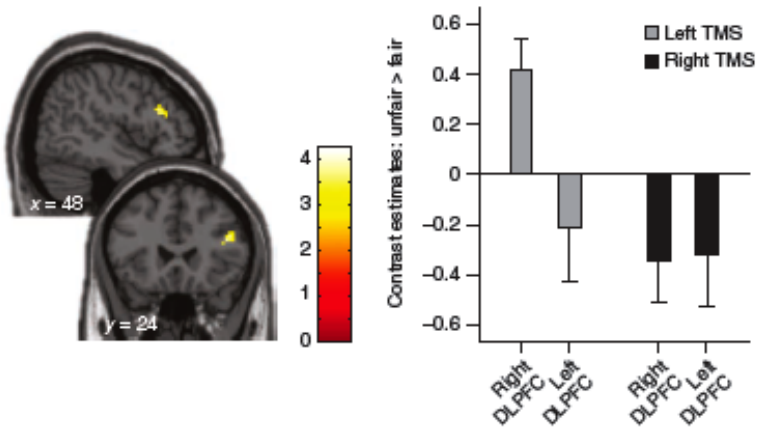


1Hz rTMS over the R dlPFC

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.

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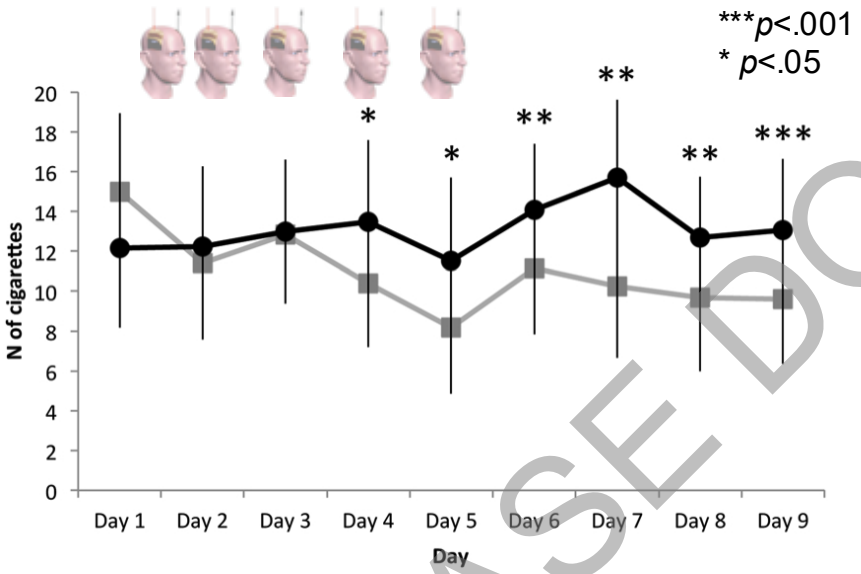
Self-interest, smoking

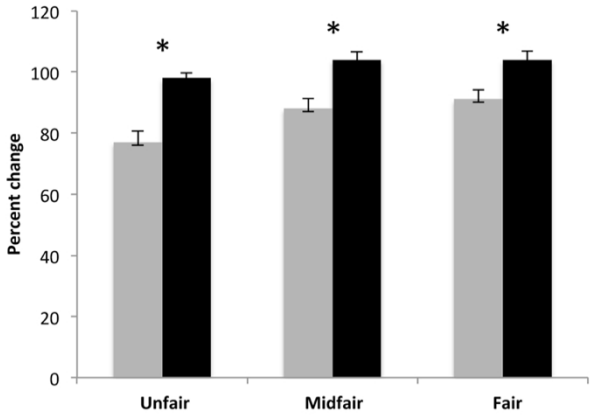
This was a 2-arm, crossover, sham controlled, blind at 3 levels (subjects, tDCS provider, outcome assessors) study with smokers receiving two 5-day tDCS regimens (real, sham).

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)

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

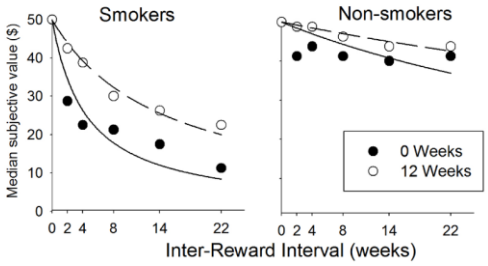
Impulsivity, delayed gratification, craving

Would you prefer to receive (Marshmallow task):

$20 now

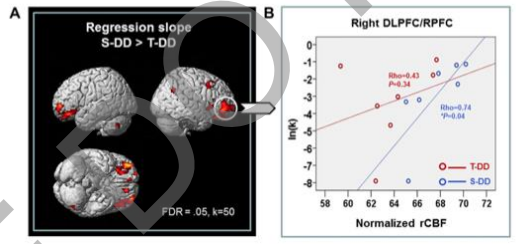
$26 tomorrow

Smokers choose more often the smaller, immediate offer of money



Mitchell & Wilson, *Psychopharmacology* 2012.

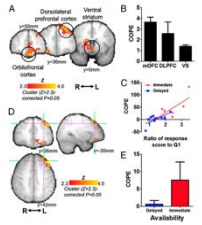
cTBS over the R dlPFC in healthy adults



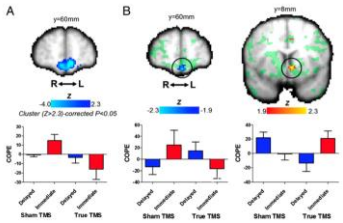
Cho, Pellecchia, Ko, Ray, Obeso, Houle, Strafella. *Brain Stimul* 2012.

1Hz rTMS over the L dlPFC in smokers

Delayed gratification



Decreased craving



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

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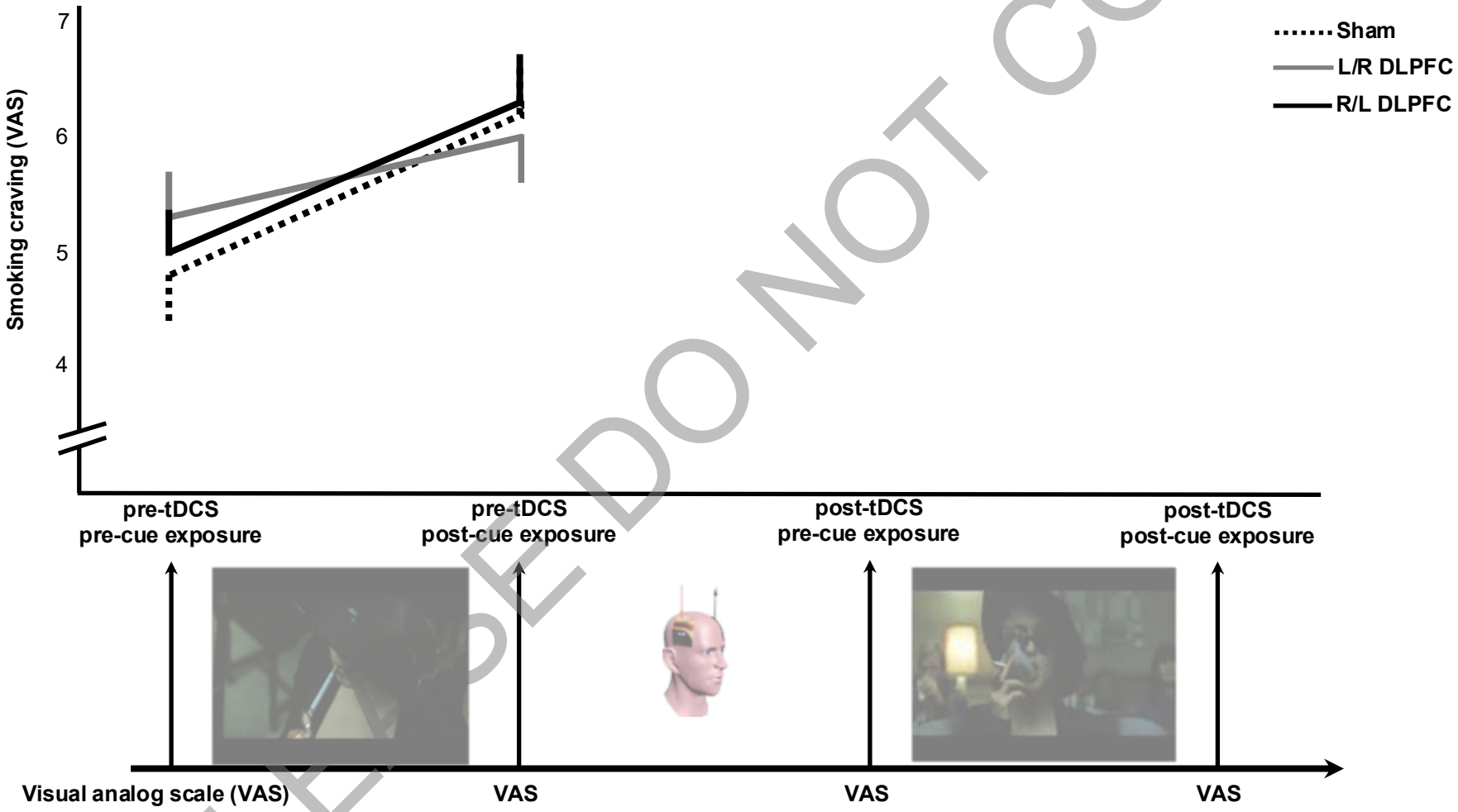
Craving

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



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

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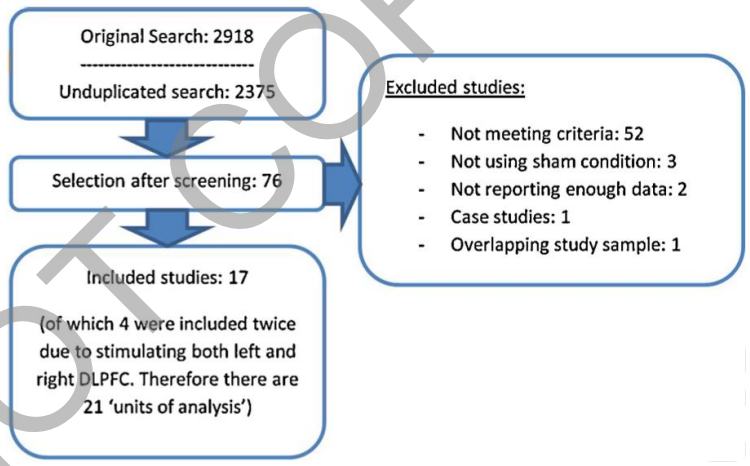
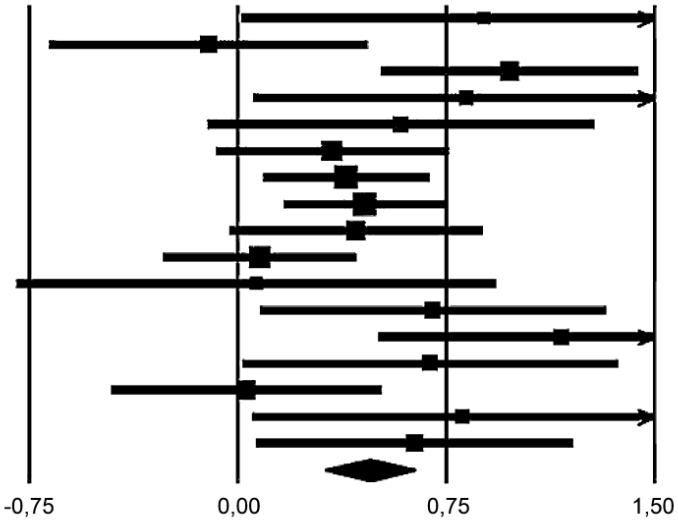
rTMS and tDCS can reduce craving for:

- 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	0.639
						0.476



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

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rTMS on smoking in Tobacco Use Disorder.

The US FDA cleared the use 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.**

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

Individual sham-controlled rTMS trials 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 cig/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.
Dieler et al. 2014	↓	continuous abstinence	n.s.
Lechner et al. 2022	n.s.	delay to smoking analog task	n.s.
Addicott et al. 2024	n.s.	7-d abstinence cotinine	n.s.
Bellini et al. 2024	n.s.	2-wk abstinence cig/d, CO, cotinine	n.s.

When NIBS reduces smoking, it does not always reduce craving.

Fecteau, *Brain Stimulation Conference* 2025.

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Key message

1. Value of cognition:

To identify the functions related to our NIBS target.

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When rTMS promotes smoking abstinence, does it modulate brain networks related to craving and/or executive functions?

There are only a few rTMS RCT that include fMRI outcomes.

- rTMS over the left dlPFC following symptom provocation:

correlations between changes in brain activity (OFC, dACC) and reduced self-reported number of cigarettes smoked, but not with cotinine, nor craving level[1,2].

- Standalone rTMS over the left dlPFC:

correlations between changes in brain activity (left MFG) and craving reduction[3].

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

The value of neuroimaging outcome.

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[1] Li, Caulfield, Hartwell, Henderson, Brady, George, *Brain Imaging Behav* 2024.
[2] Li, Caulfield, Carpenter, Ramakrishnan, Hermann, Dancy, George, *J Psychiatr Res* 2026.
[3] Li, Caulfield, Chen, McMahan, Hartwell, Brady, George, *Brain Connect* 2025.

Sham-controlled NIBS trials in other substance related and addictive disorders?

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]

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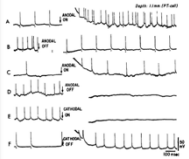
[1] Spindler, Trautmann, Alexander, Broning, Bartscher, Stuppe, Muellhan, Sci Rep 2021; Yang, Tian, Zhang, Zeng, Chen, Wang, Jia, Gong, *Neurosci Biobehav Rev* 2016.

[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?



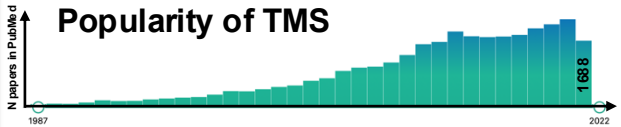
- More than a century ago… There were some behavioral changes, but the effects were unreliable.
- The current was presumably <u>not going through the brain</u>.



- 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.

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

Do we reach the cortex?

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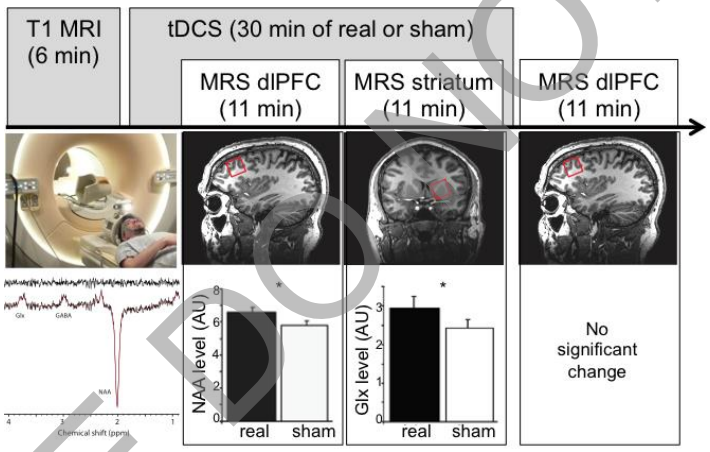
Does NIBS reach the cortex?



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

Concurrent tDCS-MRSI



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

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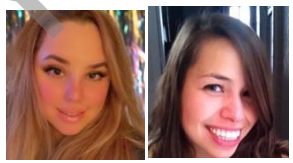
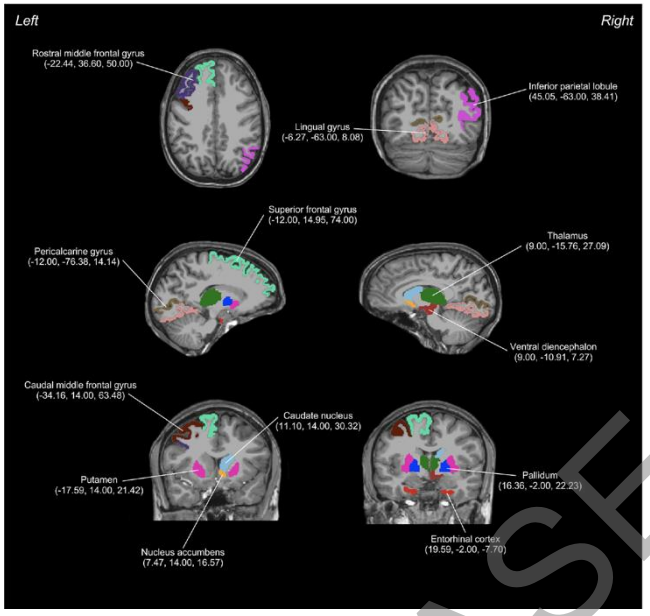
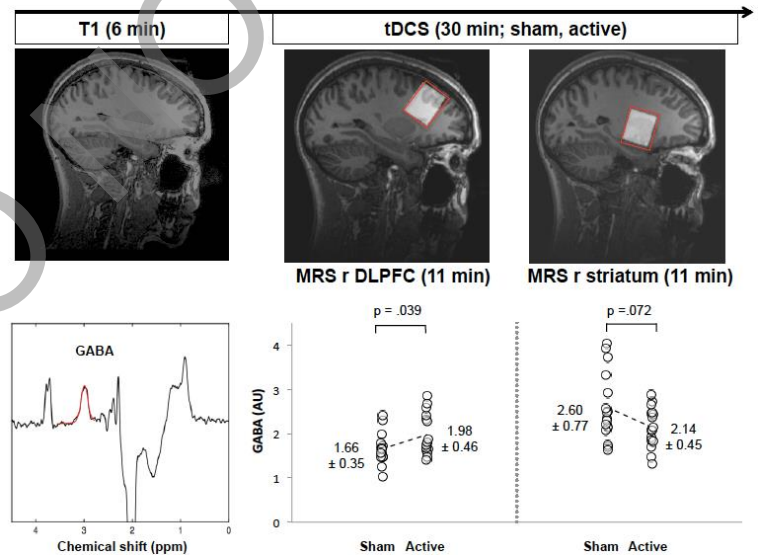
Does NIBS reach the cortex of adults with gambling disorder?



Adults with gambling disorders compared to healthy controls displayed smaller volume of the left dlPFC[1].



Concurrent tDCS-MRS, sham controlled, blind at 3 levels studies to identify the neural effects of tDCS applied over the dlPFC[2].

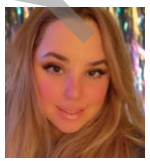


Potential intervention targeting the GABAergic system?

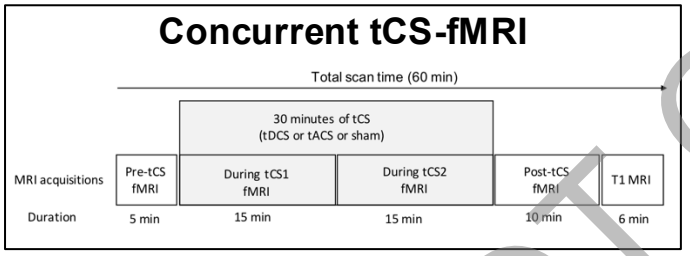
PLEASE DO NOT COPY

[1]Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau. *J Psychiatr Res* 2021.
[2]Dickler, Lenglos, Renauld, Ferland, Edden, Leblond, Fecteau, *Neuropharmacology* 2018.

Does NIBS modulate a *relevant* network?

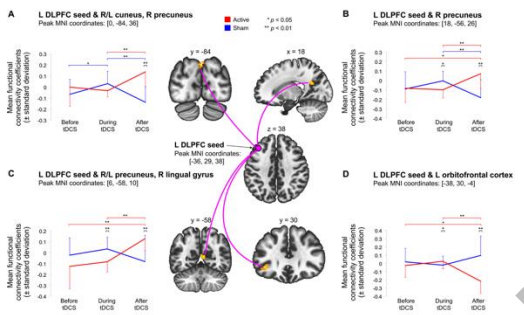



Concurrent tCS-fMRI

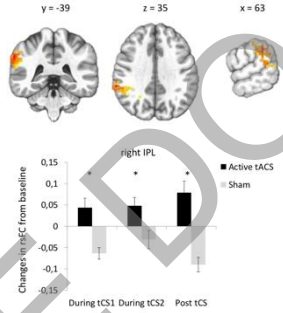


Healthy adults

tDCS-fMRI[1]

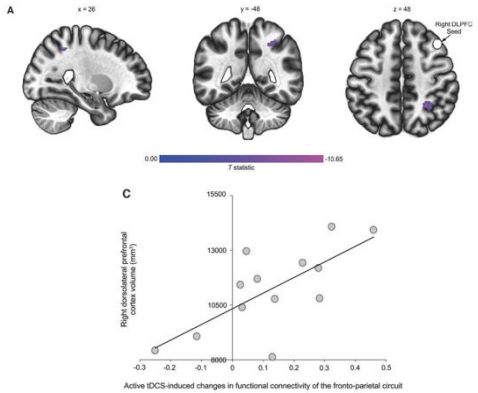


tACS-fMRI[2]



Adults with gambling disorder

tDCS-fMRI[3]



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

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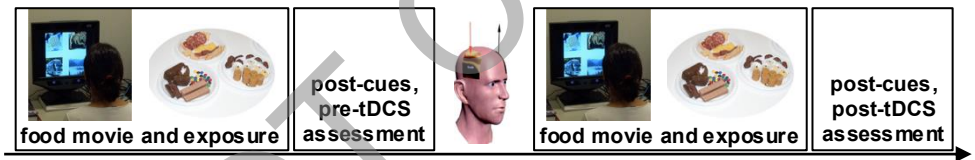
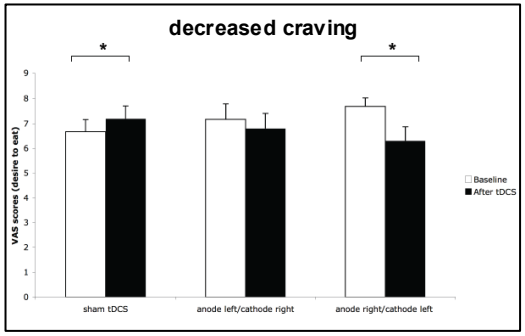
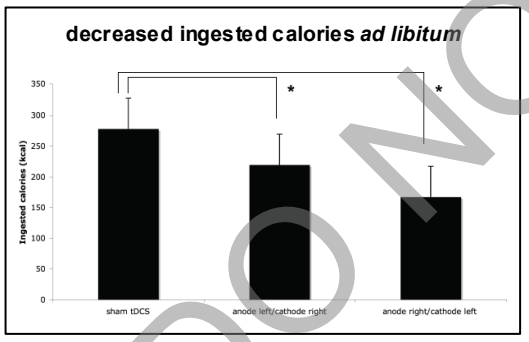
[1]Bouchard, Renauld, Fecteau, *Front Hum Neurosci* 2023.
[2]Mondino, Ghumman, Gane, Renauld, Whittingstall, Fecteau, *Front Hum Neurosci* 2020.
[3]Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau, *Brain Connect* 2021.

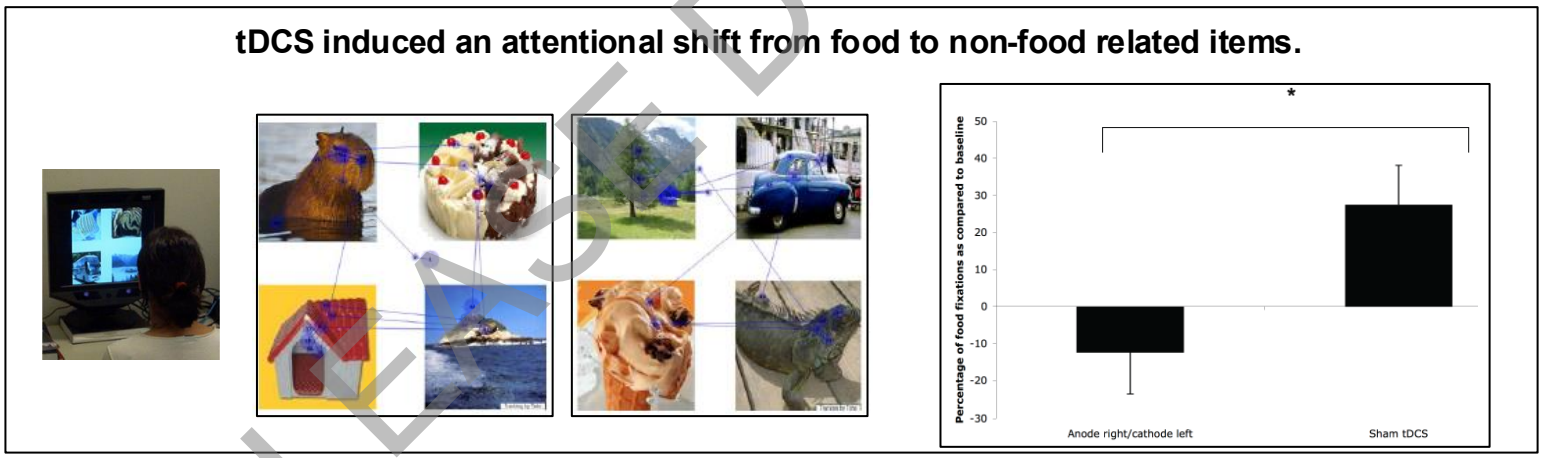
NIBS can modulate fronto-parietal connectivity, known to be involved in attentional processes: impact on craving and consumption?

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









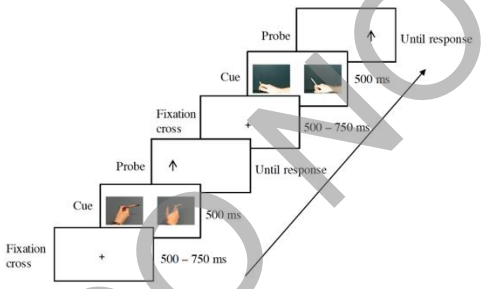
Fregni, Orsati, Pedrosa, Fecteau, Tome, Nitsche, Mecca, Macedo, Pascual-Leone, Boggio. *Appetite* 2008.

PLEASE DO NOT COPY

NIBS can modulate fronto-parietal connectivity, known to be involved in attentional processes: impact on craving and decision-making 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.

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

Key messages

1. Value of cognition:

To identify the functions related to our NIBS target.

2. Value of neuroimaging:

To identify if NIBS *sufficiently* reaches the cortex.

If so, to identify which brain networks it modulates.

To examine if these networks are relevant to our outcome.

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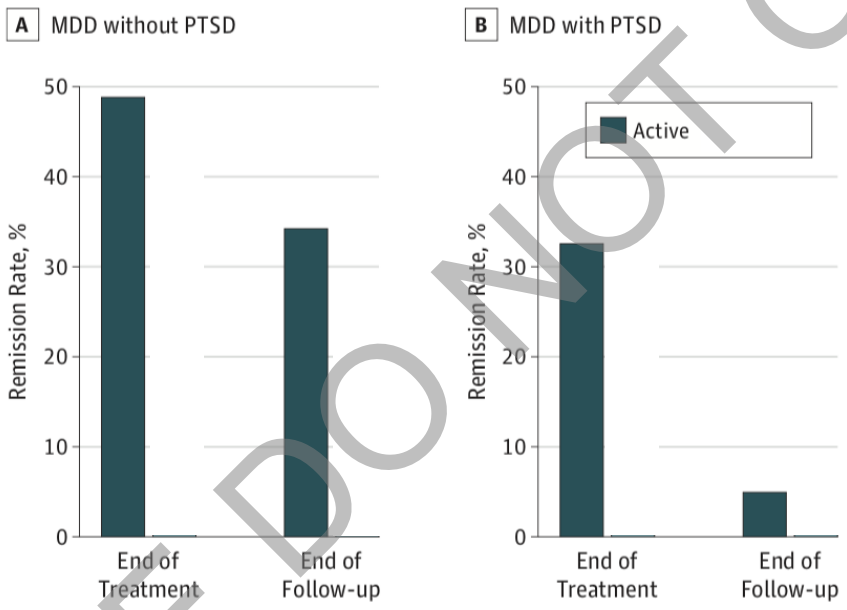
rTMS over the dlPFC to treat depression in military veterans.



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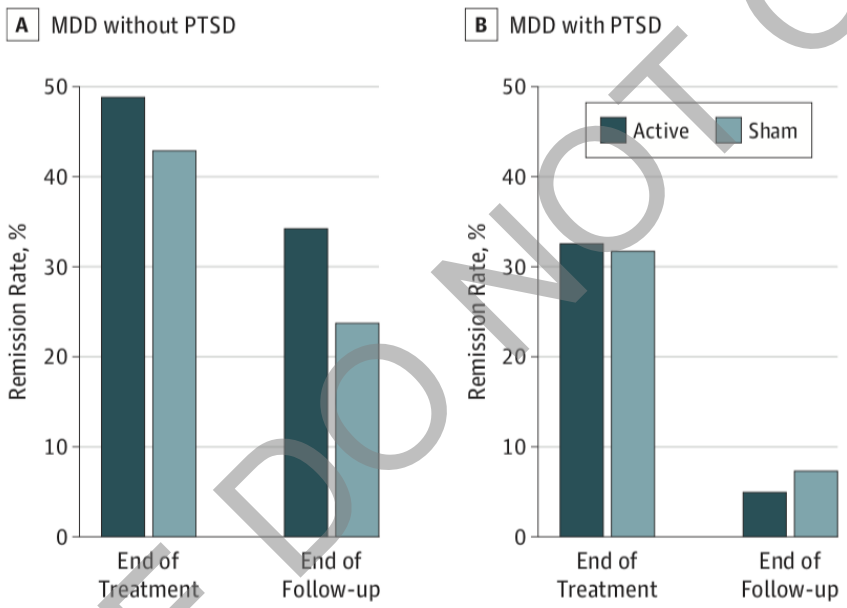
Yesavage, Fairchild, Mi, Biswas, Davis-Karim, Phibbs, Forman, Thase, Williams, Etkin, O'Hara, Georgette, Beale, Huang, Noda, George; VA Cooperative Studies Program Study Team, *JAMA Psychiatry* 2018.

rTMS over the dlPFC to treat depression in military veterans.



Another key message:
The value of sham-controlled condition to develop NIBS treatments.

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Yesavage, Fairchild, Mi, Biswas, Davis-Karim, Phibbs, Forman, Thase, Williams, Etkin, O'Hara, Georgette, Beale, Huang, Noda, George; VA Cooperative Studies Program Study Team, *JAMA Psychiatry* 2018.

Sham-controlled rTMS trial in PTSD: The value of neuroimaging outcome.

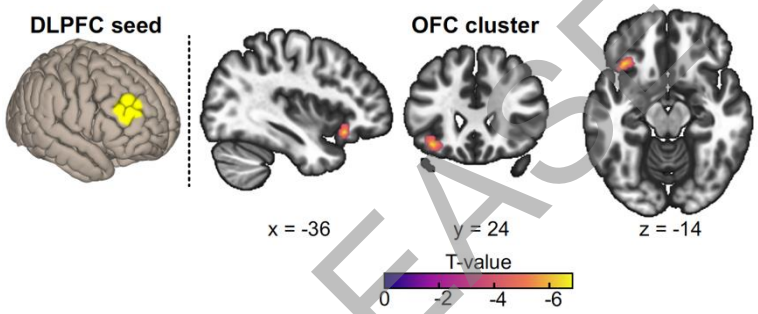
iTBS over the dlPFC to treat PTSD in military personnel

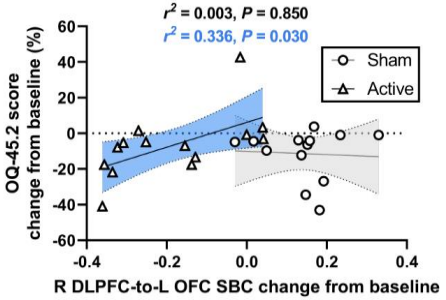
- 32% of remission 1-month after active or sham iTBS.

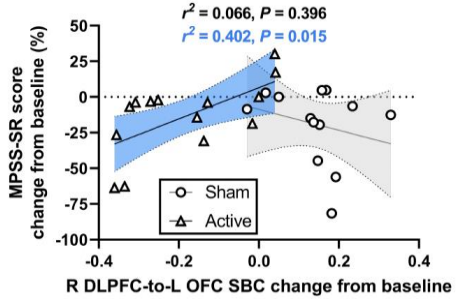
- Quality of Life improved 1-month after active, but not sham iTBS.

- Group differences of functional connectivity between the right DLPFC seed and the left orbitofrontal cortex.

- Alleviation of PTSD symptoms and improved Quality of Life correlated with reduced connectivity in the active, but not the sham group.







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Roy, Levasseur-Moreau, Mondino, Renauld, Hébert, Beaulieu, Bilodeau, Fecteau. *Transcranial Magnetic Stimulation* 2026.

Key messages

1. Value of cognition:

To identify the functions related to our NIBS target.

2. Value of neuroimaging:

To identify if NIBS sufficiently reaches the cortex.

If so, to identify which brain networks it modulates.

To examine if these networks are relevant to our outcome.

The value of cognition and neuroimaging:

So, we do not treat the brain as a black box.

We do not assume the "mechanisms" underlying NIBS-induced clinical benefits.

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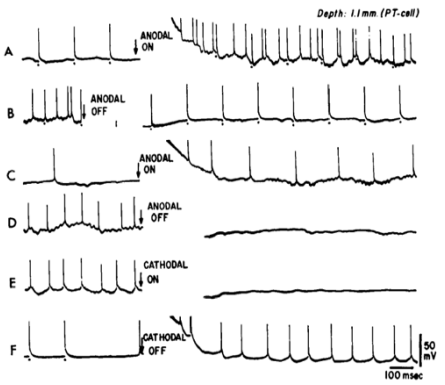
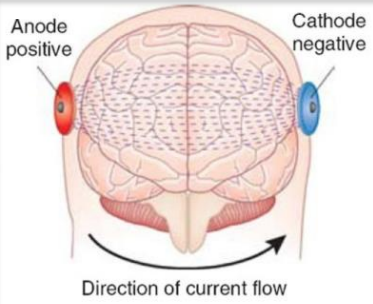
Eliminating the dosing dogma of rTMS and tDCS (and others…)



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.

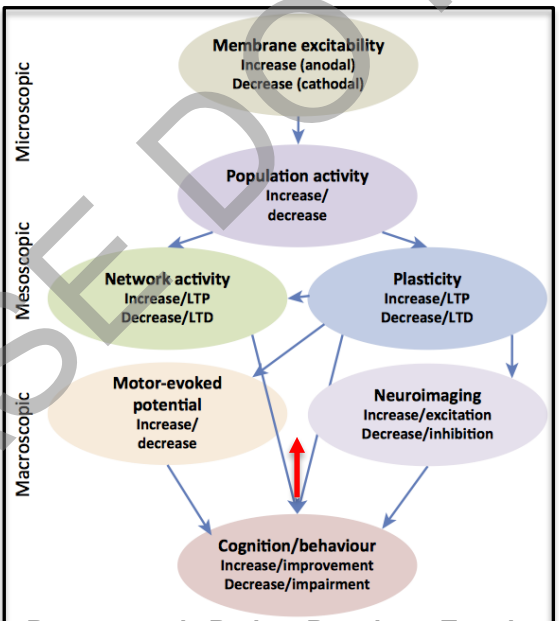
The Pitfalls

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

rTMS TBS tDCS	High freq Intermittent Anodal	Low freq Continuous Cathodal
	Excitatory	Inhibitory

rTMS	High freq	Low freq
TBS	Continuous	Intermittent
tDCS	Anodal	Cathodal
	Excitatory &	Inhibitory

Lisanby, Transcranial Electric Stimulation Workshop, NIH 2016.



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

CORTEX 139 (2021) 43–59

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ScienceDirect

Journal homepage: www.elsevier.com/locate/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
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[e] Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, United Kingdom

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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.

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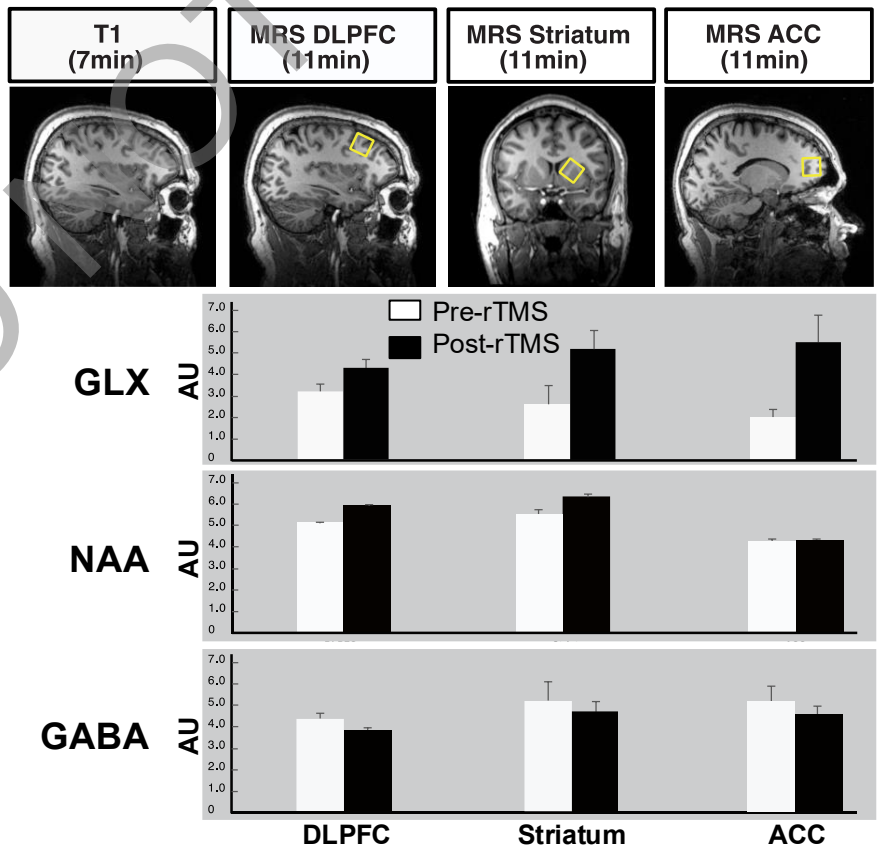
An example, the value of neuroimaging in NIBS treatment.

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.

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The value of cognition and neuroimaging to develop NIBS treatments.



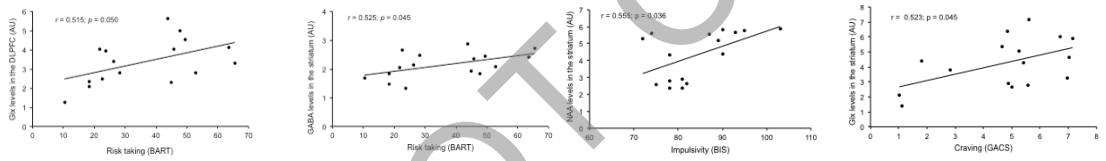
Effects of NIBS can be impacted by:

1. Cognition and symptom [1] :

Greater risk taking, impulsivity, craving level

=

Greater tDCS impact on neurotransmitter levels in the dlPFC and striatum.



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

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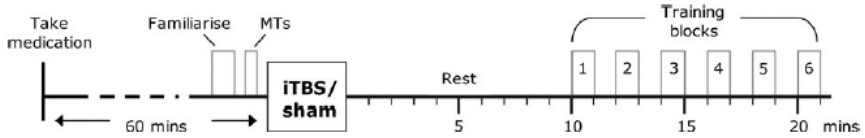
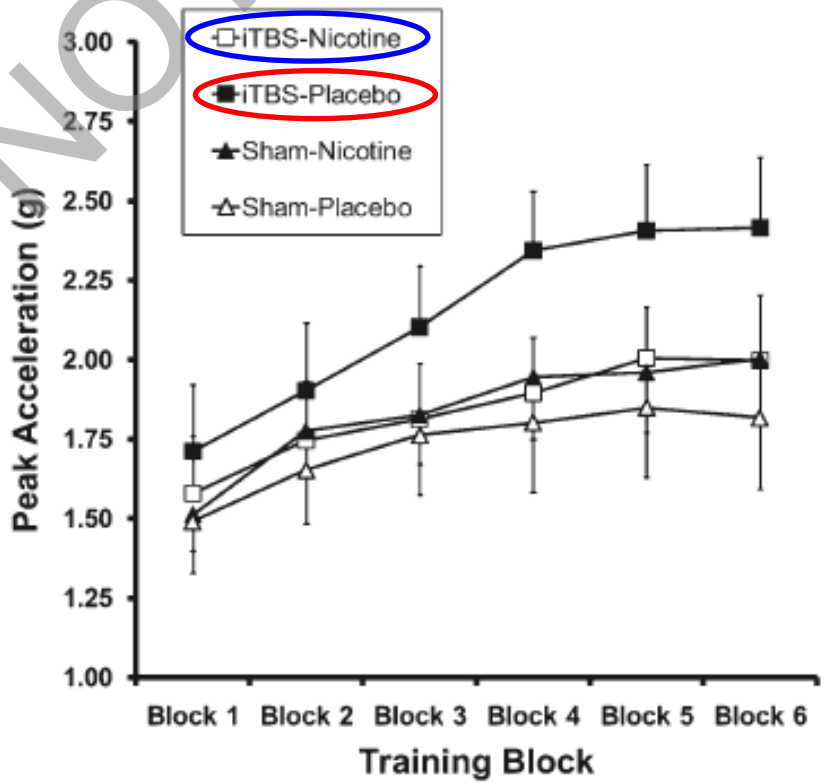
The impact of brain state on NIBS effects

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.

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The value of cognition and neuroimaging to develop NIBS treatments.



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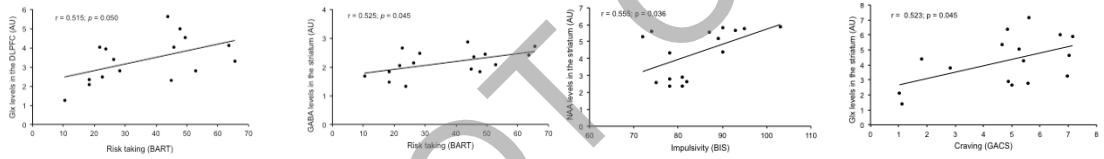
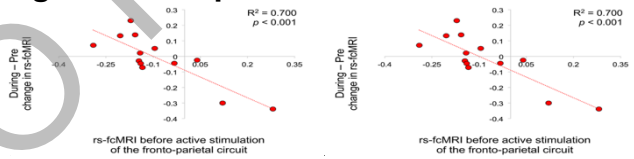


2. Functional connectivity [2] :

Stronger baseline functional connectivity

=

Stronger tDCS impact on functional connectivity.

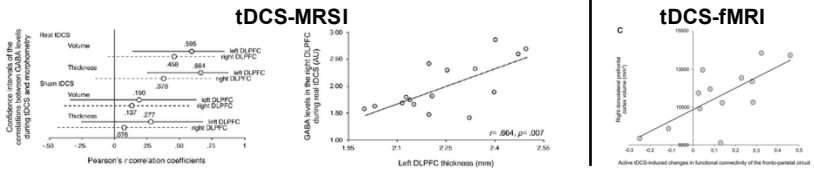


3. Brain morphometry [3,4] :

Greater dlPFC volume and thickness

=

Greater tDCS impact on neurotransmitter levels and functional connectivity.



An opportunity to personalize protocols based on individual's *characteristics*.

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

[2] Bouchard, Renauld, Fecteau, *Front Hum Neurosci* 2023.

[3] Bouchard, Dickler, Renauld, Lenglos, Ferland, Edden, Rouillard, Leblond, Fecteau, *Brain Stimul* 2020.

[4] Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau, *Brain Connect* 2021.

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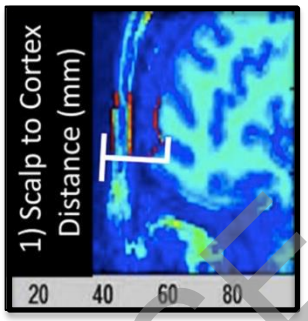
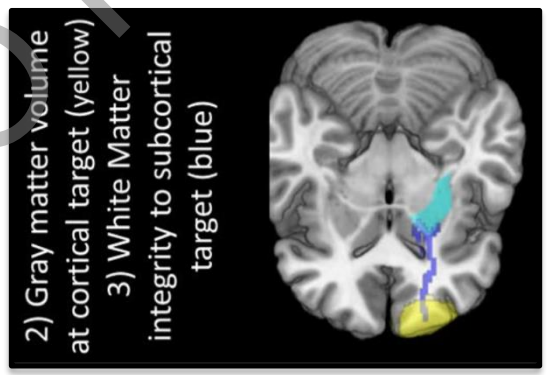
The impact of scalp-to-cortex distance on the neural effects of rTMS.

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).





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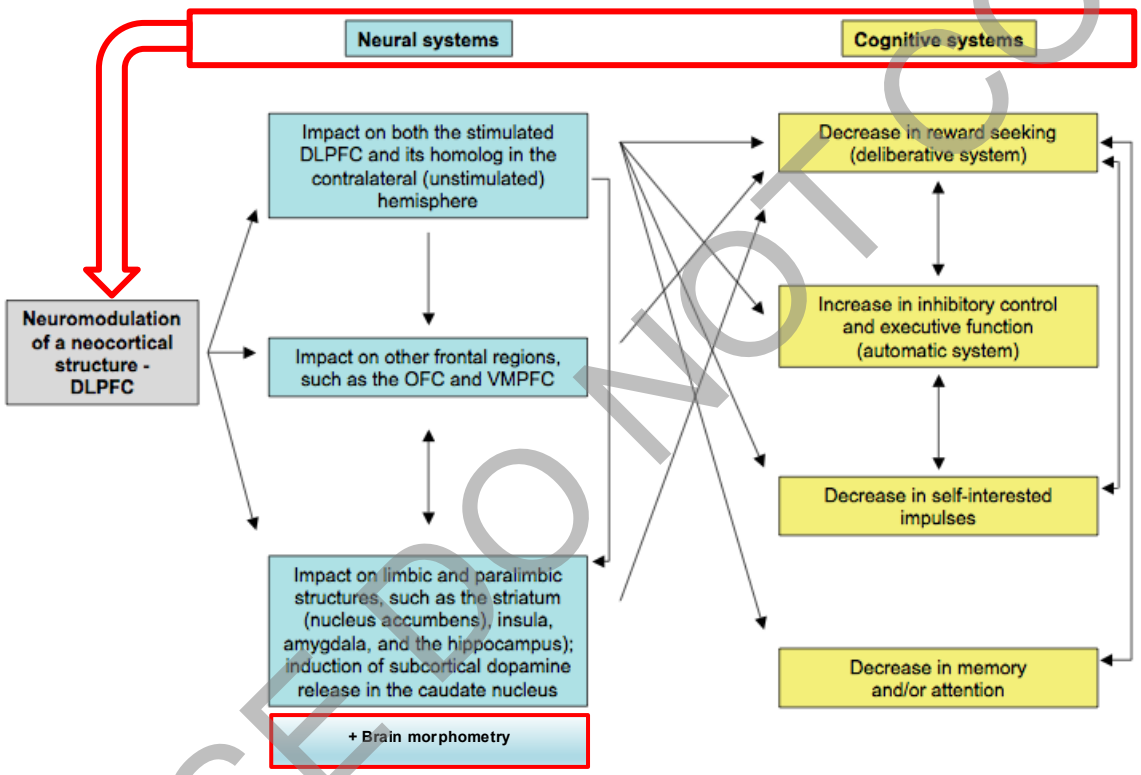
Effects of NIBS over the dlPFC… and Impact of the dlPFC on NIBS effects.



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

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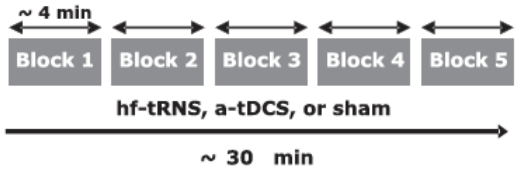
Other questions such as: When to prime the brain?

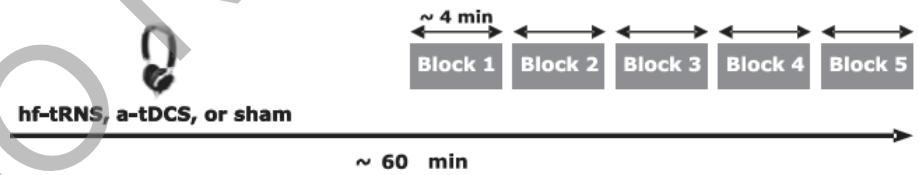
Effects of NIBS on an orientation discrimination task testing:

- **online tDCS, offline tDCS,**
- **online transcranial random noise stimulation (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.

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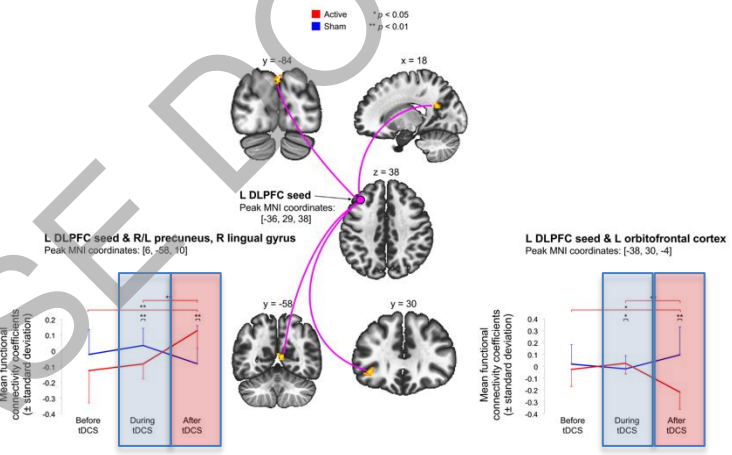
Pirrulli, Fertonani, Miniussi. *Brain Stimul* 2013.

When to prime the brain?: The value of neuroimaging to develop NIBS treatments.

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

tDCS induced changes in functional connectivity

during ≠ after tDCS



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

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Summary 1

NIBS can modulate behaviours in healthy adults:

Improve behaviours: **- clinical relevance** **- neuroenhancement** ***Can this be beneficial for my patients?***	**Impair behaviours:** **- clinical relevance** **- virtual lesion** ***Can this be a concern for my patients?***

Is there translational value of NIBS studies in healthy adults into clinical applications?
Yes, but to some extent.

The effects of NIBS can be impacted by baseline:

behavioural trait and state	**brain activity**	**brain morphometry**

These can be different:

between groups (healthy vs. patients)	**within a clinical population** (e.g., patients with MDD, with/without comorbid AUD)	**within an individual** (e.g., sobriety)

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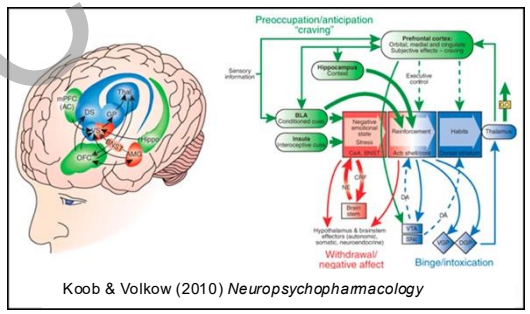
What's next to further develop NIBS treatments?

We want to know how to modulate brain substrates that are clinically relevant for a given patient.

1. Value of neuroimaging

Want is to reach and stimulate a *receptive* network

This is not trivial in substance related and addictive disorders

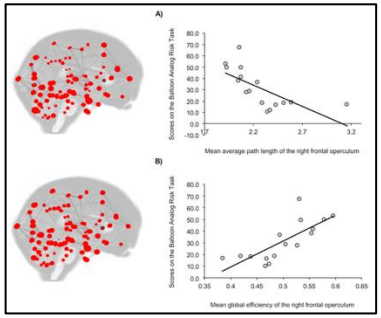


Koob & Volkow (2010) *Neuropsychopharmacology*

2. Value of cognition

- Identification of the individual's target before neuromodulation

Target the efficiency of the right frontal cortex to reduce risk taking level in adults with Gambling Disorder[1].



- Know the functionS related to this target (e.g., and not only the tested outcome).

The brain is agnostic to your primary outcome measure.

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[1] **Bouchard, Dickler, Renauld, Lenglos, Ferland, Rouillard, Leblond, Fecteau. *Eur Neuropsychoparmacol* 2023.**

Know the functions related to the NIBS target

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.

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

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

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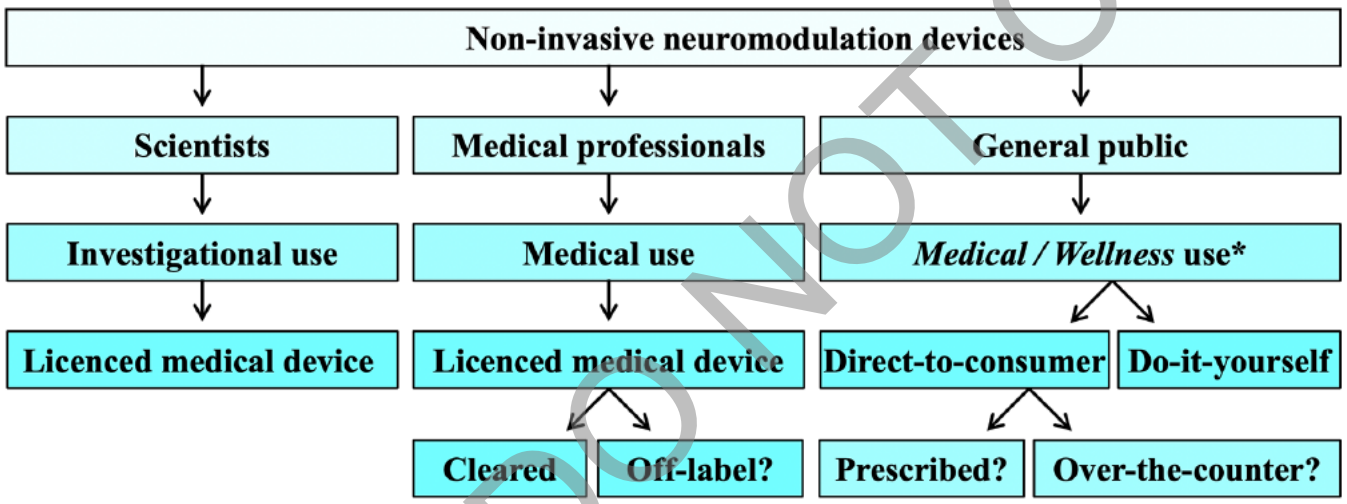
Ethical considerations



Fecteau (2023) *The Neuroscientist*

Vulnerable populations: children, etc.

Special issue "Ethico-Legal Issues in Brain Stimulation" *Brain Stimulation*, 2024

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How may NIBS induce enhancement?

Conceptual framework of neuroenhancement

Three potential mechanisms :

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

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Brem, Fried, Horvath, Robertson, Pascual-Leone. *Neuroimage* 2014.
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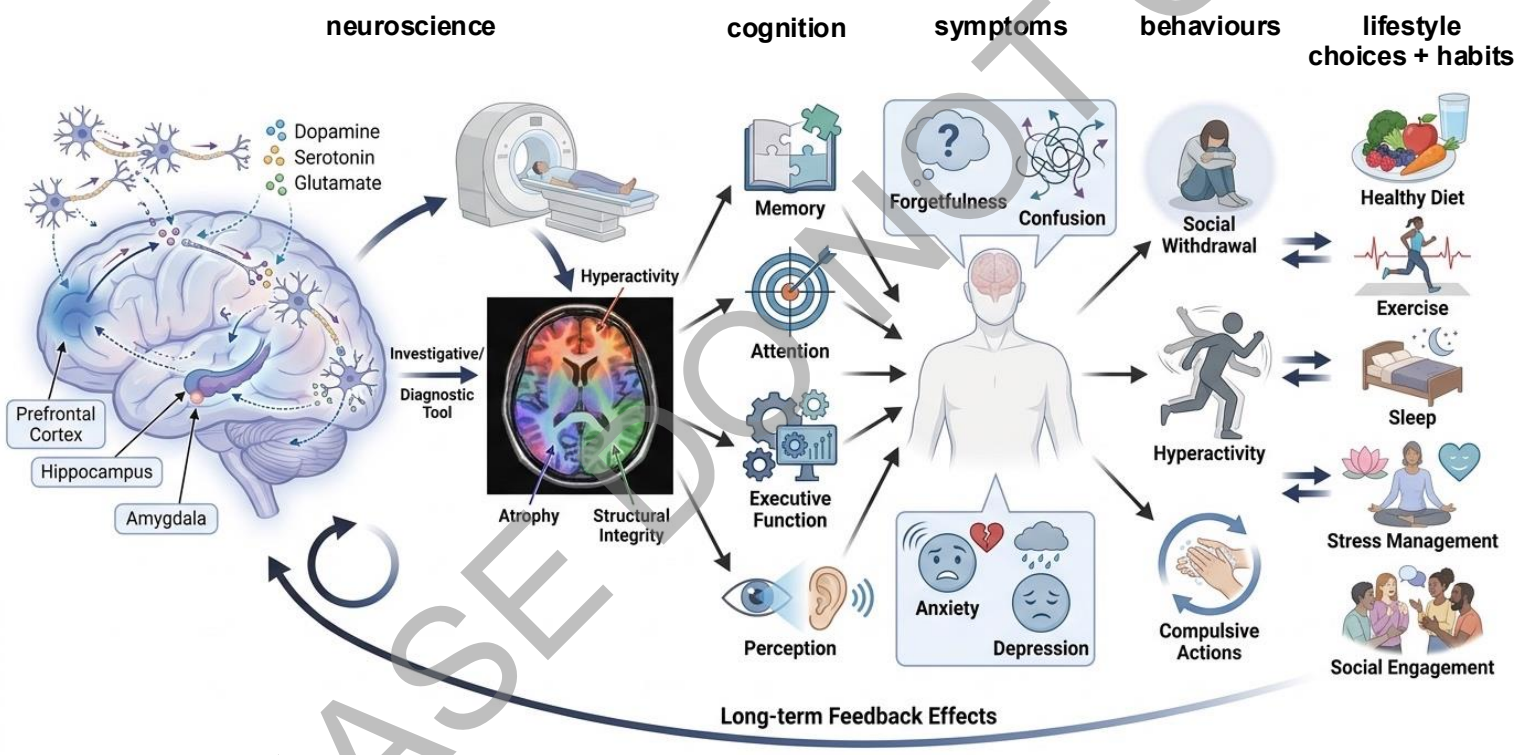
Finally, “mechanisms” related to clinical benefits

From neuroscience to cognition, symptoms, behaviours and lifestyle choices and habits… and back.



An opportunity to act on multiple fronts.

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Thank you!

Questions?

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