NEUROMODULATION EN DÉPENDANCE: DÉCOUVERTES RÉCENTES ET ORIENTATIONS FUTURES

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UNITÉ DE NEUROMODULATION PSYCHIATRIQUE (UNP) DU CHUM

CPMD 2021

CONFLITS D'INTÉRÊTS

- Aucun en lien avec cette présentation

OBJECTIFS

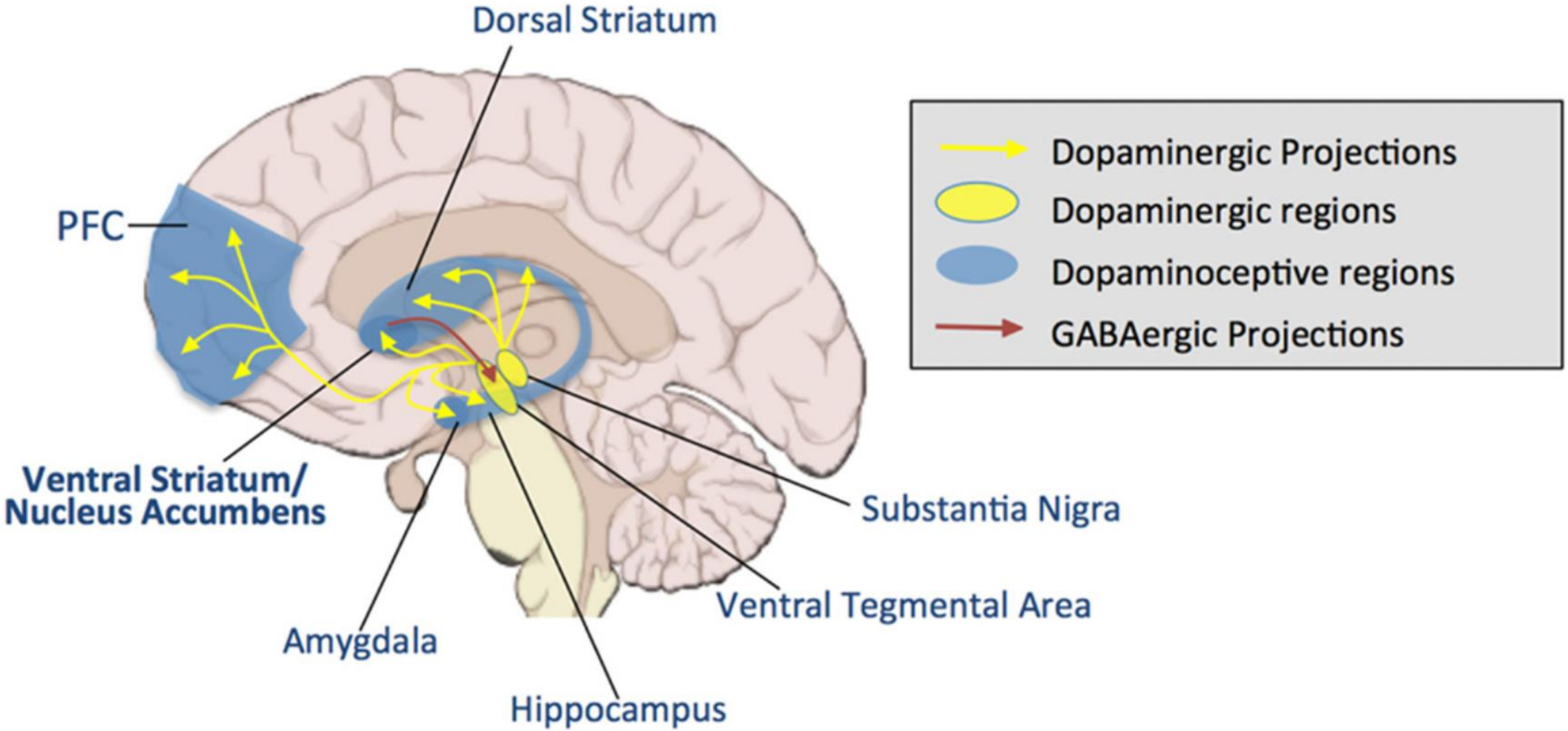
- Comprendre les substrats neurobiologiques de la toxicomanie
- Résumer les mécanismes des approches de neuromodulation
- Situer le rôle potentiel des approches de neuromodulation dans le traitement de la toxicomanie

ADDICTION

- Phénomène biologique et social
- Thérapies psychosociales et pharmacologiques reconnues, mais…
- Efficacité reste à optimiser
- Certains types de dépendance restent orphelines au niveau du traitement (cocaïne)
- Compréhension neurobiologique permet de conceptualiser de nouvelles interventions

ADDICTION

- Phénomène initialement lié à l'impulsivité qui migre éventuellement vers la compulsivité, dysfonction du système dopaminergique
- Un état de sevrage suit l'intoxication (physique court-terme, émotionnel long terme), augmentation de la sévérité à travers le temps
- Entraîne une recherche compulsive de la substance, phénomène compensatoire pour diminuer la souffrance
- Perte de contrôle

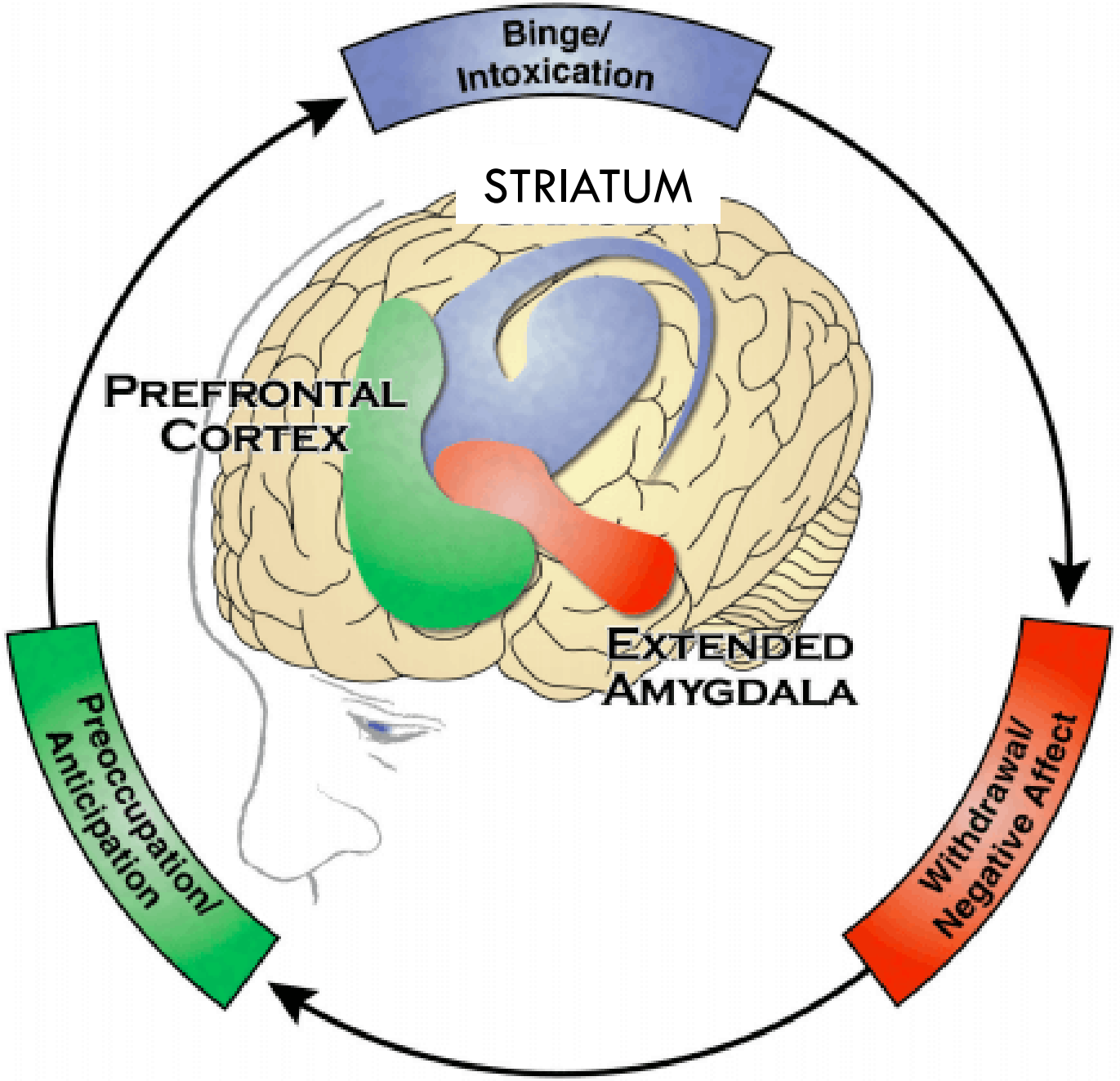


Telzer EH. Dopaminergic reward sensitivity can promote adolescent health: A new perspective on the mechanism of ventral striatum activation. Dev Cogn Neurosci. 2016 Feb;17:57-67. doi: 10.1016/j.dcn.2015.10.010. Epub 2015 Nov 24. PMID: 26708774; PMCID: PMC4727991.

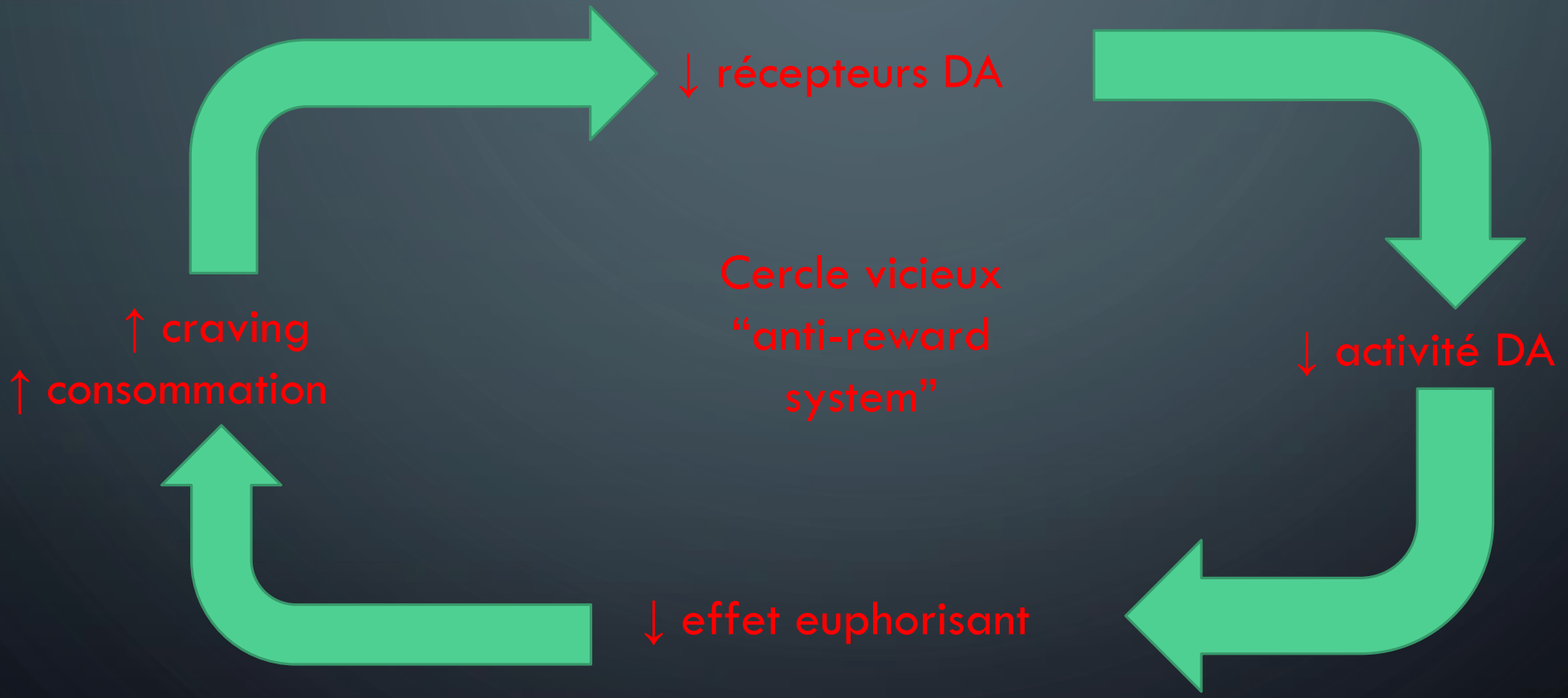
RÉGIONS CÉRÉBRALES IMPLIQUÉS

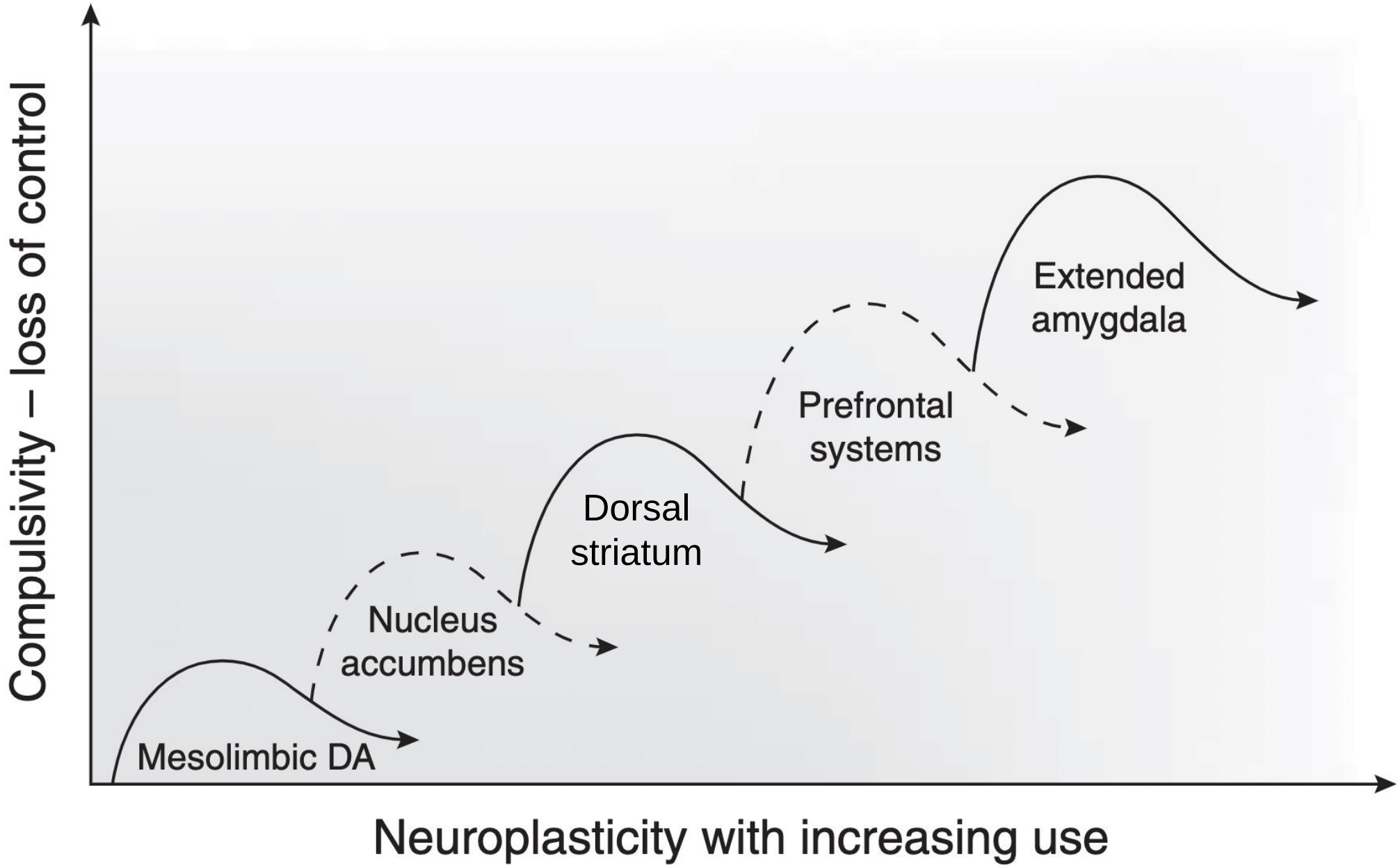
- Binge/intoxication (impulsivité)
  - Aire tegmentaire ventrale
  - Striatum ventral/**Noyau accumbens**
- Renforcement/habituation (compulsivité)
  - Striatum dorsal
- Sevrage
  - Perte du tonus dopaminergique du striatum ventral
  - Suractivation de l'axe HPA
  - Désinhibition de l'amygdale

- Anticipation (*craving*)
  - Cortex préfrontal, noyau accumbens (*drug-induced*)
  - Amygdale basolatérale (*cue-induced*)
  - Amygdale étendue (*stress-induced*)
  - Insula
  - Hippocampe
- Contrôle inhibitoire
  - Cortex cingulaire
  - Cortex préfrontal dorsolatéral
  - Gyrus frontal inférieur


Binge/
Intoxication
STRIATUM
PREFRONTAL
CORTEX
EXTENDED
AMYGDALA
Withdrawal/
Negative Affect
Preoccupation/
Anticipation

ADDICTION


↓ récepteurs DA
↓ activité DA
↓ effet euphorisant
↑ craving
↑ consommation
Cercle vicieux
"anti-reward
system"


Compulsivity – loss of control
Mesolimbic DA
Nucleus accumbens
Dorsal striatum
Prefrontal systems
Extended amygdala
Neuroplasticity with increasing use

STIMULATION MAGNÉTIQUE TRANSCRÂNIENNE (TMS)

source : MagVenture

THE LANCET, MAY 11, 1985

NON-INVASIVE MAGNETIC STIMULATION OF HUMAN MOTOR CORTEX

SIR,—This note describes a novel method of directly stimulating the human motor cortex by a contactless and non-invasive technique using a pulsed magnetic field. Merton et al[1] have drawn attention to the electrical stimulation of human brain and spinal cord using external electrodes on the skin. Interesting results have been reported on the cortical threshold in Parkinson's disease,[2] on pyramidal conduction velocity in multiple sclerosis,[3] and on pelvic neuropathy related to faecal incontinence.[4]

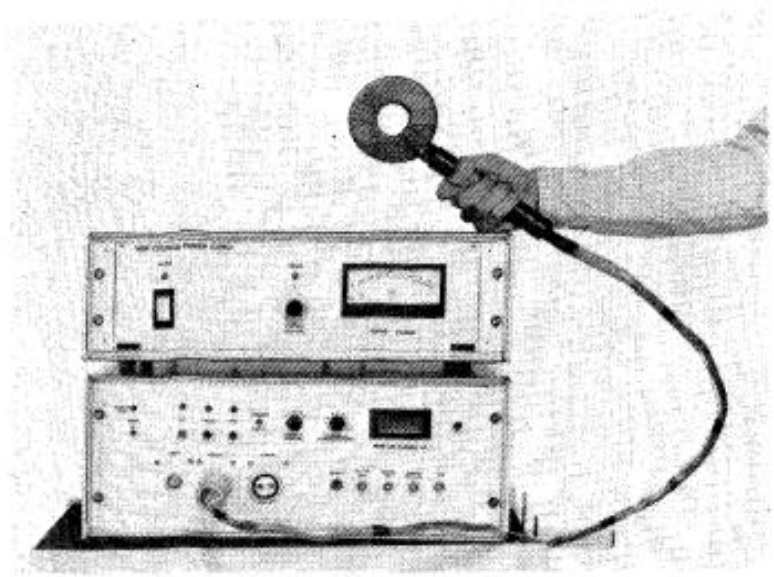


Fig 1—Magnetic stimulator and coil.

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Department of Medical Physics
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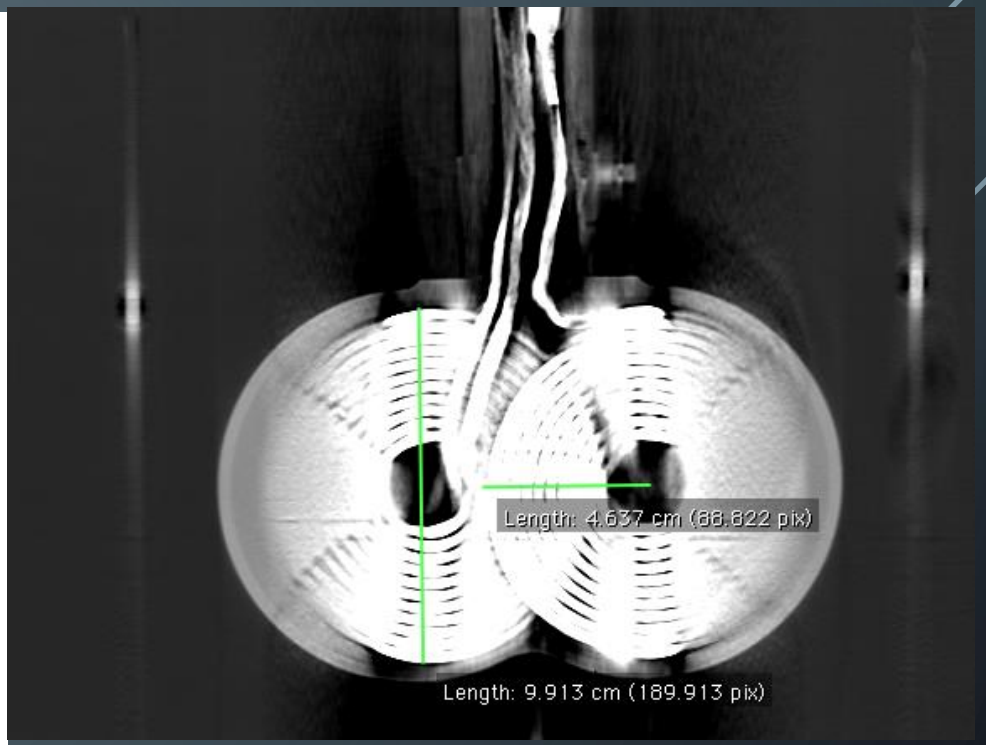
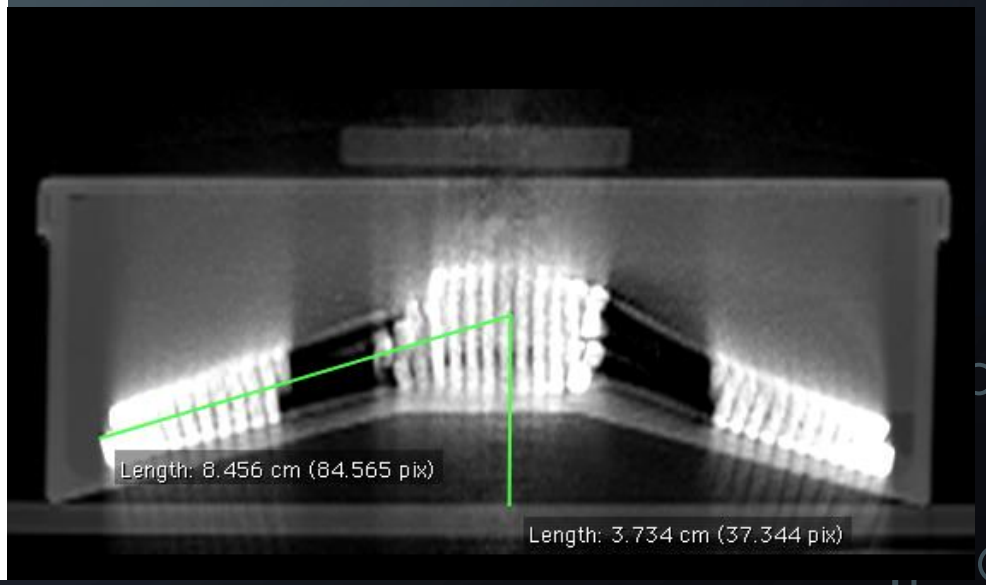
Royal Hallamshire Hospital,
Sheffield S10 2JF

A. T. BARKER
R. JALINOUS

Department of Electronic
and Electrical Engineering,
University of Sheffield

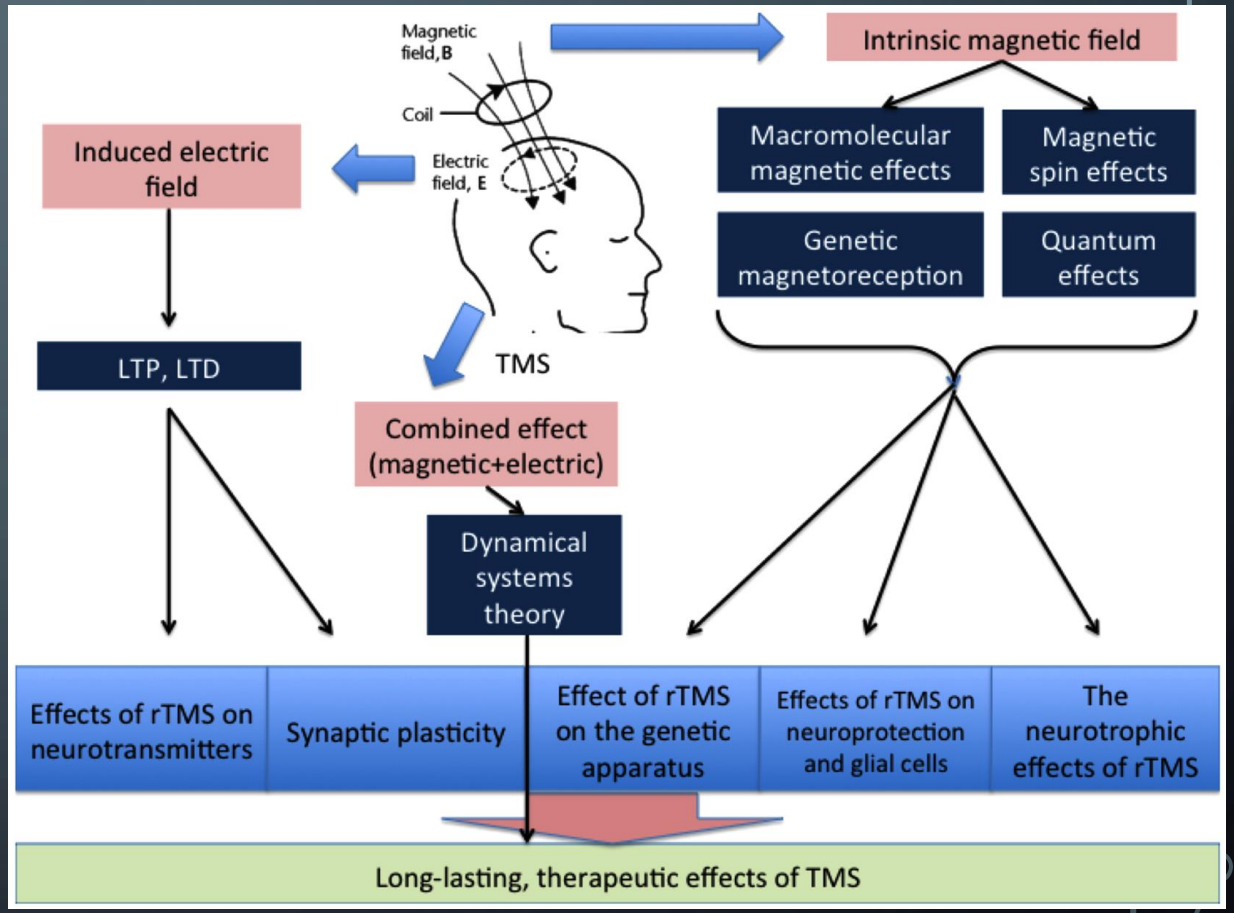
I. L. FREESTON





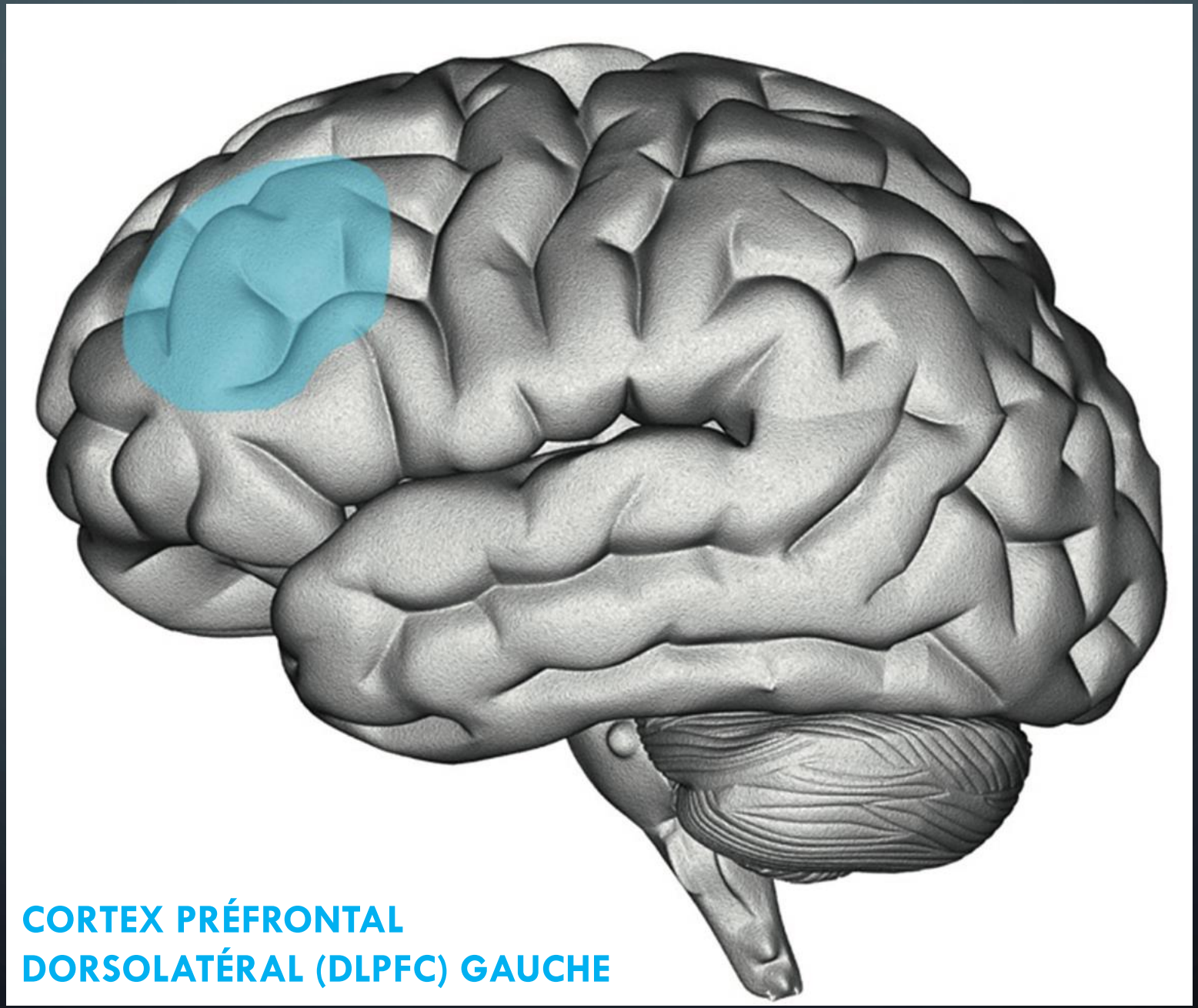
BASES DE LA rTMS

- Champ magnétique induit un courant électrique dans le tissu neural, mécanismes de LTP/LTD (excitation/inhibition) entraînent des changements neuroplastiques à long terme



BASES DE LA rTMS

- Indication principale: dépression majeure réfractaire
- Récemment aussi: approbation FDA pour TOC et tabagisme
- Classiquement, tx complet 20-30 séances (1 séance/j, 5x/sem, 4-6 sem)
- Protocoles accélérés permettraient de réduite durée du traitement en préservant efficacité



CORTEX PRÉFRONTAL DORSOLATÉRAL (DLPFC) GAUCHE

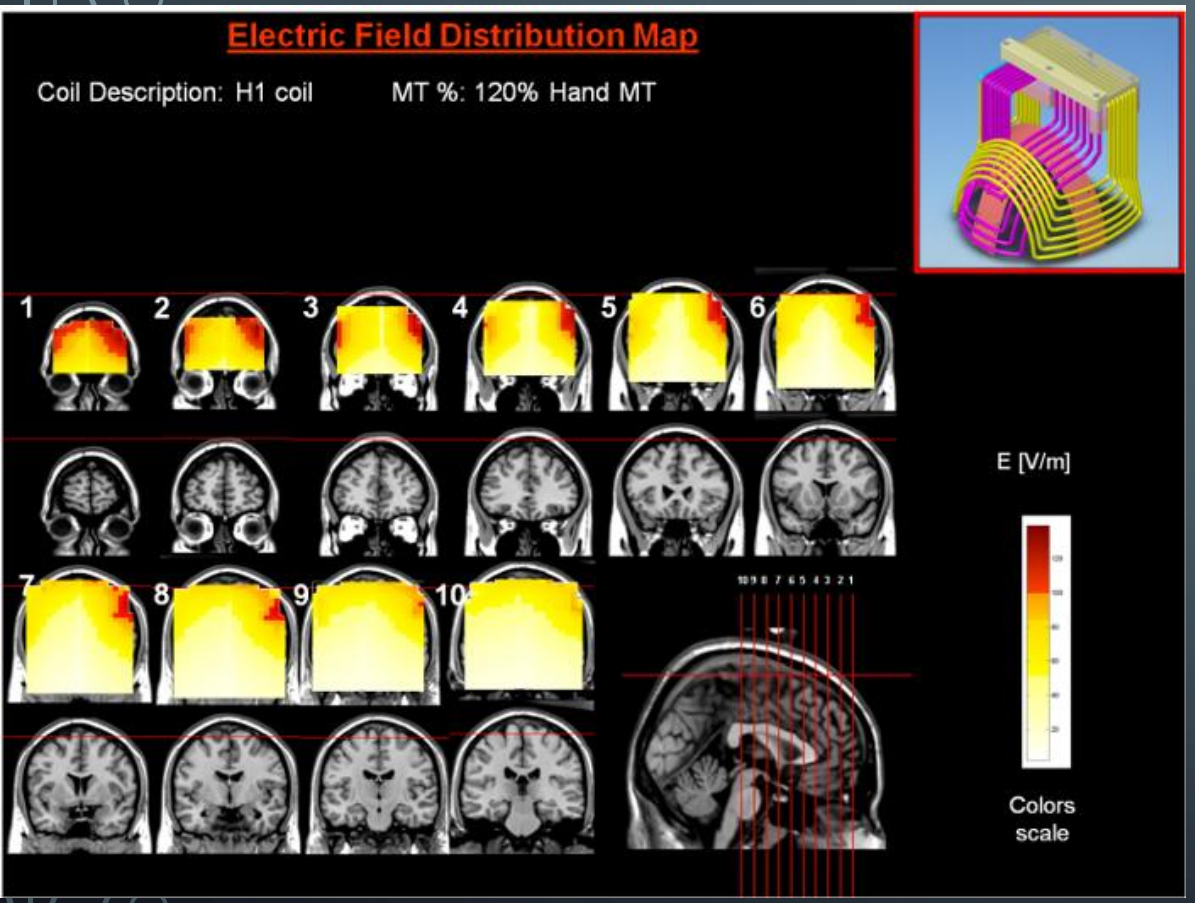
source: *Research Institute Brainclinics* ©

TMS CONVENTIONNELLE

Source: FIU

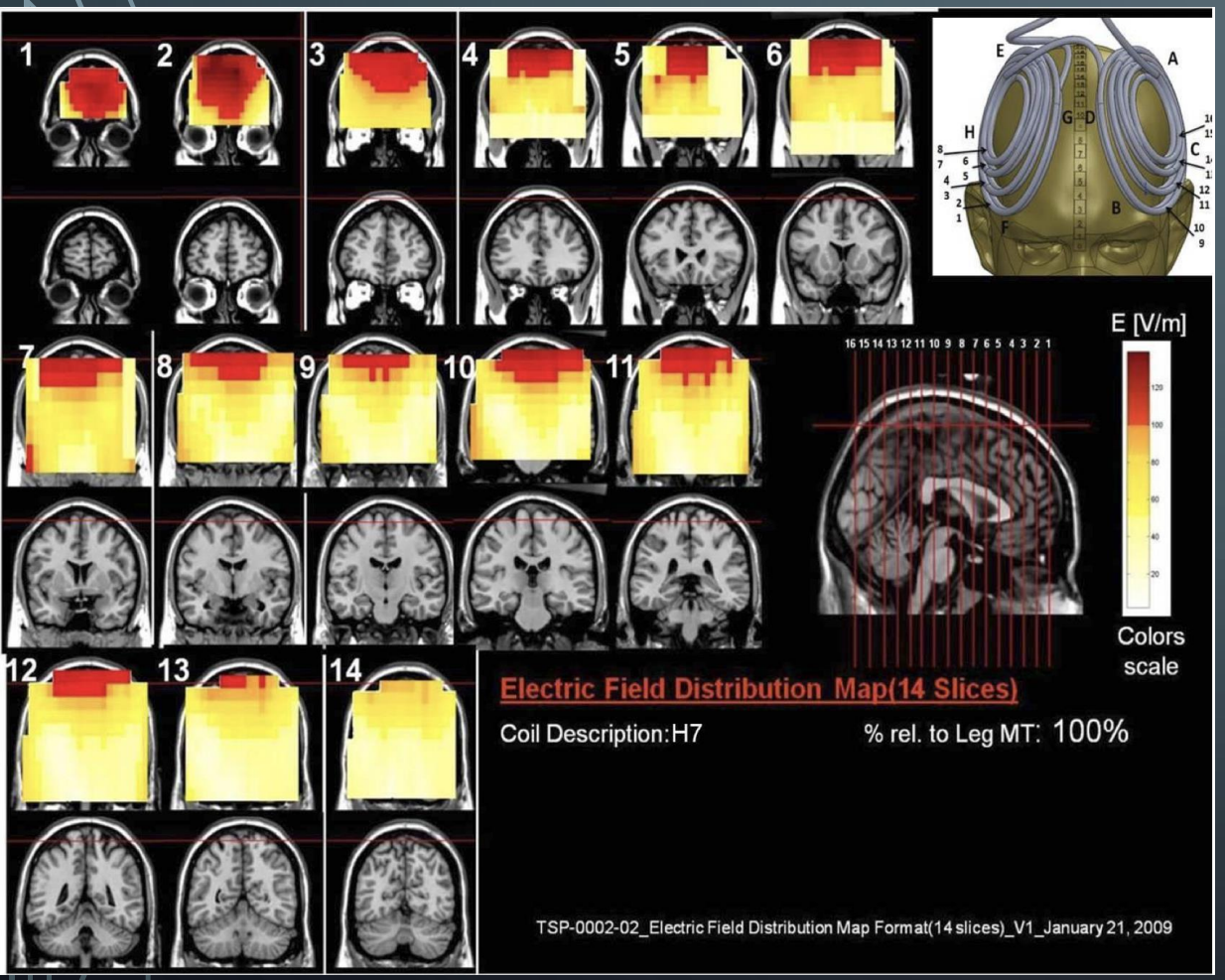
DEEP TMS

Source: Brainsway



Source: Brainsway

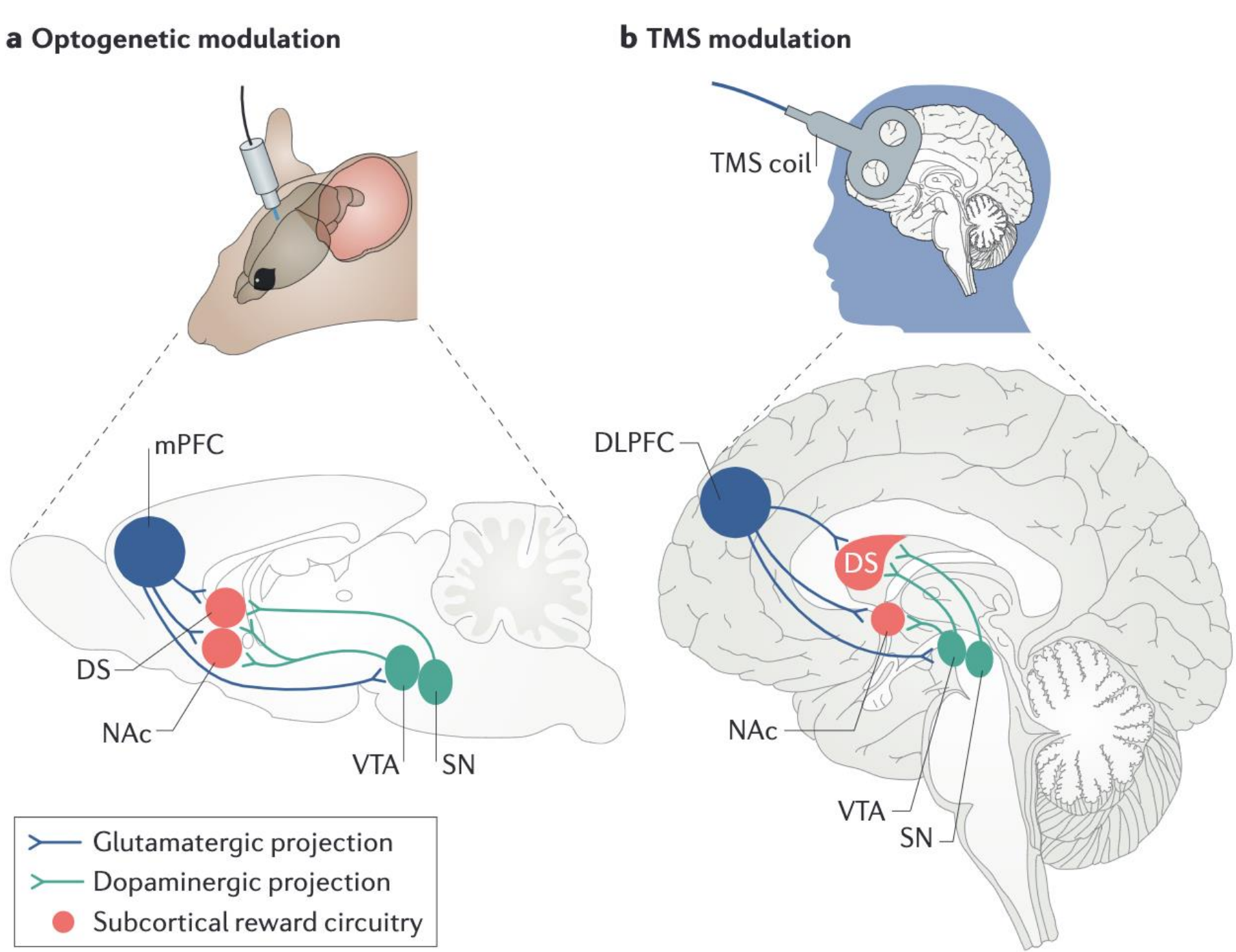
TOC



Carmi, L. *et al*. Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Prospective Multicenter Randomized Double-Blind Placebo-Controlled Trial. *Am J Psychiat* (2019) doi:10.1176/appi.ajp.2019.18101180.

EFFETS SECONDAIRES

- Aucun effet cognitif néfaste, au contraire serait pro-cognitif (Martin et al. 2017)
- Champs magnétiques ne sont pas dangereux pour le corps humain (http://www.hydroquebec.com/champs/)
- Effets secondaires communs: inconfort per-stimulation, céphalées et fatigue post-stimulation
- Effets secondaires rares: convulsions (25 cas rapportés dans la littérature), augmentation des symptômes/idées suicidaires (temporaire), hypomanie/manie, syncope, perte auditive (besoin de protection auditive pendant le traitement)
- C-I: tatouage/maquillage permanent, épilepsie, implants métalliques au niveau cérébral (stimulateurs/électrodes, implants cochléaires, clips d'anévrysmes), pacemaker, usage de BZD


a Optogenetic modulation
b TMS modulation
TMS coil
mPFC
DS
NAc
VTA
SN
DLPFC
DS
NAc
VTA
SN
Glutamatergic projection
Dopaminergic projection
Subcortical reward circuitry

Repetitive Transcranial Magnetic Stimulation of the Human Prefrontal Cortex Induces Dopamine Release in the Caudate Nucleus

Antonio P. Strafella, Tomáš Paus, Jennifer Barrett, and Alain Dagher

Montreal Neurological Institute, McGill University, Montréal, Québec, Canada H3A 2B4

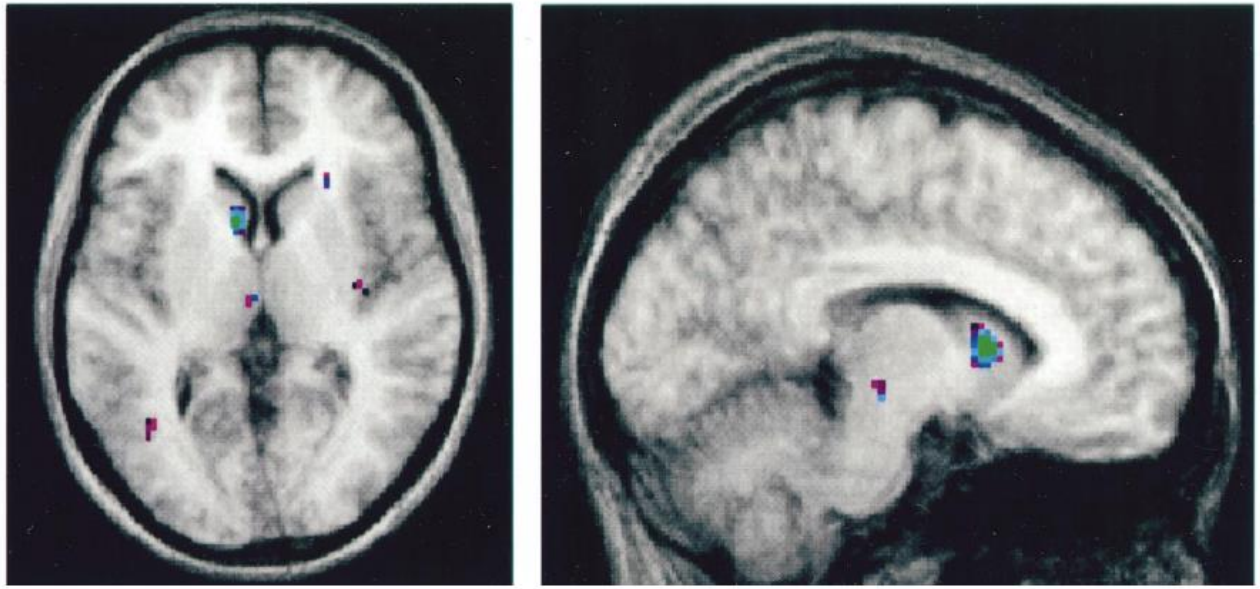
OPEN ACCESS Freely available online

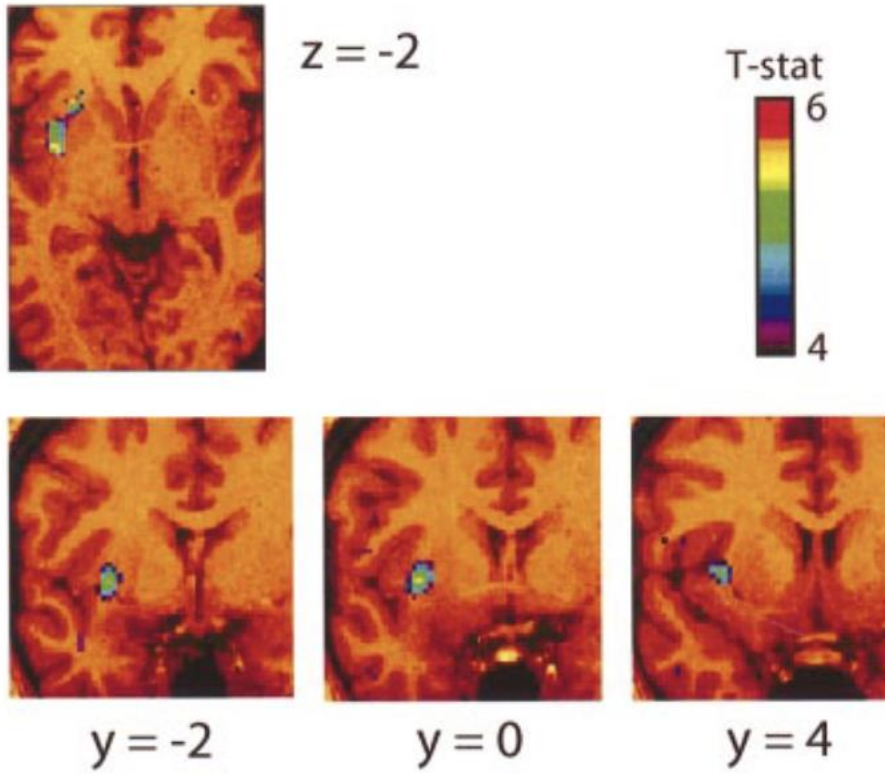
PLoS one

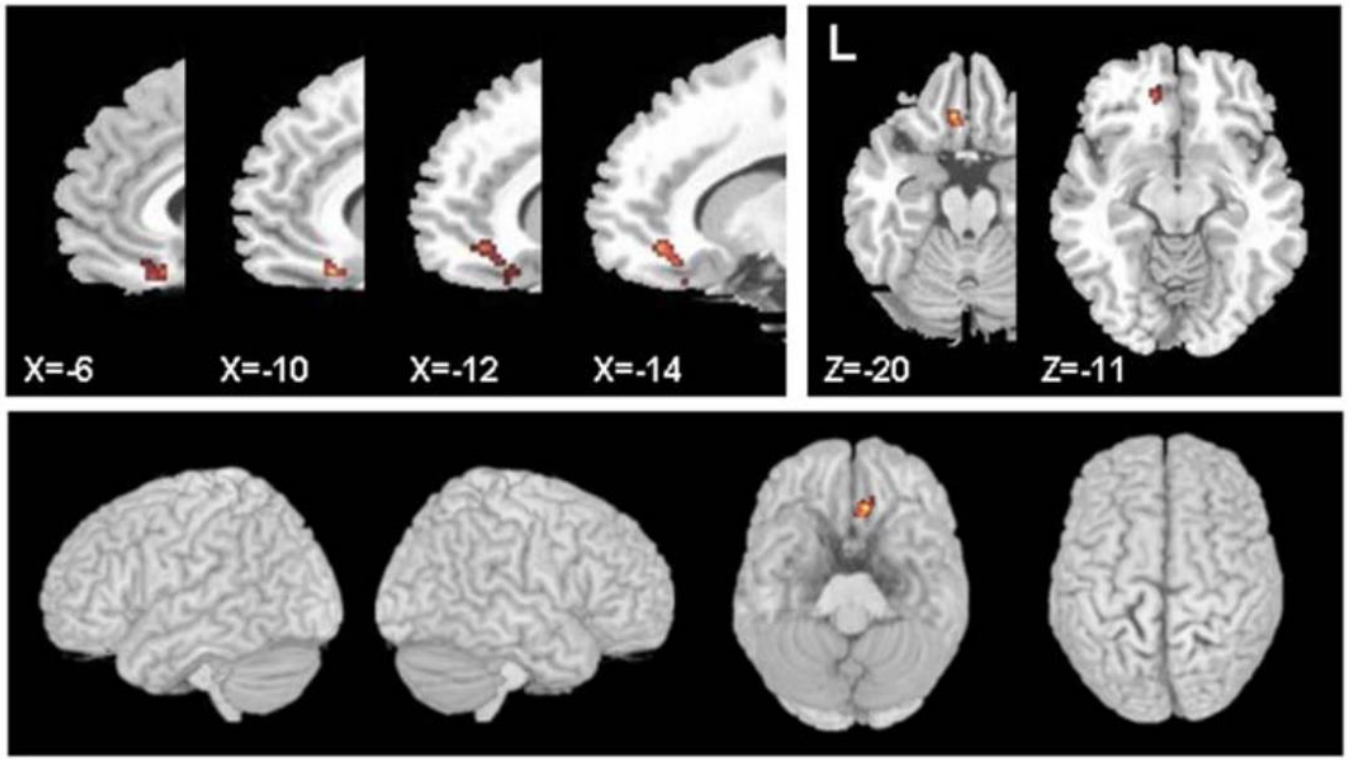
rTMS of the Left Dorsolateral Prefrontal Cortex Modulates Dopamine Release in the Ipsilateral Anterior Cingulate Cortex and Orbitofrontal Cortex

Sang Soo Cho[1,2], Antonio P. Strafella[1,2]*

1 Toronto Western Research Institute and Hospital, UHN, University of Toronto, Toronto, Canada, **2** PET Imaging Centre, Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada


t
-6
-3


z = -2
T-stat
6
4
y = -2
y = 0
y = 4


X=-6
X=-10
X=-12
X=-14
L
Z=-20
Z=-11
Z-value
4
3
2
1
0

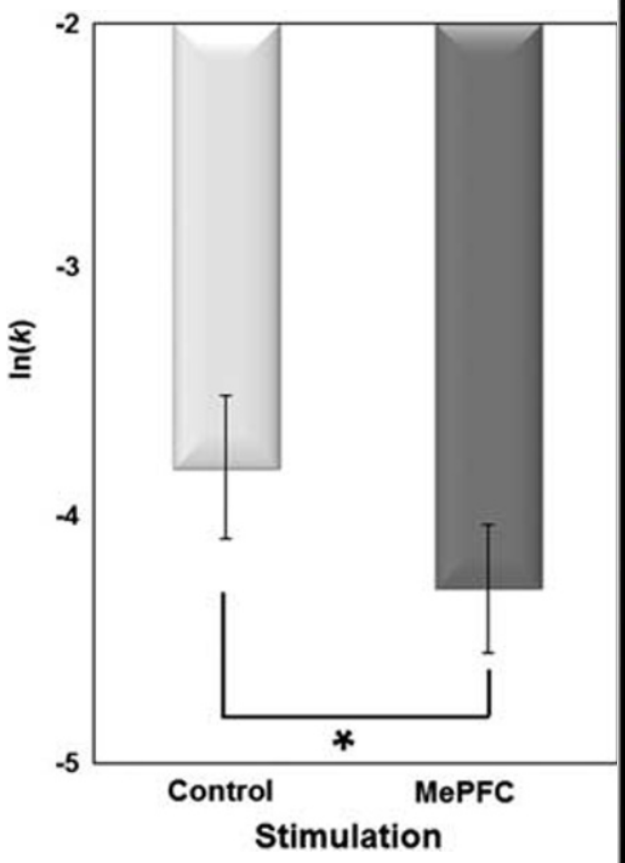
Neuropsychopharmacology (2015) 40, 546–553

www.neuropsychopharmacology.org

Investing in the Future: Stimulation of the Medial Prefrontal Cortex Reduces Discounting of Delayed Rewards

Sang Soo Cho[1,2], Yuko Koshimori[1,2], Kelly Aminian[1,2], Ignacio Obeso[1,2], Pablo Rusjan[2], Anthony E Lang[3], Zafiris J Daskalakis[4], Sylvain Houle[2] and Antonio P Strafella*[,1,2,3]

[1]Division of Brain, Imaging and Behaviour—Systems Neuroscience, Toronto Western Research Institute, UHN, University of Toronto, Ontario, Canada; [2]Research Imaging Centre, Centre for Addiction and Mental Health, University of Toronto, ON, Canada; [3]Movement Disorder Unit & E.J. Safra Parkinson Disease Program, Toronto Western Hospital, UHN, University of Toronto, ON, Canada; [4]Temerty Centre for Therapeutic Brain Intervention, Department of Psychiatry, Centre for Addiction and Mental Health, University of Toronto, ON, Canada



Contents lists available at SciVerse ScienceDirect

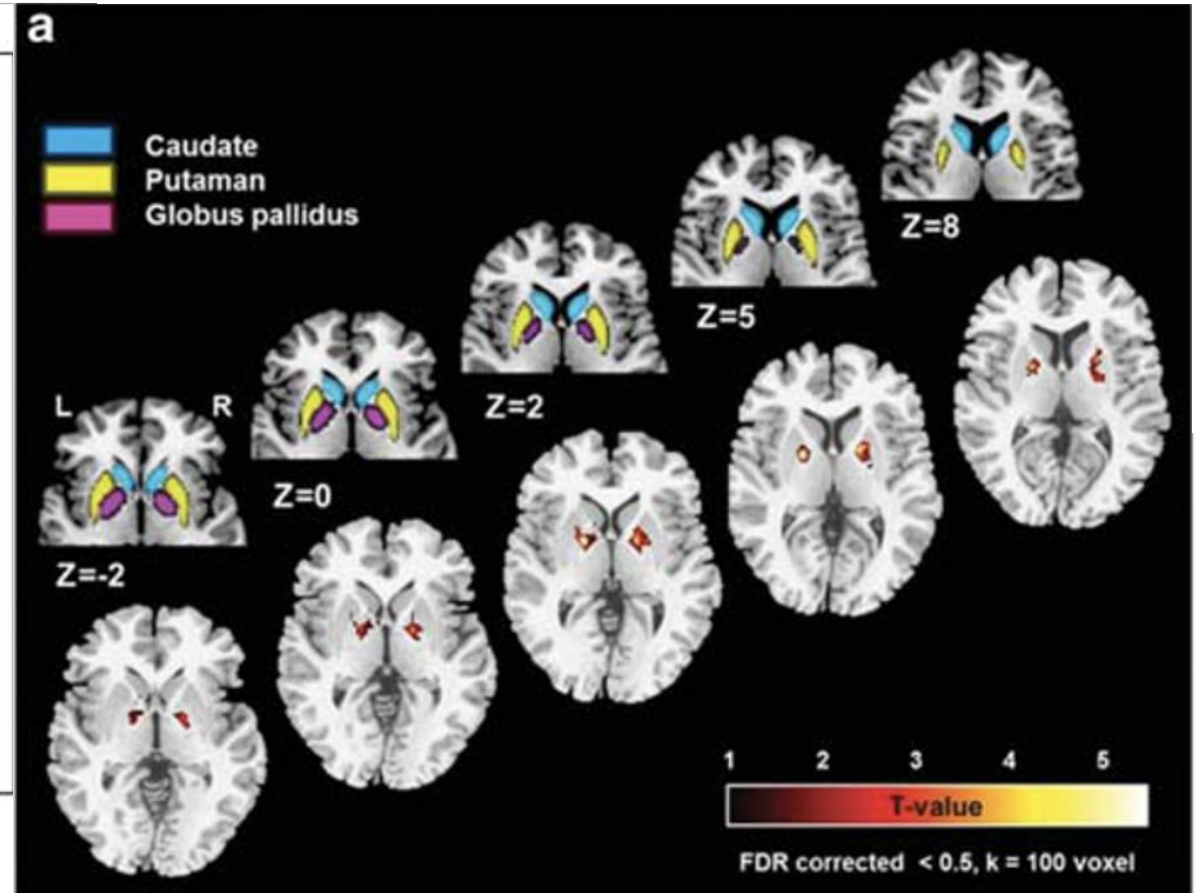
Brain Stimulation

journal homepage: www.brainstimjrnl.com

Effect of continuous theta burst stimulation of the right dorsolateral prefrontal cortex on cerebral blood flow changes during decision making

Sang Soo Cho[a,b], Giovanna Pellecchia[a,b], Ji Hyun Ko[a,b], Nicola Ray[a,b,c], Ignacio Obeso[a,b,c], Sylvain Houle[b], Antonio P. Strafella[a,b,c,*]

[a]*Division of Brain, Imaging and Behaviour – Systems Neuroscience, Toronto Western Research Institute, UHN, University of Toronto, Ontario, Canada*
[b]*Imaging Research Centre, Centre for Addiction and Mental Health, University of Toronto, Ontario, Canada*
[c]*Morton and Gloria Shulman Movement Disorder Unit & E.J. Safra Parkinson Disease Program, Toronto Western Hospital, UHN, University of Toronto, Ontario, Canada*

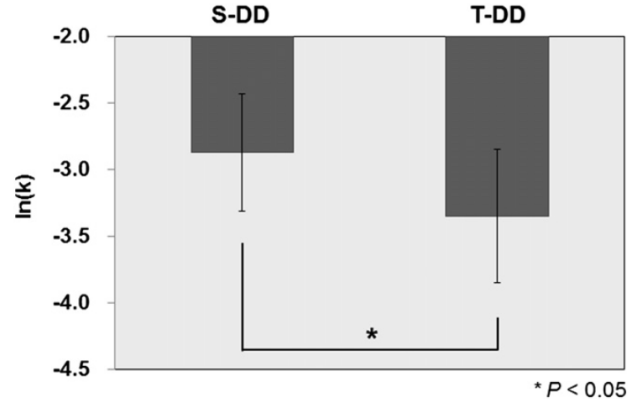


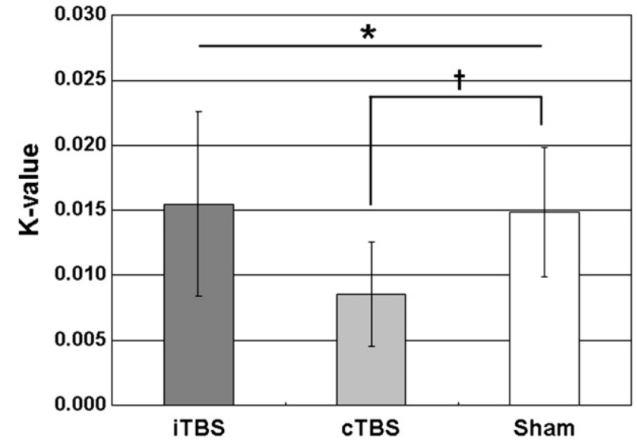
Brain Stimulation (2010) 3, 170–6

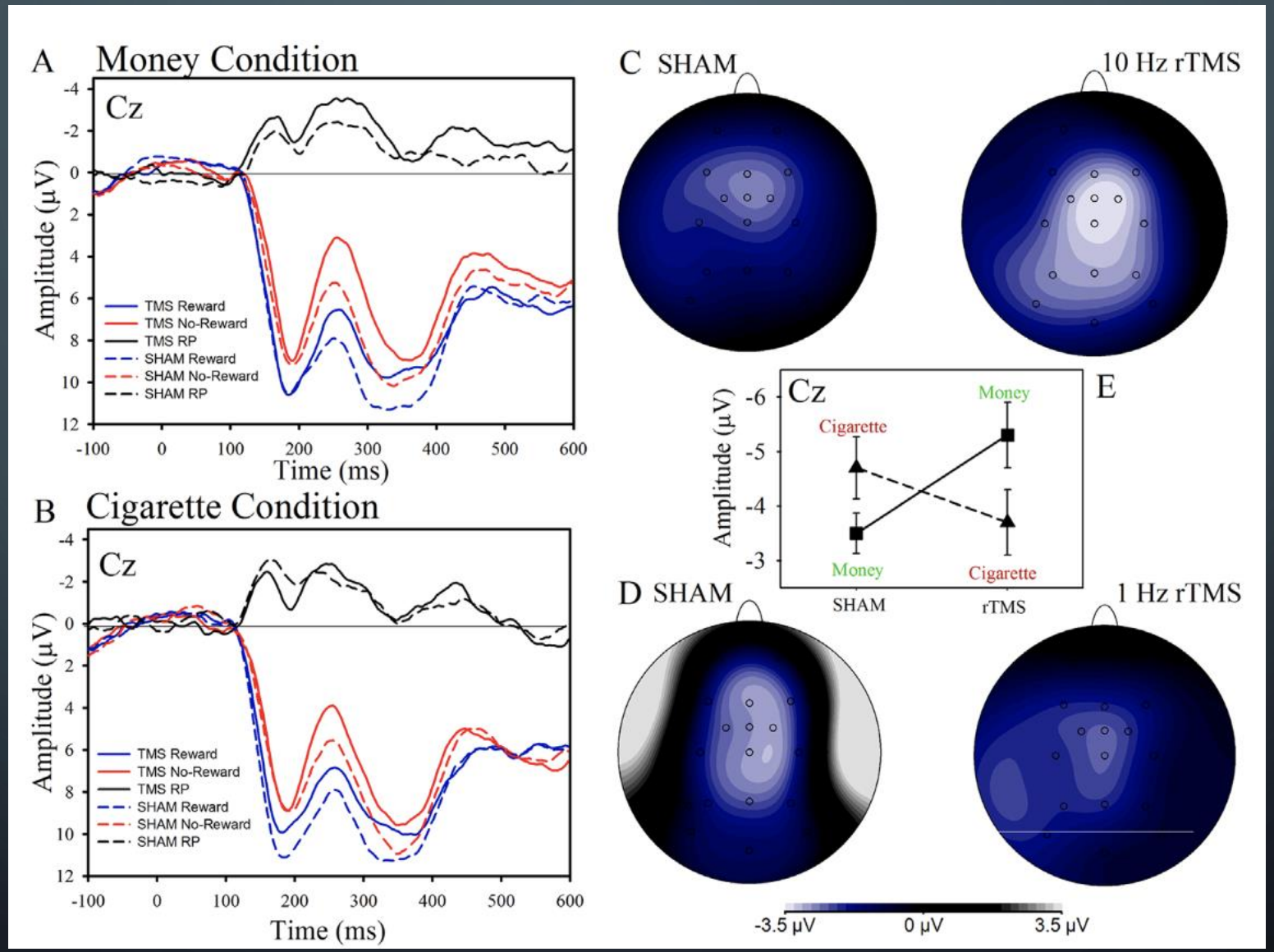
Continuous theta burst stimulation of right dorsolateral prefrontal cortex induces changes in impulsivity level

Sang Soo Cho,[a] Ji Hyun Ko,[a] Giovanna Pellecchia,[a,b] Thilo Van Eimeren,[a,b] Roberto Cilia,[a,b] Antonio P. Strafella[a,b]

[a]*PET Imaging Centre, Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada*
[b]*Toronto Western Research Institute and Hospital, University Health Network, University of Toronto, Toronto, Canada*



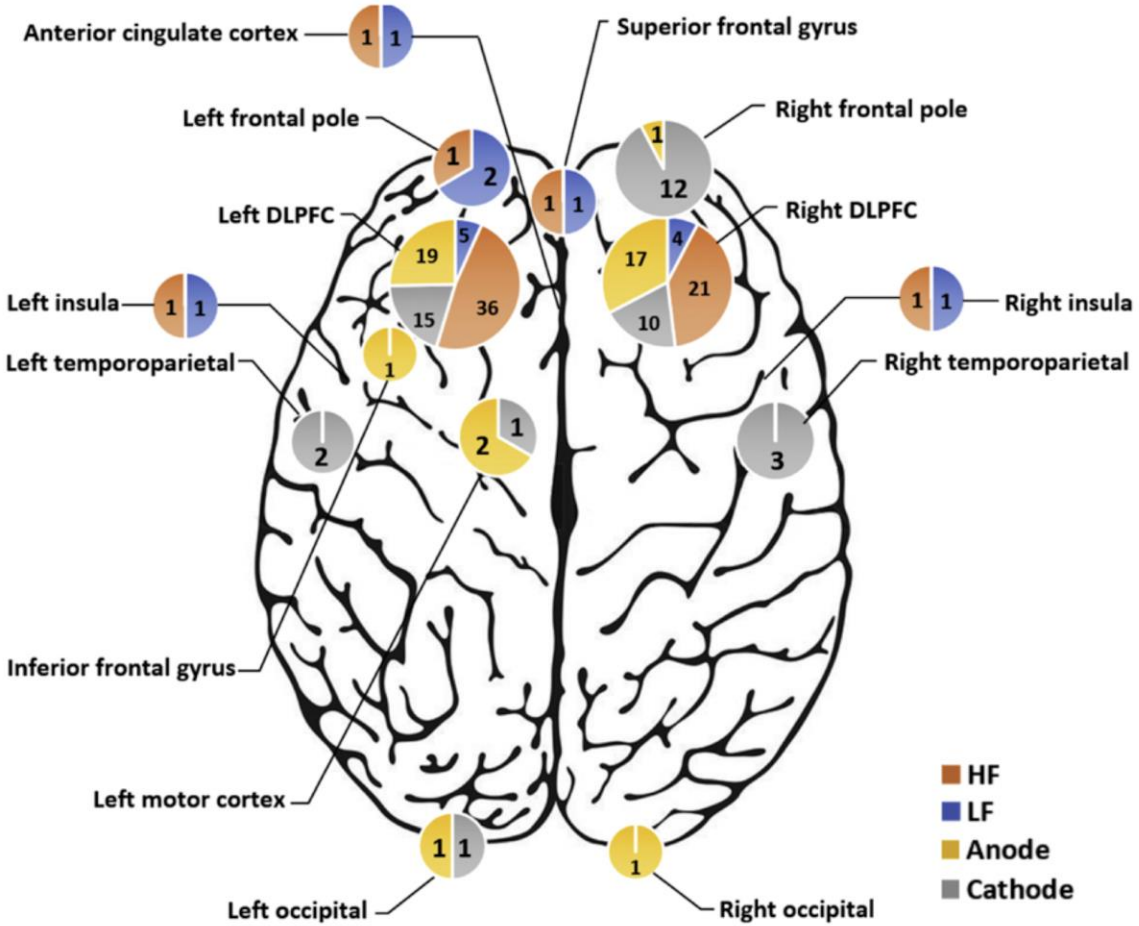


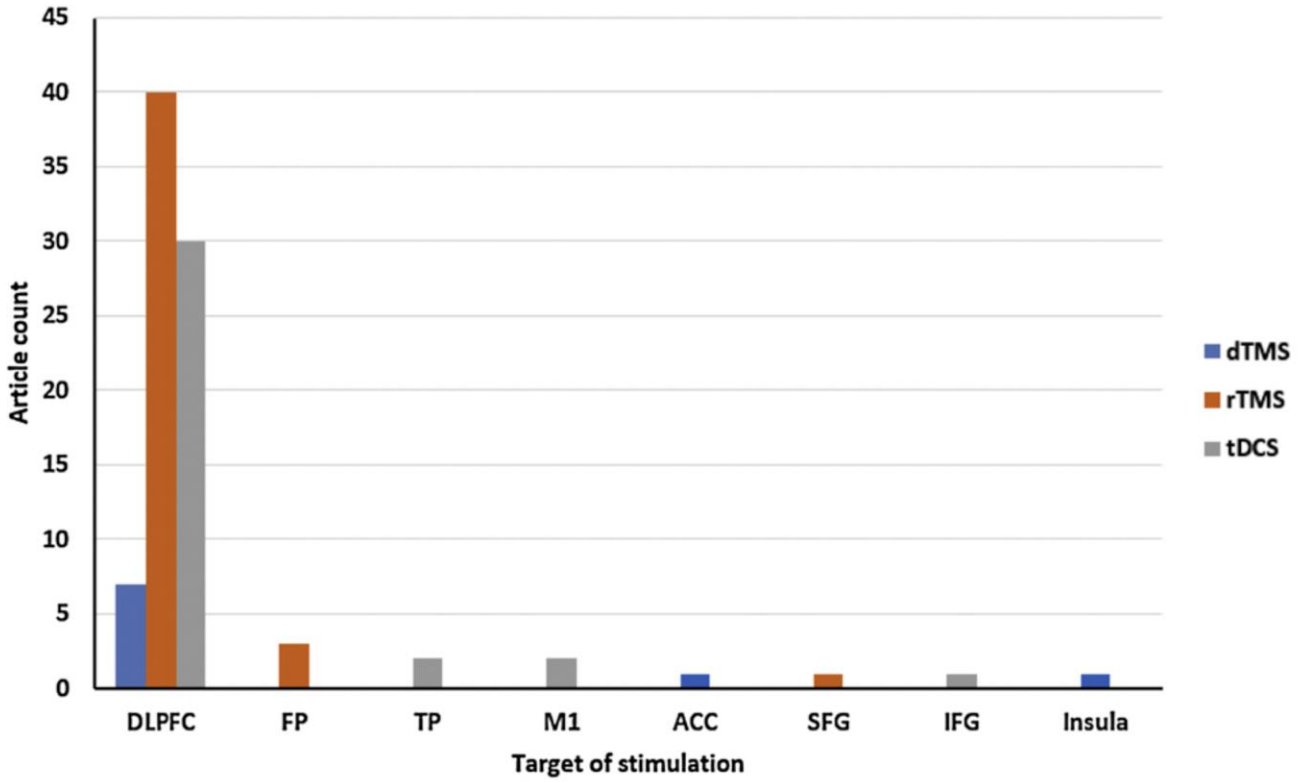


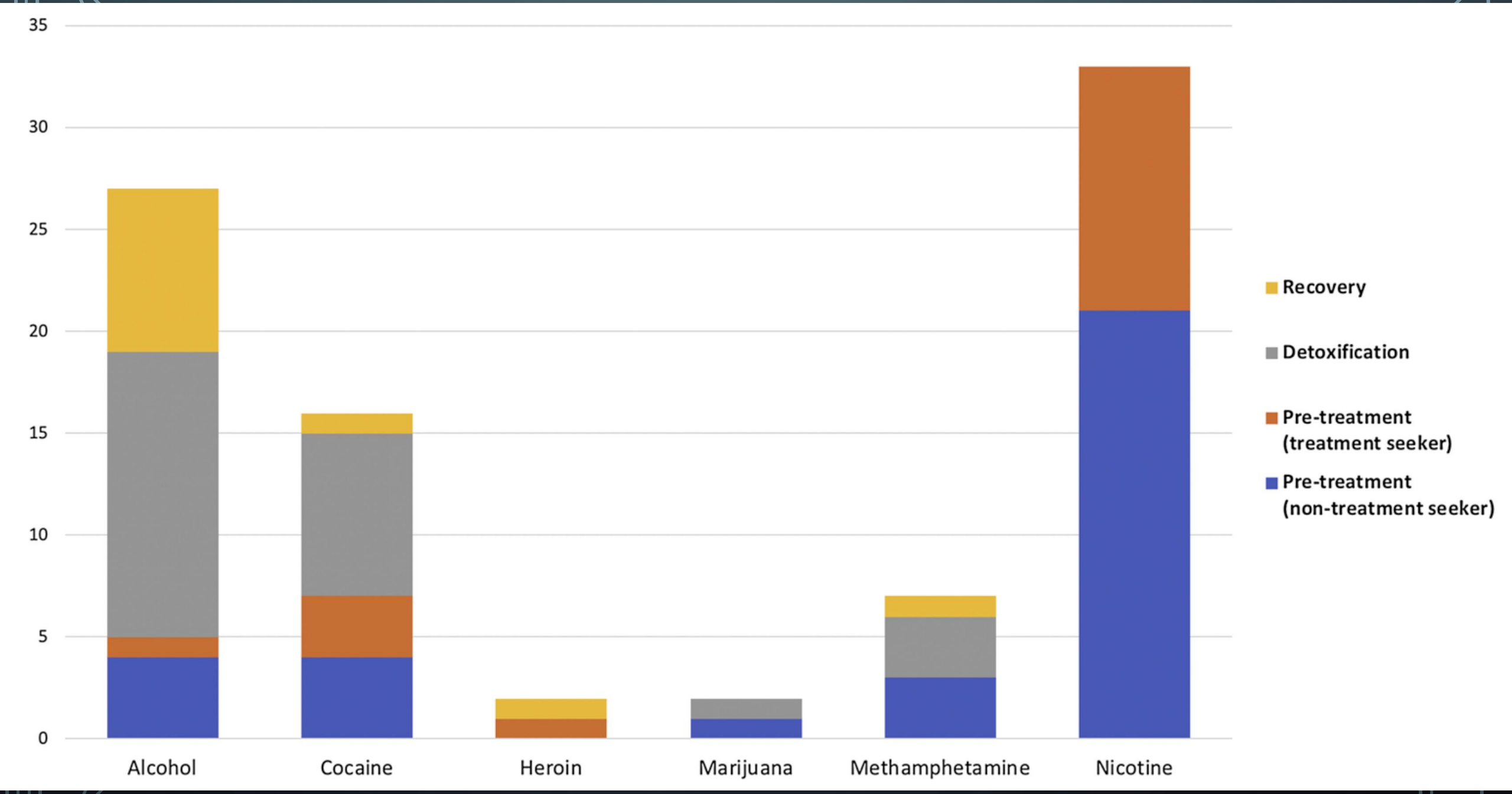
Baker, T., Lespérance, P., Tucholka, A., Potvin, S., Larcher, K., Zhang, Y., Jutras-Aswad, D., Conrod, P. (2017). **Reversing the Atypical Valuation of Drug and Nondrug Rewards in Smokers Using Multimodal Neuroimaging** BPS 82(11), 819 - 827. https://dx.doi.org/10.1016/j.biopsych.2017.01.015

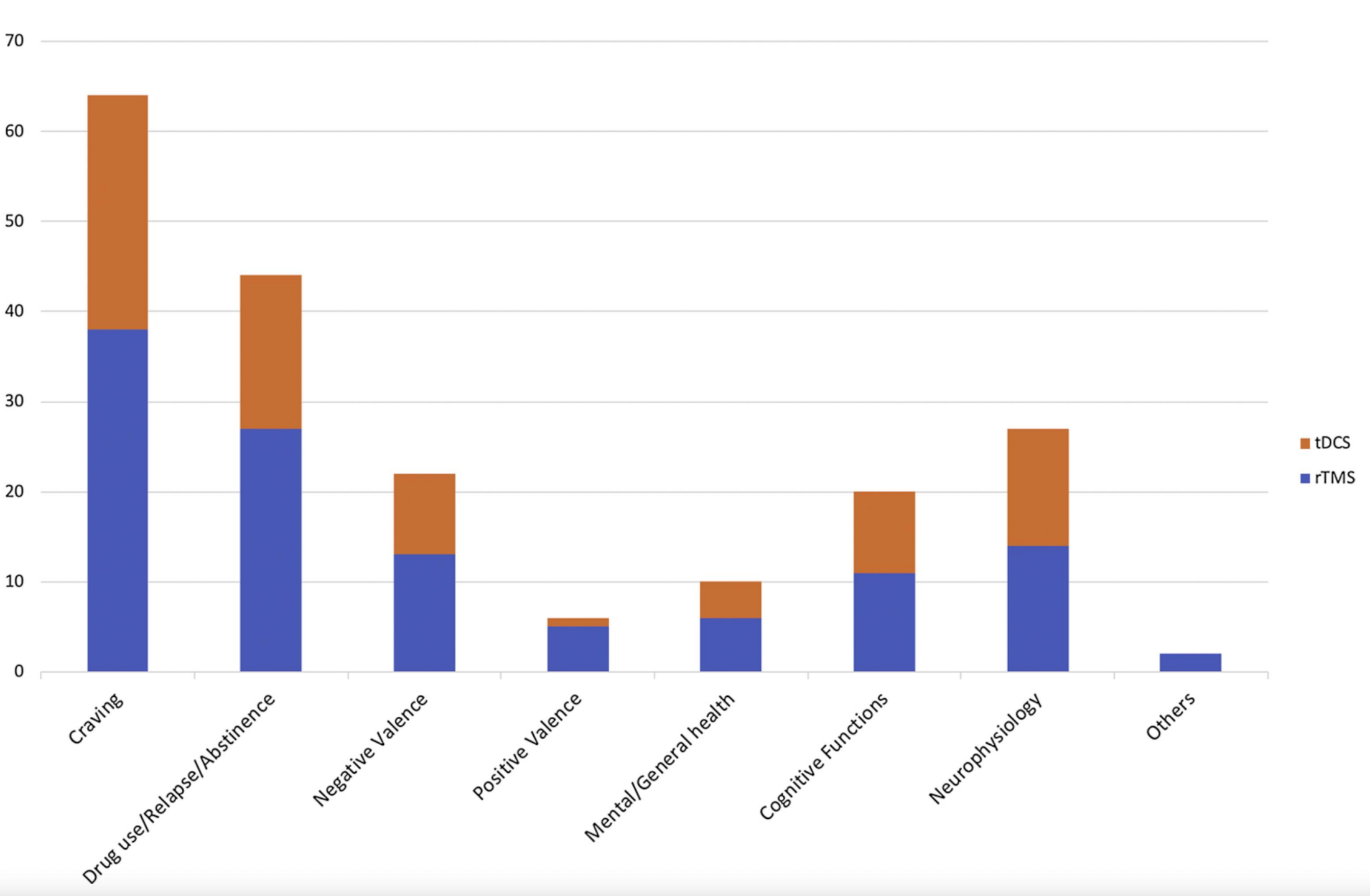
CONSENSUS PAPER 2019

- Ekhtiari 2019
- 50 articles (initialement 218)
- 7 études avec dTMS
- Seulement 11% des études ont administré plus que 15 séances


Anterior cingulate cortex
Superior frontal gyrus
Left frontal pole
Right frontal pole
Left DLPFC
Right DLPFC
Left insula
Right insula
Left temporoparietal
Right temporoparietal
Inferior frontal gyrus
Left motor cortex
Left occipital
Right occipital
HF
LF
Anode
Cathode


Article count
45
40
35
30
25
20
15
10
5
0
DLPFC
FP
TP
M1
ACC
SFG
IFG
Insula
Target of stimulation
dTMS
rTMS
tDCS

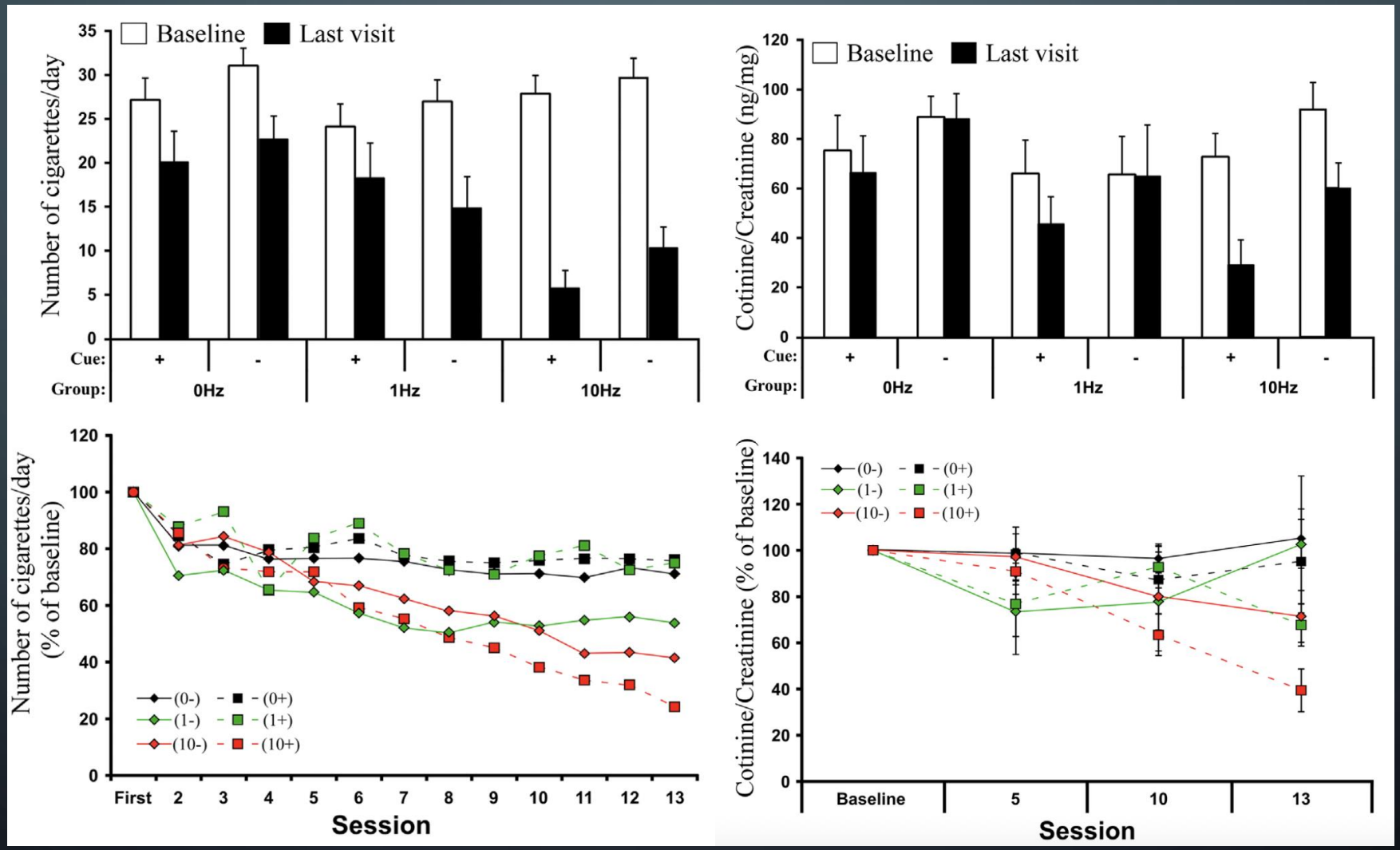

35
30
25
20
15
10
5
0
Alcohol
Cocaine
Heroin
Marijuana
Methamphetamine
Nicotine
Recovery
Detoxification
Pre-treatment (treatment seeker)
Pre-treatment (non-treatment seeker)


70
60
50
40
30
20
10
0
Craving
Drug use/Relapse/Abstinence
Negative Valence
Positive Valence
Mental/General health
Cognitive Functions
Neurophysiology
Others
tDCS
rTMS

CONSENSUS PAPER 2019

- Littérature mixte
- Plusieurs études ont démontré effet positif sur le craving et la consommation, mais études très hétérogènes

NICOTINE



Dinur-Klein, L. *et al*. Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices: A Prospective, Randomized Controlled Trial. *Biol Psychiat* **76**, 742–749 (2014).

NICOTINE

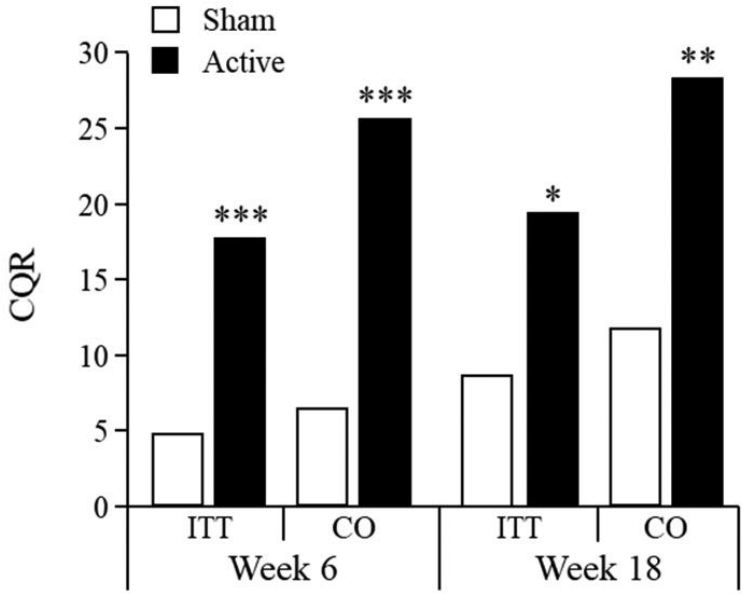


Figure 2 Four-week continuous quit rate (CQR) until Week 6 and Week 18 in patients receiving active or sham repetitive transcranial magnetic stimulation. Only participants who were abstinent at Week 6 were followed up to Week 18. ITT – intent-to-treat set, CO – completer analysis set. *p<0.05, **p<0.01, ***p<0.001.

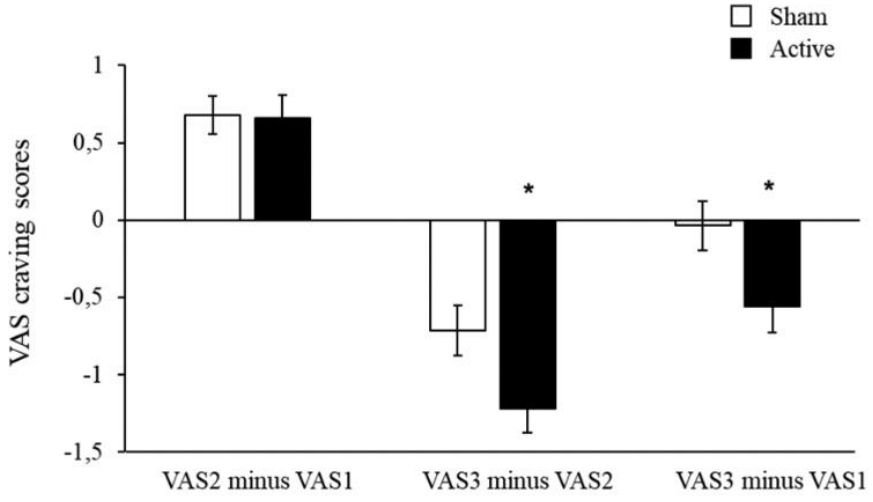


Figure 3 Acute changes in Visual Analogue Scale (VAS) craving scores following provocation (VAS2 minus VAS1) and following repetitive transcranial magnetic stimulation (VAS3 minus VAS2) in patients receiving active or sham treatment in the first session. Overall changes in craving during the first session (VAS3 minus VAS1) indicate that craving in the sham group returns to baseline, whereas it is reduced in the active group ($F_{1,253}$=5.00, p=0.026). *p<0.05.

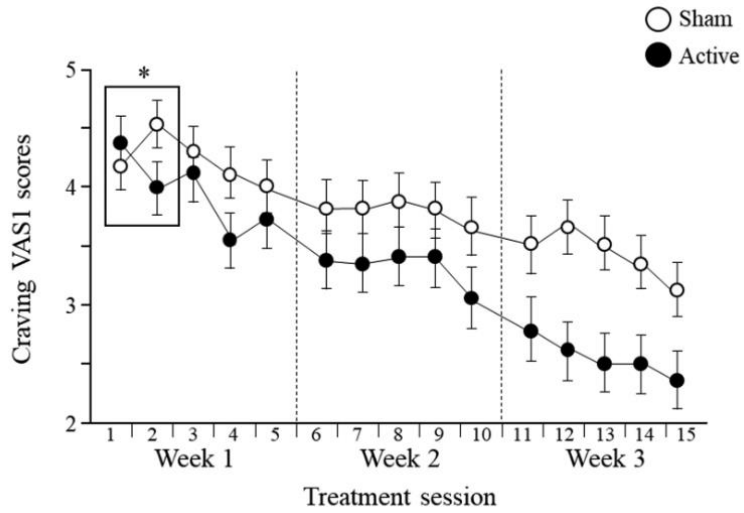


Figure 4 Daily changes in baseline craving (VAS1) scores during the first three weeks of treatment in patients receiving active or sham repetitive transcranial magnetic stimulation. ANOVA comparing VAS1 scores on the second vs. the first day of treatment (see box) revealed a significant interaction effect ($F_{1,165}$=3.70, p=0.025). Repeated measure ANOVA during the treatment period revealed main effects for group ($F_{1,159}$=4.50, p=0.035) and time ($F_{14,2226}$=16.79, p<0.0001), as well as for group x time interaction ($F_{14,2226}$=1.79, p=0.034). *p<0.05.

Zangen, A. *et al*. Repetitive transcranial magnetic stimulation for smoking cessation: a pivotal multicenter double-blind randomized controlled trial. *World Psychiatry* **20**, 397–404 (2021).

COCAINE

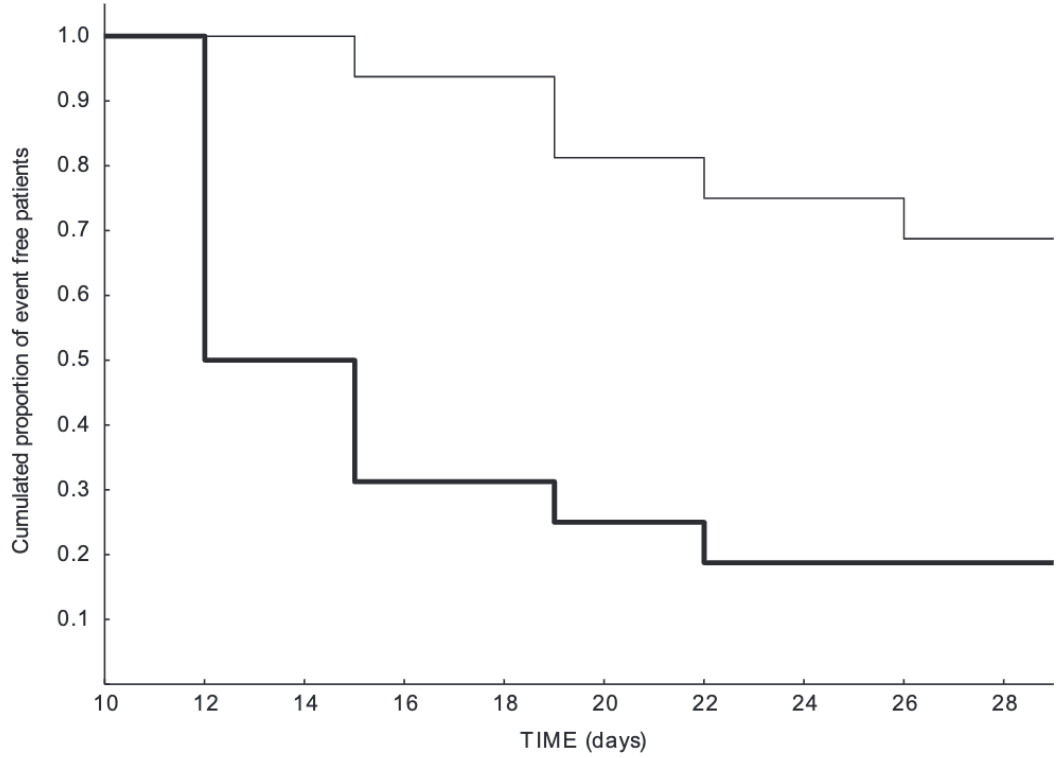


Figure 2 Kaplan Meier curve for comparison between rTMS (thin line) and controls (thick line) during Stage 1. Event is positive drug urine screen (log rank $p=0.0013$).

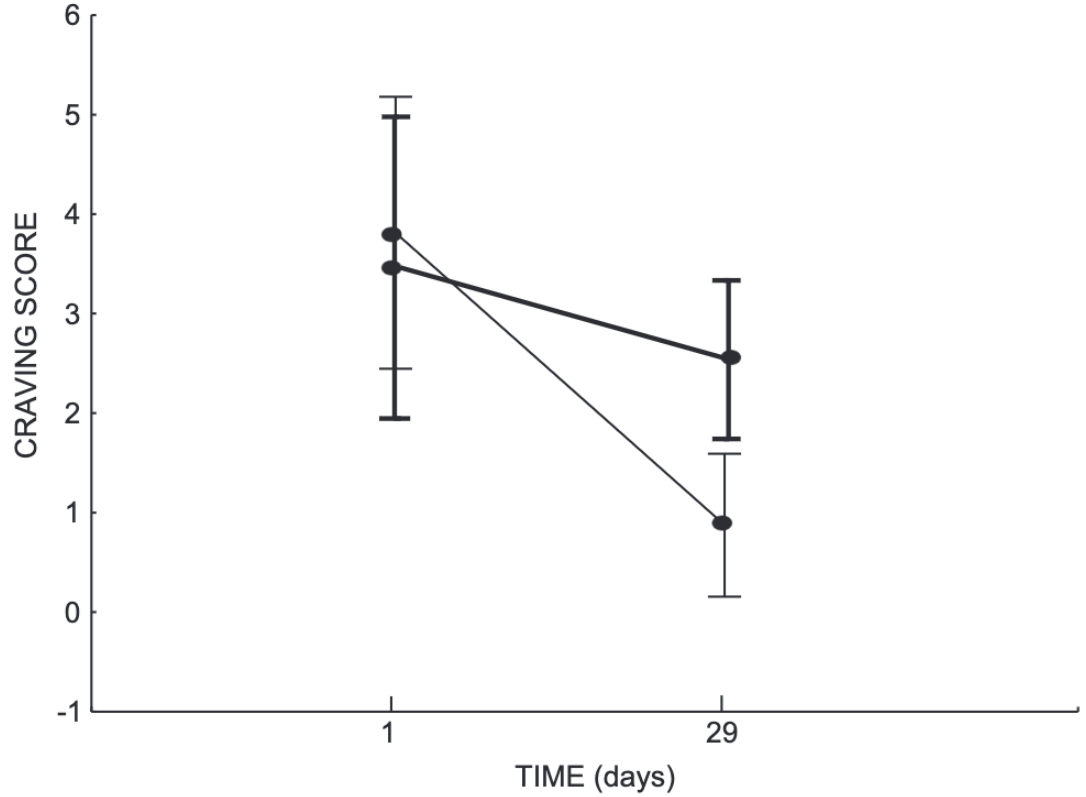


Figure 3 Significant differences in craving scores between the rTMS (thin line) and control (thick line) groups.

Terraneo, A., Leggio, L., Saladini, M., Ermani, M., Bonci, A., Gallimberti, L. (2016). **Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study** European Neuropsychopharmacology 26(1), 37-44. https://dx.doi.org/10.1016/j.euroneuro.2015.11.011

COCAINE

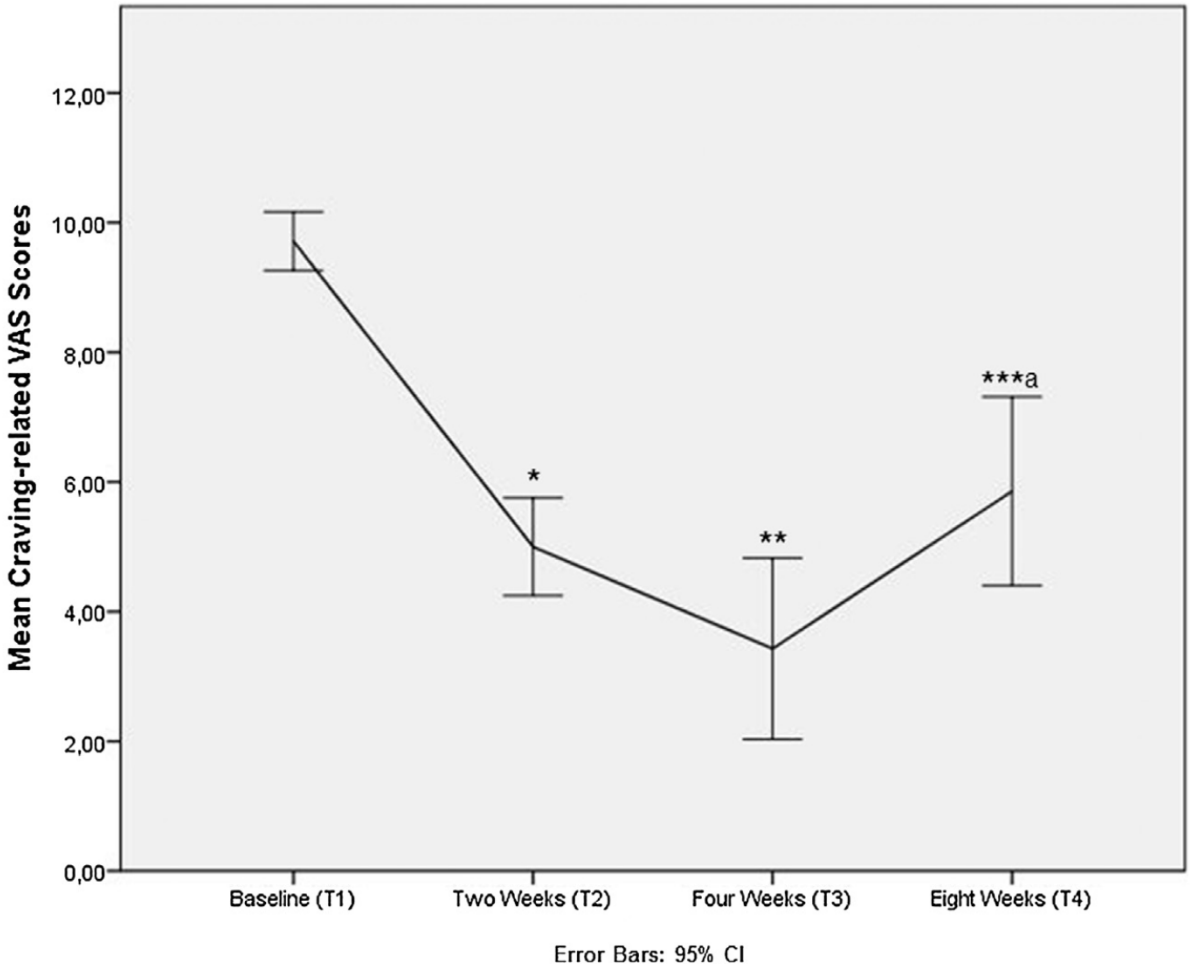


Fig. 1. Within-subjects main effect of time of treatment: ANOVA, $F[3,18] = 46.154$; $p < 0.001$; $\eta 2 = 0.88$.
*Baseline vs. Two weeks of treatment $p < 0.001$; **Four weeks $p < 0.001$; ***Eight weeks $p = 0.003$.
[a]The increase of craving was significant from T3 (end of dTMS treatment) to T4 ($p = 0.014$).

Rapinesi, C., Casale, A., Pietro, S., Ferri, V., Piacentino, D., Sani, G., Raccah, R., Zangen, A., Ferracuti, S., Vento, A., Angeletti, G., Brugnoli, R., Kotzalidis, G., Girardi, P. (2016). **Add-on high frequency deep transcranial magnetic stimulation (dTMS) to bilateral prefrontal cortex reduces cocaine craving in patients with cocaine use disorder** Neuroscience Letters 629(), 43-47. https://dx.doi.org/10.1016/j.neulet.2016.06.049

COCAINE

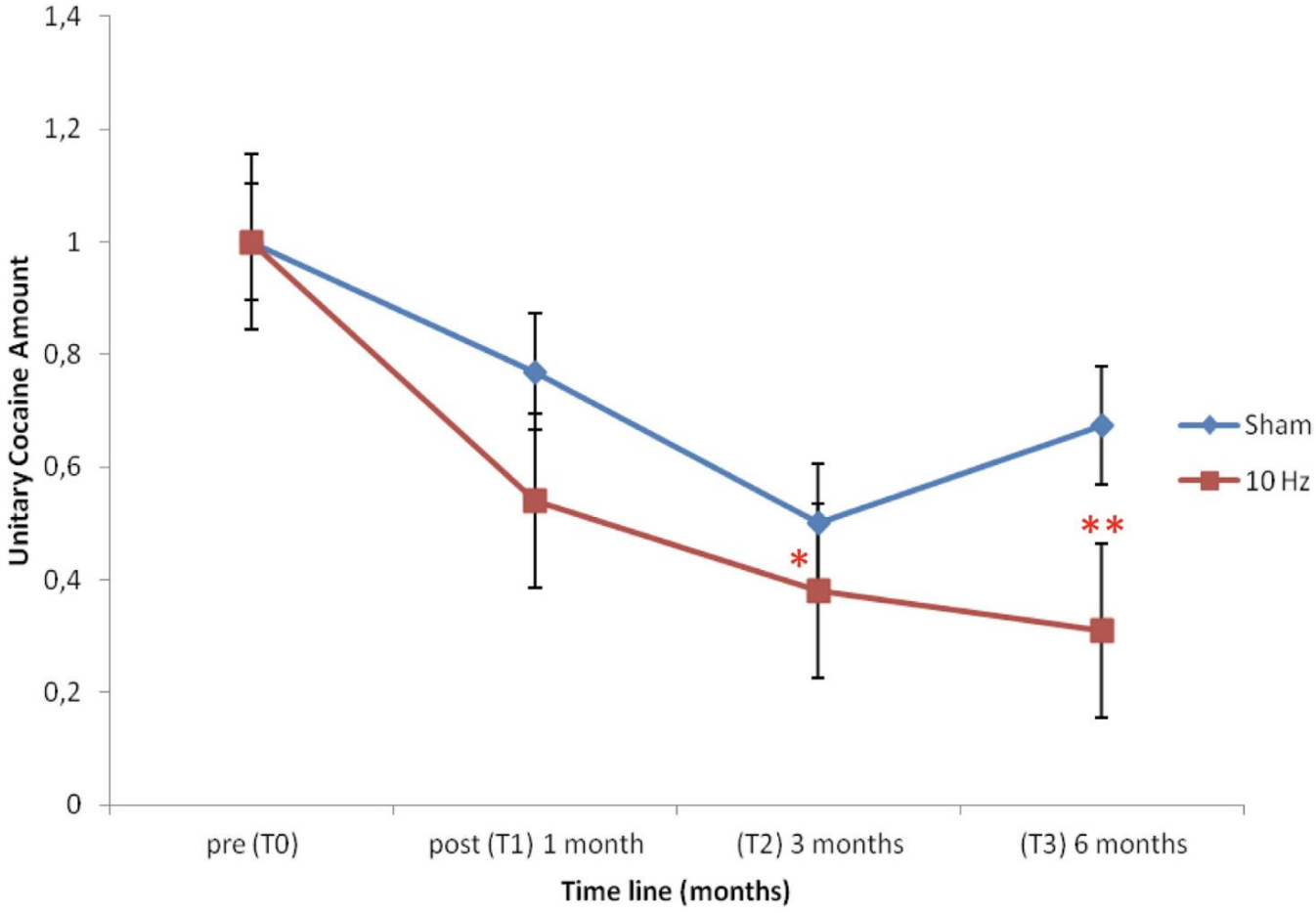


FIGURE 1 | Depicts the unitary cocaine amount in the two experimental groups along the time line considered from the baseline (T0) till 6 months later (T3). Note that only in the active group (10 Hz) there is a significant reduction in the unitary cocaine amount as indexed by T0–T2 (*$p = 0.02$) and T0–T3 (**$p = 0.01$) comparison over the time line.

Bolloni, C., Panella, R., Pedetti, M., Frascella, A., Gambelunghe, C., Piccoli, T., Maniaci, G., Brancato, A., Cannizzaro, C., Diana, M. (2016). **Bilateral Transcranial Magnetic Stimulation of the Prefrontal Cortex Reduces Cocaine Intake: A Pilot Study** Frontiers in Psychiatry 7(), 133. https://dx.doi.org/10.3389/fpsyt.2016.00133

COCAINE

- Revue systématique récente (Torres-Castano 2021)
- $k = 12$
- Techniques et mesures hétérogènes, mais résultats plus consistants
- Petites études, $N < 40$
- 2 études plus larges $N = 147$ (Madeo 2020) et $N = 87$ (Gomez 2020)
- Madeo 2020: temps ad rechute presque doublé avec rTMS (91 jours) vs TAU (51 jours)
- Gomez 2020: réduction de 95-97% consommation cocaine à 1 et 3 mois, réduction craving ~90% et ~70% à 1 et 3 mois

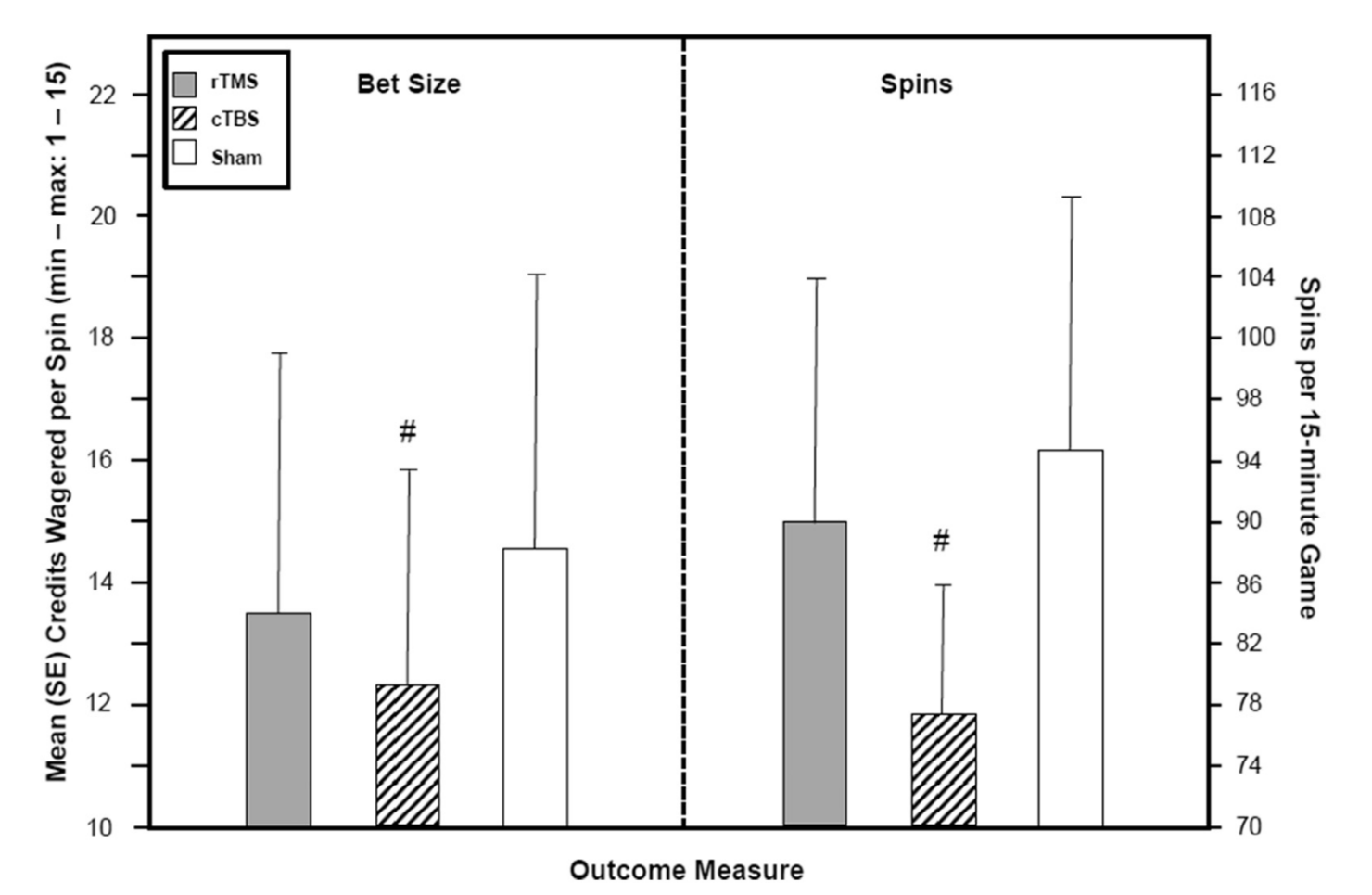
ALCOOL

- Revue récente de la littérature (Maatoug 2021)
- $k = 10$ (7 RCT), petites étude N ~ 20
- 1 RCT N = 45, seulement 10 séances, effet significatif sur craving, mais pas sur le taux de rechute
- Petites études, nombres limitées de séances, protocoles et instruments de mesure hétérogènes, conditions contrôles inadéquates

OPIACÉS

- 2 revues systématiques récentes (Young 2020 et Ward 2020)
- Petites études uniquement, aucune RCT détox ou maintien
- Effet positif sur craving dans 3 RCT, la plus grande N = 60
- Pas encore possible de faire analyse quantitative étant donné le trop petit nombre d'études

JEU PATHOLOGIQUE



Zack, M., Cho, S., Parlee, J., Jacobs, M., Li, C., Boileau, I., Strafella, A. (2016). **Effects of High Frequency Repeated Transcranial Magnetic Stimulation and Continuous Theta Burst Stimulation on Gambling Reinforcement, Delay Discounting, and Stroop Interference in Men with Pathological Gambling** Brain Stimulation 9(6), 867-875. https://dx.doi.org/10.1016/j.brs.2016.06.003

EN RÉSUMÉ

- Sauf pour la cessation tabagique, aucune RCT de qualité avec grand échantillon
- Plusieurs petites études prometteuses, mais protocoles restent à peaufiner
- Plusieurs études positives sur des substituts (*surrogates*): craving, *cue reactivity*, inhibition, contrôle exécutif, etc.)
- Étalon d'or reste la diminution de la consommation ou des méfaits
- Rôle potentiel de la neuromodulation en dépendance: en support aux approches psychosociales

PROJET À VENIR AU CHUM

- Étude pilote TU cocaïne
- N = 30 avec appareil Brainsway bobine H7
- Protocole intensif sur 2 semaines (~60 séances)
- Recrutement débutera en 2022, diffuserons une annonce

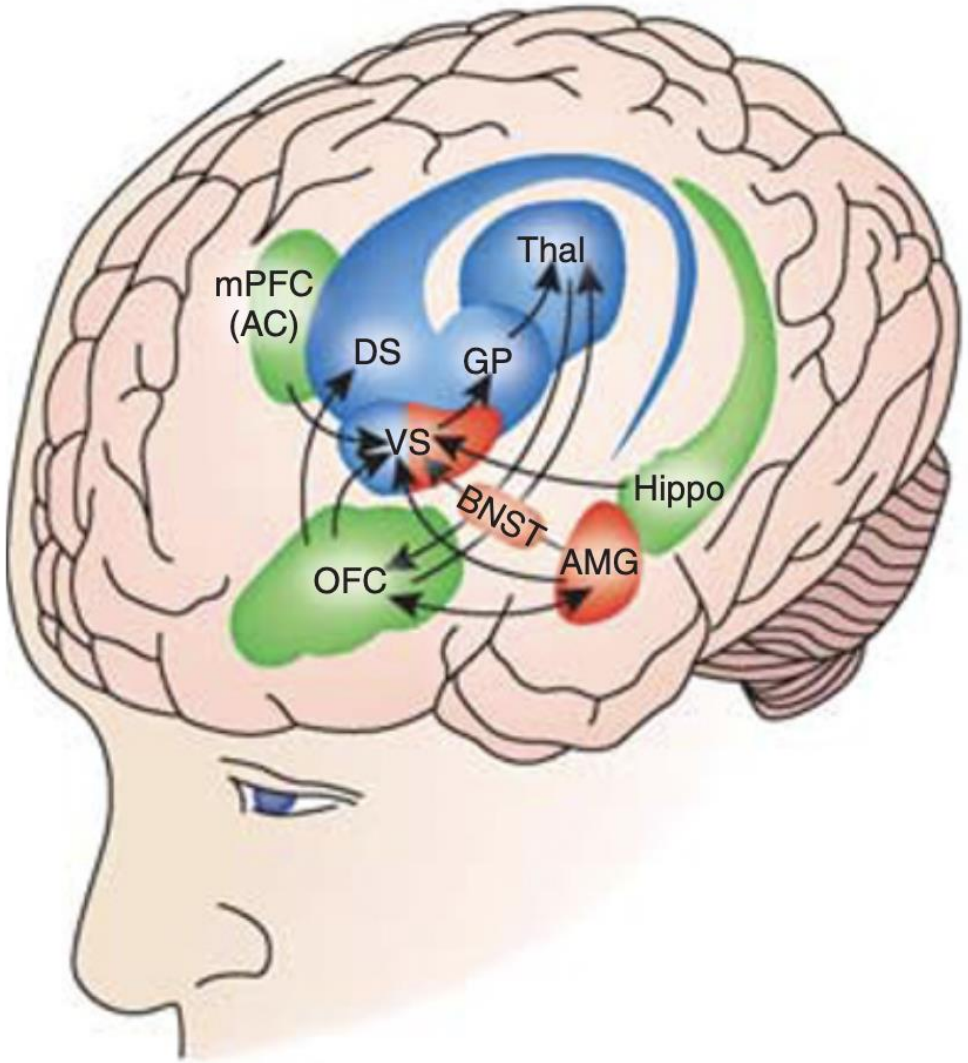
REMERCIEMENTS

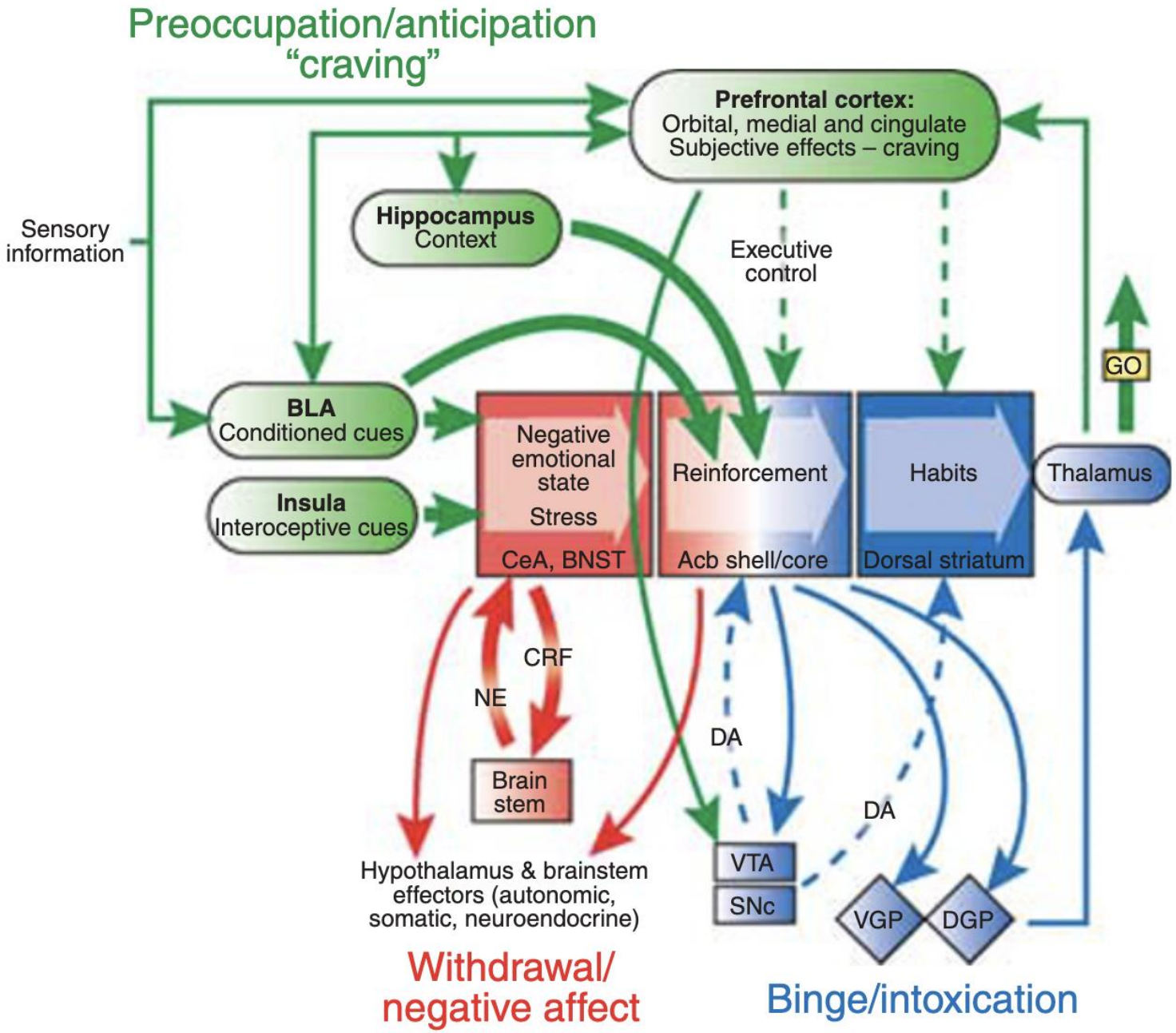
Équipe de neuromodulation psychiatrique du CHUM

RÉSEAU QUÉBÉCOIS SUR LE SUICIDE, LES TROUBLES DE L'HUMEUR ET LES TROUBLES ASSOCIÉS

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

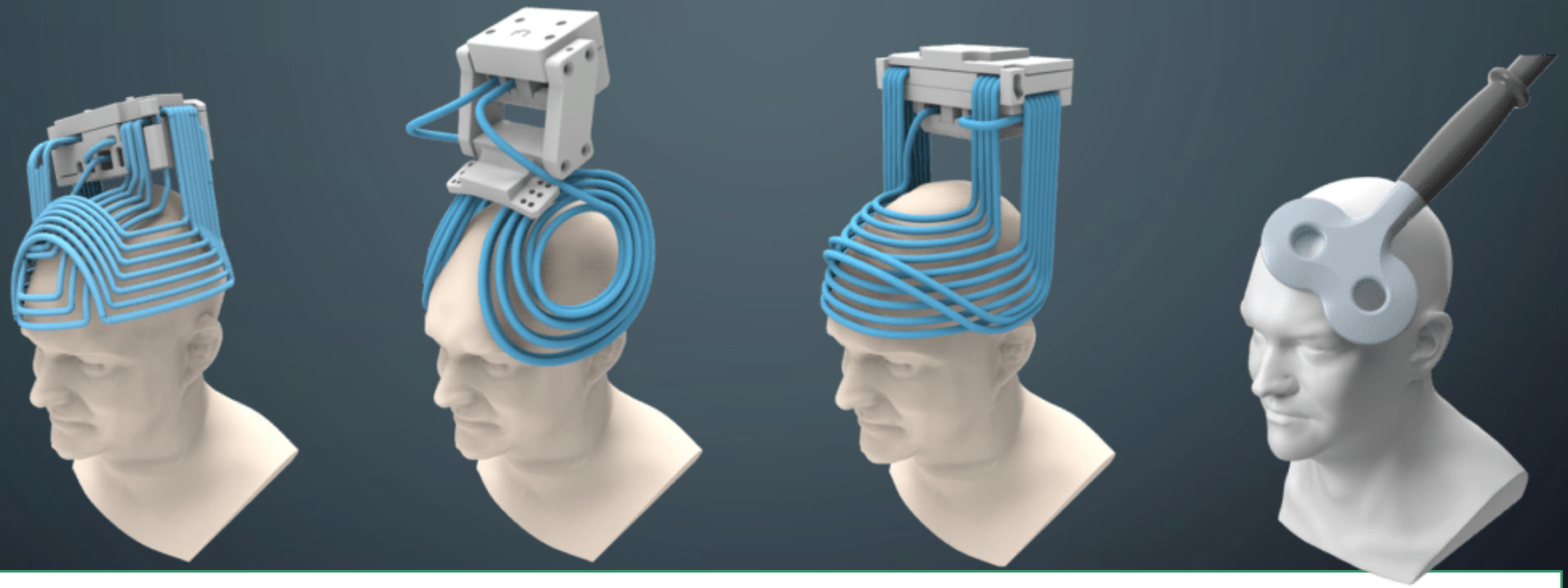
CRISM-ICRAS
Canadian Research Initiative in Substance Misuse
Initiative Canadienne de Recherche en Abus de Substance





Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016 Aug;3(8):760-773. doi: 10.1016/S2215-0366(16)00104-8. PMID: 27475769;

NICOTINE



H1-Coil for Major Depressive Disorder (MDD)	**H7-Coil** for Obsessive-Compulsive Disorder (OCD)	**H4-Coil** for Smoking Cessation	**Traditional TMS Coil** for Major Depressive Disorder (MDD)

Source: Brainsway