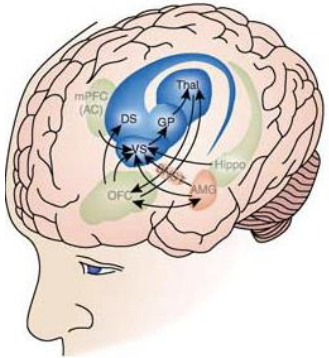
“Nuove frontiere per il trattamento del Disturbo da Uso di cocaina: outcome clinici e follow-up”.

12 febbraio 2020

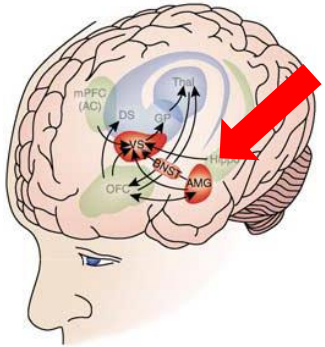
Graziella Madeo, M.D., Ph.D
Novella Fronda Foundation

Addiction is a disease of dysregulated circuits and networks

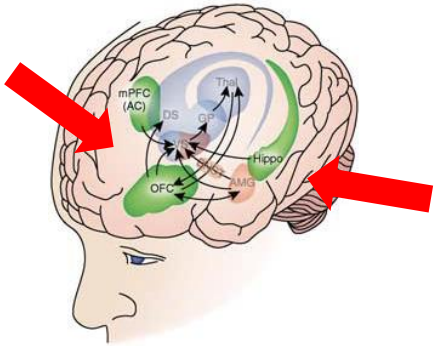


Binge /Intoxication Stage
(Incentive salience)

- Cue reactivity
- Reward processing
- Executive control (e.g. attention, inhibitory control)

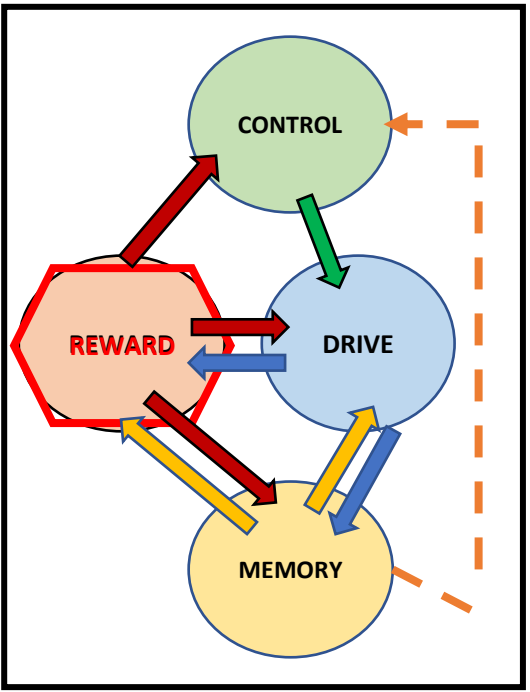


Withdrawal/Negative affect Stage
(Reward deficit and Stress surfeit)



Preoccupation/Anticipation «Craving» Stage
(Executive Function Deficit)

Treating the ADDICTED Brain



Adapted from Volkow et al Neuron 2011

MEDICATION

PSYCHOTHERAPY

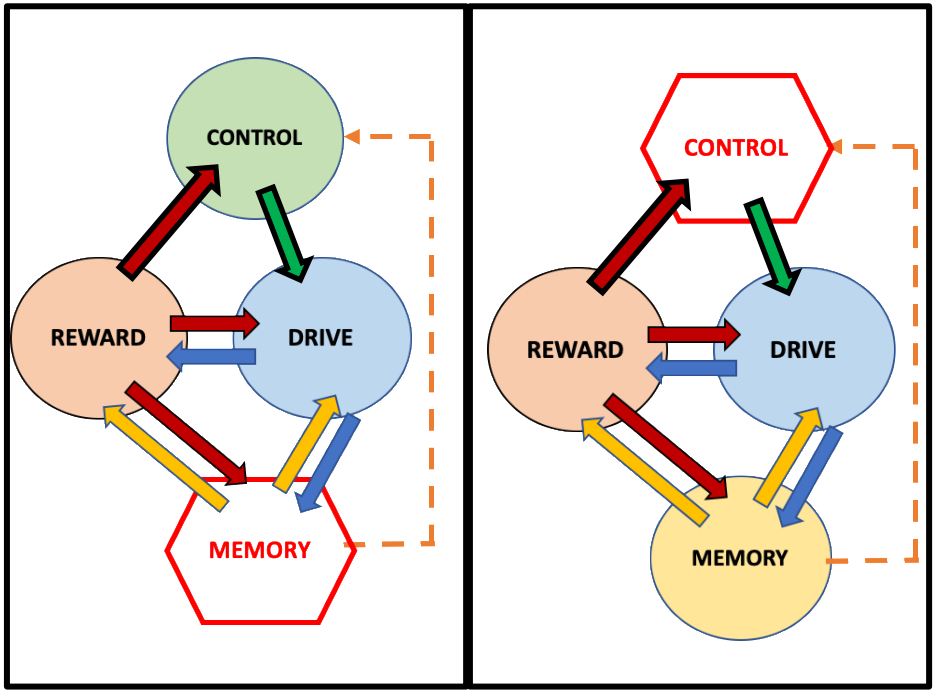
REHAB

Decrease the reward value of the drug

or

Increase the rewarding value of non-drug reinforcers

Treating the ADDICTED Brain



Adapted from Volkow et al Neuron 2011

MEDICATION

PSYCHOTHERAPY

REHAB

Weaken learned positive associations with drugs and drugs cues

or

Strengthen Frontal Control

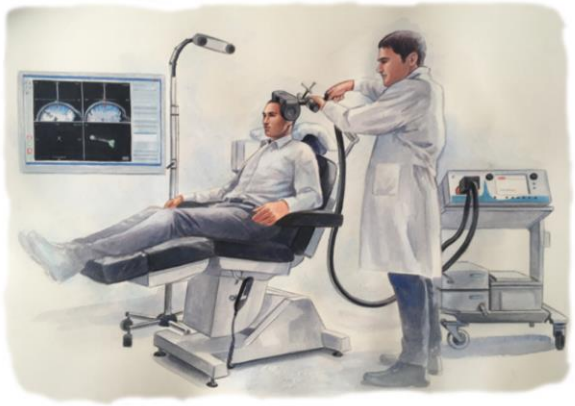
Treating the ADDICTED Brain

MEDICATION

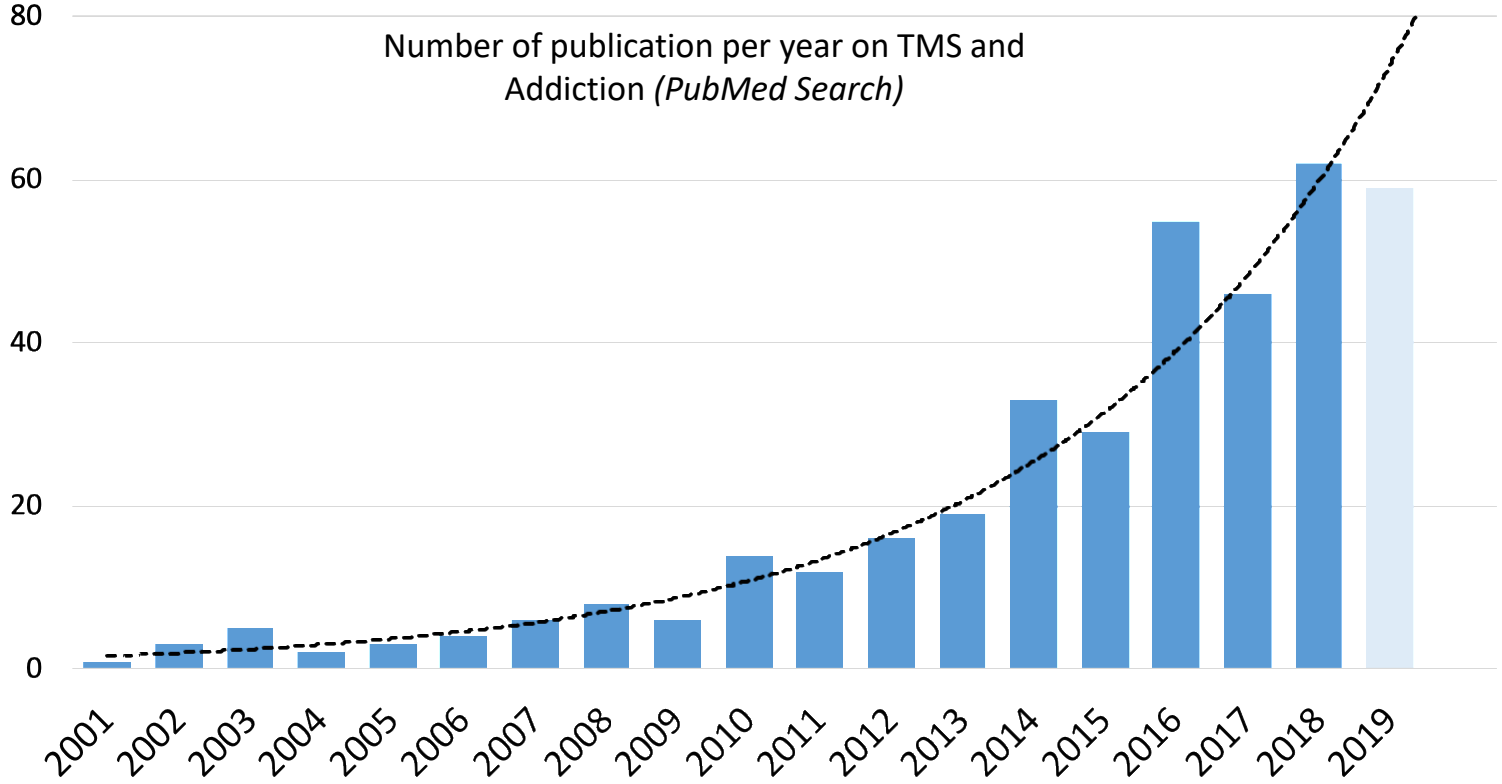
PSYCHOTHERAPY

REHAB

THE FOURTH TOOL

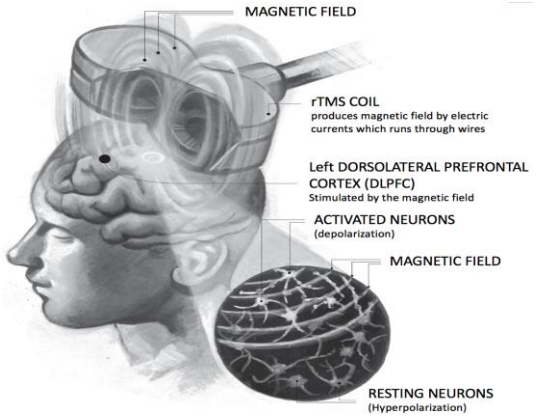


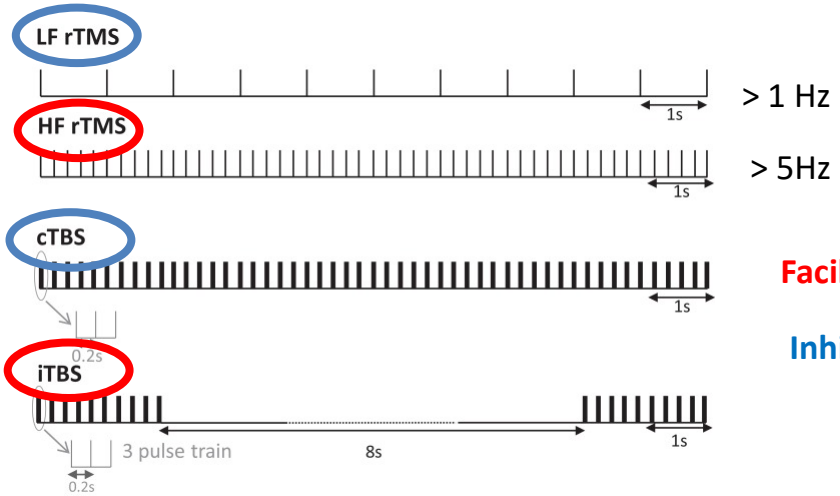
Why neuromodulation as potential treatment for addictions



TMS for the ADDICTED Brain

Courtesy of National Geographic



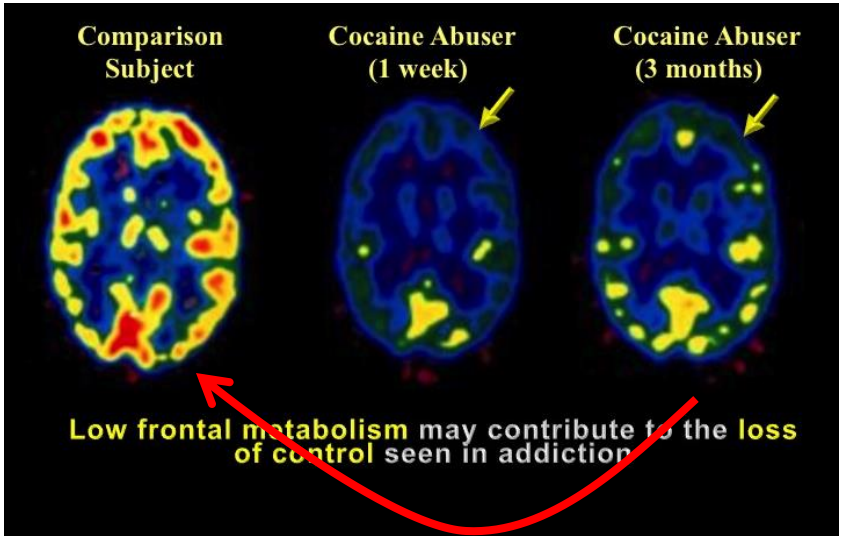


Facilitatory LTP-like

Inhibitory LTD-like

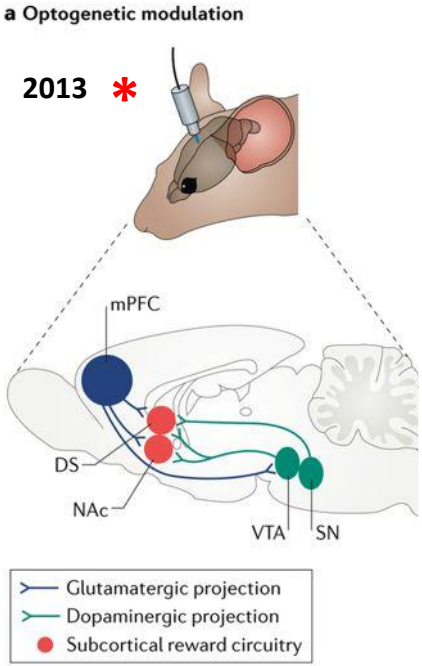
Why neuromodulation as potential treatment for addictions

Volkow et al ***1992, 1993*** *



rTMS

Reduced activity of the prefrontal brain areas, involved with salience attribution, motivation and compulsive behaviors.



Nature Reviews | Neuroscience

Chen et al, Nature 2013
Deisseroth eta al, Nature Reviews

rTMS stimulation protocol of l-DLPFC reduces cocaine use

European Neuropsychopharmacology (2016) 26, 37-44

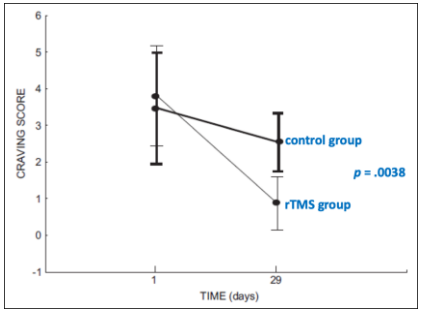
ELSEVIER

2016 *

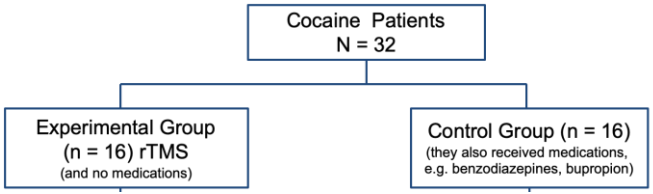
www.elsevier.com/locate/euroneuro

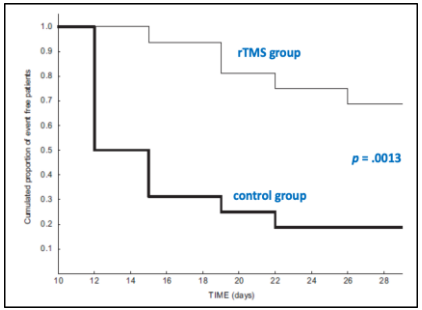
Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study

Alberto Terraneo[a], Lorenzo Leggio[b,c,d], Marina Saladini[e], Mario Ermani[e], Antonello Bonci[b,f,g,*], Luigi Gallimberti[a]



Craving score is significantly reduced in rTMS group





Proportion of cocaine free patients is significantly higher in rTMS group compared to control group.

rTMS Protocol Parameters

15 Hz,
100% of rMT,
40 trains,
60 pulses per train,

15 s intertrain-interval,
2400 pulses over the left-DLPFC
(x=-50, y=30, z=36)

rTMS studies on CUDs

Studies	N	Design	Number of sessions	Stimulation site	F (Hz)/ % MT	Total pulses per session	Effects	Adverse Events
Camprodon et al., (2007)	6	Randomized, cross-over study	2 (left or right side)	Left and Right DLPFC	10/ 90%	2000	Right but not left rTMS reduced craving	Not reported
Politi et al. (2008)	36	Open-label study	10	Left DLPFC	15/ 100%	600	Reduction in spontaneous craving	Not reported
Hanlon et al. (2015)	11	Single-blind, sham-controlled, crossover study	2 (occurring within 7–14 days of each other)	left mPFC (cTBS)	5/110%	1800	Significant reduction in self-reported cue induced craving after active cTBS but not after sham cTBS	Transient painfulness subsiding after the first 15-30 s
Bolloni et al., (2016)	10	Double-blind randomized, sham-controlled, parallel group trial	12	Bilateral PFC	10/ 100%	1000	No effect on cocaine intake in the active group but long-term reduction on cocaine intake observed in active group when considered the time as factor	Mild headache after active stimulation
Terraneo et al., (2016)	32	Open-label, randomized study. rTMS or standard pharmacological treatment	8	Left DLPFC	15/ 100%	2400	Reduction in cocaine use and craving	Mild discomfort at the start of stimulation
Rapinesi et al., (2016)	7	Open-label study	12	Left DLPFC	15 / 100%	720	Significant reduction in craving following rTMS	Not reported
Sanna et al. (2019)	47	Between-group study design with 2 treatment conditions (HF rTMS vs iTBS)	20 (HF rTMS or iTBS)	Bilateral PFC	15/100% (HF rTMS) 5/80% (iTBS)	2400 (HF rTMS) 600 (iTBS)	reductions in cocaine craving and intake after treatment	Mild head discomfort

Main limitations of available studies

Small sample size

Short-period of follow-up

Long-term effects of rTMS on drug consumption, relapses and craving

Stimulation parameters variability: intensity, frequency, number of sessions, brain target.

Clinical assessment of outcome measures

Sham-controlled, RCTs

INTAM Network
International Collaborative Network of TES/TMS Trials for Addiction Medicine

Transcranial Electrical and Magnetic Stimulation (tES and TMS) for Addiction Medicine: A consensus paper on the present state of the science and the road ahead

Authors:
Hamed Ekhtiari[1*], Hosna Tavakoli[2, 3], Giovanni Addolorato[4, 5], Chris Baeken[6], Antonello Bonci[7, 8, 9], Salvatore Campanella[10], Luis Castelo-Branco[11], Gaëlle Challet-Bouju[12], Vincent P. Clark[13], Eric Claus[14], Pinhas N. Dannon[15], Alessandra Del Felice[16], Tess den Uyl[17], Marco Diana[18], Massimo di Giannantonio[19], John R. Fedota[20], Paul Fitzgerald[21], Luigi Gallimberti[22], Marie Grall-Bronnec[12], Sarah C. Herremans[6], Martin J. Herrmann[23], Asif Jamil[24], Eman Khedr[25], Christos Kouimtsidis[26], Karolina Kozak[27, 28], Evgeny Krupitsky[29, 30], Claus Lamm[31], William V. Lechner[32], Graziella Madeo[7], Nastaran Malmir[3], Giovanni Martinotti[19], William McDonald[33], Chiara Montemitro[19], Ester Nakamura-Palacios[34], Mohammad Nasehi[35], Xavier Noël[10], Masoud Nosratabadi[36], Martin Paulus[1], Mauro Pettorruso[19], Basan Pradhan[37], Samir K. Praharaj[38], Haley Rafferty[11], Gregory Sahlem[39], Betty jo Salmeron[7], Anne Sauvaget[40, 41], Renée S. Schluter[17], Carmen Sergiou[42], Alireza Shahbabaie[23], Christine Sheffer[43], Primavera A. Spagnolo[44], Vaughn R. Steele[20], Ti-fei Yuan[45], Josanne van Dongen[42], Vincent Van Waes[46], Ganesan Venkatasubramanian[47], Antonio Verdejo-García[48], Ilse Verveer[42], Justine Welsh[33], Michael J. Wesley[49], Katie Witkiewitz[14], Fateme Yavari[24], Mohammad-Reza Zarrindast[50], Laurie Zawertailo[28], Xiaochu Zhang[51], Yoon-Hee Cha[1], Tony P. George[27, 28], Flavio Frohlich[52], Anna E. Goudriaan[17, 53], Shirley Fecteau[54], Stacey Daughters[52], Elliot A. Stein[20], Felipe Fregni[11], Michael A. Nitsche[24, 55], Abraham Zangen[56], Marom Bikson[57], Colleen A. Hanlon[39].

Main limitations of available studies

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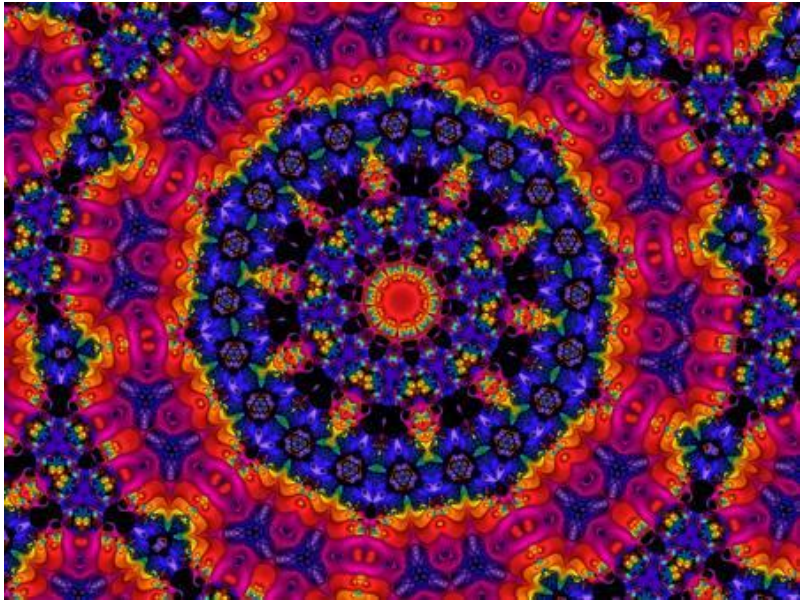
Long-term effects of rTMS on drug consumption, relapses and craving

Stimulation parameters variability: intensity, frequency, number of sessions, brain target.

Clinical assessment of outcome measures

Sham-controlled, RCTs

Patient Population treated with rTMS:
1000 + patients as of beginning of June 2019.
Pro and cons of a naturalistic approach



Long-term follow-up study

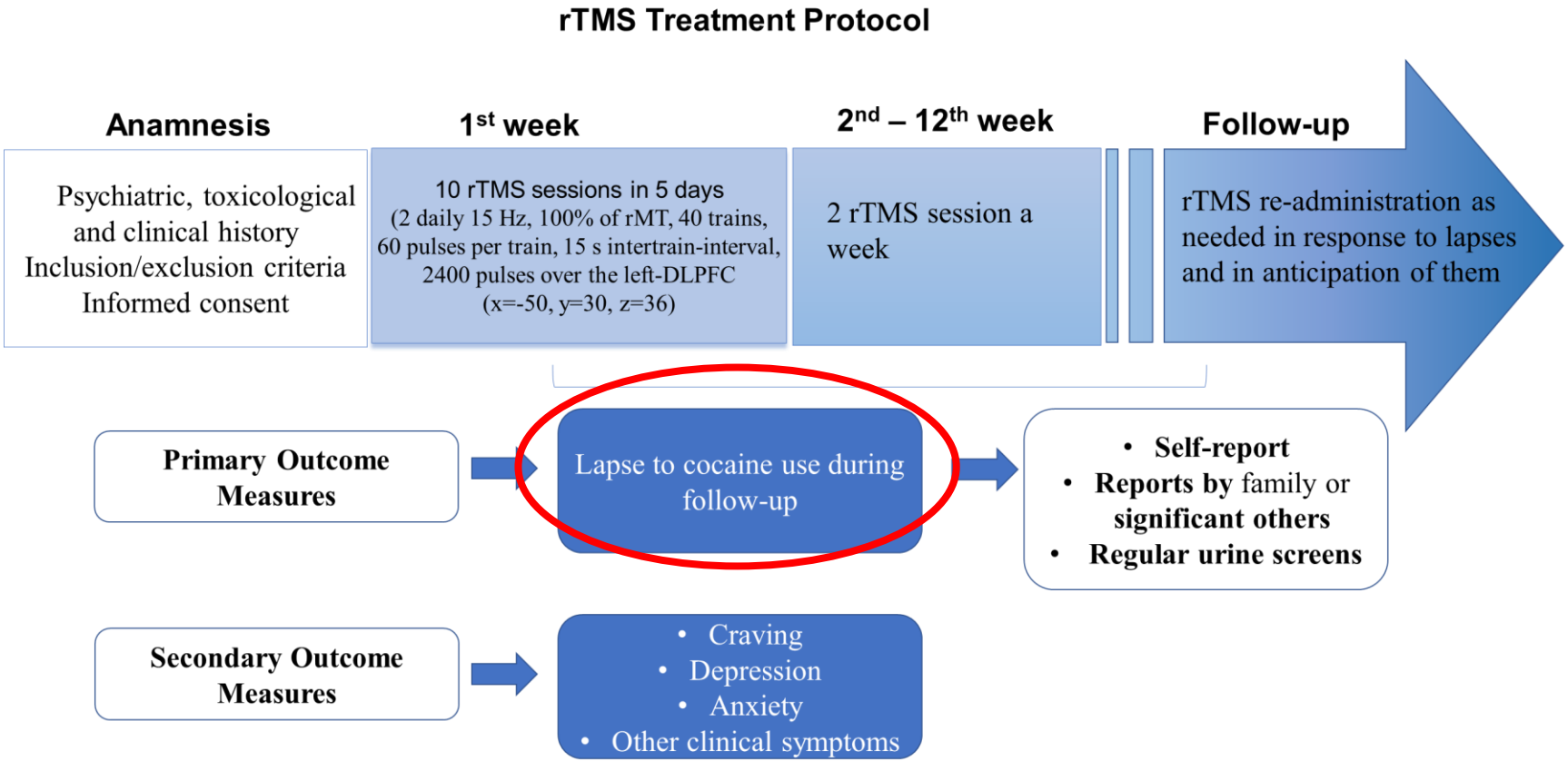
2-years and 8 months follow-up of cocaine use in 284 patients undergoing rTMS over left-DLPFC

- **Large Cohort of patients** → 284 patients with CUD (268M, 16F);
- **Period of observation** → 2-years and 8 months (median 164 days) 2013 – 2017;
- **Main Goal**→ Safety and efficacy of rTMS on long-term follow-up.

Madeo G et al, 2019 Manuscript under revision

Long-term follow-up study

2-years and 8 months follow-up of cocaine use in 284 patients undergoing rTMS over left-DLPFC



Demographic characteristics

	Total sample (n=284)	Closely followed subsample (n=147)
Age (mean, SD)	38.3 (8.4)	36.6 (7.7)
Sex		
Male	268 (94%)	139 (95%)
Female	16 (6%)	8 (5%)
Cocaine use before treatment entry*		
Daily	45%	30%
Weekly or more (not daily)	45%	51%
Monthly or more (not weekly)	2%	5%
Less than monthly	7%	14%
Cocaine route of administration*		
Snorting	90%	86%
Smoking	9%	11%
Both	1%	3%

147 cases had accurate data about patterns of cocaine use and abstinence

137 cases had only the time of initial lapse to cocaine use or loss to follow-up

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Safety on long-term follow-up

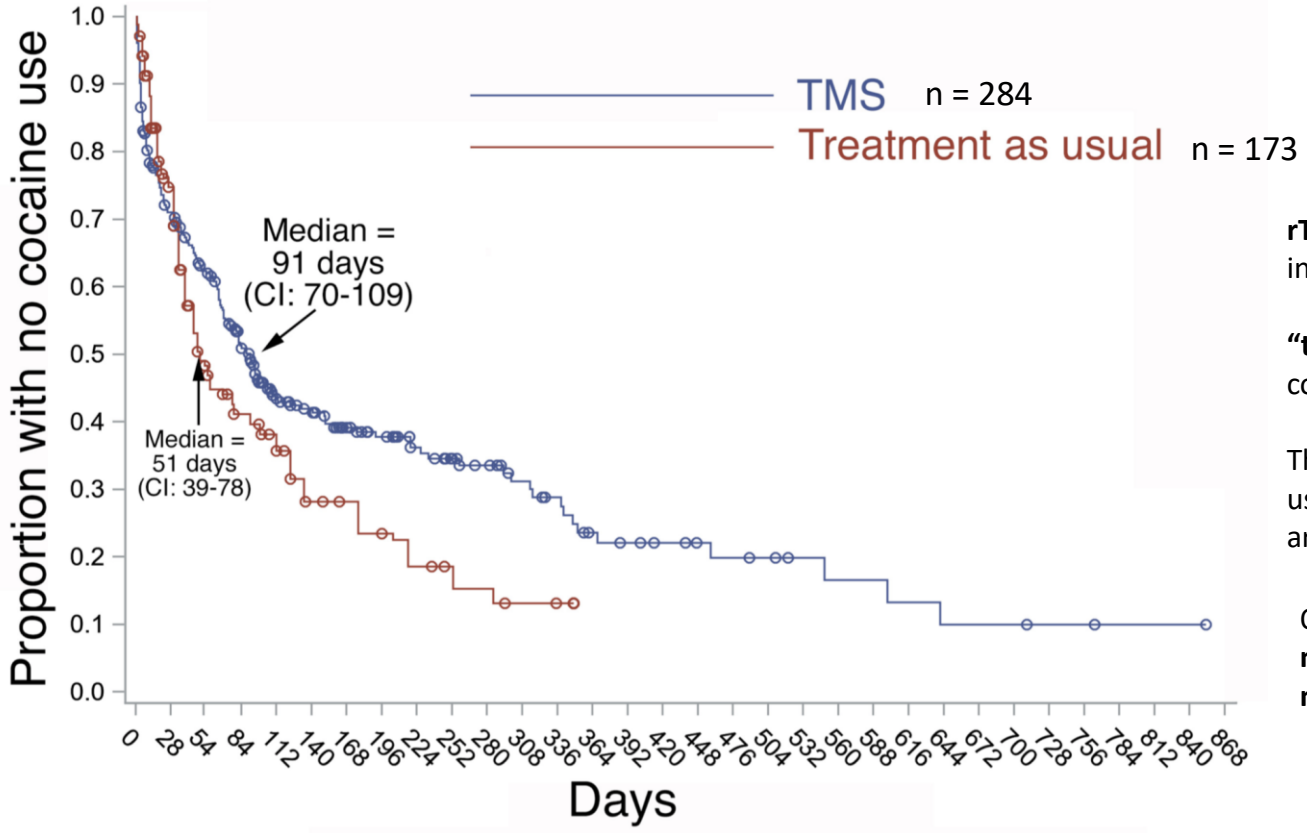
Adverse events (AEs) reported by 41 of the 284 patients.

Adverse Events	Case n
Headache	23
Hypomania	5
Anxiety	2
Irritability	2
Teeth pain	2
Scalp discomfort	1
Angioedema and urticaria	1
Distractibility	1
Dizziness	1
Nausea	1
Nausea and numbness	1
Seizure	1

The seizure occurred in a 27-year-old woman 66 days after her first rTMS session. She has used cocaine shortly before; she had not recently undergone rTMS.

Madeo G et al, 2019 Manuscript under revision

Time to first lapse of cocaine use in full sample and comparison cohort (Dodge et al 2011).



rTMS cohort: 91 days (95% confidence interval 70-109 days).

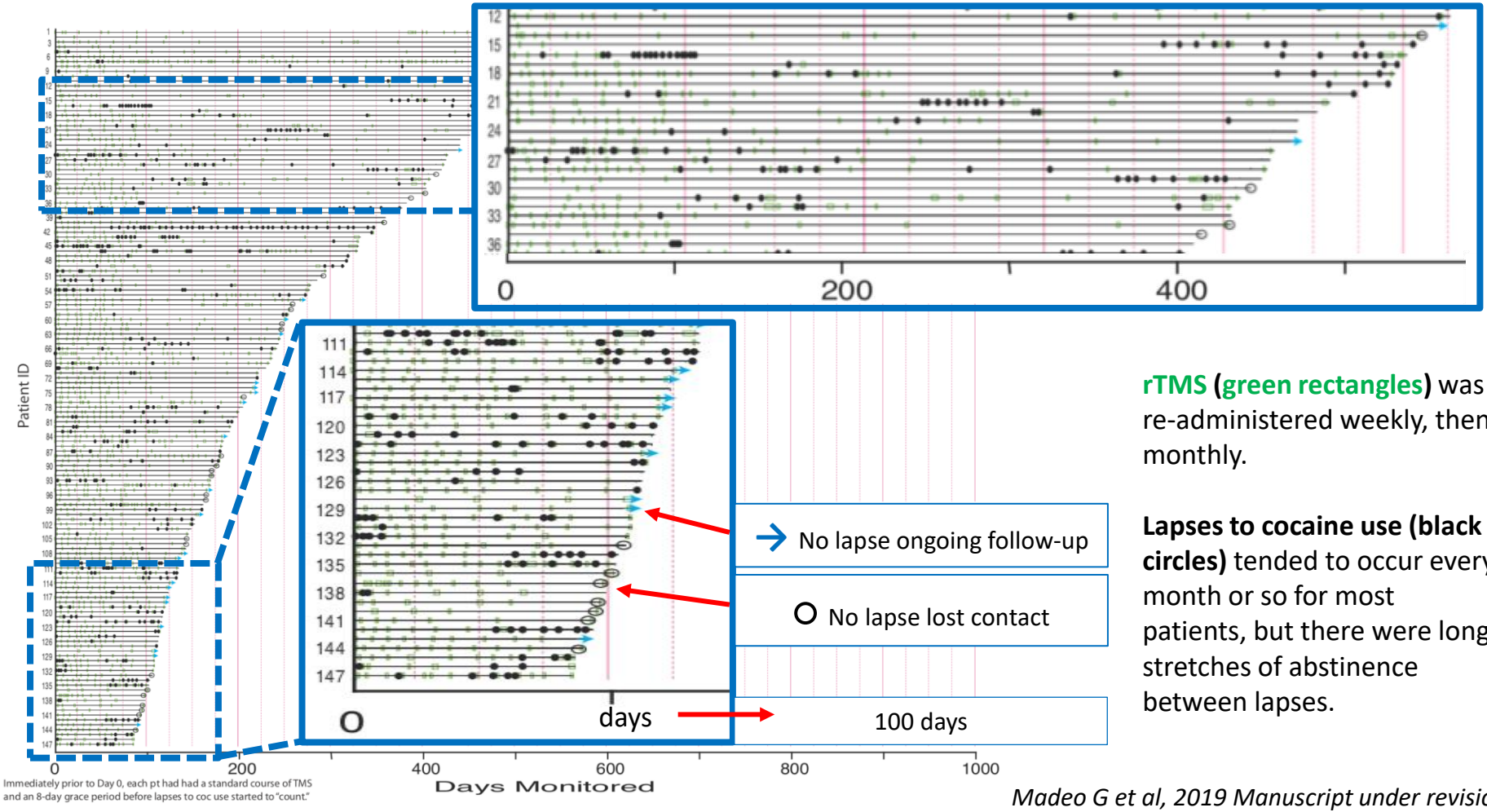
"treatment as usual" cohort: 51 days (95% confidence interval 39-78 days).

The difference between "treatment as usual" patients and rTMS patients emerges around 80 days.

Of the patients who had at least **12 months** of follow-up, 10 out of 55 (**18%) maintained abstinence throughout**.

In both cases patients had just been discharged from an inpatient stay, and both received treatment as needed during a lengthy outpatient follow-up.

Patterns of cocaine use and abstinence in the closely followed subsample



rTMS (green rectangles) was re-administered weekly, then monthly.

Lapses to cocaine use (black circles) tended to occur every month or so for most patients, but there were long stretches of abstinence between lapses.

Immediately prior to Day 0, each pt had had a standard course of TMS and an 8-day grace period before lapses to coc use started to "count."

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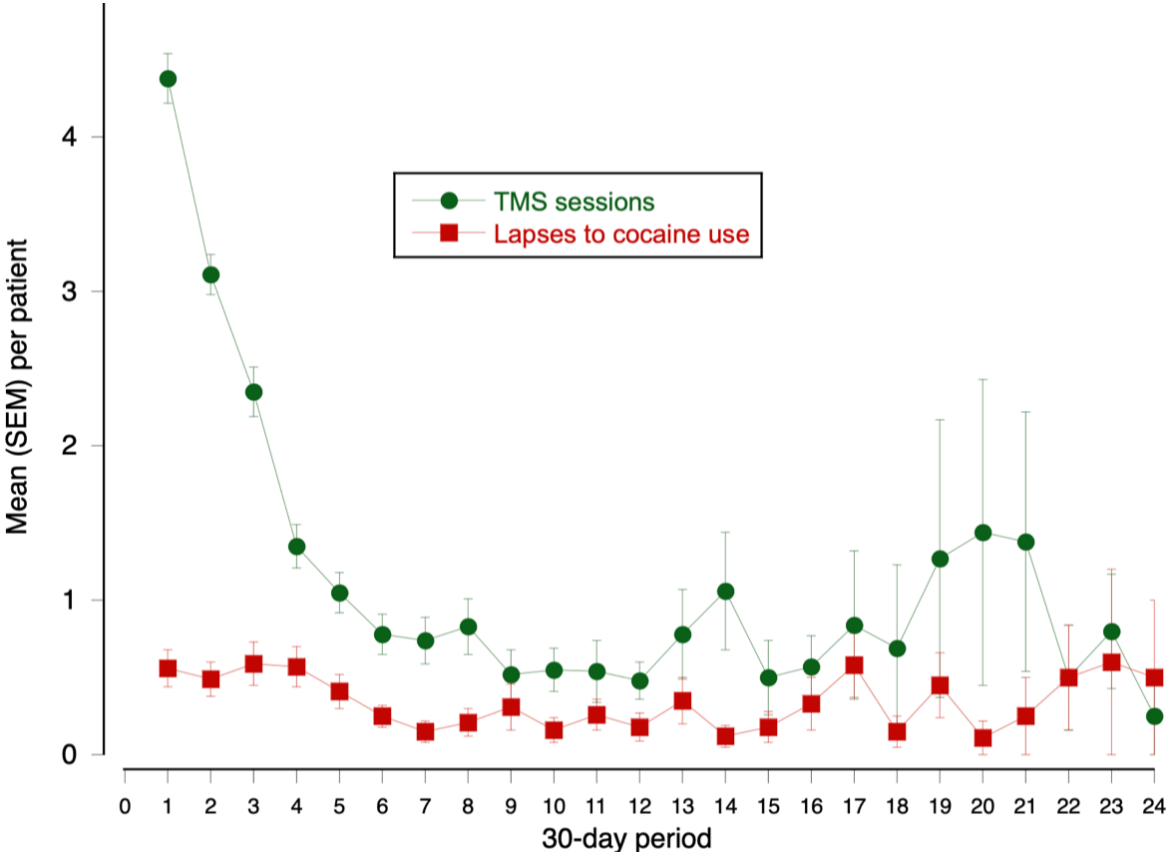
Maintenance rTMS sessions and lapses in closely followed subsample, month by month



The graph illustrates more clearly that the gradual decrease in re-administration of rTMS (green circles) did not leave patients more vulnerable to lapses to cocaine use (red circle).

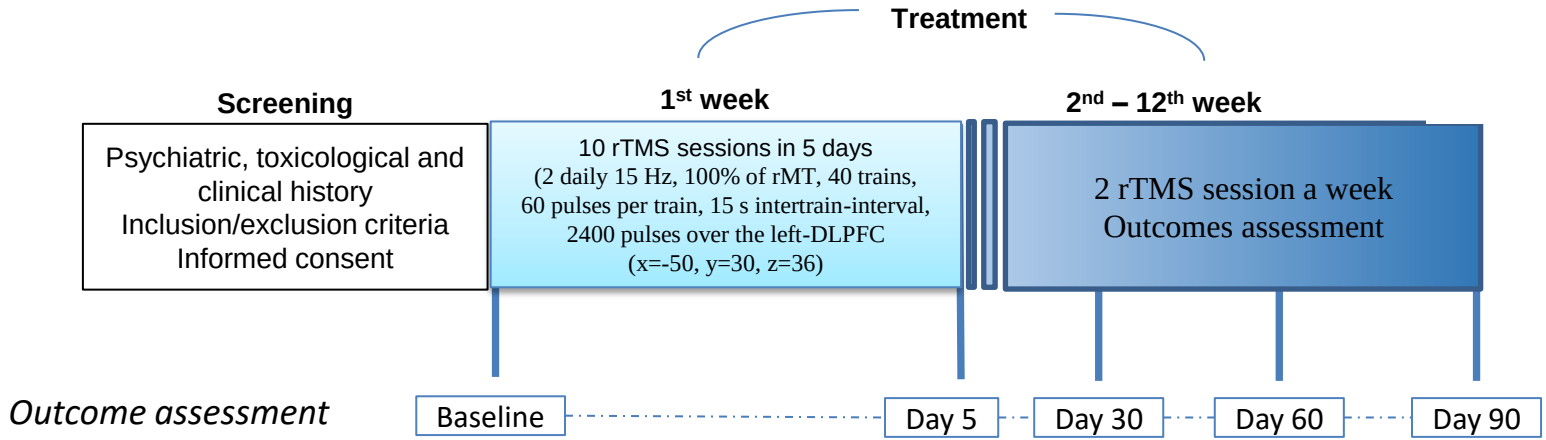
The mean quantity of cocaine use per patient was less than 1·gr/month.

Mean frequency of cocaine use significantly decreased from a mean of 18.7 day/month to less than 1.0 day/month.

The reduction of the rTMS sessions is not coupled with an increase of the number of lapses. The number of lapses remains stable over time.

Secondary Outcome Measures: effects on sleep and negative affect symptoms

Retrospective chart review of 87 patients diagnosed with CUD treated with rTMS protocol over the left DLPFC.



- **PSQI**: Pittsburgh Sleep Quality Index
- **CCQ:** Cocaine Craving Questionnaire
- **BDI-II:** Beck Depression Inventory II
- **SAS:** Self-rating anxiety scale
- **GSI:** Global Severity Index from Symptoms Checklist - 90

(Gomez-Perez, Cardullo et al., 2019, Manuscript under revision)

Secondary Outcome Measures: effects on sleep and negative affect symptoms

	Active group (n=10) §		Wait-list group (n=10)	
	Day 0	**Day 30**	**Day -30**	**Day 0**
PSQI[a]	9.00 (4.85)	3.3 (1.56)	6.4 (3.33)	6.9 (3.54)
Change from first assessment		-5.7 (1.57) *		0.5 (1.57)
CCQ[b]	18.8 (9.25)	1.00 (2.82)	24.8 (13.79)	21.9 (12.93)
Change from first assessment		-17.8 (4.74) *		-2.9 (4.74)
BDI-II[c]	18.7 (8.17)	2.7 (2.31)	15.6 (7.48)	14.1 (7.35)
Change from first assessment		-16 (3.01) *		-1.5 (3.01)
SAS[d]	47.62 (9.04)	32.62 (6.54)	45.12 (8.21)	43.00 (8.94)
Change from first assessment		-15 (3.68) *		-2.12 (3.68)
GSI[e]	68.13 (17.90)	42.08 (7.31)	61.95 (9.70)	57.85 (11.74)
Change from first assessment		-26.05 (5.50) *		-4.1 (5.5)

Data are presented as Mean (SD);

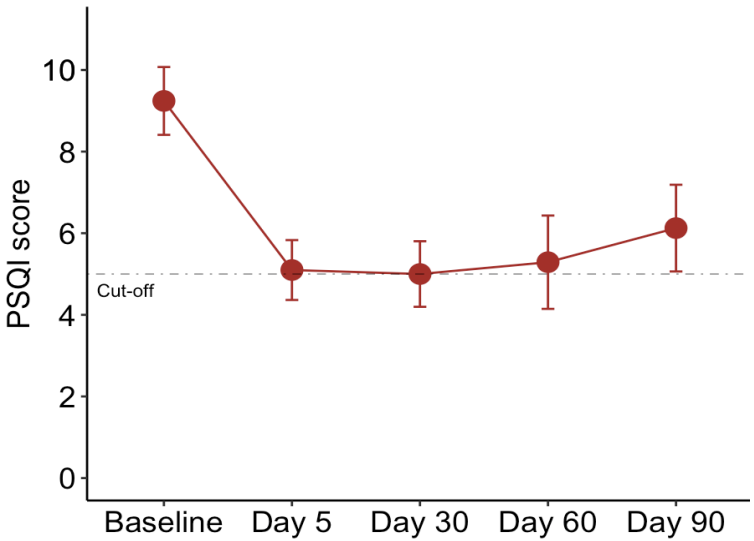
* *p* value <.001; § A small sample of equal numerosity and clinical characteristics of wait-list randomly selected from the 87 patients recruited for the study.

[a] Pittsburgh Sleep Quality Inventory – general sleep quality index; [b] Cocaine Craving Questionnaire; [c] Beck Depression Inventory – II; [d] Self-rating Anxiety Scale; [e] Global Severity Index from Symptoms Checklist – 90 – Revised

Secondary Outcome Measures: effects on sleep and negative affect symptoms

Research question 1: Are the scores at each timepoint significantly different from the baseline?

	Baseline	Day 5	Day 30	Day 60	Day 90
PSQI	9.24 (3.89)	5.09 (3.33)	5 (3.13)	5.28 (3.47)	6.12 (3.32)
Change from Baseline		-4.14 (0.53) *	-4.24 (0.58) *	-3.95 (0.67) *	-3.11 (0.66) *
Notes: Data are presented as Mean (SD); * p value <.001;					



PSQI score is significantly reduced after 5 days rTMS treatment and persist after 90 days compared to the assessment at T0.

No significant changes of PSQI scores are among T1, T2 and T3.

Percentage with PSQI score ≥ 5
Baseline: 88.5%
Day 90: 62.5%

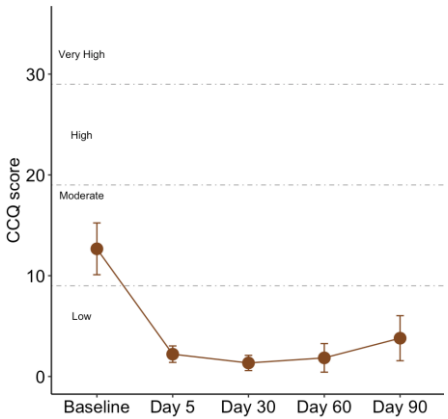
(Gomez-Perez, Cardullo et al., 2019, Manuscript under revision)

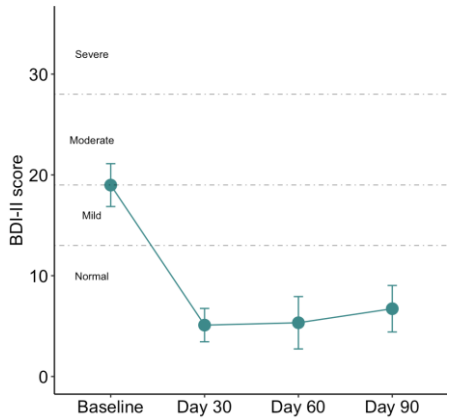
Secondary Outcome Measures: effects on sleep and negative affect symptoms

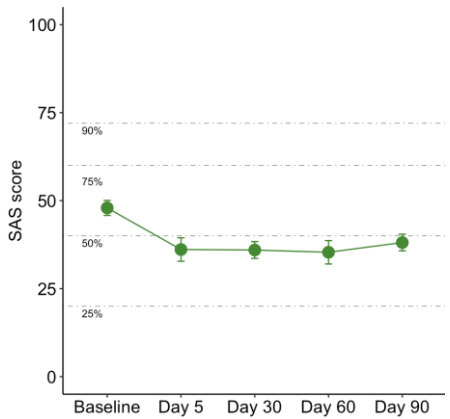
Research question 1: Are the scores at each timepoint significantly different from the baseline?

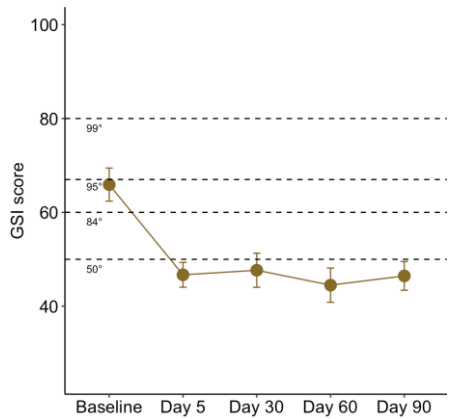
	Baseline	Day 5	Day 30	Day 60	Day 90
CCQ	12.67 (10.93)	2.21 (3.29) *	1.34 (2.79) *	1.84 (4) *	3.8 (6.5) *
BDI-II	18.99 (9.91)	-§	5.09 (6.45) *	5.33 (7.67) *	6.72 (7.2) *
SAS	47.93 (10.01)	36.11 (8.45) *	35.97 (9.44) *	35.33 (9.52) *	38.09 (7.38) *
GSI	65.91 (16.53)	46.69 (12.17) *	47.67 (14.46) *	44.49 (10.92) *	46.46 (9.56) *

Notes: Data are presented as Mean (SD); * Comparison to baseline p value <.001; § BDI-II was not administered at day 5 because it refers to the last two weeks









(Gomez-Perez, Cardullo et al., 2019, Manuscript under revision)

Secondary Outcome Measures: effects on sleep and negative affect symptoms

Research question 2: Which are the best predictors of the outcomes?

Predictors	PSQI	CCQ	BDI	SAS	GSI
TMS last 30 days	-0.11 (0.03) *	-0.22 (0.07) *	-0.37 (0.08) **	-0.34 (0.08) **	-0.40 (0.13) *
Use last 30 days	0.13 (0.02) **	0.37 (0.06) **	0.20 (0.07) *	0.18 (0.07) *	0.33 (0.10) *
Time			-0.09 (0.02) **	-0.07 (0.01) **	-0.13 (0.02) **
First experience				-0.50 (0.17) *	
Addiction age					
Age					
Education					
Notes: Data are presented as estimate (Standard Error); * p < 0.01; ** p < 0.001;					

Both the number of rTMS sessions and the use of cocaine in the preceding 30 days correlate with clinical improvements

(Gomez-Perez, Cardullo et al., 2019, Manuscript under revision)

CONCLUSIONS

TMS is a non-invasive neuromodulation technique offering a new circuit-based therapeutic intervention for addictions, including CUD.

TMS protocol stimulation, targeting the prefrontal areas, seems effective in reducing craving and cocaine consumption.

Despite the limitations of a naturalistic clinical setting, our study following-up patients for more than 2 years is supporting TMS as a safe therapeutic intervention:

- for reducing lapse to cocaine use over time,
- cocaine consumption
- prolong abstinence.

Common self-reported withdrawal/abstinence symptoms, including sleep disturbances, anxiety, depression, and other negative affect states appear to benefit from rTMS treatment

TMS should be integrated in clinical settings with conventional treatments, including psychotherapy and medication.

Sham-controlled RCTs with more uniform reporting standards in TMS research are needed already ongoing (ClinicalTrials.gov identifiers NCT03607591, NCT03333460, and NCT02986438).

Likewise, shared research questions, protocols and data repository will help to FuturiZe research and clinical practice for Addictions.

Thank you!

Luigi Gallimberti
Antonello Bonci
Alberto Terraneo
Sonia Chindamo
Sonia DeMarchi
Graziella Madeo
Stefano Cardullo
Luis Gomez Perez
Veronica Farruggia
Diego Cuppone
Silvia Soldatesca
Marta Ballin
Elena Marini
Linda Marconi
Giulia Bussolotto
Sonia Specie
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Novella Fronda Foundation
Research Advances for Brain Health

Secondary Outcome Measures: effects on sleep and negative affect symptoms

Demographic Features	All (n=87)
Age (years) [Mean (SD)]	37.67 (7.53)
Gender (female/male)	2/85
Education (years) [Mean (SD)]	12.51 (3.2)
Age at first experience (years) [Mean (SD)]	20.55 (5.65)
Age at addiction (years) [Mean (SD)]	28.62 (8.8)
rTMS sessions number [Mean (SD)]	29.17 (6.34)
PSQI score $\geq$ 5 at baseline [%]	88.5
CCQ score at baseline [Mean (SD)]	12.66 (10.93)
BDI-II score at baseline [Mean (SD)]	18.98 (9.91)
SAS score at baseline [Mean (SD)]	47.93 (10.01)
GSI score at baseline [Mean (SD)]	65.91 (16.53)

Analyses

- Repeated-measures analysis of variance (ANOVA) with *post-hoc* pairwise comparisons **to assess the change overtime**
- linear mixed-effects model **to assess the best predictors of change**

(Gomez-Perez, Cardullo et al., 2019, Manuscript under revision)