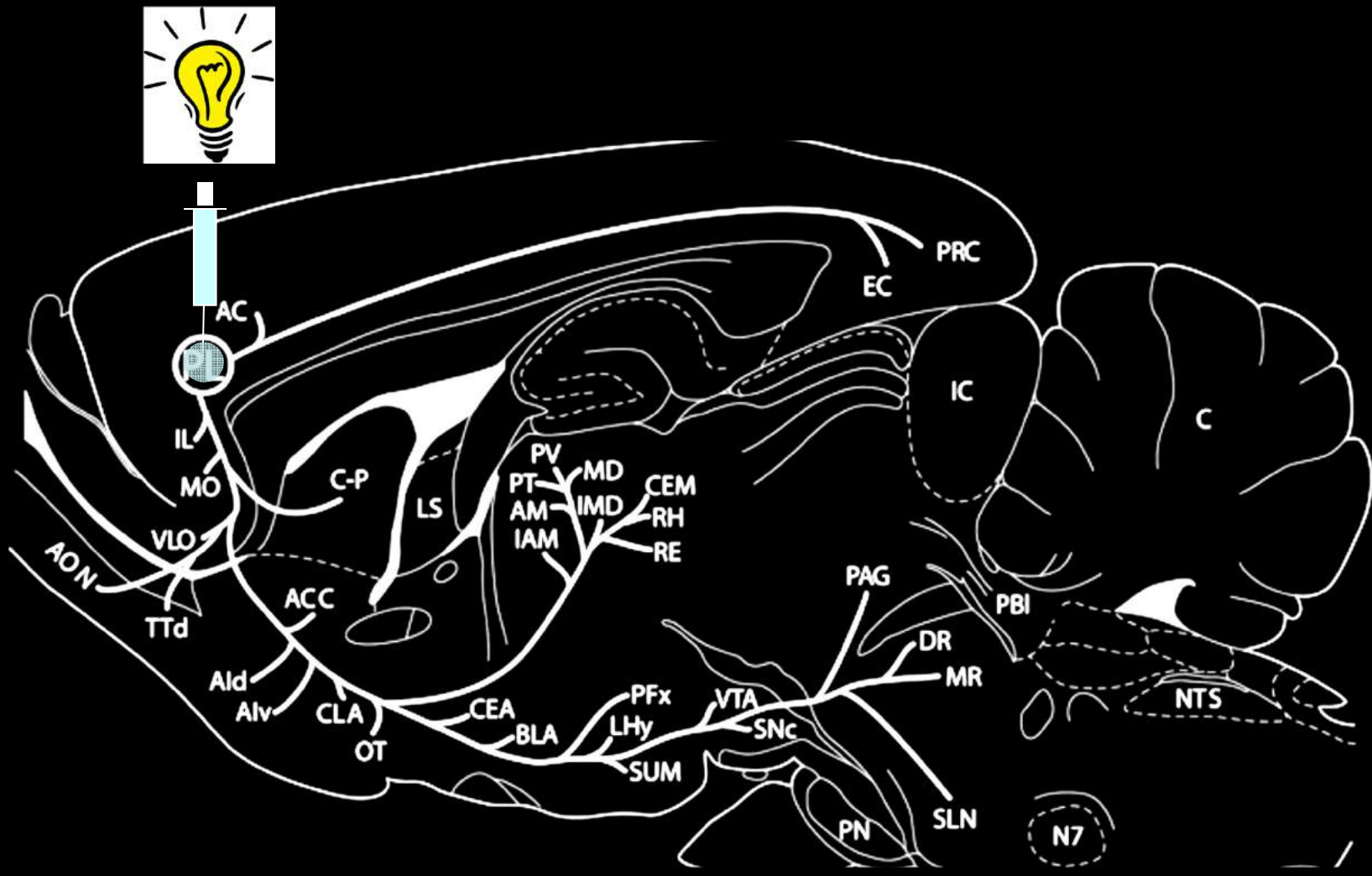
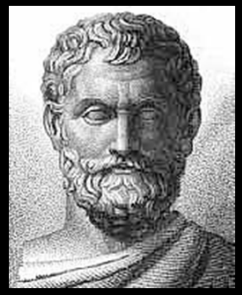
Stimulation of the prelimbic via optogenetics, produces a network effect, widespread throughout the brain



Adapted from Vertes, Neuroscience 2006; 142 1-20

Transcranial Magnetic Stimulation (TMS)

History of Transcranial Magnetic Stimulation (TMS)



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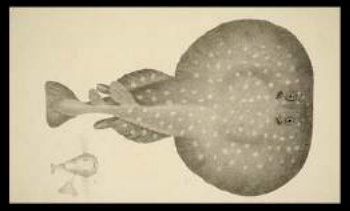
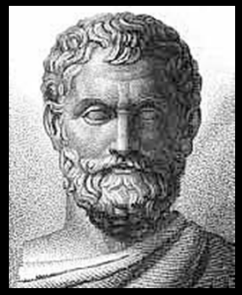


= TMS

Scribonius Largus
43 AD

History of Transcranial Magnetic Stimulation (TMS)



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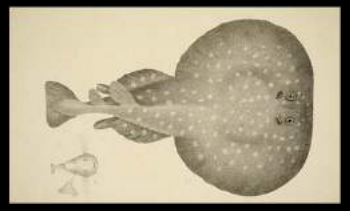
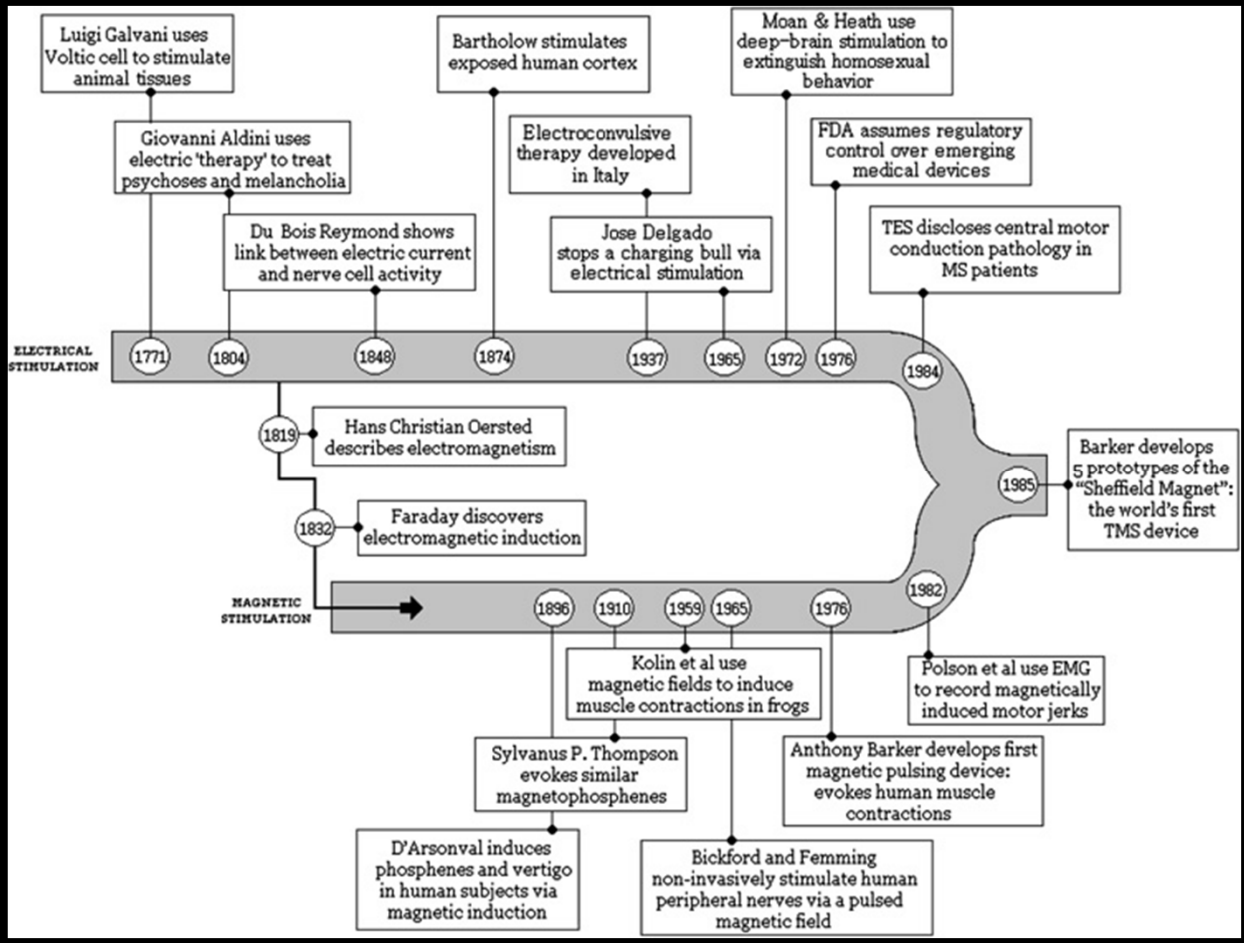


= TMS



From Horvath et al., 2011

Do rat and human PFC have anything in common?

Do rat and human PFC have anything in common?

Not the anatomy

Rat Prelimbic Area and Human/Monkey DL PFC share functional roles

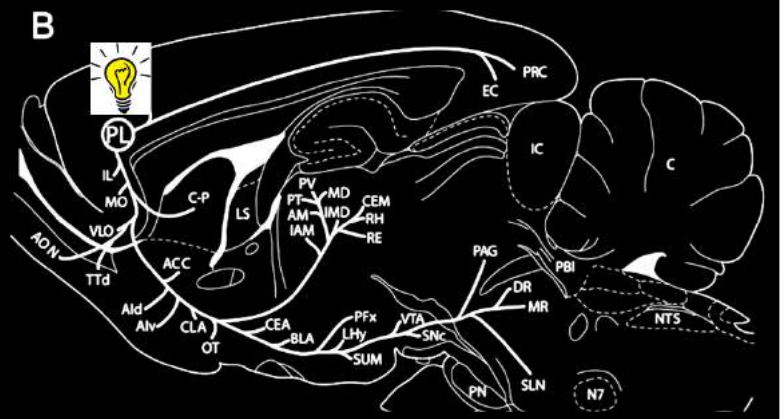
- The prelimbic area in rats and dlPFC in human/monkey are implicated in "executive functions"

Inhibitory control in rats (Jonkman et al 2009; Moorman and Aston-Jones, 2015) and self-control in humans (Hare et al 2009) are mediated by the prelimbic cortex and dlPFC, respectively

- Executive functions include:
  - Working memory
  - Temporal processing
  - Behavioral flexibility
  - Decision Making
- The Prelimbic/Infralimbic region in rats and dorsal and ventral lateral PFC in monkeys and humans support working memory for objects and places, temporal order for object and places, reversal learning, delay discounting and uncertainty-decision making (Kesner et al. 2011)

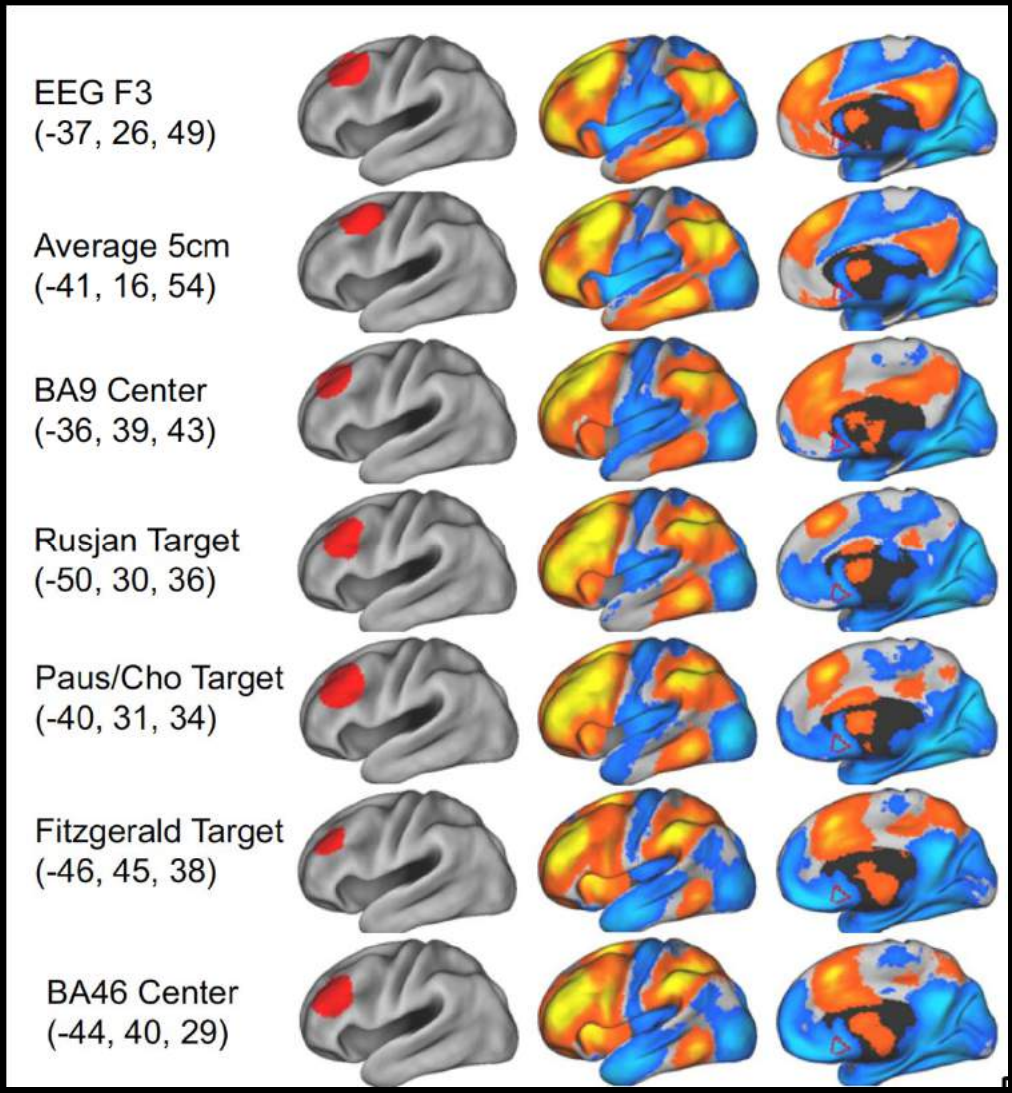
Stimulation of the DL PFC via rTMS, produces a widespread network effect

Rat



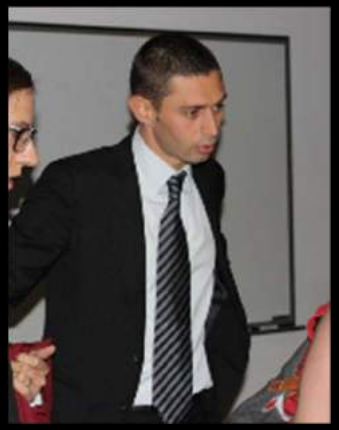
Vertes, 2006

Human



Fox et al., 2012

From optogenetics to the clinic



-**Site:**

- Addiction Center, Padova, Italy
- Luigi Gallimberti MD and Alberto Terraneo PhD
- Outpatient Clinic setting

-**Population:**

- Female and male patients with cocaine use disorder
- Treatment-seekers for cocaine use disorder
- “Guardian” assigned to each patient

Terraneo et al., 2015

repeated Transcranial Magnetic Stimulation (rTMS) Preliminary Results

Treatment:

-General medical management provided by addiction specialist physicians and other health care providers

- Assessment of adverse events, urine drug tests (UDTs), craving for cocaine, medical history, physical exam, psychological assessments (SCL-90-R)

- While AUD was exclusionary, patients were asked to abstain completely from any alcohol use during the duration of the study: disulfiram 400mg/day was used to assure compliance

Terraneo et al., 2015

repeated Transcranial Magnetic Stimulation (rTMS)
Preliminary Results

Treatment:

Table 2 Participant characteristics at baseline [*M* ±(*SD*) or percentage (%)].

	rTMS group ($n=16$)	Control group ($n=16$)
Age*	43.50 (9.75)	37.06 (5.95)
Women (*N*)	2	0
Race: Caucasians (%)	100	100
Age of first cocaine use	26.69 (9.34)	24.06 (6.23)
Years of cocaine use	16.81 (7.95)	13.00 (5.55)
Cocaine use during the last month (days per week)	4.81 (1.94)	4.31 (2.02)
Cocaine use during the last month (grams per day)	1.81 (1.11)	1.75 (0.77)
Tobacco smokers (%)	62.5%	56.25%
Last use		
Less than 24 h	37.50%	43.75%
Between 24 *and* 48 h	18.75%	25.00%
More than 48 h	43.75%	31.25%

*$p<0.05$; unless otherwise noted, there were no significant differences between the groups on these measures [$p>0.05$]

Terraneo et al., 2015

repeated Transcranial Magnetic Stimulation (rTMS)
Preliminary Results

Treatment:

-rTMS:

- Dorsolateral Prefrontal Cortex (MNI coordinates, left side)
- 15 Hz frequency, 60 pulses, 40 sec intervals (13 minutes per session)

- Duration of treatment:
  - ❖ Week 1: once a day for 5 consecutive days
  - ❖ Weeks 2-4: twice a week

Terraneo et al., 2015

repeated Transcranial Magnetic Stimulation (rTMS)
Preliminary Results

-**Primary aims:**

- Assess SAFETY of the use of rTMS in a population of patients with cocaine use disorder

- Assess FEASIBILITY of the use of rTMS in this population

Terraneo et al., 2015

repeated Transcranial Magnetic Stimulation (rTMS) Preliminary Results

-**Primary aims:**

- Assess SAFETY of the use of rTMS in a population of patients with cocaine use disorder

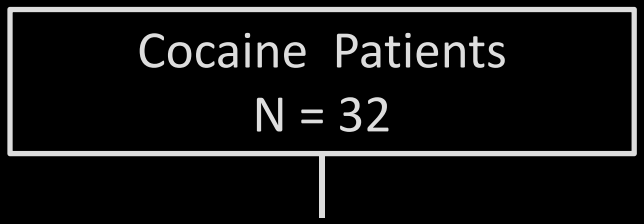
- Assess FEASIBILITY of the use of rTMS in this population

-**Secondary aim:**

- Explore signal for efficacy to inform fully-powered controlled trials by comparing the experimental group to a control group via a randomized open-label design

Terraneo et al., 2015

repeated Transcranial Magnetic Stimulation (rTMS)
Preliminary Results



Terraneo et al., 2015

repeated Transcranial Magnetic Stimulation (rTMS)
Preliminary Results

Cocaine Patients
N = 32

Control Group (n = 16)
(they also received medications,
e.g. benzodiazepines, bupropion)

- No serious or unanticipated side-effects
- 13 (81%) participants completed treatment
- **All cocaine-negative UDTs: 3 (19%)***

Terraneo et al., 2015

repeated Transcranial Magnetic Stimulation (rTMS)
Preliminary Results

Cocaine Patients
N = 32

Experimental Group (n = 16)
rTMS
(and no medications)

- ❑ No serious or unanticipated side-effects
- ❑ 16 (100%) participants completed treatment
- ❑ **All cocaine-negative UDTs: 11 (69%)***

Control Group (n = 16)
(they also received medications,
e.g. benzodiazepines, bupropion)

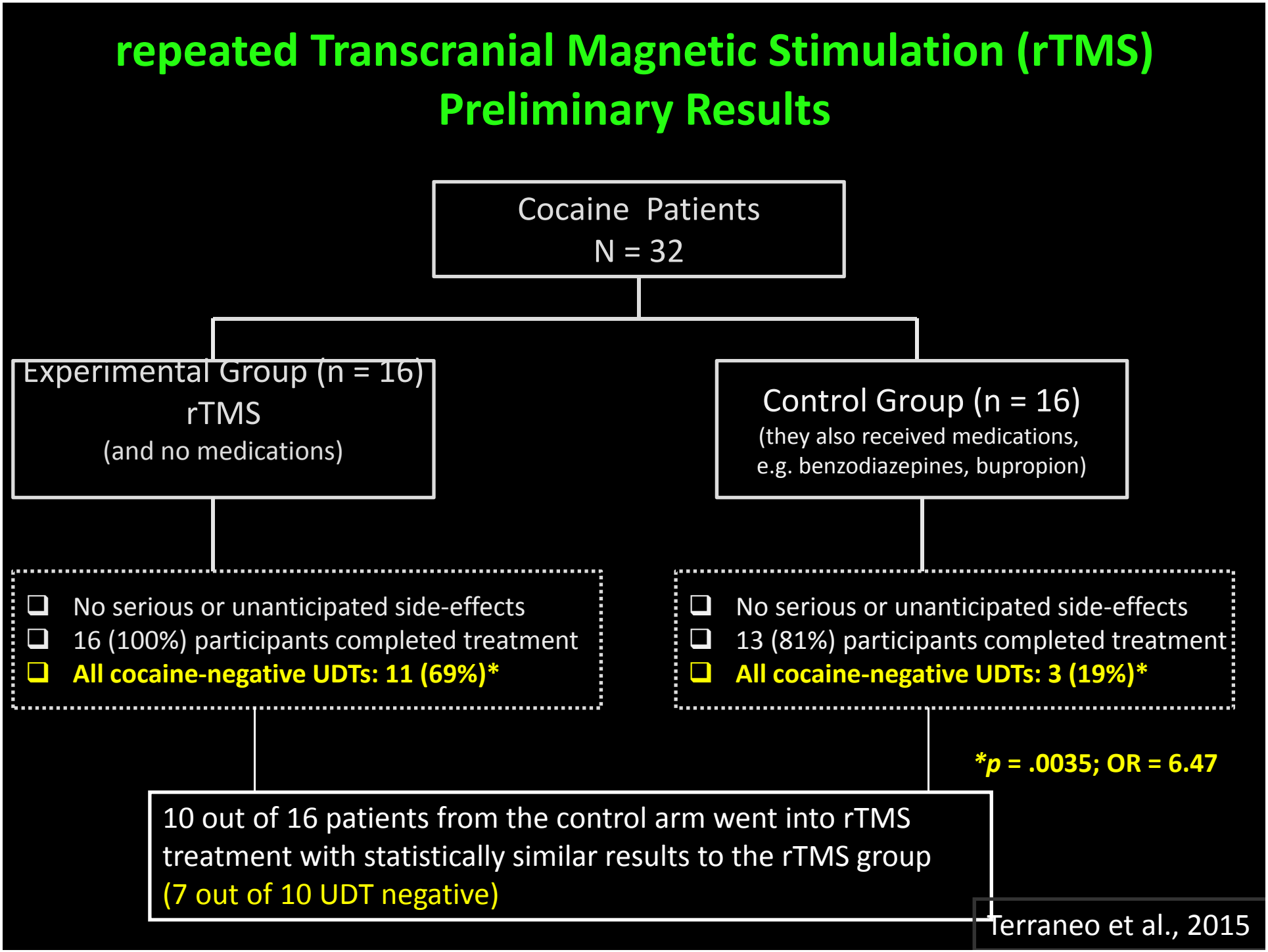
- ❑ No serious or unanticipated side-effects
- ❑ 13 (81%) participants completed treatment
- ❑ **All cocaine-negative UDTs: 3 (19%)***

***p* = .0035; OR = 6.47**

Urines monitored twice a week in both groups

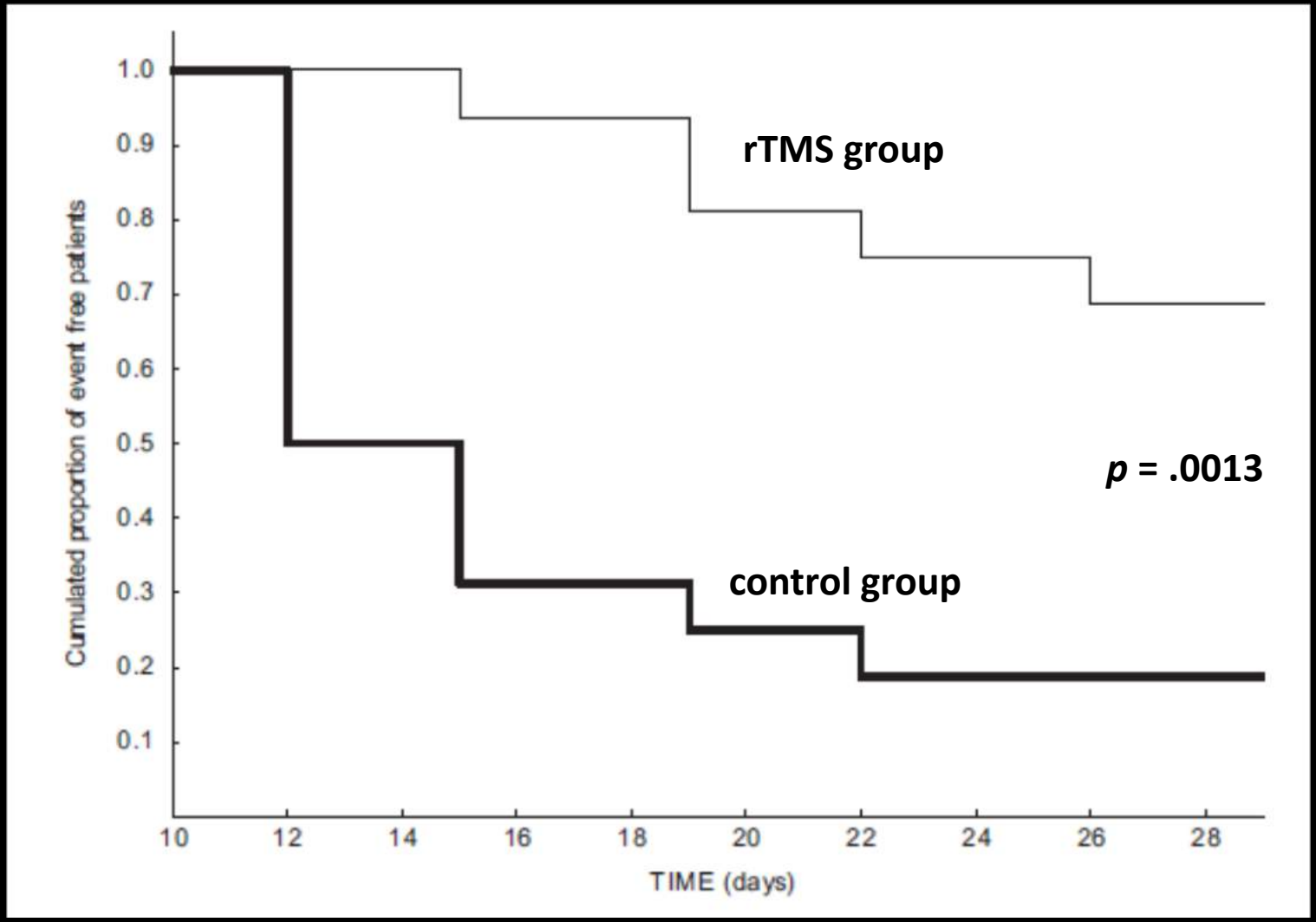
Terraneo et al., 2015

repeated Transcranial Magnetic Stimulation (rTMS)
Preliminary Results



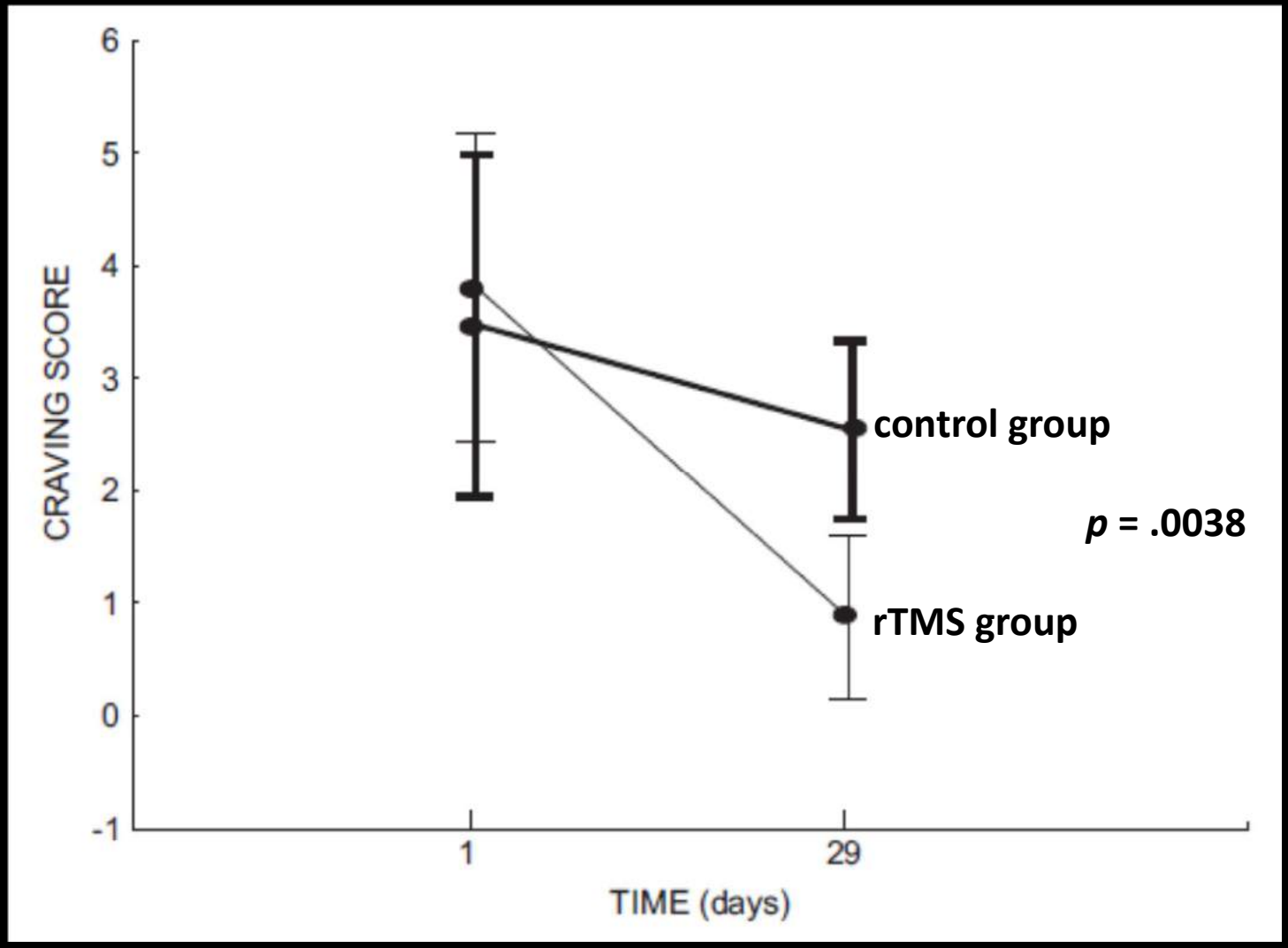
Terraneo et al., 2015

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



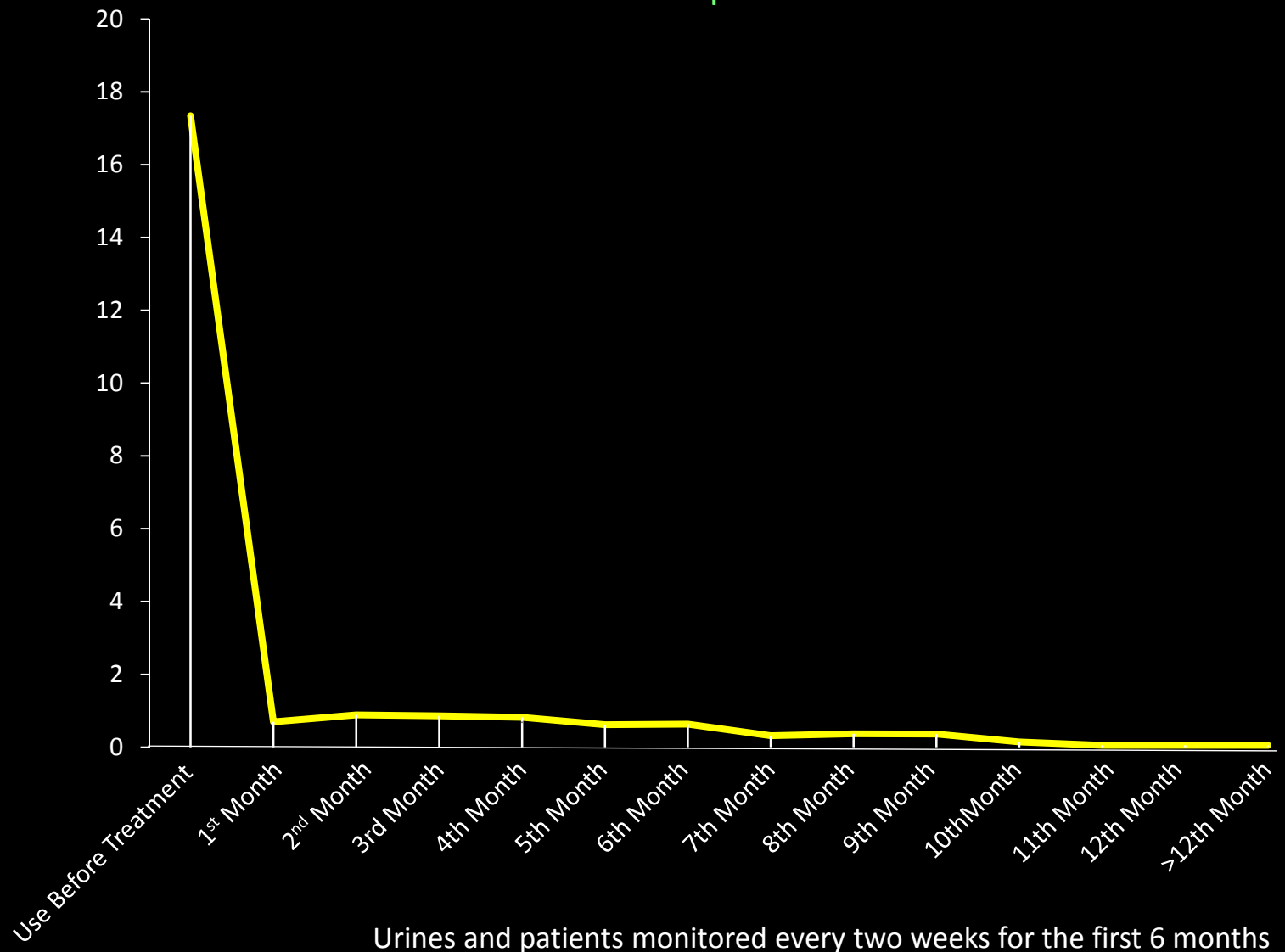
Terraneo et al., 2015

Craving score is significantly reduced in rTMS group

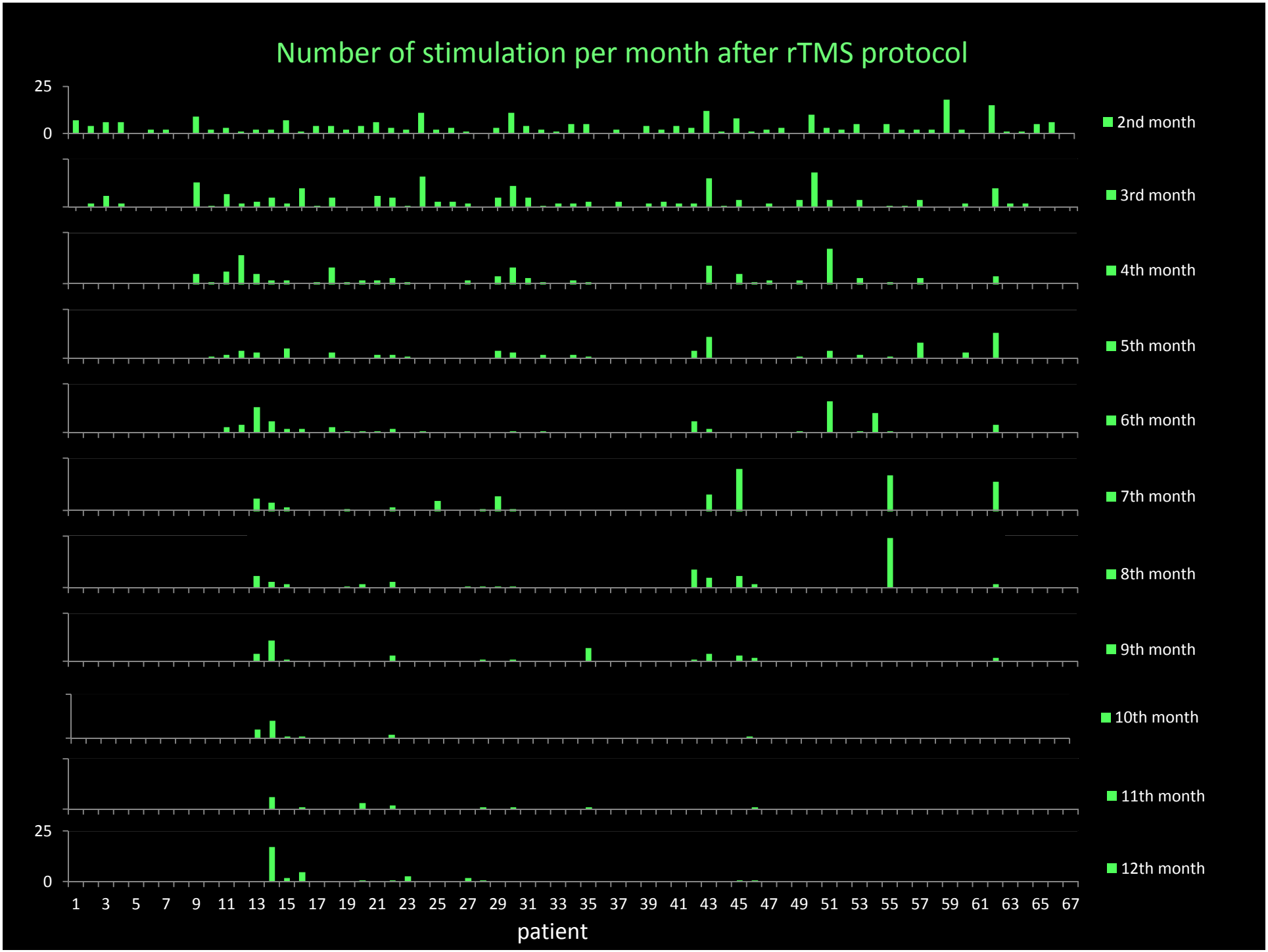


Terraneo et al., 2015

Average days of cocaine use per month, after the end of rTMS protocol

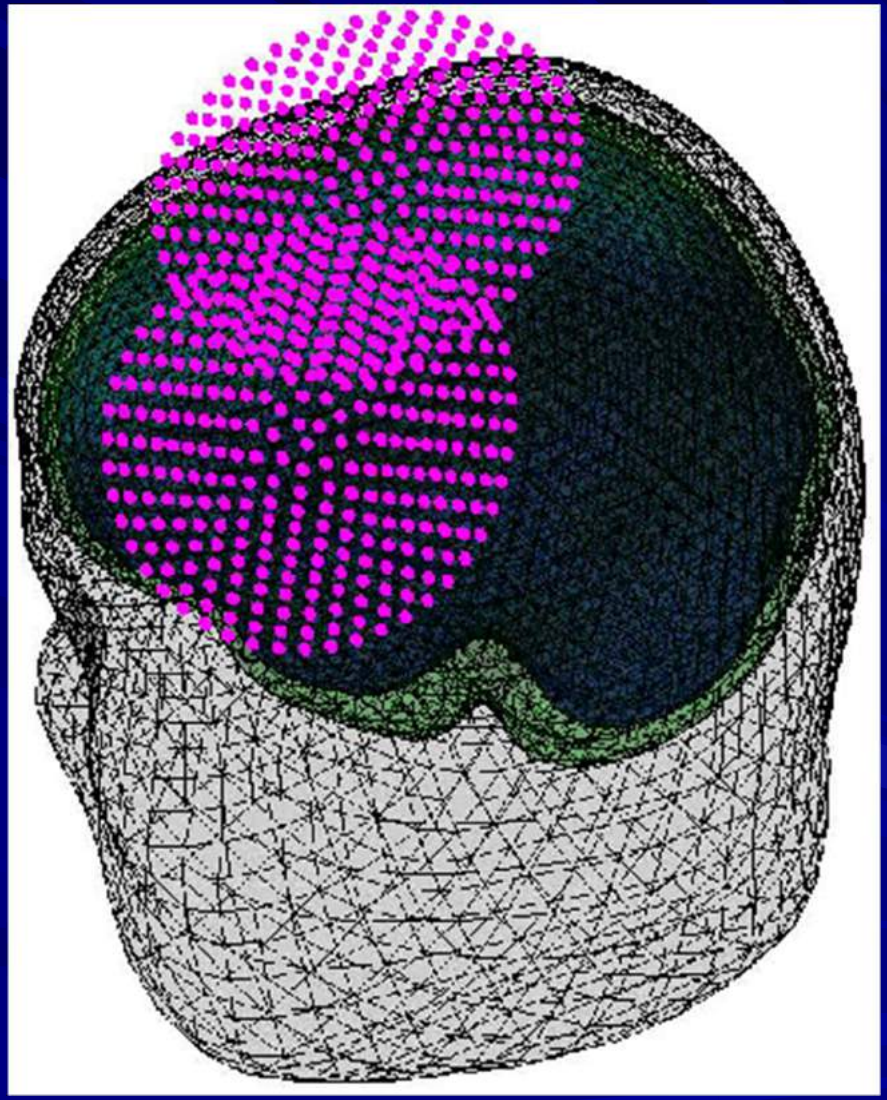


Urines and patients monitored every two weeks for the first 6 months
Then once a month


Number of stimulation per month after rTMS protocol
25
0
2nd month
3rd month
4th month
5th month
6th month
7th month
8th month
9th month
10th month
11th month
12th month
25
0
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65 67
patient

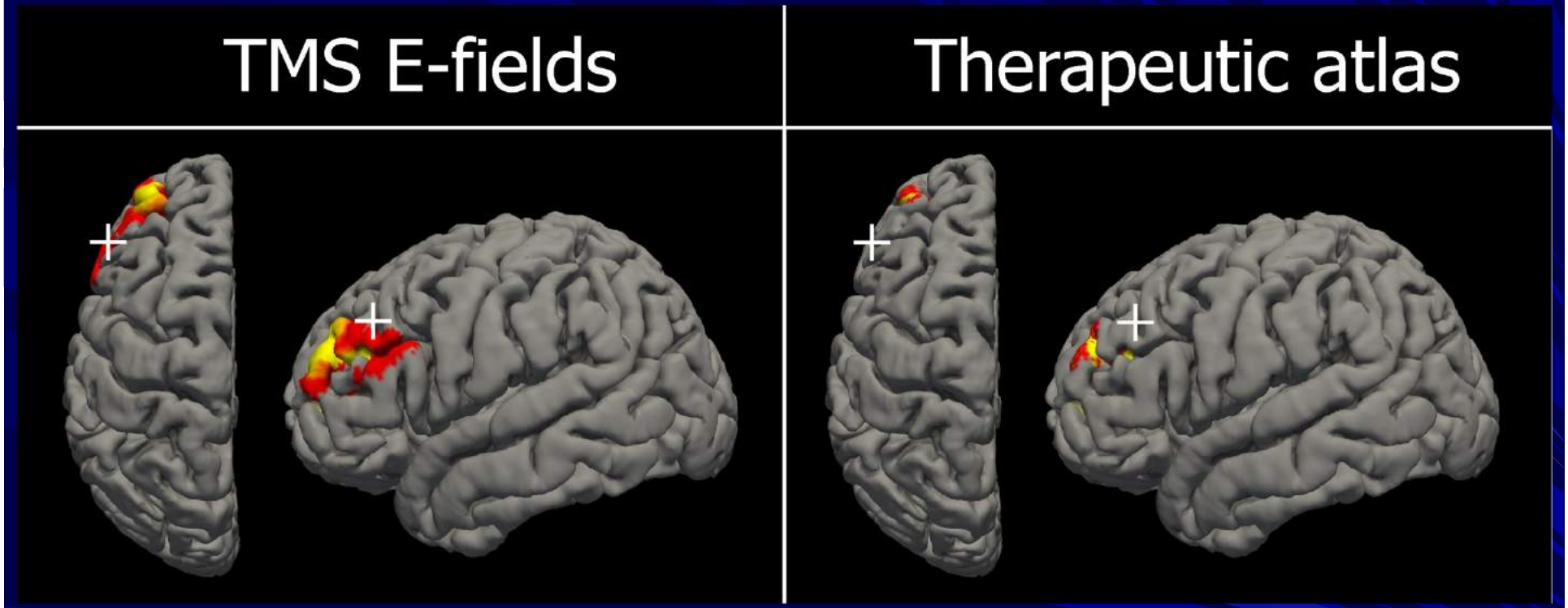

Generalized effects versus Specificity
rTMS
Optogenetics

1. Computing TMS E-fields



Courtesy of Tommi Raij

Treatment Atlas: First Results (N=15)



- MNI coordinates versus foci of stimulation
- Importance of realistically shaped volume conductor model
- Building a probabilistic treatment atlas

Raij et al. (2015) In Preparation

Current plans and objectives

- Relationship between locus of stimulation and effectiveness
- Brain regions involved
- Standardization of rTMS protocol(s) versus “personalized” rTMS

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Conclusions

1. Optogenetic based-rTMS study. Its rationale is based on the demonstration of a causal role of the prelimbic cortex in bidirectionally shaping cocaine seeking and taking.

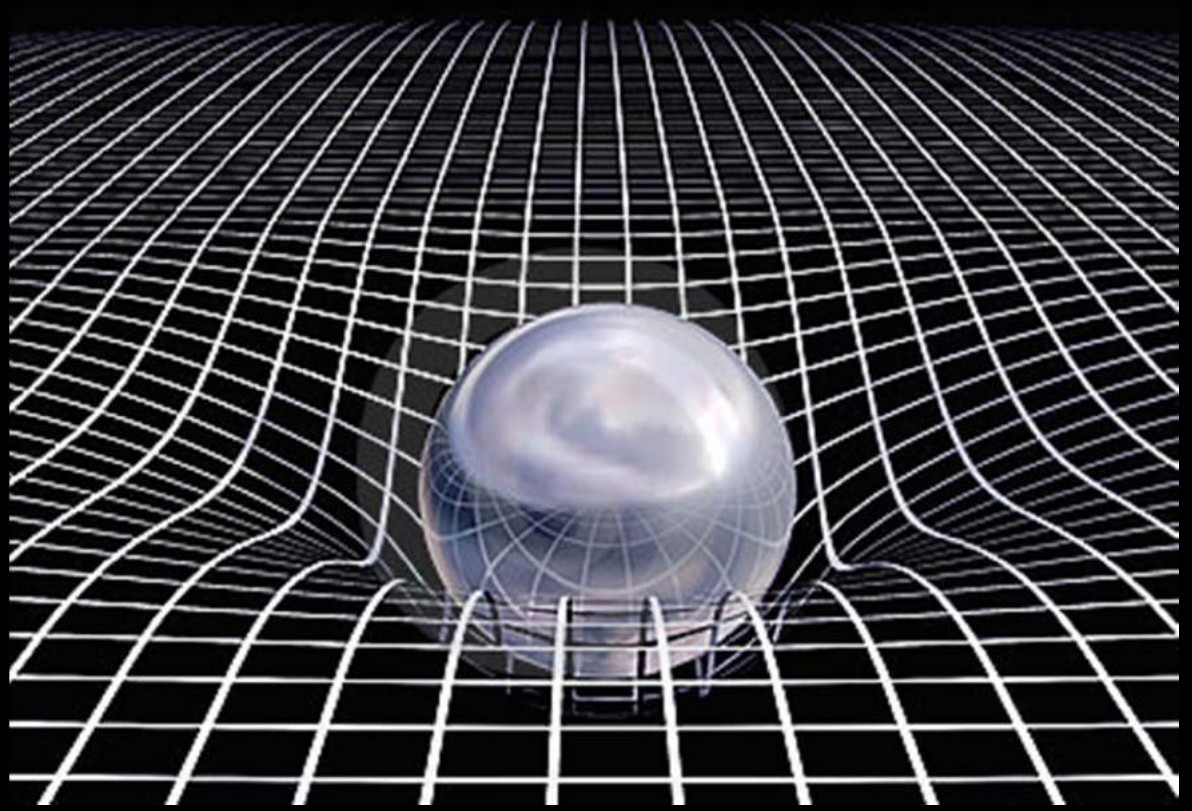
2. It provides the first clear evidence supporting the SAFETY of rTMS in cocaine-addicted patients and suggest its potential therapeutic role for rTMS-driven prefrontal cortex (PFC) stimulation in reducing cocaine use.

3. It provides preliminary clinical evidence for rTMS efficacy in treating cocaine use disorders in patients.

4. It provides a strong rationale for developing larger placebo-controlled studies and create standardized rTMS treatment.

5. 99% of work still to be done

The Future of Neuroscience



The Future of Neuroscience

Acknowledgements

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Collaborations

Extramural

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Glia project
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