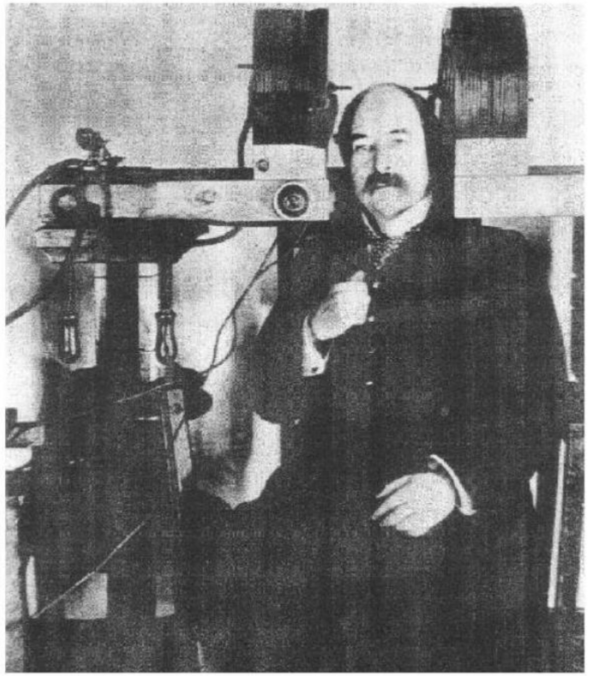
Transcranial Magnetic Stimulation

Dr. Masoud Nosratabadi
PhD in Health Psychology

Past



Present

Barker, 1984

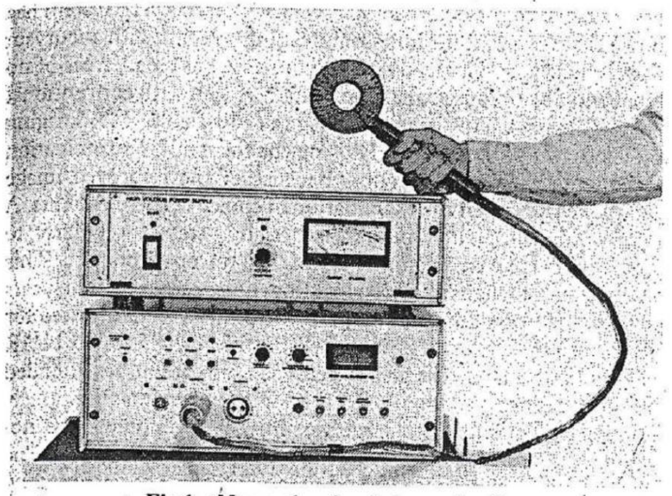


Fig 1—Magnetic stimulator and coil.

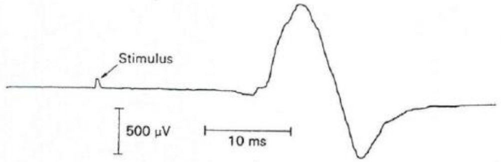
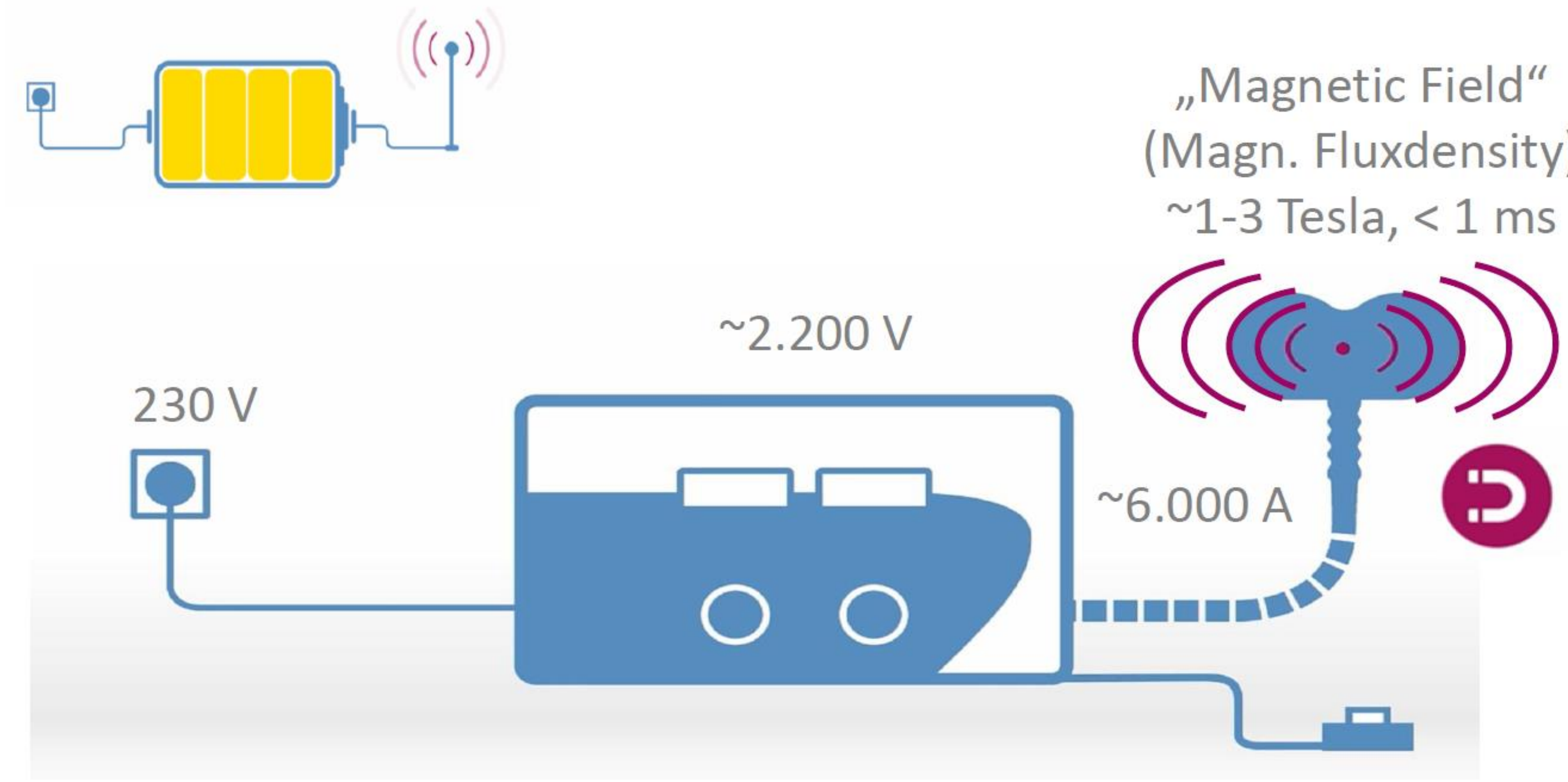


Fig. 1. Action potential (surface electrodes) in forearm flexor muscles, after a magnetic stimulus to the opposite motor area.

TMS at a glance

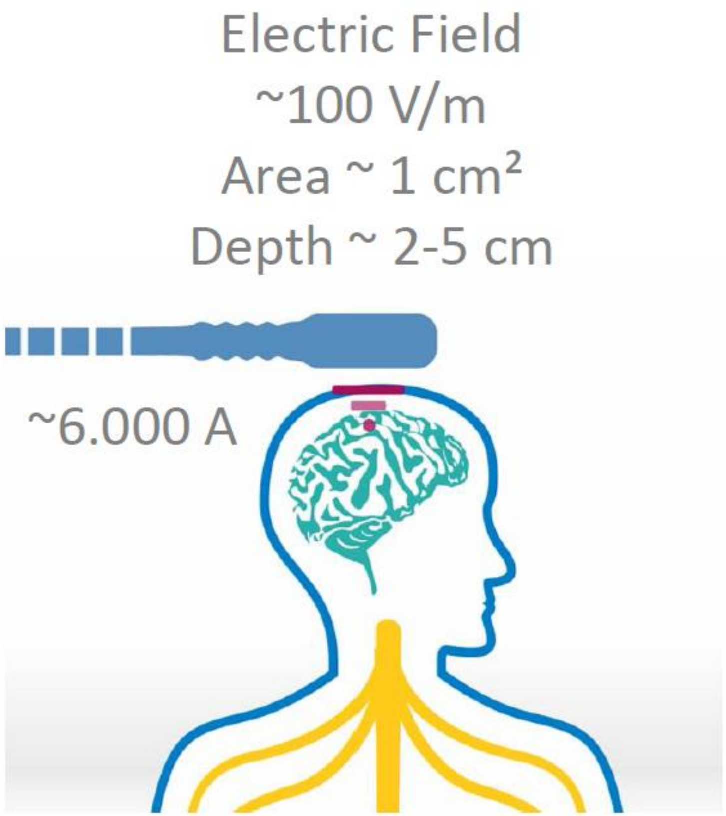
- **Non-invasive**
- **Well-tolerated**
- **Little side effects**
- **No anasthesia**
- **Normal activities possible after treatment**
- **Treatment session takes approx. 20-30 min**
- **Typical treatment is 20-30 session in 4-6 weeks**
- **Technology platform for variety of indications**

Magnetic Stim Basics

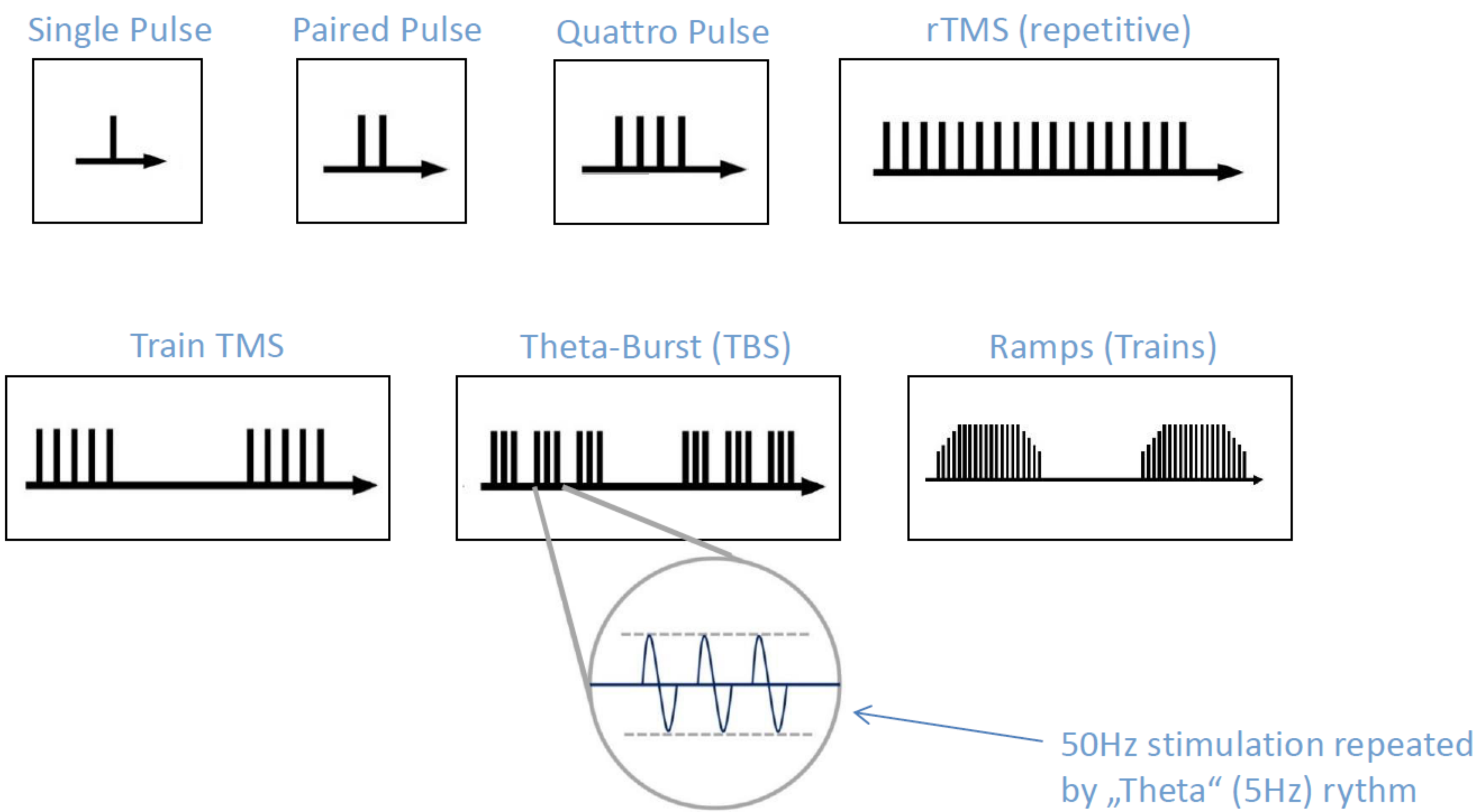


Magnetic Stim Basics

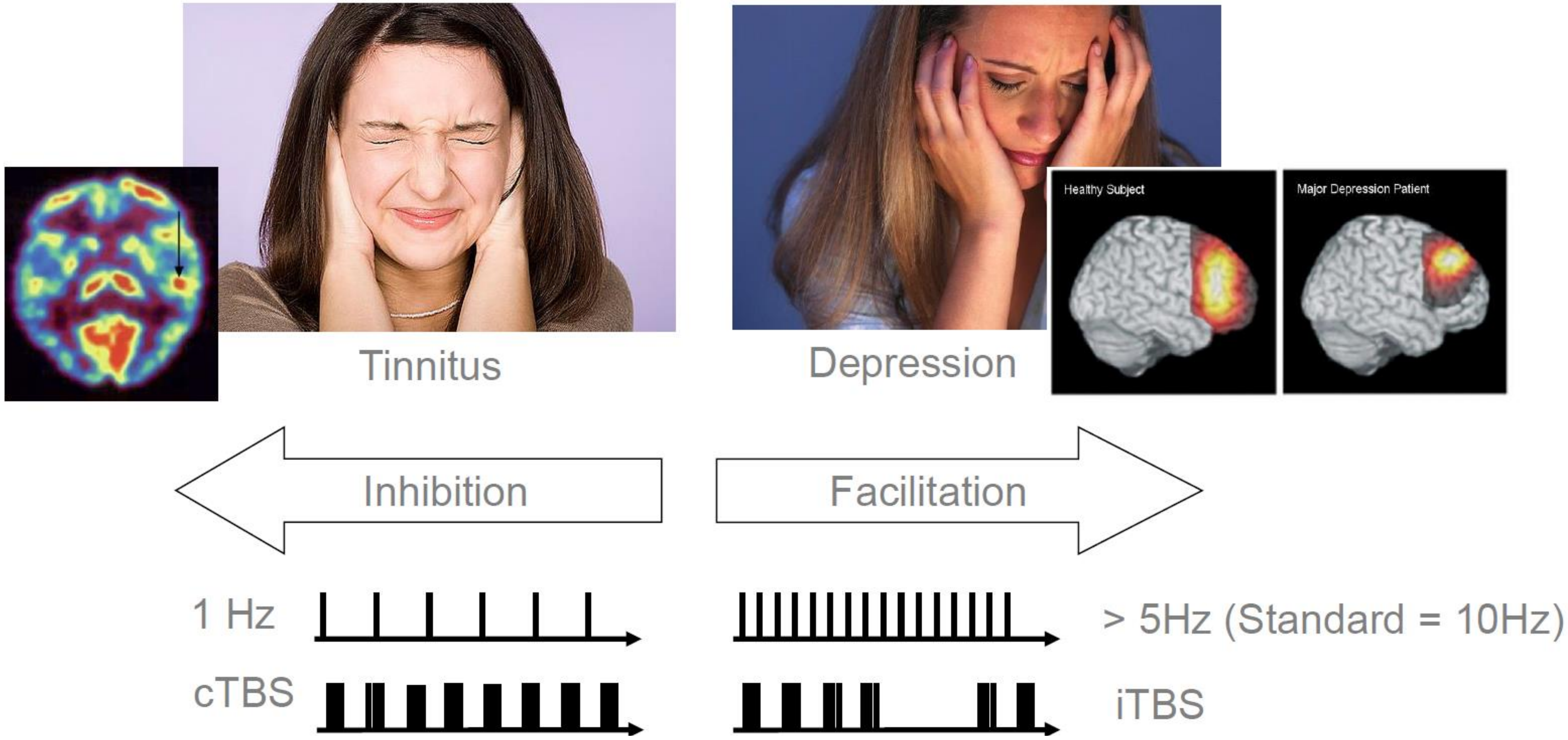
- Magnetic coil is placed tangentially over the target area (cortex, periphery)
- Magnetic pulse causes a „click“ sound – however its painless and non-invasive
- Various stimulation parameters determine the effectiveness (intensity, frequency, pulse pattern, ...)



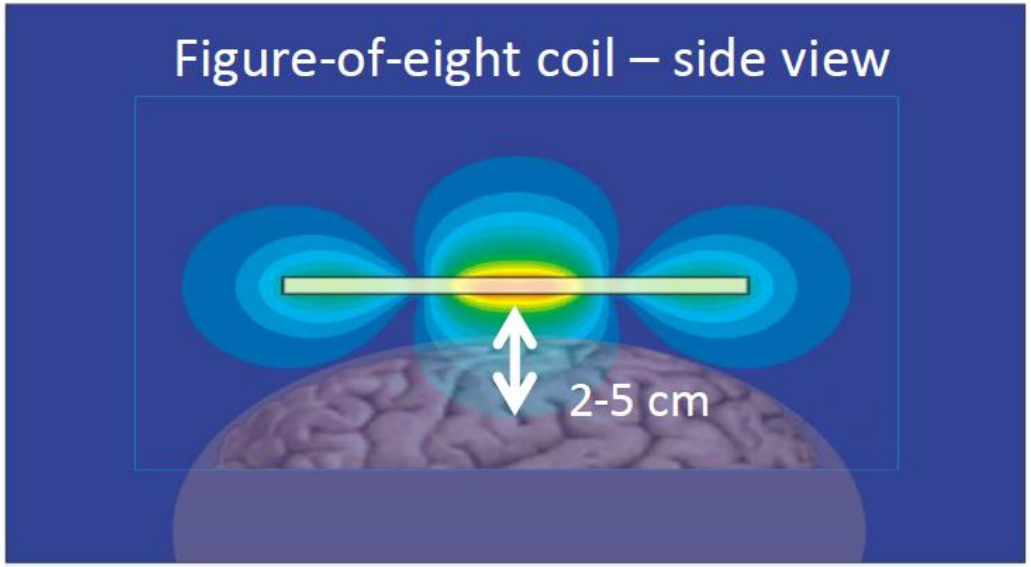
Pulse Patterns

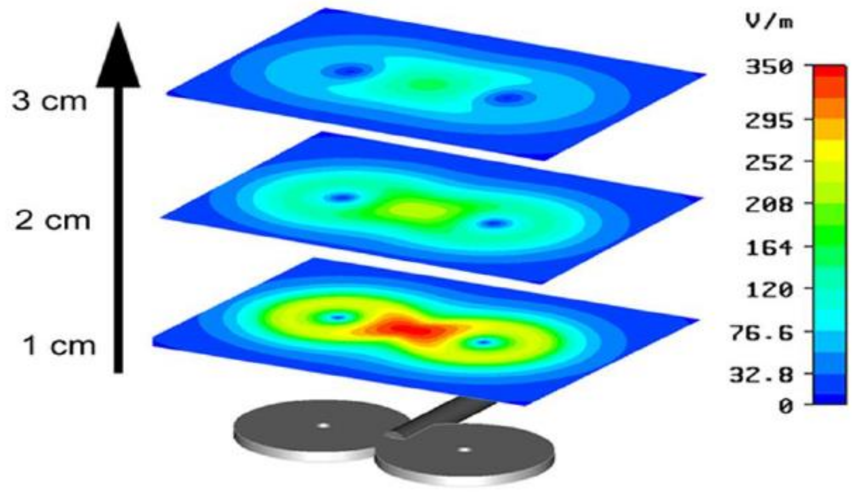


Stimulation Protocols

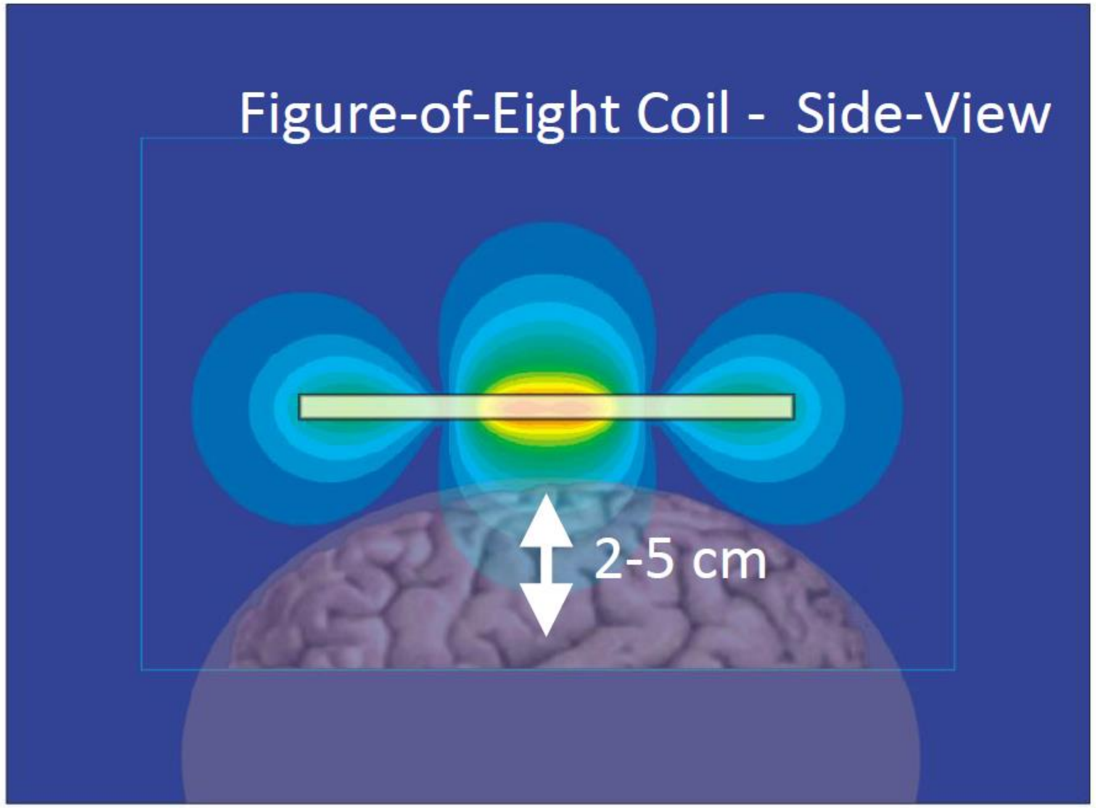


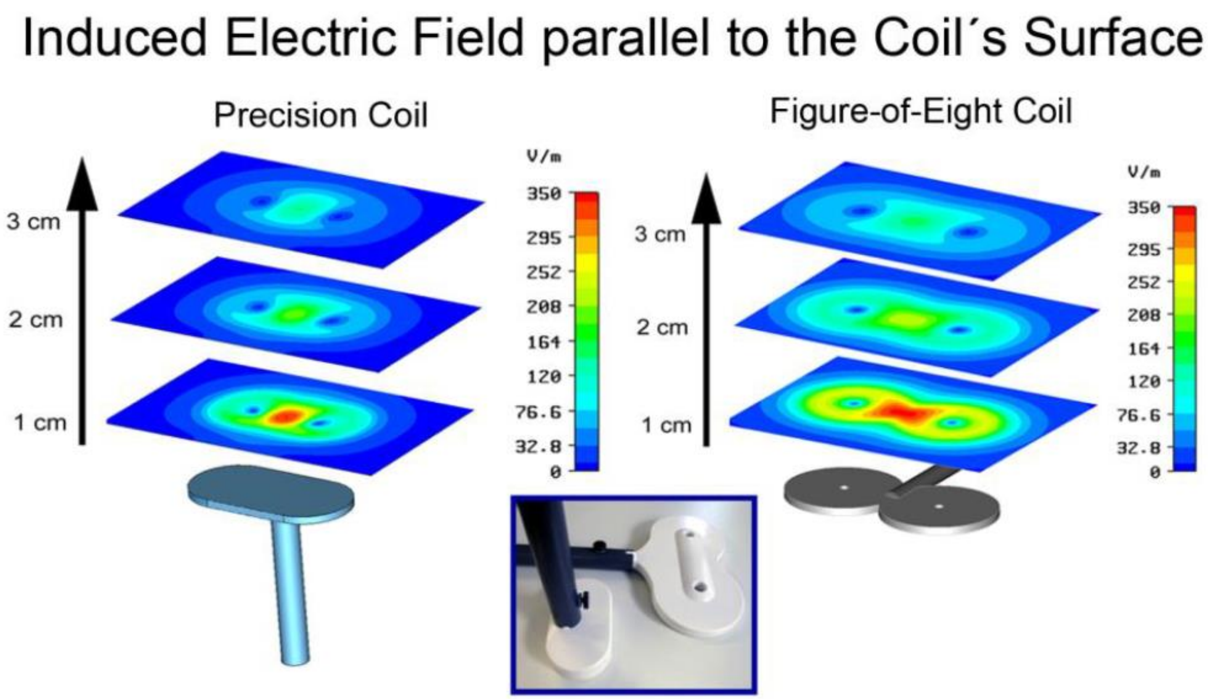
Depth of Stimulation





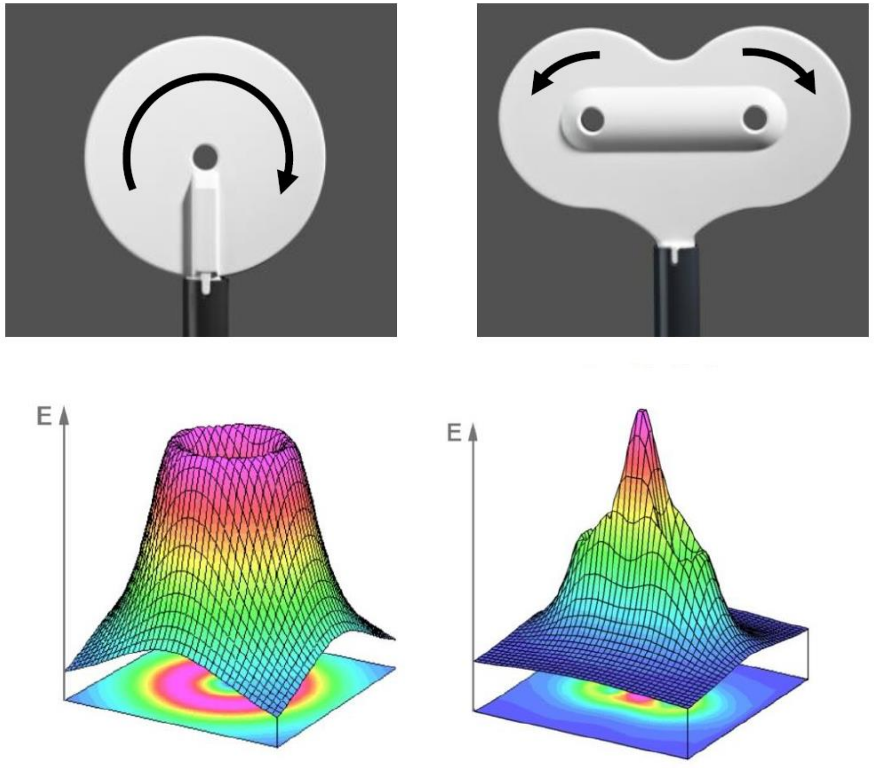
- Focal TMS has a depth of penetration of 2-3 (max.5) cm
- Deep TMS Stimulation only through network stimulation
- Special coil designs can increase depth of penetration (but also widespread)
- **It is not possible to focus in the depth!**





Small coil = focal

Big coil = deeper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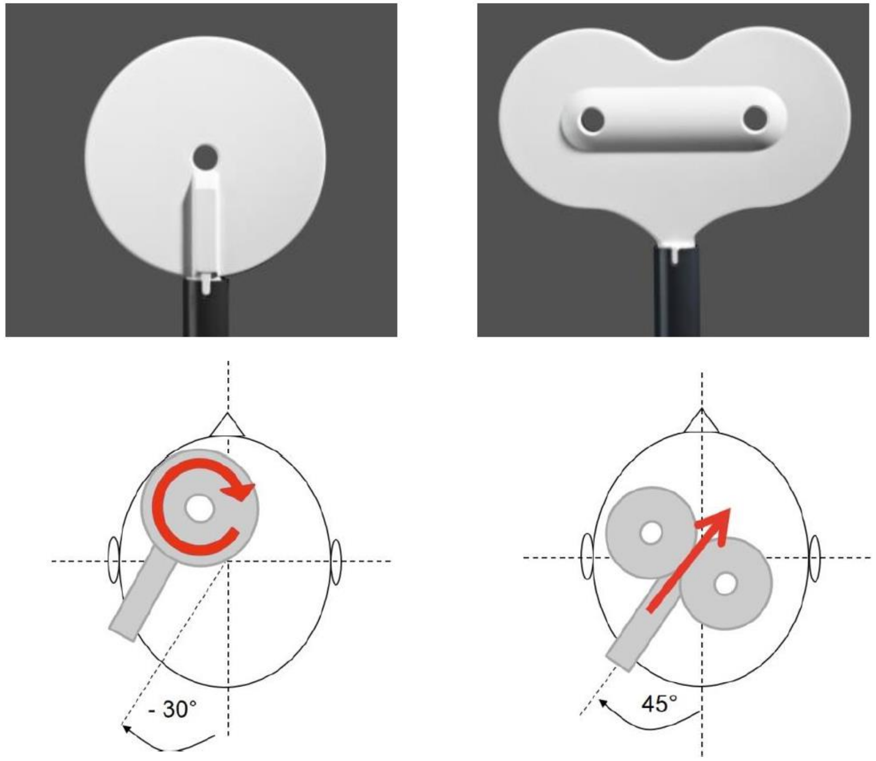
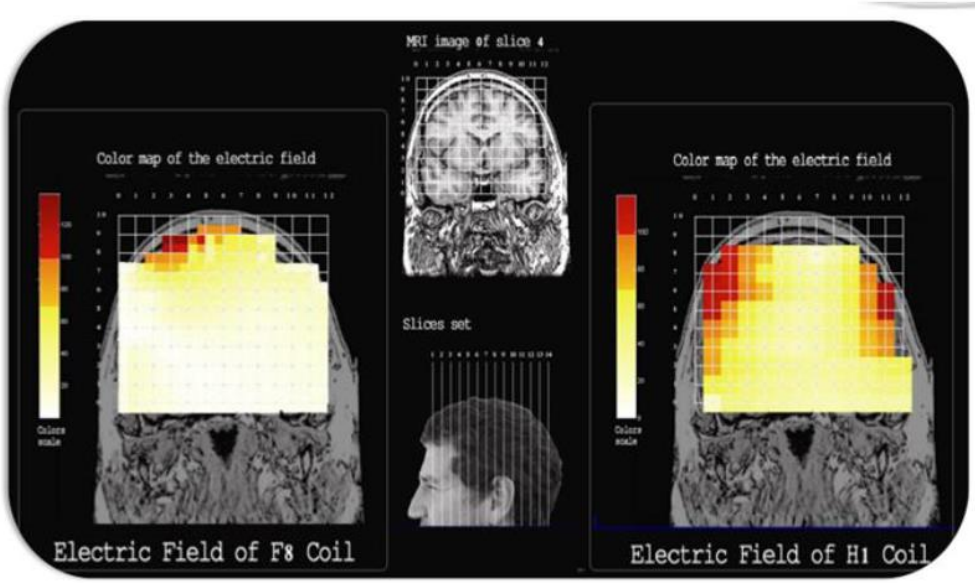
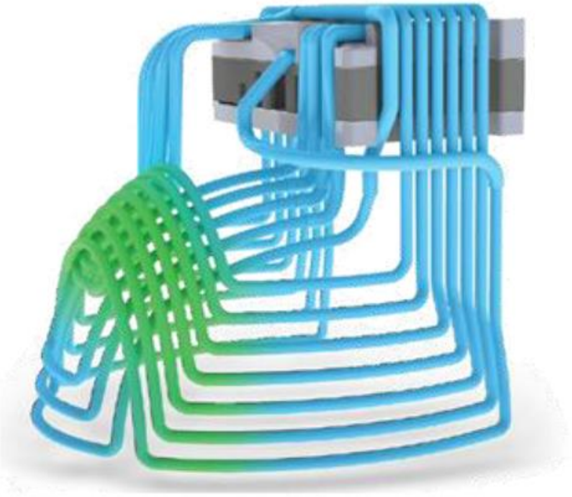

- 30°
45°

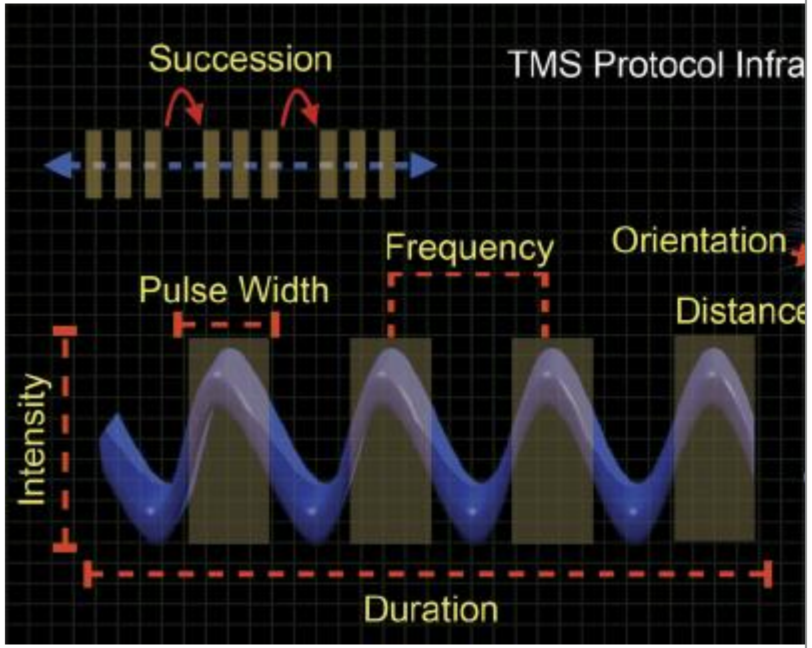
Depth of Stimulation

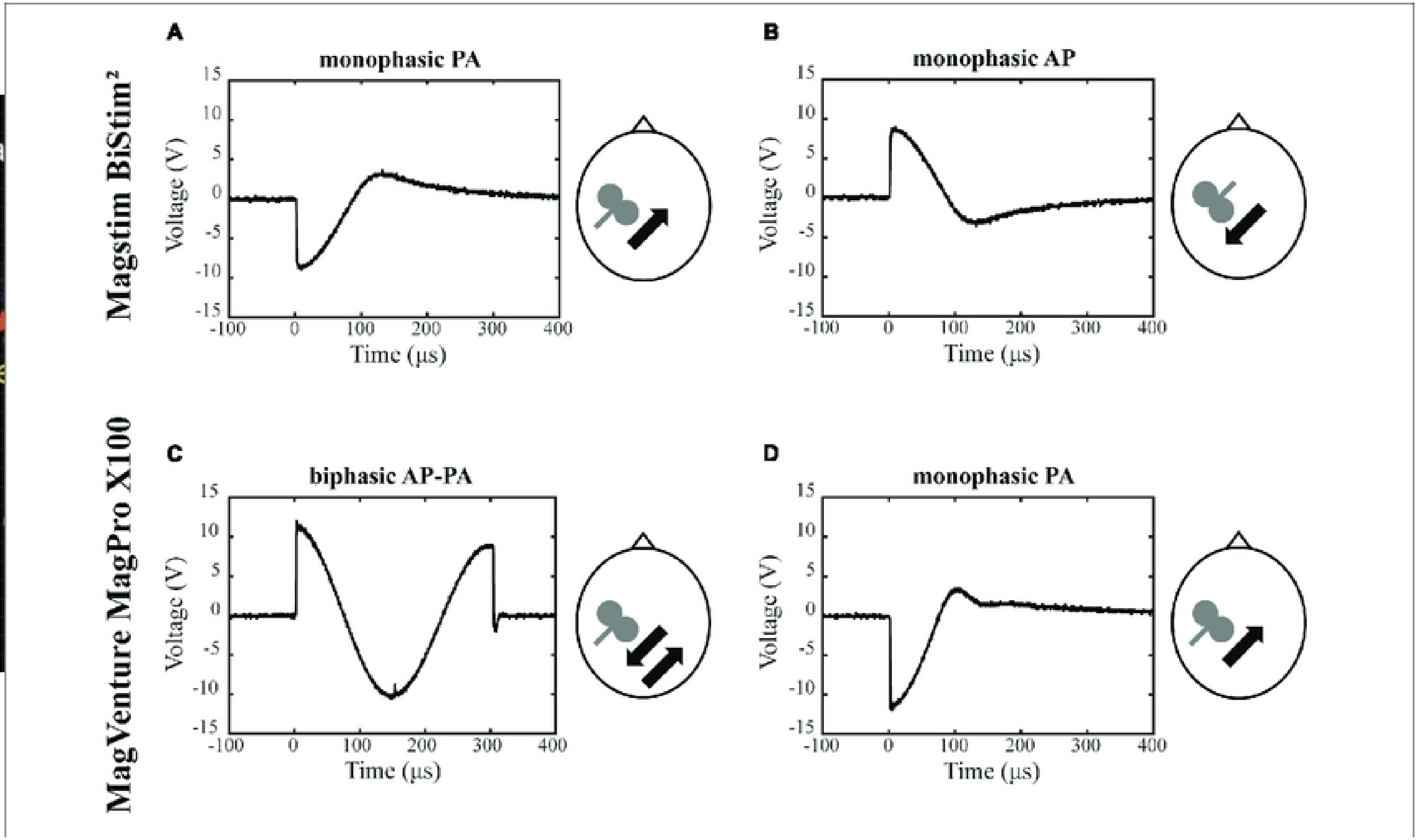




- A novel coil design (BrainWay) to stimulate deeper brain regions
- Deeper means up to 3(-5) cm **AND** more widespread (17cm^2)

Pulse Width


Succession
TMS Protocol Infra
Frequency
Orientation
Pulse Width
Distance
Intensity
Duration


Magstim BiStim²
A
monophasic PA
Voltage (V)
Time (µs)
B
monophasic AP
Voltage (V)
Time (µs)
MagVenture MagPro X100
C
biphasic AP-PA
Voltage (V)
Time (µs)
D
monophasic PA
Voltage (V)
Time (µs)

Contraindications

- Unwilling or unable to consent
- Heart pacemaker
- Brain pacemaker (Deep Brain Stimulation, DBS)*
- Intracerebral metal implants (electrodes, plates, clips, artificial cochlea implants or similar)*
- Indication of lower seizure threshold or a history of epileptic seizures *
- Pregnancy or lactation period #
- ** Exception: Centers with comprehensive clinical and scientific experience in applying the method and patient base*
- *# Recommendation only due to lack of studies*

Efficacy and Safety of TMS :

- Alternative for patients not responding on the first medication
- Meta Analysis of 29 randomised, double blind- and Sham-controlled studies with 1.371 patients (Berlim et al, Psy Med, vol. 44 (2), Jan 2014)
  - Response rate = 29,3%
  - Remission rate = 18,6%
- Save application if you follow the guidelines

Advantages of TMS compared to other treatments:

- Targeted modulation of prefrontal networks
- Non-invasive and well tolerated
- No systemic side effects and safe
- Suitable for long-term treatment

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Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Guidelines

Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research ☆

Simone Rossi [a,*], Mark Hallett [b], Paolo M. Rossini [c,d], Alvaro Pascual-Leone [e] and The Safety of TMS Consensus Group [1]

[a] Dipartimento di Neuroscienze, Sezione Neurologia, Università di Siena, Italy
[b] Human Motor Control Section, NINDS, NIH, Bethesda, USA
[c] Università Campus Biomedico, Roma, Italy
[d] Casa di Cura S. Raffaele, Cassino, Italy
[e] Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, USA

Safety Aspects:

Table 1
Potential side effects of TMS. Consensus has been reached for this table.

Side effect	Single-pulse TMS	Paired-pulse TMS	Low frequency rTMS	High frequency rTMS	Theta burst
Seizure induction	Rare	Not reported	Rare (usually protective effect)	Possible (1.4% crude risk estimate in epileptic patients; less than 1% in normals)	Possible (one seizure in a normal subject during cTBS) (see para 3.3.3)
Transient acute hypomania induction	No	No	Rare	Possible following left prefrontal stimulation	Not reported
Syncope	Possible as epiphenomenon (i.e., not related to direct brain effect)				Possible
Transient headache, local pain, neck pain, toothache, paresthesia	Possible [illegible]	Likely possible, but [illegible]	Frequent (see para. 3.3)	Frequent (see para. 3.3)	Possible
Transient hearing changes	[illegible]	[illegible]	Possible	Possible	Not reported
Transient cognitive/ neuropsychologial changes	[illegible]	[illegible]	Overall negligible (see Section 4.6)	Overall negligible (see Section 4.6)	Transient impairment of working memory
Burns from scalp electrodes	No	No	Not reported	Occasionally reported	Not reported, but likely possible
Induced currents in electrical circuits	Theoretically possible, but described malfunction only if TMS is delivered in close proximity with the electric device (pace-makers, brain stimulators, pumps, intracardiac lines, cochlear implants)				
Structural brain changes	Not reported	Nor reported	Inconsistent	Inconsistent	Not reported
Histotoxicity	No	No	Inconsistent	Inconsistent	Not reported
Other biological transient effects	Not reported	Not reported	Not reported	Transient hormone (TSH), and blood lactate levels changes	Not reported

Beware of:
relative frequency of side effects are increasing compared to SP-TMS(!)

Side effect	Single-pulse TMS	Paired-pulse TMS	Low frequency rTMS	High frequency rTMS	Theta burst
Seizure induction	Occasional	Not reported	Occasional (usually protective effect)	Possible (1.4% crude risk estimate in epileptic patients; less than 1% in normals)	Not reported
Transient acute hypomania induction	No	No	Rare	Possible following left prefrontal stimulation	Not known
Syncope	Possible as epiphenomenon (i.e, not related to direct brain effect)				Not reported
Transient headache, local pain, neck pain, toothache, paresthesia	Possible	Likely possible, but not reported/addressed	Frequent (see para. 3.3)	Frequent (see para. 3.3)	Not reported
Transient hearing changes or tinnitus	Possible	Likely possible, but not reported	Possible	Possible (avoid rTMS in cochlear implants)	Not known
Transient cognitive/ neuropsychological changes	Not reported	No reported	Overall negligible (see para. 3.5)	Overall negligible (see para. 3.5)	Not known
Burns from scalp electrodes	No	No	Not reported	Occasionally reported	Not known, but likely possible
Induced currents in electrical circuits	Theoretically possible, but described malfunction only if TMS is delivered in close proximity with the electric device (pace-makers, brain stimulators, pumps, intacardiac lines)				
Structural brain changes	Not reported	Nor reported	Inconsistent	Inconsistent	Not known
Histoxicity	No	No	Inconsistent	Inconsistent	Not known
Other biological transient effects	Not reported	Not reported	Not reported	Transient hormone changes (Prolactine, TSH)	Not known

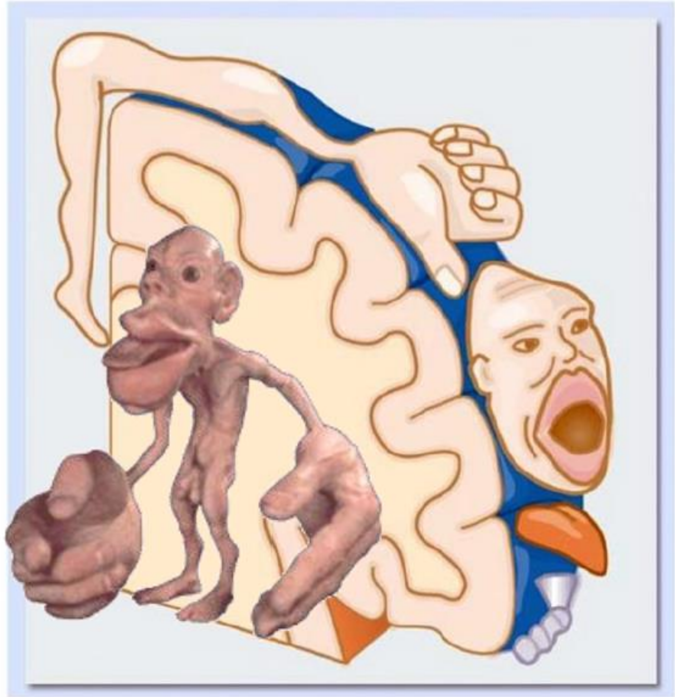
Rossi., Hallett, Rossini, & Pascual-Leone (2009)

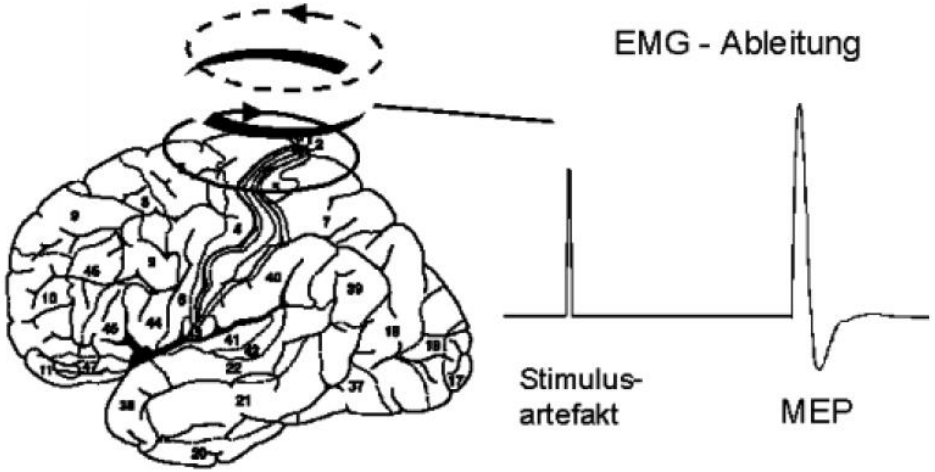
Safety Aspects:

- Induction of epileptic seizure (focal or generalized) - significant risk of TMS
- When considering the safety criteria → **Risk very low**
- Particular caution:
  - Anamnesis
  - Neuro-active medication
  - Sleep deprivation, alcohol withdrawal / dependency
  - Cerebral pathologies (tumors, cysts, infarct scars)

Basic rule: risk increases with growing stimulation **intensity**, growing stimulation **length**, growing stimulation **frequency** and **reduced break** periods

Motor Threshold



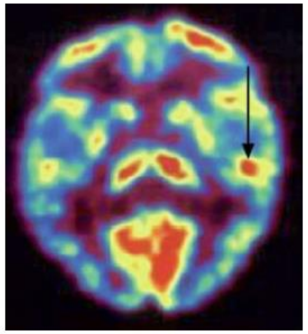


http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/bilder/inhalt/forschung/tms/tms.gif

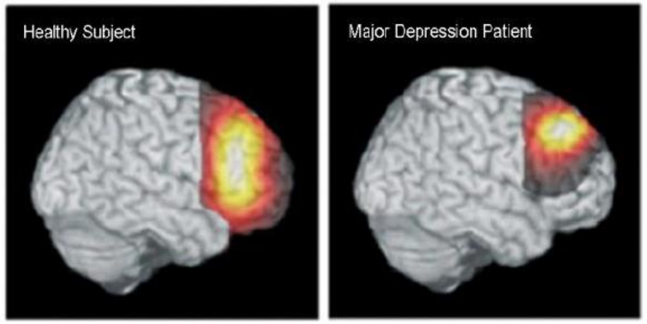
The motor threshold is defined as that intensity, which with a probability of 50% evokes a MEP (motor evoked potential)

Why must MT determined accurately?

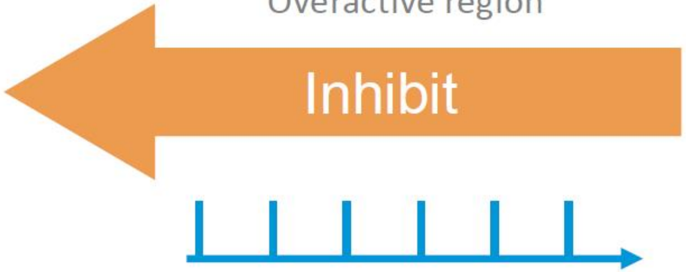
- Examples:



PET Tinnitus
Overactive region



PET Depression – underactive region



1 Hz Pulse at
90 % motor threshold

10 Hz Trains at
120 % motor threshold

De Riddler, et al: Transcranial Magnetic Stimulation for Tinnitus: Influence of Tinnitus Duration on Stimulation Parameter Choice and Maximal Tinnitus Suppression

O'Reardon et al: Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial

Numerical example

- Lets assume a patient's actual motor threshold (MT) is: 40 %
- O'Reardon Protocol uses trains at 10 Hz for 4 seconds with 120 % MT
  - Goal Intensity 48 %
- Assumption: Determined MT at 44 % → resulting intensity of 53 %
- Assumption: Determined MT at 48 % → resulting intensity of 58 %

Maximum safe duration (s) of single trains of rTMS based on the NINDS experience

Frequency (Hz)	Intensity (% of MEP threshold)												
	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

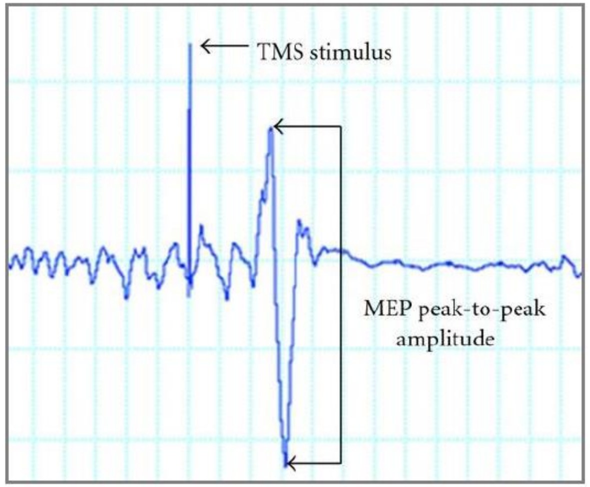
Wassermann (1996): Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation

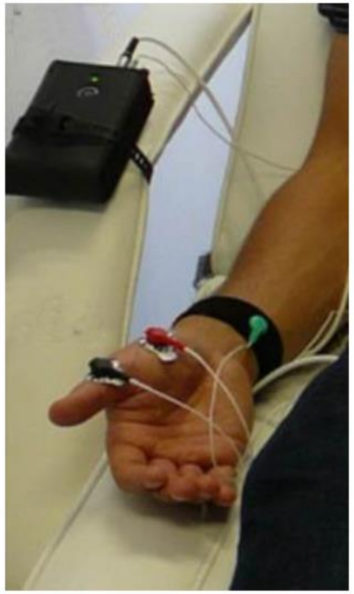
MT determination: Visual or by EMG

- Studies have shown that visually determined MEPs significantly higher and thus inaccurate

  Westin, et al (2014); Clin Neurophysiol. 2014 Jan;125(1); Determination of motor threshold using visual observation overestimates transcranial magnetic stimulation dosage: safety implications.

- EMG with a 50mV threshold should be used





Rossini & Rothwell

I Start	II Increase	III Finish
- 10 low intensity pulses, count MEPs 3 out of 10	- Increase intensity, emit 10 pulses, count MEPs Example: 4 out of 10	- Repeat II until at least 5 MEPs out of 10 are determined Example: 6 out of 10

- Relative Frequency methods are mathematically disadvantageous
- In fact, it is highly likely that an incorrect MT will be determined

➢ State of the Art because simple and (fairly) fast, but very inaccurate…

Adaptive Methods

- Determines next intensity dependent upon ALL previously measured data

- Primarily by maximizing a log-likelihood function

$$p(m,\mu,\sigma) = \frac{1}{\sigma\sqrt{2\pi}}\int_{-\infty}^{m} e^{-\frac{(\tau-\mu)^2}{2\sigma^2}}\,d\tau$$

$$L(\mu,\sigma) = \sum_{i=1}^{j} \ln(p(ms_i,\mu,\sigma)) + \sum_{i=1}^{k} \ln(1 - p(mf_i,\mu,\sigma))$$

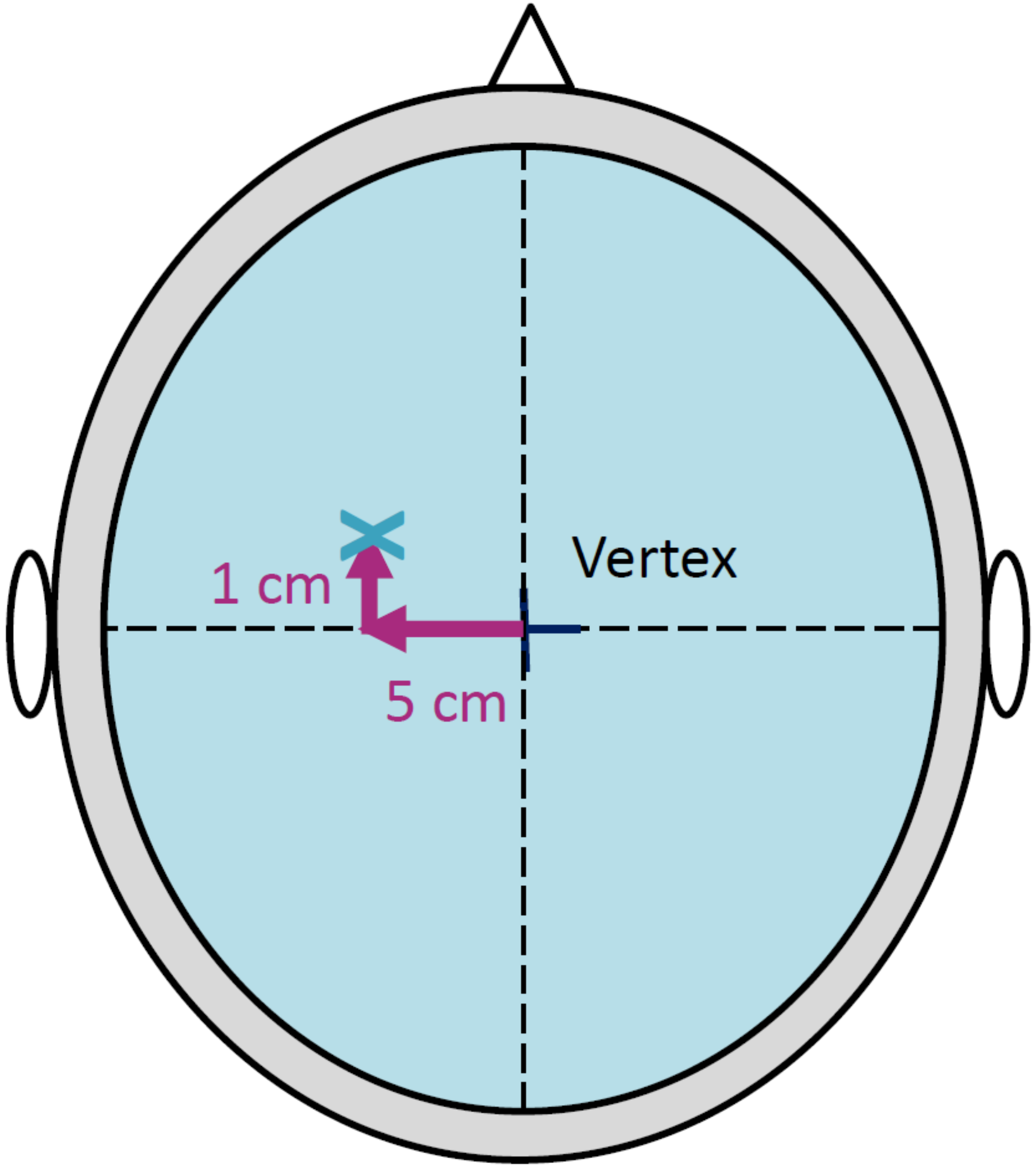
➢ Mathematically quite mighty and hence also very accurate and fast

Awiszus (2003): TMS and threshold hunting

Qi et at (2011): Fast estimation of transcranial magnetic stimulation motor threshold

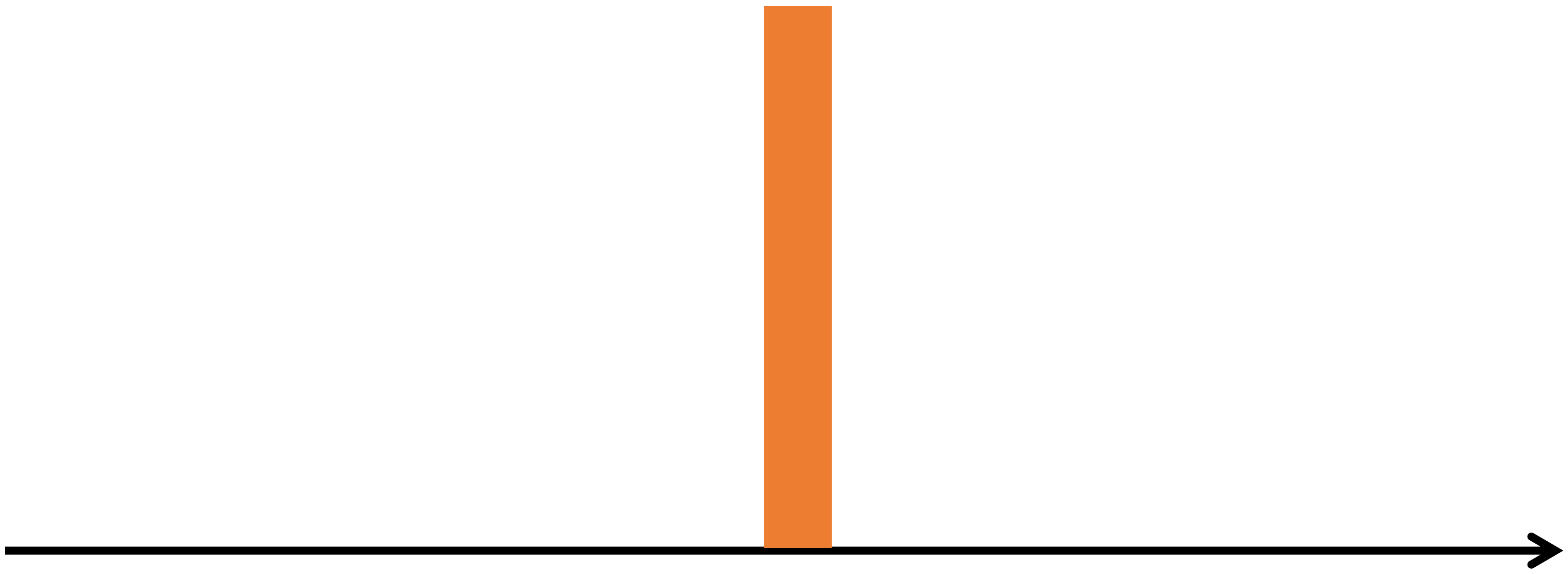
Step 4: Determine starting point for hand area

- Mark starting point for localization 5 cm lateral and 1 cm anterior from Vertex

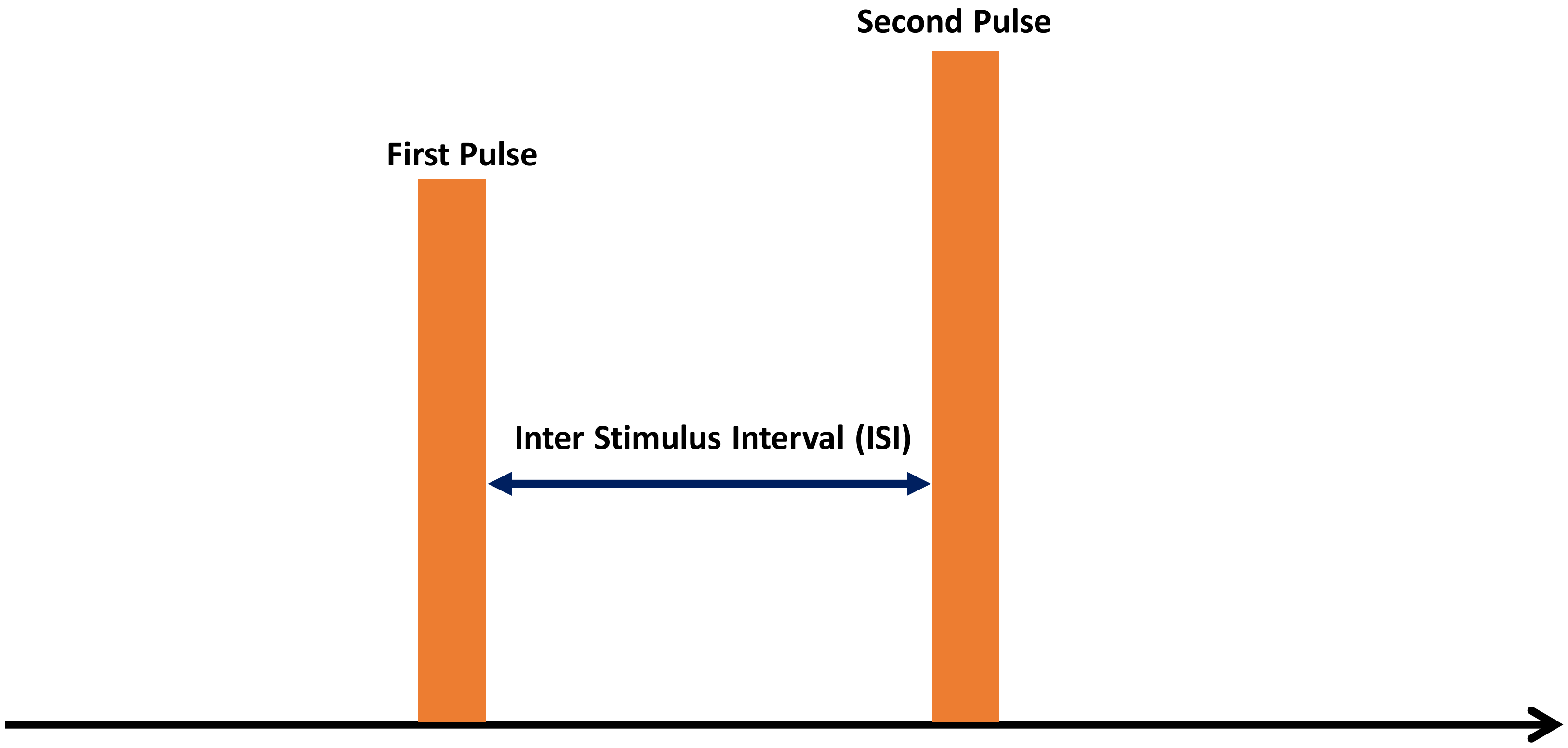


Stimulation Types

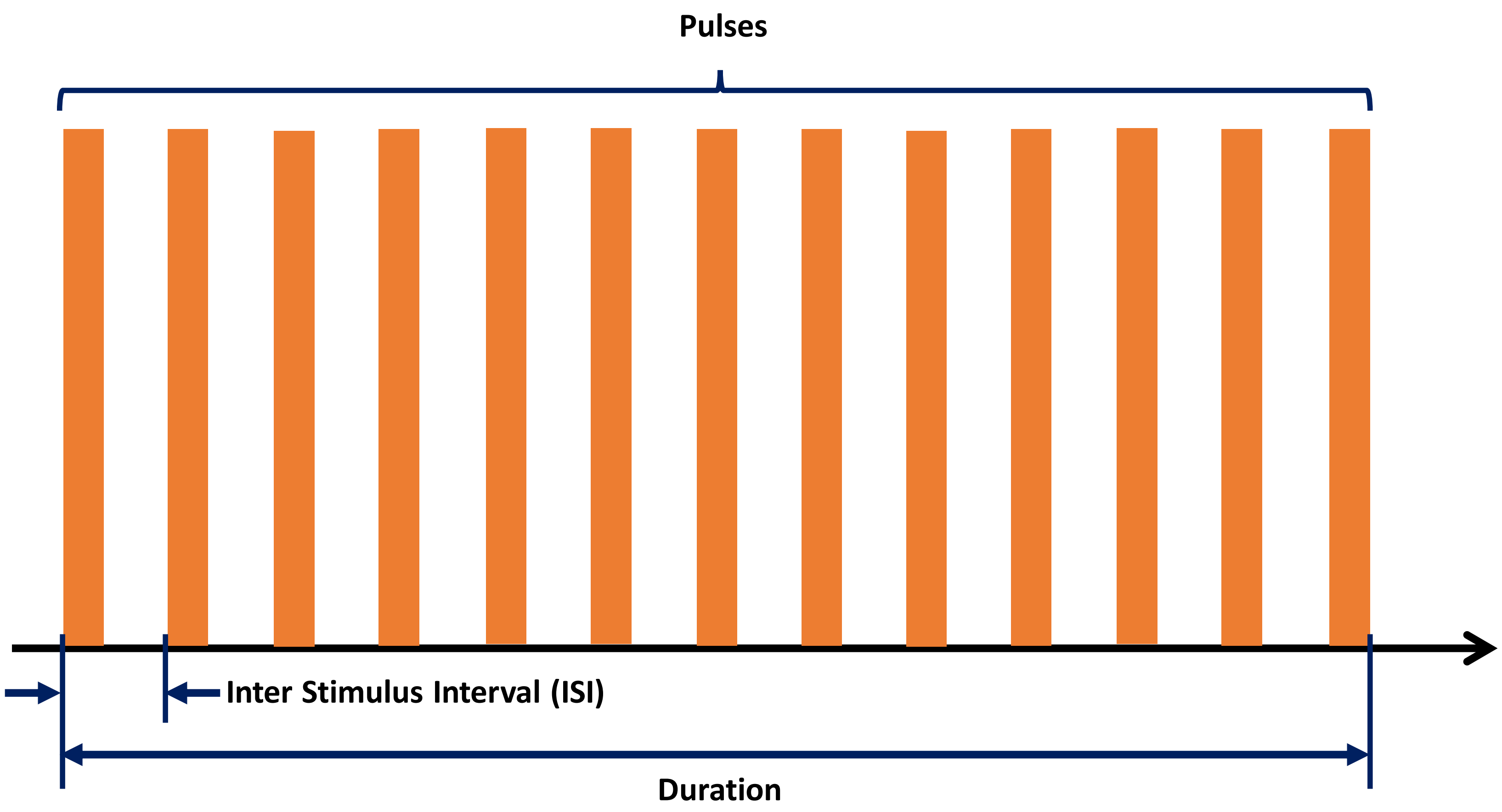
Single Pulse



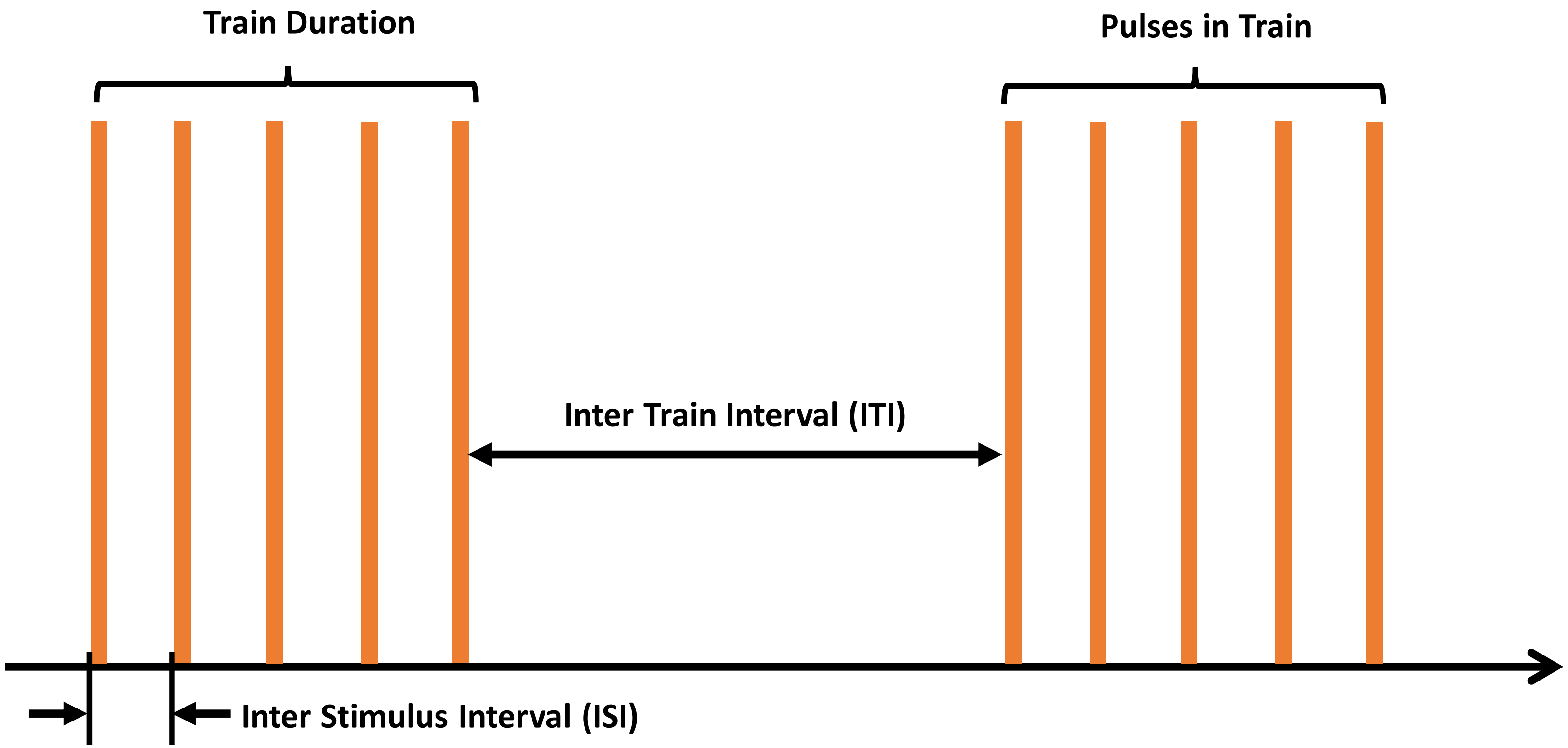
Paired-Pulse



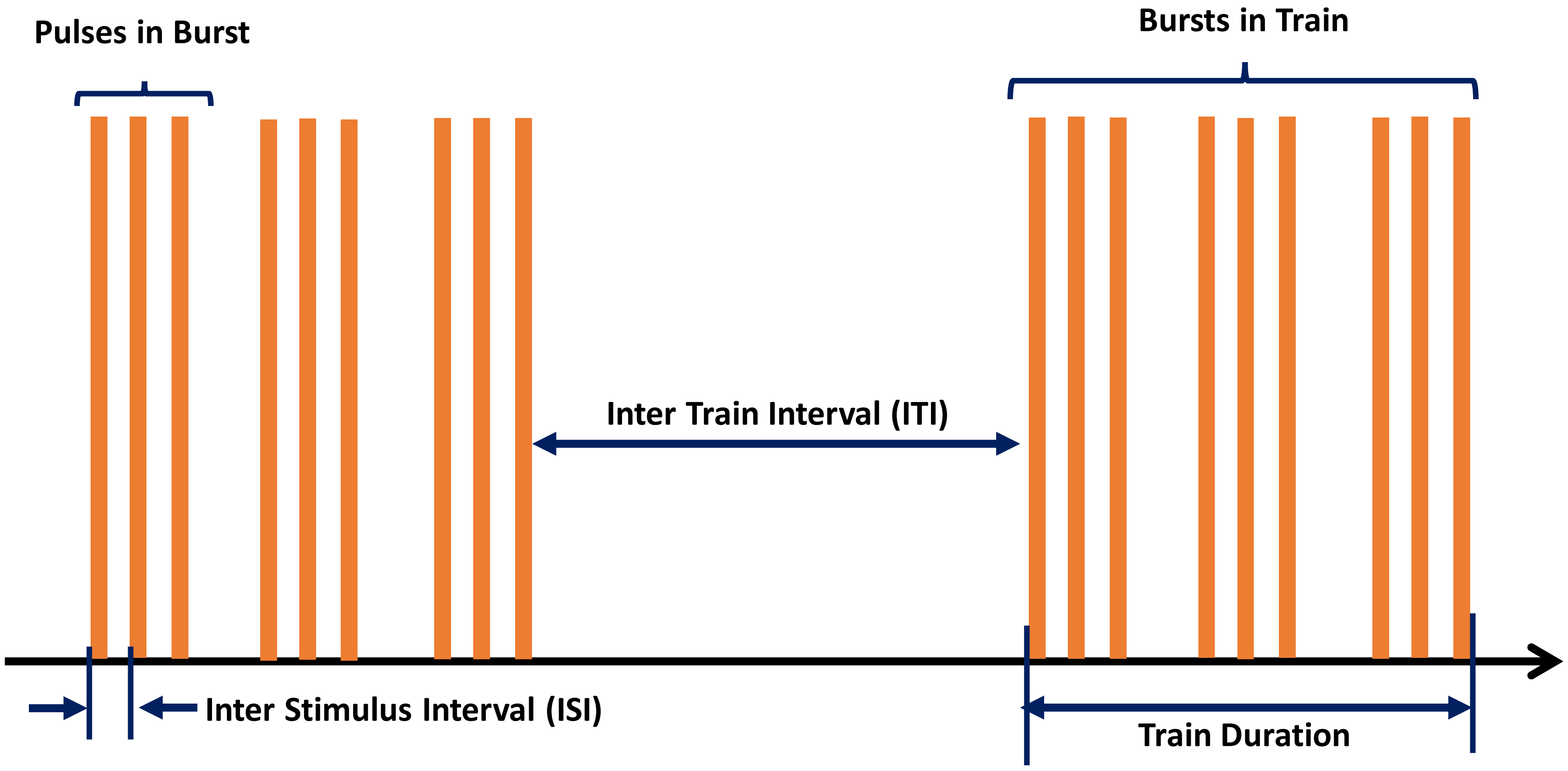
Repeated Pulse



Patterned Pulse (Train)

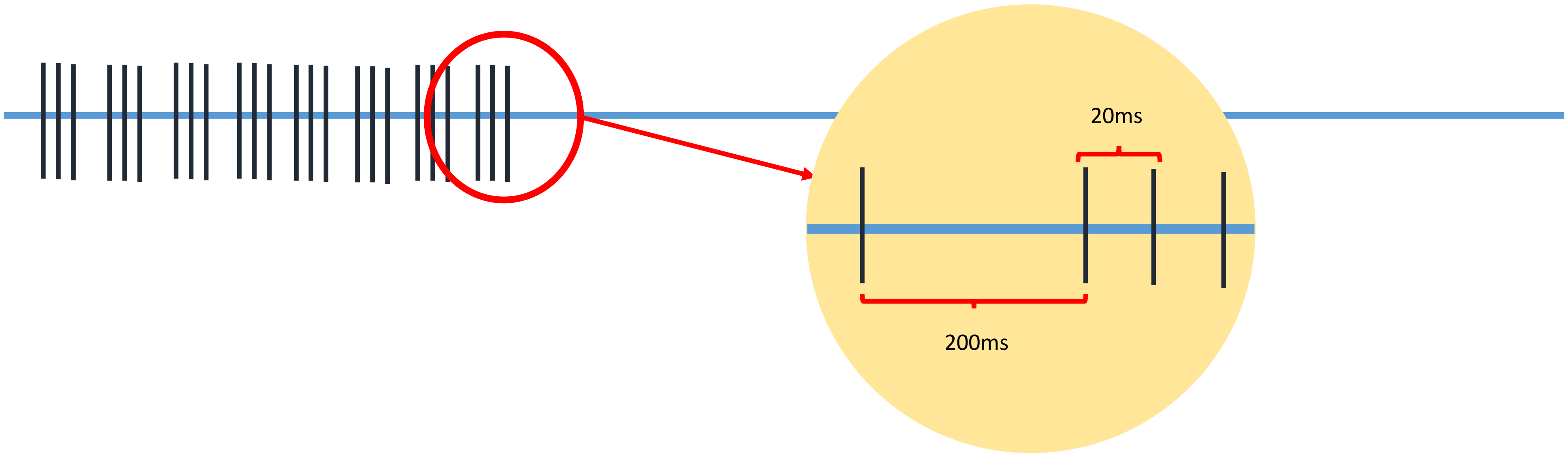


Theta burst


Pulses in Burst
Bursts in Train
Inter Train Interval (ITI)
Inter Stimulus Interval (ISI)
Train Duration

cTBS (Continuous Theta Burst Stimulation)

- 3 Pulse, at 50 Hz (Inter Burst Interval=20ms)
- with 5Hz carrying Wave (Inter Train Interval=200ms)
- For 20 or 40S (40s=600 Pulses)
- Intensity=80% MT

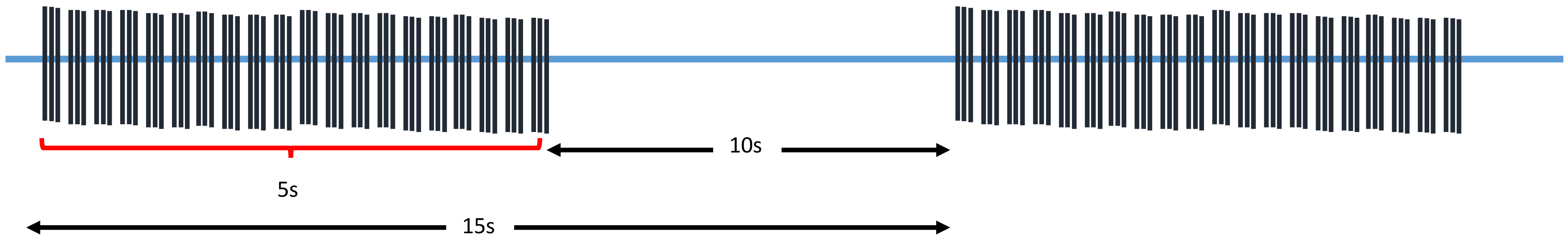


iTBS (Intermittent Theta Burst Stimulation)

- 3 Pulse, at 50 Hz (Inter Burst Interval=20ms)
- with 5Hz carrying Wave (Inter Train Interval=200ms)
- a 2s train of TBS is repeated every 10s for a total of 190 s (600 pulses)
- Intensity=80% MT

imTBS (intermediate theta burst stimulation paradigm)

- 3 Pulse, at 50 Hz (Inter Burst Interval=20ms)
- with 5Hz carrying Wave (Inter Train Interval=200ms)
- a 5s train of TBS is repeated every 15s for a total of 110s (600 pulses)
- Intensity=80% MT



Future Indications

- Addiction / craving
- Alzheimer’s disease
- Auditory hallucinations
- Epilepsy
- Movement disorders
- Obsessive compulsive disorder (OCD)
- Parkinson‘s disease
- …
- *Degrees of evidence and efficacy vary strongly between these indications!*

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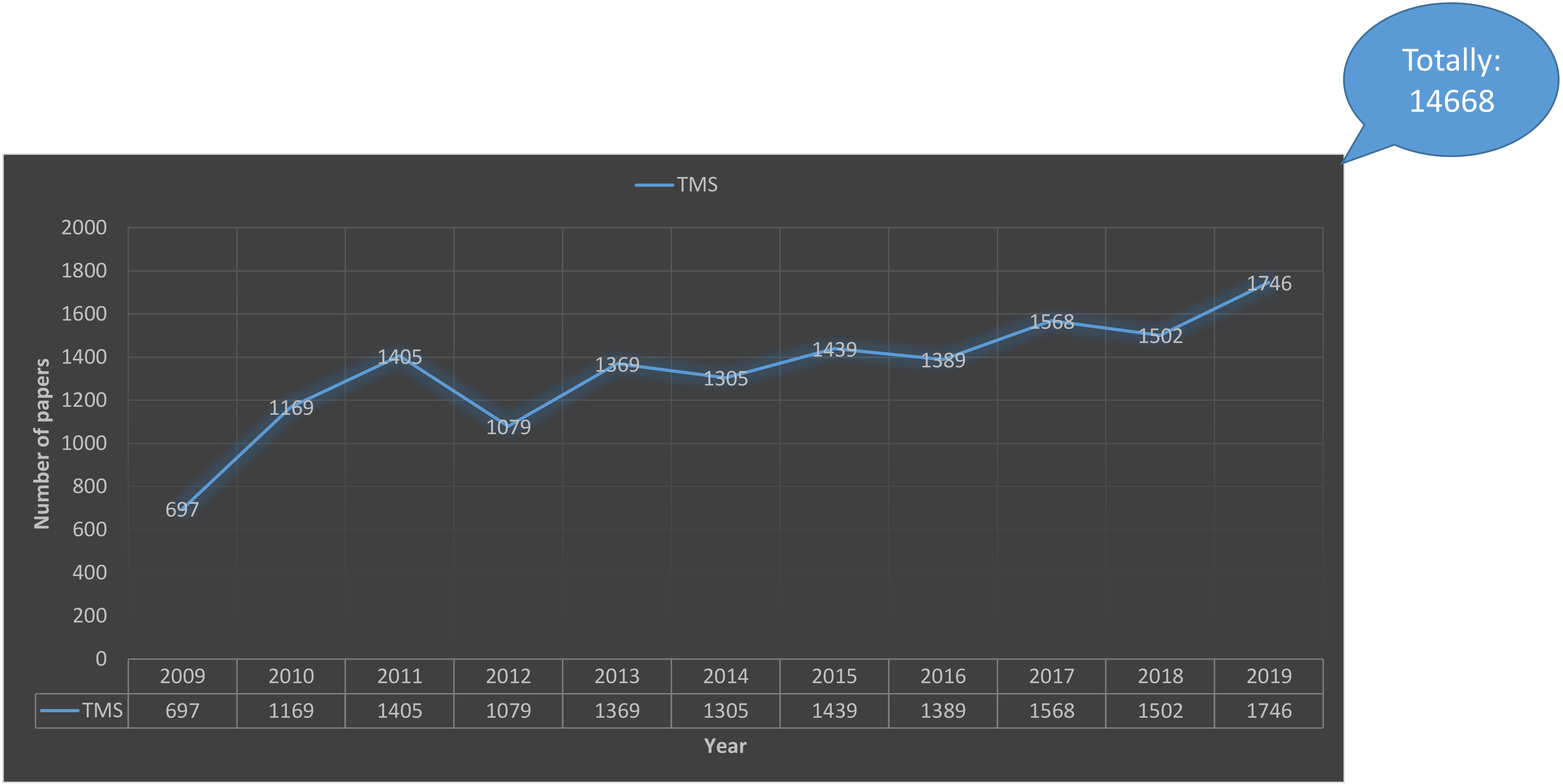
ELSEVIER

Guidelines

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)

Jean-Pascal Lefaucheur [a,b,*], Nathalie André-Obadia [c,d], Andrea Antal [e], Samar S. Ayache [a,b], Chris Baeken [f,g], David H. Benninger [h], Roberto M. Cantello [i], Massimo Cincotta [j], Mamede de Carvalho [k], Dirk De Ridder [l,m], Hervé Devanne [n,o], Vincenzo Di Lazzaro [p], Saša R. Filipović [q], Friedhelm C. Hummel [r], Satu K. Jääskeläinen [s], Vasilios K. Kimiskidis [t], Giacomo Koch [u], Berthold Langguth [v], Thomas Nyffeler [w], Antonio Oliviero [x], Frank Padberg [y], Emmanuel Poulet [z,aa], Simone Rossi [ab], Paolo Maria Rossini [ac,ad], John C. Rothwell [ae], Carlos Schönfeldt-Lecuona [af], Hartwig R. Siebner [ag,ah], Christina W. Slotema [ai], Charlotte J. Stagg [aj], Josep Valls-Sole [ak], Ulf Ziemann [al], Walter Paulus [e,1], Luis Garcia-Larrea [d,am,1]



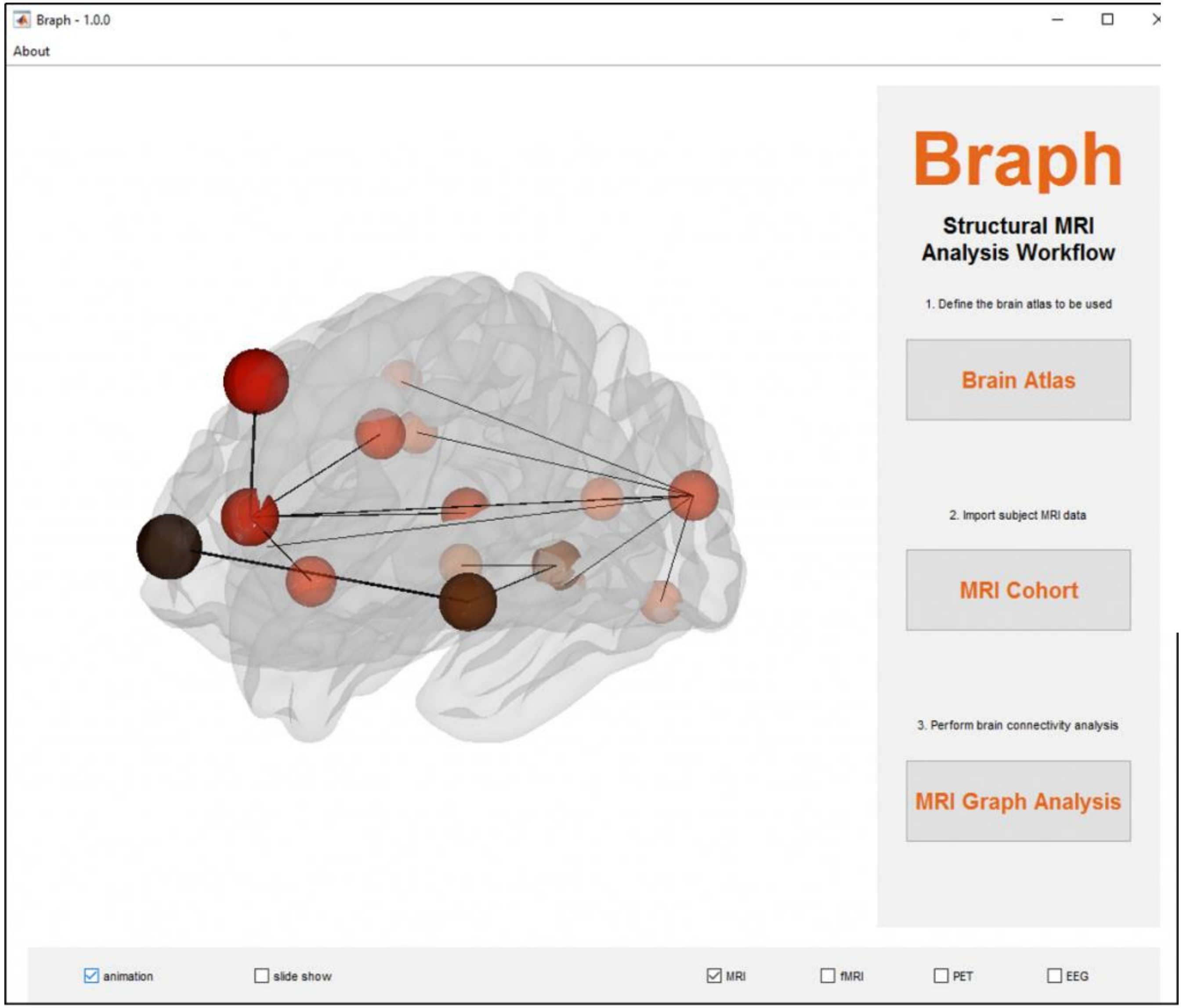
Totally: 14668
TMS
Number of papers
2000
1800
1600
1400
1200
1000
800
600
400
200
0
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
TMS 697 1169 1405 1079 1369 1305 1439 1389 1568 1502 1746
Year

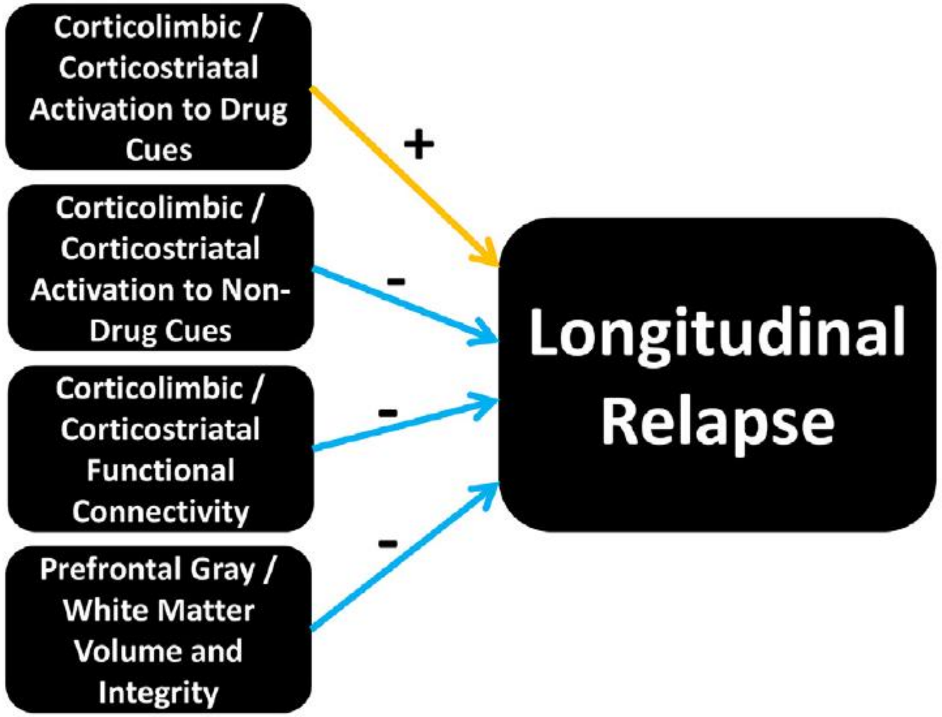
TABLE 1 | The top 20 journals that published articles on rTMS research.

Rank	Journal title	Count	IF 2018	Citations WoS	Citations per paper	Country
1	*Brain Stimulation*	199	6.919	4,566	22.94	USA
2	*PLoS One*	89	2.776	1,269	14.26	USA
3	*Clinical Neurophysiology*	66	3.675	4,000	60.61	Ireland
4	*Neuropsychologia*	61	2.872	1,015	16.64	England
5	*Frontiers in Human Neuroscience*	56	2.870	986	17.61	Switzerland
6	*Neuroscience Letters*	51	2.173	542	10.63	Netherlands
7	*Restorative Neurology and Neuroscience*	50	1.839	761	15.22	Netherlands
8	*Journal of Ect*	49	2.280	492	10.04	USA
9	*Journal of Affective Disorders*	47	4.084	799	17.00	Netherlands
10	*Cerebral Cortex*	44	5.437	1,762	40.05	USA
11	*Neuroimage*	44	5.812	1,157	26.3	USA
12	*Journal of Neuroscience*	42	6.074	2,256	53.71	USA
13	*Psychiatry Research*	36	2.208	507	14.08	Netherlands
14	*European Journal of Neuroscience*	35	2.784	671	19.17	England
15	*Cortex*	30	4.275	685	22.83	Italy
16	*Experimental Brain Research*	30	1.878	791	26.37	Germany
17	*Frontiers in Neuroscience*	25	3.648	92	3.68	Switzerland
18	*Scientific Reports*	25	4.011	82	3.28	England
19	*Human Brain Mapping*	24	4.554	620	25.83	USA
20	*Journal of Cognitive Neuroscience*	24	3.029	556	23.17	USA

IF, impact factor; WoS, Web of Science.

Biomarker Based TMS

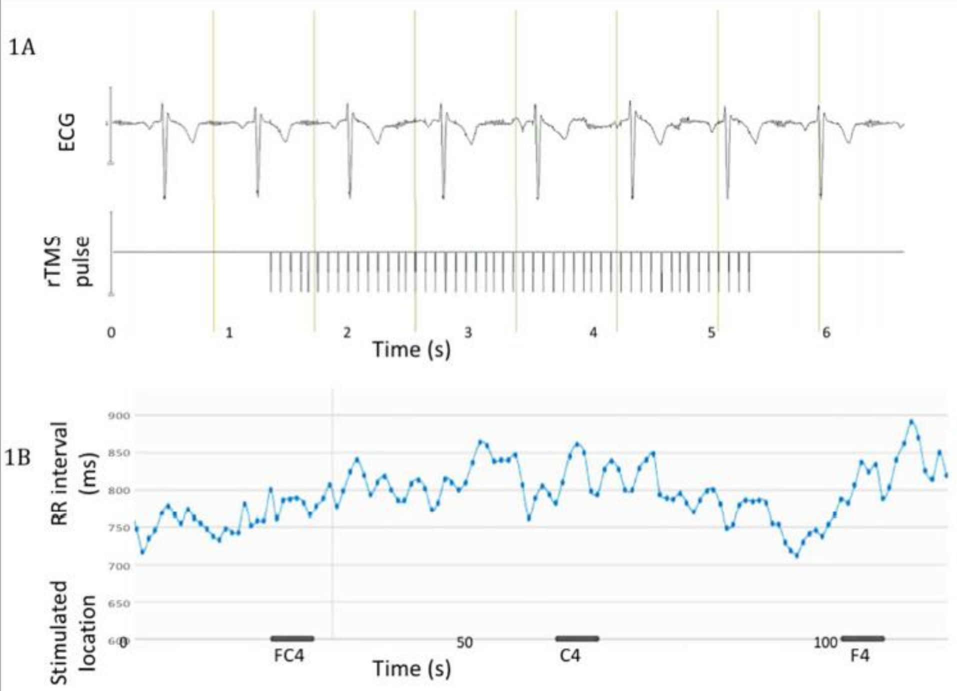


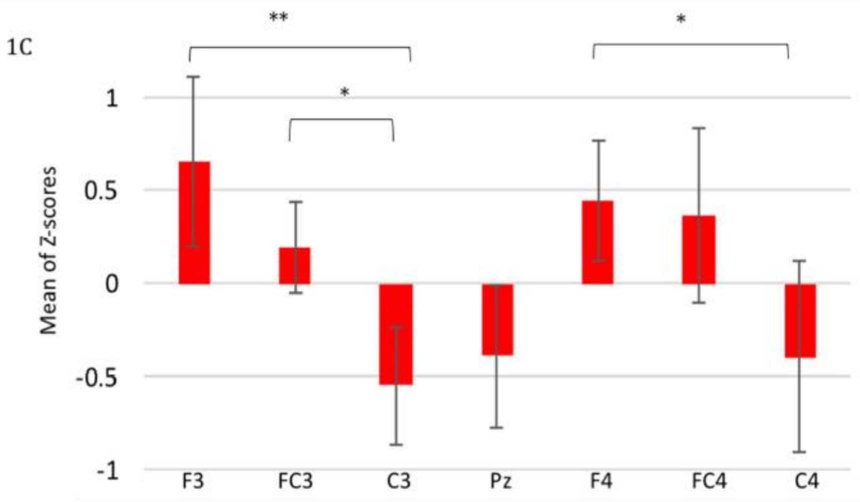


- Alpha peak, Alpha Asymmetry
- Hub Assessment

Neuro-Cardiac-Guided TMS (NCG-TMS)

Increased HRV= Individualized location for stimulation





1D

F3	FC3	C3	F4	FC4	C4
8/10	2/10	0/10	6/10	4/10	0/10
80%	20%	0%	60%	40%	0%

Transcranial Magnetic Stimulation (TMS)

Biomarker-Informed
EEG+HRV

Online TMS

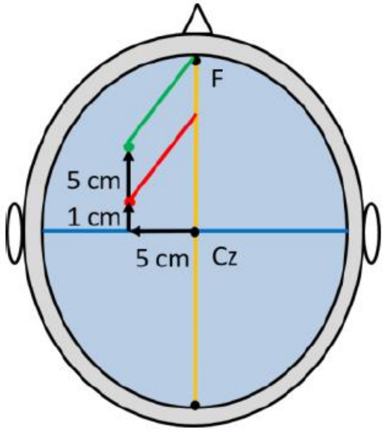
Stim Pattern

- rTMS
- Theta Burst
- Pulse Width

Location

- LDLPFC
- RDLPFC
- Insula
- Individual DLPFC

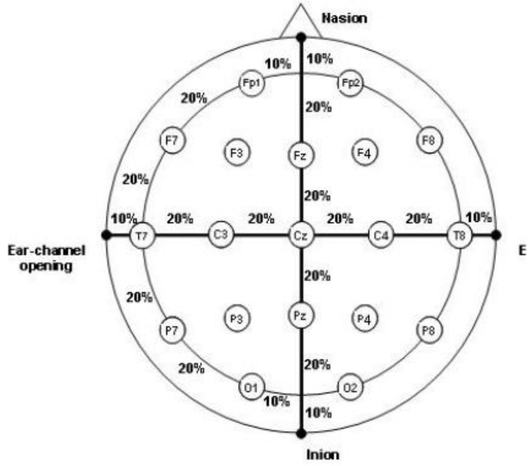
TMS cap and e.g. 5cm rule



+ Inexpensive
+ Simple rules

- No exact reproducibility possible

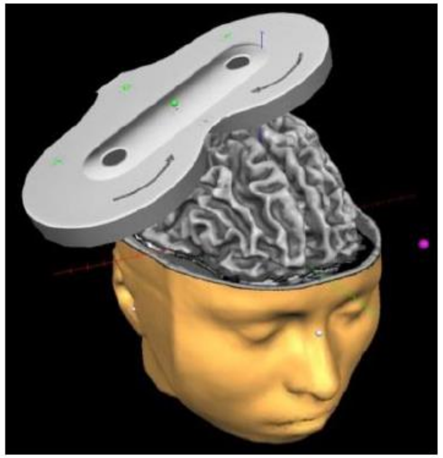
EEG-10-20-System



+ easy to use
+ medical product

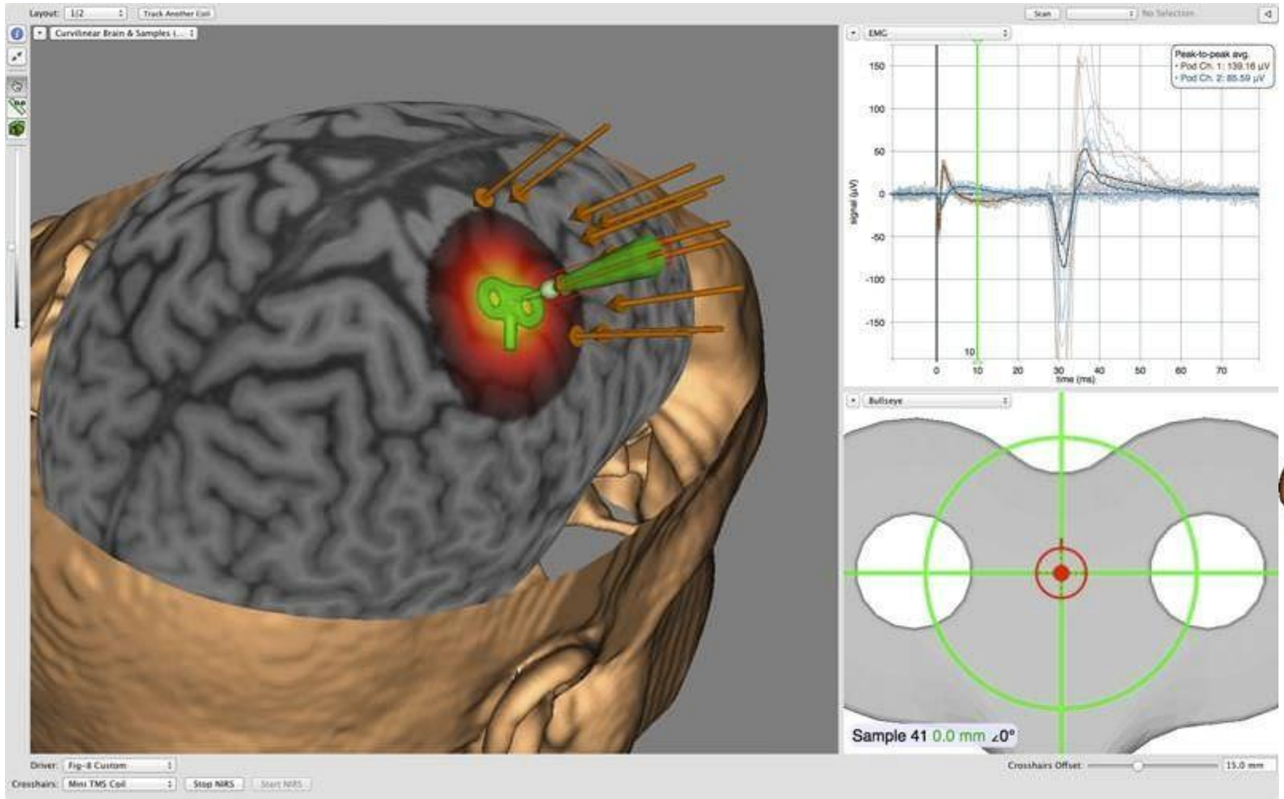
- not cheap
- No exact reproducibility possible

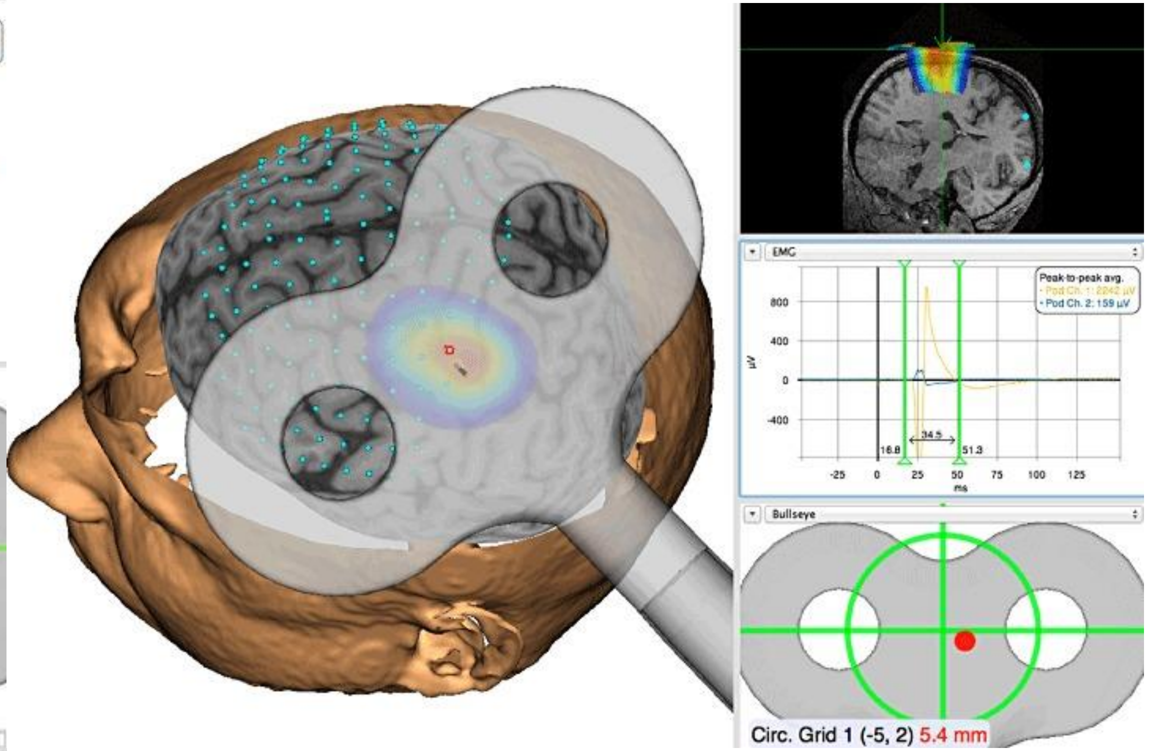
Neuronavigation



+ only option for exact reproducibility
+ extensive reporting

- individual MRI-Scans are necessary
- Acquisition cost


Layout:
Track Another Coil
Scan
EMG
Peak-to-peak avg.
Bullseye
Sample 41 0.0 mm ∠0°
Driver:
Crosshairs:
Crosshairs Offset


EMG
Peak-to-peak avg.
Pod Ch. 1: 2242 µV
Pod Ch. 2: 159 µV
Bullseye
Circ. Grid 1 (-5, 2) 5.4 mm