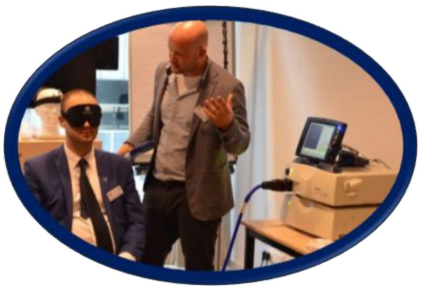
CLINICAL TMS CERTIFICATION COURSE



Dear TMS Course Participants, dear colleagues

The International Clinical TMS Certification Course supports a new **important initiative** from internationally renowned researchers and clinicians from Maastricht University and other prestigious academic and clinical institutes aiming to **bridge the gap between scientific research and clinical practice** in the field of noninvasive brain stimulation.

On our **LinkedIn page**, we now provide free access to relevant scientific publications from the international brain stimulation literature and inform about new developments on clinical efficacy, safety, and application expansion of TMS and TES.

Our aim is to **facilitate the free and open access to latest scientific evidence** in order to keep all clinical practitioners informed and connected to the most recent scientific and clinical developments in the field of noninvasive brain stimulation.

Follow the International Clinical TMS Certification Courses on LinkedIn to benefit from this free access to important publications and new scientific developments in the field of TMS and TES.

Here is the plain link to copy and paste in your browser:
https://www.linkedin.com/company/international-clinical-tms-certification-course/

I hope to welcome many of you again in one of our future Clinical TMS Certification Courses. We recommend updating your knowledge and skills every 3 years in order to stay up to date with this dynamically developing field.

Best wishes,

Prof. Dr. Alexander Sack
Course Director
Maastricht University

The Academy of Brain Stimulation
Education and Certification

Stay in touch and stay connected

TMS is dynamically developing. Our TMS Certification Courses are continuously updated. We recommend following our courses again in the future!

www.linkedin.com/company/international-clinical-tms-certification-course/

You can now become full member of the Academy of Brain Stimulation at
www.brainstimulation-academy.com
(access to advanced lectures, evidence-based protocols, and much more)

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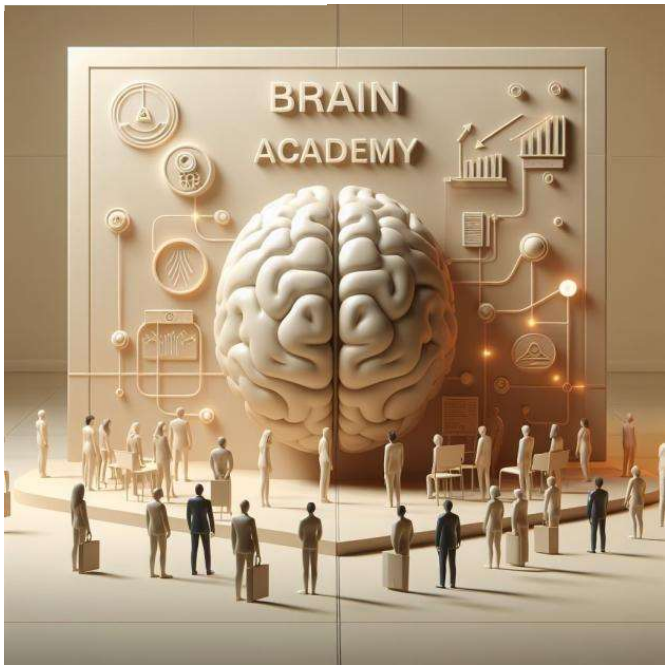

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www.brainstimulation-academy.com

Membership Benefits

- **Receive the prestigious Academy Member Certificate**, issued in your name
- **Benefit from priority status (seat guaranteed) and discounts** when registering for our (online) TMS Certification Program
- **Connect directly with TMS experts** from the Academy to ask questions, exchange insights, and gain valuable guidance
- **Access to updated clinical protocols** for rTMS therapies in psychiatry, neurology, and rehabilitation (FDA, CE, off-label)
- **Enjoy 24-hour access** to an updated online library of video recordings from leading scientists and clinical TMS practitioners
- **Learn about a variety of brain stimulation solutions** suited for clinical applications
- **Become an active member** of a global community of TMS professionals, sharing insights and supporting each other in using TMS to help patients

The Academy of Brain Stimulation
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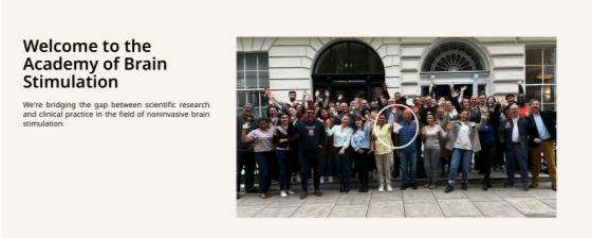

Join the **Academy of Brain Stimulation** as a full member

Discount code = UHCUBA8Z

Teaching Staff

Prof. Dr. Alexander T. Sack is full Professor of Brain Stimulation at Maastricht University and the Maastricht University Medical Center (MUMC+), and Director of the Center for Integrative Neuroscience. Prof. Dr Sack has more than twenty years of experience with TMS and has published >200 articles on TMS in high-ranking international peer-reviewed journals. He is co-founder and board member of the Dutch-Flemish Society for Brain Stimulation. Prof. Sack and colleagues are also advising national health policy makers and insurances, negotiating terms for reimbursement of TMS treatment costs, and providing quality standards for the accreditation of TMS practitioners.

Prof. Dr. Teresa Schuhmann is Professor of Clinical Applications of Non-invasive Brain Stimulation and a Neuropsychologist with 20 years of experience with TMS. Her clinical specialisation includes TMS/TCS in neurorehabilitation, especially for the recovery of cognitive deficits following stroke/CVA or traumatic brain injury. As the head of clinical trials at the Maastricht Brain Stimulation Centre, she also is affiliated with the Maastricht University Medical Center (MUMC+).

Dr. Felix Duecker is Assistant Professor in cognitive neuroscience and expert in the methodology of TMS. His main research focus concerns the combination of TMS and neuroimaging, and TMS method improvement, including, e.g., the systematic investigation of TMS placebo effects following sham stimulation.

Dr. Tahnée Engelen is a cognitive neuroscientist whose research focuses on brain-body interactions and emotions. Her research employs various neuroimaging methods, including brain stimulation, and she has special interest in multi-modal approaches in which brain stimulation can be combined with other imaging methods.

Dr. Lukas Schilberg is a clinical scientist affiliated with Maastricht University. He is the founder and director of BrainStim, a private institute offering brain stimulation related education, consultancy, and clinical treatments. Dr. Schilberg has more than fifteen years of experience with brain stimulation research and clinical application of TMS. He has several years of teaching experience at university level and has published multiple articles in high-ranking international journals.

Fundamentals of TMS

Prof. Dr. Alexander Sack

The Academy of Brain Stimulation
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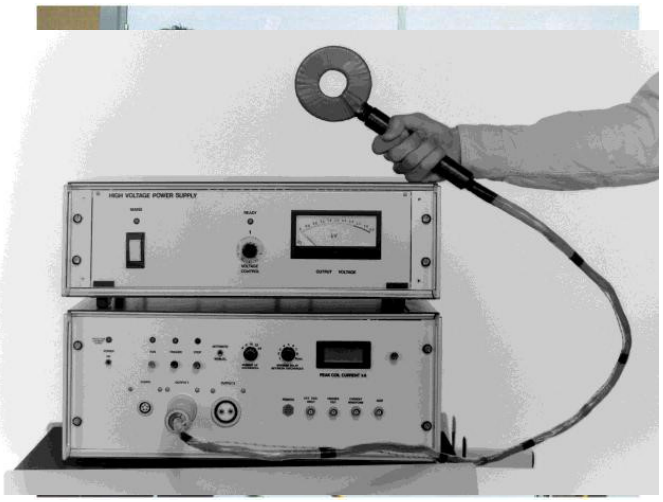
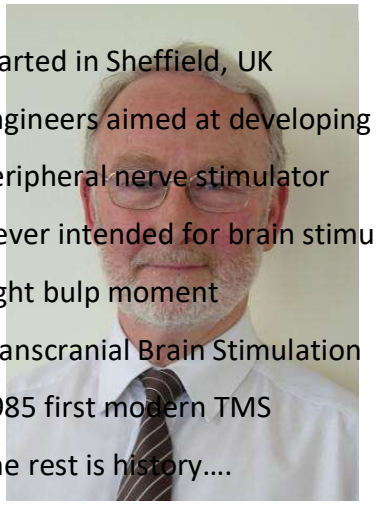
Fundamentals of TMS

TMS History - TMS Physics – TMS Physiology – What TMS can do

Prof. Dr. Alexander Sack
Department of Psychiatry and Neuropsychology
School for Mental Health and Neuroscience (MHeNs) Brain+Nerve Centre
Maastricht University Medical Centre+ (MUMC+)

The History of TMS – a Great Story of Science





- Started in Sheffield, UK
- Engineers aimed at developing peripheral nerve stimulator
- Never intended for brain stimulation
- Light bulp moment
- Transcranial Brain Stimulation
- 1985 first modern TMS
- The rest is history….

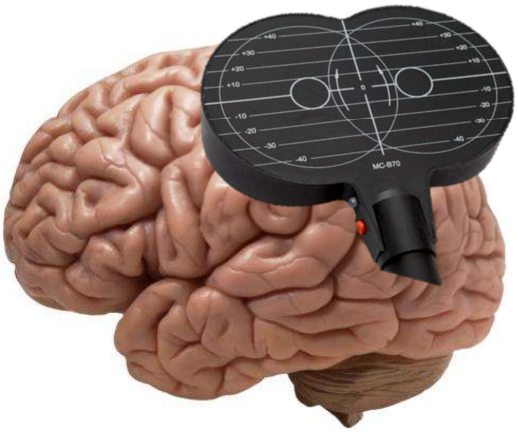
Coming soon: Interview Series with Prof. Anthony Barker: www.brainstimulation-academy.com or our LinkedIn Page

Overview

1 – TMS Physics

2 – TMS Physiology

3 – What can TMS do



TMS Hardware

A switch closes a circuit, allowing current to flow through a (TMS) coil

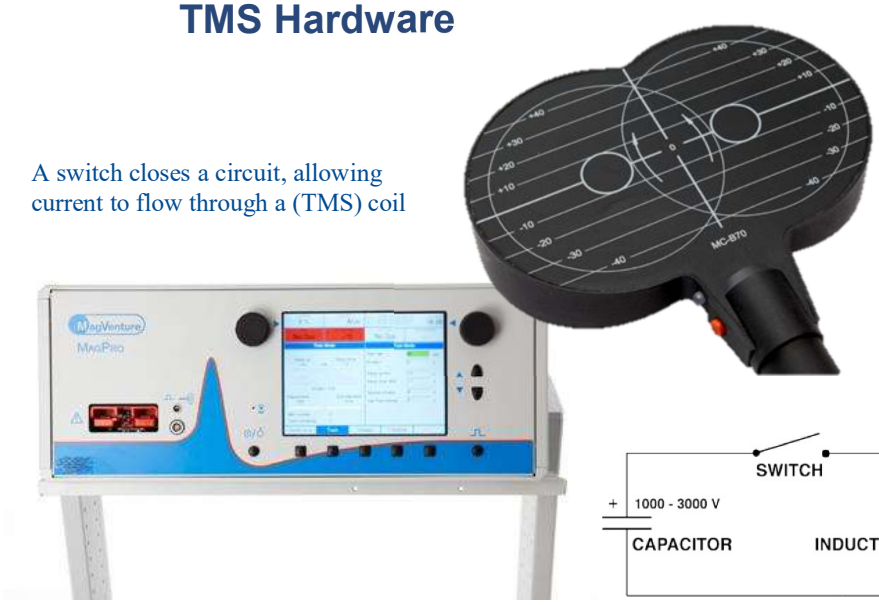


Image source:
neupsykey.com/transcranial-magnetic-stimulation/

Epstein, 2008

Physical Laws in TMS

Faraday's law

Describes how a magnetic field interacts with an electric circuit to generate an electromotive force

Maxwell-Faraday Equation

A time-varying magnetic field is always accompanied by a spatially-varying electric field, and vice-versa.

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}$$

Physical Laws in TMS

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TMS pulse

neuronal tissue

induced currents that can depolarize neurons

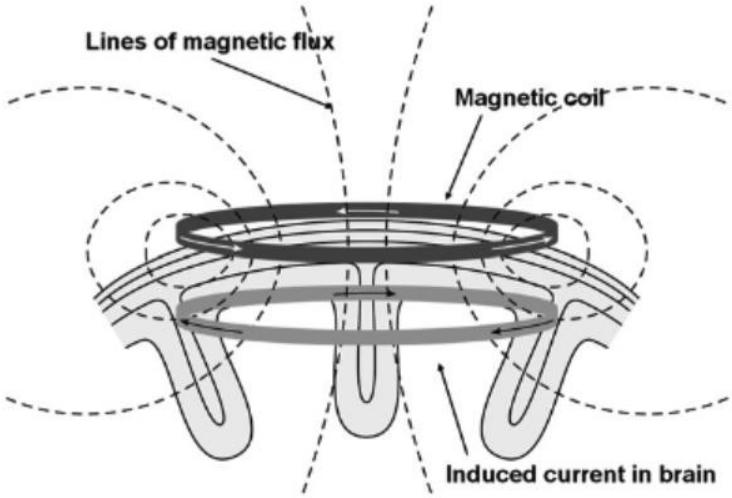
$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}$$

spatially varying electric field

change in magnetic field ... over time

A TMS Pulse I

Hallett, 2007

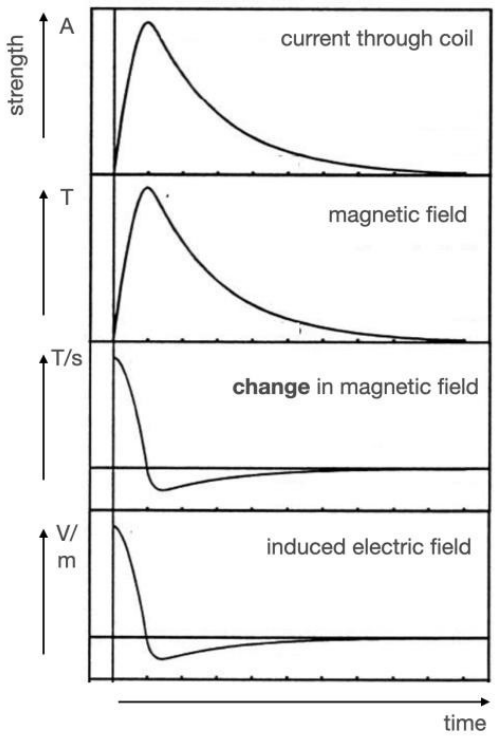


A TMS Pulse II

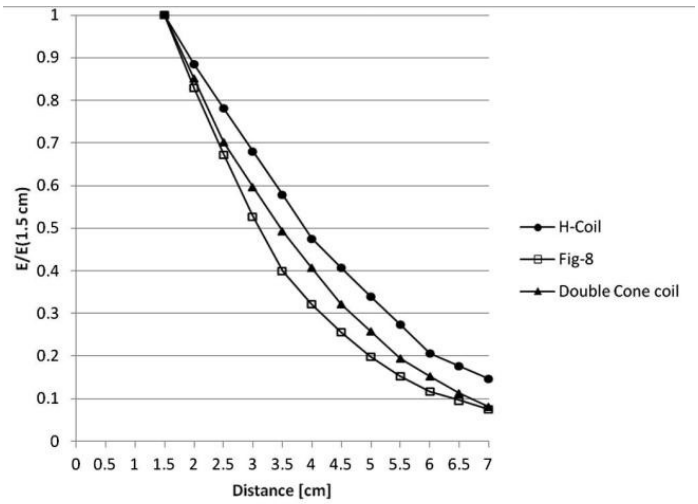
current in TMS coil produces magnetic field pulse

rate of change is essential

induced electric field matches change in magnetic field



Stimulation strength vs. Distance

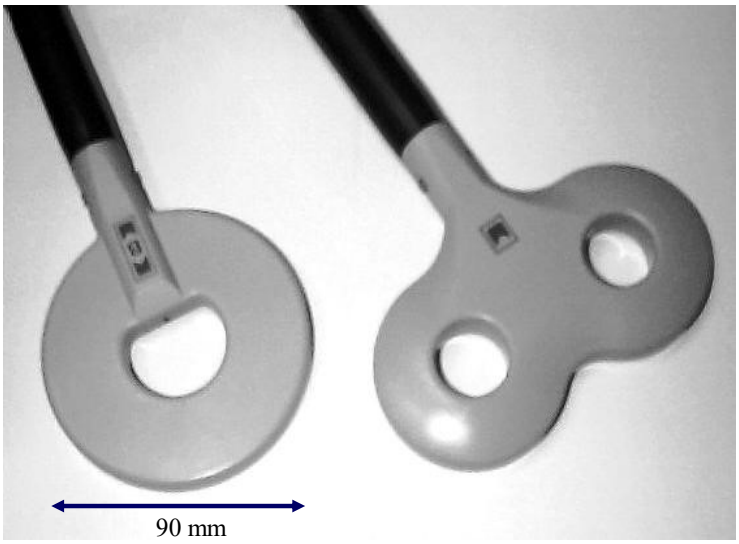


→ limited to cortical stimulation

Roth et al., 2015

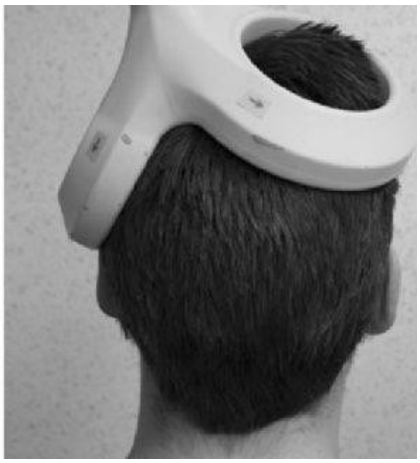
TMS Coil Geometry I

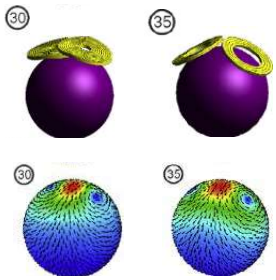
Cohen et al. 1990



TMS Coil Geometry II: Double-cone coils

Deng et al 2013





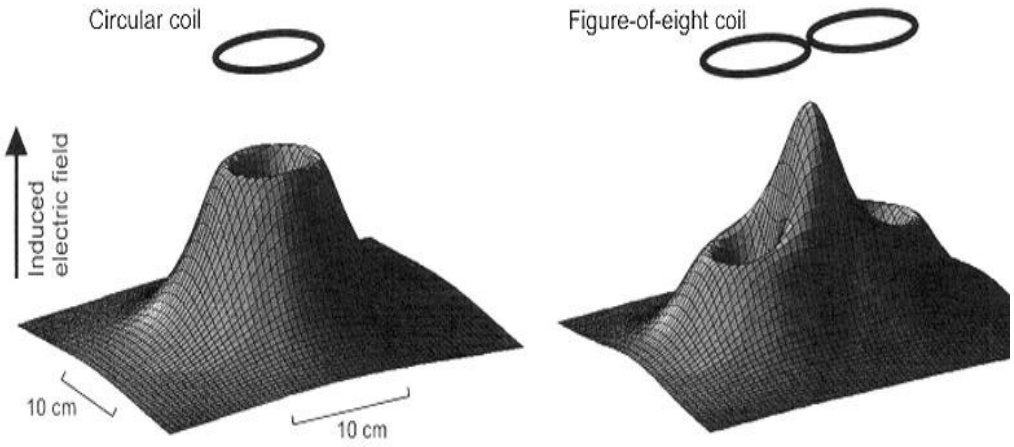
- **Slightly deeper, but less focal (5-6 cm's reasonable)**

TMS Coil Geometry II: H-coils (BrainSway)

- Multiple differently oriented coil loops
- Coil elements mostly radially oriented
- Adding different electric fields
- **Slower decay**: same stimulation deep, less stimulation on surface

TMS Coil Geometry III

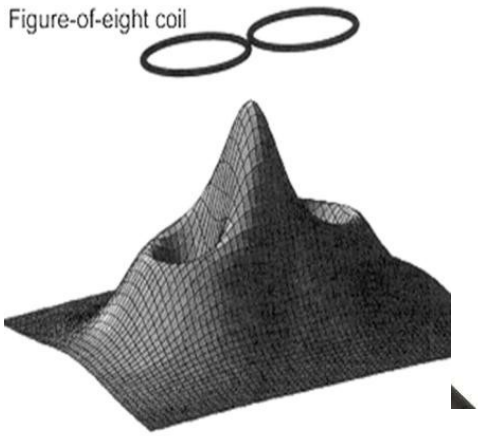
Cohen et al. 1990

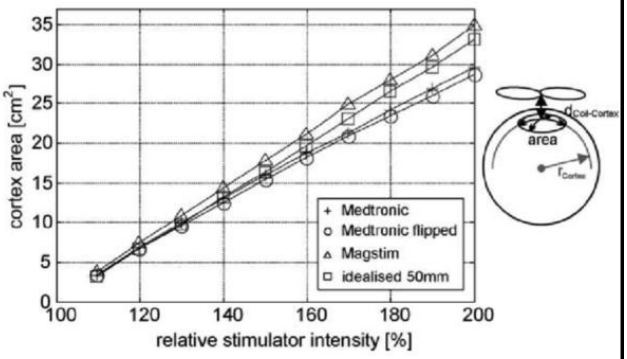


rule of thumb: ~1 cm^2

TMS Coil Geometry III

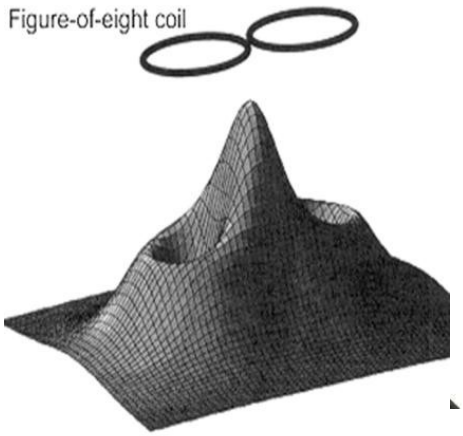
Thielscher & Kammer 2004





But focality depends also on intensity

TMS Coil Geometry III

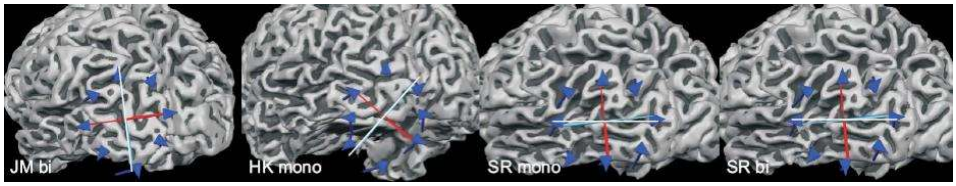


Butterfly Coil

Cohen et al. 1990

TMS coil orientation

Kammer et al 2007



Optimal current direction is perpendicular to the underlying gyrus

The coil orientation matters for stimulation efficacy

Coil orientation is part of a recommended protocol

Physics: Summary

a changing magnetic field induces an electric field in the brain

most cortical areas can be stimulated with TMS

figure-of-eight coil is most focal, but consider other geometries

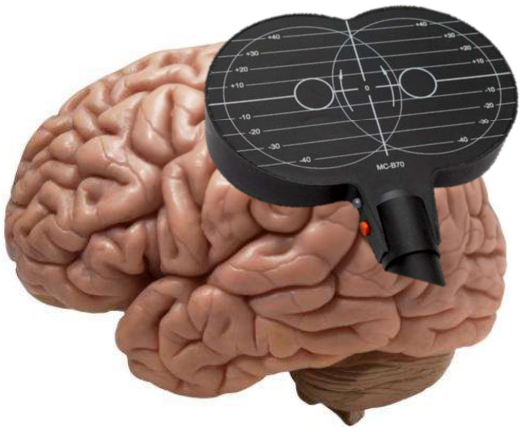
TMS coil orientation is important (to be explored in practical)

Overview

1 – TMS Physics

2 – TMS Physiology

3 – What can TMS do



Neurons

membrane potential

action potential

neurotransmitters

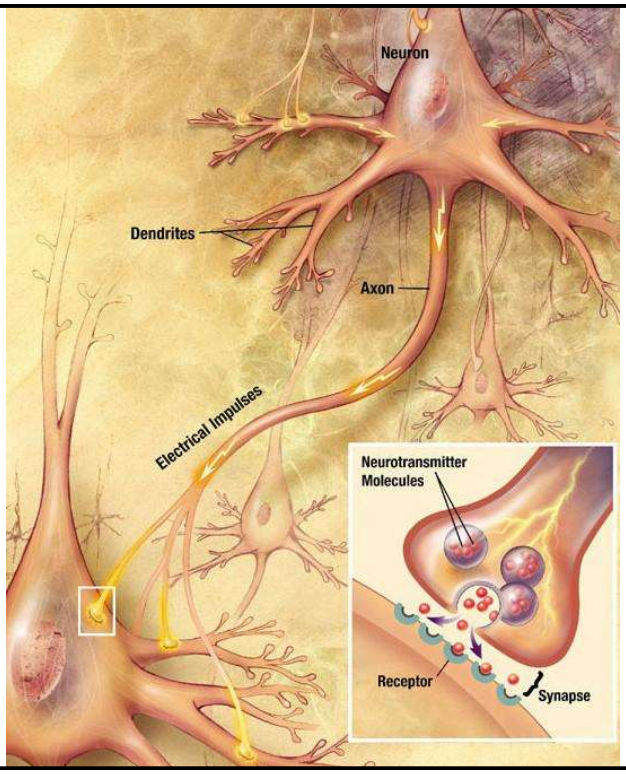
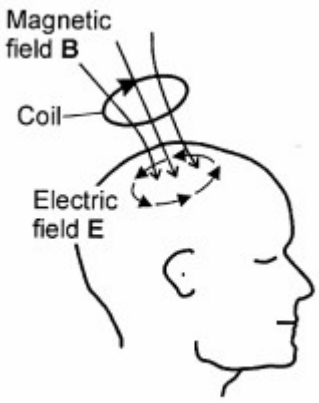
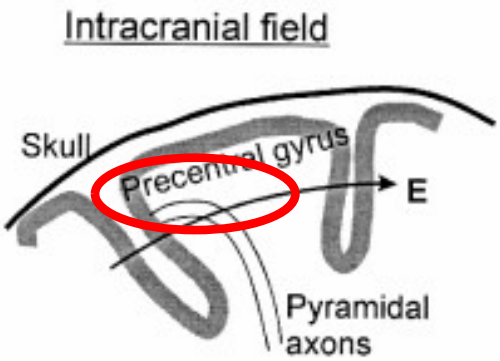


Image source:
www.biomens.eu

Physiology: A TMS Pulse

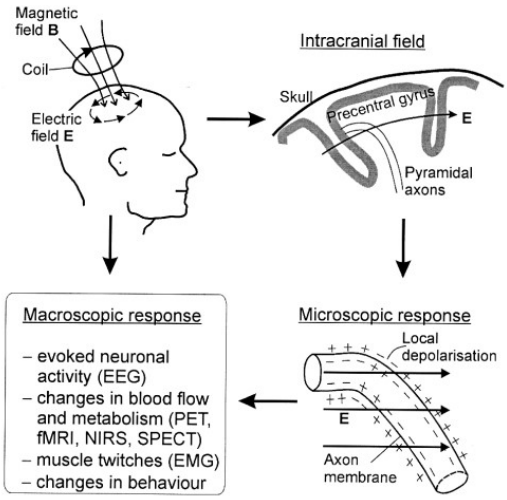
Sack and Linden 2003



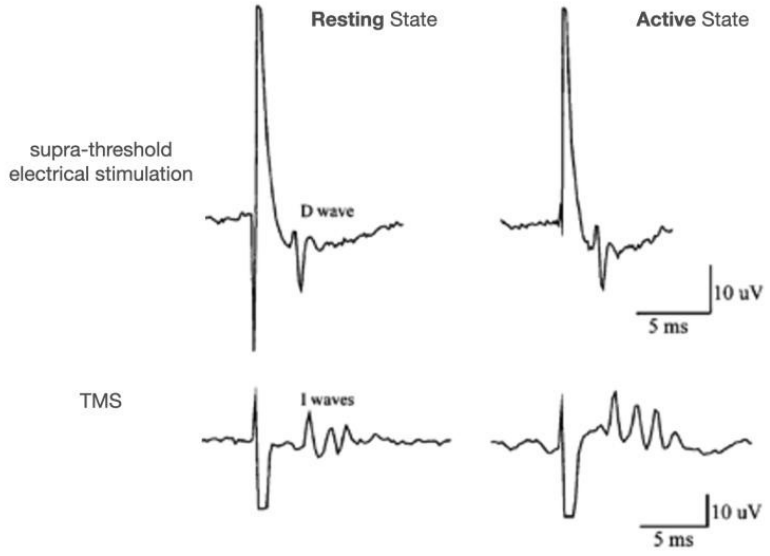


Physiology: A TMS Pulse I

Sack and Linden 2003



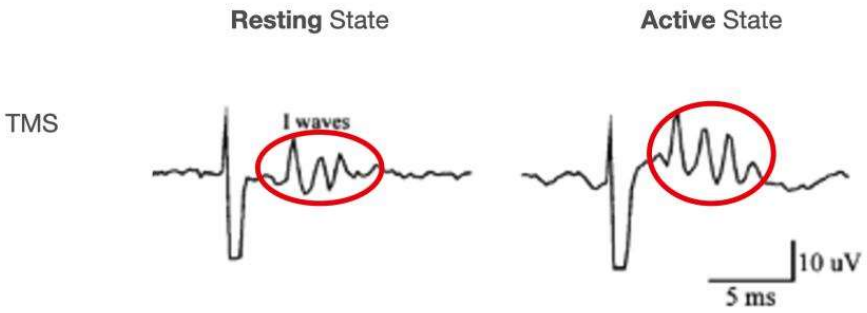
Physiology: A TMS Pulse II



Di Lazarro et al. 2008

Physiology: A TMS Pulse II

Physiological effects of a single TMS pulse depend on the state of the brain!



Di Lazarro et al. 2008

Motor evoked potentials (MEPs)

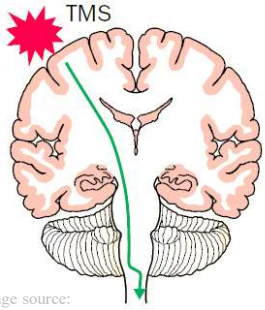


Image source: unknown

- TMS pulse to M1
- Muscle response measured with EMG
- Motor evoked potential

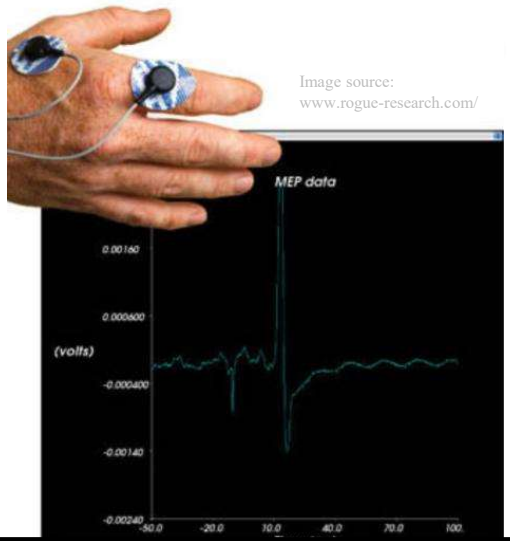
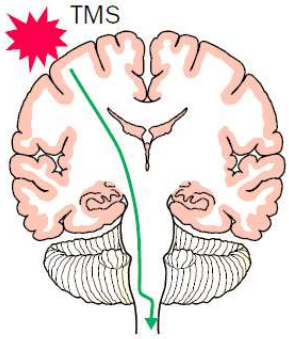
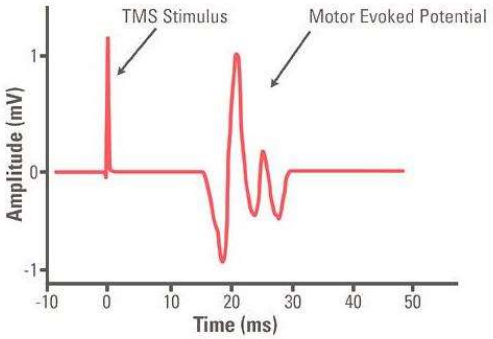


Image source: www.rogue-research.com/

Motor Threshold





- Motor threshold: TMS intensity required to elicit a minimal motor response (e.g. visible twitch, EMG -0.05 to +0.05 mV)
- **Biomarker**, reference for TMS intensity dosage

Physiology: Summary

TMS influences neuronal communication that is based on electro-chemical signals

Single TMS pulse elicits action potential(s) if sufficiently strong

TMS effects depend on brain state (to be explored in the practical)

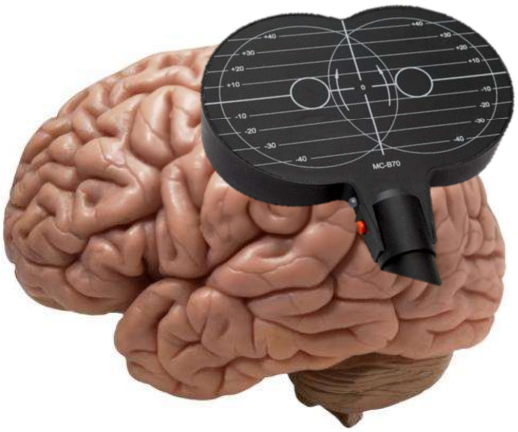
Every head and brain (area) is different, TMS intensity should be adjusted accordingly, we use motor threshold

Overview

1 – TMS Physics

2 – TMS Physiology

3 – What can TMS do



What can TMS do?

Stimulation

Disruption

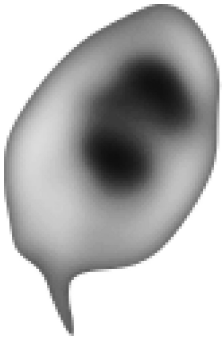
Modulation

What can TMS do?

Stimulation

Disruption

Modulation



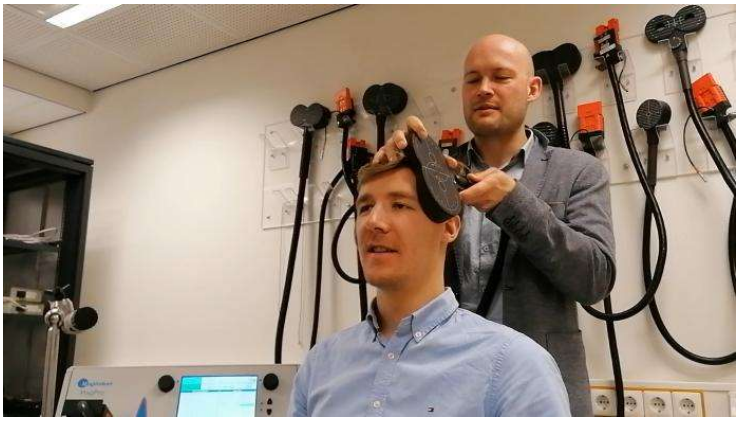
phosphene

What can TMS do?

Stimulation

Disruption

Modulation

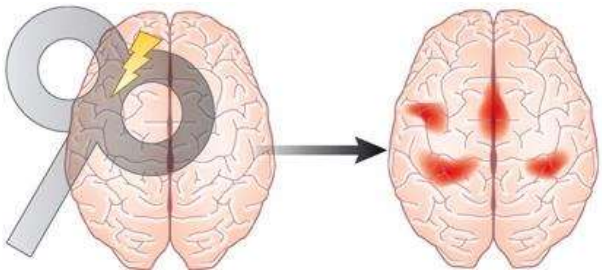


What can TMS do?

Stimulation

Disruption

Modulation



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What can TMS do?

Stimulation

Disruption

“online” TMS, immediate effects

Modulation

“offline” rTMS, after-effects

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Fundamentals of TMS

TMS History - TMS Physics – TMS Physiology – What TMS can do

Prof. Dr. Alexander Sack

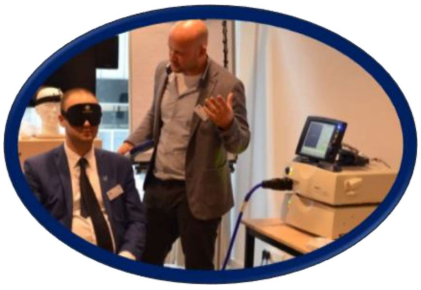
Department of Psychiatry and Neuropsychology

School for Mental Health and Neuroscience (MHeNs) Brain+Nerve Centre

Maastricht University Medical Centre+ (MUMC+)

TMS Protocols

Dr. Lukas Schilberg



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TMS Protocols

Single Pulse TMS - Paired-pulse TMS - Repetitive TMS - Theta Burst TMS - Primed TMS

Dr. Lukas Schilberg

BrainStim
Düsseldorf, Germany

Department of Cognitive Neuroscience
Faculty of Psychology and Neuroscience
Maastricht University

lukas.schilberg@maastrichtuniversity.nl

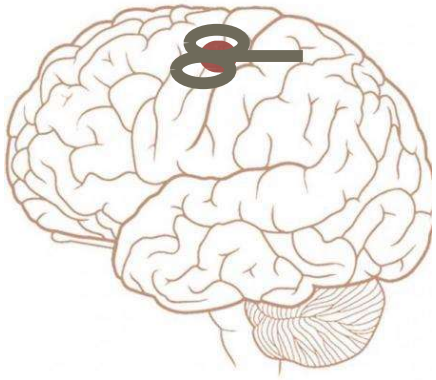
What can TMS do?

Stimulation } "online" TMS, immediate effects

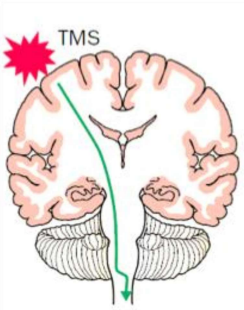
Disruption }

Modulation "offline" rTMS, after-effects

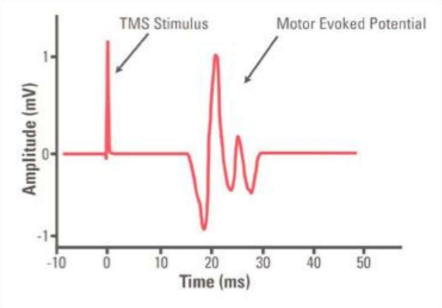
Single-Pulse TMS (spTMS)



immediate local effect



motor evoked potential



MEPs are a very rich signal

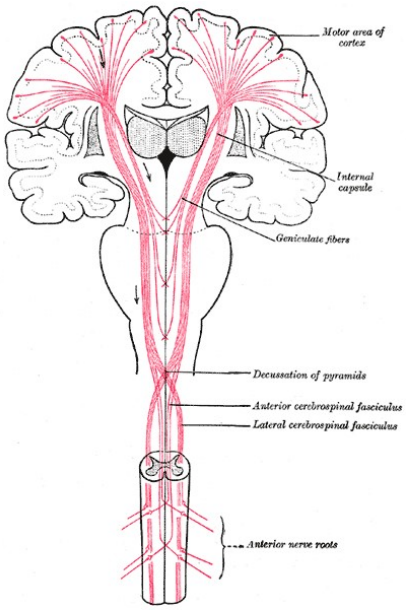
motor threshold

intra-cortical inhibition/facilitation

silent period

central motor conduction time

transcallosal conduction



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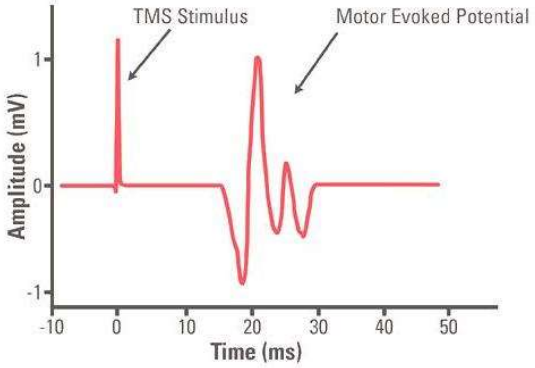


MT is a measure of cortical excitability
but depends on scalp-to-cortex distance

MEPs are a very rich signal

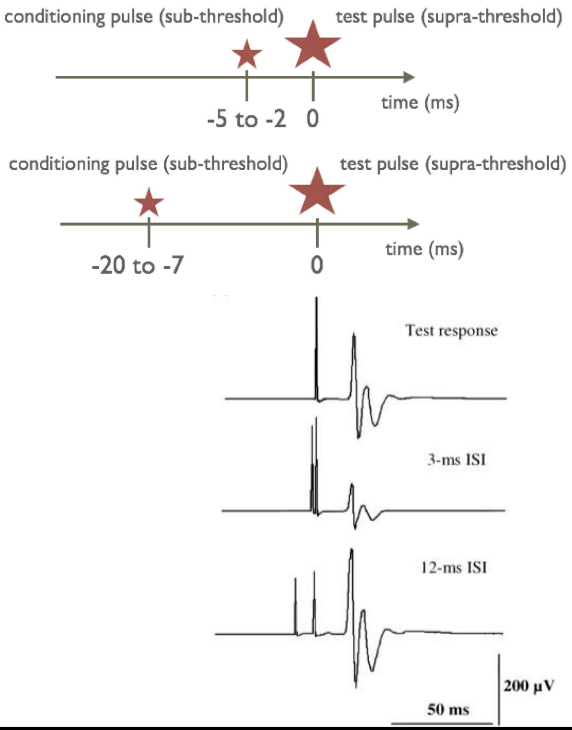
motor threshold

intra-cortical inhibition/facilitation

silent period

central motor conduction time

transcallosal conduction



MEPs are a very rich signal

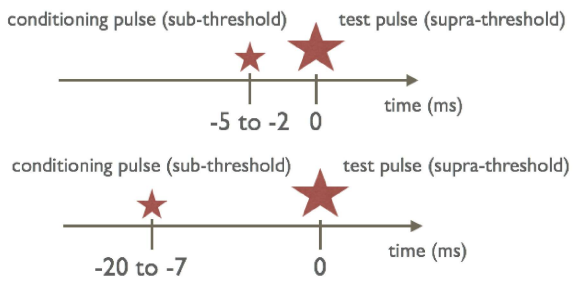
motor threshold

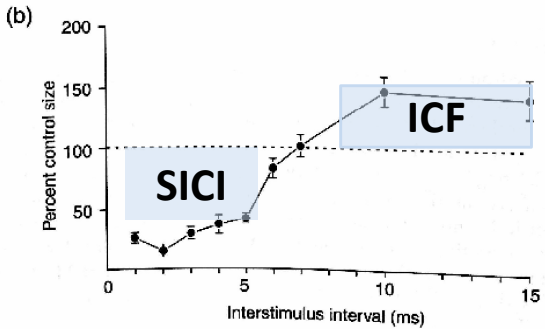
intra-cortical inhibition/facilitation

silent period

central motor conduction time

transcallosal conduction





MEPs are a very rich signal

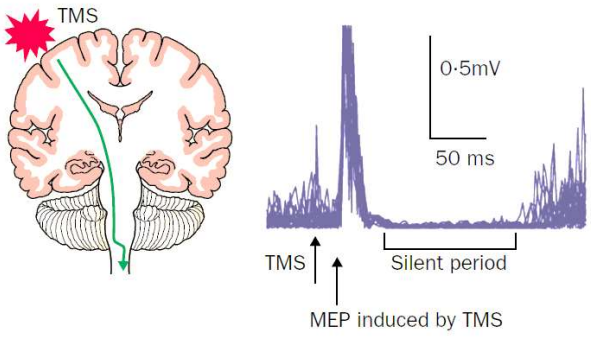
motor threshold

intra-cortical inhibition/facilitation

silent period

central motor conduction time

transcallosal conduction



GABA-mediated inhibitory mechanisms in motor cortex

MEPs are a very rich signal

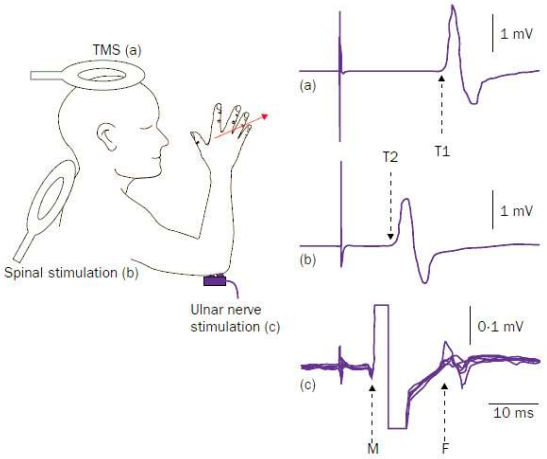
motor threshold

intra-cortical inhibition/facilitation

silent period

central motor conduction time

transcallosal conduction



latency differences between different stimulation sites

MEPs are a very rich signal

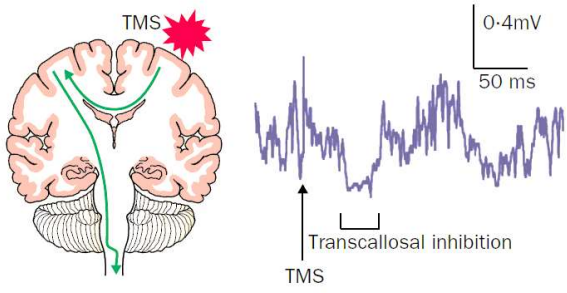
motor threshold

intra-cortical inhibition/facilitation

silent period

central motor conduction time

transcallosal conduction



interhemispheric interaction between motor cortices

TMS Effects are Complex

many measures of cortical excitability

various pharmacological profiles

many unknown interactions

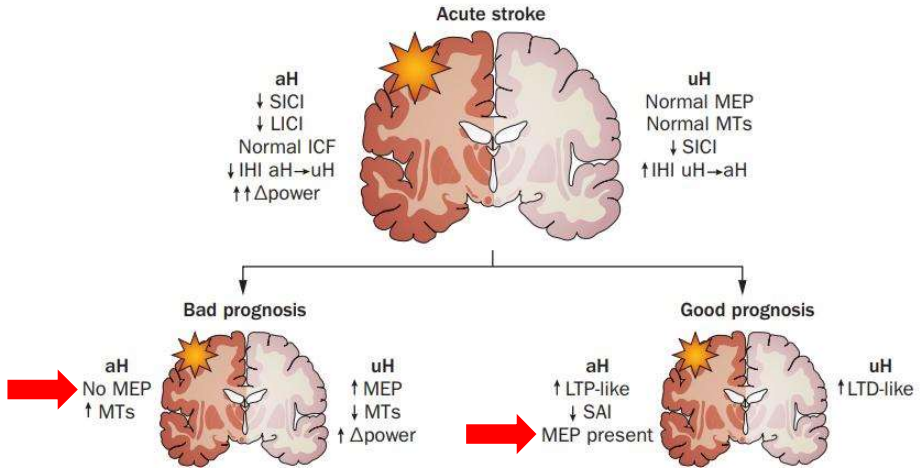
gene-dependence(!?)

Ziemann et al. (2008)

Acute drug effects on TMS measures of motor cortical excitability

Drug	Mode of action	MT	MEP	CSP	SICI	ICF	SICF	Literature
Carbamazepine	Na^+	▲○	○	○	○○	○▼	○	Ziemann et al. (1996c)
								Schulze-Bonhage et al. (1996)
Phenytoin	Na^+	▲▲	○○	○○				Chen et al. (1997)
								Mavroudakis et al. (1994)
Lamotrigine	Na^+	▲▲▲	▼	○	○○	○○	○	Ziemann et al. (1996c)
								Boroojerdi et al. (2001)
								Tergau et al. (2003)
Valproic acid	Na + /GABA	○		○	○	○		Ziemann et al. (1999)
Lorazepam	GABAA	○○○	▼▼	▲	▲▲○	▼○	▼	Ziemann et al. (1996b)
								Boroojerdi et al. (2001)
								Di Lazzaro et al. (2000a)
Diazepam	GABAA	○○	▼○	▼○	▲○	▼	▼	Inghilleri et al. (1996)
								Palmieri et al. (1999)
								Ilic et al. (2002b)
Thiopental	GABAA	○	▼	○				Inghilleri et al. (1996)
Ethanol	GABAA	○	○	▲	▲	▼		Ziemann et al. (1995)
Progesterone	GABAA	○			▲	○		Smith et al. (1999)
Flumazenil	GABAA antagonist	○	○	○	○	○		Jung et al. (2004)
Vigabatrin	GABA	○	○○	○○	○	▼	▼	Ziemann et al. (1996c)
								Mavroudakis et al. (1997)
Tiagabine	GABA	○	○	▲	▼	▲		Werhahn et al. (1999)
Baclofen	GABAB	○○	○○	○○	▲	▼	○	Ziemann et al. (1996c)
								Inghilleri et al. (1996)
Dextrometorphan	NMDA antagonist	○	○	○	▲	▼		Ziemann et al. (1998a)
Memantine	NMDA antagonist	○○	○	○	▲	▼	○	Ziemann et al. (1998c)
								Schwenkreis et al. (1999)
Riluzole	Anti-GLU	○○		○○	▲○	▼▼		Liepert et al. (1997)
								Schwenkreis et al. (2000)
Ketamine	NMDA antagonist	▼	▲	○	○	○		Di Lazzaro et al. (2003)
L-DOPA	DA precursor	○	○	▲	○	○		Priori et al. (1994)
								Ziemann et al. (1997)
Bromocriptine	DA agonist	○			▲	○		Ziemann et al. (1997)
Pergolide	DA agonist	○	○	▲	▲	○		Ziemann et al. (1996a)
Cabergoline	DA agonist	○	▼	○	▲	▼	▼	(own unpublished observations)
Selegiline	MAO-B inhibitor	○			○	○		Ziemann et al. (1997)
Haloperidol	DA antagonist	○○	▲	○	▼○	▲		Ziemann et al. (1997)
								(own unpublished observations)
								Daskalakis et al. (2003)
Sulipiride	DA antagonist	○			○	○		Ziemann et al. (1997)
Olanzapine	DA/5HT2A antagonist	○		○	○			Daskalakis et al. (2003)
Methylphenidate	NE agonist	○○	▲	○	▼○	○▲		Ilic et al. (2003)
								Moll et al. (2003)
d-Amphetamine	NE/DA agonist	○	▲		○	▲		Boroojerdi et al. (2001)
Reboxetine	NE re-uptake inhibitor	○▼	▲		▼○	▲▲		Plewnia et al. (2002)
								Herwig et al. (2002)
Yohimbine	α2 Antagonist	○	▲		○	▲		Plewnia et al. (2001)
Prazosin	α1 Antagonist	○	○		○	○		Sawaki et al. (2003)
Guanfacine	α2 Agonist	○	▼		▲	▼		Korchounov et al. (2003)
Sertraline	SSRI	○	▲	○	○	▼		Ilic et al. (2002a)
Citalopram	SSRI	○			▲	○		Eichhammer et al. (2003)
Zolmitriptan	5-HT1B/1D agonist	○	○	○	▼	○		Werhahn et al. (1998)
Atropine	M1/M2 antagonist	○	○	○	▼	▲		Liepert et al. (2001)
Scopolamine	M1 antagonist	▼	▲	○	○	○		Di Lazzaro et al. (2000b)

Stroke – Motor Deficits – Prognosis



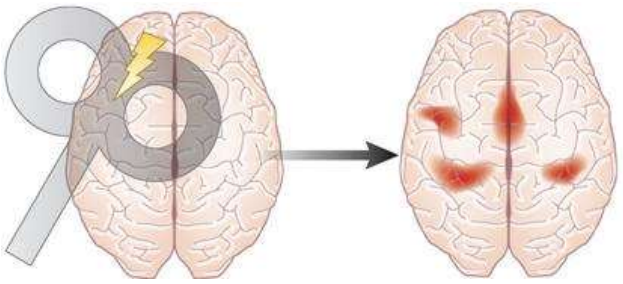
Di Pino et al. (2014). Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. Nat Rev Neurol. 10(10)

Repetitive TMS

Stimulation

Disruption

Modulation



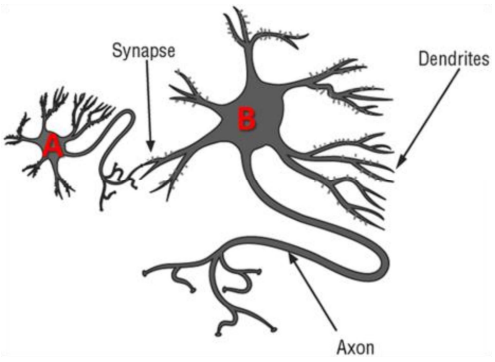
Repetitive TMS

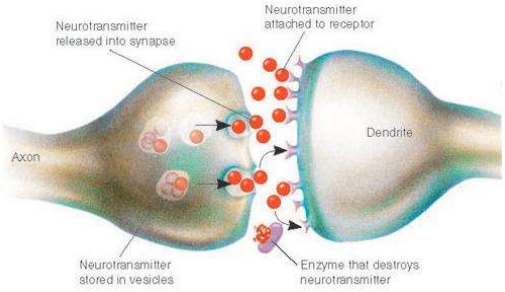
rTMS engages neuroplasticity mechanisms

“neurons that fire together, wire together”

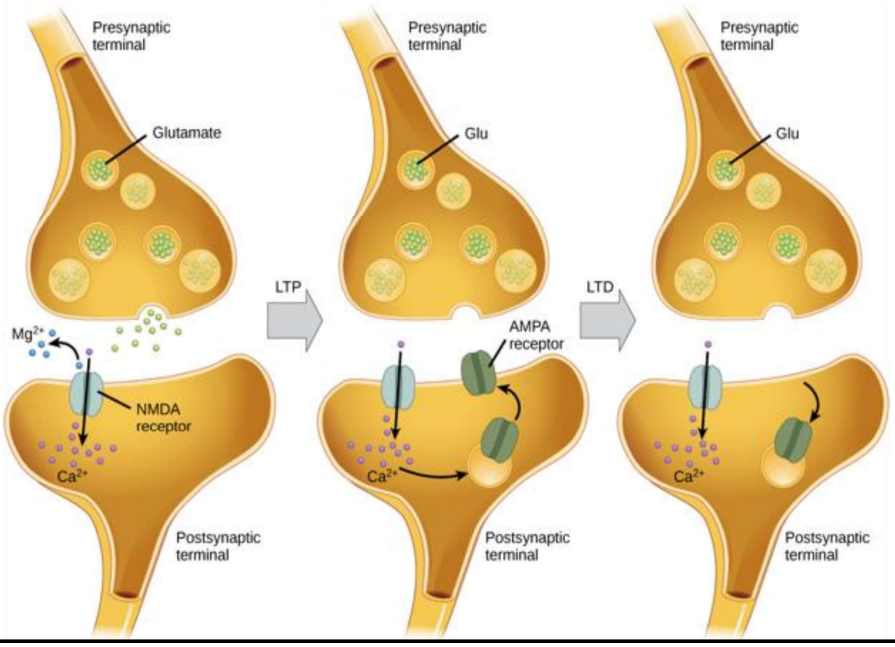
long-term depression (LTD)

long-term potentiation (LTP)

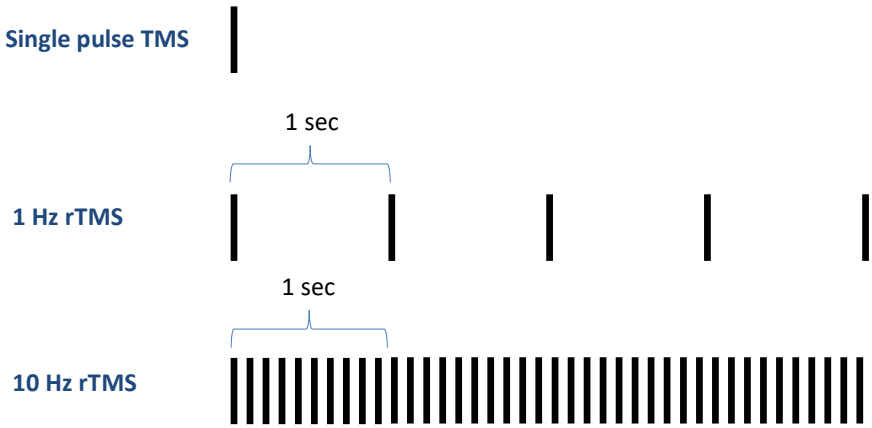




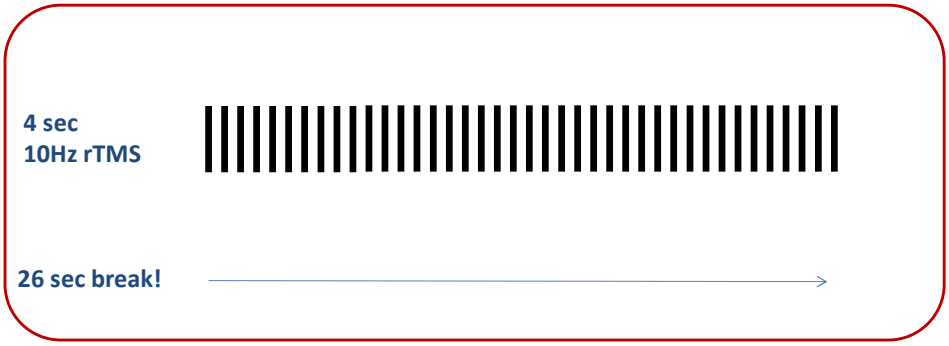
Neuroplasticity



From Single Pulses to Repetitive TMS



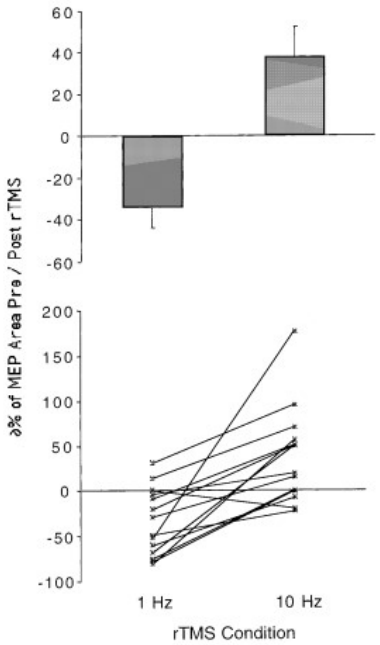
Repetitive TMS: Trains and Intervals



Repetitive TMS

low frequency rTMS (1Hz and below)
→ long-term depression (LTD)
→ inhibitory

high frequency rTMS (5Hz and above)
→ long-term potentiation (LTP)
→ excitatory



Maeda et al. (2000)

A Complete TMS Protocol

Intensity
Frequency
TMS coil type
Number of pulses in train
Inter-Train-Interval
Total number of pulses
Duration
Current direction
Stimulation site
...

Infinite
Parameter
Space
!!!

do not play around unless you know what you are doing

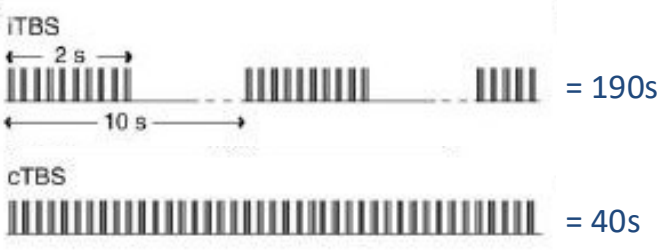
Faster Protocols: Theta Burst Stimulation

bursts of 3 pulses at 50 Hz repeated in a 5Hz rhythm

600 pulses at 80% MT (originally)

2 main stimulation paradigms:

- iTBS (intermittent)
- cTBS (continuous)

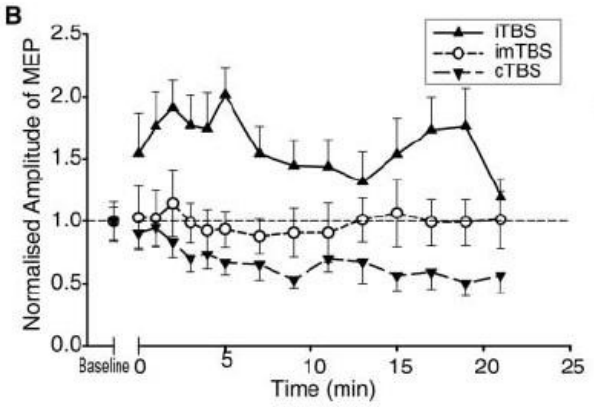


Huang et al. (2005)

Faster Protocols: Theta Burst Stimulation

iTBS (intermittent)
→ excitatory
→ similar to high frequency rTMS

cTBS (continuous)
→ inhibitory
→ similar to low frequency rTMS



(depression) treatment in 3 instead of 30+ minutes!?

Huang et al. (2005)

Primed TMS Protocols

TMS effects are brain state-dependent

brain state can be controlled / changed by "priming"
→ e.g. brain stimulation prior to the main protocol
→ metaplasticity

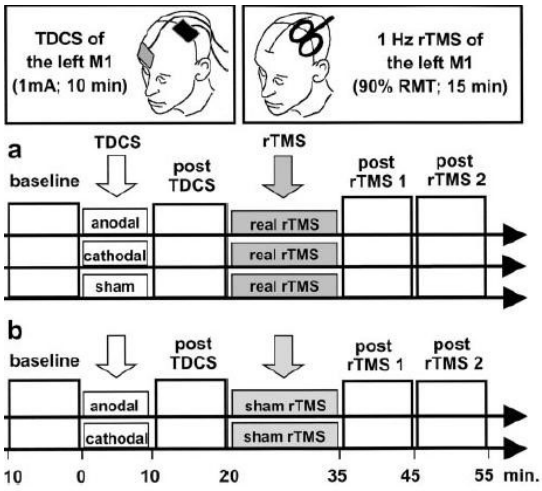
homeostatic plasticity adds complexity
→ "counteracts" TMS effects
→ potential to be used to our advantage

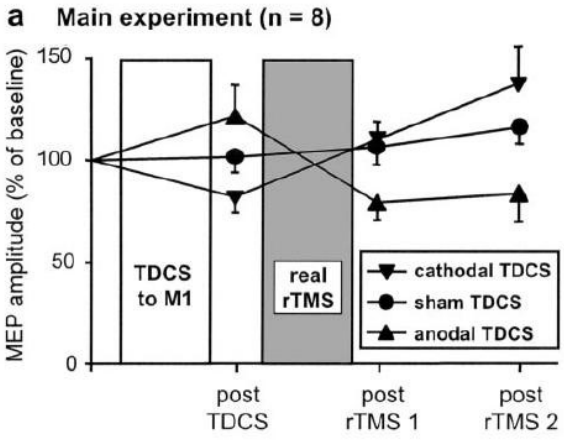
Definition Box

Metaplasticity: 'plasticity of synaptic plasticity'
Metaplasticity is a higher-order form of synaptic plasticity. The term was originally introduced by W.C. Abraham and M.F. Bear [27]. It refers to synaptic or cellular activity that primes the ability to induce subsequent synaptic plasticity, such as long-term potentiation (LTP) or depression (LTD). The priming event does not necessarily cause a change in the efficacy of normal synaptic transmission. Metaplasticity can be homeostatic or non-homeostatic.

Homeostatic plasticity: 'plasticity stabilizing synaptic plasticity'
The term homeostatic plasticity refers to a range of plasticity mechanisms that stabilize neuronal activity [24]. Homeostatic plasticity counteracts the destabilizing influence of synaptic plasticity and thus, stabilizes neural activity within a physiologically meaningful range. Homeostatic mechanisms can be metaplastic or non-metaplastic.

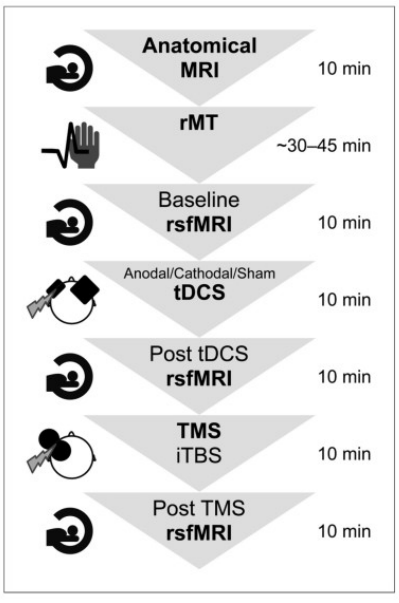
Primed TMS Protocols

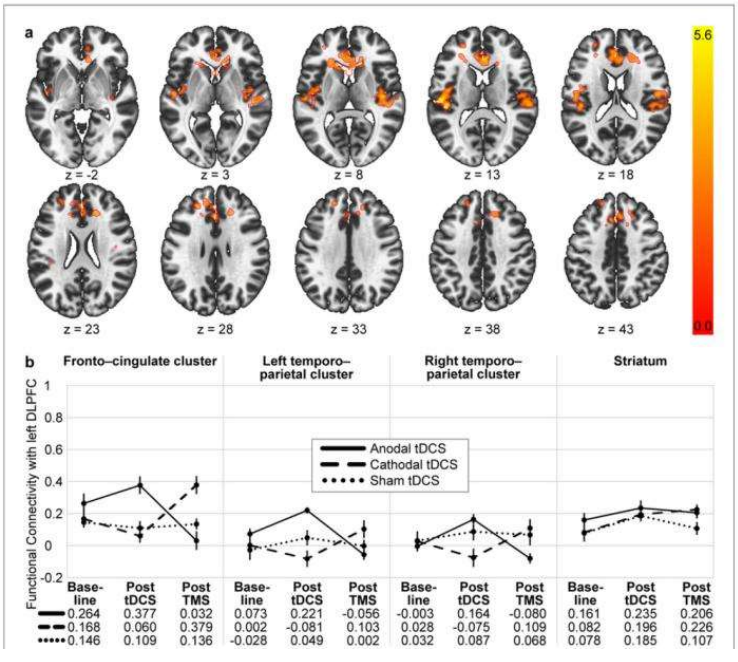




Siebner et al. (2008)

Primed TMS Protocols





Alkhasli et al. (2022)

Primed TMS Protocols

Review > JAMA Psychiatry. 2017 Feb 1;74(2):143-152. doi: 10.1001/jamapsychiatry.2016.3644.

Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis

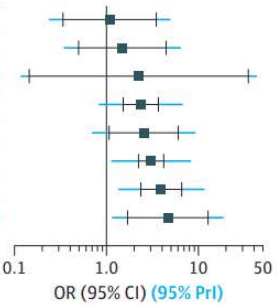
Andre R Brunoni [1], Anna Chaimani [2], Adriano H Moffa [1], Lais B Razza [3], Wagner F Gattaz [1], Zafiris J Daskalakis [4], Andre F Carvalho [5]

Affiliations + expand

PMID: 28030740 DOI: 10.1001/jamapsychiatry.2016.3644

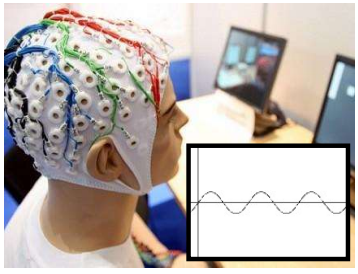
B Response

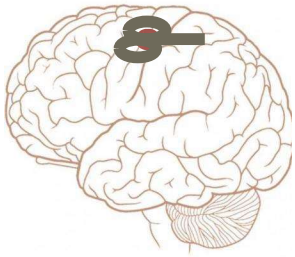
Active Device	OR (95% CI) (95% PrI)
sTMS	1.08 (0.34-3.49) (0.24-4.98)
dTMS	1.49 (0.50-4.47) (0.34-6.48)
aTMS	2.25 (0.14-35.03) (0.12-43.39)
LF-rTMS	2.37 (1.52-3.68) (0.83-6.78)
TBS	2.54 (1.07-6.05) (0.70-9.32)
HF-rTMS	3.07 (2.24-4.21) (1.12-8.37)
Bilateral rTMS	3.96 (2.37-6.60) (1.34-11.70)
pTMS	4.66 (1.70-12.77) (1.15-18.91)

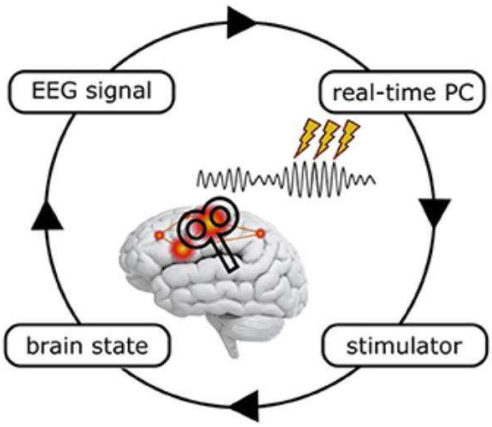


Brunoni et al. (2017)

EEG-Informed / Triggered TMS







closed-loop brain state-dependent brain stimulation

Til Ole Bergmann lab

The Academy of Brain Stimulation
Education and Certification

TMS Protocols

Single Pulse TMS - Paired-pulse TMS - Repetitive TMS - Theta Burst TMS - Primed TMS

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TMS Safety and Procedures

Dr. Teresa Schuhmann

The Academy of Brain Stimulation
Education and Certification

Clinical TMS Certfication Course

Safety and Procedures

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Safety and procedures

1 - Hardware considerations

2 - Side effects

3 - Procedures

Safety and procedures

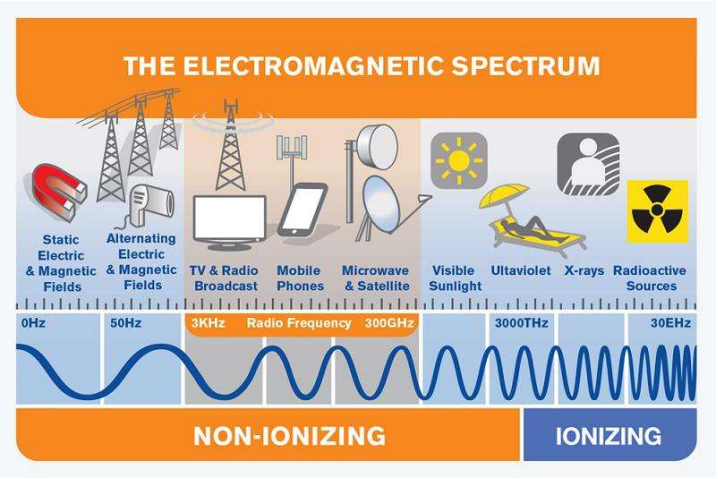
1 - Hardware considerations

2 - Side effects

3 - Procedures

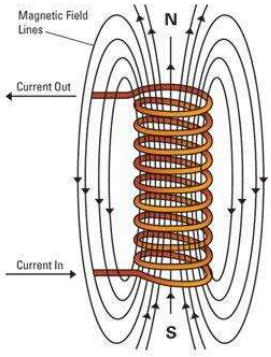
Magnetic field exposure

TMS is considered safe for patients and operators



Forces

TMS pulse exerts attractive forces on ferromagnetic objects



Magnetic Forces

Heating

COIL

TMS pulses heat up coil

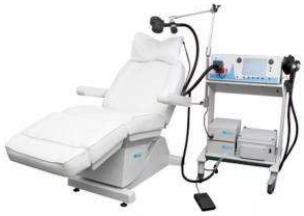
TMS devices automatically disables to prevent overheating

cooled TMS coils for extensive use

TISSUE

tissue heating is minimal

much less than deep brain stimulation



Safety and procedures

1 – Hardware considerations

2 - Side effects

3 - Procedures

Side effects

Well-tolerated in most cases

Many side effects not due to brain stimulation

Single-pulse TMS has least side effects

rTMS and patterned TMS has more side effects

pain

afterdischarges

syncope

seizures

hearing

discomfort

headaches

Pain, headaches, and discomfort

Approximately 10 in every 100 patients experience headaches

Neck stiffness, neck pain is experienced by 1 in every 100 patients

→ Simple pain killers can solve this

Transient hearing changes

Acoustic artefact that may exceed 140 dB of sound pressure

Transient increases in hearing thresholds have been reported

→ use hearing protection

→ individuals with cochlear implants should not receive TMS

EEG aftereffects

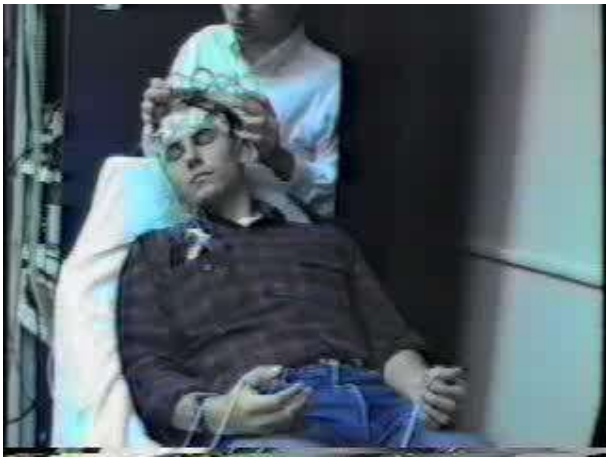
EEG aftereffects can persist in the absence of behavioural effects, including epileptiform abnormalities

Absolute duration reported 20 – 70 minutes

Take this into consideration when planning treatments and when dismissing patients

Afterdischarges

High frequency rTMS may cause rhythmic series of MEPs that persist briefly after stimulation ends



Seizures

Induction of seizures is most severe acute adverse effect of TMS

Seizures can theoretically be induced during two periods:

1) during or immediately after trains of TMS

2) during the after effects due to the modulation of cortical excitability

Accidental seizures are extremely rare (less than 0.003%)

Seizure management

Little to do other than ensure safety during an acute seizure

Patients may become hostile or violent if actively restrained

Most seizures stop by themselves

→seizures lasting more than 5 minutes should be treated as a medical emergency

Syncope

A common reaction to anxiety and psycho-physical discomfort

Behaviours considered typical of seizures:

tonic stiffening, jerking, vocalisations, oral and motor automatisms, brief head or eye version, incontinence, hallucinations, and injuries from falling

Safety of Theta Burst Stimulation

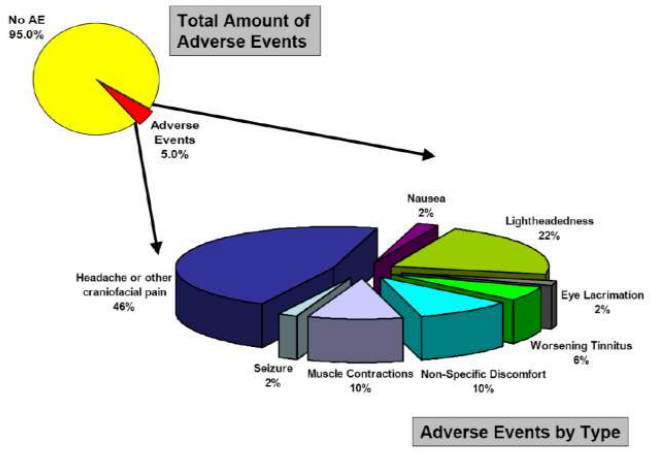


Figure 1.
Percentage of adverse events reported during or immediately following Theta Burst Stimulation.

Oberman et al., 2011

Side effects overview

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	Likely possible, but not reported/ addressed	Frequent (see para. 3.3)	Frequent (see para. 3.3)	Possible
Transient hearing changes	Possible	Likely possible, but not reported	Possible	Possible	Not reported
Transient cognitive/ neuropsychologial changes	Not reported	No reported	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

Rossi et al., 2009

Complex parameter space

- Stimulus intensity
- Frequency
- Inter-train intervals
- Length of stimulation

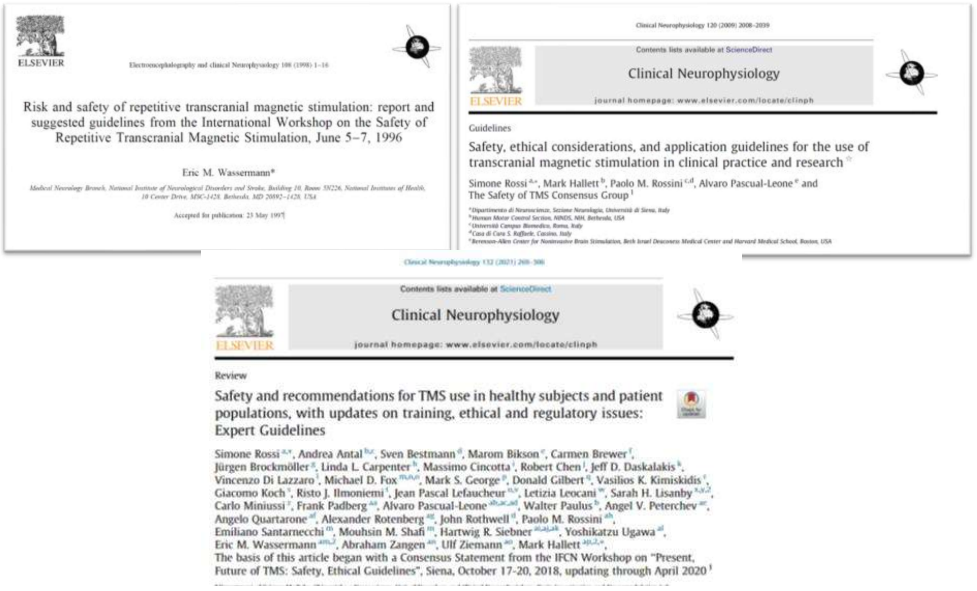
Advice: Do not “play around” with these parameters

New pulse generators/waveforms

Seizure monitoring necessary

- New waveforms with asymmetric E-field phase
- Triple-pulse or quadri-pulse with ultra-high pulse repetition rate (up to 666 Hz)
- Using pairs of coils or coil arrays

Minimizing risks



Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996

Eric M. Wassermann*

Clinical Neurophysiology

Guidelines

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

Simone Rossi, Mark Hallett, Paolo M. Rossini, Alvaro Pascual-Leone and The Safety of TMS Consensus Group

Clinical Neurophysiology

Review

Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines

Simone Rossi, Andrea Antal, Sven Bestmann, Marom Bikson, Carmen Brewer, Jürgen Brockmöller, Linda L. Carpenter, Massimo Cincotta, Robert Chen, Jeff D. Daskalakis, Vincenzo Di Lazzaro, Michael D. Fox, Mark S. George, Donald Gilbert, Vasilios K. Kimiskidis, Giacomo Koch, Risto J. Ilmoniemi, Jean Pascal Lefaucheur, Letizia Leocani, Sarah H. Lisanby, Carlo Miniussi, Frank Padberg, Alvaro Pascual-Leone, Walter Paulus, Angel V. Peterchev, Angelo Quartarone, Alexander Rotenberg, John Rothwell, Paolo M. Rossini, Emiliano Santarnecchi, Mouhsin M. Shafi, Hartwig R. Siebner, Yoshikatzu Ugawa, Eric M. Wassermann, Abraham Zangen, Ulf Ziemann, Mark Hallett

The basis of this article began with a Consensus Statement from the IFCN Workshop on "Present, Future of TMS: Safety, Ethical Guidelines", Siena, October 17-20, 2018, updating through April 2020

Further considerations – interactions

Illness-stimulation interactions

- TMS effects are state-dependent
- Illness-specific side effects

Treatment-stimulation interactions

- Antidepressants and neuroleptics increase seizure risk
- Anticonvulsants lower seizure risks

Further considerations – drugs

Strong potential hazards
imipramine, doxepine, amphetamines, clozapine, cocaine, alcohol, etc...
→ TMS should be performed with particular caution

Relative hazards
mianserin, fluaxetine, haloperidol, penicillin, antihistamines, etc...
→ TMS should be performed with caution

Strong hazard when **withdrawal** from
alcohol, barbiturates, benzodiazepines, etc...
→ TMS should be performed with caution

Note: Systematic data are not available regarding the specific medications and adverse effects

UPDATE: current data shows such a low seizure rate that recommended caution is no longer supported

for a complete list, see Rossi et al., 2009, update Rossi 2021

Further considerations – pregnancy


Brain Stimulation 12 (2019) 96–102

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Randomized controlled trial of transcranial magnetic stimulation in pregnant women with major depressive disorder

Deborah R. Kim [a, *], Eileen Wang [b], Brendan McGeehan [a], Jessica Snell [a, 1], Grace Ewing [a], Claudia Iannelli [a], John P. O'Reardon [a, 2], Mary D. Sammel [c], C. Neill Epperson [a]

[a] Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, 3535 Market Street, 3rd Floor, Philadelphia, PA, 19014, United States
[b] Department of Obstetrics and Gynecology, Perelman School of Medicine at the University of Pennsylvania, 3535 Market Street, 3rd Floor, Philadelphia, PA, 19014, United States
[c] Department of Biostatistics, Epidemiology & Informatics, Perelman School of Medicine at the University of Pennsylvania, 3535 Market Street, 3rd Floor, Philadelphia, PA, 19014, United States


Journal of Affective Disorders 272 (2020) 259–268

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Review article

"A systematic review of non-invasive neurostimulation for the treatment of depression during pregnancy"

Gerasimos N. Konstantinou[a,b], Simone N. Vigod[a,c], Shobha Mehta[b], Zafiris J. Daskalakis[a,b], Daniel M. Blumberger[a,b,*]

[a] Department of Psychiatry, University of Toronto
[b] Temerty Centre for Therapeutic Brain Intervention and Campbell Family Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada
[c] Women's College Research Institute, Women's College Hospital, Toronto, ON, Canada

Further considerations – pregnancy

- Clinical effects, tolerability, acceptability, and safety of non-invasive brain stimulation for treating depression during pregnancy
- Case studies or small open-label trial designs
- No long-term data on maternal or child outcomes
- Mild maternal discomfort, such as temporary headache and scalp pain during stimulation
- In all reviewed cases, positive clinical effects and no severe adverse outcomes have been reported
- A 30° pelvic tilt should be employed for women at or beyond 24 weeks of pregnancy to prevent supine hypotension

Further considerations – pediatrics

Children have been treated with TMS

e.g. depression, ADHD, Tourettes syndrome, migraine

Side effects very comparable to adults


Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Safety and tolerability of transcranial magnetic and direct current stimulation in children: Prospective single center evidence from 3.5 million stimulations

E. Zewdie, P. Ciechanski, H.C. Kuo, A. Giuffre, C. Kahl, R. King, L. Cole, H. Godfrey, T. Seeger, R. Swansburg, O. Damji, T. Rajapakse, J. Hodge, S. Nelson, B. Selby, L. Gan, Z. Jadavji, J.R. Larson, F. MacMaster, J.F. Yang, K. Barlow, M. Gorassini, K. Brunton, A. Kirton


Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Review Article

Safety of Noninvasive Brain Stimulation in Children and Adolescents

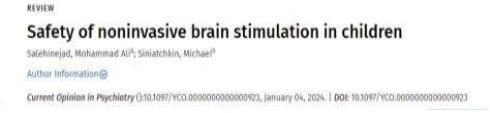
Chandramouli Krishnan, Luciana Santos, Mark D. Peterson, Margaret Ehinger


frontiers in HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE

Safety and tolerability of theta burst stimulation vs. single and paired pulse transcranial magnetic stimulation: a comparative study of 165 pediatric subjects

Yaejee H. Hong, Steve W. Wu, Ernest V. Pedapati, Paul S. Horn, David A. Huddleston, Cameron S. Laue and Donald L. Gilbert


REVIEW

Safety of noninvasive brain stimulation in children

Salehinejad, Mohammad Ali; Siniatchkin, Michael

Author Information

Current Opinion in Psychiatry (): 10.1097/YCO.0000000000000923, January 04, 2024. | DOI: 10.1097/YCO.0000000000000923

Further considerations – pediatrics

The frequency of adverse events is similar to adults

Neuromodulation: Technology at the Neural Interface

Received: January 25, 2021 Revised: April 4, 2021 Accepted: April 19, 2021

(onlinelibrary.wiley.com) DOI: 10.1111/ner.13455

A Systematic Review of the Safety and Tolerability of Theta Burst Stimulation in Children and Adolescents

Rana Elmaghraby, MD; Qi Sun, MD; Can Ozger, BS; Julia Shekunov, MD; Magdalena Romanowicz, MD; Paul E. Croarkin, DO, MS

Induced voltages

- TMS in patients with implanted stimulating/recording electrodes is possible but requires caution
- In patients with DBS or cortical stimulation electrodes, TMS can induce currents in the electrode leads which could cause unintended stimulation → potential safety hazard
- Implants in the head that are MRI safe are more likely to be TMS safe than those that are not MRI safe
- TMS coil should be at least 10 cm away from electrodes

Absolute contraindications

Cochlear implants or metallic/electronic implants in close contact with TMS coil (need to be at least >10 cm from coil)

Safety and procedures

1 - Hardware considerations

2 - Side effects

3 - Procedures

Procedures and risk management

Procedures differ between research and clinical facilities

Basic research

→ risks should be minimised

Clinical research and therapy

→ risks and clinical goals should be carefully weighted

Recommended clinical practice

Clinical Neurophysiology 132 (2021) 819–837

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Review

Training in the practice of noninvasive brain stimulation: Recommendations from an IFCN committee

Peter J. Fried [a,1], Emiliano Santarnecchi [a,1], Andrea Antal [b], David Bartres-Faz [c], Sven Bestmann [d], Linda L. Carpenter [e], Pablo Celnik [f], Dylan Edwards [g,h], Faranak Farzan [i], Shirley Fecteau [j], Mark S. George [k,l], Bin He [m], Yun-Hee Kim [n], Letizia Leocani [o], Sarah H. Lisanby [p], Colleen Loo [q], Bruce Luber [r], Michael A. Nitsche [s], Walter Paulus [b], Simone Rossi [t], Paolo M. Rossini [u], John Rothwell [v], Alexander T. Sack [w], Gregor Thut [x], Yoshikazu Ugawa [y], Ulf Ziemann [z], Mark Hallett [aa], Alvaro Pascual-Leone [ab,ac,*]

Training

- University TMS education programme
- Industry sponsored training (device specific product training)
- Peer to peer training

Establish formal standard operating procedures (SOPs)

- Standard procedure for training
- Criteria to maintain procedural skills to all staff involved
- Documentation of implementation and adherence to these procedures

Recommended clinical practice

Roles and responsibilities

Attending phycisian responsible for

- overall daily management of TMS treatment plan
- motor threshold and stimulation intensity determination
- stimulation site localisation

Establish a treatment plan

- Standard treatment high frequency, left prefrontal rTMS, five daily treatments over 4–6 weeks
- Maintenance treatments
- Advice patients to set appropriate expectations

Recommended clinical practice

Informed consent

- Give patient a thorough, accurate, and informative presentation of what a course of TMS will entail
- Brochures and videos
- Invite family members into the consultation room to address any questions they may have
- Only then written informed consent should be obtained

Recommended clinical practice

Safety considerations

- Use informed consent
- Pre-treatment clinical screening of potential seizure risk
- Continuous clinical monitoring of the TMS treatment session
- Train personnel to provide appropriate initial management of a seizure or other medical event

Recommended clinical practice

Pre-treatment screening

1. Do you have epilepsy or have you ever had a convulsion or a seizure?
2. Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s)?
3. Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?
4. Do you have any hearing problems or ringing in your ears?
5. Do you have cochlear implants?
6. Are you pregnant or is there any chance that you might be?
7. Do you have metal in the brain, skull or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, specify the type of metal.
8. Do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)?
9. Do you have a cardiac pacemaker or intracardiac lines?
10. Do you have a medication infusion device?
11. Are you taking any medications? (please list)
12. Did you ever undergo TMS in the past? If so, were there any problems.
13. Did you ever undergo MRI in the past? If so, were there any problems.

Rossi et al., 2009

Recommended clinical practice

Outcome evaluation

Objective documentation of clinical benefit

- Patient Health Questionnaire
- Inventory of depression scale – self rates
- Beck Depression Inventory

Post-treatment planning

- Slow versus immediate fade out of TMS
- Follow-up treatments?

Recommended clinical practice

Brain Stimulation 9 (2016) 336–346

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder

Tarique Perera [a], Mark S. George [b,c,*], Geoffrey Grammer [d], Philip G. Janicak [e], Alvaro Pascual-Leone [f], Theodore S. Wirecki [g,1]

[a] Contemporary Care, Greenwich, CT, USA
[b] Brain Stimulation Division, Department of Psychiatry, Medical University of South Carolina, Charleston, SC, USA
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[d] TMS NeuroHealth, McLean, VA, USA
[e] Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
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[g] TMS Center of Colorado, Denver, CO, USA

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Review

Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines

Simone Rossi [a,*], Andrea Antal [b,c], Sven Bestmann [d], Marom Bikson [e], Carmen Brewer [f], Jürgen Brockmöller [g], Linda L. Carpenter [h], Massimo Cincotta [i], Robert Chen [j], Jeff D. Daskalakis [k], Vincenzo Di Lazzaro [l], Michael D. Fox [m,n,o], Mark S. George [p], Donald Gilbert [q], Vasilios K. Kimiskidis [r], Giacomo Koch [s], Risto J. Ilmoniemi [t], Jean Pascal Lefaucheur [u,v], Letizia Leocani [w], Sarah H. Lisanby [x,y,z], Carlo Miniussi [z], Frank Padberg [aa], Alvaro Pascual-Leone [ab,ac,ad], Walter Paulus [b], Angel V. Peterchev [ae], Angelo Quartarone [af], Alexander Rotenberg [ag], John Rothwell [d], Paolo M. Rossini [ah], Emiliano Santarnecchi [ai], Mouhsin M. Shafi [ai], Hartwig R. Siebner [aj,ak,al], Yoshikatzu Ugawa [af], Eric M. Wassermann [am,z], Abraham Zangen [an], Ulf Ziemann [ao], Mark Hallett [ap,z,*],

The basis of this article began with a Consensus Statement from the IFCN Workshop on "Present, Future of TMS: Safety, Ethical Guidelines", Siena, October 17-20, 2018, updating through April 2020 [1]

TMS approval and reimbursement

- TMS approval through national bodies for clinical use in many countries
- Reimbursement differs largely between countries and health insurances

The Academy of Brain Stimulation
Education and Certification

Clinical TMS Certfication Course

Safety and Procedures

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Department of Cognitive Neuroscience
Faculty of Psychology and Neuroscience
Maastricht University
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From the Lab to the Clinic

Dr. Felix Duecker

The Academy of Brain Stimulation
Education and Certification

TMS: From the Lab to the Clinic

Basic Principles – Science ≠ FDA/CE – Levels of Evidence – Research <-> Clinic

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Department of Cognitive Neuroscience
Faculty of Psychology and Neuroscience
Maastricht University
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The First TMS Device

Anthony Barker, Sheffield

"When the coil is placed on the scalp, over the appropriate region of the motor cortex, movements of the opposite hand or leg are easily obtained without causing distress or pain. "

"Stimulation is assumed to be due to the current induced in the tissue by the rapid, time-varying magnetic field."

"The ability to stimulate corticospinal motor pathways allows their function to be assessed in many neurological conditions […] Magnetic stimulation is a major advance in the implementation of such studies."

THE LANCET, MAY 11, 1985

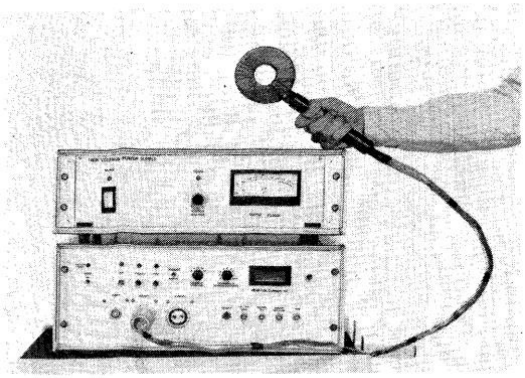
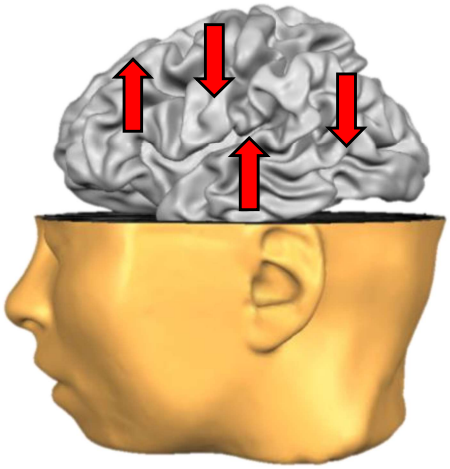


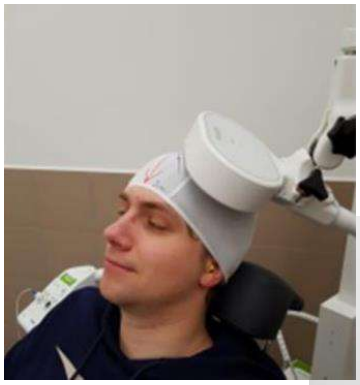
Fig 1—Magnetic stimulator and coil.

Treatment: Basic Principles

Application of long-lasting inhibitory or excitatory TMS protocols, often for many sessions, that ideally reverse the brain state back to normal



All TMS devices aim to do the same…



FDA Milestones

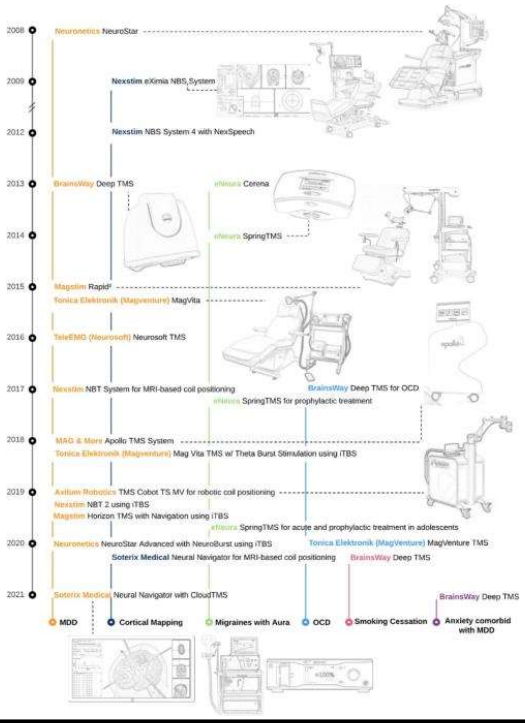
Scientific evidence

≠

FDA approval (or CE)

≠

Reimbursement



Cohen et al. (2021)

Efficacy of TMS Treatment

Clinical Neurophysiology 125 (2014) 2150–2206

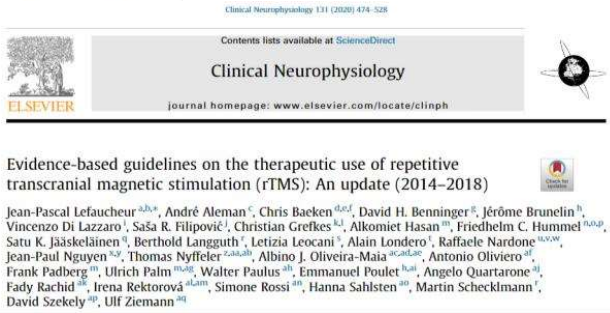
Contents lists available at ScienceDirect

Clinical Neurophysiology

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

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 David H. Benninger [h], Roberto M. Cantello [i], Massimo Cincotta [j], Mamede de Hervé Devanne [n,o], Vincenzo Di Lazzaro [p], Saša R. Filipović [q], Friedhelm C. Hu Vasilios K. Kimiskidis [s], Giacomo Koch [u], Berthold Langguth [v], Thomas Nyffele Frank Padberg [y], Emmanuel Poulet [z,aa], Simone Rossi [ab], Paolo Maria Rossini [ac] Carlos Schönfeldt-Lecuona [af], Hartwig R. Siebner [ag,ah], Christina W. Slotema [ai] Josep Valls-Sole [ak], Ulf Ziemann [al], Walter Paulus [e,1], Luis Garcia-Larrea [f,am,1]



Clinical Neurophysiology 131 (2020) 474–528

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)

Jean-Pascal Lefaucheur [a,b,*], André Aleman [c], Chris Baeken [d,e,f], David H. Benninger [g], Jérôme Brunelin [h], Vincenzo Di Lazzaro [i], Saša R. Filipović [j], Christian Grefkes [k,l], Alkomiet Hasan [m], Friedhelm C. Hummel [n,o,p], Satu K. Jääskeläinen [q], Berthold Langguth [r], Letizia Leocani [s], Alain Londero [t], Raffaele Nardone [u,v,w], Jean-Paul Nguyen [x,y], Thomas Nyffeler [z,aa,ab], Albino J. Oliveira-Maia [ac,ad,ae], Antonio Oliviero [af], Frank Padberg [m], Ulrich Palm [m,ag], Walter Paulus [ah], Emmanuel Poulet [h,ai], Angelo Quartarone [aj], Fady Rachid [ak], Irena Rektorová [al,am], Simone Rossi [an], Hanna Sahlsten [ao], Martin Schecklmann [r], David Szekely [ap], Ulf Ziemann [aq]

+ recent reviews, meta analyses, and clinical trials

Levels of Evidence - Psychiatry

A: definitely effective	major depression
B: probably effective	post-traumatic stress disorder
C: possibly effective	schizophrenia - auditory hallucinations schizophrenia - negative symptoms addiction and craving obsessive compulsive disorder

Levels of Evidence - Neurology & Rehabilitation

A: definitely effective	neuropathic pain motor stroke
B: probably effective	Fibromyalgia (quality of life and pain) Parkinson's disease (antiparkinsonian and antidepressant effects) post-stroke aphasia multiple sclerosis
C: possibly effective	complex regional pain syndrome (type I) epilepsy hemispatial neglect tinnitus Alzheimer's disease

The Academy of Brain Stimulation Education and Certification

The **International Clinical TMS Certification Course** supports a new initiative from internationally renown researchers and clinicians aiming to **bridge the gap between scientific research and clinical practice in the field of non-invasive brain stimulation**

This **LinkedIn page now** provides **free access to relevant scientific publications** from the international brain stimulation literature and inform about **new scientific developments** in the field.

https://www.linkedin.com/company/international-clinical-tms-certification-course/

Your Data Matters

Contents lists available at ScienceDirect

Psychiatry Research

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

Repetitive transcranial magnetic stimulation for major depression: A naturalistic observational study in an Australian private hospital

Nathan L. Dowling[a,*], Richard Bonwick[a], Nitin P. Dharwadkar[b,c], Chee H. Ng[a]

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[b] The Melbourne Clinic, Melbourne, Australia
[c] Monash Alfred Research Centre, Monash University, Melbourne, Australia

ARTICLE INFO

Keywords:
rTMS
Major depression
Naturalistic
Response
Remission

ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is an effective and evidence-based treatment for major depression, which is now as a mainstream treatment in clinical practice. However, there is limited data concerning its use in Australian private psychiatric hospital settings. This retrospective study examined routinely collected data of 153 inpatients, who received 20 rTMS treatments over four weeks. Primary outcomes measures were the 17-item Hamilton Depression Rating Scale (HAMD-17) and the 21-item Depression, Anxiety and Stress Scale (DASS-21). At post-treatment, response and remission rates were 54% and 28%, respectively, for the HAMD-17; and 53% response and 16% remission rates, for the DASS-21 Depression subscale, respectively. Although no gender differences were observed, younger patients demonstrated more improvements during acute rTMS but the effect was not significant after accounting for pre-treatment symptom severity. The findings of this naturalistic study suggest that an acute course of rTMS provided in private clinical settings resulted in similar response and remission rates to longer rTMS courses. Shorter rTMS courses appear to have satisfactory efficacy in treating major depression, in clinically diverse and real-world practice.

The Academy of Brain Stimulation
Education and Certification

TMS: From the Lab to the Clinic

Basic Principles – Science ≠ FDA/CE – Levels of Evidence – Research <-> Clinic

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TMS Treatment of Depression

Dr. Felix Duecker

The Academy of Brain Stimulation
Education and Certification

TMS Treatment of Depression

Why TMS in depression? – rTMS and theta-burst over DLPFC – Acute and long-term effects

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Faculty of Psychology and Neuroscience
Maastricht University
felix.duecker@maastrichtuniversity.nl

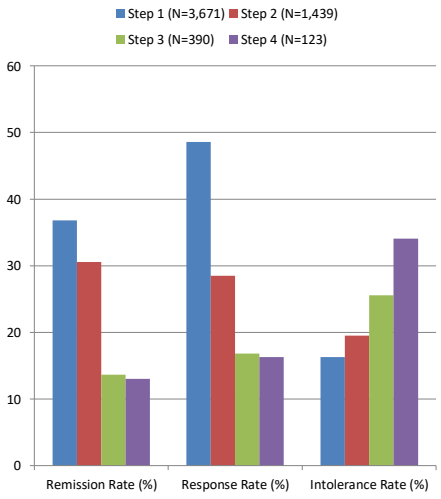
Depression: Treatment Efficacy (not TMS)

famous STAR*D study

cumulative remission rate: 67%

probability of remission decreases dramatically after two treatment attempts

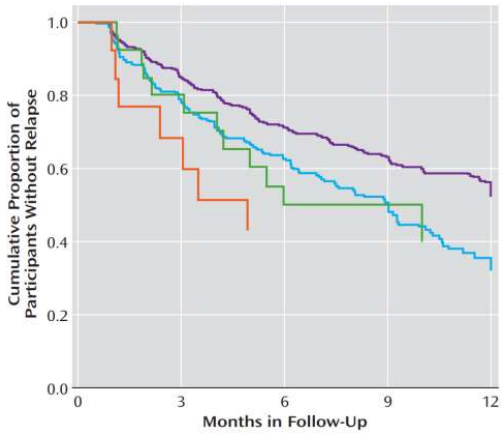
about 25% of patients do not tolerate and/or stop treatment



Rush et al. (2006)

Depression: Relapse after Remission (not TMS)

> 50% relapse within first year after remission



Rush et al. (2006)

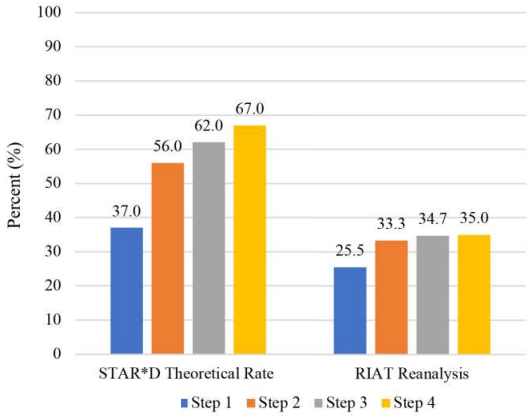
Depression: Treatment Efficacy (not TMS)

reanalysis of patient-level data

- stricter adherence to original reseach protocol in terms of outcome measure, accounting for drop-out, inclusion criteria, etc...

cumulative remssion rate was approximately half of that originally reported!

a new baseline for TMS effects



Pigott et al. (2023)

TMS Treatment of Depression

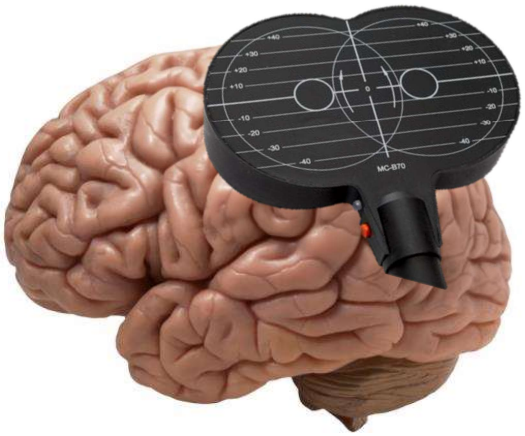
explored since the 1990s

novel treatment approach
- targets specific brain areas to induce neuro-plasticity

definite efficacy (level A)
- large multi-center trials

no severe side effects

FDA-approved in 2008; growing world-wide

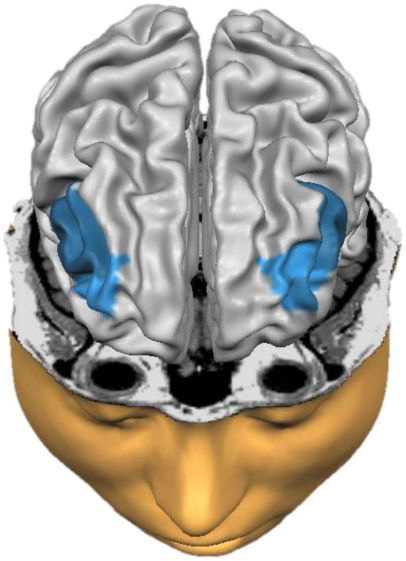


Rationale for rTMS in Depression

DLPFC as "window" to the depression network

frontal asymmetry in DLPFC
- hyperactivity right
- hypoactivity left

possible rTMS treatments
- high freq. left
- low freq. right
- both

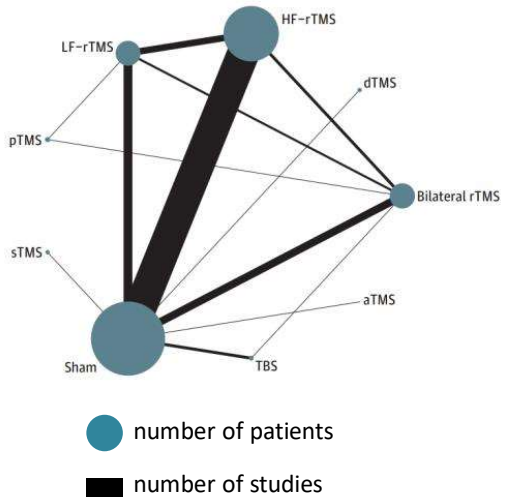


Finding the best TMS protocol is difficult

strong focus on high-freq. stimulation over left DLPFC

mostly comparisons to sham

research bias does not necessarily reflect differences in efficacy!



Brunoni et al. (2017)

The Original Depression TMS Protocol

Stimulation Site
left DLPFC
5 cm anterior to motor hotspot

Stimulation Frequency
10Hz rTMS

Stimulation Intensity
120% resting motor threshold

TMS Timing
4 seconds ON, 26 seconds OFF
75 trains/repetitions
= 37.5 minutes

Number of Sessions
5 days a week
6 weeks of treatment
= 30 sessions

Total Dosage
3,000 pulses per session
90,000 for entire treatment

→ **FDA/CE-approved protocol**
→ **Level A recommendation**

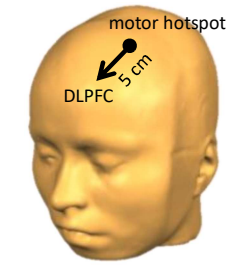
The Original Depression TMS Protocol

1 - Find motor hotspot

2 - Determine motor threshold
- → only once per week
- → essential for stimulation intensity

3 - Move TMS coil to DLPFC
- → 5 cm rule

4 - Apply treatment protocol



Depression: RCT for FDA Approval

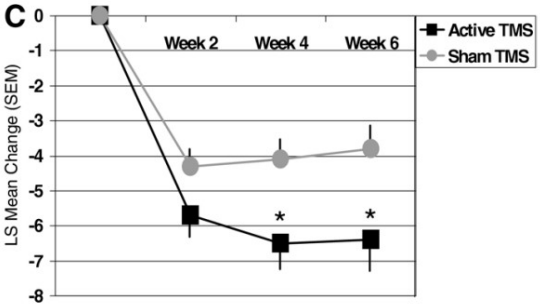
large multi-center trial led to initial FDA approval in USA

301 patients (active 155; sham 146)

treatment-resistant (1.6 failed attempts)

medication-free

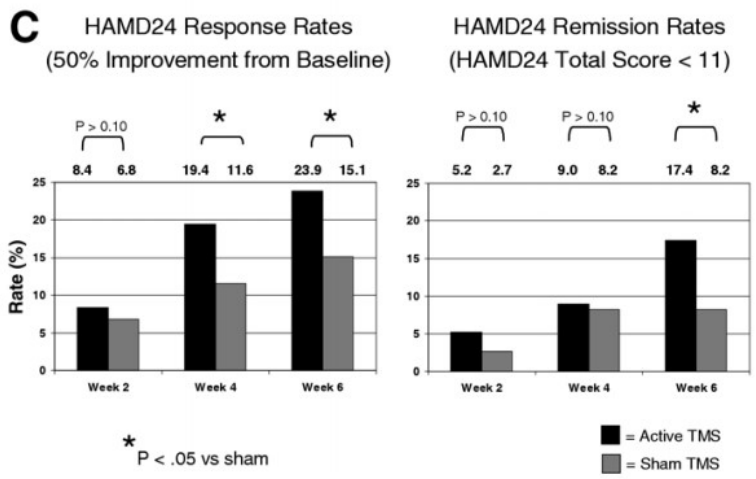
adequate sham control
- → mimicking both auditory and somato-sensory side effects of TMS
- → successful blinding



reduction of depression score

O'Reardon et al. (2007). Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression. Biological Psychiatry

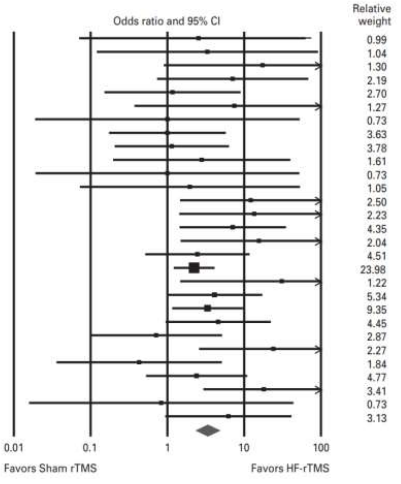
Depression: RCT for FDA Approval



O'Reardon et al. (2007). Efficacy and Saftey of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression. Biological Psychiatry

Depression: Meta-Analysis – Response Rate

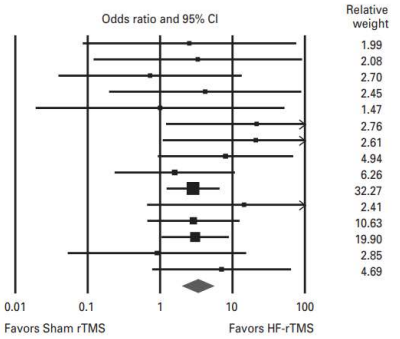
Study name	Odds ratio	Lower limit	Upper limit	z	p	Active rTMS	Sham rTMS
	Statistics for each study						
George *et al.* (1997)	2.538	0.085	75.765	0.538	0.591	1/7	0/5
Berman *et al.* (2000)	3.316	0.120	91.601	0.708	0.479	1/10	0/10
George *et al.* (2000)	17.348	0.895	336.226	1.887	0.059	9/20	0/10
Garcia-Toro *et al.* (2000)	7.083	0.731	68.607	1.690	0.091	5/17	1/18
Boutros et al. (2002)	1.167	0.151	9.006	0.148	0.882	3/12	2/9
Padberg *et al.* (2002)	7.452	0.371	149.546	1.313	0.189	5/20	0/10
Fitzgerald *et al.* (2003)	1.000	0.019	52.977	0.000	1.000	1/20	1/20
Hoppner *et al.* (2003)	1.000	0.173	5.772	0.000	1.000	5/10	5/10
Nahas *et al.* (2003)	1.143	0.205	6.366	0.152	0.879	4/11	4/12
Holtzheimer *et al.* (2004)	2.800	0.196	40.057	0.758	0.448	2/7	1/8
Koerselman *et al.* (2004)	1.000	0.019	52.362	0.000	1.000	1/26	1/26
Mosimmann *et al.* (2004)	1.966	0.072	53.478	0.401	0.688	1/15	0/9
Rossini *et al.* (2005)	12.190	1.460	101.804	2.309	0.021	16/37	1/17
Su *et al.* (2005)	13.500	1.421	128.258	2.266	0.023	12/20	1/10
Avery *et al.* (2006)	7.104	1.437	35.120	2.405	0.016	11/35	2/33
Anderson *et al.* (2007)	15.600	1.481	164.376	2.287	0.022	6/11	1/14
Loo *et al.* (2007)	2.462	0.514	11.799	1.126	0.260	6/19	3/19
O'Reardon *et al.* (2007)	2.230	1.204	4.130	2.550	0.011	37/155	18/146
Stern *et al.* (2007)	31.000	1.462	657.278	2.204	0.028	5/10	0/15
Mogg *et al.* (2008)	4.105	0.978	17.229	1.930	0.054	9/28	3/29
George *et al.* (2010)	3.338	1.151	9.680	2.220	0.026	14/92	5/98
Palliere-Martinot *et al.* (2010)	4.583	0.945	22.235	1.889	0.059	10/18	3/14
Triggs *et al.* (2010)	0.714	0.099	5.178	−0.333	0.739	4/18	2/7
Zheng *et al.* (2010)	24.000	2.574	223.790	2.790	0.005	12/19	1/15
Blumberger *et al.* (2012)	0.429	0.036	5.126	−0.669	0.503	1/22	2/20
Zhang *et al.* (2011)	2.400	0.524	10.992	1.128	0.259	8/14	5/14
Bakim *et al.* (in press)	18.000	2.937	110.307	3.125	0.002	18/23	2/12
Fitzgerald *et al.* (2012)	0.830	0.016	43.775	−0.092	0.927	1/24	1/20
Hernández-Ribas *et al.* (2013)	6.222	0.936	41.382	1.891	0.059	7/10	3/11
	3.306	2.354	4.643	6.899	0.000	214/730	67/641



Berlim et al. (2014)

Depression: Meta-Analysis – Remission Rate

Study name	Odds ratio	Lower limit	Upper limit	z	p	Active rTMS	Sham rTMS
	Statistics for each study					Remitters/total	
George *et al.* (1997)	2.538	0.085	75.765	0.538	0.591	1/7	0/5
Berman *et al.* 2000	3.316	0.120	91.601	0.708	0.479	1/10	0/10
Boutros *et al.* (2002)	0.727	0.039	13.452	−0.214	0.831	1/12	1/9
Padberg *et al.* (2002)	4.200	0.197	89.609	0.919	0.358	3/20	0/10
Koerselman *et al.* (2004)	1.000	0.019	52.362	0.000	1.000	1/26	1/26
Rossini *et al.* (2005)	21.596	1.205	387.150	2.086	0.037	14/37	0/17
Su *et al.* (2005)	21.000	1.085	406.551	2.014	0.044	10/20	0/10
Avery *et al.* (2006)	8.000	0.926	69.078	1.891	0.059	7/35	1/33
Loo *et al.* (2007)	1.594	0.235	10.817	0.477	0.633	3/19	2/19
O'Reardon *et al.* (2007)	2.853	1.228	6.633	2.436	0.015	22/155	8/146
Stern *et al.* (2007)	14.467	0.659	317.545	1.695	0.090	3/10	0/15
Mogg *et al.* (2008)	2.889	0.664	12.560	1.415	0.157	7/28	3/29
George *et al.* (2010)	3.061	1.046	8.960	2.041	0.041	13/92	5/98
Blumberger *et al.* (2012)	0.905	0.053	15.492	−0.069	0.945	1/22	1/20
Bakim *et al.* (in press)	7.071	0.774	64.575	1.733	0.083	9/23	1/12
	3.298	2.042	5.325	4.881	0.000	96/516	23/459



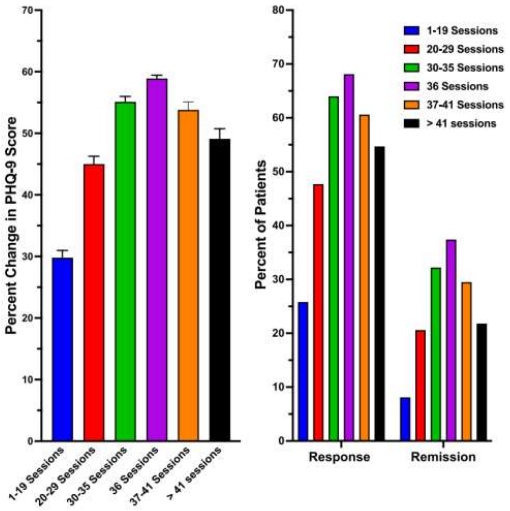
Berlim et al. (2014)

Depression: How many sessions?

large-scale study (N = 7215)

naturalistic setting
-> many factors not controlled for

30+ sessions are required for full clinical benefit in most patients



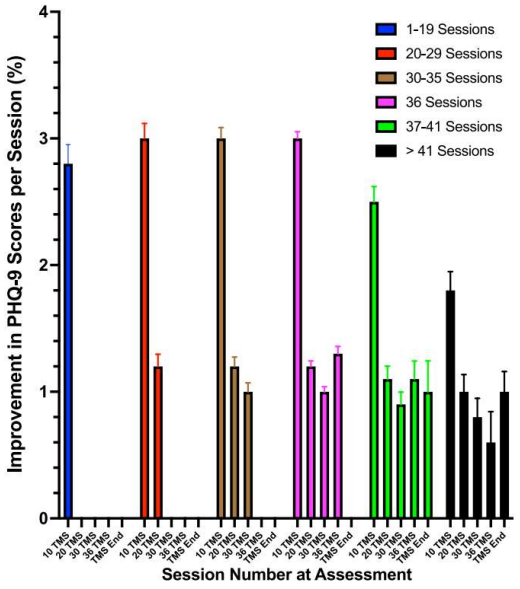
Hutton et al. (2023)

Depression: Typical Trajectory of Change

rapid improvement over the first 10 sessions is common

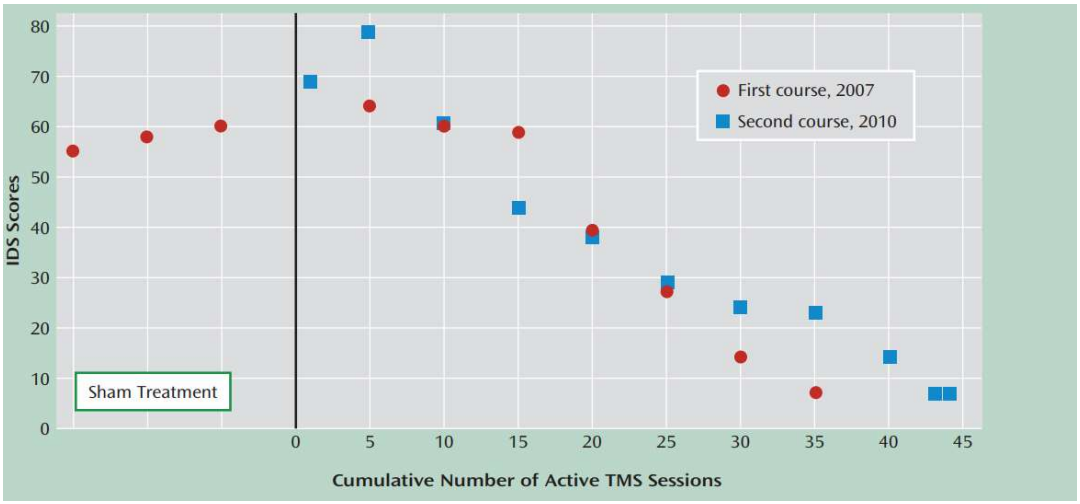
additional sessions have additional effects, but at a slower rate

no evidence for a plateau



Hutton et al. (2023)

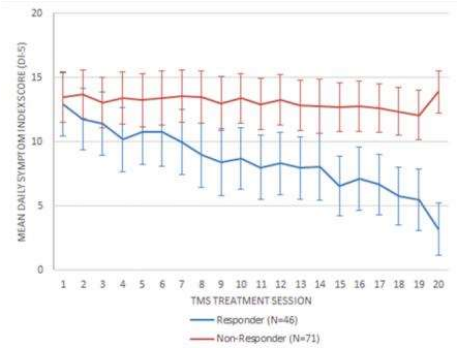
Depression: An Example Patient with Response



George and Post (2011)

Depression: Non-Responders

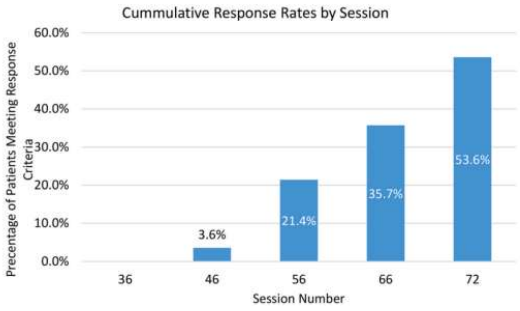
Prediction is difficult



improvement < 4 points (session 10)
-> probability non-response at session 20 is 75%

improvement ≥ 4 points (session 10)
-> probability response at session 20 is 66%.

Late Responders exist!



sample of 28 non-responders after 36 sessions

50% response rate after 72 sessions

Gillet al. (2022) & Razafsha et al. (2023)

The Updated Depression TMS Protocol(s)

Stimulation Site
left DLPFC
5/6/7 cm rule or electrode position F3

Stimulation Frequency
10Hz rTMS

Stimulation Intensity
120% resting motor treshold

TMS Timing
4 seconds ON, 11 seconds OFF
75 trains/repetitions
= 19 minutes

Number of Sessions
5 days a week
6 weeks of treatment
= 30 sessions

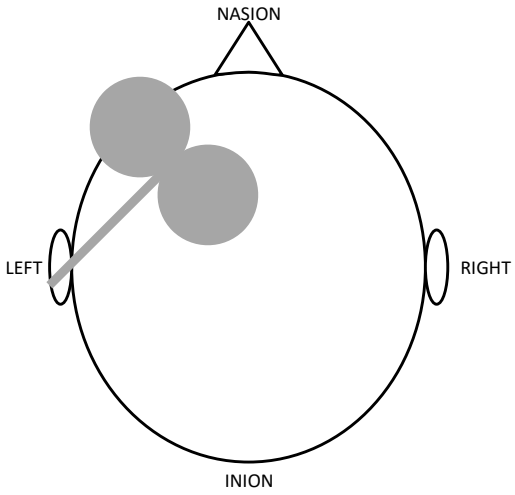
Total Dosage
3,000 pulses per session
90,000 for entire treatment

→ **FDA/CE-approved protocol**
→ **Level A recommendation**

Dorsolateral Prefrontal Cortex (DLPFC)

TMS coil position based on F3

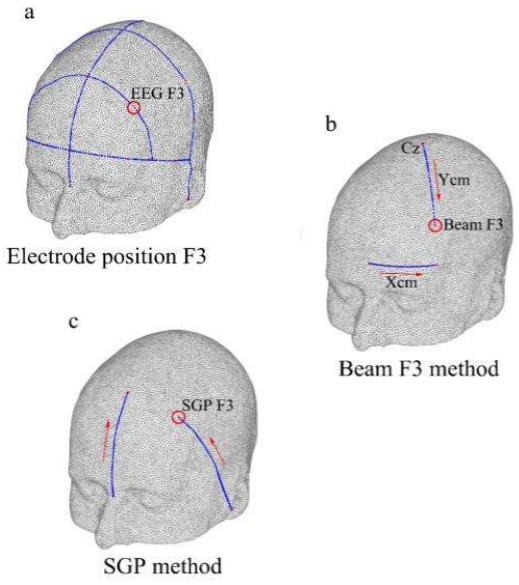
TMS coil handle points in the lateral-posterior direction, at 45 degrees relative to the midline (same as motor cortex stimulation)



Dorsolateral Prefrontal Cortex (DLPFC)

TMS coil position based on F3

TMS coil handle points in the lateral-posterior direction, at 45 degrees relative to the midline (same as motor cortex stimulation)



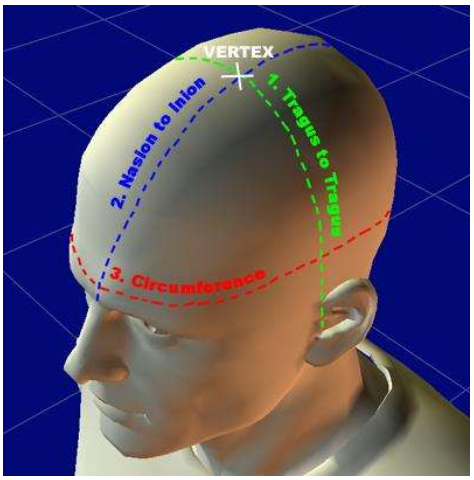
Beam F3 system

www.clinicalresearcher.org/f3

Software requires 3 skull measurements

- tragus to tragus distance
- nasion to inion distance
- head circumference

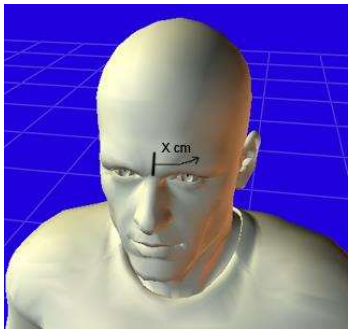
mark vertex on the head

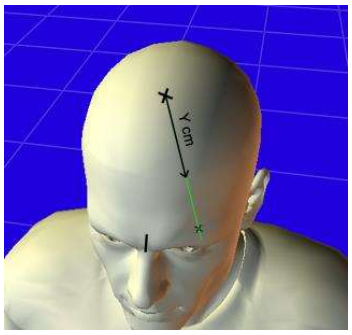


Beam F3 system

Software gives 2 output values

- distance along circumference from midline (X cm)
- distance from vertex (Y cm)





Depression: Low-Freq. TMS Over Right DLPFC

Stimulation Site
right DLPFC
5 cm rule / F4

Stimulation Frequency
1Hz rTMS

Stimulation Intensity
120% resting motor treshold

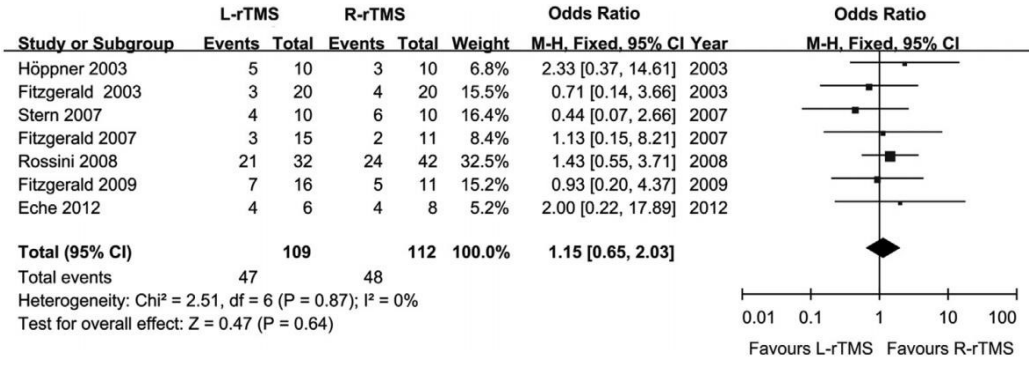
TMS Timing
continuous rTMS for 25 minutes

Number of Sessions
5 days a week
6 weeks of treatment
= 30 sessions

Total Dosage
1,500 pulses per session
45,000 for entire treatment

→ **Level B recommendation**

Depression: Left DLPFC vs. Right DLPFC



Probably no difference between left and right DLPFC stimulation (Level C)

Chen et al. (2013)

Depression: Bilateral TMS Over DLPFC

Stimulation Sites
first right then left DLPFC
5 cm anterior to motor hotspot

Stimulation Frequency
1Hz rTMS; 10Hz rTMS

Stimulation Intensity
120% resting motor treshold

TMS Timing (standard protocols)
1Hz rTMS for 10 minutes
10 Hz rTMS for 19 minutes

Number of Sessions
5 days a week
6 weeks of treatment
= 30 sessions

Total Dosage
2,100 pulses per session
63,000 for entire treatment

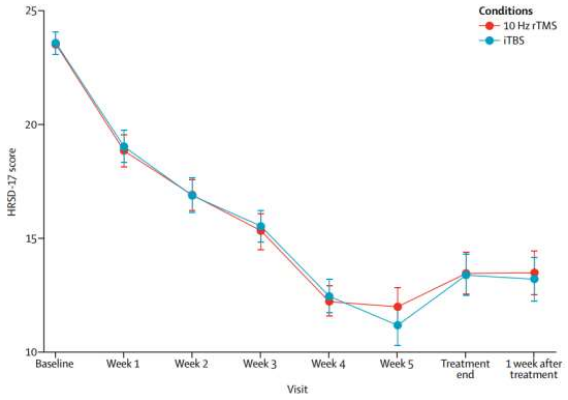
→ **Level B recommendation**

Depression: Theta Burst Stimulation

non-inferiority study
10 Hz vs. iTBS
identical efficacy and tolerability

main differences
37.5 minutes vs. 3 minutes
3000 pulses vs. 600 pulses
10 Hz vs. 50 Hz triplets

response rate: 40 % vs. 39%
remission rate: 26 %. vs 25%



Blumberger et al. (2018)

Depression: iTBS Over Left DLPFC

Stimulation Site
left DLPFC
(electrode position F3)

Stimulation Frequency
50Hz triplets, 5Hz rhythm

Stimulation Intensity
120% resting motor treshold

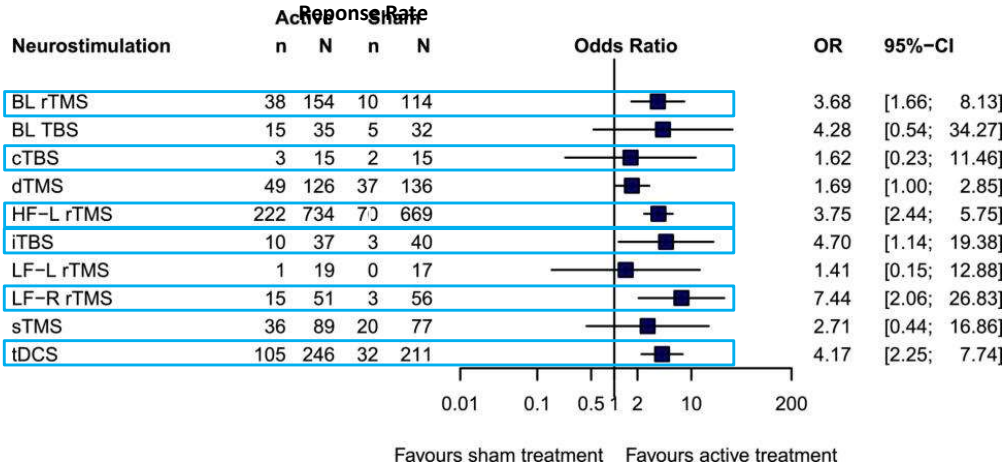
TMS Timing
2 seconds ON; 8 seconds OFF
= 190 seconds

Number of Sessions
5 days a week
6 weeks of treatment
= 30 sessions

Total Dosage
600 pulses per session
18,000 for entire treatment

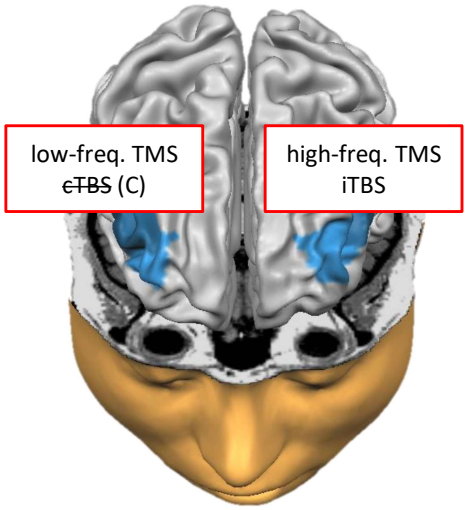
→ **FDA/CE-approved protocol**
→ **replicated in 2022; updated recommendation incoming**

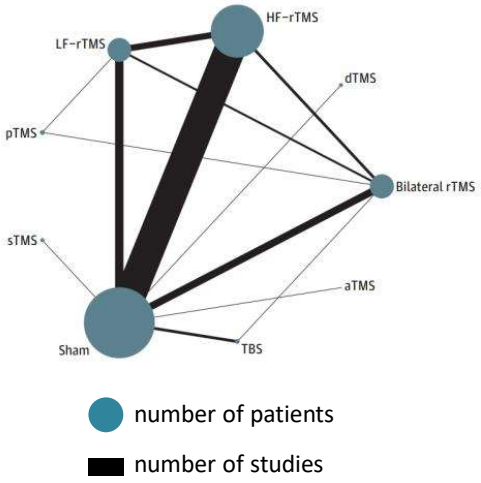
Depression: Effective Protocols



Mutz et al. (2018)

Depression: Best TMS Protocol Is Unknown





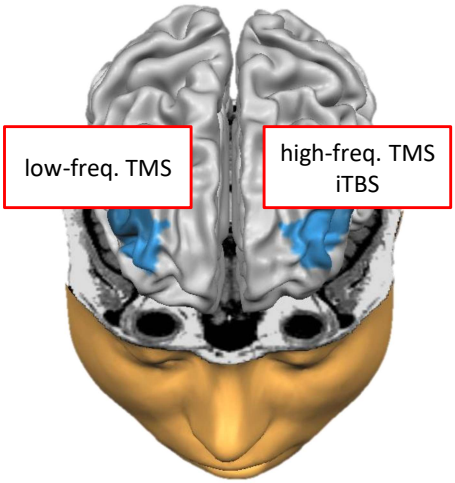
Brunoni et al. (2017)

How to choose a TMS protocol in depression?

high-frequency rTMS (left DLPFC)
- → standard protocol
- → tried and tested
- → level A recommendation

low-frequency rTMS (right DLPFC)
- → lower risk and less side effects
- → sometimes preferred if psychomotor agitation is present
- → level B recommendation

intermittent theta burst (left DLPFC)
- → very time efficient
- → particularly suited for accelerated TMS protocols
- → awaiting updated recommendation



Depression: Long-Lasting Effects?

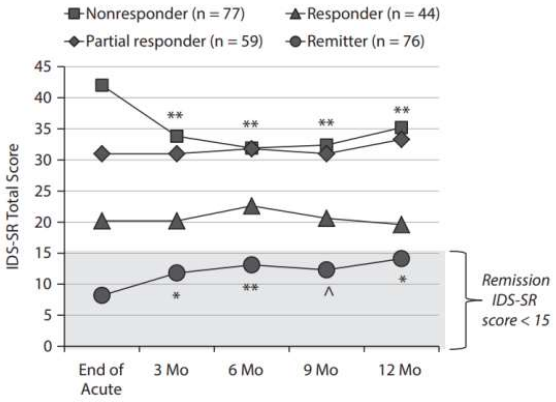
6 weeks of treatment

42 rTMS treatment sites in USA
→ real world practice setting!

standard protocol

response rate: 46.5 %
remission rate: 29.7 %

effects stable over time



Depression Scores → 12 months

Dunner et al. (2014)

Depression with comorbid anxiety disorders

no placebo control, but reduction of scores not different between groups

→ CE-approved

Table 4
Mean HAMA, HAMD21, MADRS and ZUNG scores for patients meeting the criteria for no anxiety disorders ($N = 76$) or for anxiety comorbidities ($N = 172$). p = significance between anxious and non-anxious groups (independent samples t-tests).

Mean (SD)	No anxiety	Anxiety	p-value
Baseline HAMA	16.32 (6.46)	21.55 (7.21)	<0.001
Final HAMA	10.54 (6.02)	14.58 (8.34)	<0.001
Reduction in HAMA	5.77 (7.04)	6.97 (8.19)	0.243
t-test comparing baseline and final HAMA	$p < 0.001$***	$p < 0.001$***	
Baseline HAMD	19.57 (5.59)	24.59 (6.33)	<0.001
Final HAMD	12.32 (6.77)	15.38 (8.69)	0.003
Reduction in HAMD	7.25 (6.76)	9.21 (8.80)	0.058
t-test comparing baseline and final HAMD	$p < 0.001$***	$p < 0.001$***	
Baseline MADRS	26.07 (7.10)	32.15 (7.12)	<0.001
Final MADRS	17.08 (10.70)	22.23 (11.84)	0.001
Reduction in MADRS	8.99 (9.70)	9.91 (10.90)	0.524
t-test comparing baseline and final MADRS	$p < 0.001$***	$p < 0.001$***	
Baseline ZUNG	54.76 (6.87)	58.46 (6.70)	<0.001
Final ZUNG	45.09 (9.54)	48.97 (11.35)	0.06
Reduction in ZUNG	9.67 (10.71)	9.49 (10.52)	0.903
t-test comparing baseline and final ZUNG	$p < 0.001$***	$p < 0.001$***	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Clarke et al. (2019). Journal of Affective Disorders.

Peripartum Depression

only 87 patients in published work
-> 1 RCT
-> 3 uncontrolled trials
-> 8 case studies

various TMS protocols, including...
-> HF left DLPFC
-> LF right DLPFC

TMS appears effective and no serious adverse events so far
-> no recommendation yet

Journal of Psychiatric Research 115 (2019) 142–150

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

A systematic review of the safety and effectiveness of repetitive transcranial magnetic stimulation in the treatment of peripartum depression

Jaeden Cole[a,b,c], Katherine Bright[a], Lisa Gagnon[a], Alexander McGirr[a,b,c,*]

Cole et al. (2019).

Bipolar Depression

large-scale RCTs are still missing

mixed results with various protocols
-> no recommendation

seems to be **ineffective** in cases of depression with **psychotic features**

trials do not provide evidence that TMS is associated with an increased risk of hypomanic switch, but…

Brain Stimulation 13 (2020) 705–706

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Treatment-emergent mania with psychosis in bipolar depression with left intermittent theta-burst rTMS

The Academy of Brain Stimulation
Education and Certification

TMS Treatment of Depression

Why TMS in depression? – rTMS and theta-burst over DLPFC – Acute and long-term effects

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Faculty of Psychology and Neuroscience
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TMS Treatment in Psychiatry
Beyond Depression

Dr. Felix Duecker

The Academy of Brain Stimulation
Education and Certification

TMS in Psychiatry beyond Depression

OCD – PTSD – schizophrenia – addiction and craving

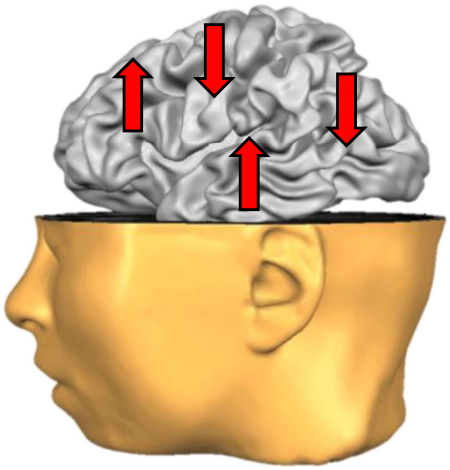
Felix Duecker, PhD
Department of Cognitive Neuroscience
Faculty of Psychology and Neuroscience
Maastricht University
felix.duecker@maastrichtuniversity.nl

Levels of Evidence - Psychiatry

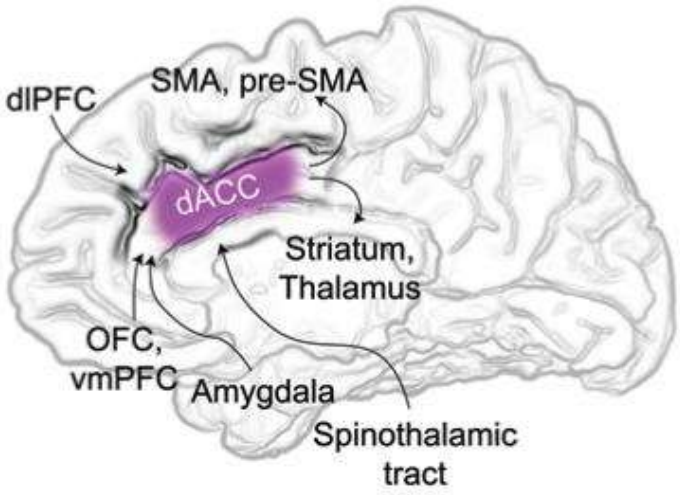
A: definitely effective	major depression
B: probably effective	post-traumatic stress disorder
C: possibly effective	schizophrenia - auditory hallucinations schizophrenia - negative symptoms addiction and craving obsessive compulsive disorder

Treatment: Basic Principles

Application of long-lasting inhibitory or excitatory TMS protocols, often for many sessions, that ideally reverse the brain state back to normal

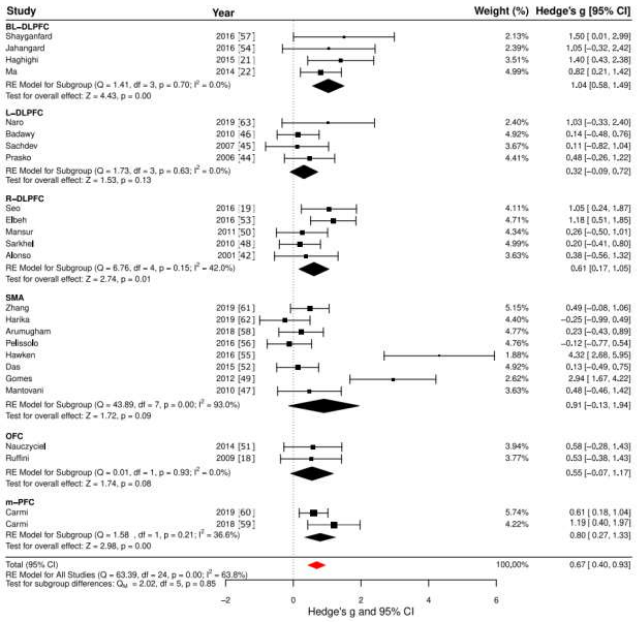


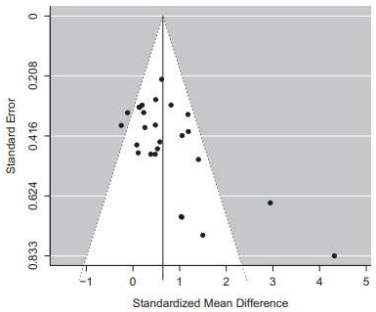
Obsessive Compulsive Disorder



McGovern & Sheth (2017). J. Neurosurg.

Obsessive Compulsive Disorder





Prabhavi (2021). Biological Psychiatry

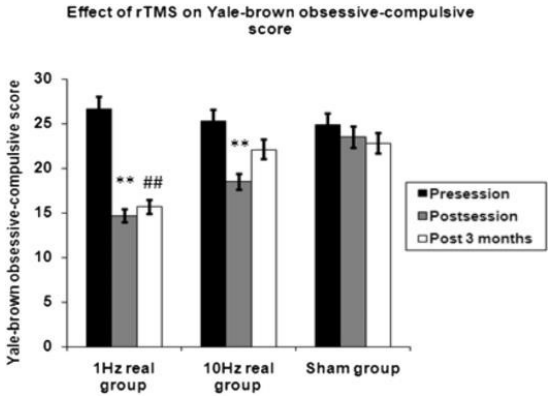
Obsessive Compulsive Disorder (right DLPFC)

Hyperactivity in frontal cortex

10 sessions over right DLPFC

- 1 Hz rTMS
- 10 Hz rTMS
- Sham

1 Hz rTMS effects still present after 3 months



Elbeh et al. (2016). Repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorders. Psychiatry Research

OCD: Low-Freq. TMS Over Right DLPFC

Stimulation Site
right DLPFC
5 cm rule / F4

Stimulation Frequency
1Hz rTMS

Stimulation Intensity
120% resting motor treshold

TMS Timing
continuous rTMS for 25 minutes

Number of Sessions
5 days a week
4+ weeks of treatment

Total Dosage
1,500 pulses per session

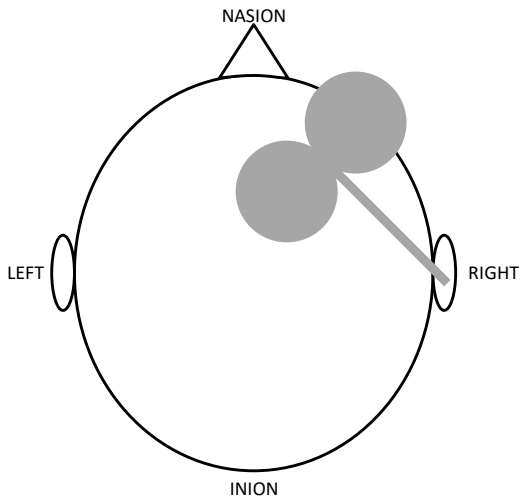
-> Level C recommendation

-> No established protocol!
We advise to follow the depression approach.

Right Dorsolateral Prefrontal Cortex (DLPFC)

TMS coil position based on “Beam F4”

TMS coil handle points in the lateral-posterior direction, at 45 degrees relative to the midline (same as motor cortex stimulation)

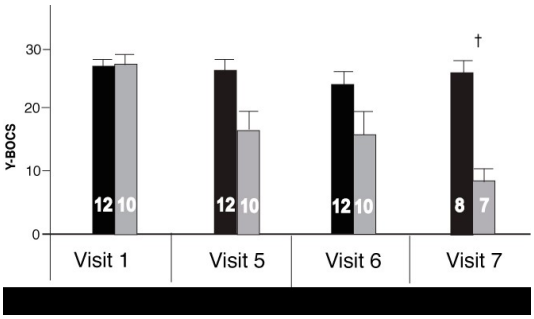


Obsessive Compulsive Disorder (Pre-SMA)

(Pre-)Supplementary motor area involved in behavioural inhibition (hyperactivity)

25 sessions of 1 Hz rTMS

Effects still present at 6 weeks post-treatment



Hawken et al. (2016). Transcranial Magnetic Stimulation of the Supplementary Motor Area in the Treatment of Obsessive-Compulsive Disorder. Int J Molecular Sciences

OCD: Low-Freq. TMS Over Pre-SMA

Stimulation Site
Bilateral Pre-SMA
15% anterior to Cz
(on the nasion-inion line)

Stimulation Frequency
1Hz rTMS

Stimulation Intensity
120% resting motor treshold

TMS Timing
continuous rTMS for 25 minutes

Number of Sessions
5 days a week
4+ weeks of treatment

Total Dosage
1,500 pulses per session

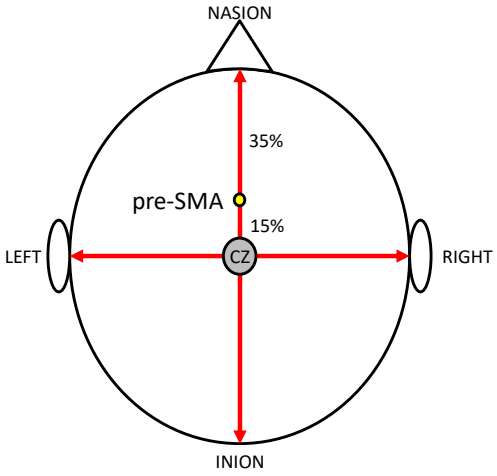
-> No recommendation considered to be very promising

Pre-Supplementary Motor Area (pre-SMA)

TMS coil on the midline to target the pre-supplementary motor area in both hemisphere simultaneously

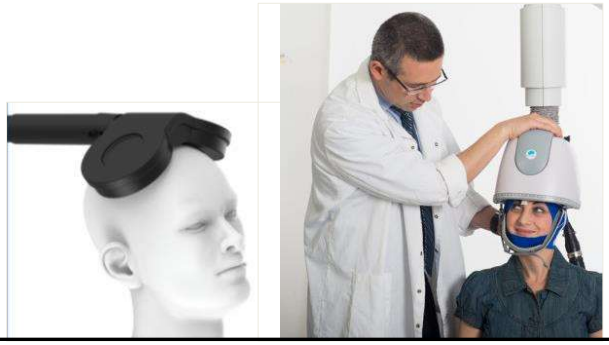
TMS coil position based on nasion-inion distance, either...
...15% anterior of CZ, or
...35% posterior of nasion.

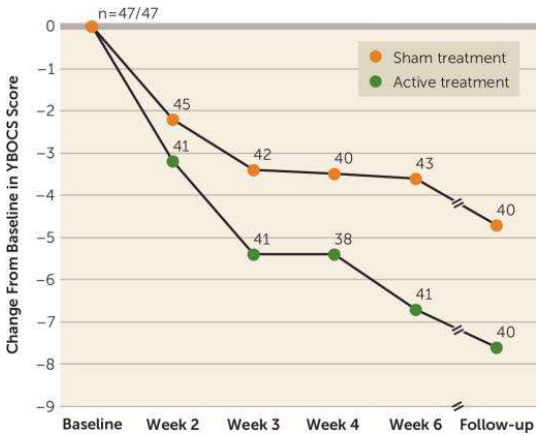
TMS coil handle points in the posterior direction



Obsessive Compulsive Disorder (DMPFC)

N = 99, 11 centers
30 sessions of high-freq rTMS
20 Hz protocol
1 month follow-up





Carmi et al. (2019)

OCD: High-Freq. TMS Over DMPFC

Stimulation Site
dorsomedial prefrontal cortex
25% nasion-to-inion distance

Stimulation Frequency
20Hz rTMS

Stimulation Intensity
100% resting **leg** motor treshold

TMS Timing
2 seconds ON, 20 seconds OFF
50 trains/repetitions
= 18 minutes

Number of Sessions
5 days a week
6 weeks of treatment
= 30 sessions

Total Dosage
2,000 pulses per session

-> FDA/CE-approved protocol

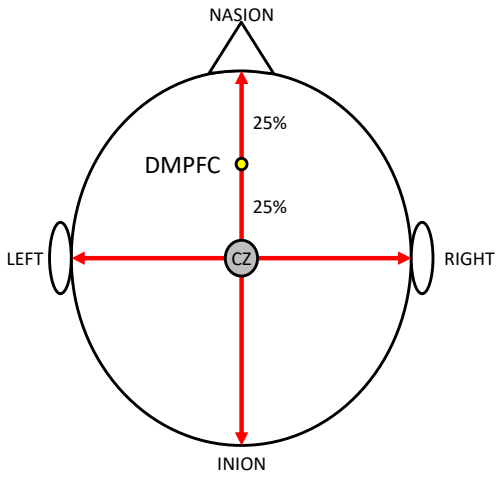
-> but no recommendation yet

Dorsomedial Prefrontal Cortex (DMPFC)

TMS coil on the midline to target the dorsomedial prefrontal cortex in both hemisphere simultaneously

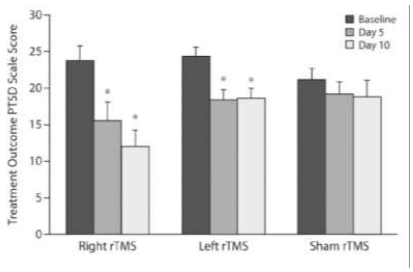
TMS coil position based on nasion-inion distance,...
...25% anterior of CZ, or
...25% posterior of nasion.

TMS coil handle points in the posterior direction (unlike DMPFC TMS in depression)

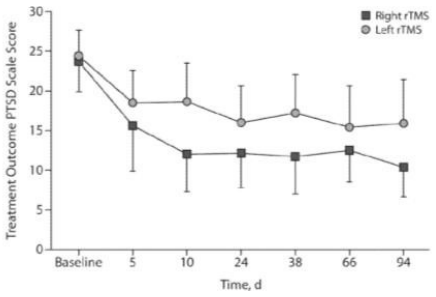


Post-Traumatic Stress Disorder (PTSD)

20 Hz rTMS, 10 sessions



long-term effects



hypo-activity in prefrontal areas
high-freq. rTMS over right and left DLPFC reduces PTSD scores
right DLPFC might be more effective

Boggio et al. (2010). Noninvasive Brain Stimulation With High-Frequency and Low-Intensity Repetitive Transcranial Magnetic Stimulation Treatment for PTSD. J Clin Psychiatry

PTSD: High-Freq. TMS Over Right DLPFC

Stimulation Site
right DLPFC
5 cm rule / F4

Stimulation Frequency
10Hz rTMS

Stimulation Intensity
120% resting motor treshold

TMS Timing
4 seconds ON, 26 seconds OFF
75 trains/repetitions
= 37 minutes

Number of Sessions
5 days a week
6 weeks of treatment

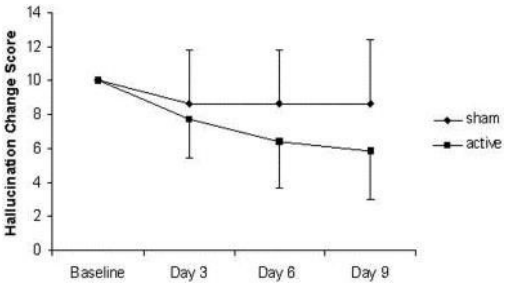
Total Dosage
3,000 pulses per session

-> Level B recommendation

-> No established protocol! We advise to copy depression parameters.

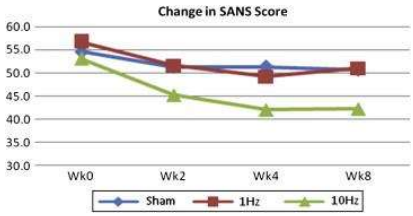
Schizophrenia

Positive Symptoms



low-freq. rTMS over temporo-parietal cortex reduces auditory hallucinations

Negative Symptoms



high-freq. rTMS over left DLPFC reduces negative symptoms (link to depression?)

Hoffman et al. (2005). Teomporoparietal Trancranial Magnetic Stimulation of Auditory Hallucinations. Biological Psychiatry
Schneider et al. (2008). Repetitive Transcranial Magnetic Stimulation as an Augmentation Treatment for the Negative Symptoms of Schizophrenia. Brain Stimulation

Substance abuse, addiction and craving

Alcohol craving → no recommendation

Nicotine craving → Level C recommendation

Drug craving → no recommendation

Eating disorders → no recommendation

Gambling disorder → no recommendation

mostly high-freq. rTMS over left DLPFC

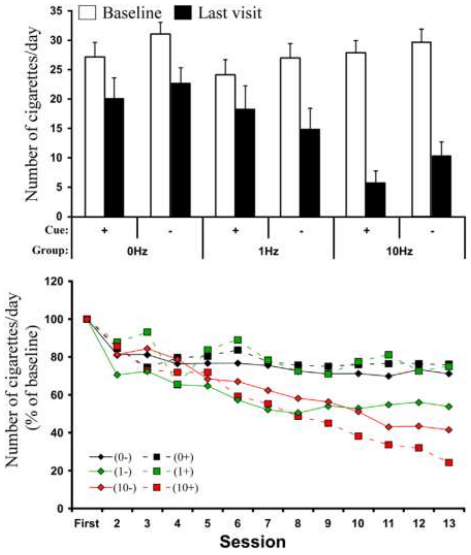
Nicotine Craving - Cigarettes

13 sessions with special H-coil, targeting lateral PFC and the insula

10 Hz stimulation decreased cigarette consumption (44% abstinence)

Effects still present at 6 months post-treatment

FDA/CE-approved protocol

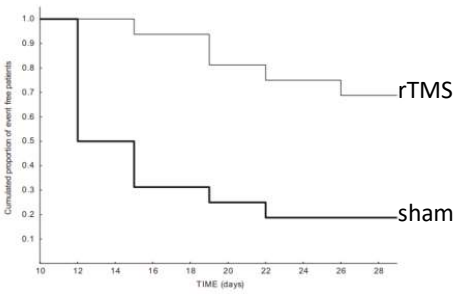


Dinur-Klein et al. (2014). Smoking Cessation Induced by Deep Repetitive Transcranial Magnetic Stimulation of the Prefrontal and Insular Cortices. Biol Psychiatry

Cocaine Addiction

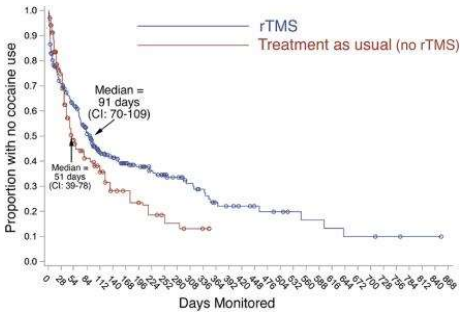
Pilot study (N = 32)

daily TMS for one week
weekly maintence session



Observational study (N = 284)

lapses to cocaine use
decreased to once per month



Terraneo et al. (2017). Brain Stimulation; Madeo et al. (2020). Front. Psychiatry

Cocaine Addiction: High-Freq. TMS Over Left DLPFC

Stimulation Site
- left DLPFC
- Beam F3 or MRI-based
- (MNI coordinates [x= -50, y=30, z=36])

Stimulation Frequency
- 15Hz rTMS

Stimulation Intensity
- 100% resting motor treshold

TMS Timing
- 4 seconds ON, 15 seconds OFF
- 40 trains/repetitions
- = 13 minutes

Number of Sessions
- daily TMS in week 1
- continue with weekly sessions
- option to do 2 sessions per day

-> CE-approved protocol
-> but no recommendation yet

Levels of Evidence - Psychiatry

A: definitely effective	major depression
B: probably effective	post-traumatic stress disorder
C: possibly effective	schizophrenia - auditory hallucinations schizophrenia - negative symptoms addiction and craving obsessive compulsive disorder

the end

The Academy of Brain Stimulation
Education and Certification

TMS in Psychiatry beyond Depression

OCD – PTSD – schizophrenia – addiction and craving

Felix Duecker, PhD
Department of Cognitive Neuroscience
Faculty of Psychology and Neuroscience
Maastricht University
felix.duecker@maastrichtuniversity.nl

TMS Therapies in Neurology

Prof. Dr. Alexander Sack

The Academy of Brain Stimulation
Education and Certification

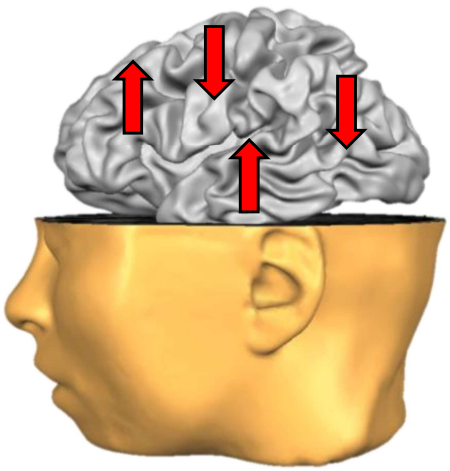
TMS in Neurology

Neuropathic Pain & Fibromyalgia – Multiple Sclerosis – Epilepsy – Tinnitus
Parkinson's Disease – Dementia – Disorders of Consciousness

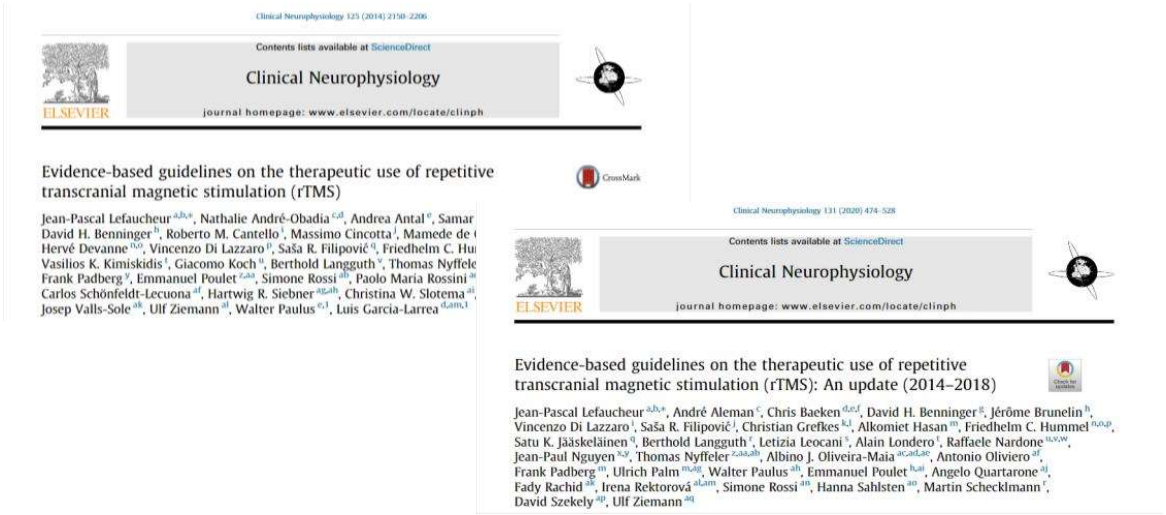
Prof. Dr. Alexander Sack
Department of Psychiatry and Neuropsychology
School for Mental Health and Neuroscience (MHeNs) Brain+Nerve Centre
Maastricht University Medical Centre+ (MUMC+)

Treatment: Basic Principles

Application of long-lasting inhibitory or excitatory TMS protocols, often for many sessions, that ideally reverse the brain state back to normal



Efficacy of TMS Treatment



Clinical Neurophysiology 125 (2014) 2150–2206

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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 David H. Benninger [b], Roberto M. Cantello [f], Massimo Cincotta [f], Mamede de Hervé Devanne [b,g], Vincenzo Di Lazzaro [h], Saša R. Filipović [i], Friedhelm C. Hu Vasilios K. Kimiskidis [j], Giacomo Koch [k], Berthold Langguth [l], Thomas Nyffele Frank Padberg [y], Emmanuel Poulet [z,aa], Simone Rossi [ab], Paolo Maria Rossini [ac] Carlos Schönfeldt-Lecuona [ad], Hartwig R. Siebner [ae,af,ah], Christina W. Slotema [ai], Josep Valls-Sole [ak], Ulf Ziemann [al], Walter Paulus [e,*], Luis Garcia-Larrea [d,am,*]

Clinical Neurophysiology 131 (2020) 474–528

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Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)

Jean-Pascal Lefaucheur [a,b,*], André Aleman [c], Chris Baeken [d,e,f], David H. Benninger [g], Jérôme Brunelin [h], Vincenzo Di Lazzaro [i], Saša R. Filipović [j], Christian Grefkes [k,l], Alkomiet Hasan [m], Friedhelm C. Hummel [n,o,p], Satu K. Jääskeläinen [q], Berthold Langguth [r], Letizia Leocani [s], Alain Londero [t], Raffaele Nardone [u,v,w], Jean-Paul Nguyen [x,y], Thomas Nyffeler [z,aa,ab], Albino J. Oliveira-Maia [ac,ad,ae], Antonio Oliviero [af], Frank Padberg [m], Ulrich Palm [m,ag], Walter Paulus [ah], Emmanuel Poulet [h,ai], Angelo Quartarone [aj], Fady Rachid [ak], Irena Rektorová [al,am], Simone Rossi [an], Hanna Sahlsten [ao], Martin Schecklmann [r], David Szekely [ap], Ulf Ziemann [aq]

+ recent reviews, meta analyses, and clinical trials

Levels of Evidence - Neurology & Rehabilitation

A: definitely effective	**neuropathic pain** motor stroke
B: probably effective	**fibromyalgia (quality of life and pain)** **Parkinson's disease (antiparkinsonian and antidepressant effects)** post-stroke aphasia **multiple sclerosis**
C: possibly effective	**complex regional pain syndrome (type I)** **epilepsy** hemispatial neglect **tinnitus** **Alzheimer's disease**

Neuropathic Pain

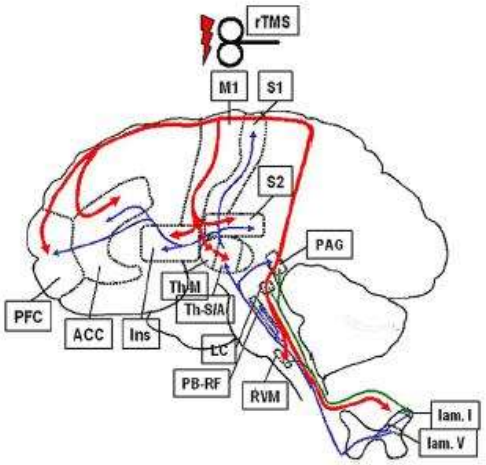
inspired by motor cortex stimulation implant;
mechanisms unclear!

high freq. rTMS (10Hz or 20Hz) over
primary motor cortex, contralateral to pain

effects often within a few sessions, but with current protocols rarely long-lasting effects

no evidence for other targets

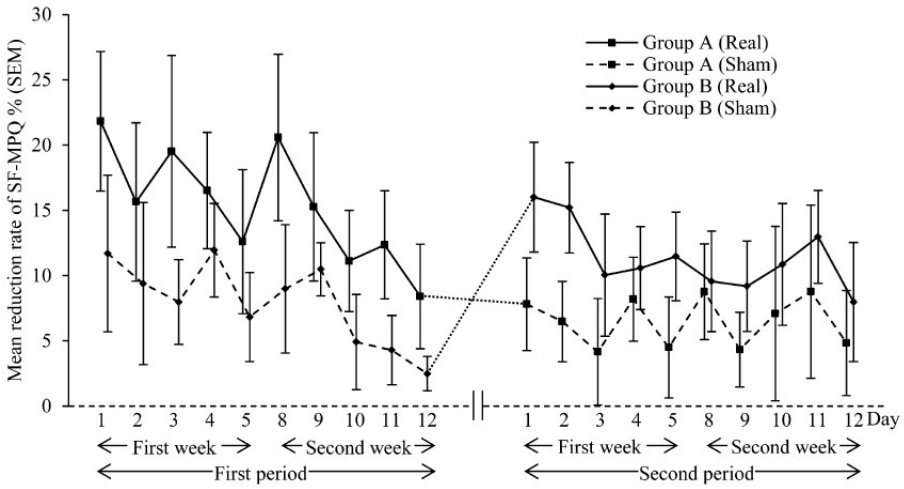
- DLPFC, dPMC, S1, SMA



Lefaucheur J.P. (2006). The Use of Repetitive Transcranial Magnetic Stimulation (rTMS) in Chronic Neuropathic Pain . Neurophysiologie Clinique

Neuropathic Pain

5 Hz, 90%rMT
64 patients, realistic placebo



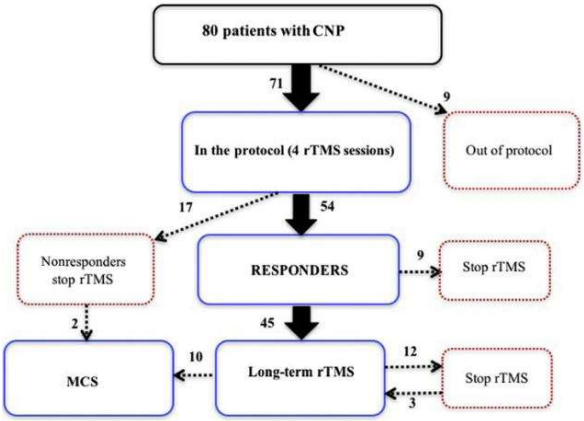
Hosomi et al. (2013). Daily Repetitive Transcranial Magnetic Stimulation of Primiary Motor Cortex for Neuropathic Pain... Pain

Neuropathic Pain

long-term effects by maintenance treatment

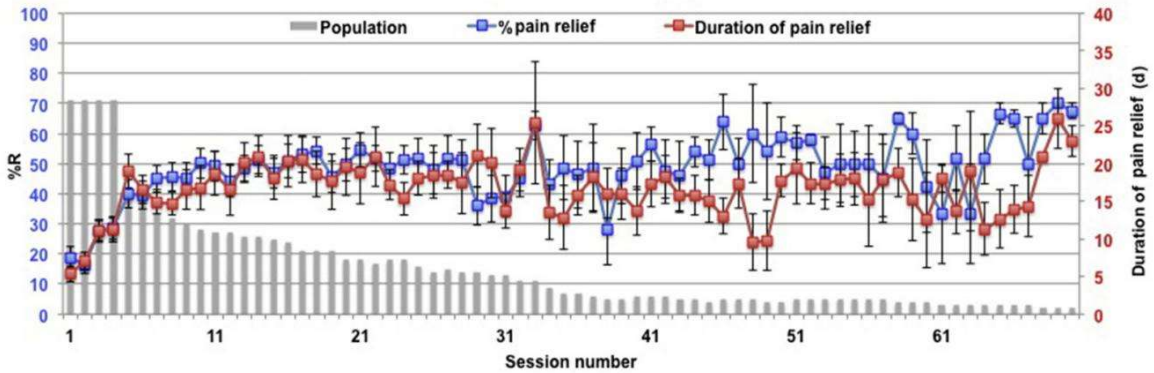
20 Hz rTMS over M1
first evaluation after 4 sessions over the course of 9 – 12 weeks

patients could freely decide on continuation and time between sessions!



Quesada et al. (2018). Robot-guided neuronavigated rTMS in central neuropathic pain. Archives of Physical Medicine and Rehabilitation

Neuropathic Pain



Quesada et al. (2018). Robot-guided neuronavigated rTMS in central neuropathic pain. Archives of Physical Medicine and Rehabilitation

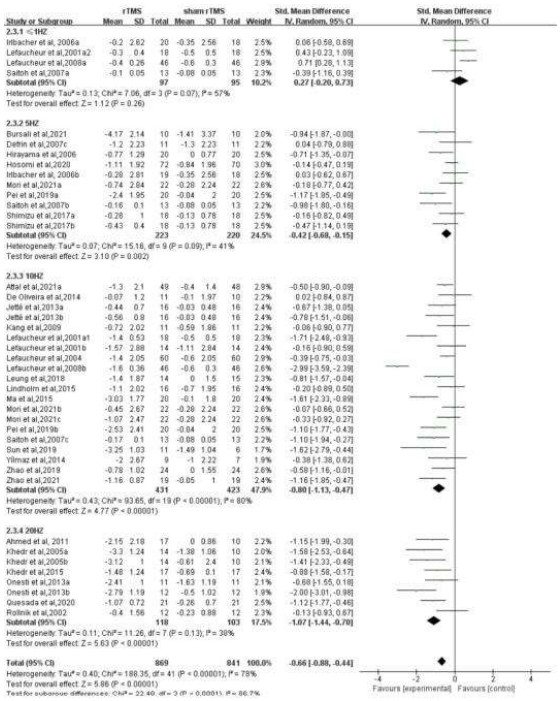
Neuropathic Pain

Robust effects across many studies

No general difference between peripheral pain vs. central pain, but...

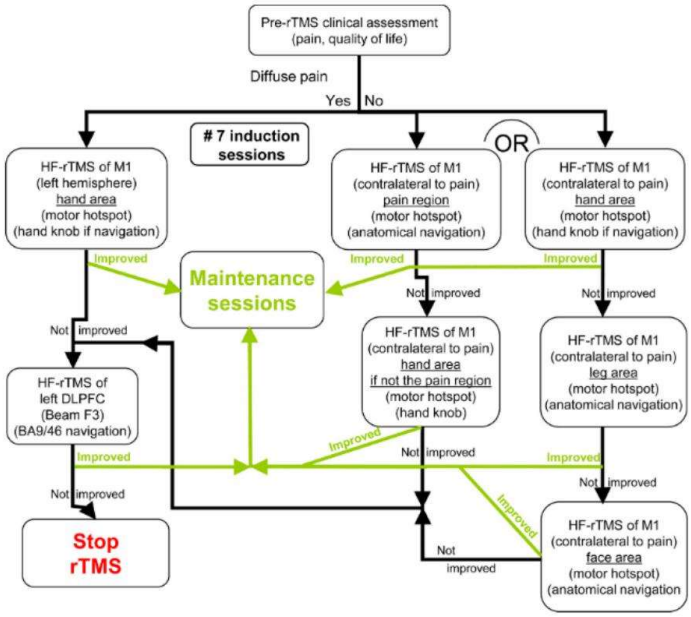
... subgroups matter!

+ postherpetic neuralgia
+ diabetic neuropathy
- trigeminal neuralgia
- brachial plexus injury
+ spinal cord injury
- post-stroke
- brain stem lesion
- phantom limb pain



Jiang at a. (2022)

Neuropathic Pain – Practical Algorithm



Lefaucheur et al. (2019)

Neuropathic Pain

High-Freq. rTMS over M1 contralateral to pain

Stimulation Site
primary motor cortex (M1) contralateral to pain
Coil handle pointing forward (PA-AP)

Stimulation Frequency
10Hz rTMS

Stimulation Intensity
80% resting motor threshold

TMS Timing
10 seconds ON, 20 seconds OFF
30 trains/repetitions
= 15 minutes

Number of Sessions
5-10 acute treatment sessions
subsequent maintenance TMS

Total Dosage
3000 pulses per session

→ **Level A recommendation**
→ **No consensus on exact protocol!**

Lefaucheur et al. (2020)

Fibromyalgia

"pain protocol":
- quality of life improvements (level B)
- but no pain reduction

"depression protocol":
- analgesic effects in fibromyalgia (level B)
- but no quality of life

→ Surprising, inconsistent with smaller earlier work, and hard to explain.

Lefaucheur et al. (2020)

Fibromyalgia – Quality of Life

High-Freq. rTMS over left primary motor cortex

Stimulation Site
left primary motor cortex (M1)

Stimulation Frequency
10Hz rTMS

Stimulation Intensity
80% resting motor threshold

TMS Timing
10 seconds ON, 20 seconds OFF
30 trains/repetitions
= 15 minutes

Number of Sessions
5-10 acute treatment sessions
subsequent maintenance TMS

Total Dosage
3000 pulses per session

→ **Level B recommendation**
→ **No consensus on exact protocol!**
→ **No evidence of pain relief!**

Lefaucheur et al. (2020)

Fibromyalgia – Pain

High-Freq. rTMS over left DLPFC

Stimulation Site
Left DLPFC / F3

Stimulation Frequency
10Hz rTMS

Stimulation Intensity
120% resting motor threshold

TMS Timing
4 seconds ON, 11 seconds OFF
75 trains/repetitions
= 19 minutes

Number of Sessions
20 acute treatment sessions

Total Dosage
3000 pulses per session

→ **Level B recommendation**
→ **No consensus on exact protocol!**

Lefaucheur et al. (2020)

Complex Regional Pain Syndrome

Level C recommendation

Following the procedure in neuropathic pain

- HF-rTMS on contralateral M1

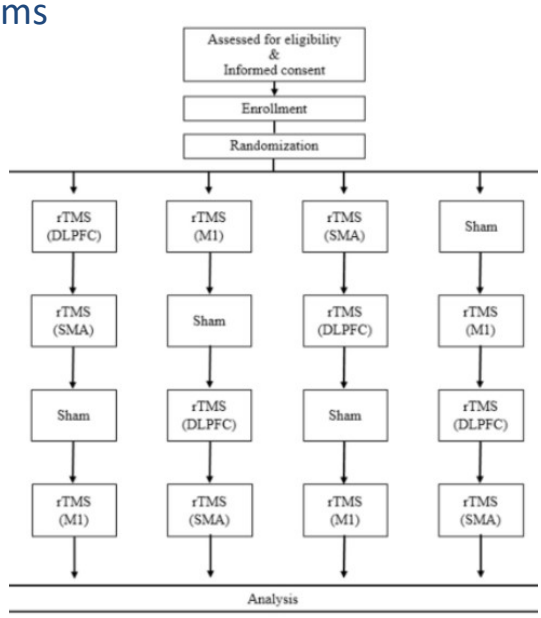
Hardly any new evidence since 2014

Parkinson's Disease – Motor Symptoms

Approach: Increase excitability in motor areas
-> high-freq. rTMS over M1 or SMA
-> bilateral stimulation (consecutively)

Level B recommendation for M1

Positive effects on...
...UPDRS-III motor score
...freezing of gait
...walking velocity



Lefaucheur et al. (2020) & Yokoe et al. (2018)

Parkinson's Disease – Motor Symptoms

Table 2
Results of changes in clinical scores after stimulations (n = 19).

	Mean (SD)				P-values (vs. sham)		
	M1	SMA	DLPFC	Sham	M1	SMA	DLPFC
UPDRS-III total score	3.28(2.25)	1.90 (2.27)	1.37 (2.12)	−0.23 (1.69)	<0.001***	0.012*	0.085 (n.s.)
Axial score	0.46 (0.89)	0.47 (0.60)	0.35 (0.87)	0.26 (0.78)	1.000 (n.s.)	1.000 (n.s.)	1.000 (n.s.)
Upper limb score	2.19 (1.62)	1.12 (1.66)	0.82 (1.63)	−0.58 (1.58)	<0.001***	<0.001***	0.059 (n.s.)
Lower limb score	1.98 (1.72)	0.95 (1.41)	0.82 (1.48)	0.16 (0.76)	0.001**	0.170 (n.s.)	0.383 (n.s.)
Tremor	0.49 (0.96)	0.11 (0.61)	0.37 (0.92)	−0.05 (0.34)	0.054 (n.s.)	0.730 (n.s.)	0.212 (n.s.)
Rigidity	1.00 (1.29)	0.49 (0.88)	0.39 (0.91)	0.21 (0.56)	0.058 (n.s.)	0.899 (n.s.)	1.000 (n.s.)
Postual stability	0.11 (0.30)	0.14 (0.37)	0.18 (0.30)	0.19 (0.30)	0.861 (n.s.)	1.000 (n.s.)	1.000 (n.s.)
Akinesia	1.28 (1.26)	0.40 (1.01)	0.19 (1.11)	−0.46 (1.00)	<0.001***	0.088 (n.s.)	0.164 (n.s.)
Bradykinesia	0.12 (0.32)	0.16 (0.26)	0.18 (0.39)	0.09 (0.31)	1.000 (n.s.)	1.000 (n.s.)	1.000 (n.s.)
Walk time (sec)	2.49 (3.88)	4.21 (8.74)	2.62 (7.01)	−1.74 (9.26)	0.743 (n.s.)	0.742 (n.s.)	1.000 (n.s.)
Number of steps	1.70 (3.89)	2.93 (3.76)	0.83 (5.50)	2.20 (8.70)	1.000 (n.s.)	1.000 (n.s.)	1.000 (n.s.)
Self-assessment score	2.72 (4.04)	3.54 (4.32)	3.47 (3.65)	2.83 (4.04)	1.000 (n.s.)	1.000 (n.s.)	1.000 (n.s.)
VAS	0.24 (0.84)	0.12 (0.14)	0.07 (0.11)	0.06 (0.08)	1.000 (n.s.)	0.220 (n.s.)	1.000 (n.s.)
AES	1.47 (5.15)	1.16 (5.10)	1.63 (5.68)	0.90 (5.25)	1.000 (n.s.)	1.000 (n.s.)	1.000 (n.s.)
MADRS-S	−2.11 (8.08)	−2.42 (7.87)	−0.95 (6.98)	−3.16 (8.23)	1.000 (n.s.)	1.000 (n.s.)	0.247 (n.s.)
SDS	−0.52 (7.96)	−0.37 (6.37)	−1.53 (7.02)	0.63 (6.33)	1.000 (n.s.)	1.000 (n.s.)	0.625 (n.s.)
PDQ-39	6.26 (24.00)	7.16 (24.92)	7.58 (26.78)	2.63 (29.25)	1.000 (n.s.)	1.000 (n.s.)	0.247 (n.s.)

*: p < .05; *: p < .01; **: p < .001***, n.s.: not significant.
UPDRS-III; the Unified Parkinson's Disease Rating Scale part III, VAS; visual analogue scale, AES; Apathy Evaluation Scale, MADRS-S; Self-Rated the Montgomery Åsberg Depression Rating Scale version, SDS; Self-Rating Depression Scale, PDQ-39; 39-item Parkinson's Disease Questionnaire, SD: standard deviation.

Yokoe et al. (2018)

Parkinson's Disease – Motor Symptoms

High-Freq. rTMS over primary motor cortex

Stimulation Site
Bilateral M1, leg area

Stimulation Frequency
10Hz rTMS

Stimulation Intensity
80% resting motor threshold

TMS Timing
10 seconds ON, 20 seconds OFF
20 trains/repetitions
= 10 minutes

Number of Sessions
10+ sessions

Total Dosage
2000 pulses per session

→ **Level B recommendation**
→ **No consensus on exact protocol!**

Parkinson's Disease – Depression

High-Freq. rTMS over left DLPFC

Stimulation Site
Left DLPFC, F3

Stimulation Frequency
10Hz rTMS

Stimulation Intensity
120% resting motor threshold

TMS Timing
4 seconds ON, 11 seconds OFF
75 trains/repetitions

Number of Sessions
5 sessions per week
2+ weeks

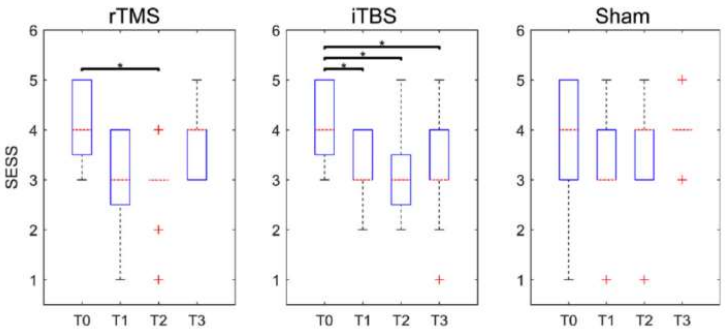
Total Dosage
3000 pulses per session

→ **Level B recommendation**
→ **No consensus on exact protocol!**

Multiple Sclerosis

Bilateral M1 stimulation

Example study: rTMS vs. iTBS vs. sham



Subjective spasticity scale

Korzhova et al. European journal of neurology (2019)

Multiple Sclerosis

iTBS over bilateral M1 contralateral to pain

Stimulation Site
Bilateral M1, leg area

Stimulation Frequency
50Hz triplets at 5Hz

Stimulation Intensity
80% resting motor threshold

TMS Timing
2 seconds ON, 8 seconds OFF
20 trains/repetitions

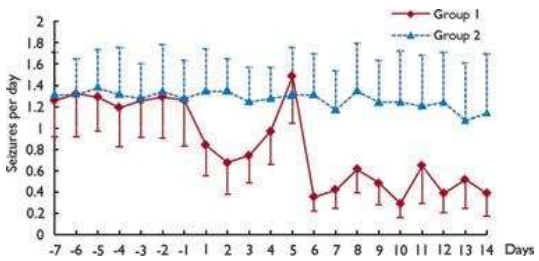
Number of Sessions
5 sessions per week
2 weeks

Total Dosage
600 pulses per session

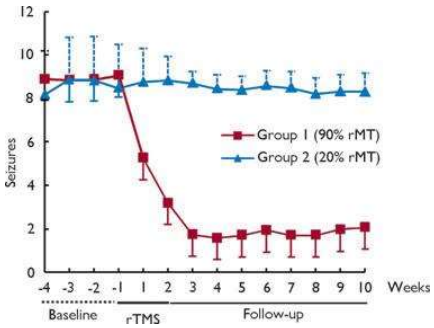
→ **Level B recommendation**
→ **No consensus on exact protocol!**

Refractory Partial Epilepsy

during treatment period



follow-up



two weeks of low frequency rTMS over epileptic focus
reduction of number of seizures for > 10 weeks

Sun et al. (2012). Low-Frequency Repetitive Transcranial Magnetic Stimulation for the Treatment of Refractory Partial Epilepsy: A Controlled Clinical Study. Epilepsia

Epilepsy

Stimulation Site
area of epileptic focus

Stimulation Frequency
1Hz rTMS

Stimulation Intensity
90% resting motor threshold

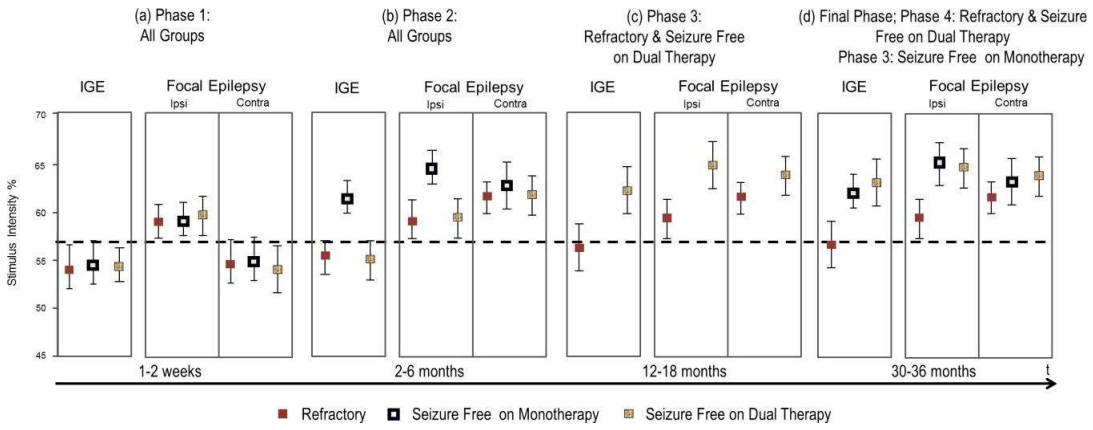
TMS Timing
25 minutes (continuous)

Number of Sessions
5+ consecutive days

Total Dosage
1500 pulses per session

→ **Level C recommendation**
→ **No consensus on exact protocol!**

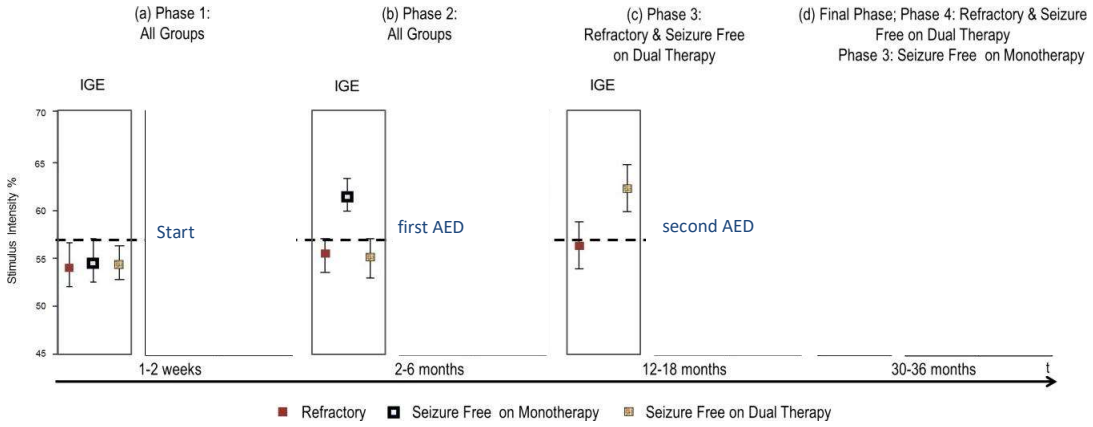
Epilepsy – Biomarker for Treatment Success



effectiveness of AEDs is generally assessed based on occurrence of clinical events
changes in motor threshold can serve as an early biomarker

Badawy et al. (2013). Cortical Excitabilty and Refractory Epilepsy: A Three-Year Longitudinal Transcranial Magnetic Stimulation Sutdy. International Journal of Neural Systems

Epilepsy – Biomarker for Treatment Success



Motor threshold increase when starting AED, if the AED will later turn out to be effective

Badawy et al. (2013). Cortical Excitabilty and Refractory Epilepsy: A Three-Year Longitudinal Transcranial Magnetic Stimulation Sutdy. International Journal of Neural Systems

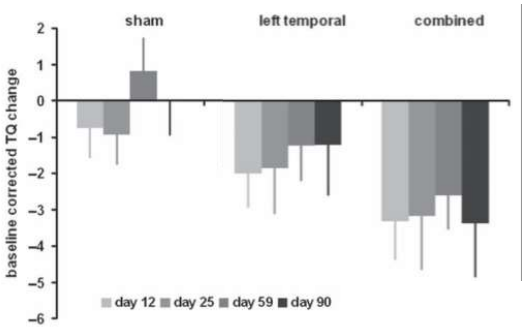
Tinnitus

alterations in neuronal activity of auditory and non-auditory brain areas

48 patients per group

- 1Hz rTMS over left auditory cortex
- 20 Hz rTMS over the left frontal cortex, followed by 1 Hz rTMS over left auditory cortex

10 sessions



promising, but non-significant reduction of tinnitus scores

Langguth et al. (2014).

Tinnitus

Low-freq. rTMS over auditory cortex

Stimulation Site
Left auditory cortex
between electrodes T3 and T5

Stimulation Frequency
1Hz rTMS

Stimulation Intensity
110% resting motor threshold

TMS Timing
Continuous rTMS for 25 minutes

Number of Sessions
5 days per week
2+ weeks

Total Dosage
1500 pulses per session

→ **Level C recommendation**
→ **No consensus on exact protocol!**

Alzheimer's Disease – Multi-Site Strategy

multi-site rTMS with cognitive training

Stimulation Site
3 target site per session
Broca's, Wernicke's, both DLPFCs,
both parietal somatosensory
association cortices (PSAC)

Stimulation Frequency
10Hz rTMS

Stimulation Intensity
90% - 110% resting motor threshold

TMS Timing
2 seconds ON, 40 seconds cognitive task
20 trains/repetitions

Number of Sessions
5 sessions per week
6 weeks

Total Dosage
1200 pulses per session

→ **Level C recommendation**
→ **No consensus on exact protocol!**
→ **Best efficacy at mild/early stage AD**

possibly effective to improve apathy, cognitive function, memory, and language in AD patients

Alzheimer's Disease – An Emerging Alternative Target..

https://doi.org/10.1093/brain/awac285 BRAIN 2022: 145; 3776–3786 | 3776

BRAIN
CLINICAL TRIAL

Precuneus magnetic stimulation for Alzheimer's disease: a randomized, sham-controlled trial

Giacomo Koch,[1,2] Elias Paolo Casula,[1] Sonia Bonnì,[1] Ilaria Borghi,[1]
Martina Assogna [1,3] Marilena Minei [1] Maria Concetta Pellicciari [1] Caterina Motta [1]

Alzheimer's Disease – Precuneus

50 AD mild-moderate (mean age 74 yrs)
25 SHAM, 25 precuneus rTMS

2 weeks:
5 rTMS per week (daily)
22 weeks:
1 rTMS per week (maintenance)

Clinical Dementia Rating Scale
Sum of Boxes
(+ others)

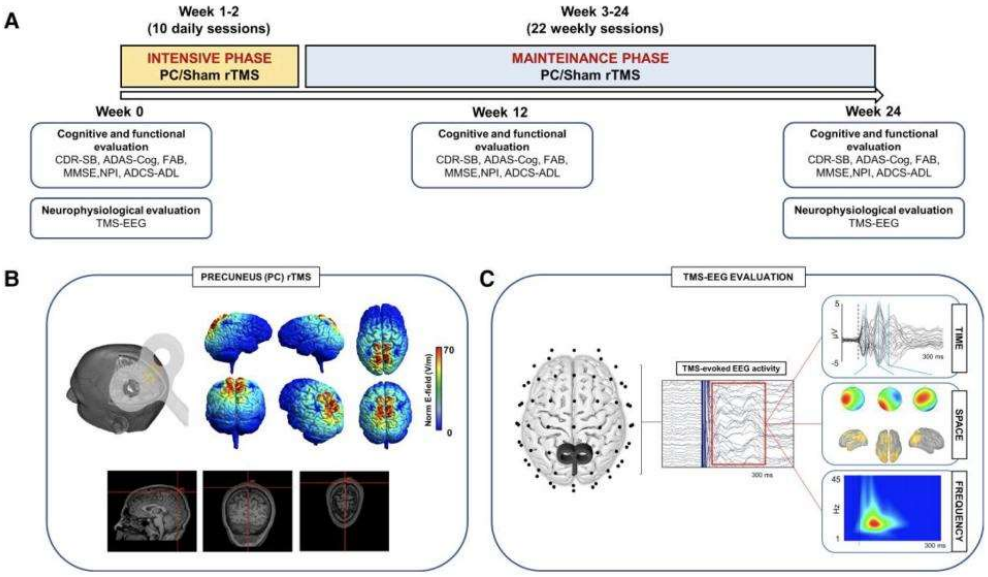
rTMS:
20 Hz, 40 2s trains, 28s inter-train interval
= 1600 pulses

Coil handle parallel to midline

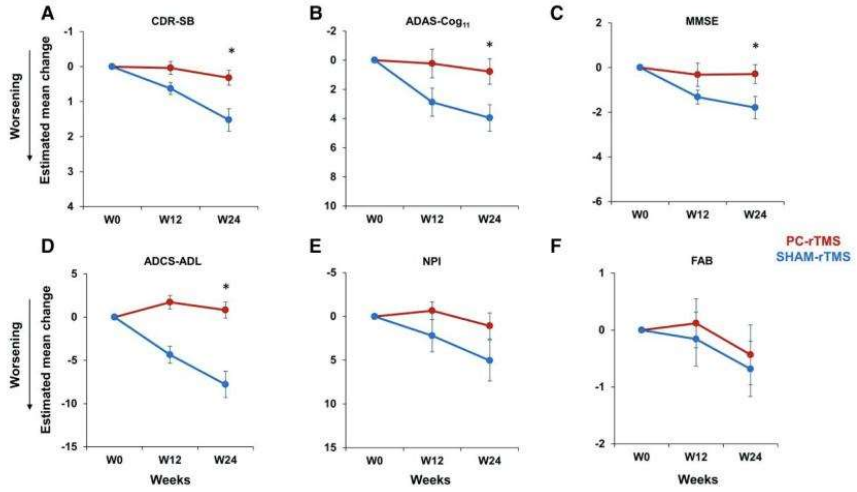
Neuronavigation

Intensity based on distance-adjusted MT and additional EEG response criteria

Alzheimer's Disease – Precuneus



Alzheimer's Disease – Precuneus



Precuneus rTMS prevents worsening of symptoms

Levels of Evidence - Neurology & Rehabilitation

A: definitely effective	**neuropathic pain** motor stroke
B: probably effective	**Fibromyalgia (quality of life and pain)** **Parkinson's disease (antiparkinsonian and antidepressant effects)** post-stroke aphasia **multiple sclerosis**
C: possibly effective	**complex regional pain syndrome (type I)** **epilepsy** hemispatial neglect **tinnitus** **Alzheimer's disease**

The Academy of Brain Stimulation
Education and Certification

TMS in Neurology

Neuropathic Pain & Fibromyalgia – Multiple Sclerosis – Epilepsy – Tinnitus
Parkinson's Disease – Dementia – Disorders of Consciousness

Prof. Dr. Alexander Sack
Department of Psychiatry and Neuropsychology
School for Mental Health and Neuroscience (MHeNs) Brain+Nerve Centre
Maastricht University Medical Centre+ (MUMC+)

TMS in Rehabilitation

Prof. Dr. Alexander Sack

The Academy of Brain Stimulation
Education and Certification

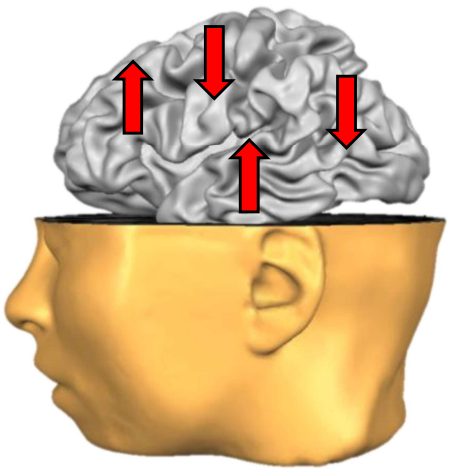
Clinical TMS Certfication Course

TMS in Stroke Rehabilitation

Prof. Dr. Alexander Sack
Department of Psychiatry and Neuropsychology
School for Mental Health and Neuroscience (MHeNs) Brain+Nerve Centre
Maastricht University Medical Centre+ (MUMC+)

Treatment: Basic principles

Application of long-lasting inhibitory or excitatory TMS protocols, often for many sessions, that ideally reverse the brain state back to normal



Efficacy of TMS treatment

Clinical Neurophysiology 125 (2014) 2150–2206

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

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 [f,am,1]

Clinical Neurophysiology 131 (2020) 474–528

Contents lists available at ScienceDirect

Clinical Neurophysiology

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Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)

Jean-Pascal Lefaucheur [a,b,*], André Aleman [c], Chris Baeken [d,e,f], David H. Benninger [g], Jérôme Brunelin [h], Vincenzo Di Lazzaro [i], Saša R. Filipović [j], Christian Grefkes [k,l], Alkomiet Hasan [m], Friedhelm C. Hummel [n,o,p], Satu K. Jääskeläinen [q], Berthold Langguth [r], Letizia Leocani [s], Alain Londero [t], Raffaele Nardone [u,v,w], Jean-Paul Nguyen [x,y], Thomas Nyffeler [z,aa,ab], Albino J. Oliveira-Maia [ac,ad,ae], Antonio Oliviero [af], Frank Padberg [m], Ulrich Palm [m,ag], Walter Paulus [ah], Emmanuel Poulet [h,ai], Angelo Quartarone [aj], Fady Rachid [ak], Irena Rektorová [al,am], Simone Rossi [an], Hanna Sahlsten [ao], Martin Schecklmann [r], David Szekely [ap], Ulf Ziemann [aq]

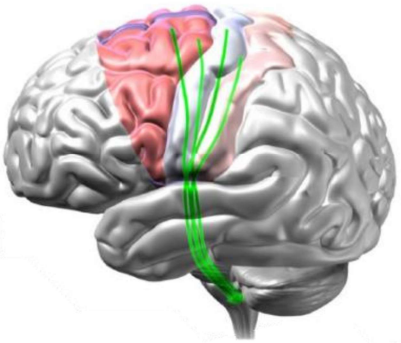
+ recent reviews, meta analyses, and clinical trials

Levels of evidence - Neurology & Rehabilitation

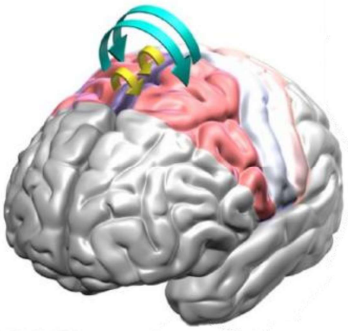
A: definitely effective	neuropathic pain **motor stroke**
B: probably effective	Fibromyalgia (quality of life and pain) Parkinson's disease (antiparkinsonian and antidepressant effects) **post-stroke aphasia** multiple sclerosis
C: possibly effective	complex regional pain syndrome (type I) epilepsy **hemispatial neglect** tinnitus Alzheimer's disease

Core Concepts in Stroke Rehabilitation

Ipsilesional Corticospinal Plasticity



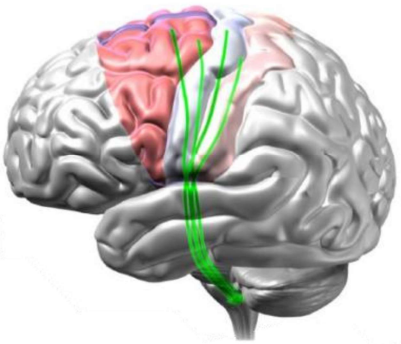
Inter-hemispheric Balance



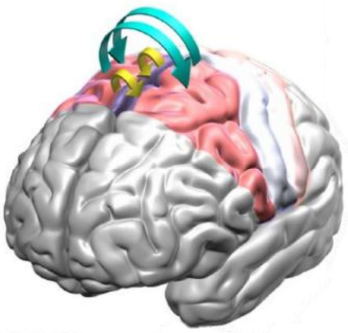
Plow et al. (2015). Rethinking stimulation of the brain in stroke rehabilitation… Neuroscientist. 21(3): 225-40

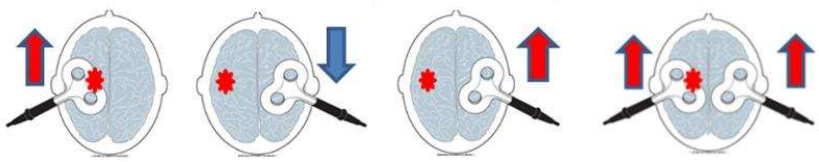
Core concepts in stroke rehabilitation

Ipsilesional Corticospinal Plasticity



Inter-hemispheric Balance

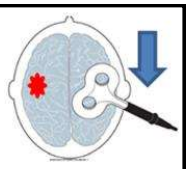




boost supportive brain plasticity and counteract maladaptive changes

Plow et al. (2015). Rethinking stimulation of the brain in stroke rehabilitation… Neuroscientist. 21(3): 225-40

Motor stroke

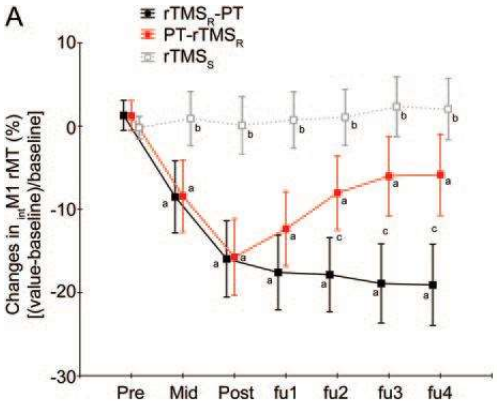


Chronic stroke patients with mild motor disabilities

10 sessions of 1Hz rTMS over intact M1 combined with physical therapy

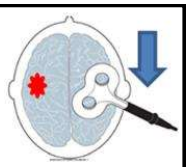
Follow-up for 3 months

→ Reduction of motor threshold in affected M1 (increased excitability)

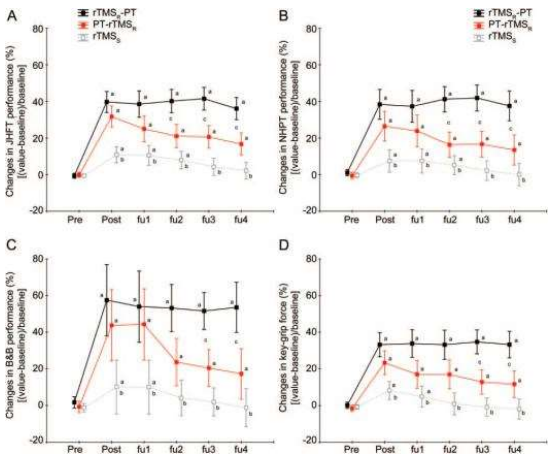


Avenanti et al. (2012). Low-frequency rTMS promotes use-dependent motor plasticity in chronic stroke. Neurology

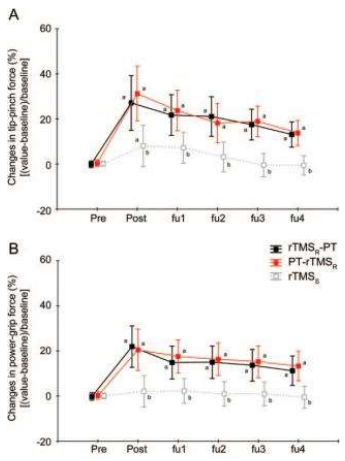
Motor stroke



Jebsen-Taylor Hand Function



Untrained motor functions

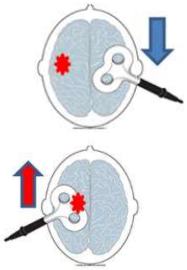


Avenanti et al. (2012). Low-frequency rTMS promotes use-dependent motor plasticity in chronic stroke. Neurology

Motor Stroke

2020 Lefaucheur et al. update:

- **Level A** evidence for contralesional LF-rTMS
  - At least for hand function
  - Especially when rTMS is used to prime physical therapy
- **Level B** evidence for ipsilesional HF-rTMS
  - At least for upper limb function

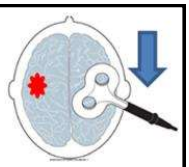


- One study suggesting equal efficacy HF-rTMS/LF-rTMS
- Two studies suggesting superiority contralesional LF-rTMS

- This may apply to postacute (subacute) stroke only.
  Updated LF-rTMS recommendation for chronic stroke is **Level C:** for **mixed** results

Lefaucheur et al. (2020)

Motor Stroke – Hand Recovery



Low-Freq. rTMS over contralesional M1

Stimulation Site
Primary motor cortex
Contralesional

Stimulation Frequency
1Hz rTMS

Stimulation Intensity
90% resting motor threshold

TMS Timing
Continuous rTMS for 25 minutes

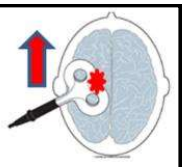
Number of Sessions
5 days a week
4+ weeks of treatment
During postacute stage

Total Dosage
1,500 pulses per session

→ **Level A recommendation**
→ **No consensus on exact protocol!**

Lefaucheur et al. (2020)

Motor Stroke – Hand Recovery



High-Freq. rTMS over ipsilesional M1

Stimulation Site
Primary motor cortex
Ipsilesional

Stimulation Frequency
10Hz rTMS

Stimulation Intensity
80% resting motor threshold

TMS Timing
10 seconds ON, 20 seconds OFF
10 trains/repetitions

Number of Sessions
5 days a week
2 weeks of treatment
During postacute stage

Total Dosage
1000 pulses per session

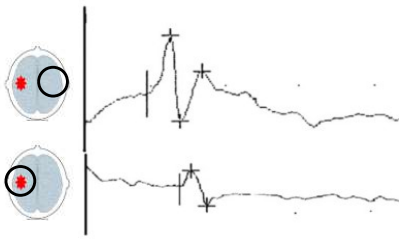
→ **Level B recommendation**
→ **No consensus on exact protocol!**
→ **In addition to standard rehabilitation therapies**

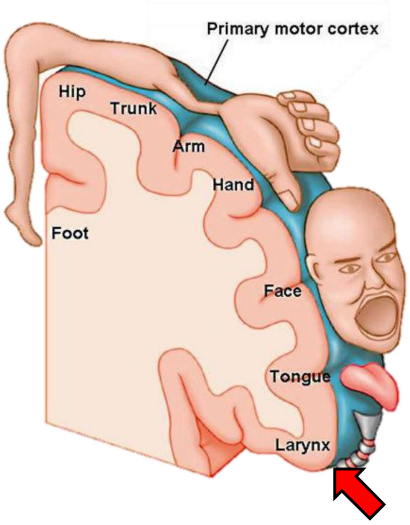
Lefaucheur et al. (2020)

Dysphagia

TMS can be used to stimulate pharyngeal motor cortex

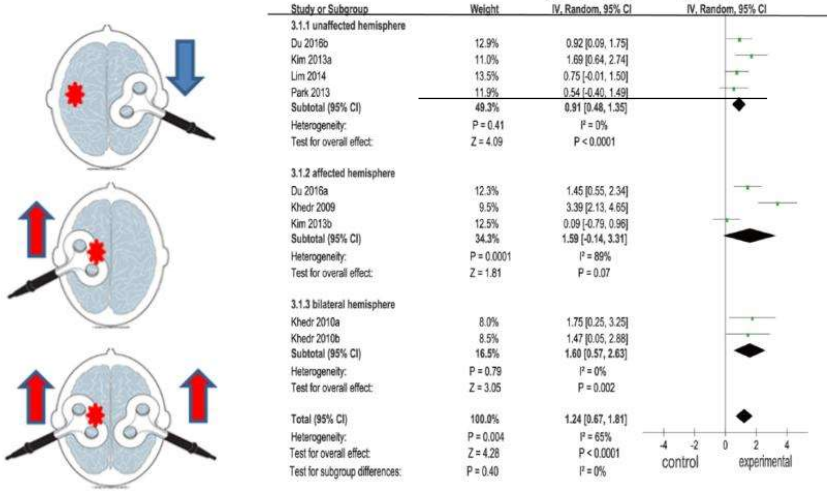
MEPs obtained via catheter





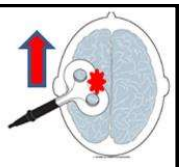
Michou et al. (2006) & Khedr et al. (2008)

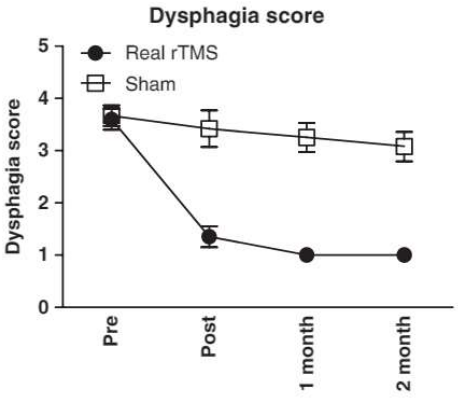
Dysphagia

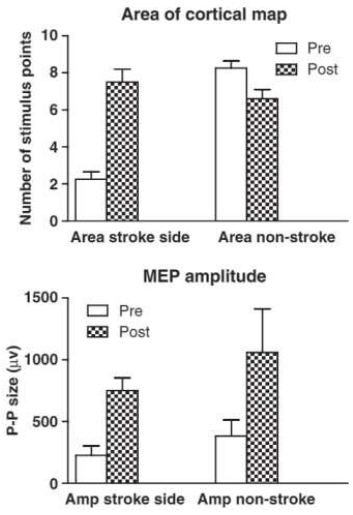


Michou et al. (2006) & Liao et al. (2017)

Dysphagia



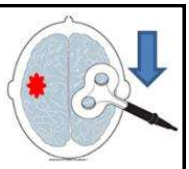




1 week of high-frequency rTMS (3Hz) over affected hemisphere
reduction of symptoms and functional recovery of motor cortex

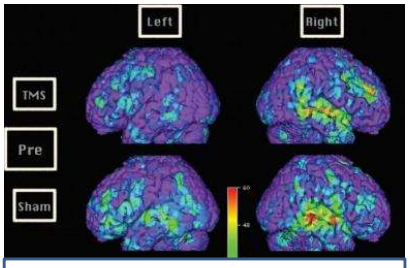
Khedr et al. (2009)

Aphasia



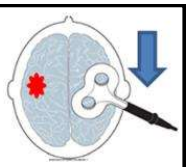
Aphasia is characterized by higher activity in right hemisphere (maladaptive?)

Low-freq rTMS over right hemisphere leads to more balanced activity pattern



Thiel et al. (2013). Effects of Noninvasive Brain Stimulation on Language Networks and Recovery in Early Poststroke Aphasia. Stroke. 44(8)

Aphasia



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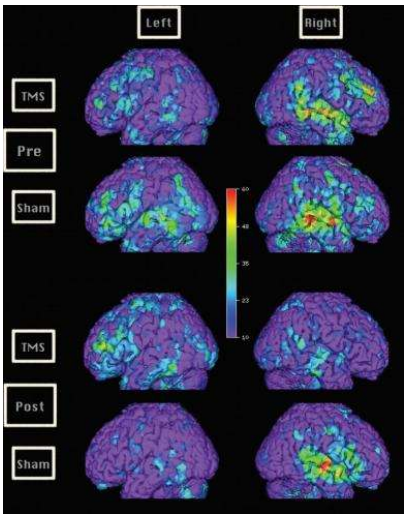

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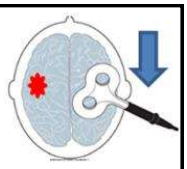
Aphasia

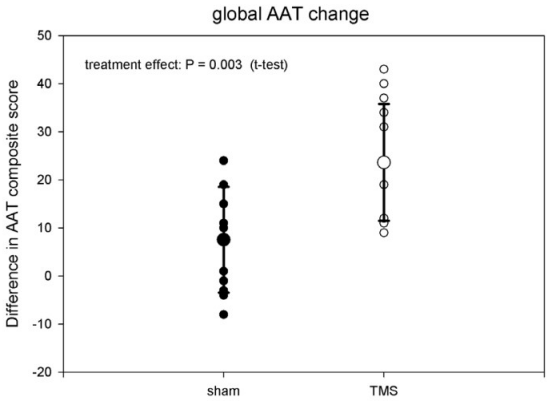


1Hz rTMS for 20 minutes over pars triangularis

2 weeks of treatment

just prior to speech and language therapy sessions

subacute phase (~6 weeks)



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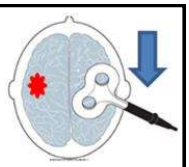
Aphasia



Low-Freq. rTMS over right IFG

Stimulation Site
Right IFG (BA 45)

Stimulation Frequency
1Hz rTMS

Stimulation Intensity
90% resting motor threshold

TMS Timing
Continuous rTMS for 20 minutes

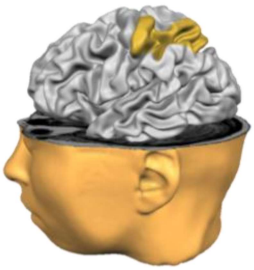
Number of Sessions
10 sessions
During chronic stage

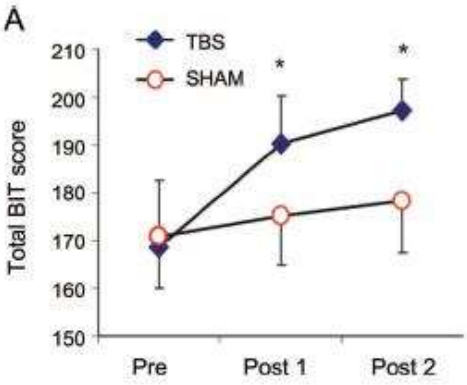
Total Dosage
1200 pulses per session

→ **Level B recommendation**
→ **No consensus on exact protocol!**

Lefaucheur et al. (2020)

Hemispatial Neglect





cTBS over left PPC
10 sessions
2 weeks

Koch et al. (2012). Theta Burst Stimulation of the Left Hemisphere Accelerates Recovery of Hemispatial Neglect. Neurology

Hemispatial Neglect

cTBS over contralesional posterior parietal cortex

Stimulation Site
Contralesional PPC (P3/P4 or P5/P6)

Stimulation Frequency
Adapted cTBS
3-pulse bursts (30Hz) repeated at 5Hz

Stimulation Intensity
90% resting motor threshold

TMS Timing
2 x 40s, 15 minute break

Number of Sessions
5 sessions per week
2 weeks
During postacute stage

Total Dosage
2 x 600 pulses per session

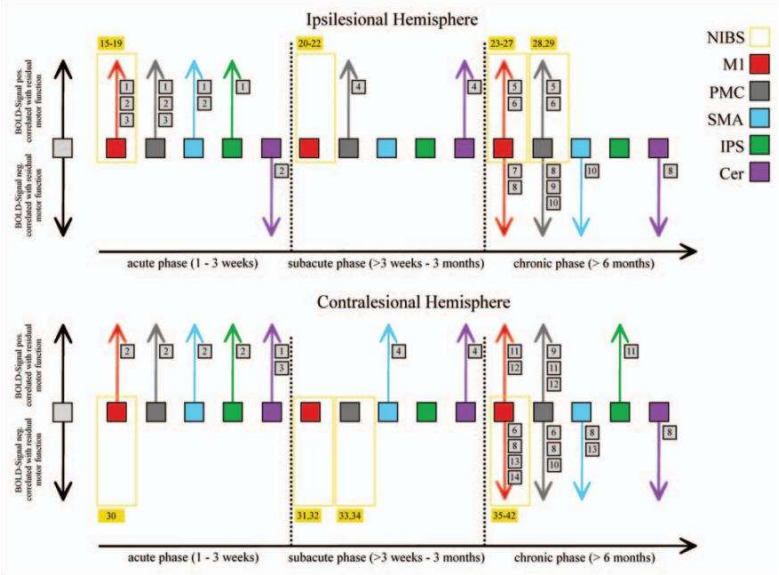
→ **Level C recommendation**
→ **No consensus on exact protocol!**

Lefaucheur et al. (2020)

TMS after stroke – When? Where? What?

Bold activity in key motor areas during the course of stroke recovery.

The activity level of BOLD-signaling in key motor areas is differently positively or negatively correlated with residual motor function in fifferent phases of motor recovery after stroke in the ipsilesional or contralesional hemisphere



Koch & Hummel (2017). Toward precision medicine: tailoring interventional strategies based on noninvasive brain stimulation for motor recovery after stroke. Current opinion in neurology. 30(4)

The Academy of Brain Stimulation
Education and Certification

Clinical TMS Certfication Course

TMS in Stroke Rehabilitation

Prof. Dr. Alexander Sack

Department of Psychiatry and Neuropsychology

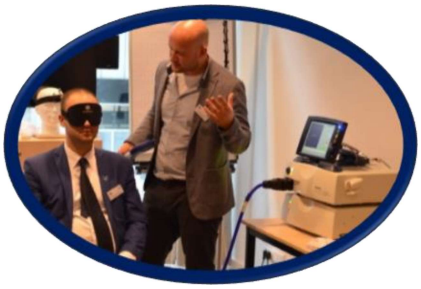
School for Mental Health and Neuroscience (MHeNs) Brain+Nerve Centre

Maastricht University Medical Centre+ (MUMC+)

Optimised and Personalised TMS Depression Therapies

Prof. Dr. Alexander Sack



The Academy of Brain Stimulation
Education and Certification

Optimised and Personalised TMS Depression Therapies

Optimizing TMS Efficacy – Stratification – Alternative targets for DLPFC nonresponders – SAINT
Accelerated TMS - State-dependent TMS Therapy - Combining TMS with other Interventions

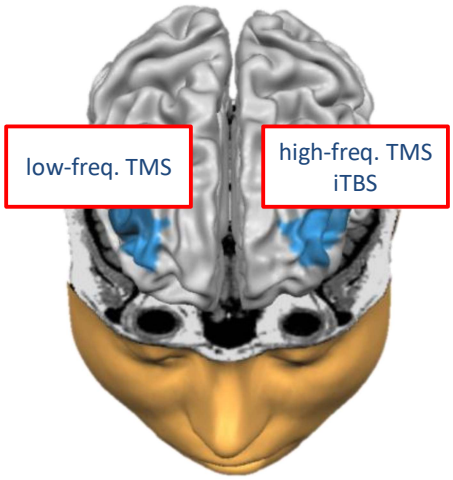
Prof. Dr. Alexander Sack
Department of Psychiatry and Neuropsychology
School for Mental Health and Neuroscience (MHeNs) Brain+Nerve Centre
Maastricht University Medical Centre+ (MUMC+)

Three effective protocols: combine and escalate

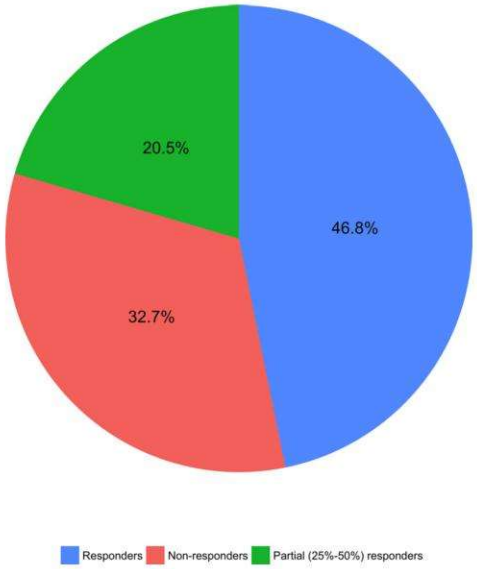
high-frequency rTMS (left DLPFC)
- → standard protocol
- → tried and tested

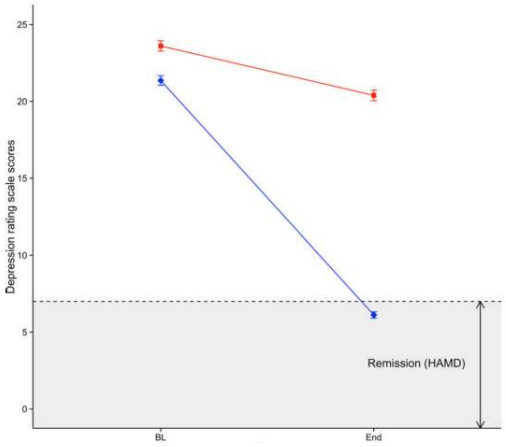
low-frequency rTMS (right DLPFC)
- → lower risk and less side effects
- → sometimes preferred if psychomotor agitation is present

intermittent theta burst (left DLPFC)
- → very time efficient
- → particularly suited for accelerated TMS protocols



Bimodal Response Pattern indicates sub types



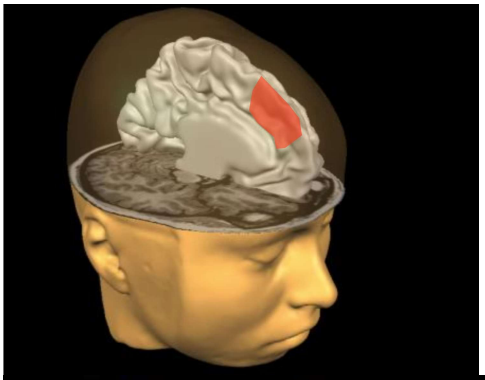


(Fitzgerald, Hoy et al. 2016)

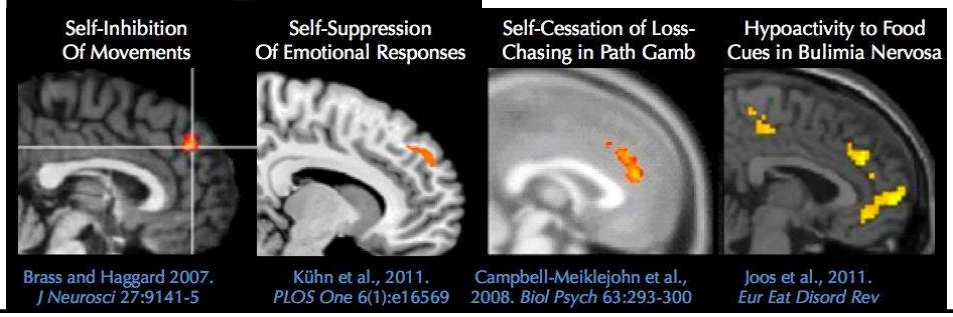
Sub types may need different targets

- **lDLPFC target seems to be highly effective in some patients….**
- **….whereas other patients don't benefit at all**
- **Prefrontal cortex can be partialized into various sub regions connected to distinct networks**
- **Maybe DLPFC not optimal target for all depressed patient (sub types)?!**

DMPFC: A new target for rTMS



Cortical Locus of Self-Control



Candiates for dmPFC Treatment

Overall *hypoactivity* in areas involved in self control

Symptoms include:

- Pervasive deficiency of cognitive control
- Cluster B traits (Dramatic, Erratic)
- Features of Bipolar, ADHD, some BPD traits
- History of binge eating / purging
- History of substance misuse / abuse
- Features of PTSD, OCD
- Intrusive thoughts / recollections
- Lack of control of emotion, cognition, action

Drysdale et al. (2016)

TMS over Dorsomedial Prefrontal Cortex

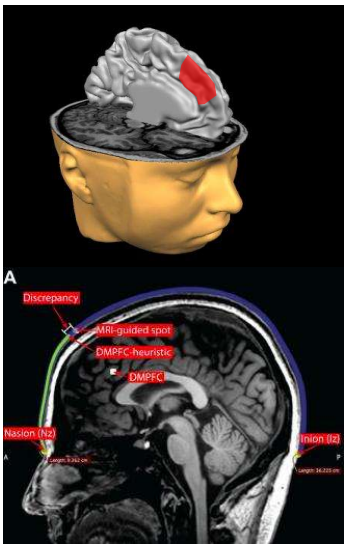
same principle as in DLPFC stimulation

25% nasion-to-inion distance

Cool D-B80 Butterfly Coil

10Hz protocol at 120% rMT

target is quite deep, requires appropriate TMS coils and intensities



Mir-Moghtadaei et al. (2016)

Dorsomedial Prefrontal Cortex (DMPFC)

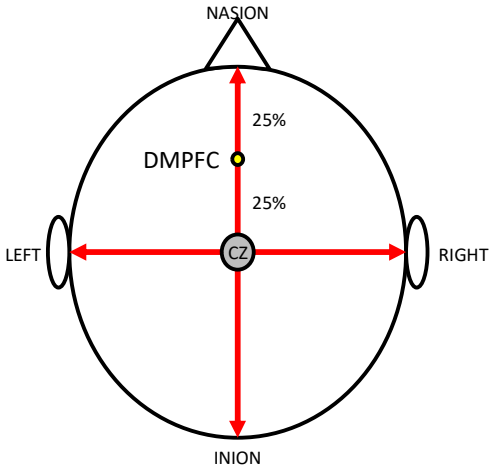
TMS coil on the midline to target the dorsomedial prefrontal cortex in both hemisphere simultaneously

TMS coil position based on nasion-inion distance,...

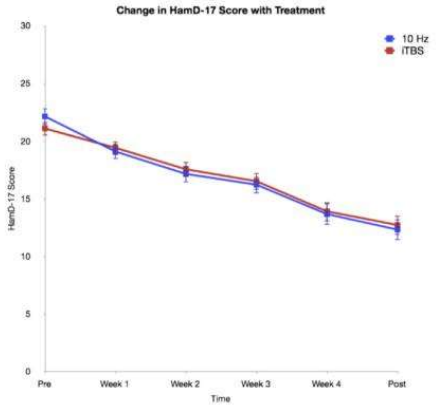
...25% anterior of CZ, or

...25% posterior of nasion.

TMS coil handle points in the lateral direction, claimed to result in preferential stimulation of the opposite hemisphere



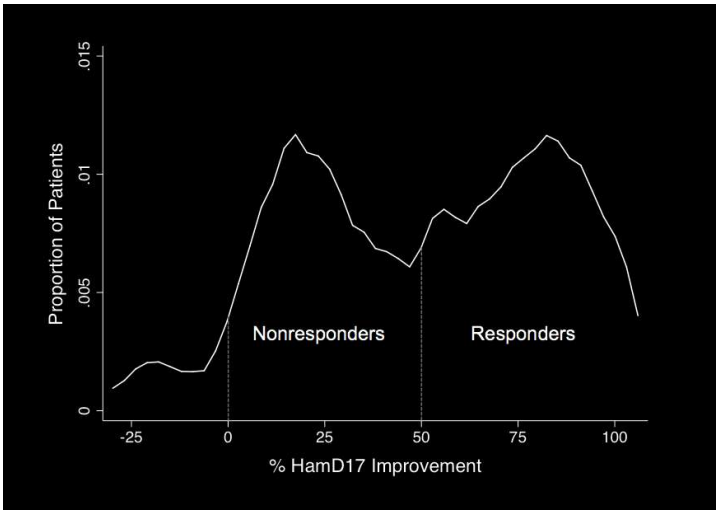
TMS over Dorsomedial Prefrontal Cortex



49.7% Response, 33.5% Remission

Downar et al. (2014) & Bakker et al. (2015)

TMS over Dorsomedial Prefrontal Cortex



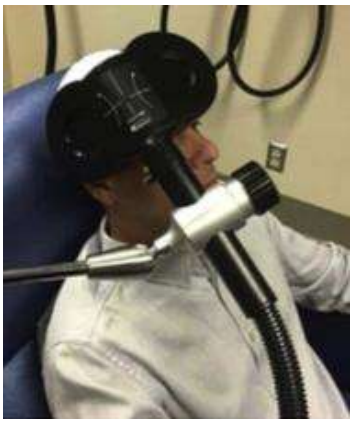
Downar et al. (2014) & Bakker et al. (2015)

Lateral Orbitofrontal Cortex (rOFC)

enhanced connectivity of the non-reward/punishment system
→ low frequency rTMS (1Hz)

patients characterized by…

- high anxiety
- pessimism
- obsessive negativity
- preoccupation



10% nasion-to-inion distance
10% head circumference to the right

Keffer 2018 (European Psychopharmacology).

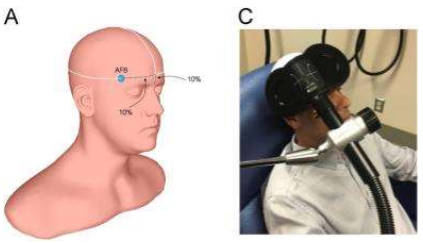
Orbitofrontal Cortex (OFC)

TMS coil at electrode position AF8 or Fp2 to target the orbitofrontal cortex (OFC)

TMS coil position based on 10/20 EEG system…

1) move 10% of the nasion-inion distance above the nasion

2) move 10% or 5 % of the circumference towards the right hemisphere



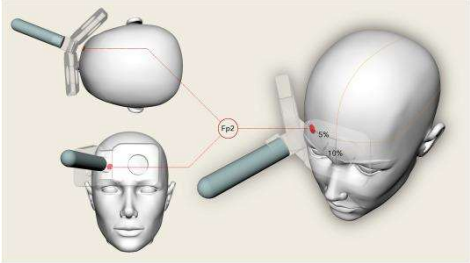
Feffer et al. (2018). European Neuropsychopharmacology

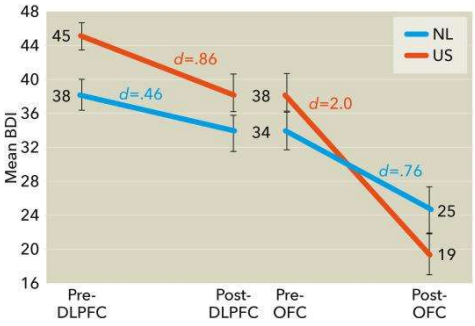
OFC–TMS for patients unresponsive to DLPFC-TMS

OFC Protocol:

NL:
- 1Hz, 60s on, 30s off, 15 trains, 120 % lower limb RMT), targeting Fp2, using a figure-8 coil with 120°-angled windings (Deymed DuoMag XT-100 with 90BFVT-LQC coil or MagVenture R30 with D-B80 coil)

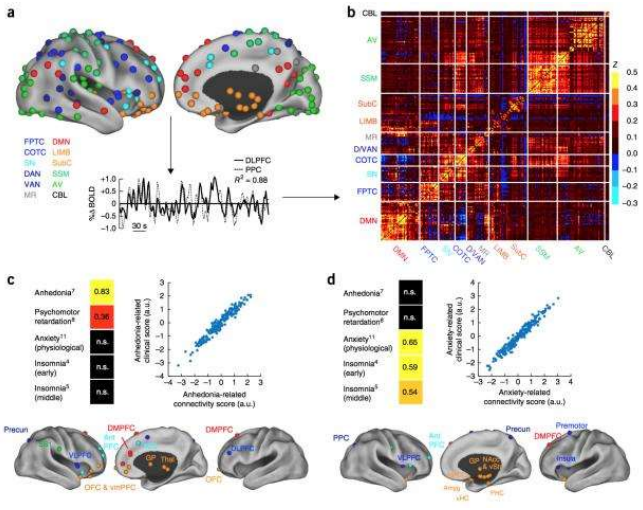
US:
- 1Hz-R–OFC–TMS augmented to DLPFC stimulation (1Hz, 1200 pulses continuously, 120 % finger twitch RMT), targeting AF8, using a NeuroStar iron-core coil, positioned at an angle of +35°

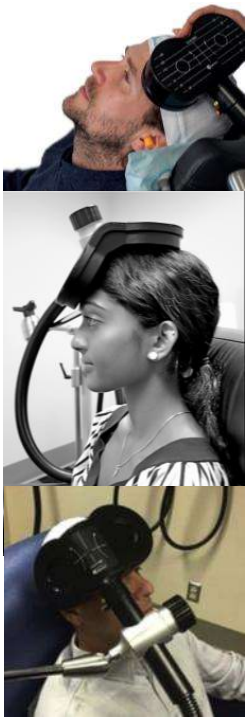




Prentice A, Kolken Y, Tuttle C, van Neijenhof J, Pitch R, van Oostrom I, Kruiver V, Downar J, Sack AT, Arns M, van der Vinne N. 1Hz right orbitofrontal TMS benefits depressed patients unresponsive to dorsolateral prefrontal cortex TMS. Brain Stimul. 2023 Oct 13;16(6):1572-1575

Stratification in TMS Treatment

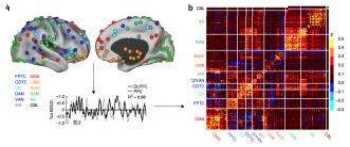


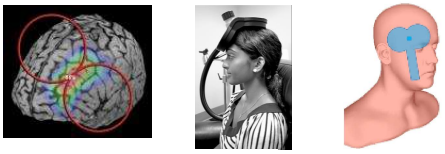


Stratification: Future Perspectives vs Practical Approach

Predict and Personalise

rs-fMRI biomarker

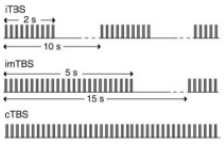




DLPFC **DMPFC** **rOFC**

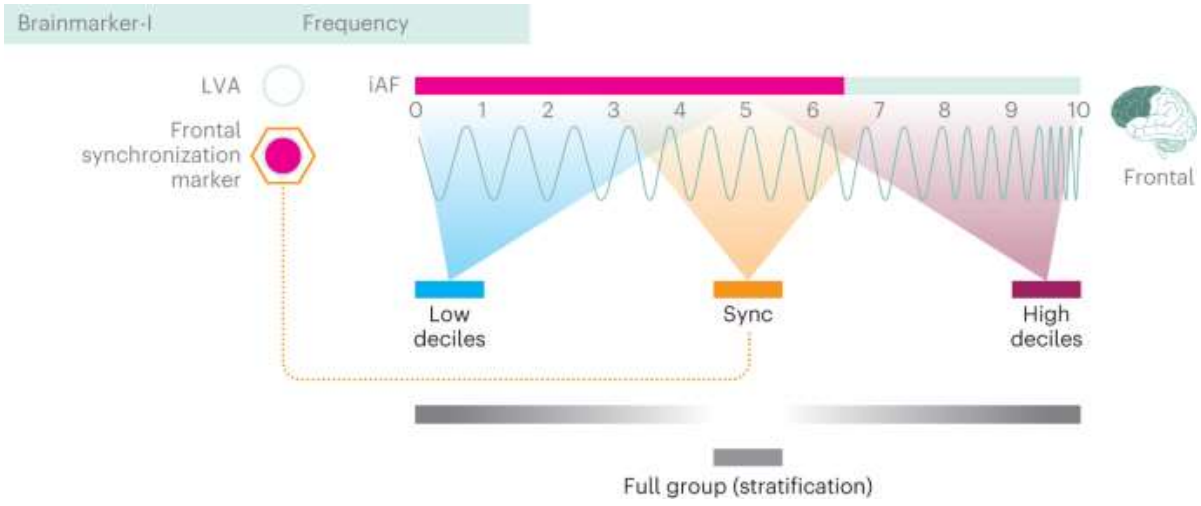
Cover all Bases

rapid, low-cost treatment



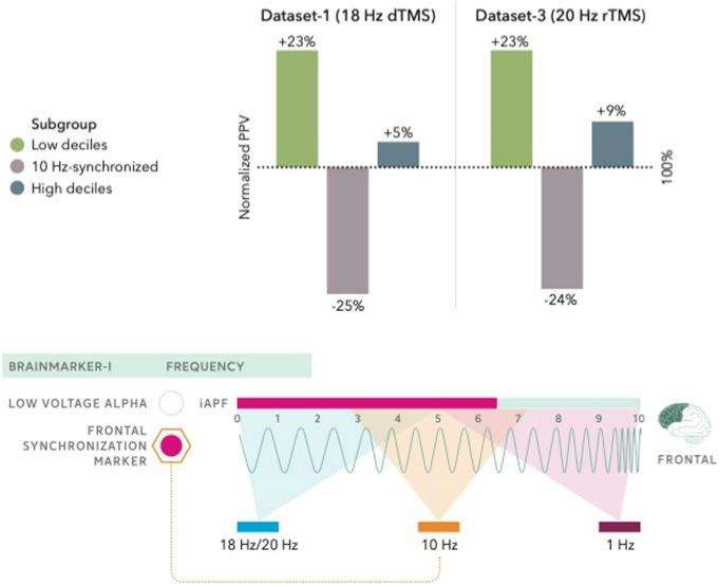
DLPFC **DMPFC** **rOFC**

Stratification: EEG Biomarkers ?!



Voetterl, H.T.S., Sack, A.T., Olbrich, S. *et al.* Alpha peak frequency-based Brainmarker-I as a method to stratify to pharmacotherapy and brain stimulation treatments in depression. *Nat. Mental Health* **1**, 1023–1032 (2023). https://doi.org/10.1038/s44220-023-00160-7

Stratification: EEG Biomarkers ?!

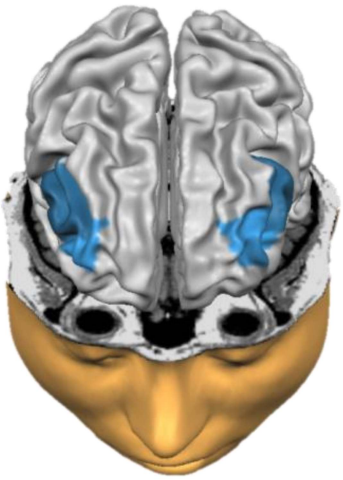


Voetterl H, Alyagon U, Middleton VJ, Downar J, Zangen A, Sack AT, van Dijk H, Halloran A, Donachie N, Arns M. Does 18 Hz deep TMS benefit a different subgroup of depressed patients relative to 10 Hz rTMS? The role of the individual alpha frequency. Eur Neuropsychopharmacol. 2024 Oct 11;89:73-81. doi: 10.1016/j.euroneuro.2024.09.007. Epub ahead of print. PMID: 39395357.

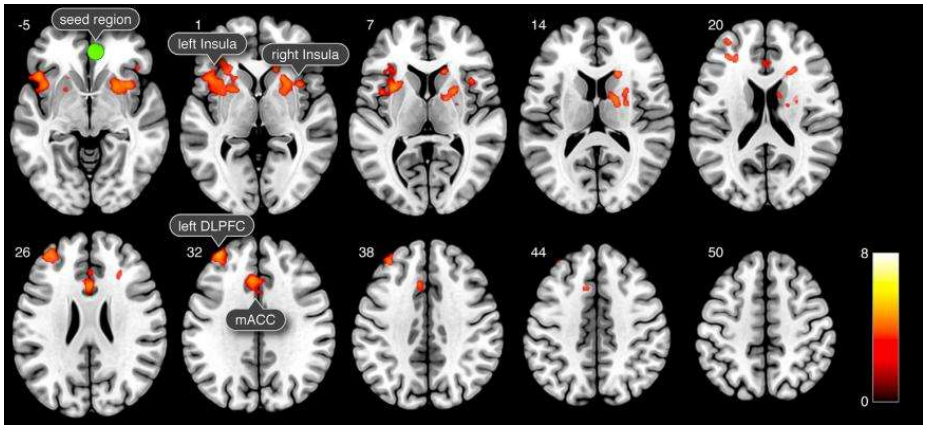
Individualizing Treatment: a network disorder

Idea of high frequency rTMS over left DLPFC to counteract hypo-activity is overly simplistic

Move from brain regions to brain networks



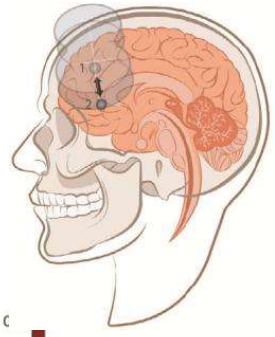
Network Changes Underlying Depression



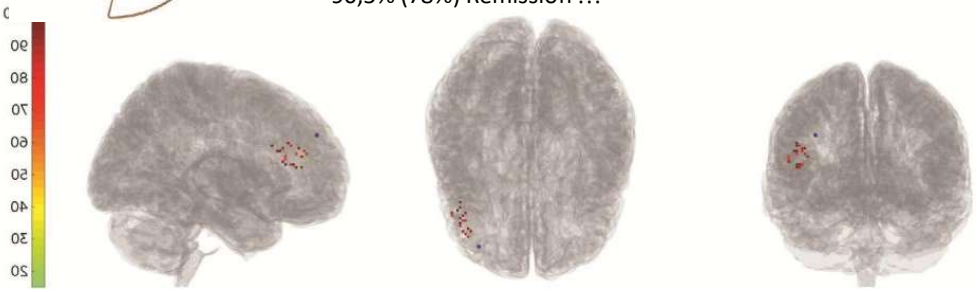
particular focus on altered function and connectivity between **DLPFC and sgACC**

Tik et al. (2017). Towards understanding rTMS mechanism of action. NeuroImage

Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression

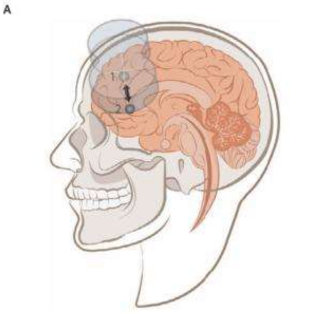


- 22 TRD patients treated with iTBS
- fcMRI was used to individually target the region of the left DLPFC most anti- correlated with sgACC in each participant
- Fifty iTBS sessions (1,800 pulses per session, 50-minute intersession interval) were delivered as 10 daily sessions over 5 consecutive days at 90% resting motor threshold
- 90,5% (78%) Remission !!!



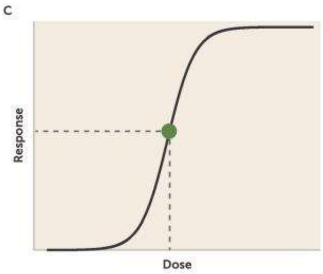
Cole et al., Am J Psychiatry 177:8, August 2020

Stanford Accelerated Neuromodulation Therapy (SNT)



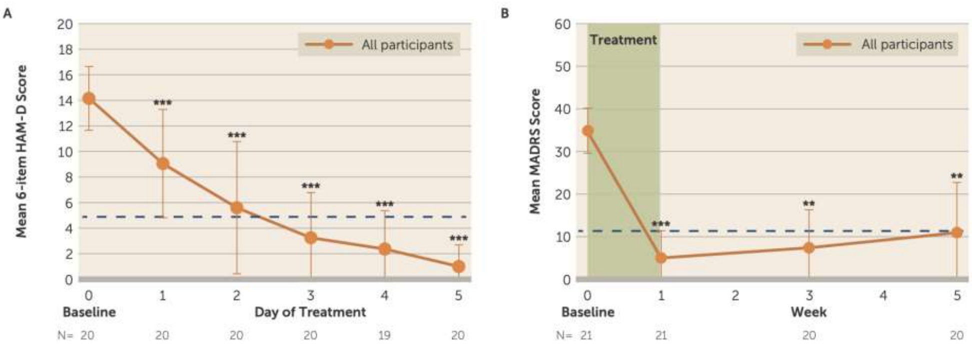
B

Day 1	Day 2	Day 3	Day 4	Day 5
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI
iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800	iTBS 1800
50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI	50 minute ISI



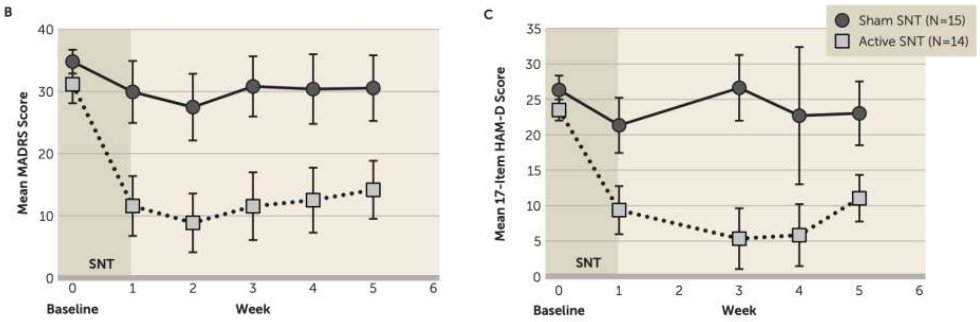
Cole et al. (2020)

Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT)



Cole et al. (2020)

Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT)

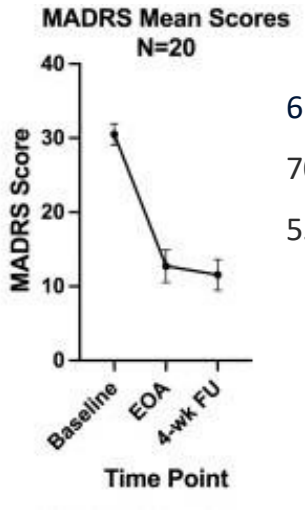


85% response and 78% remission

52.5% MADRS reduction

Cole et al. (2021)

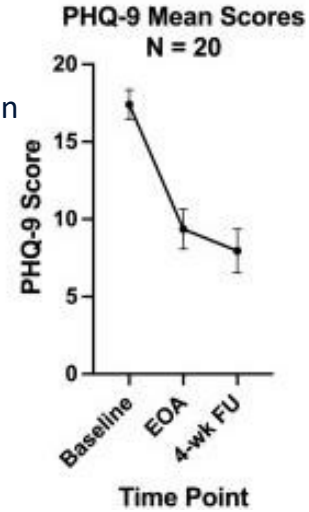
Pragmatic "SAINT"
36 sessions over 5 days (68886), 600 iTB, Beam F3



62% MADRS Reduction

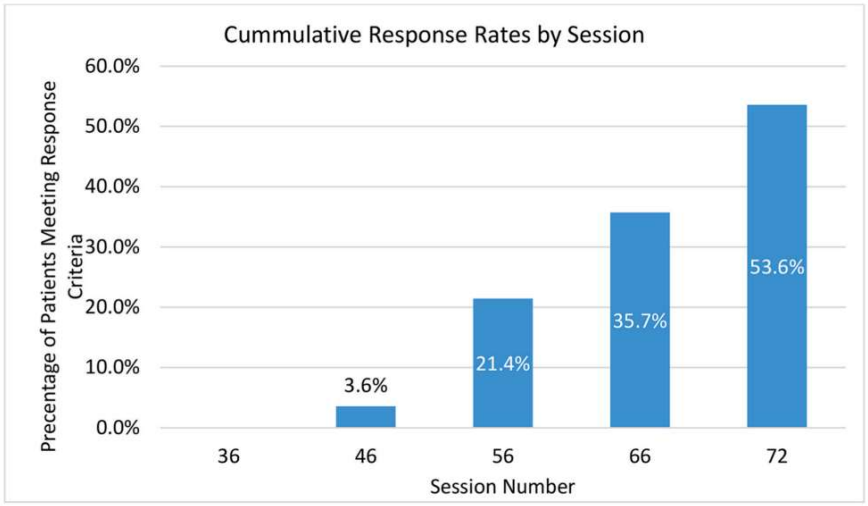
70 % Response

55 % Remission



Accelerated transcranial magnetic stimulation: A pilot study of safety and efficacy using a pragmatic protocol. Luehr, John G.Sackeim, Harold A. et al. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, Volume 17, Issue 4, 860 - 863

It is never to late - consider more sessions!



Razafsha et al. (2023)

Accelerated TMS

frontiers in Neurology

OPINION
published: 05 November 2020
doi: 10.3389/fneur.2020.599918

How to Design Optimal Accelerated rTMS Protocols Capable of Promoting Therapeutically Beneficial Metaplasticity

*Alix C. Thomson [1,2,3] and Alexander T. Sack [1,2,3]**

[1] Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, Netherlands, [2] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNS), Maastricht, Netherlands, [3] Centre for Integrative Neuroscience, Faculty of Psychology and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands

Keywords: metaplasticity, homeostatic plasticity, hebbian plasticity, transcrancial magnetic stimulation (TMS), accelerated rTMS

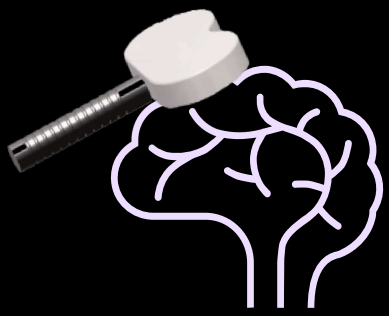
INTRODUCTION

OPEN ACCESS

Edited by:
Mariagiovanna Cantone, Sant'Elia Hospital, Italy

Our brain is comprised of billions of neurons, which can connect via synapses that rely on electrical signaling and the release of chemical messengers to communicate and propagate signals through neural networks. By forming such networks, neurons are capable of monitoring previous firing activity, and using this information to adapt subsequent firing rate. This so-called activity-dependent plasticity is critical for the encoding of new information, and the tuning of (low activity)

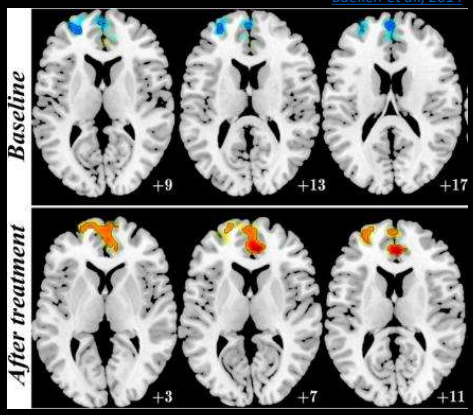
TMS Depression Therapy: what we *do* know



TMS is a successful depression treatment

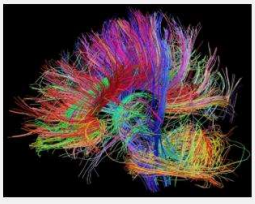
Doesn't work equally well for everyone

Baeken et al., 2014

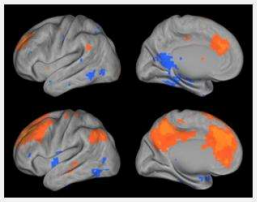


sgACC – dLPFC FC seems relevant

Personalising Treatment: The *WHERE* of TMS

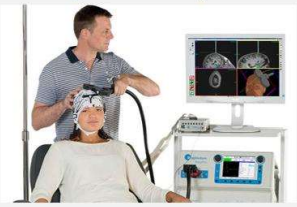


Diffusion Tensor Imaging

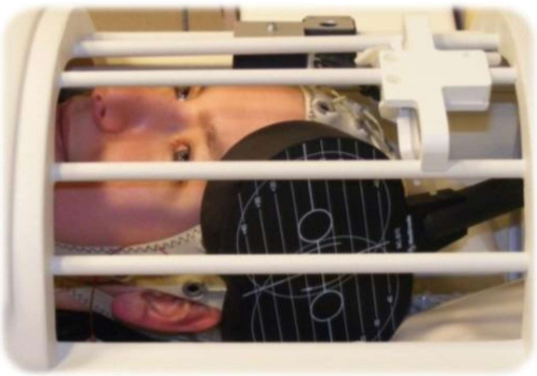


Resting state functional MRI

Individualized neuronavigated TMS target localization approach



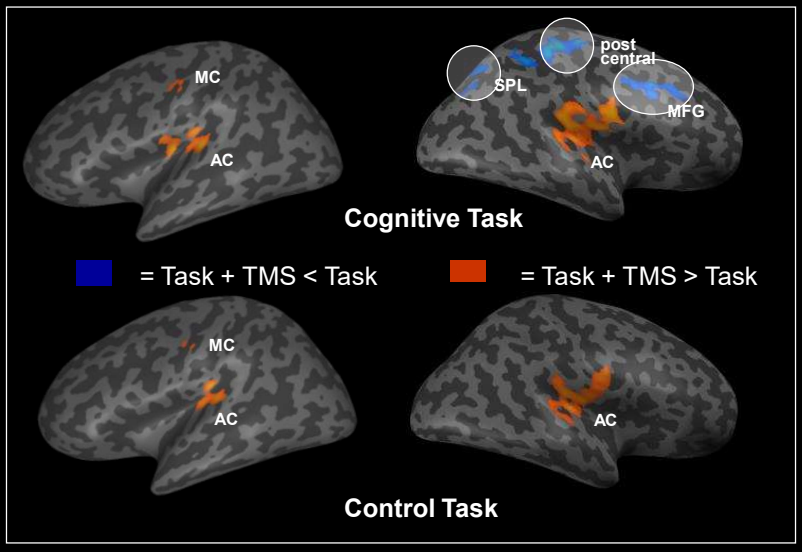
Personalising Treatment
But what about the ***WHEN*** of TMS



Simultaneous TMS and FMRI to identify state-dependent network effects of TMS

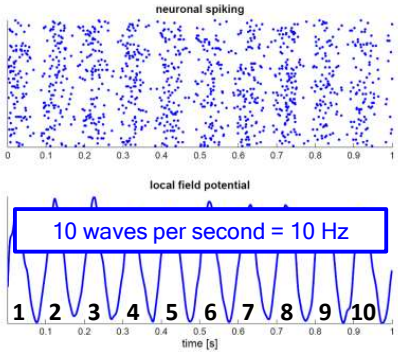
TMS causes (state-dependend) network effects

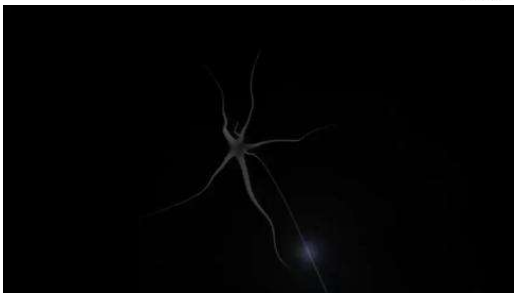
TMS during different Cognitive Brain States



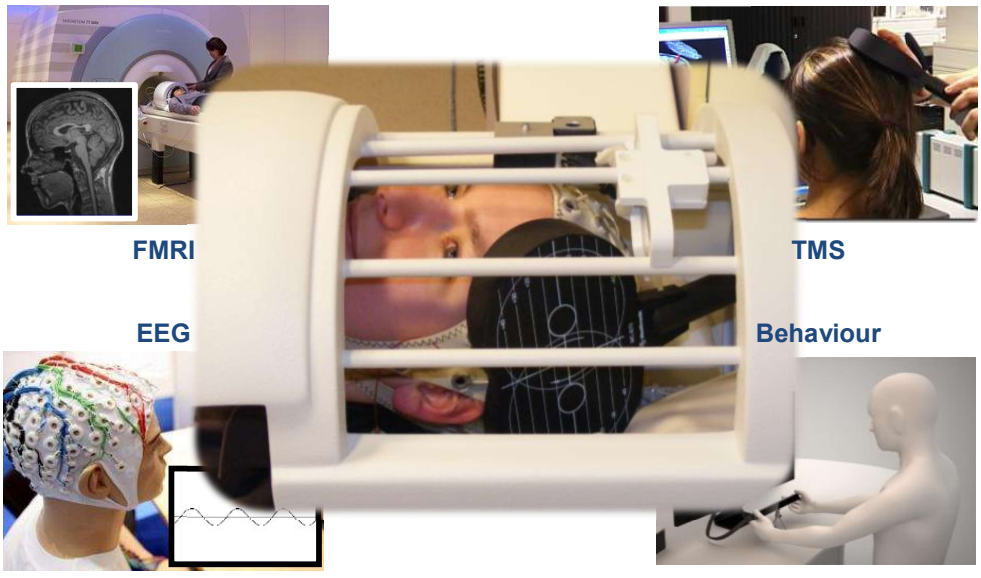
Sack et al., 2007

Cognitive State = Oscillatory Brain State
The Rhythms of Network Communication





Integrate oscillation-network coupling



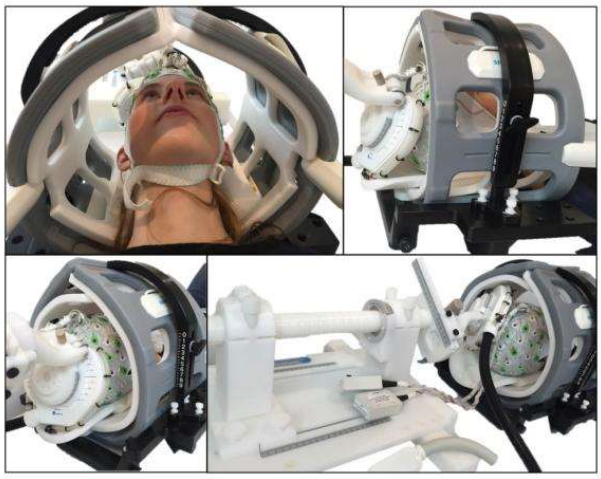
FMRI

TMS

EEG

Behaviour

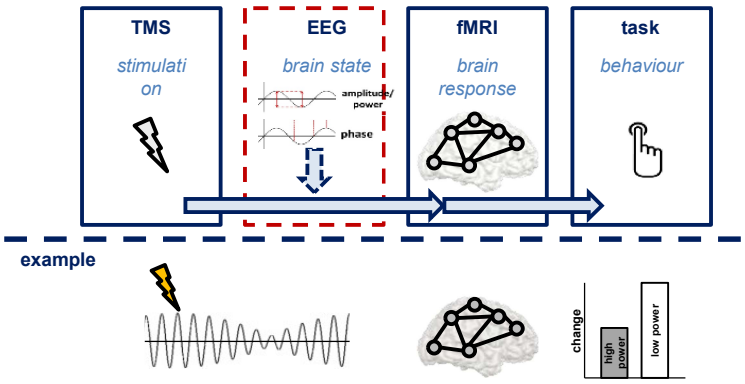
Combining EEG+fMRI+TMS



Peters*, Reithler*, Schuhmann, de Graaf, Uludag, Goebel, Sack. *Journal of Neurophysiology (2013)*

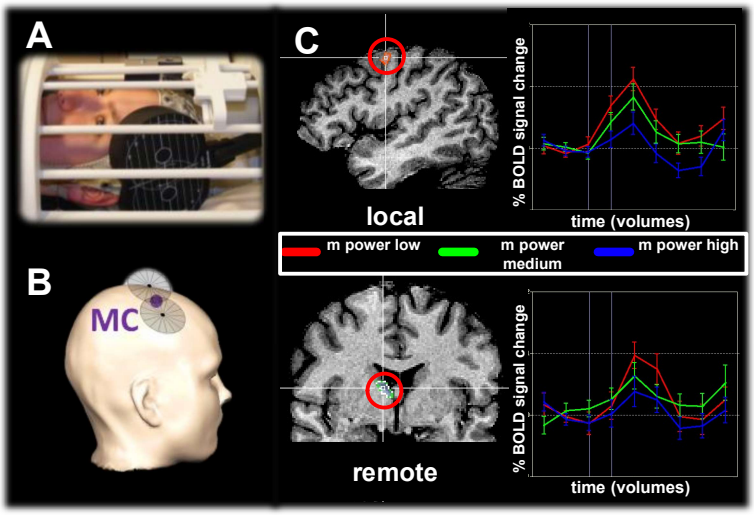
Personalising Treatment
But what about the ***WHEN*** of TMS

oscillation-network coupling



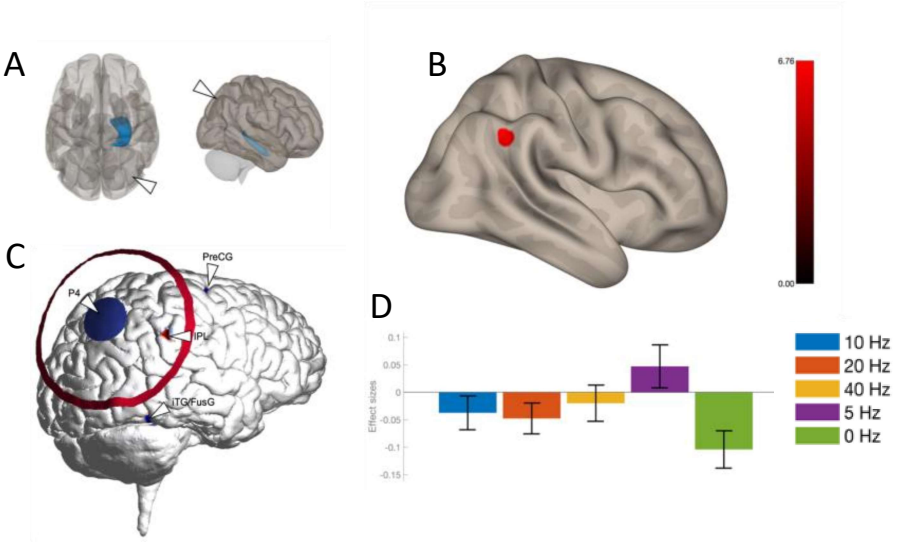
Peters*, Reithler*, Schuhmann, de Graaf, Uludag, Goebel, Sack. *Journal of Neurophysiology (2013)*

Oscillatory-state-dependent TMS network effects

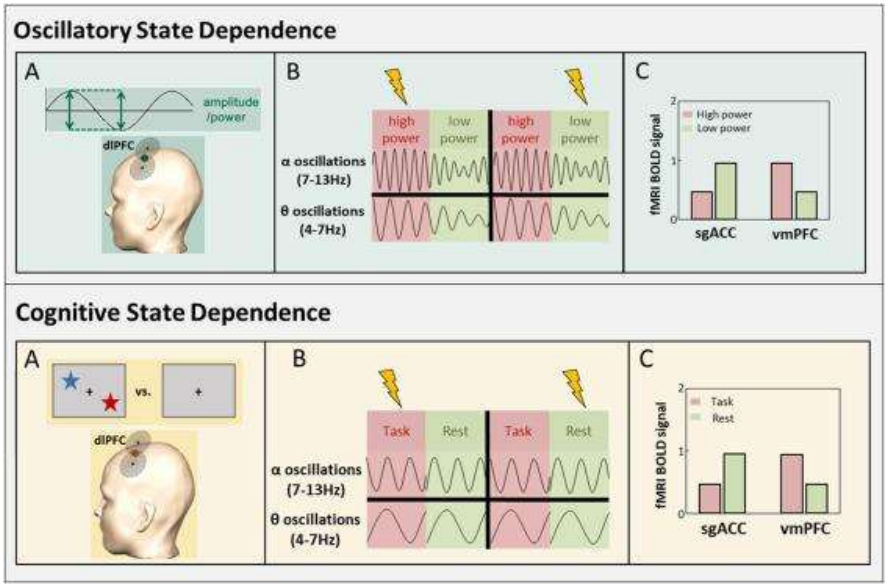


Peters*, Reithler*, de Graaf, Schuhmann, Goebel, Sack. Nature Communications Biology (2020)

HD-tACS - Functional connectivity IPS-Hippocampus

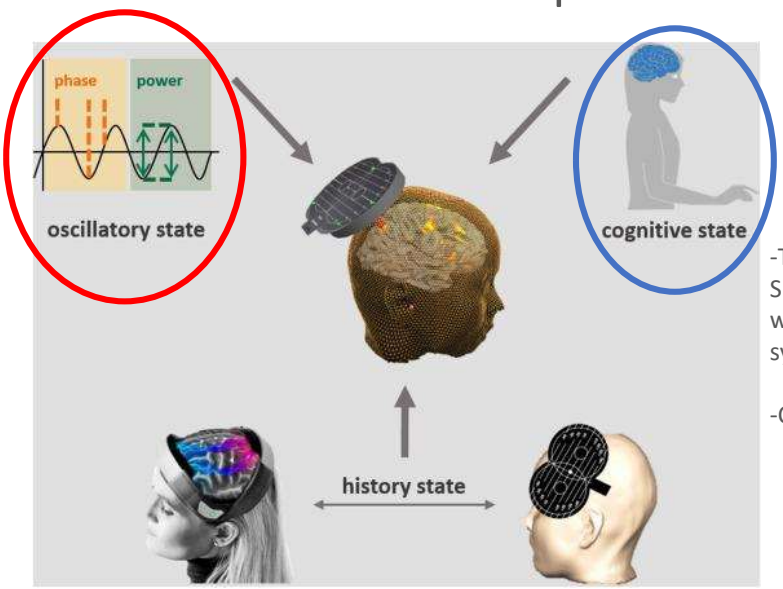


Personalising Treatment:
The ***WHEN*** and ***HOW*** of TMS!



What to do in clinical practice

Closed-loop TMS

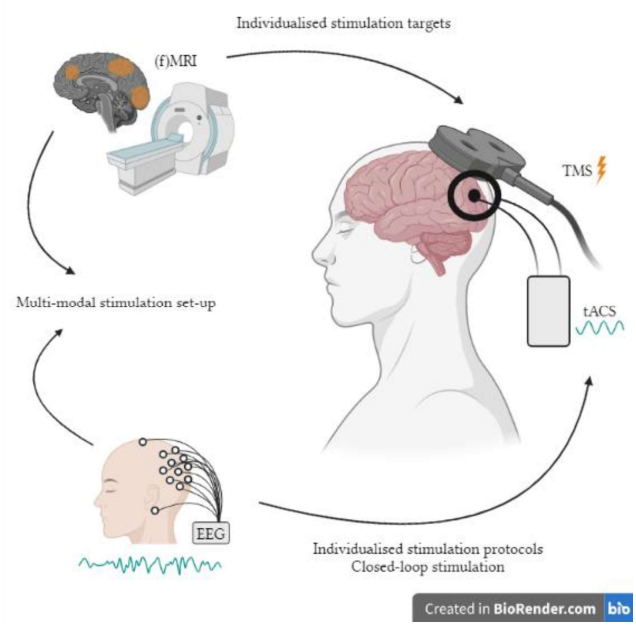


-TMS for OCD, PTSD, SUD often concurrent with cue-triggered symptom provocation

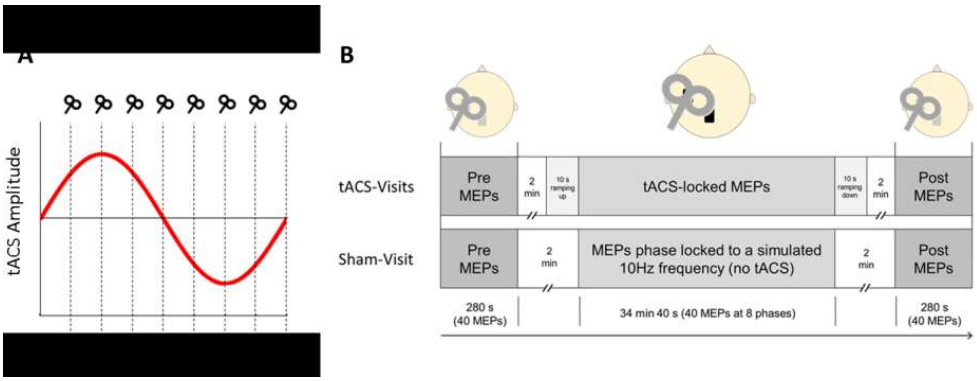
-Cognitive Task

Sack AT, Paneva J, Küthe T, Dijkstra E, Zwienenberg L, Arns M, Schuhmann T. Target engagement and brain state dependence of transcranial magnetic stimulation: implications for clinical practice. Biol Psychiatry. 2023 Sep 20:S0006-3223(23)01571-8.

Simplified Closed-loop TMS
TMS at EEG/TACS-controlled Brain States

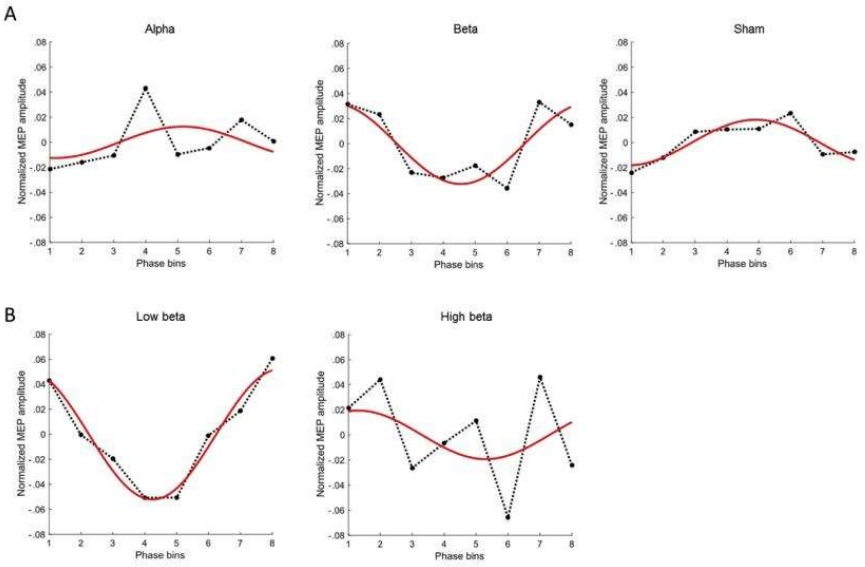


tACS-controlled phase-dependent TMS effects



(Schilberg, …, and Sack (2018)

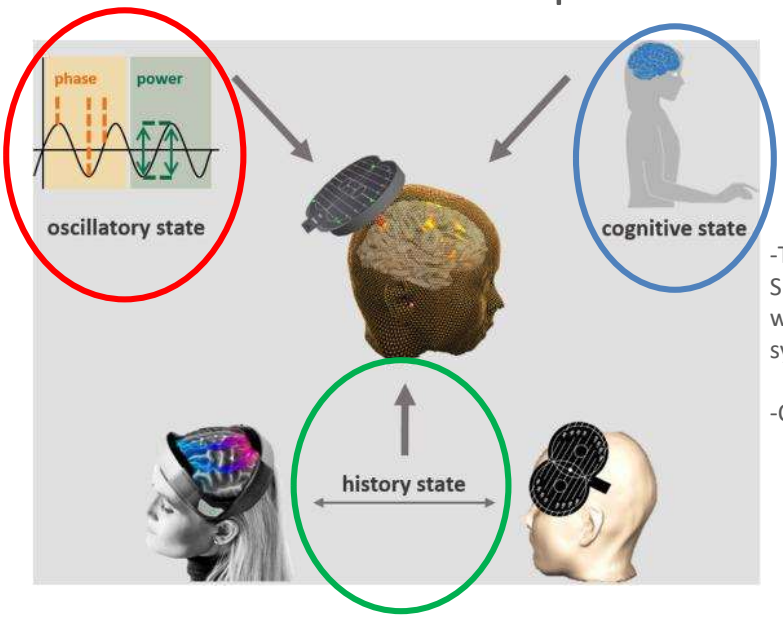
tACS oscillation **phase**-locked TMS effects



(Schilberg, …, and Sack (2018)

What to do in clinical practice

Closed-loop TMS



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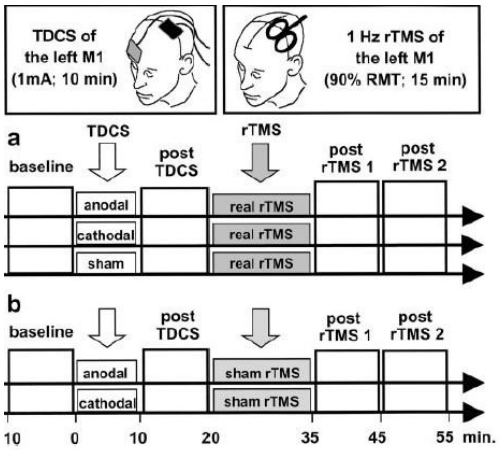
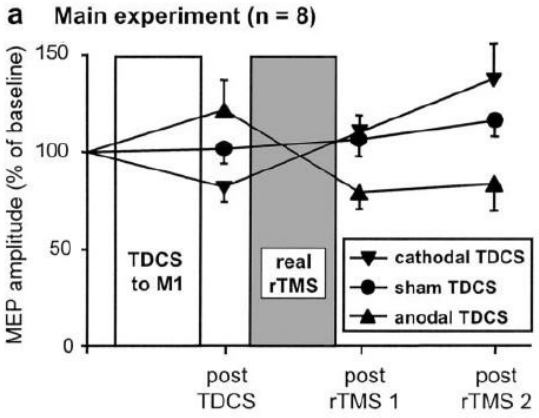
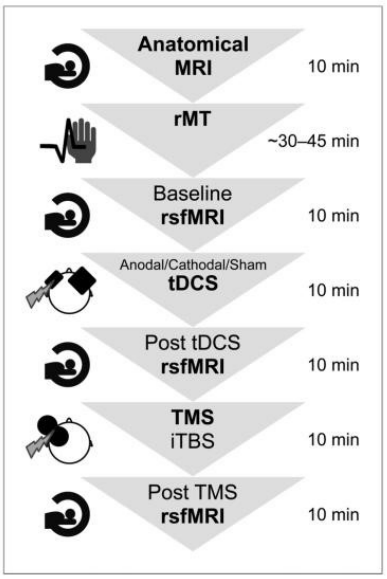
Primed TMS Protocols

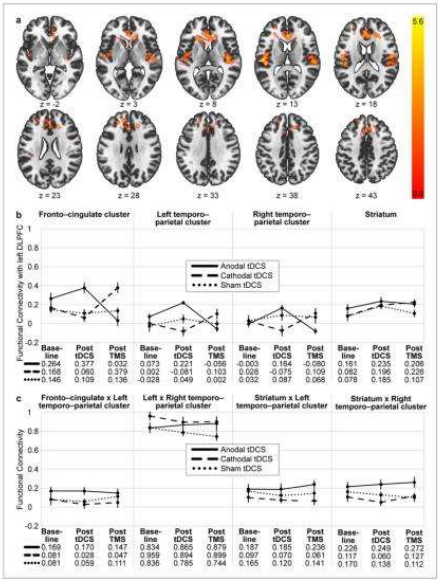




Siebner et al (2004). The Journal of Neuroscience, March 31, 2004 • 24(13):3379 –3385 • 3379

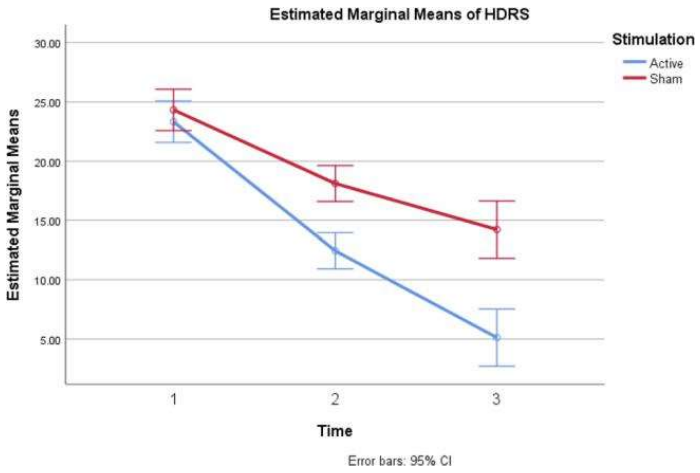
Primed TMS Protocols: Stronger Functional Network Effects!





Isabel Alkhasli et al (2022). Preconditioning Prefrontal Connectivity Using Transcranial Direct Current Stimulation and Transcranial Magnetic Stimulation. Preprint

Primed TMS Protocols: Better Clinical Oucomes !



High-Definition Transcranial Direct Current Stimulation–Primed Intermittent Theta Burst Stimulation in Treatment-Resistant Depression
A Controlled Study Alankrit Jaiswal, MBBS,∗ Nishant Goyal, MD, DPM,† and Umesh Shreekantiah, MD, DPM‡

The Academy of Brain Stimulation
Education and Certification

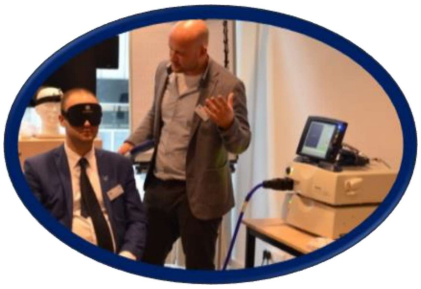
Optimised and Personalised TMS Depression Therapies

Optimizing TMS Efficacy – Stratification – Alternative targets for DLPFC nonresponders – SAINT
Accelerated TMS - State-dependent TMS Therapy - Combining TMS with other Interventions

Prof. Dr. Alexander Sack
Department of Psychiatry and Neuropsychology
School for Mental Health and Neuroscience (MHeNs) Brain+Nerve Centre
Maastricht University Medical Centre+ (MUMC+)

Precision TMS

Dr. Lukas Schilberg



The Academy of Brain Stimulation
Education and Certification

Clinical TMS Certification Course

Precision TMS

Neuronavigation and Electric Field Modelling

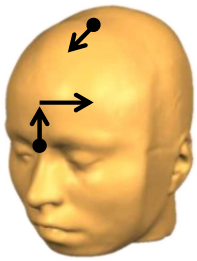
Dr. Lukas Schilberg

BrainStim
Düsseldorf, Germany

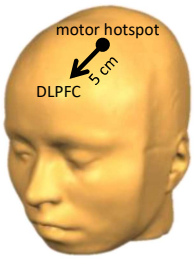
Department of Cognitive Neuroscience
Faculty of Psychology and Neuroscience
Maastricht University

lukas.schilberg@maastrichtuniversity.nl

TMS Coil Positioning



Where do we need to place the TMS coil to reach treatment specific targets?



Anatomical landmarks

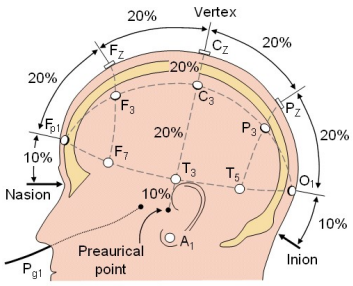
- nasion, inion, vertex

Functional landmarks

- muscle twitch, phosphene, speech arrest

EEG electrode positions

- F3, P4, etc.
- Beam F3



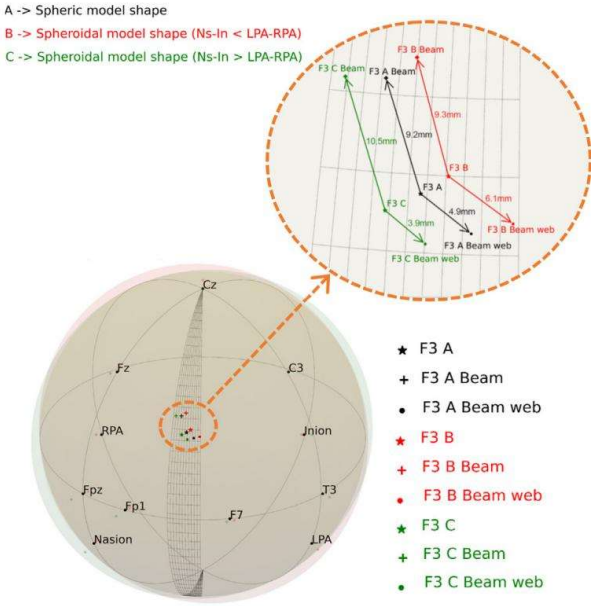
Neuronavigation

Current Issues with Beam “F3”

Beam F3 is not F3

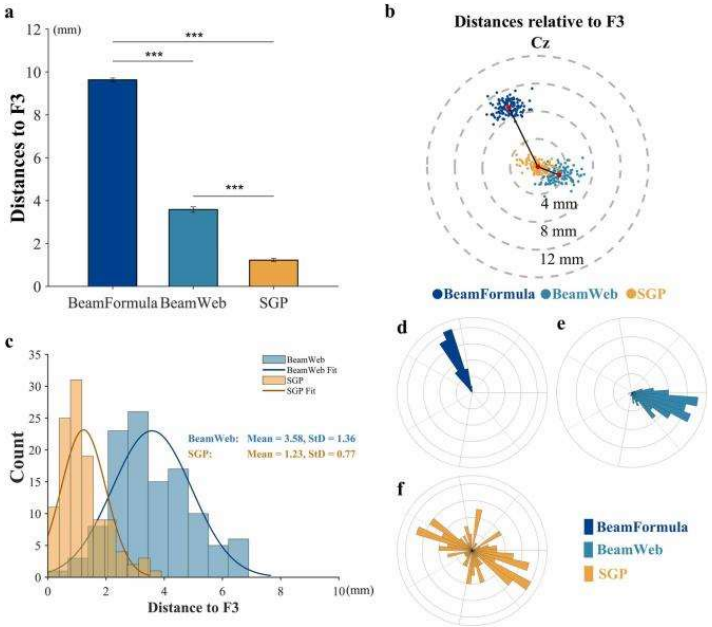
Beam F3 software implementation is not the same as published equations

Impact currently unclear



Fabregat-Sanjuan et al. (2022). Brain Stimulation

Current Issues with Beam “F3”



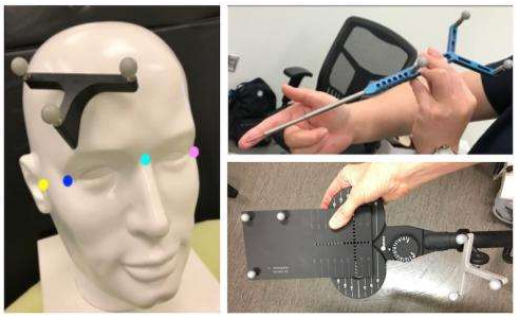
Li, Z., Sack, A.T., Duecker, F. (2025). Transcranial Magnetic Stimulation

Considerations for Coil Positioning Methods

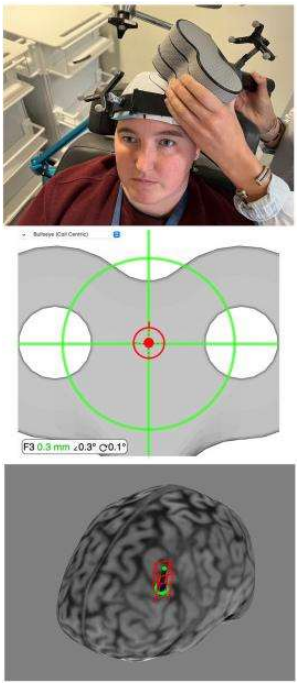
	Landmark approach	10/20 Beam F3	Neuronavigation
Costs	+	+	−
Time	+	+	+ −
Required expertise	+	+	−
Between expert reliability	−	+	+
Day to day reliability	−	+	+
Individual head size	−	+	+
Individual neuro-anatomy	−	−	+

TMS Neuronavigation

TMS Neuronavigation



Credits: Dianne Patterson



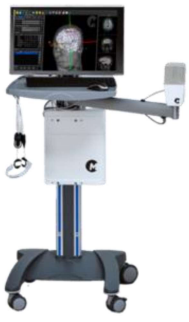
Caulfield et al. (2022). Brain Stimulation

TMS Neuronavigation

Assisted coil poisitioning system

Guided **targeting of scalp based landmarks** (5cm rule, F3, Beam DLPFC)

Neuronavigation system



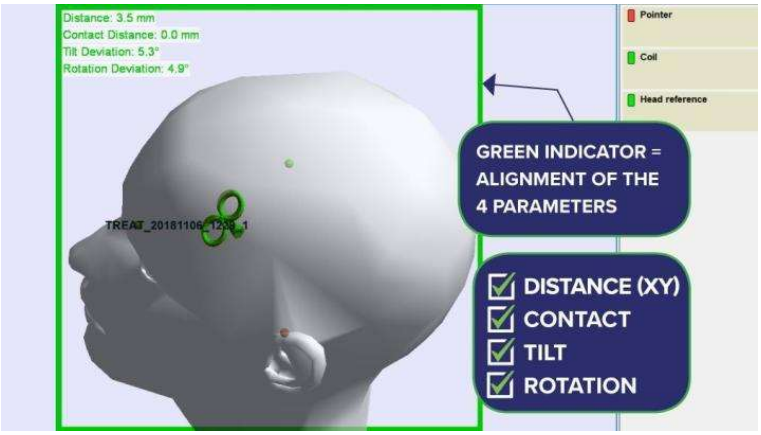
Neuronavigation **based on individual MRI data** (anatomical, functional, connectivity)

TMS Neuronavigation

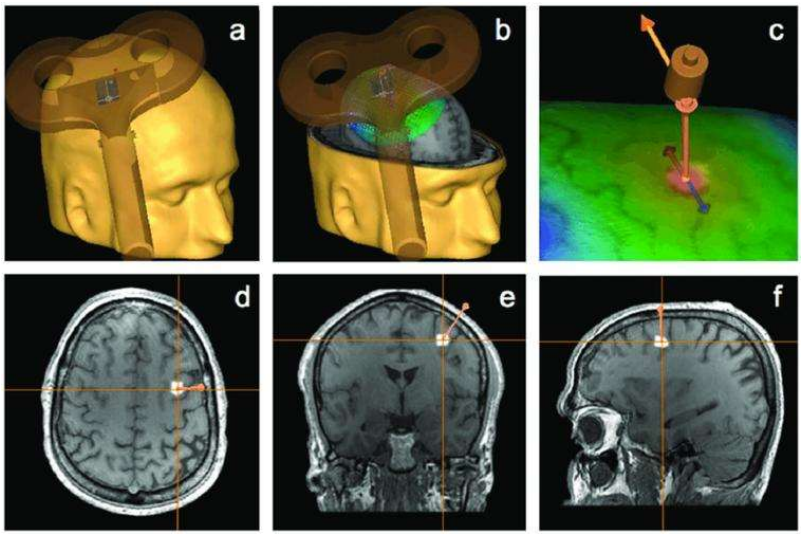
- **Higher day-to-day treatment accuracy**
- **Reduced between operator variability**

by tracking

- Distance
- Contact
- Tilt
- Rotation



TMS Neuronavigation

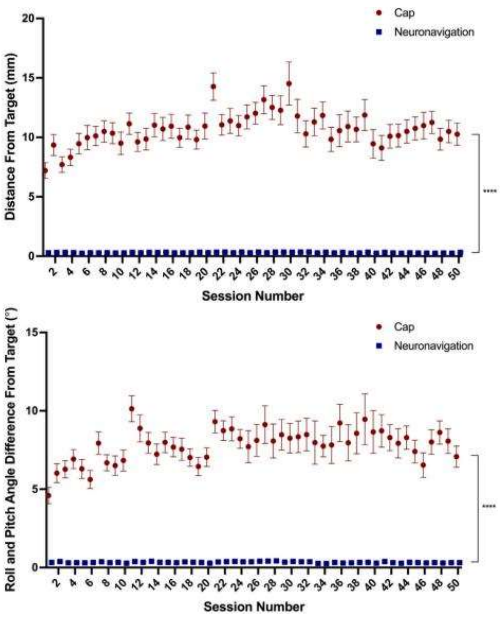


Chanes et al. (2012). PLoS One

TMS Neuronavigation in Action

Direct comparison of cap-based coil positioning versus neuronavigation, targeting the Beam “F3” point in both cases!

Near-perfect control over all TMS coil position paramters at all times (distance, angle, etc.)

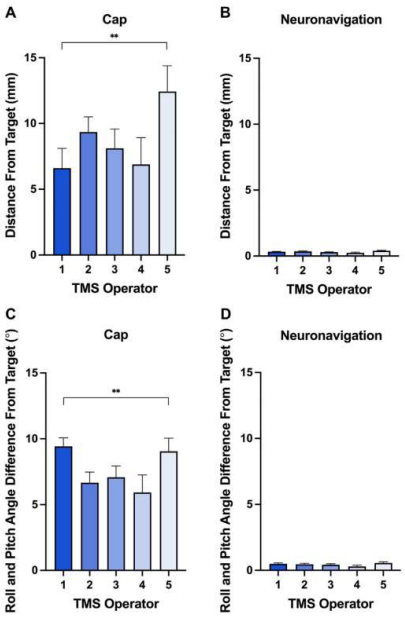


Caulfield et al. (2022). Brain Stimulation

TMS Neuronavigation in Action

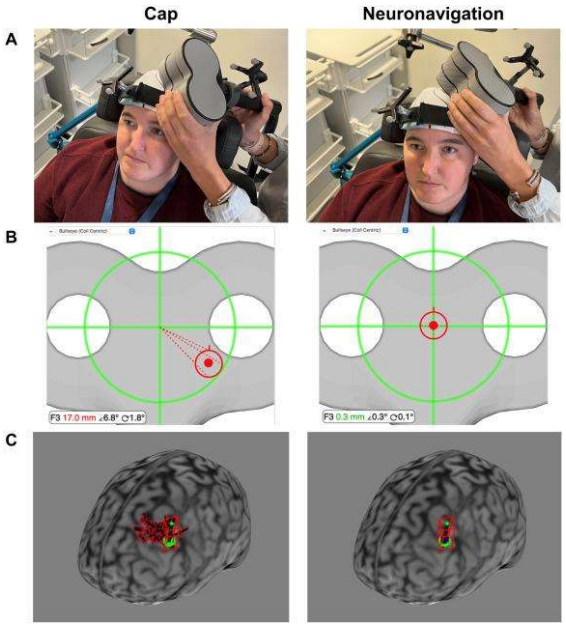
Neuronavigation essentially eliminates all variability across TMS operators

Yet, clinical relevance remains unclear...



Caulfield et al. (2022). Brain Stimulation

TMS Neuronavigation in Action



Caulfield et al. (2022). Brain Stimulation

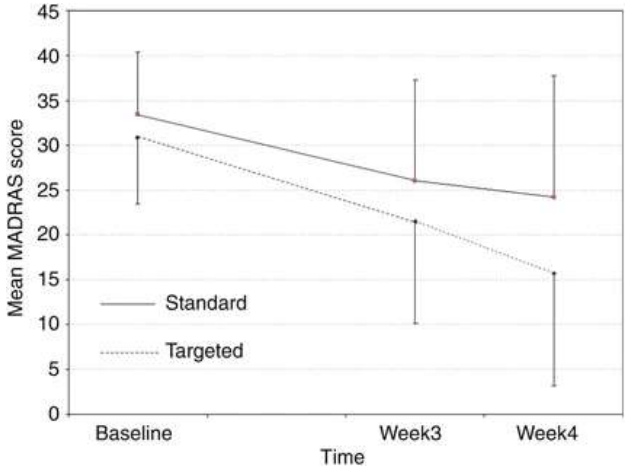
The Benefit of Neuronavigation in Depression

10Hz rTMS to lDLPFC in TRD

Standard:
5cm method

Targeted:
Neuronavigation based on structural MRI (between BA9 and 46)

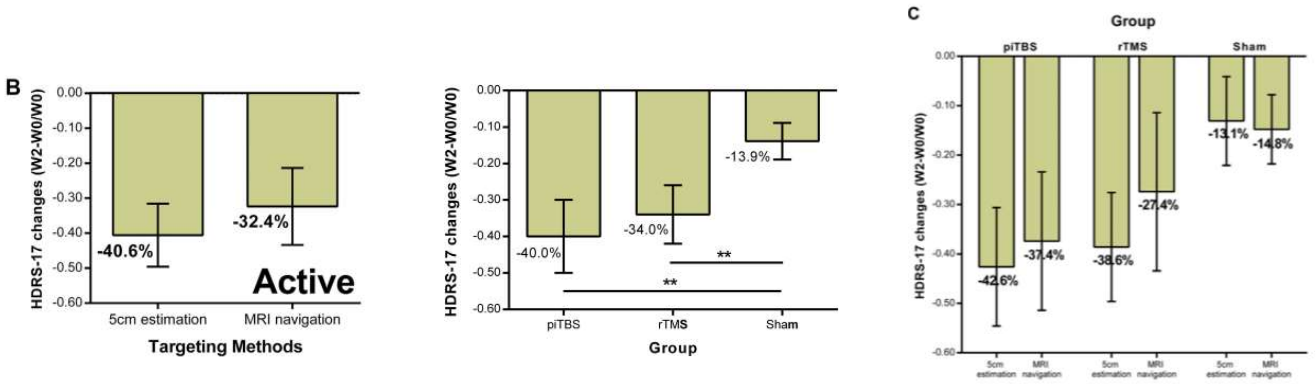
Neuronavigation
-> Lower MADRS scores at week 4



Fitzgerald et al. (2009)

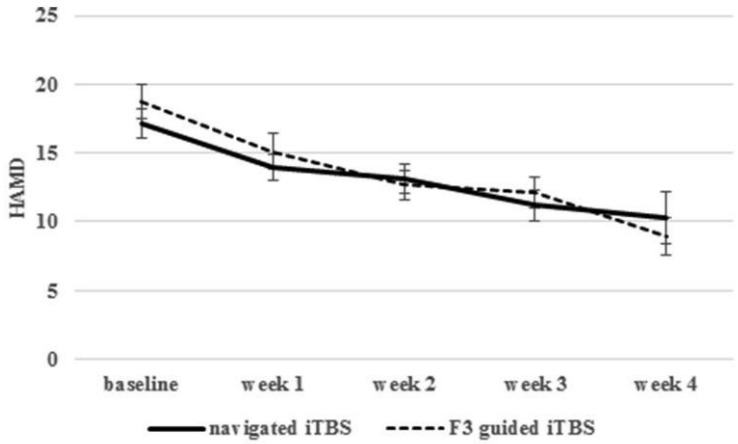
The Benefit of Neuronavigation in Depression

Recent study shows no difference in antidepressant TMS effects between coil positioning based on 5cm and MRI-guided neuronavigation



Li et al. (2020)

The Benefit of Neuronavigation in Depression



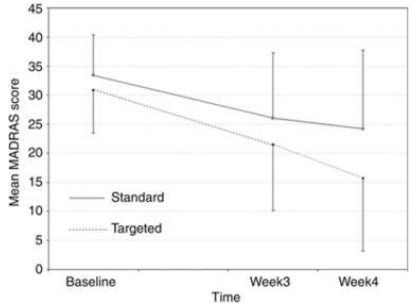
Hebel et al. (2021)

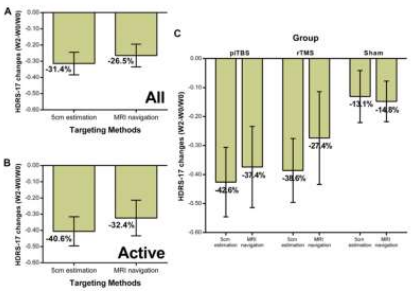
The Benefit of Neuronavigation in Depression

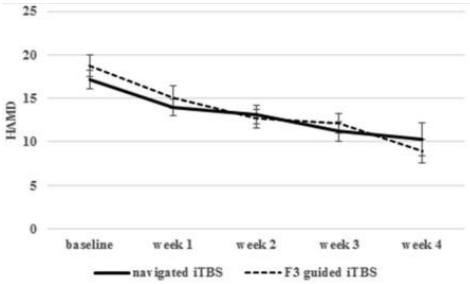
Although neuronavigation is precise

➔ Studies used no clear anatomical or functional target

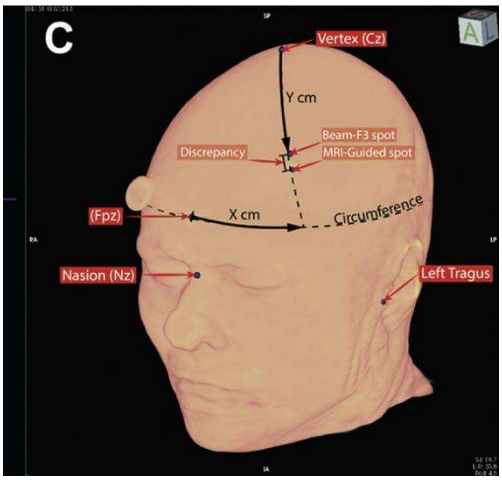
➔ No convincing clinical benefit of Neuronavigation

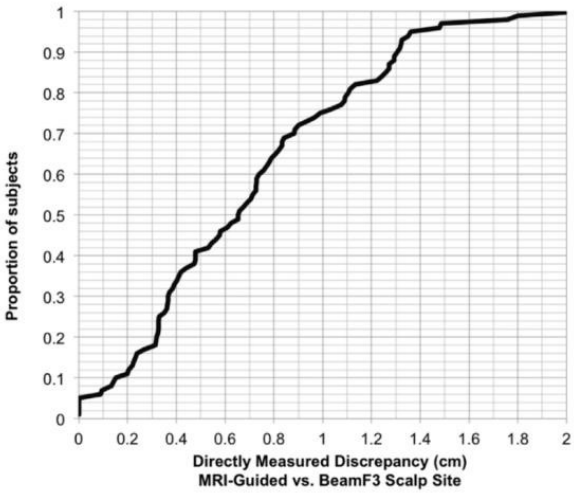






Beam "F3" Provides a Good Estimation of MRI-guided Target Sites





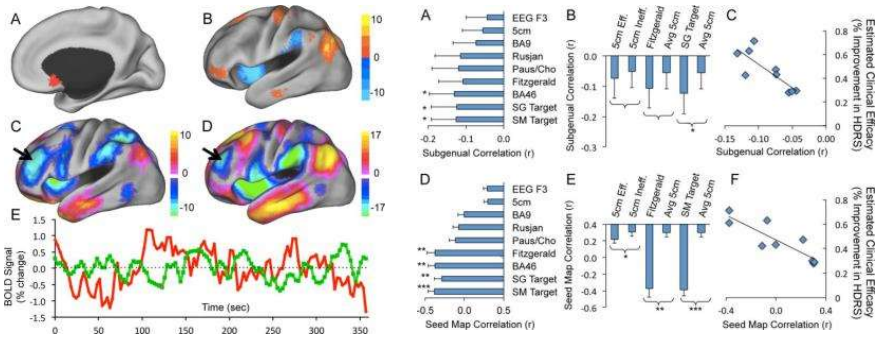
Mir-Moghtadaei et al. (2015)

Personalized TMS Targeting in Depression

Network connectivity:
sgACC - DLPFC

Optimized cortical targets defined by peak anticorrelations in DLPFC

More effective sites
= more anticorrelated

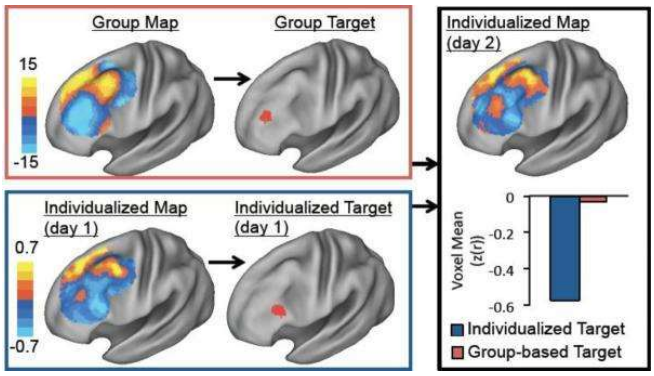


Fox et al. (2012). Biological Psychiatry

Personalized TMS Targeting in Depression

Individualized targeting is more negatively correlated than population-based targeting

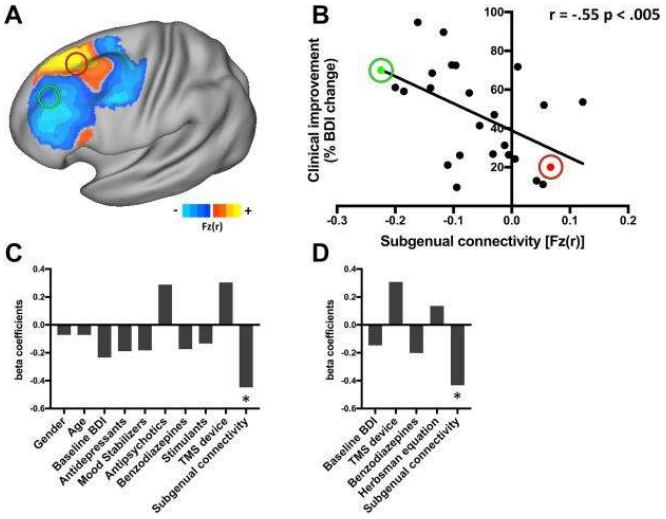
Possibly better clinical response via prospective connectivity-guided targeting



Fox et al. (2013). Neuroimage

Personalized TMS Targeting in Depression

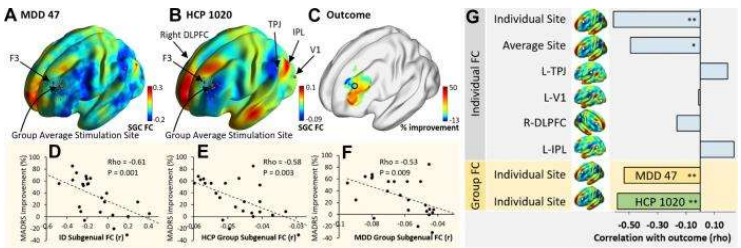
Functional connectivity between sgACC and DLPFC as predictor of antidepressant response

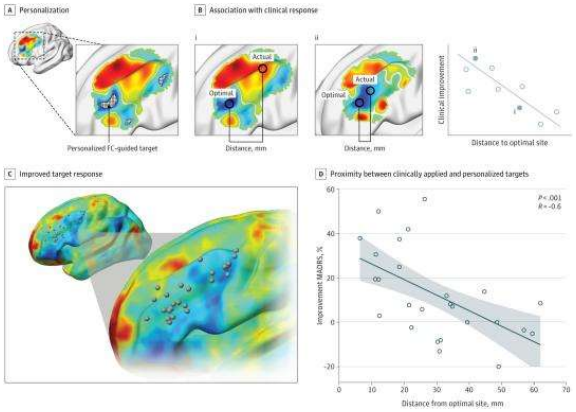


Weigand et al. (2018). Biological Psychiatry

Personalized TMS Targeting in Depression

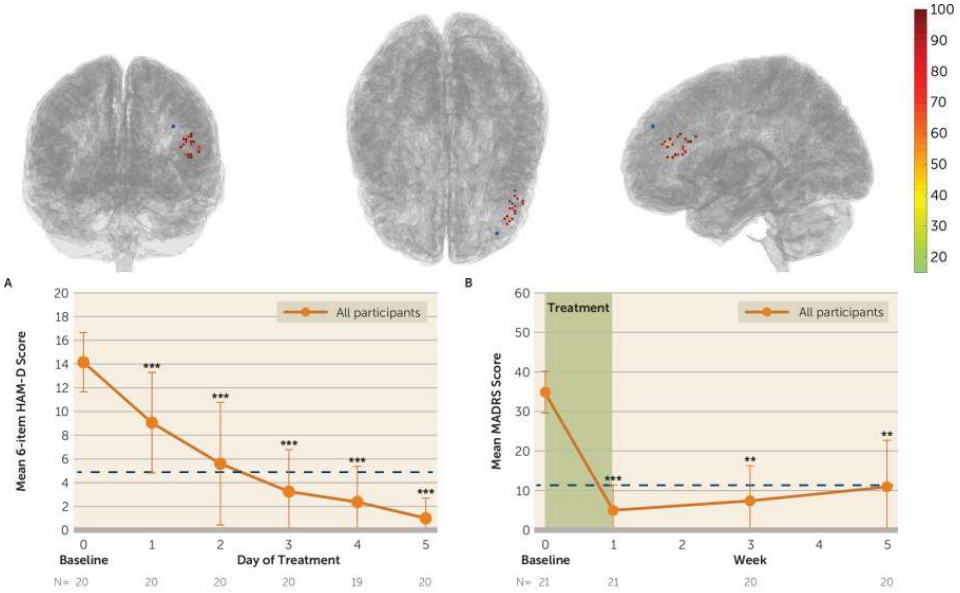
Target site personalization may improve rTMS clinical efficacy





Cash et al. (2019). Biological Psychiatry & Cash et al. 2020 JAMA Psychiatry

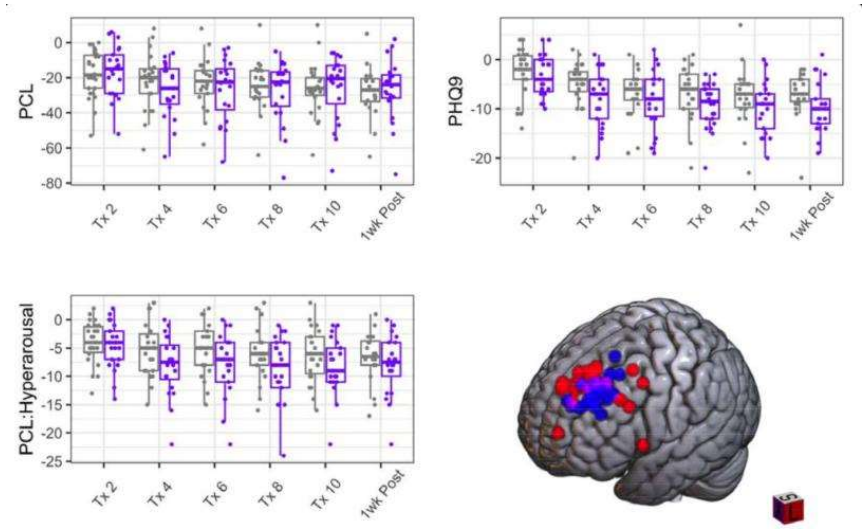
Personalized TMS Targeting in Depression



Cole et al. (2020). Am J Psychiatry

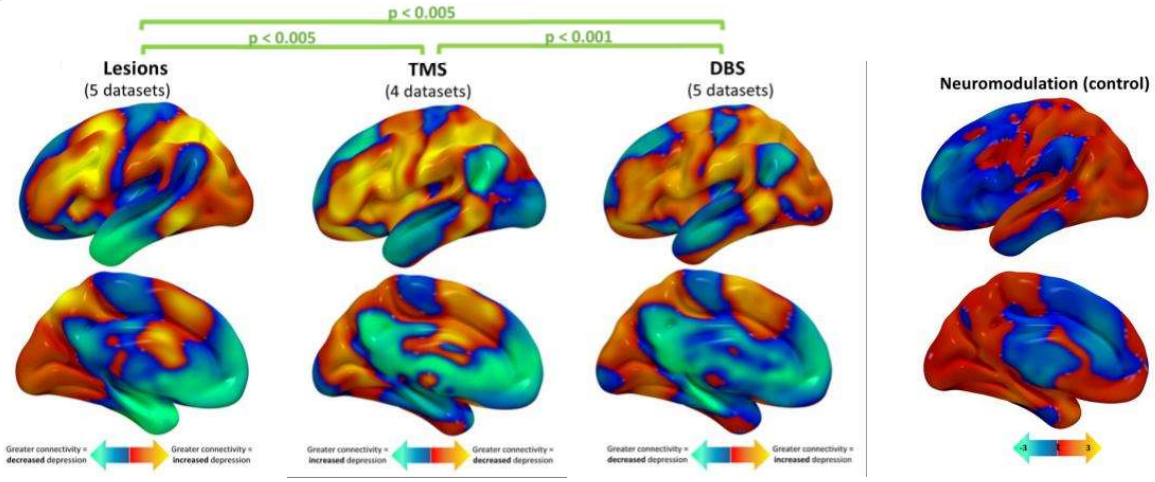
Personalized TMS Targeting in Depression

Targeting: **fMRI-guided** vs. **standard scalp-based** (6cm)



Oathes et al. (2024). medRxiv (preprint)

Personalized TMS Targeting in Depression

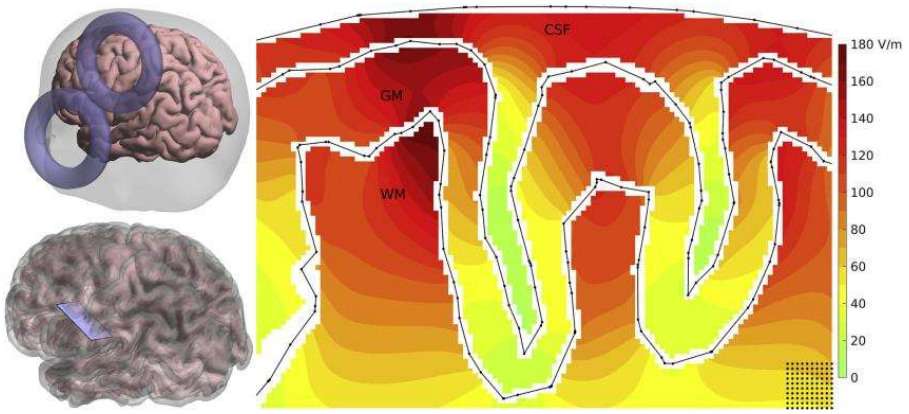


Depression circuit maps were similar between lesion datasets, TMS datasets, and DBS datasets

→ Connectivity to depression circuit predicted clinical outcomes better than connectivity to sgACC

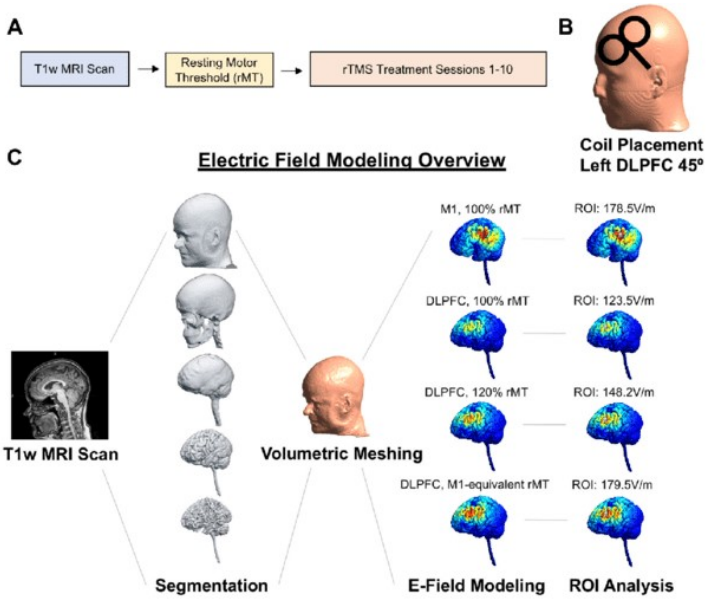
Siddiqi et al. (2021). Nat Hum Behav.

TMS Electric Field Modeling



Stenroos & Koponen (2019) NeuroImage

TMS Electric Field Modeling



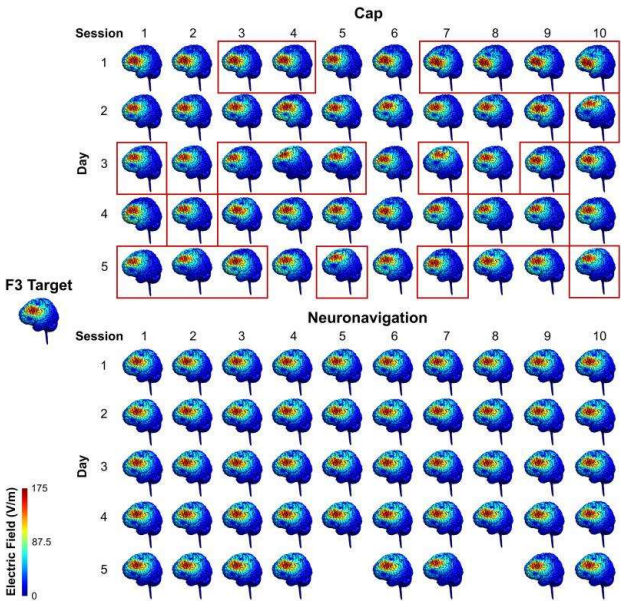
Caulfield et al. (2021). Clinical Neurophysiology

TMS Electric Field Modeling

Electric field produced from the coil at the targeted Beam F3 location

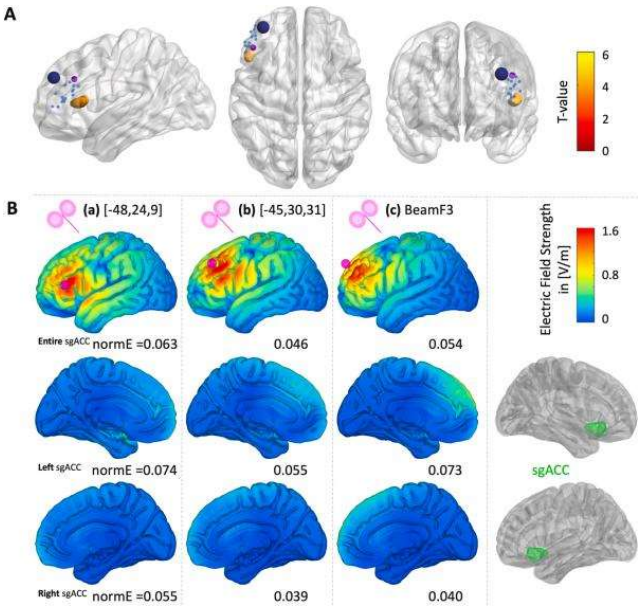
Squares indicate
≥ 10% lower E-field

Neuronavigated TMS at 120% MT produced equivalent E-fields as 119.9% MT TMS compared to 110.7% from cap-based targeting



Caulfield et al. (2022). Brain Stimulation

VLPFC Targeting in Depression



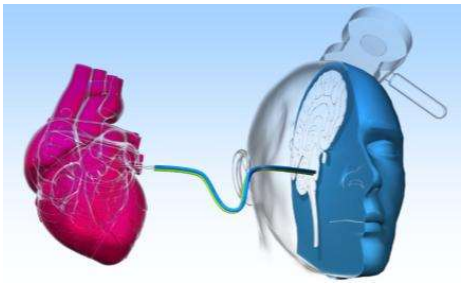
Wu & Baeken (2023). Brain Stimulation

Alternative Individualized Approach

Neurocardiac-guided TMS / Heart-brain coupling (HBC)

rTMS–induced heart rate deceleration to confirm activation of the frontal-vagal pathway

- possible biomarker of clinical response
- determination of the best target site



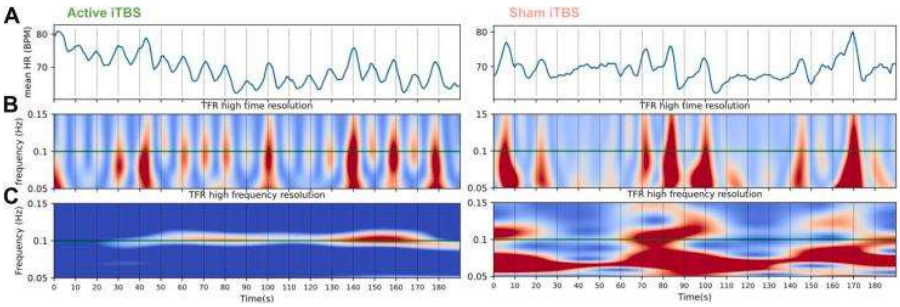
Brainclinics Foundation

Iseger et al., (2020) Brain Stimulation

Alternative Individualized Approach

Neurocardiac-guided TMS / Heart-brain coupling (HBC)

rTMS entrained heart rate oscillation



HBC as a marker for:

- Target engagement based on highest HBC power (e.g. Beam vs. 5cm)
- Stimulation intensity (dose-response effect of rTMS-induced HBC) → Frontal thresholding

Dijkstra et al., (2023) BPSGOS

Precision TMS - Summary

- Neuronavigation is the most accurate way of TMS coil positioning
  - ➢ Reduced variability between operators and across session
- Connectivity-based personalized targeting with precision stimulation using neuronavigation shows great clinical effects (e.g. SAINT/SNT)
- E-field modelling can serve as a potent tool to examine TMS effects and to determine the optimal stimulation site and intensity
- However, no scientific evidence yet that MRI targeting produces better clinical effects

➢ **Need for prospective studies**

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Precision TMS

Neuronavigation and Electric Field Modelling

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Maintenance TMS

Dr. Tahnée Engelen

The Academy of Brain Stimulation
Education and Certification

Clinical TMS Certfication Course

Maintenance TMS

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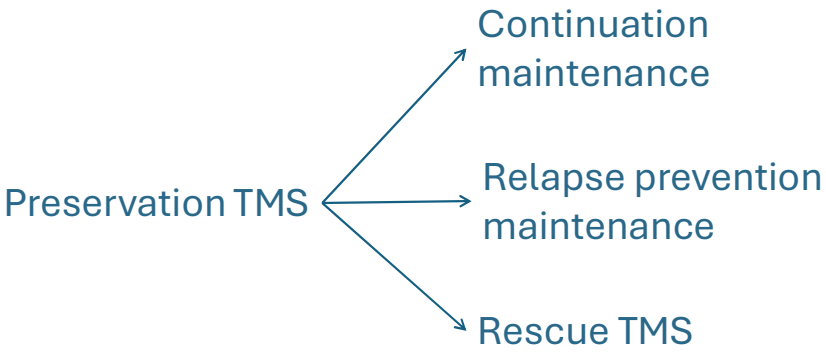
Maintenance TMS

>> TMS used to sustain a clinical response after a succesful acute course of treatment



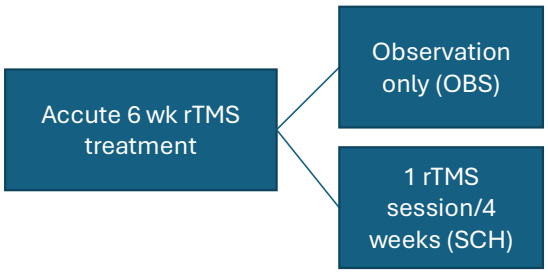
Wilson et al., Journal of Affective Disorders (2022)

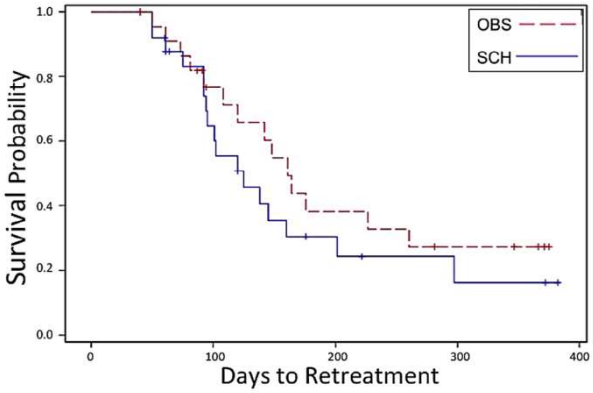
Structuring maintenance treatment

- When? Fixed schedule vs. symptom triggered
- How many sessions? Clustered, tapered, acute..
- How to assess response preservation?
- When to stop maintenance?
- Which dosing parameters?

Wilson et al., Journal of Affective Disorders (2022)

Structuring maintenance treatment



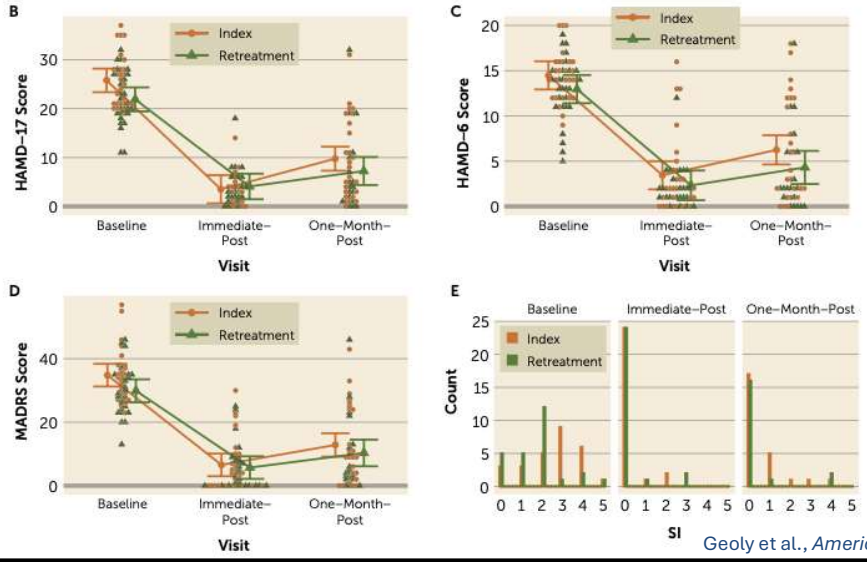


1 session per month might not be enough!

Philip et al. (2016). *Brain Stim*

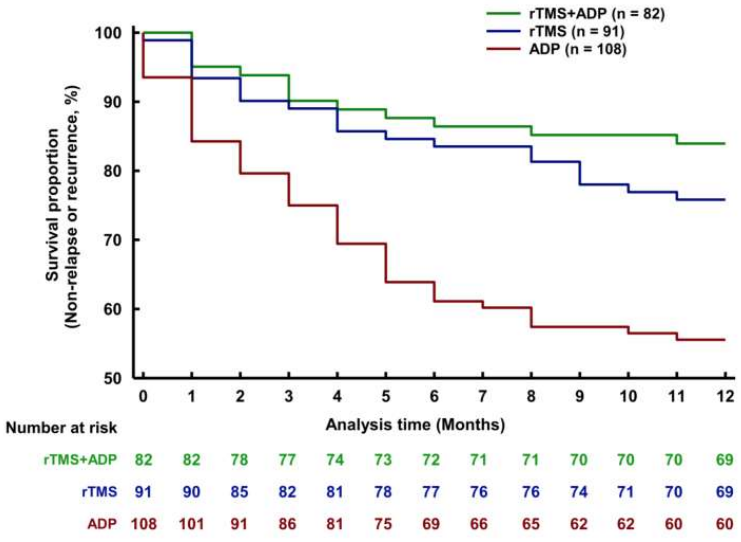
SNT retreatment

~26 weeks after initial treatment with retreatment criteria of major depressive episode



Geoly et al., *American Journal of Psychiatry*, 2024

Maintenance TMS to prevent relapse after ADP treatment



Wang et al. (2017). *Translational Psychiatry*

Maintenance TMS – general advice

- Most effective continuation rTMS (directly after acute treatment) so far is monthly administration of 3-5 sessions over 2.5-5 days
- No fixed protocol yet for relapse prevention maintenance, although literature suggests efficacy

Currently strong recommendations difficult due to large variability in examined protocols

Possible Solution: Cloud-based HOME-USE TES

PlatoScience Medical

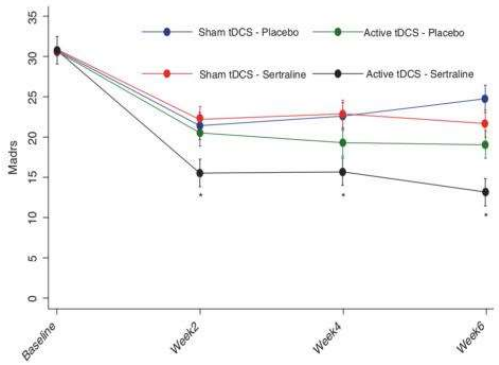
First at-home tDCS medical devices arising with full control & remotely supervised

A Clinical Case Series of Acute and Maintenance Home Administered Transcranial Direct Current Stimulation in Treatment-Resistant Depression

- First report of remotely supervised, home-administered tDCS for depression in a clinical setting
- Clinical, cognitive, and safety outcomes from 16 highly treatment-resistant depressed patients up to 2.5 years of treatment
- 12 patients = acute treatment and 4 = tDCS maintenance therapy after responding to ECT or rTMS
- 5/12 patients responded to acute tDCS within 6 weeks, and 9 patients who received tDCS for more than 12 weeks maintained improvements over several months
- Conclusion: TDCS given for at least 6 weeks may be of clinical benefit even in highly treatment-resistant depression. Results provide support for **long-term effectiveness, safety, and feasibility of remotely supervised tDCS and suggest a role for maintenance tDCS after acute treatment with tDCS, rTMS, or ECT**

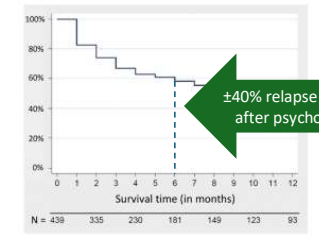
Le, Brandon BPsych (Hons); Alonzo, Angelo PhD; Bull, Michael FRANZCP; Kabourakis, Michael BPsych (Hons); Martin, Donel PhD, MClinNeuro; Loo, Colleen FRANZCP, MDThe Journal of ECT: June 2022 - Volume 38 - Issue 2 - p e11-e19

TDCS can also be used as an adjunct or maintenance treatment

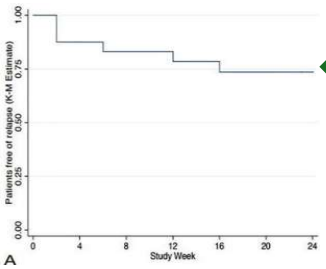


Increased effects as adjunct

- Pharmacotherapy
- Psychotherapy
- Cognitive training
- Physical therapy



±40% relapse 6 months after psychotherapy



±25% relapse 6 months after tDCS treatment

Source: Ali et al (2017), Aparicio et al. (2019), Brunoni et al. (2016), Brunoni et al. (2019), Moffa et al. (2020)

10

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Maintenance TMS

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Combining TMS with TES

Prof. Dr. Alexander Sack

The Academy of Brain Stimulation
Education and Certification

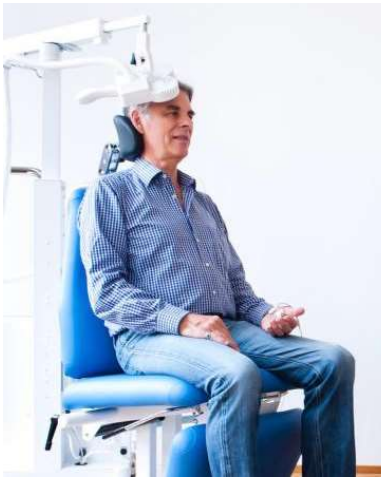
Combine TMS with tDCS / tACS

Basic Principles of tDCS – Safety - Clinical Efficacy

Prof. Dr. Alexander Sack
Department of Psychiatry and Neuropsychology
School for Mental Health and Neuroscience (MHeNs) Brain+Nerve Centre
Maastricht University Medical Centre+ (MUMC+)

Noninvasive Transcranial Brain Stimulation

TES



TMS

Transcranial electrical stimulation (tDCS / tACS)

tDCS: transcranial direct current stimulation

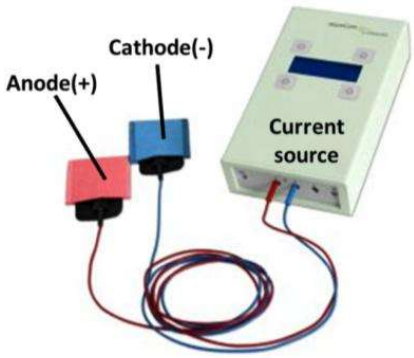


Image source:
www.neuroconn.de

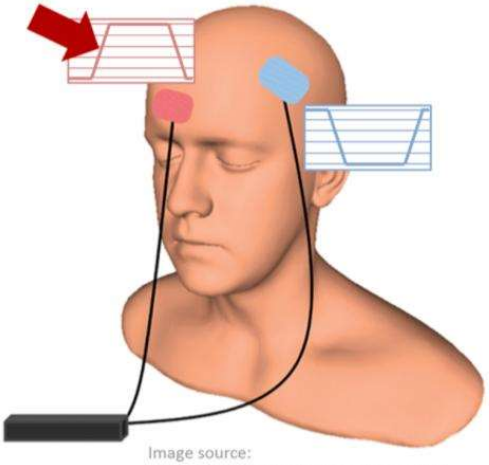
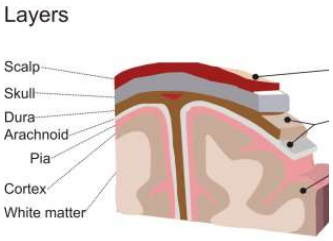
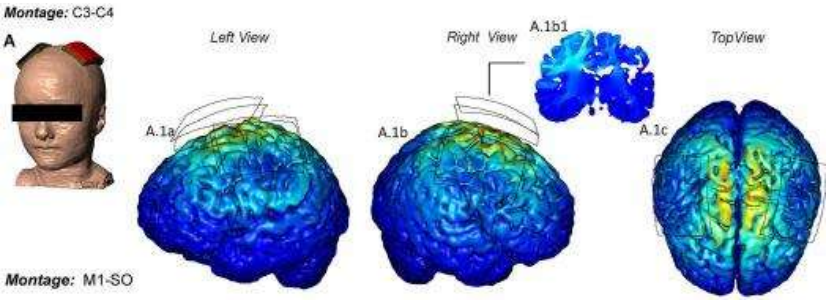


Image source:
Dayan et al., Nature Neuroscience, 2013

Transcranial electrical stimulation

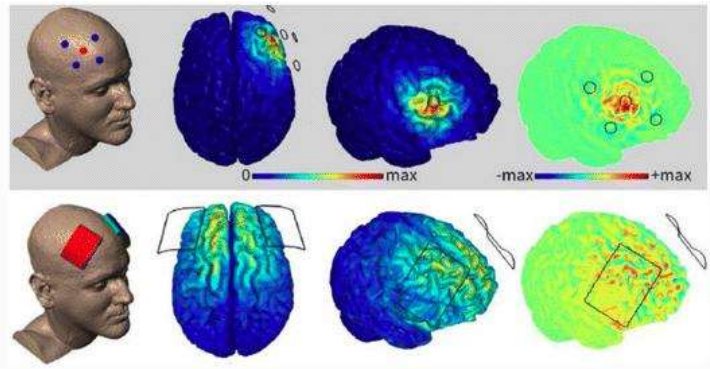
"Electric field modeling"





TES - Montages

High-definition TES: a center electrode and a set of surrounding electrodes



HD-tDCS

tDCS

Reinhart et al., 2016

TES - Physiology

Threshold for voltage-dependent Na+ channels: +/- -55 mV

Enough EPSPs: action potential

TES modulates resting state!

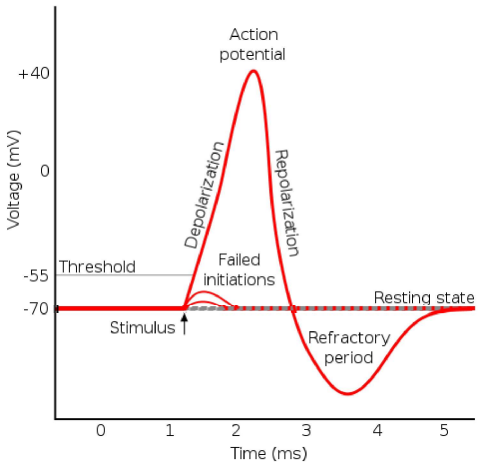


Image source: Wikipedia

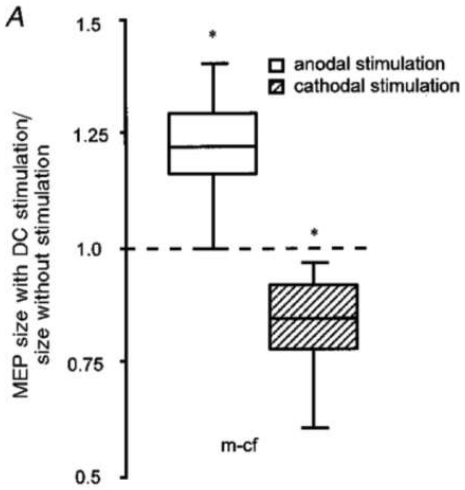
TES: physics

- An electric current flows between two (sets of) electrodes
- Current flows from anodal electrode to cathodal electrode
- Not focal, and the location of both (sets of) electrodes impacts stimulation sites
- HD-TES allows more focality (reasonably established)
- Future developments may include individual dosing (very new)

tDCS – Physiology – similar to rTMS after effects

anodal tDCS:
increase in MEPs

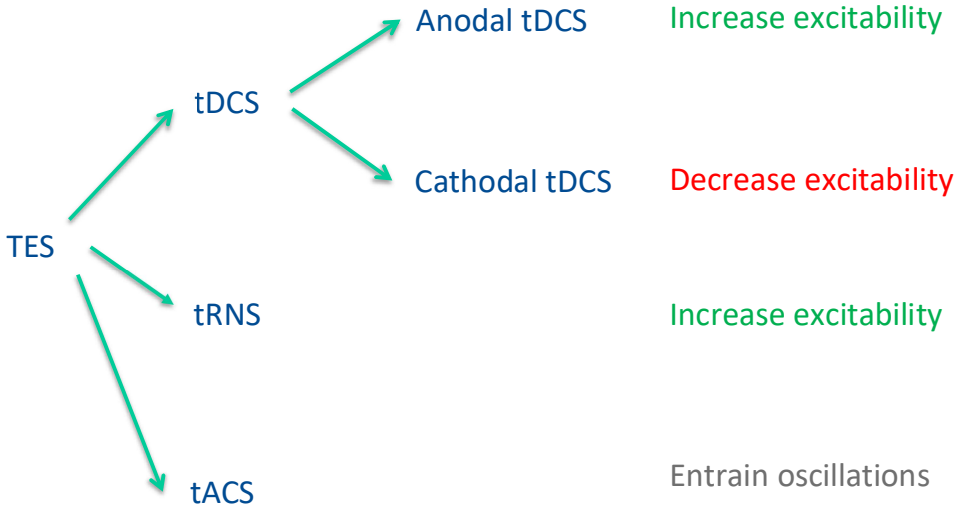
cathodal tDCS:
decrease in MEPs



Effects of tDCS measured with TMS!

Nitsche & Paulus, 2000

Types of TES



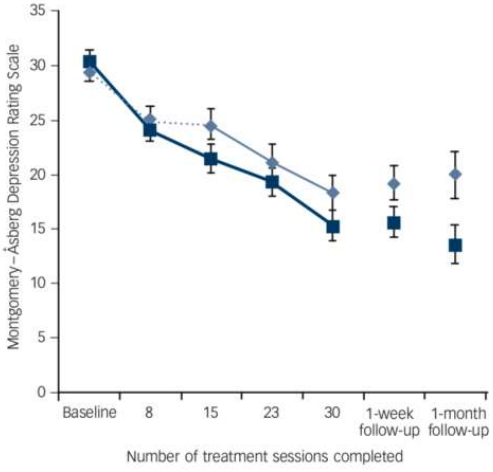
TES is safe to use in MDD
TES is effective in treating MDD

tDCS, 2mA
Anodal left DLPFC
Cathodal right orbito-frontal

15 masked sessions
15 open label sessions

60 patients total

Significant, lasting reduction in MADR

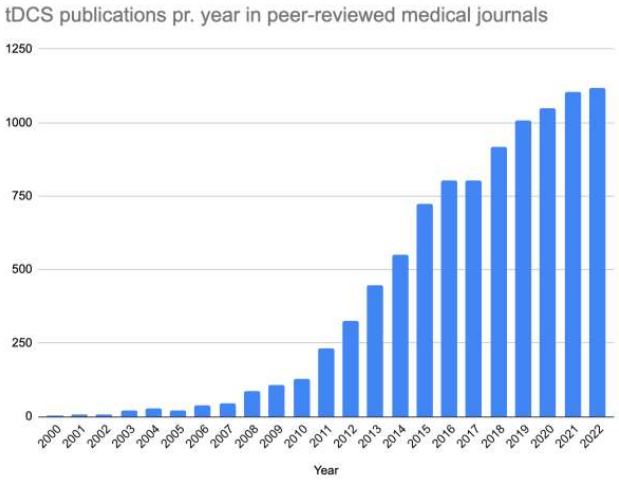


Loo et al., 2012

Current state of TDCS

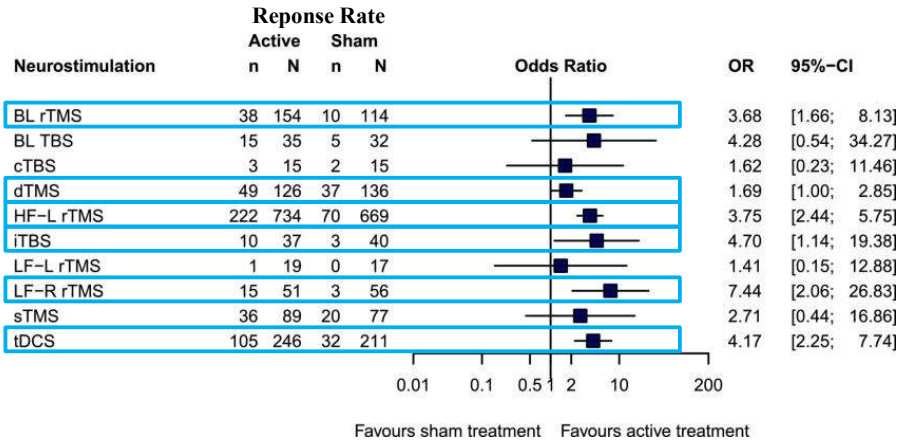
TDCS is one of the fastest growing methods in neuroscience, its affordability, ease of use and tolerability makes it an intriguing option for modifying brain activity.

Around 9000 studies since the inception of the technology in 2000.



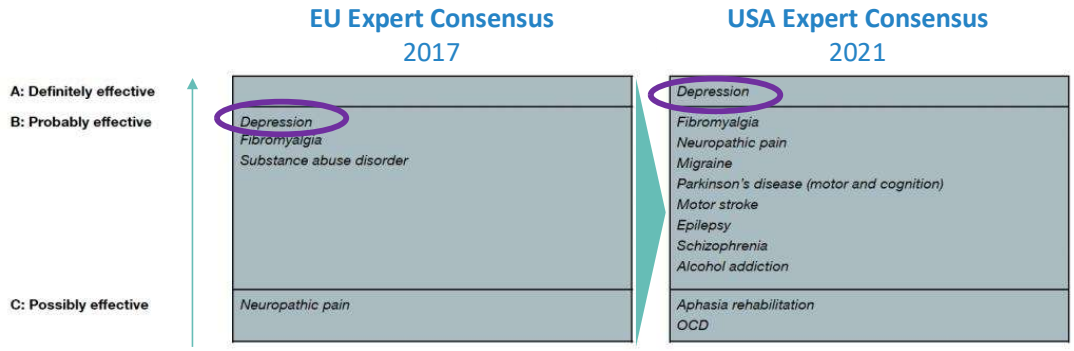
Peer reviewed TDCS publication pr. Year (april 2023, Pubmed)

Depression: Effective Protocols



Mutz et al. (2018)

TDCS is RATED ‘definitely effective’ in depression



Source: Fregni et al. (2021), Lefaucheur et al. (2017)

Clinical use: efficacy

- The therapeutic relevance of tDCS is increasing and may be complementary to rTMS
- Sufficient evidence to label tDCS probably (2017) or definitely (2021) effective in treating several disorders
- tDCS does have potential as safe and portable therapy for home use
- The potential and relevance of TES will likely increase
  (e.g. as transition from in-clinic to at-home maintenance therapy)

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Combine TMS with tDCS / tACS

Maintenance TMS - remotely supervised home-use tDCS/tACS - Scalibility

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Department of Psychiatry and Neuropsychology
School for Mental Health and Neuroscience (MHeNs) Brain+Nerve Centre
Maastricht University Medical Centre+ (MUMC+)

Maastricht TMS Depression Clinic

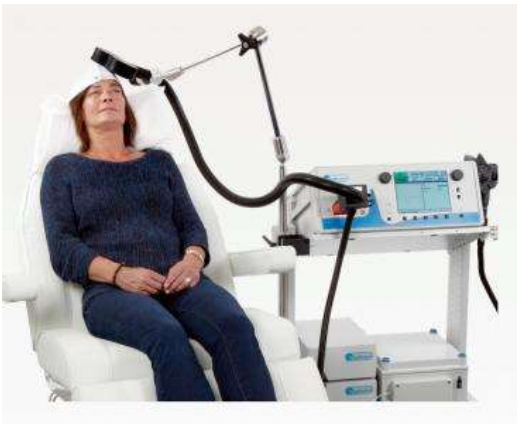
+ Proven efficacy (FDA and CE)

+ Health insurance coverage in growing number of countries

- Requires daily visits to clinic

- Relapse problem unsolved

- Not scalable

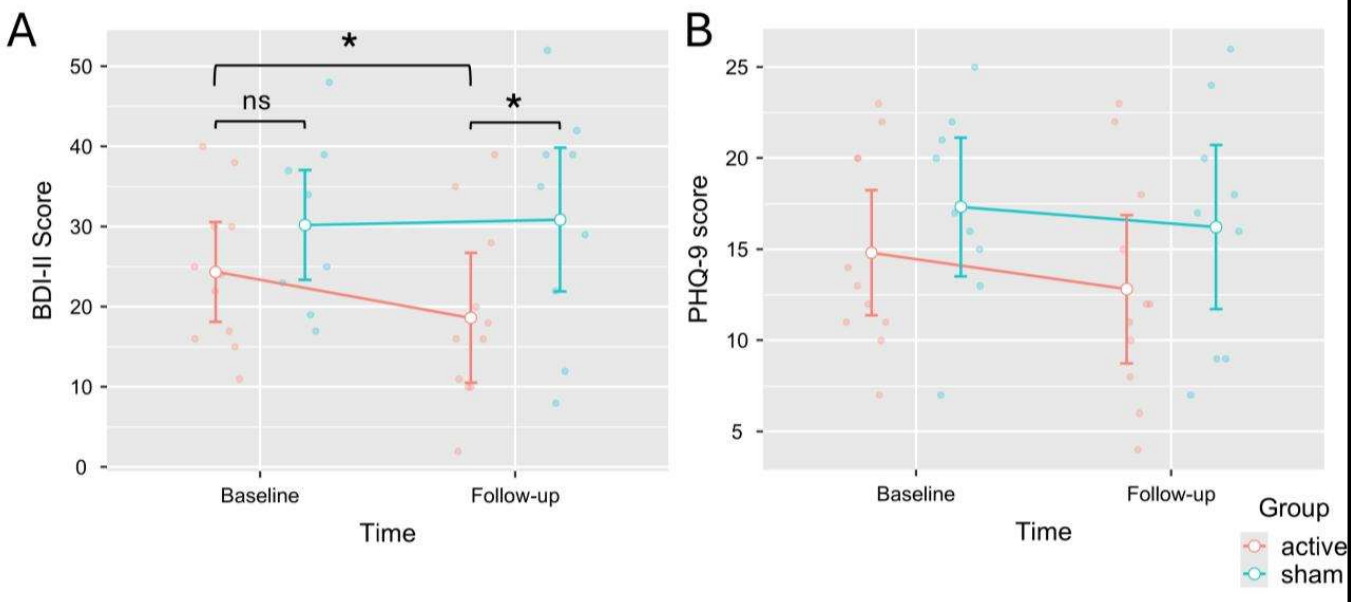


Possible Solution: HOME-USE TES

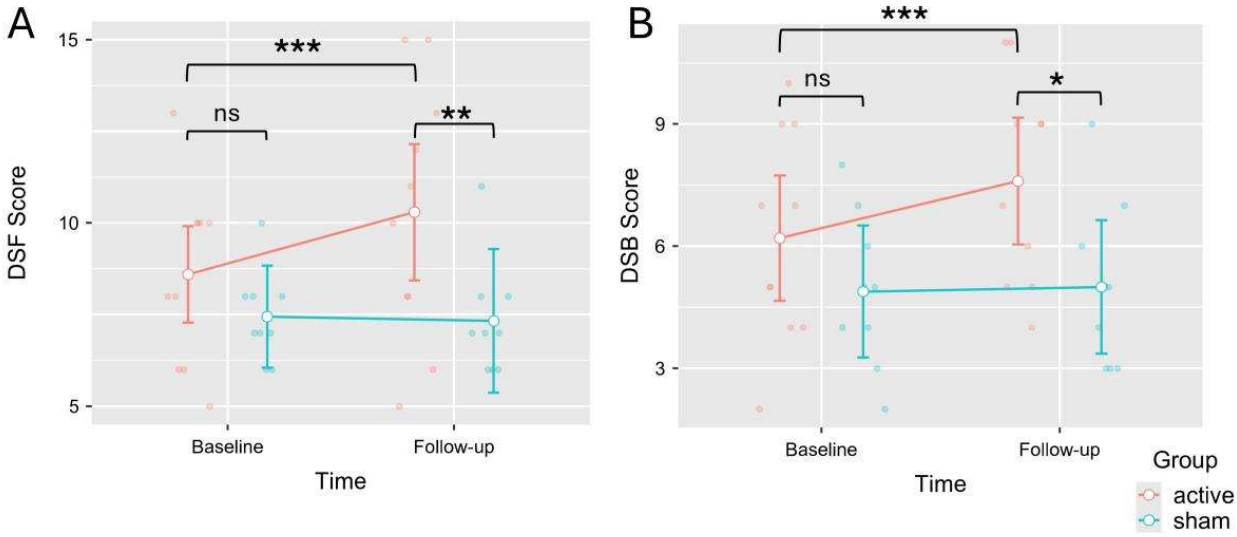
PlatoScience
Medical

First at-home tDCS medical devices arising with full control & remotely supervised

TDCS improved Depression

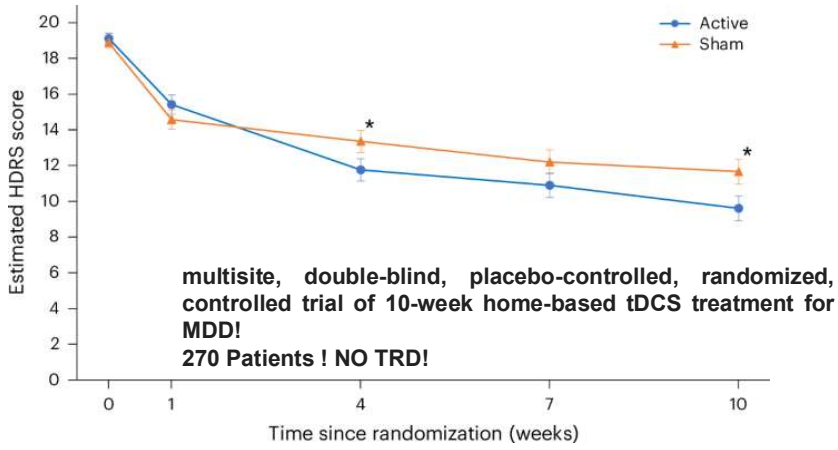


TDCS also improved Cognition in MDD patients



DSF: Digit span forward (STM), DSB: Digit span backward (WM).

Home-based transcranial direct current stimulation treatment for major depressive disorder: a fully remote phase 2 randomized sham-controlled trial



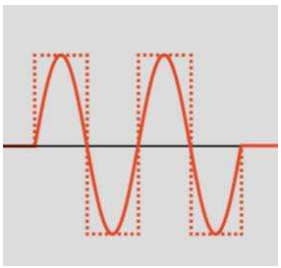
multisite, double-blind, placebo-controlled, randomized, controlled trial of 10-week home-based tDCS treatment for MDD!
270 Patients ! NO TRD!

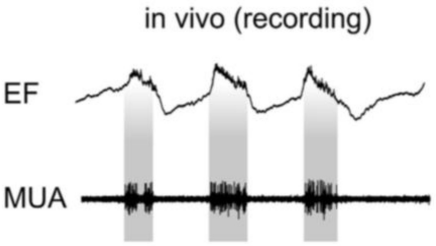
Woodham, R.D., Selvaraj, S., Lajmi, N. *et al.* Home-based transcranial direct current stimulation treatment for major depressive disorder: a fully remote phase 2 randomized sham-controlled trial. *Nat Med* (2024). https://doi.org/10.1038/s41591-024-03305-y

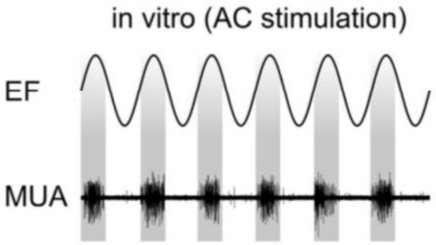
TES is also able to do tACS

"up-phase" tACS:
depolarize membrane

"down-phase" tACS:
hyperpolarize membrane





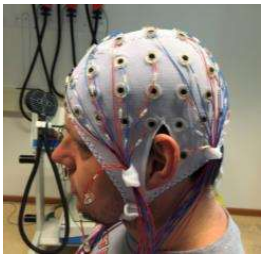


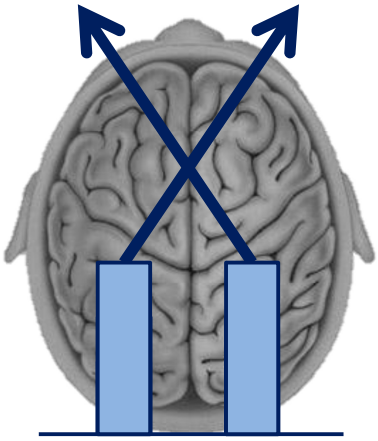
"Entrainment":
study/modulate oscillations

Fröhlich & McCormick, *Neuron*, 2010

The Role of Oscillations in Spatial Attention

Attention left Attention right



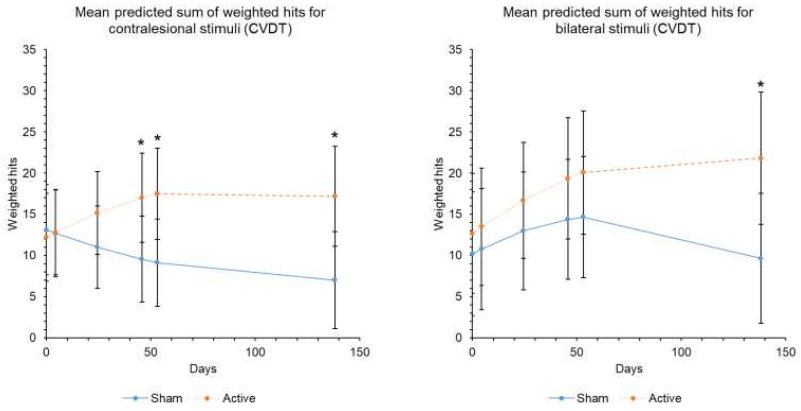


alpha power

Stroke Rehabilitation

Alpha transcranial alternating current stimulation improves chronic neglect: a randomised trial

Computerized visual detection task



Group x Time ***p* = .005**, *n* = 21

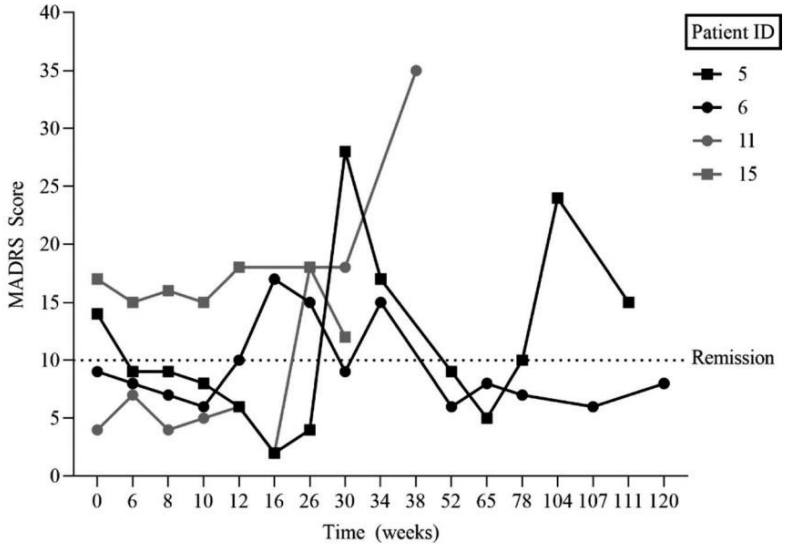
Group x Time ***p* = .010**, *n* = 21

Middag-van Spanje M, Nijboer TCW, Schepers J, van Heugten C, Sack AT, Schuhmann T. Alpha transcranial alternating current stimulation as add-on to neglect training: a randomized trial. Brain Commun. 2024 Aug 30;6(5):fcae287.

Combining TMS with tDCS / TACS
Evidence-based Use Cases

- Replace / Substitute in-clinic TMS with home-use tDCS (cost effectiveness)
- Increase scalability and accessibility (no waiting lists, no capacity limits)
- Priming / Precondition TMS with tDCS
- Maintenance home-use tDCS after in-clinic TMS (relapse prevention)

Results – maintenance patients

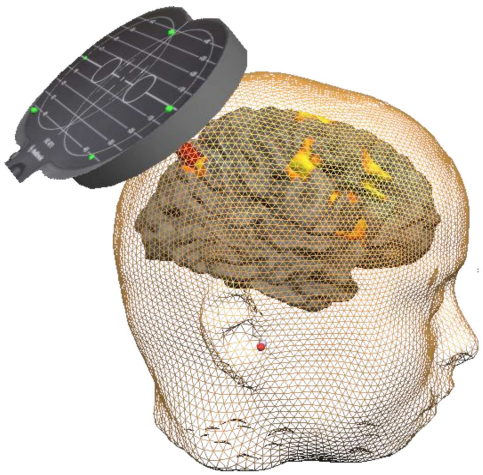


Patients 6 and 15 stayed in remission switching from TMS to HA-tDCS

Patient 5 improved switching from ECT to HA-tDCS

Patient 11 – relapsed

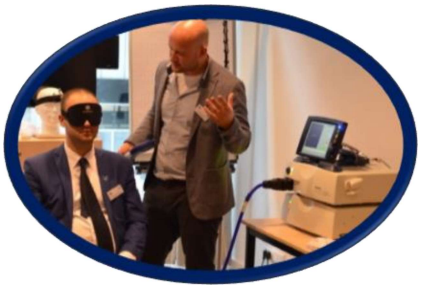
The Academy of Brain Stimulation
Education and Certification



Clinical TMS Certification Course

Prof. Dr. Alexander Sack
Department of Psychiatry and Neuropsychology
School for Mental Health and Neuroscience (MHeNs)
Brain+Nerve Centre
Maastricht University Medical Centre+ (MUMC+)

Screening Forms



Screening questionnaire for

Transcranial Magnetic Stimulation (TMS)

(as suggested by the Safety of TMS Consensus group; Rossi et al. 2009)

1. Do you have epilepsy or have you ever had a convulsion or a seizure?
2. Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s)?
3. Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?
4. Do you have any hearing problems or ringing in your ears?
5. Do you have cochlear implants?
6. Are you pregnant or is there any chance that you might be?
7. Do you have metal in the brain, skull or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, specify the type of metal.
8. Do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)?
9. Do you have a cardiac pacemaker or intracardiac lines?
10. Do you have a medication infusion device?
11. Are you taking any medications? (please list)
12. Did you ever undergo TMS in the past? If so, were there any problems.
13. Did you ever undergo MRI in the past? If so, were there any problems.

SCREENING QUESTIONNAIRE FOR TRANSCRANIAL ELECTRICAL STIMULATION (TES)

		YES	NO
1	Do you have metal (except titanium) or electronic implants in the brain/skull (e.g., splinters, fragments, clips, cochlear implants, deep brain stimulation etc.)? If yes, please specify the type of metal and the location _____ _____		
2	Do you have metal or any electronic device at other sites in your body, such as a cardiac pacemaker or traumatic metallic residual fragments? If yes, please specify the device and the location _____		
3	Did you ever have surgical procedures involving your head or spinal cord? If yes, please specify the locations _____		
4	Have you ever had a head trauma followed by impairment of consciousness?		
5	Do you have skin problems, such as dermatitis, psoriasis or eczema? If yes, please specify the location _____		
6	Do you have epilepsy or have you ever had convulsions, a seizure?		
7	Did you ever have fainting spells or syncope?		
8	Are you pregnant or is there any chance that you might be?		
9	Are you taking any medications? If yes, please specify: _____		
10	Did you ever undergo transcranial electric or magnetic stimulation in the past? If yes, were there any adverse events? Please specify: _____		

An affirmative answer to one or more of questions do not represent an absolute contraindication to TES, but the risk-benefit ratio should be carefully balanced by the Principal Investigator of the research project or by the responsible (treating) physician.

Name _____ Surname _____

Date _____ Signature _____