World Society for Stereotactic and Functional Neurosurgery

Transcranial Magnetic Stimulation: Applications in Neuromodulation, Perioperative monitoring and Neurorestoration

Monday 18 February 2019

Prof J. Rothwell

TMS: Basics and management of movement disorders

Prof S. Taylor

Transcranial Magnetic Stimulation: Treatment of Depression

Prof D. De Ridder

TMS: Managing tinnitus

Prof L. Oberman

Transcranial Magnetic Stimulation: Applications in Autism spectrum disorder

Dr F. Vergani

TMS: Experience and use of Experience and use of pre-operative functional mapping in brain tumours

Possible advantages of controllable pulse TMS devices

John Rothwell

UCL Institute of Neurology, London, UK

Disclosures. John Rothwell PhD

- No industry involvement in this presentation
- No clinical responsibilities
- Editorial boards of Brain Stimulation, Movement Disorders and Neurorehabilitation and Neural Repair

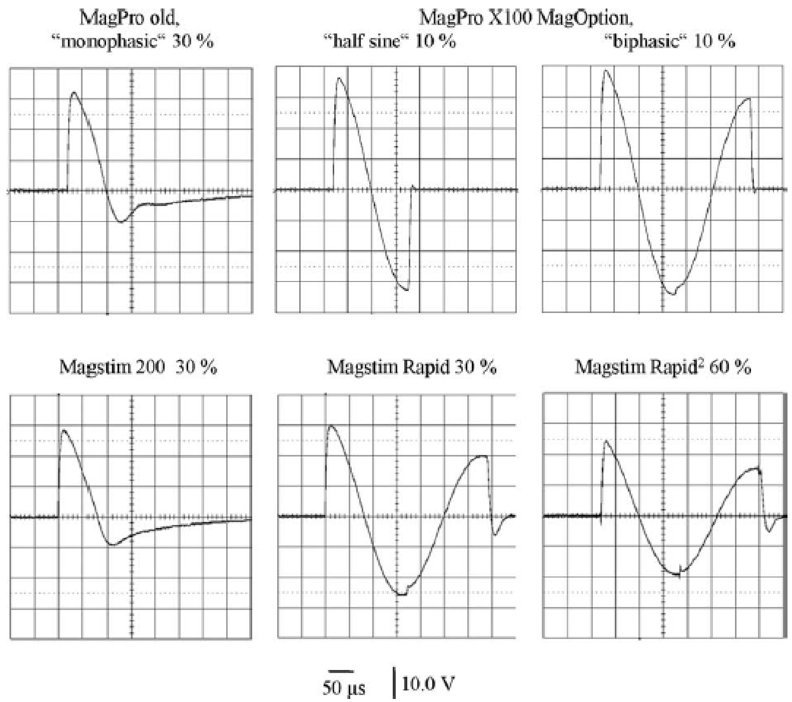
Variability of response to rTMS

- Common in all conditions: some people respond well, others not at all.

- WHY?
- Many reasons that differ between individuals, such as age, circulating hormones, genetics
- Many reasons why people differ from moment to moment, such as brain state when stimulus applied
  - Maybe control for this by using EEG state to decide when to stimulate
- Individuals may also differ because the stimulus activates different sets of neurones by different amounts in different people
  - Usually try to control for this by adjusting stimulus intensity to individual thresholds
  - **BUT individual brain anatomy may also be important. This is where cTMS comes in**

Most TMS machines produce very similar pulse waveforms

Single Repetitive



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Most nerve stimulators have more than one knob

…because different types of pulses activate different types of axons.
E.g. 1ms for H-reflexes; wider for pain

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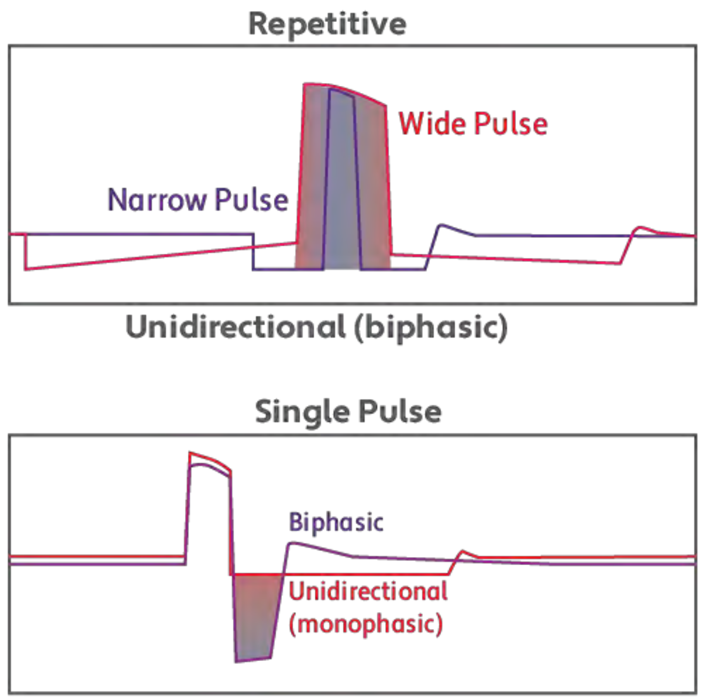
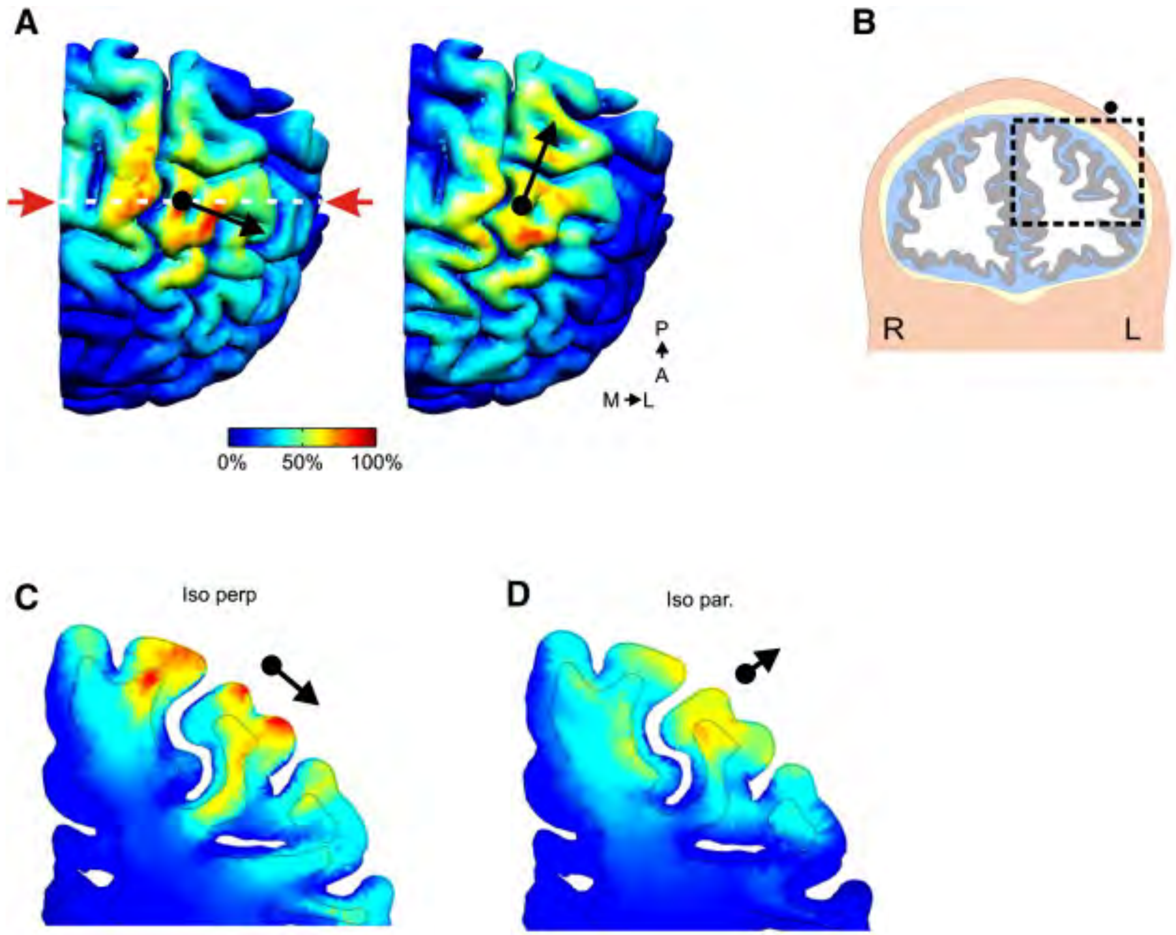
Controllable TMS can produce

1) unidirectional rTMS
2) different pulse durations
3) different waveforms

Rogue Research





TMS direction is important (i.e. coil orientation) because stimulation is more effective if the current is perpendicular to a sulcus

[in the surface of the gyri either side of a sulcus, the electric field strength is highest if the TMS coil is oriented perpendicular to the sulcus.]

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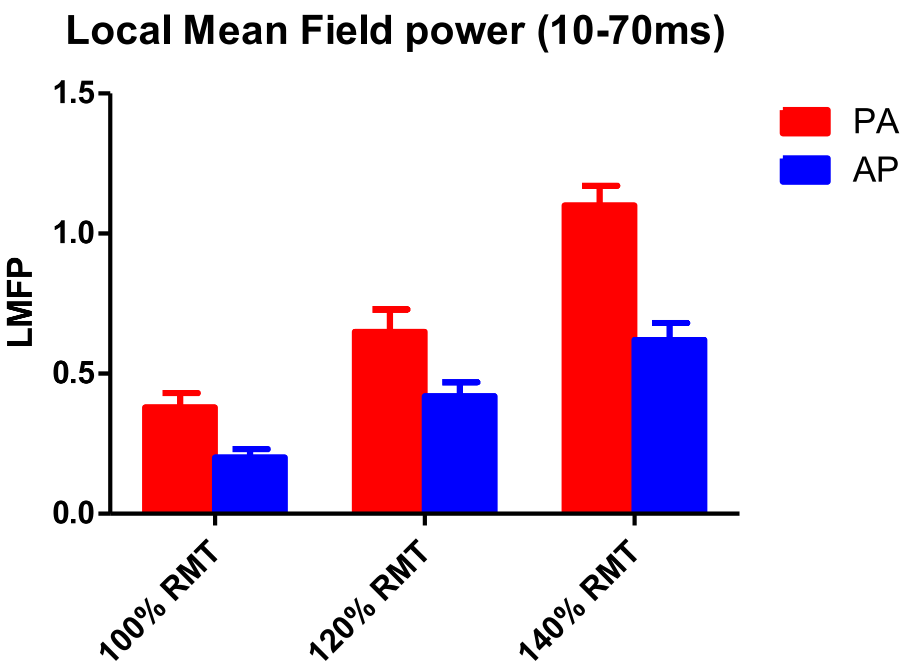
- The previous pictures show electric field strength (max perpendicular to sulcus)
- Opposite current directions create the same maximum field and therefore you might expect them to stimulate the same things, BUT….
- The direction is important

- E.g. Motor cortex threshold is much lower for Posterior-Anterior stimulation than Anterior-Posterior stimulation.

- So, if you are stimulating a site outside of motor cortex, you might neuronavigate to produce a perpendicular stimulation. But which of the two possible directions would be best?

TMS-EEG of the SMA in two opposite directions



TMS direction is important because one direction can have a lower threshold than the opposite direction, even outside the motor cortex

Bar graph shows amount of EEG activity evoked locally around the TMS site. For a given TMS intensity there is much more EEG activity with a PA pulse than an AP pulse

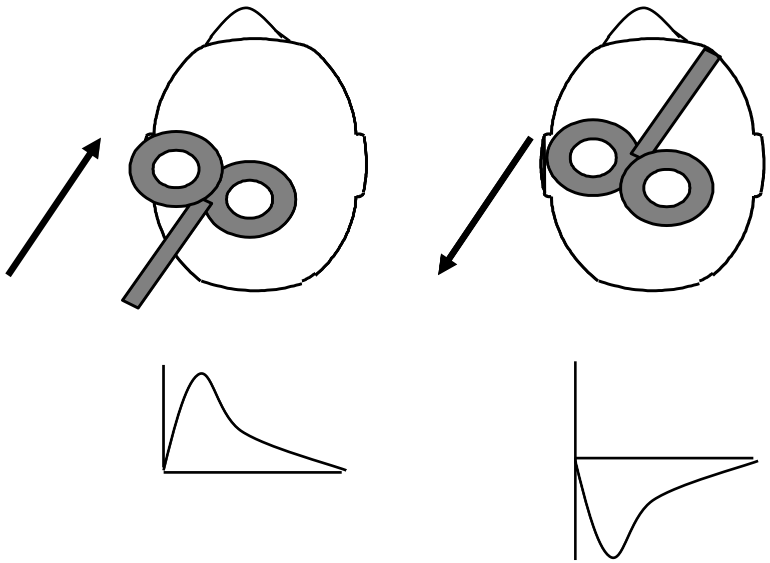
(unpublished data from Dr L Rocchi)

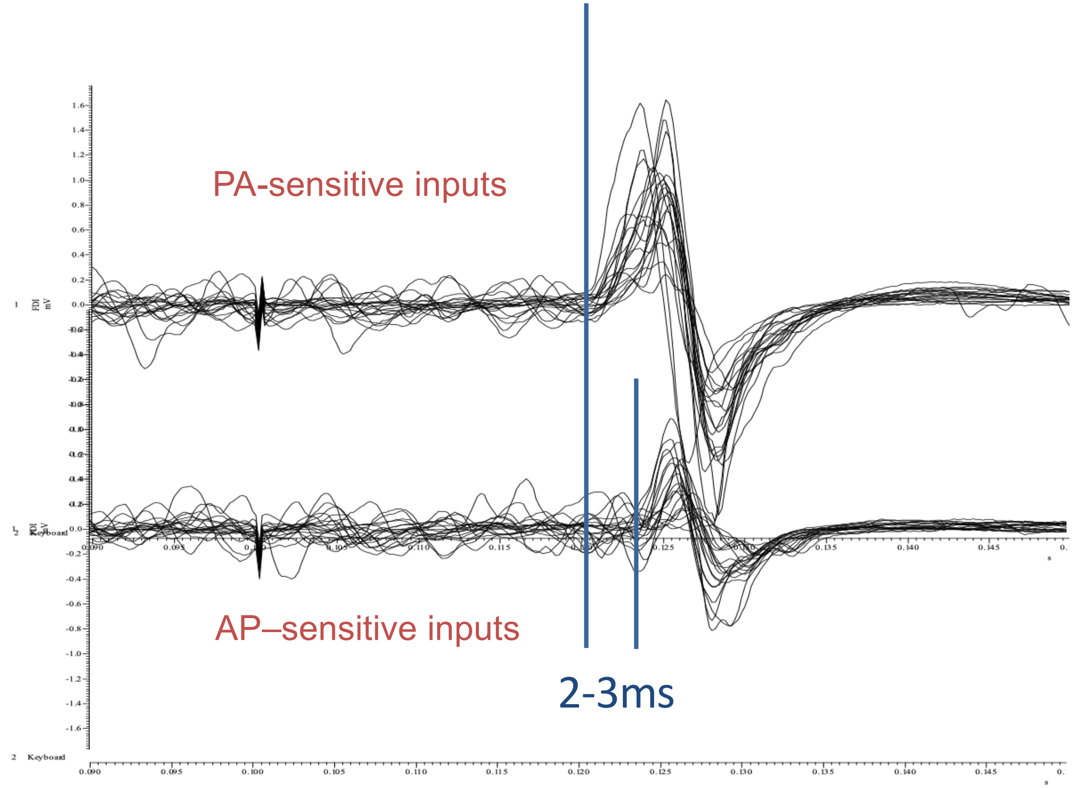
Besides differences in threshold, different directions of current stimulate different things

Different TMS directions activate different sets of inputs to corticospinal neurones

PA induced (early I-inputs)

AP induced (late I- inputs)





Note that this preferential recruitment is seen with low intensity stimuli. High intensity stimuli recruit all inputs.

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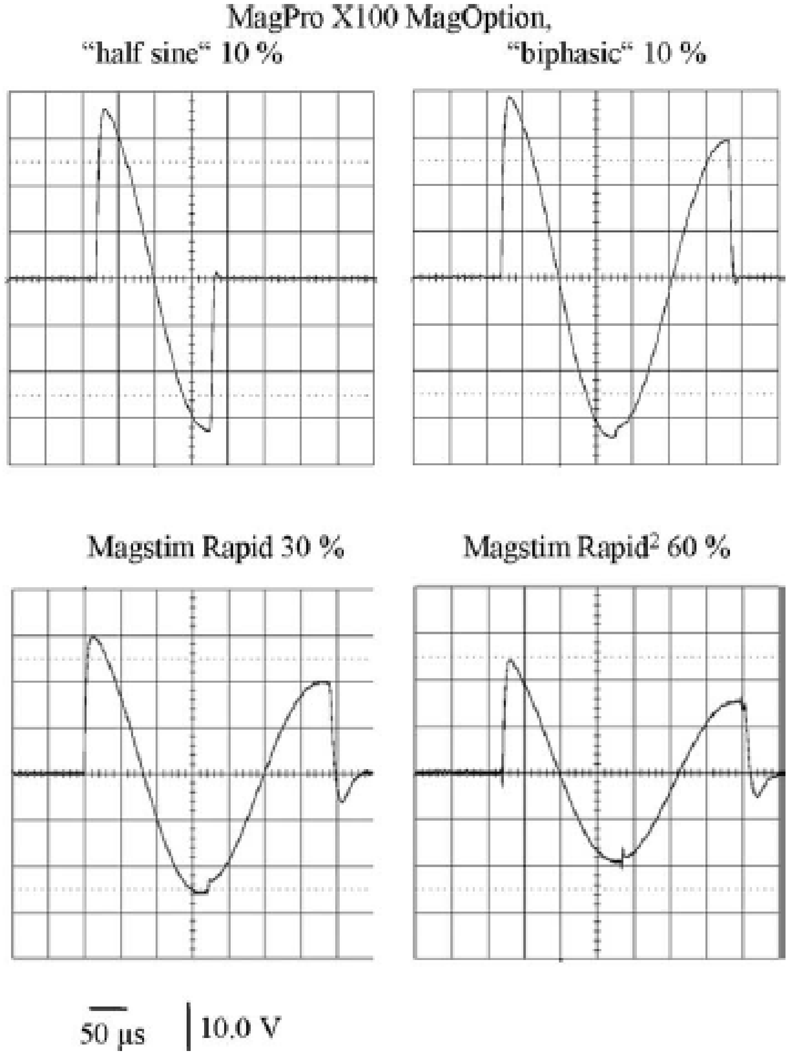
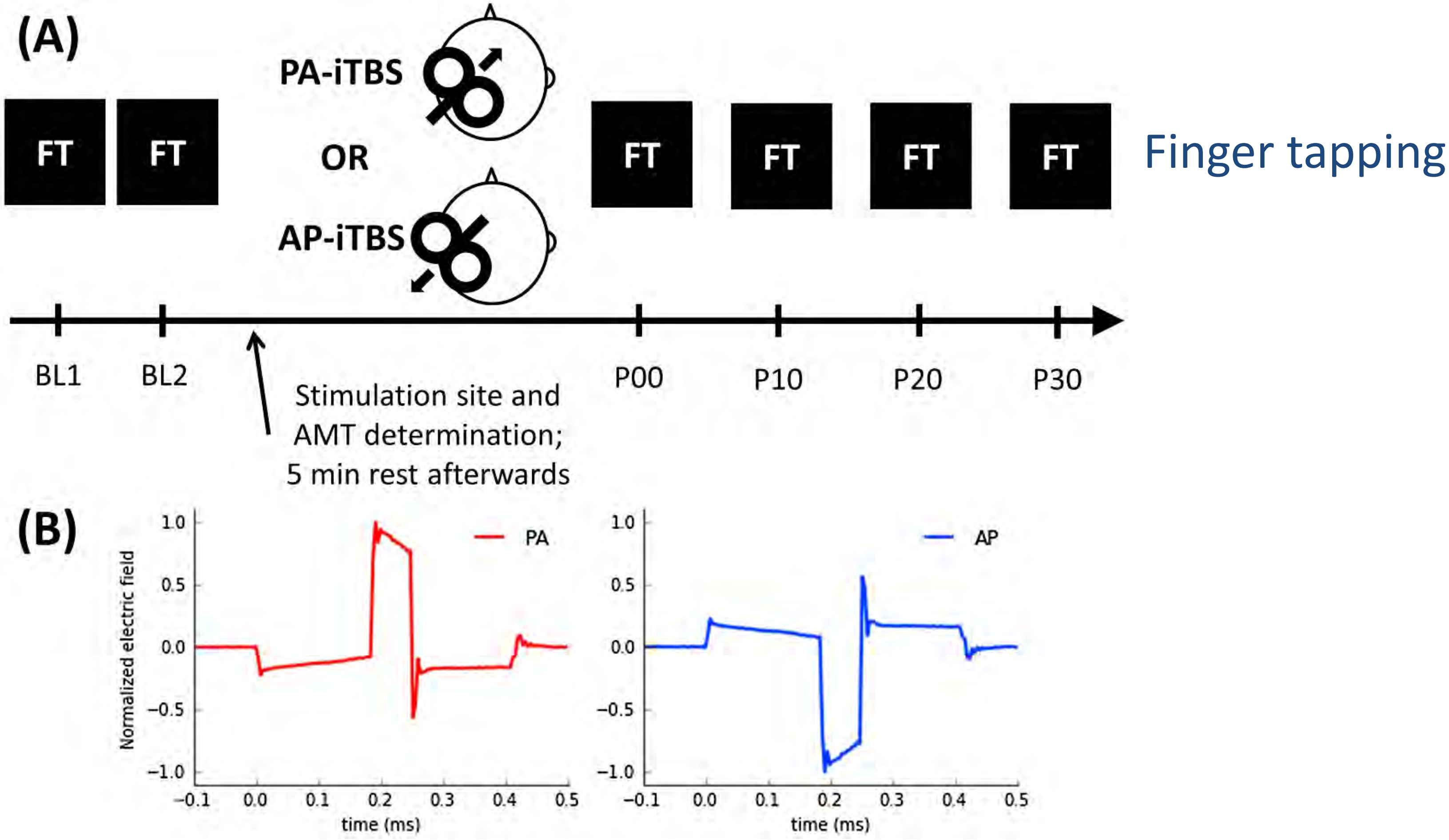


Direction is important because it determines which neurones are activated

BUT most rTMS devices used clinically have a biphasic pulse, potentially stimulating in two diametrically opposite directions

Motor cortex: Effects of rTMS depend on current direction



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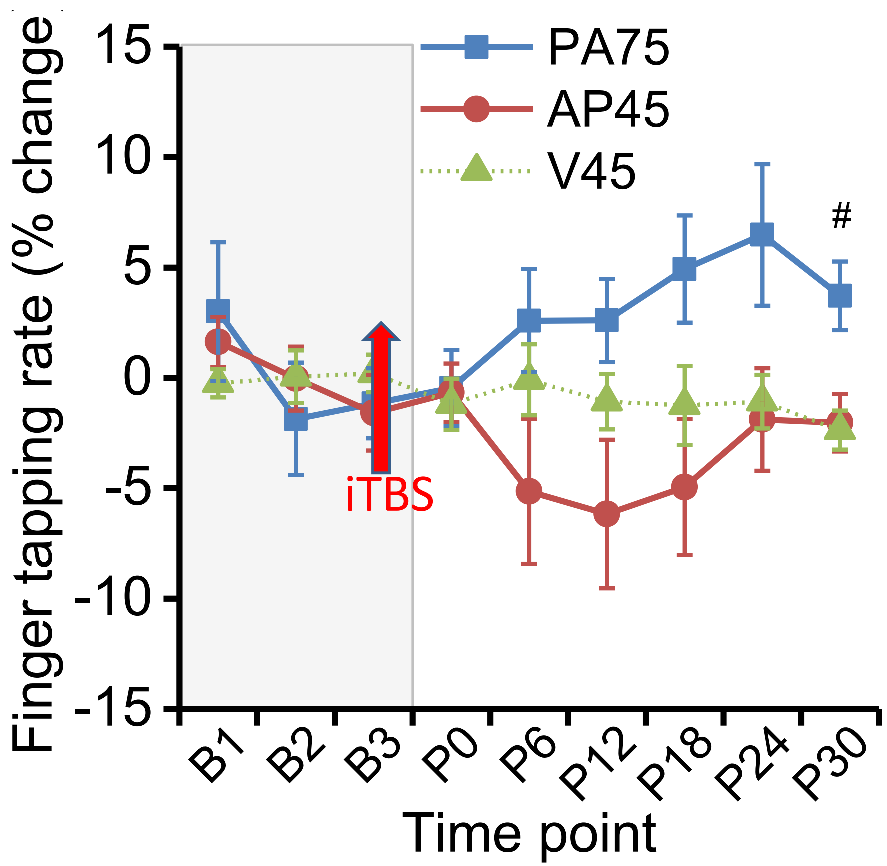
Importance of targeting the correct circuits

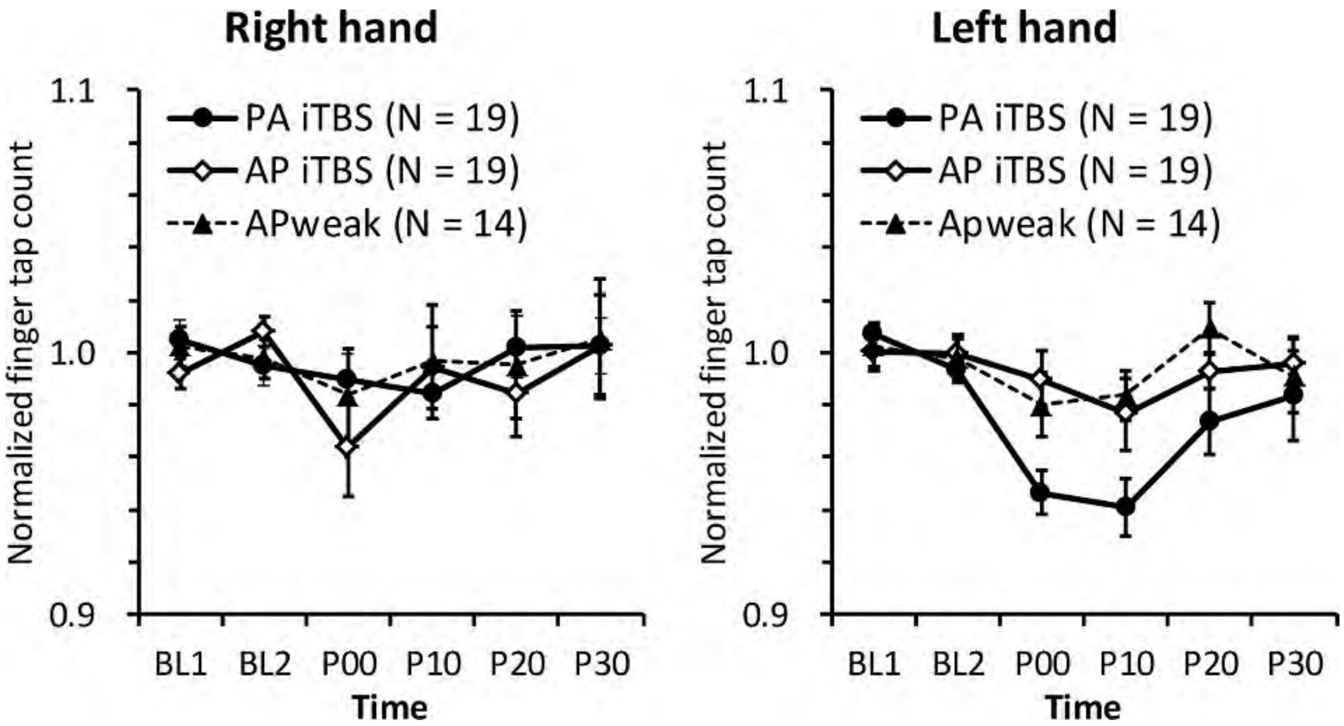
(unpublished Sommer et al)



Look at a single behaviour (finger tapping rate in 15 healthy volunteers) and ask whether this affected differently if the rTMS is delivered in one or other direction to the contralateral motor cortex (PA-rTMS or AP-rTMS)

Compared with sham (rTMS at vertex)

Different directions of the same rTMS protocol have opposite effects on finger tapping rate in healthy people. [Previous work with a different rTMS (bidirectional) protocol showed no effect on tapping rate]



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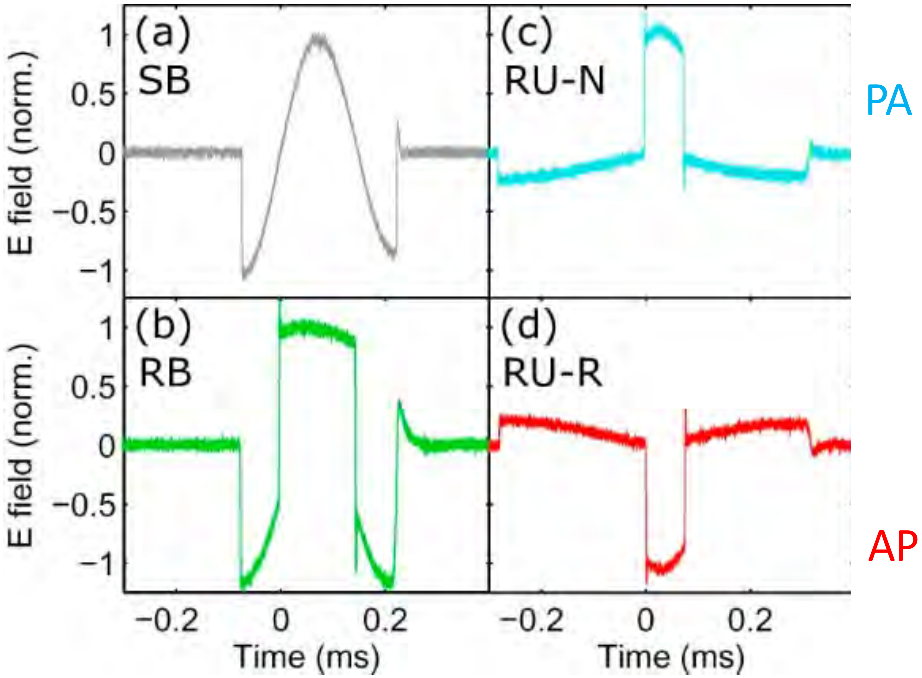
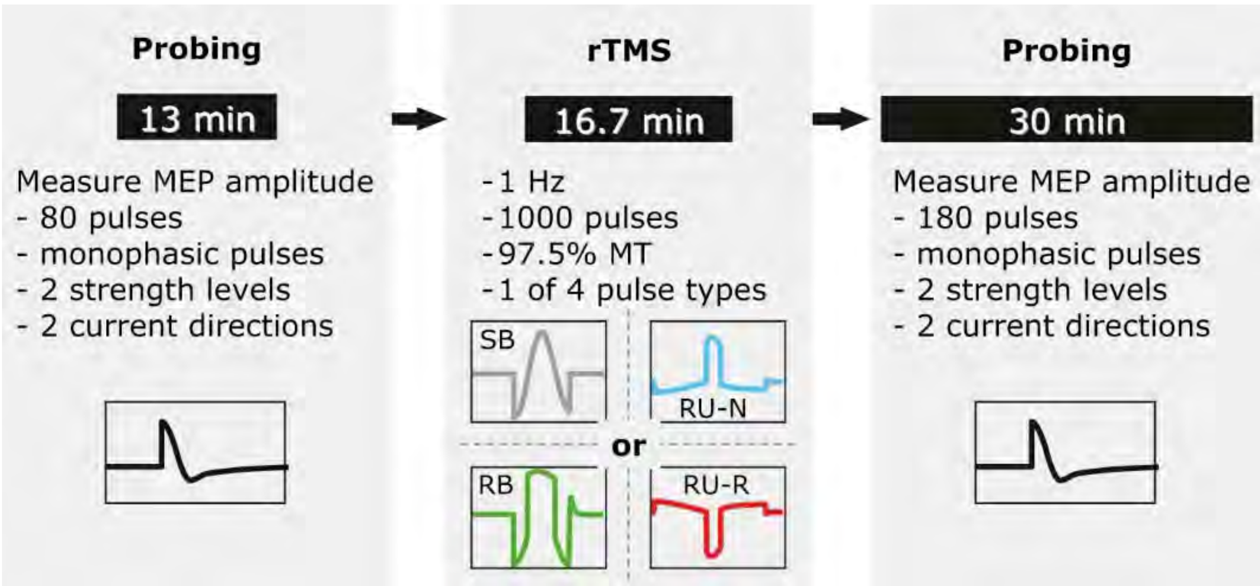


Another motor cortex example of the importance of current direction in rTMS

Goetz et al 2016



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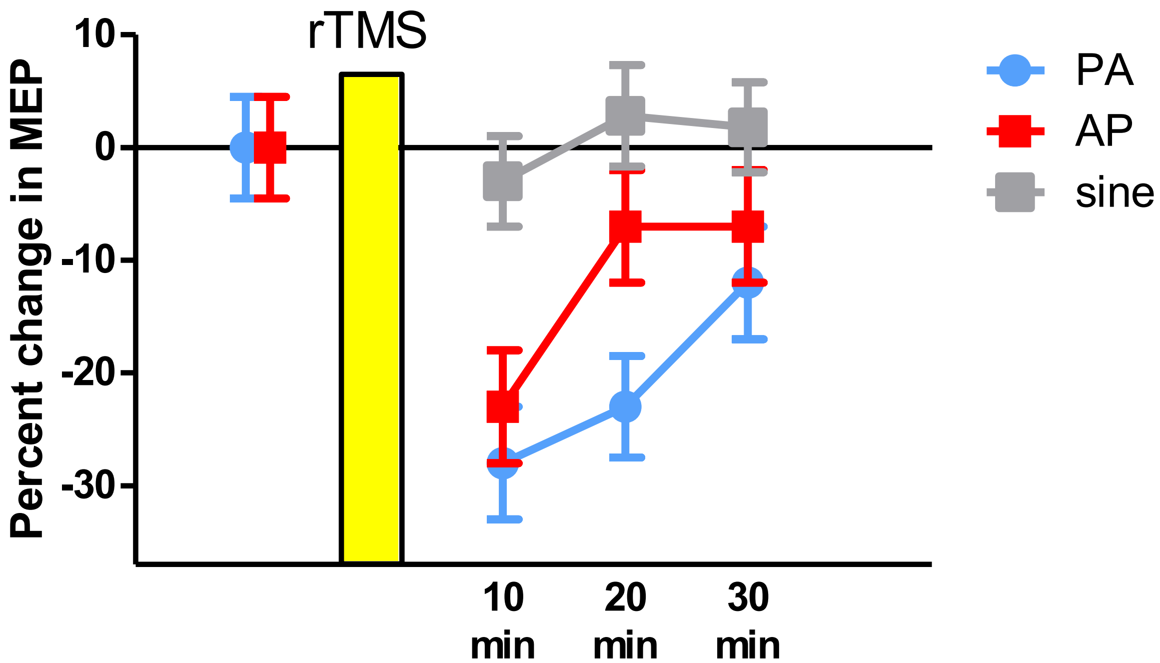
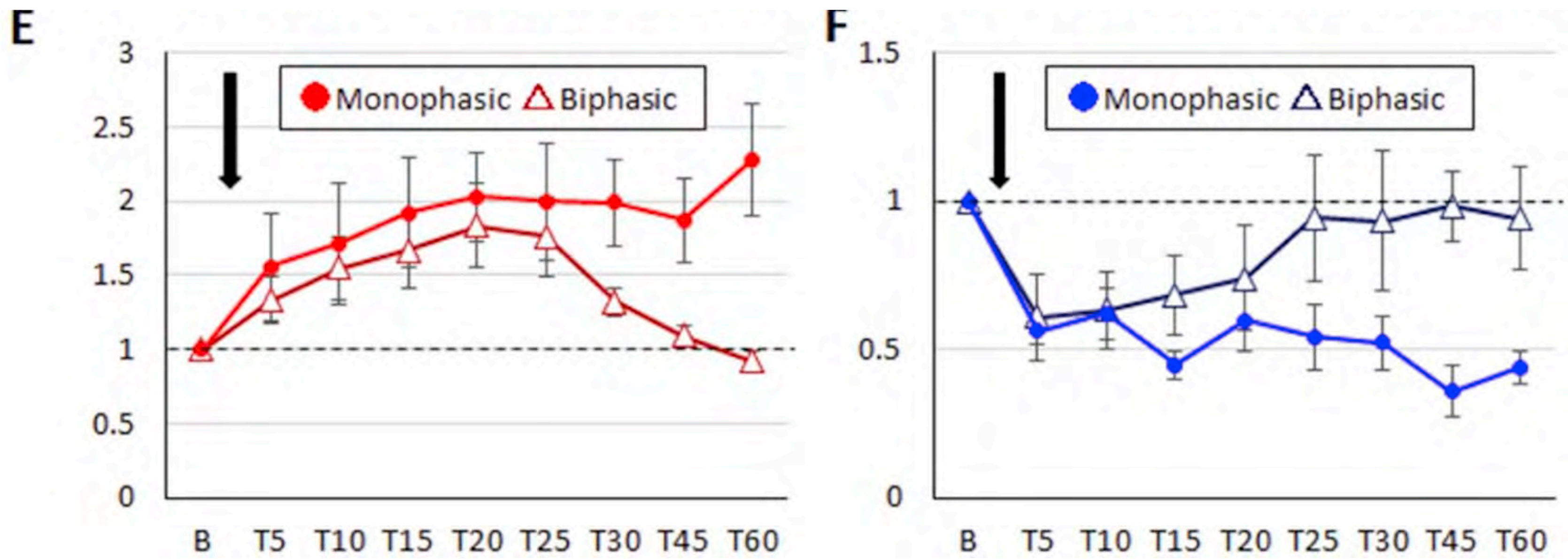


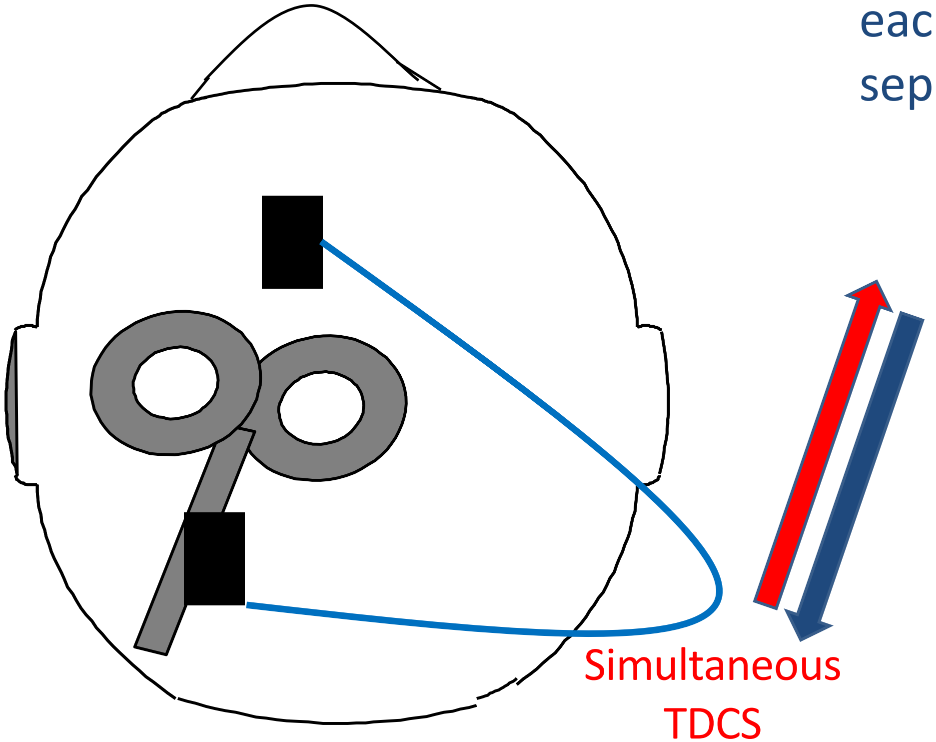
PA rTMS (1 Hz) reduces motor cortex excitability much more and for longer than AP rTMS. Sine wave rTMS had no effect at all (replotted from Goetz et al 2016)



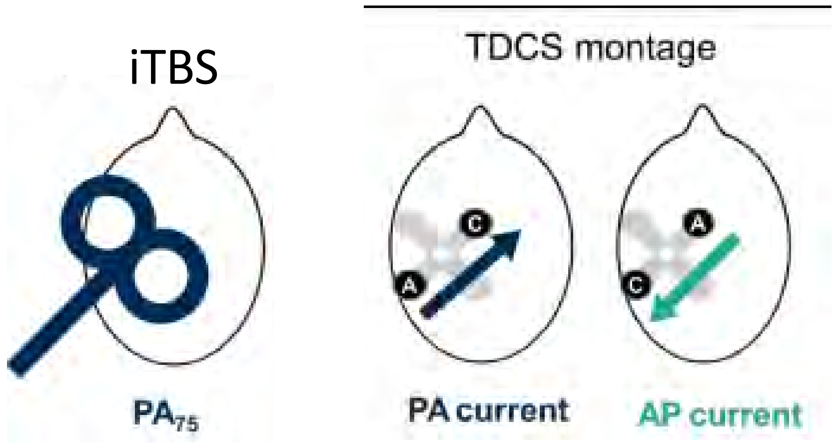
Another example from motor cortex showing that the effects of monophasic rTMS (quadripulse stimulation) are different from biphasic stimulation. Monophasic rTMS gives a longer lasting effect.

(Nakamura et al, Brain Stim 2016)

Can we improve the response to directional rTMS with directional TDCS?



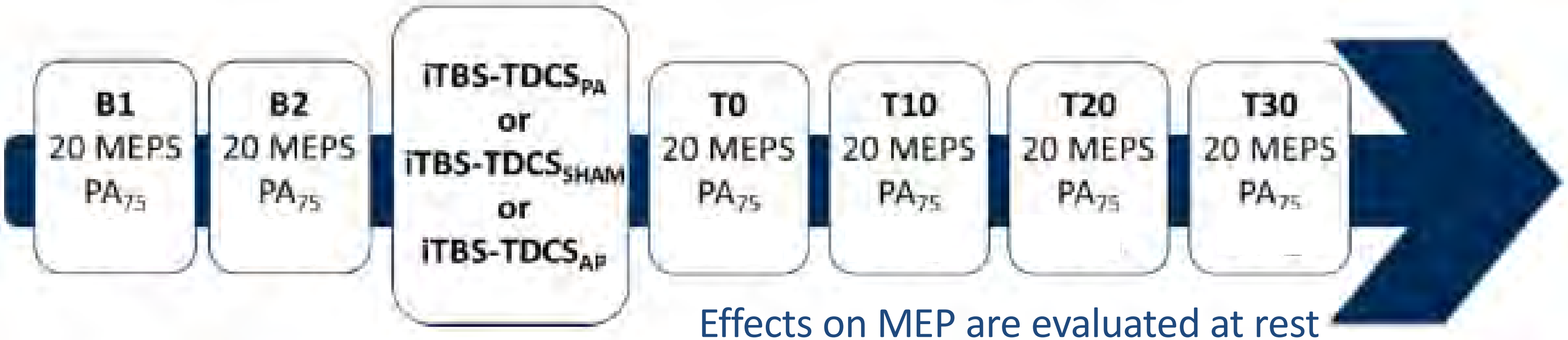
Apply a monophasic PA-iTBS protocol
Combine with sham or real TDCS (in each direction: 3 experimental sessions separated by > 1 week)



iTBS is unidirectional PA

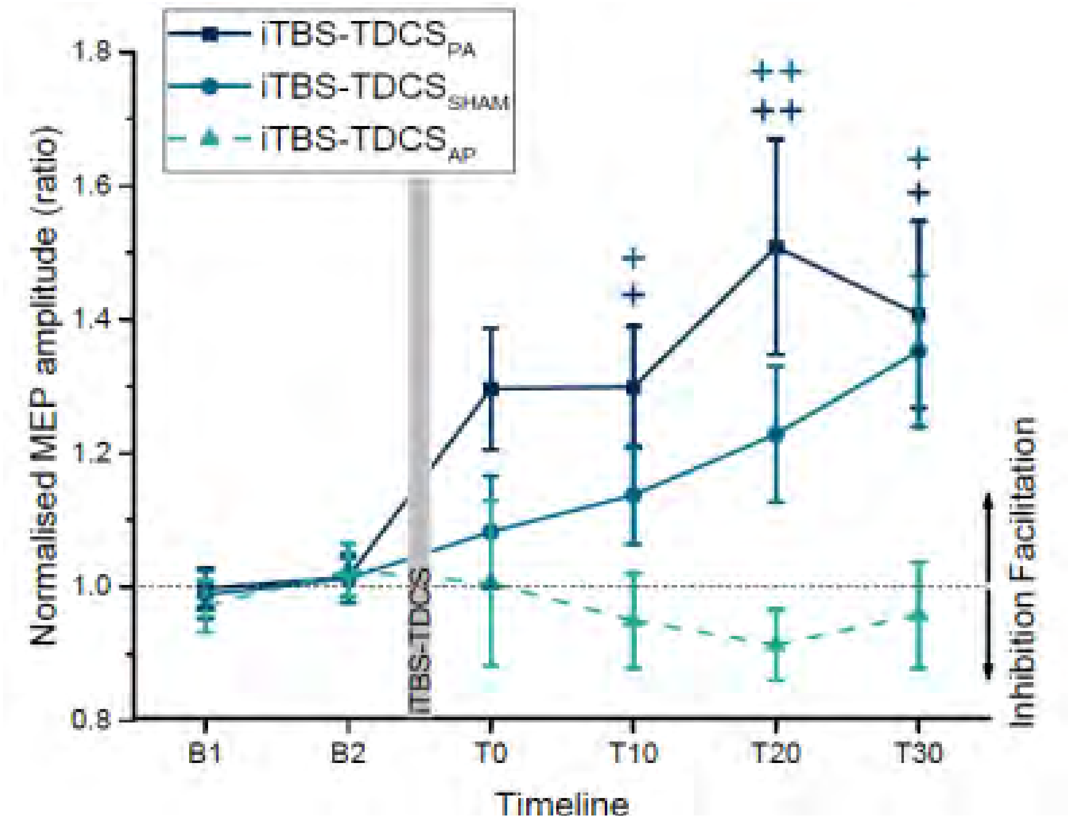
(Tremblay et al Brain Stim 2017)

N=20



Effects on MEP are evaluated at rest

Monophasic PA-iTBS is increased by concurrent PA-TDCS and reduced by AP-TDCS (Tremblay et al, Brain Stim 2017)

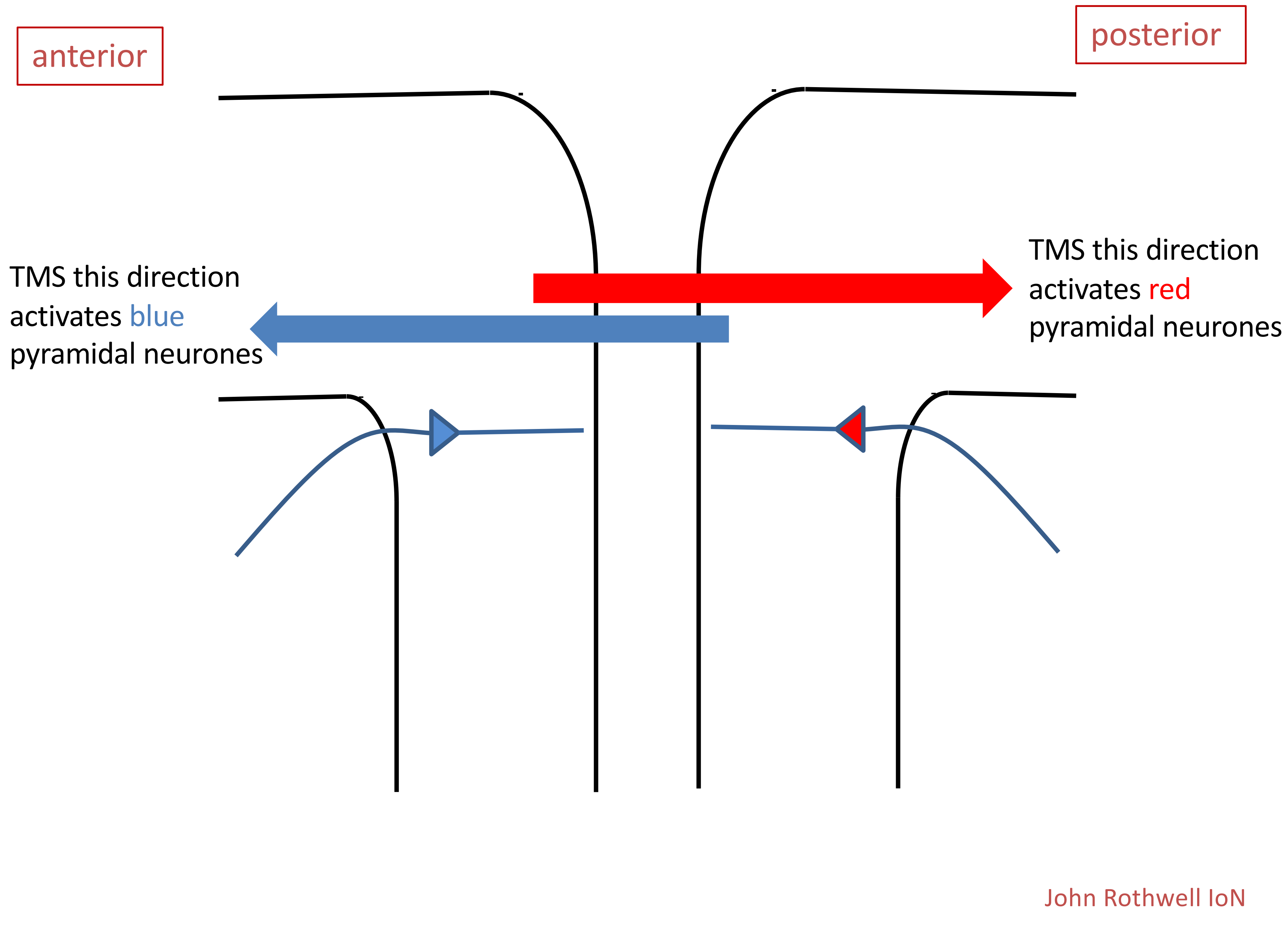


Summary 1

- Direction is important for brain stimulation
- Perpendicular to sulcus
- Best direction across sulcus to achieve lowest threshold
- Direction also determines which neurones are activated

- **RESULT:** rTMS with a conventional biphasic pulse will not produce the same effects as with unidirectional rTMS
  - Unidirectional may be more effective

  - How do I understand how direction is important?


anterior
posterior
TMS this direction activates blue pyramidal neurones
TMS this direction activates red pyramidal neurones
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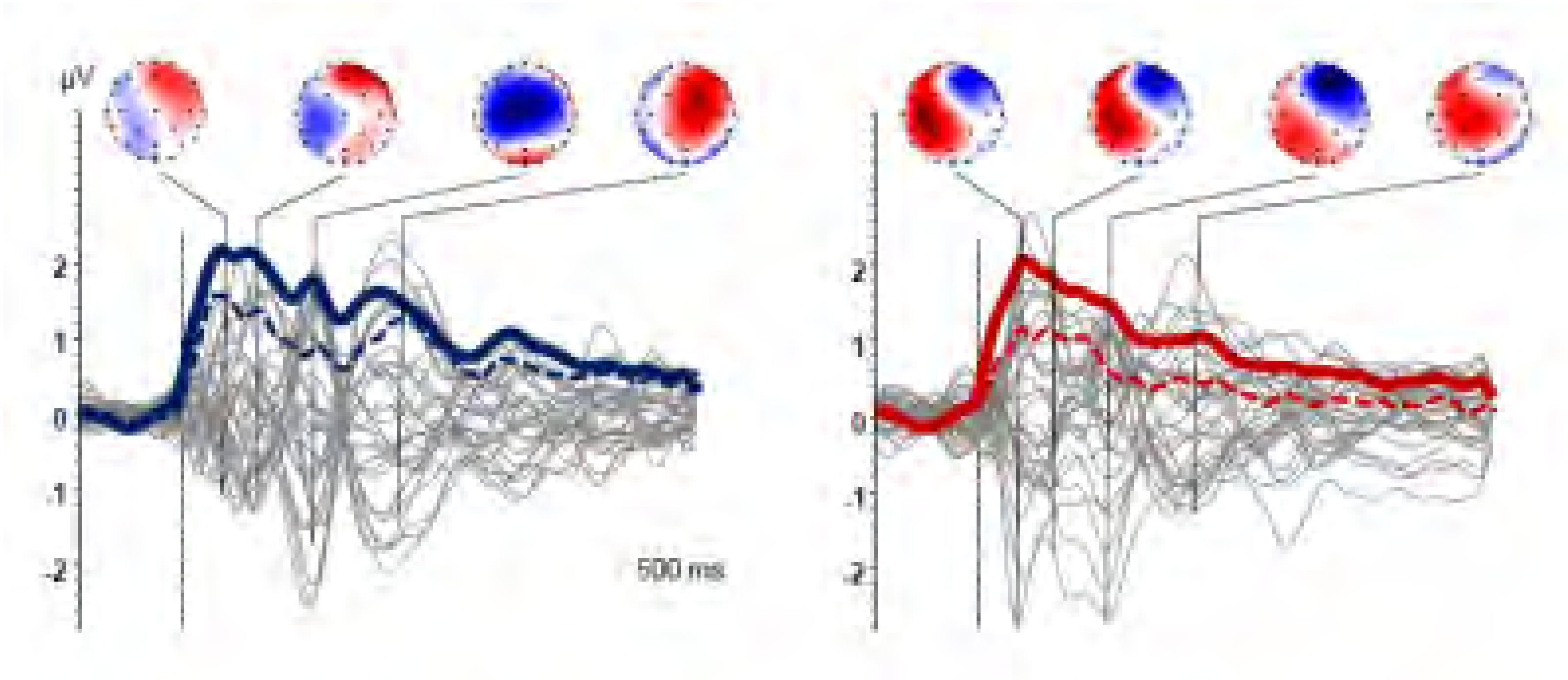
AP stimulation PA stimulation



Polarity makes a difference to the evoked EEG from a given point…..maybe PA stimulation activates the anterior wall of the central sulcus and AP stimulation activates the posterior wall. The result is a dipole that points either forwards or backwards

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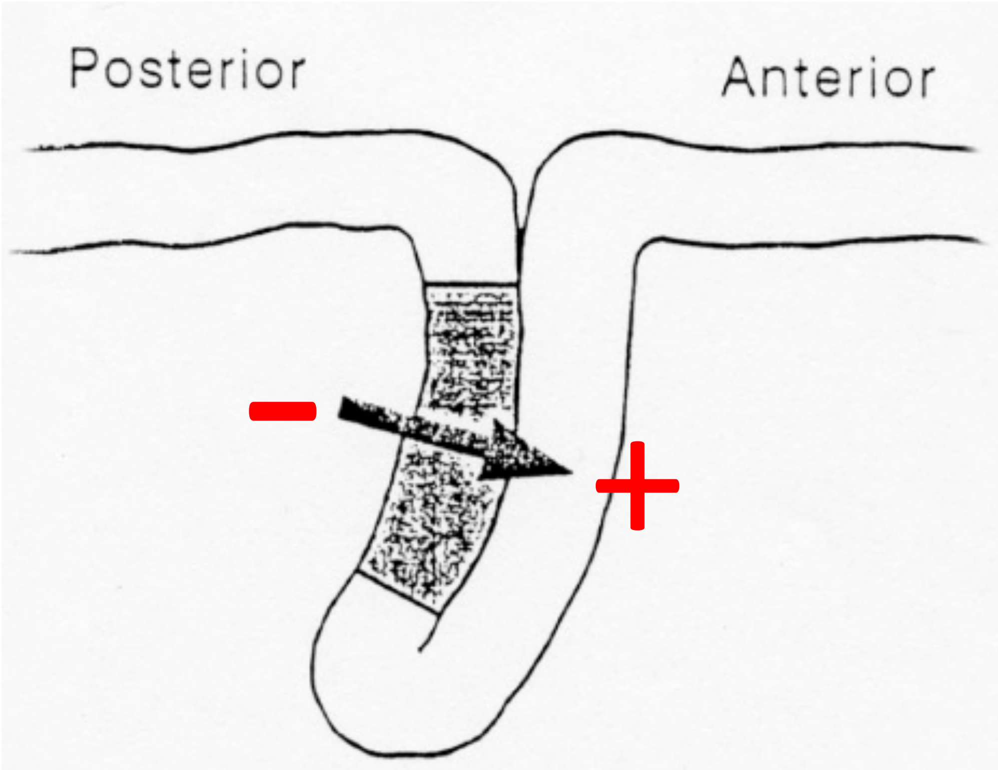
Generator of N20 component of SEP

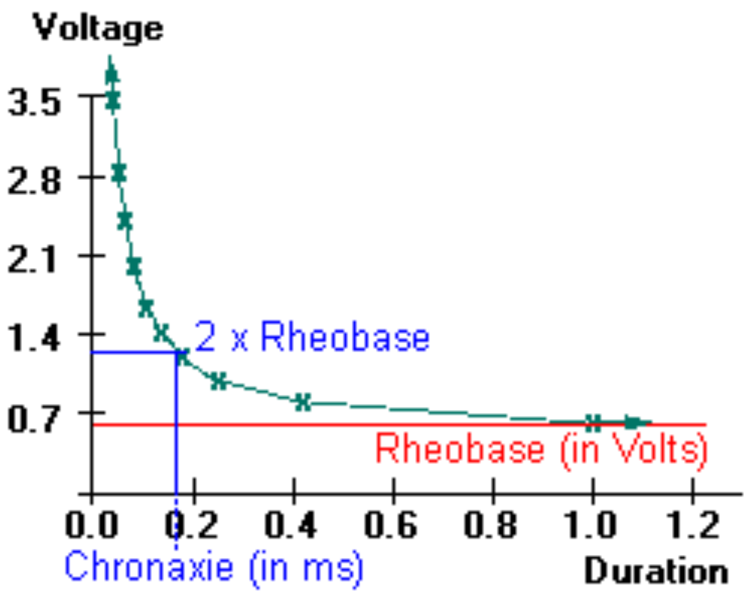


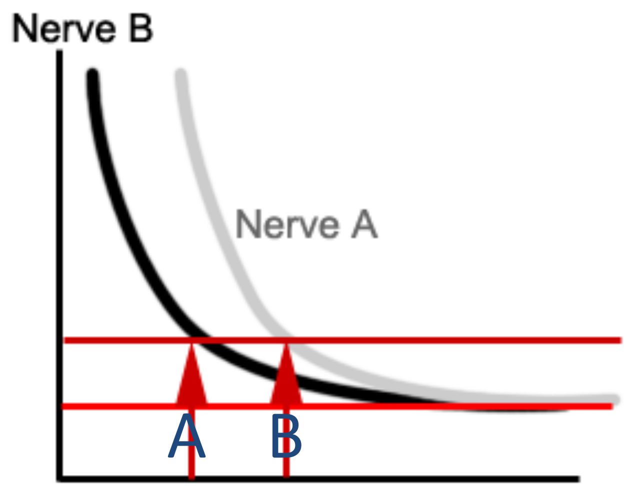
In the SEP, a deep negativity and surface positivity produces a posterior N20 and an anterior P20 in the EEG

If a similar pattern occurred in the anterior bank of the central sulcus, it would give an oppositely directed response in the EEG.

Changing pulse width can also change the neurons that are activated:

Strength-duration curves

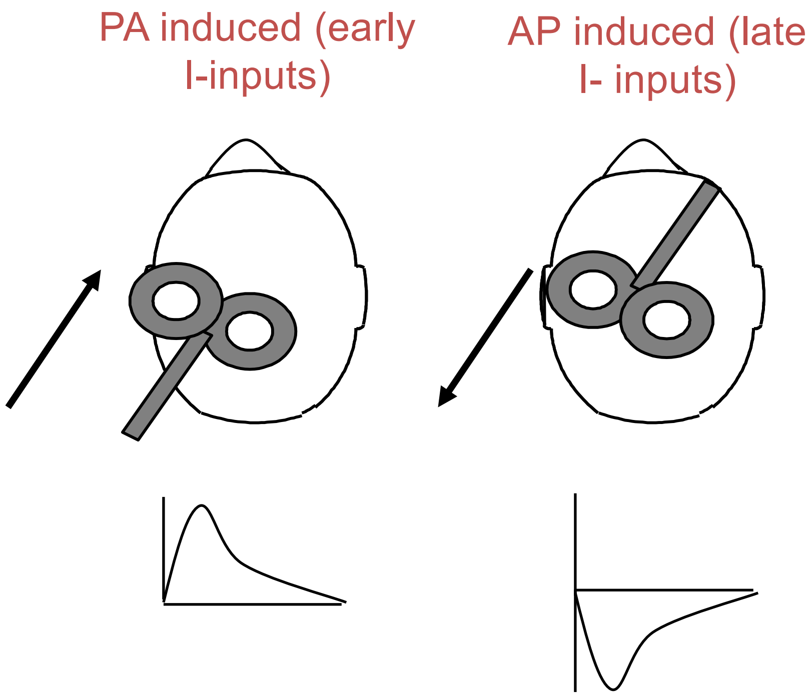


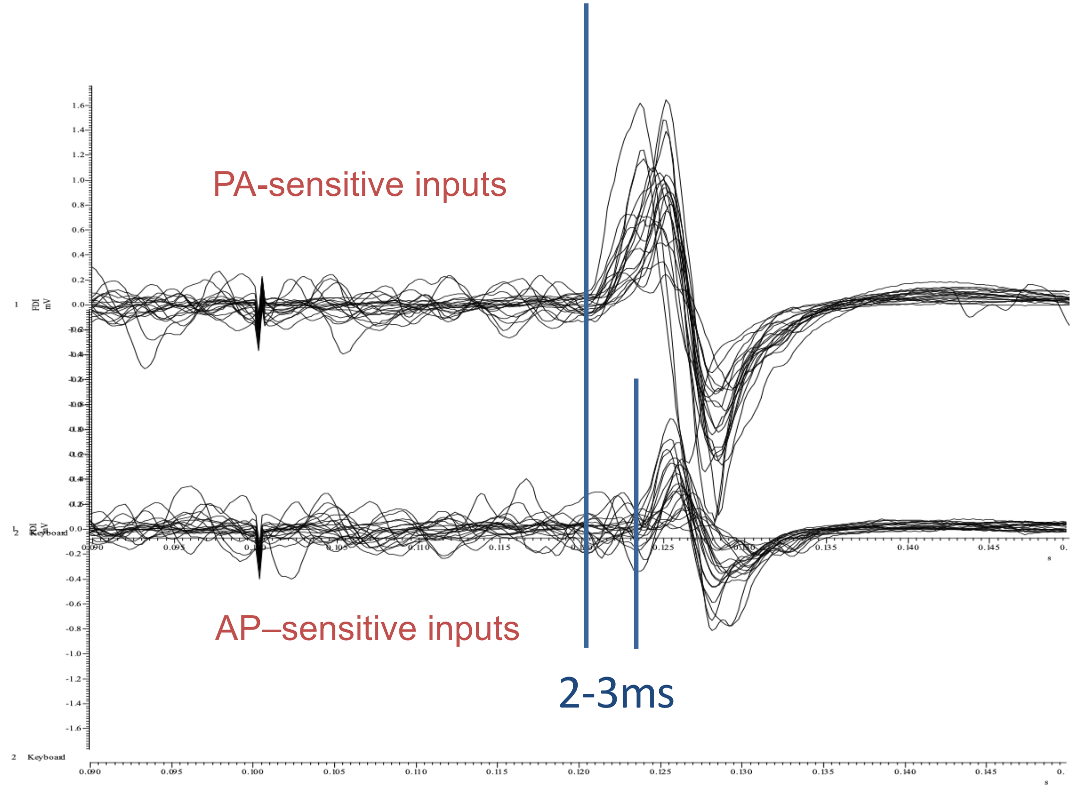


Stimulate using a pulse width of B and both nerves are activated. Us same intensity but reduce pulse duration to A and only nerve B is activated.

Different current directions evoke MEPs of different latencies in the same hand muscle.

Different TMS directions activate different sets of inputs to corticospinal neurones





Note that this preferential recruitment is seen with low intensity stimuli. High intensity stimuli recruit all inputs.

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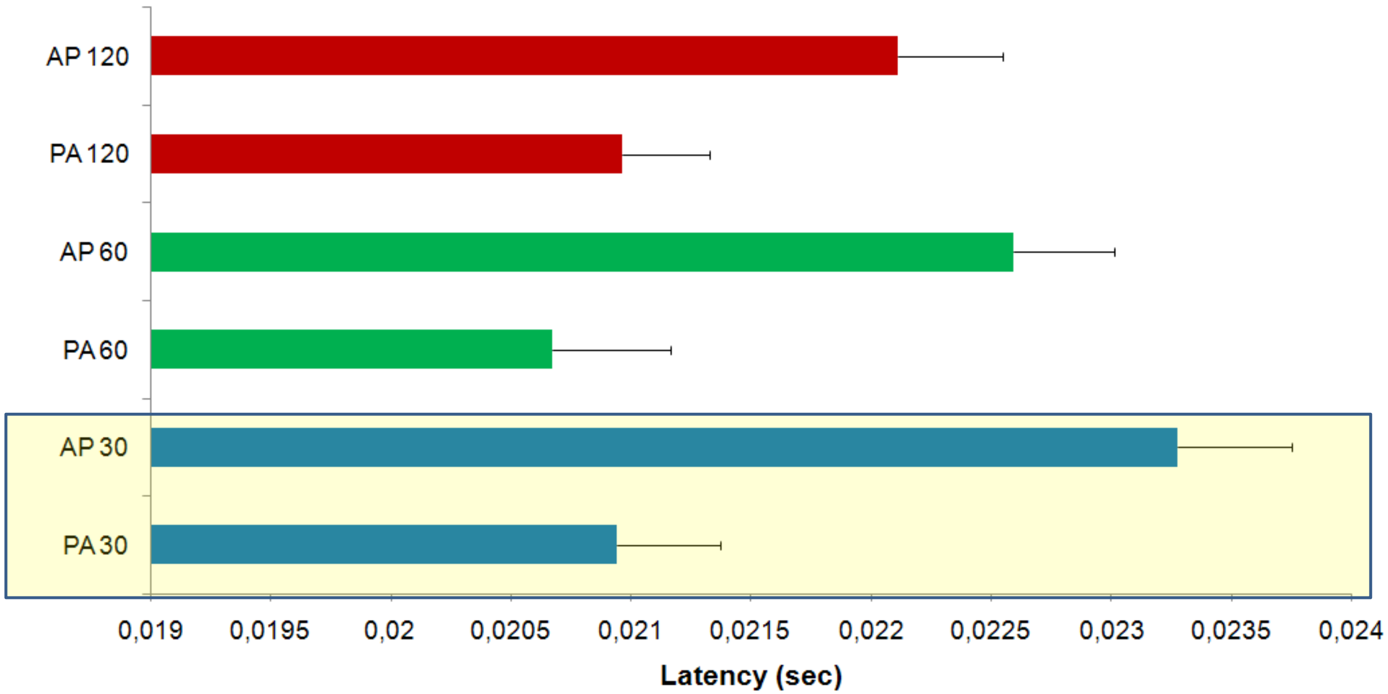
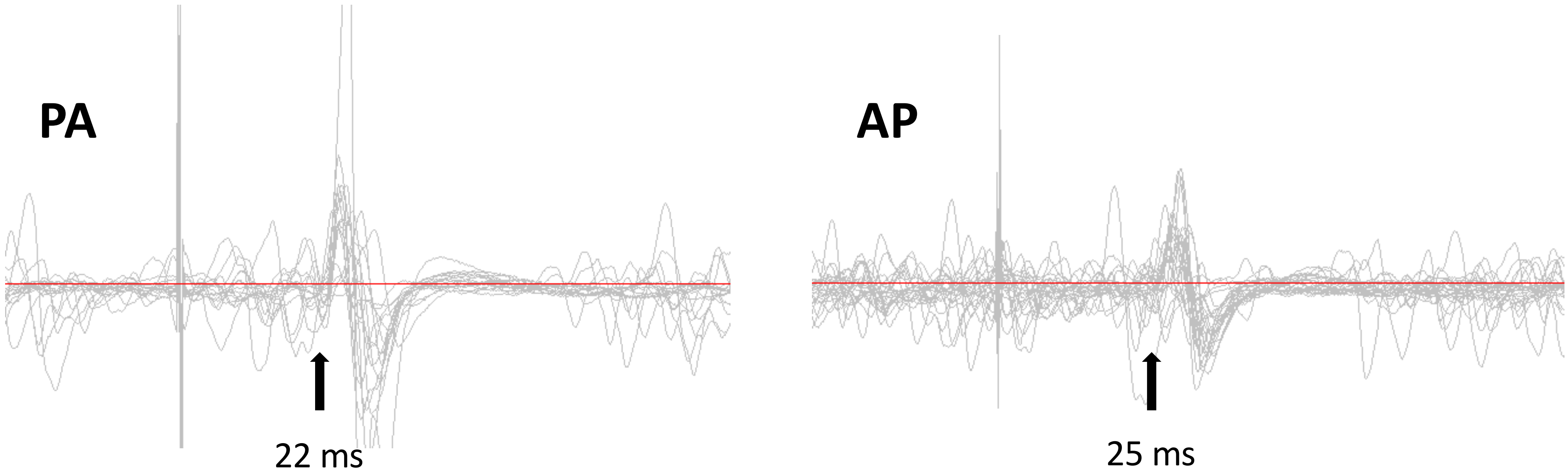
Controllable TMS

Short duration AP pulses produce MEPs with the longest latency. Note this distinction best seen during active muscle contraction when stimulus intensities relatively low

Use short duration AP in following expts





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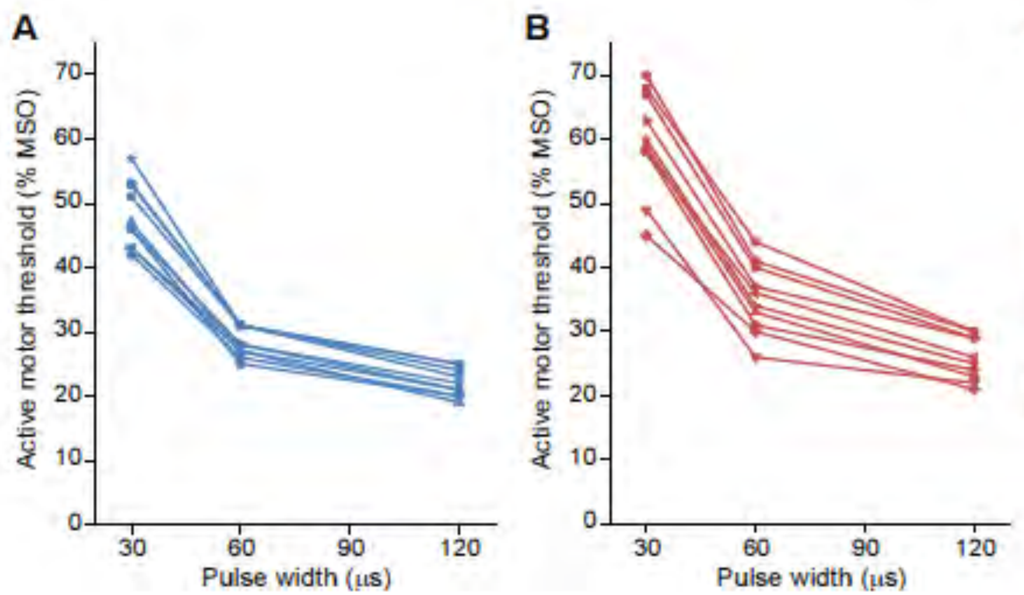
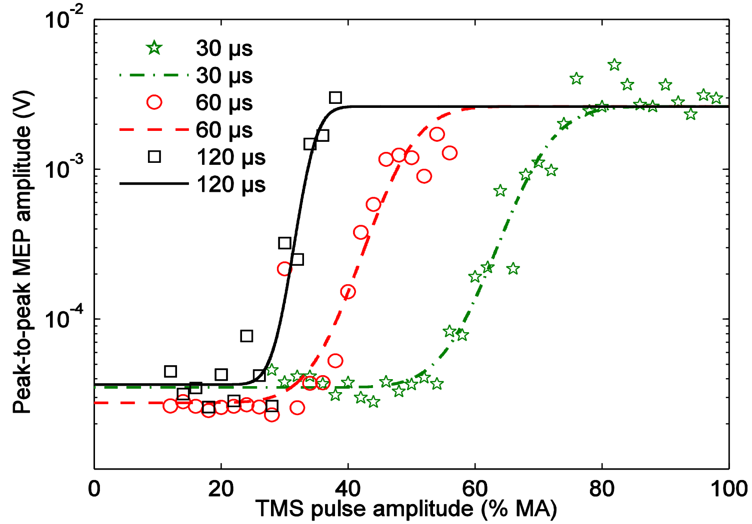
PA and AP strength-duration curves
(to calculate S-D time constant for activation)





	PA REST	AP REST	PA ACTIVE	AP ACTIVE
Time constant (μs)	251.02 ± 54.76	268.09 ± 97.28	230.95 ± 97.16	294.19 ± 90.85

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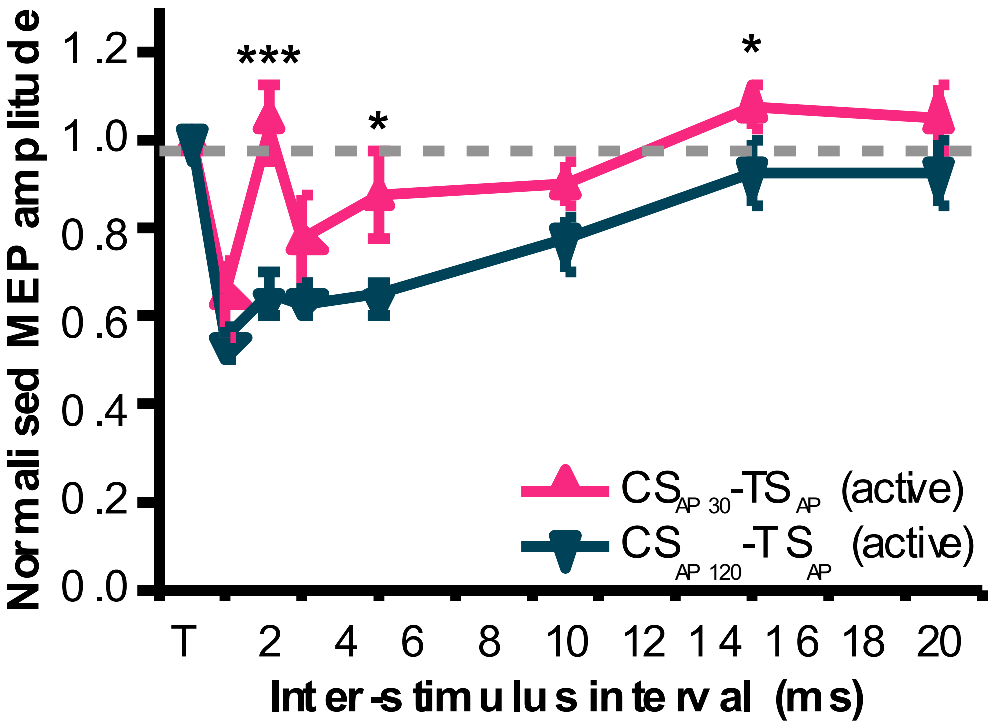
Effect of CS pulse duration and ISI on SICI with AP CS and AP TS during contraction (n = 15)

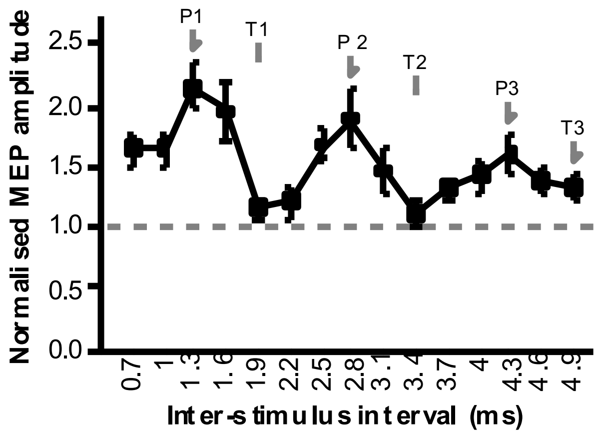


The conditioning stimulus was oriented AP. Examine the effect of changing the pulse width from 30µs to 120µs. The intensity of each pulse was set to be 80% of the active motor threshold evaluated using that pulse width (i.e. the pulses were equal in terms of their excitatory effects on MEPs)

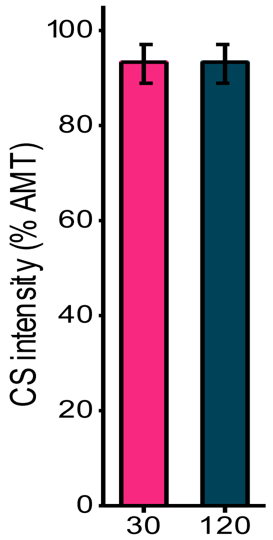
A narrow pulse is much less effective in producing SICI, even though the pulses are matched in terms of their ability to generate an MEP.

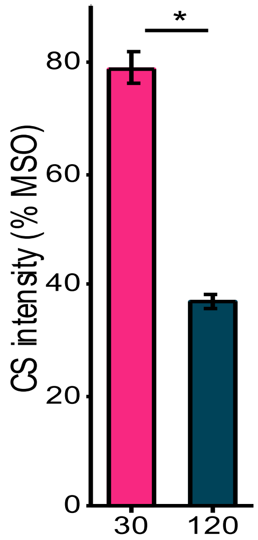
rTMS with a narrow pulse may activate fewer inhibitory neurones than if a wide pulse is used.

Effect of CS pulse duration and ISI on SICI with PA CS and PA TS(n = 15)

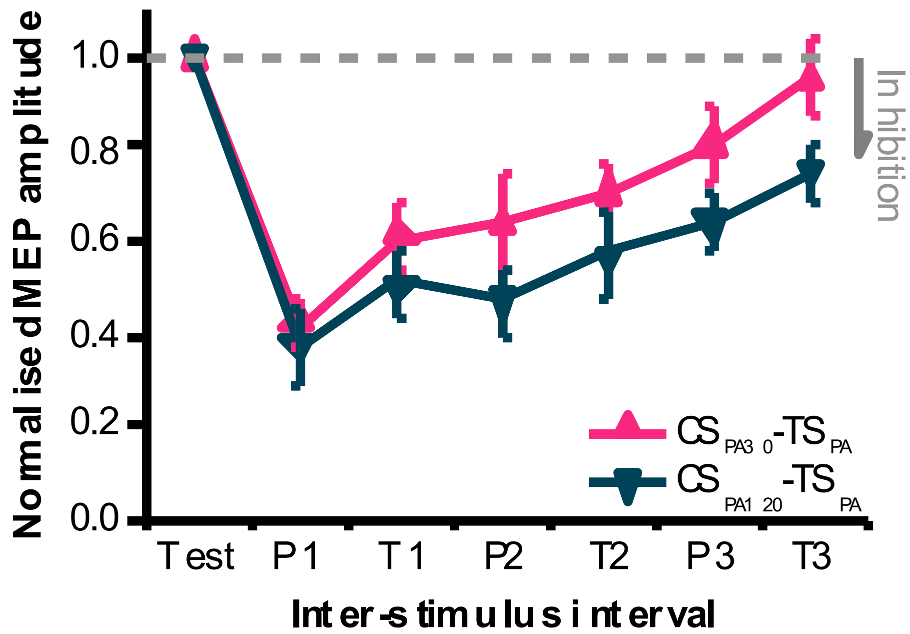


SICI ISIs based on peaks and troughs of SICF





CS were 30 and 120 microsecond pulses delivered at same % AMT (i.e. same in relative terms, but different in absolute terms)



SICI with PA CS and PA TS was greater (main effect of pulse width) for 120 versus 30 CS pulses

Why is all this important clinically?

- Stimulus direction is important because it affects threshold.
  - If you are in the wrong direction then the stimulus can be ineffective

- Stimulus direction and pulse shape are important because they affect which neurones get activated by the stimulus
- The importance of this depends on how you think rTMS works in your particular context
  - If you want to target particular neurones (e.g. that project to deeper structures like cingulate or amygdala) then you may need to be particular about how you stimulate
  - If you just want to disrupt function of an area, then subtleties like this don't matter, so long as you are orientated in the right direction

- Biphasic or monophasic?
  - In motor cortex monophasic may be more effective and longer lasting. It also can be combined with TDCS

Department of
Psychiatry

Depression
Center

Transcranial Magnetic Stimulation for the Treatment of Depression

Stephan F. Taylor, M.D.

University of Michigan

Transcranial Magnetic Stimulation: Applications in Neuromodulation, Perioperative monitoring and Neurorestoration, 18 February 2019

The World Society for Stereotactic and Functional Neurosurgery

Disclosures: Stephan F. Taylor
(last 2 years)

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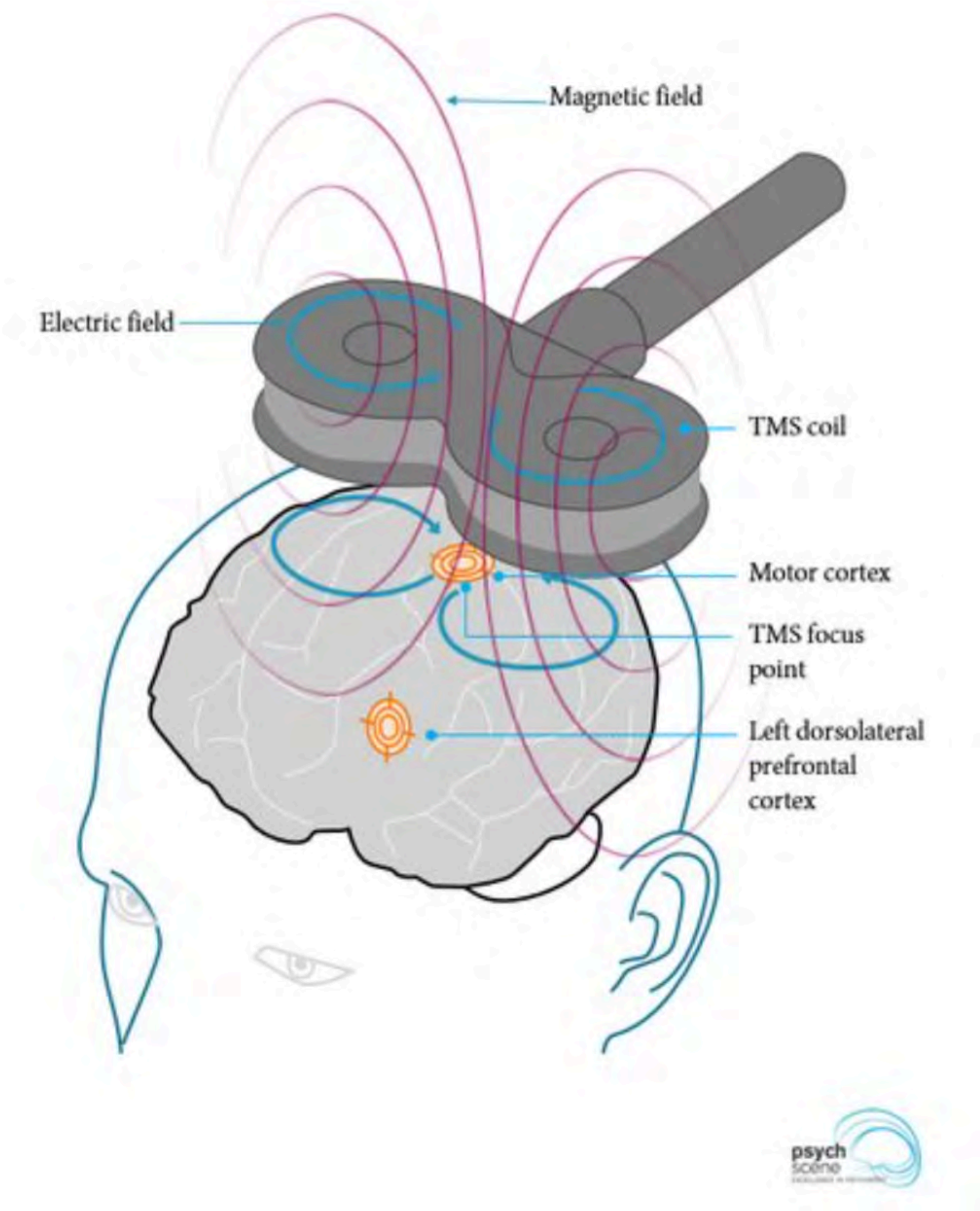
  - Otsuka/Vanguard Research
- Advisory boards: None
- Equity interest: None

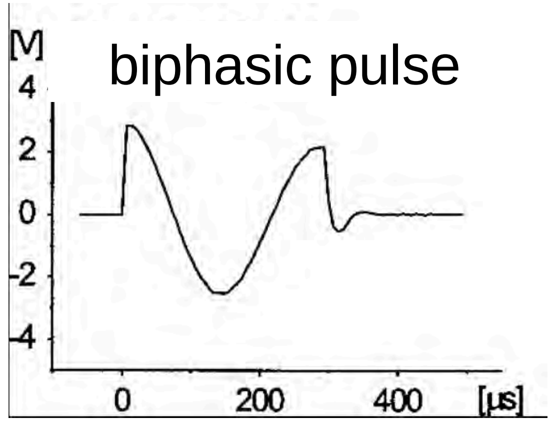
Today's off-label discussion: various forms TMS

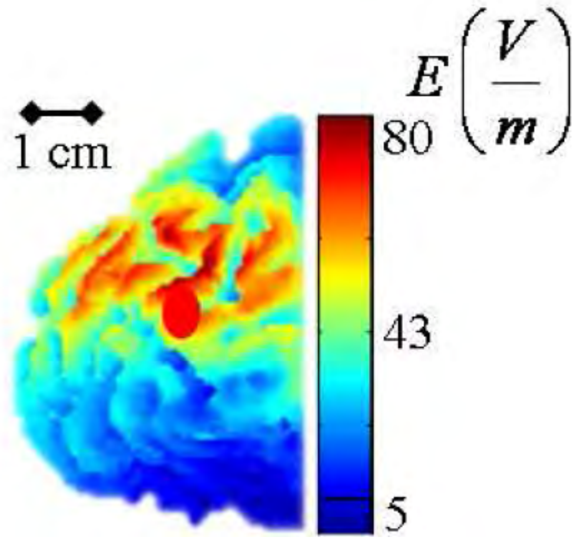
TMS for MDD: An overview

- TMS – Brief introduction
- TMS for treatment of depression
  – High frequency left-sided stimulation (FDA approved)
  – Other forms - deep TMS (dTMS), theta-burst stimulation (TBS), etc
- TMS in clinical use: Future directions

Transcranial Magnetic Stimulation





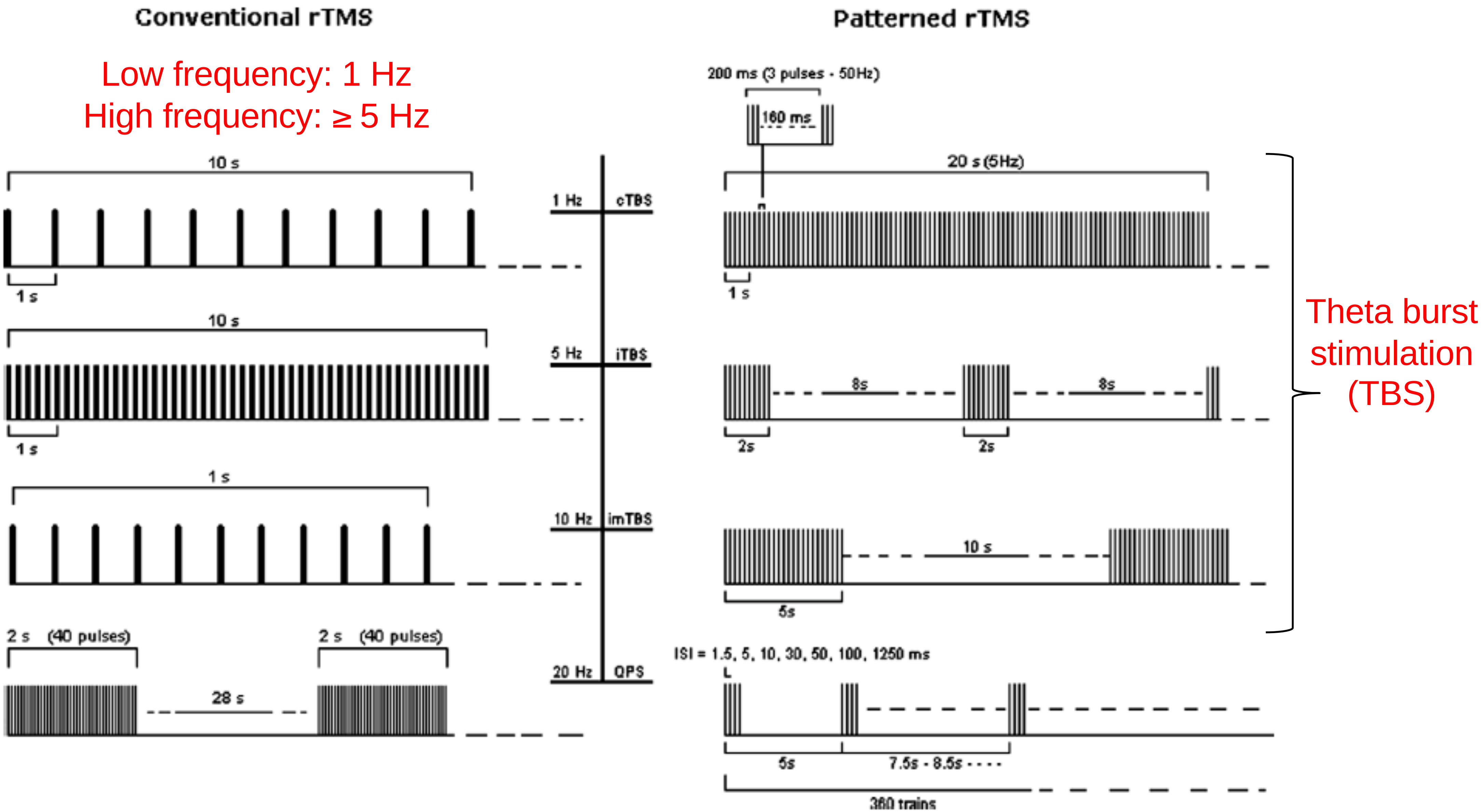


Gomez et al, 2014

Parameters that affect TMS effects on neural tissue

- Coil design
- Pulse shape
- Direction of current/orientation of coil & geometry of neurons
- Frequency of stimulation
- Pattern of stimulation
- Location of stimulation
- State of neurons/brain when stimulated

The many varieties of repetitive TMS (rTMS)



Rossi et al, 2010

Major Depressive Disorder

- World wide prevalence: 11.1 – 14.5% lifetime; 5.5 – 5.9% annual (Bromet et al, 2011)
- Second leading cause of morbidity amongst all diseases (Global Burden of Disease 2013)
- Complex, multi-factorial and heterogeneous
- One-third are not responsive to multiple treatments (Rush et al, 2006)

Clinical rTMS system

Outpatient treatment

No anesthesia required

Sessions around 25-40 min

Typical course: 30-35

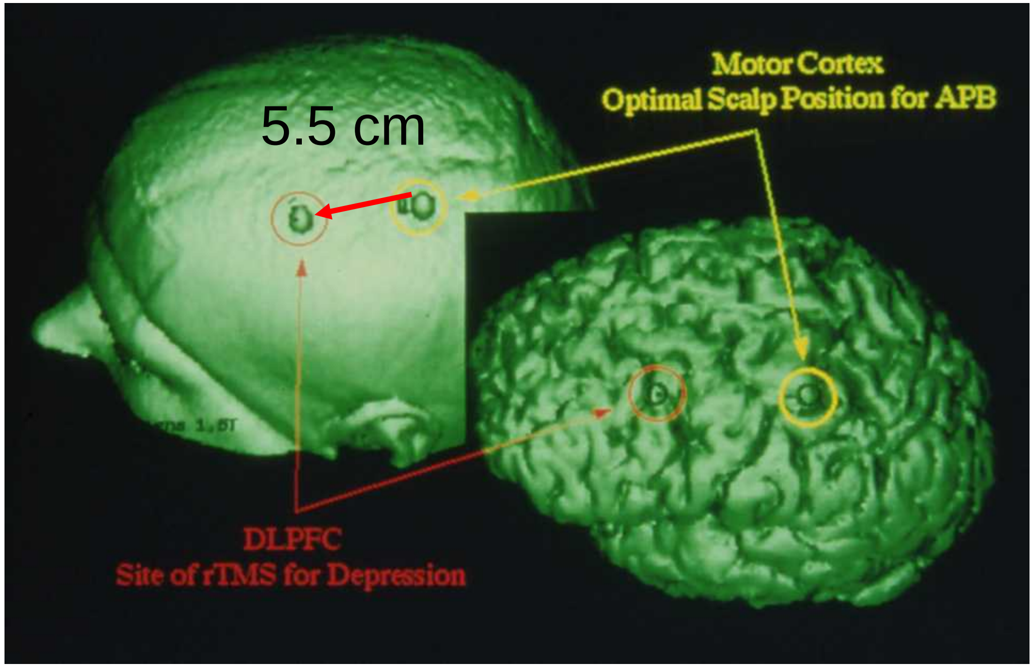
sessions over 6-8 weeks

In USA:

FDA clearance for 3 types of rTMS for MDD, 4 different systems

Administering rTMS for MDD

- Calibration: Obtain motor threshold (intensity at which 50% probability of causing thumb/finger movement)
- Targeting: Locate target (Left dlPFC: 5.5 cm anterior of motor cortex, or F3 in 10-20 system)
- Treatment: Move coil to target & stimulate: 10 Hz for 4 sec trains @ 120% motor threshold, q 12 – 26 sec
- Patient state usually uncontrolled – urged not to sleep

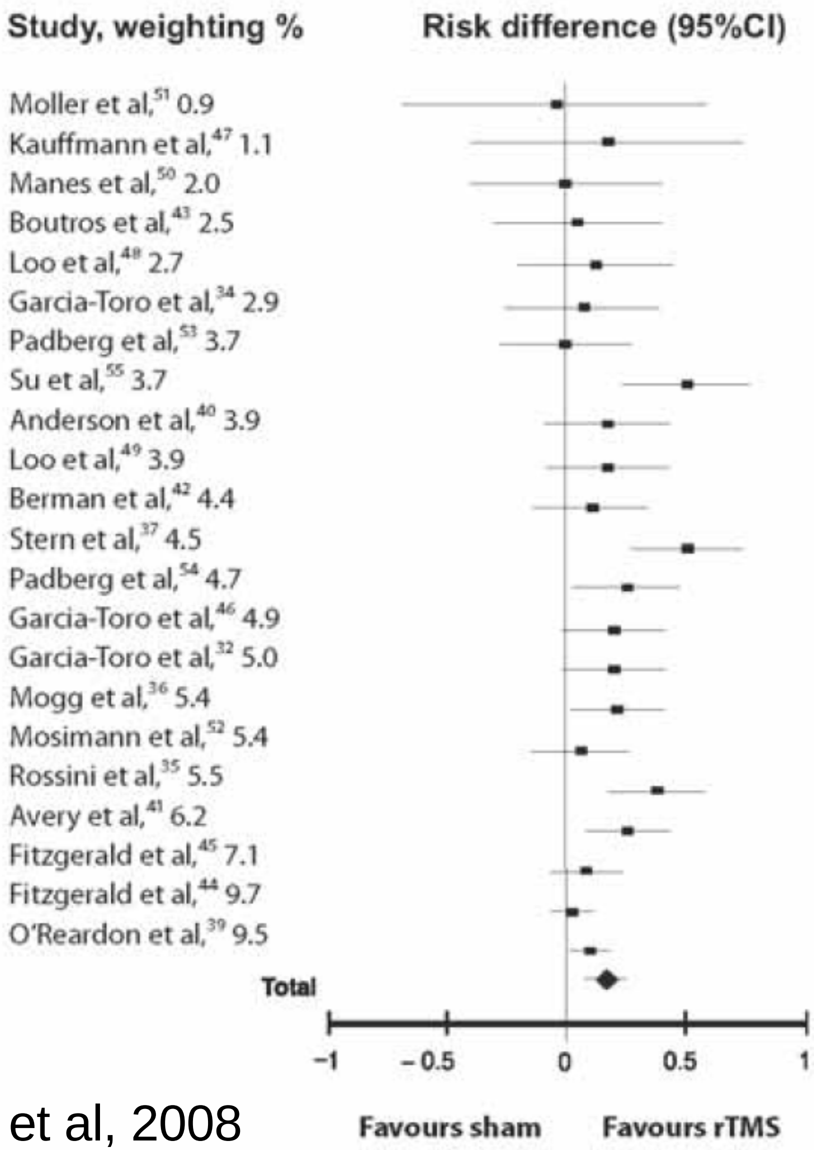


rTMS in clinical use - Side effects

- Seizure risk (1/1000): Contra-indicated for individuals with high risk of seizure
- Pain with stimulation (35 - 50 %) -- managed with changes in coil position, reduced stimulation intensity, change to LF stim
- Scalp muscle contractions with stimulation (~20 %)
- Toothache (7 %)
- Hearing impairment (earplugs used)
- In pivotal trial (n = 325), discontinuation rate of 4.5 % not different from sham stimulation (Janicak et al 2008)

TMS for MDD:
Does it actually work?

Meta-analysis of 24 randomized, controlled trials



Lam et al, 2008

1092 patients

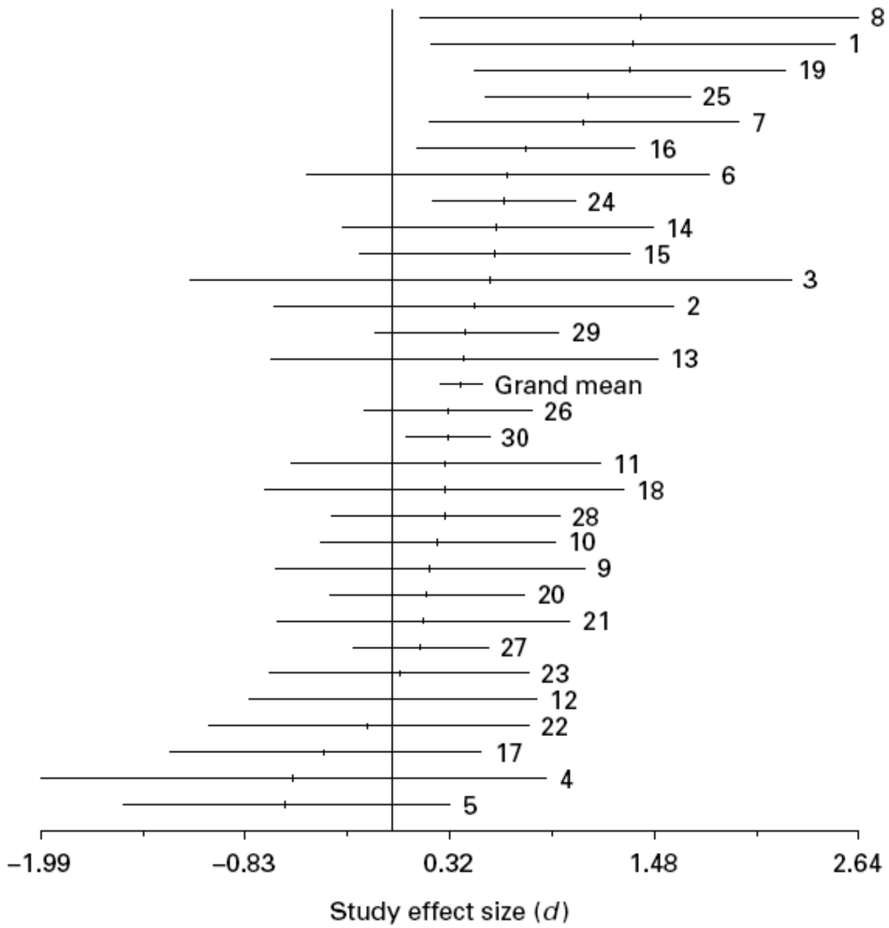
Pooled response rate (> 50 % improvement): 25 %

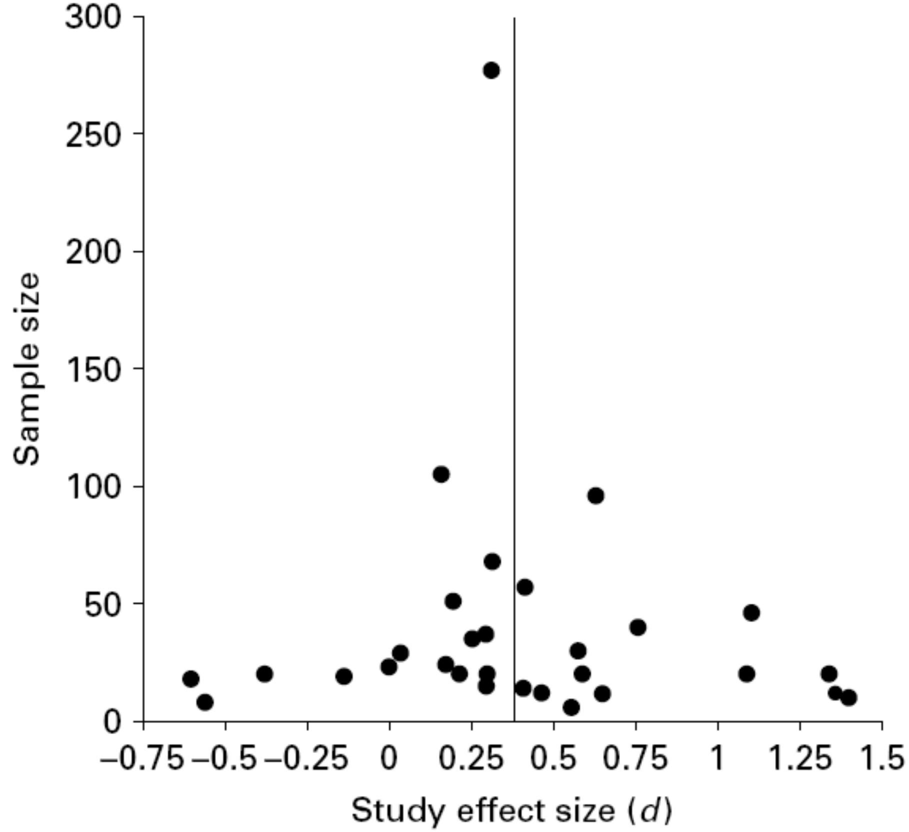
Pooled remission rate: 17 %

Effect size: 0.48

Possible predictors:
- Younger age
- Longer treatment (> 2 weeks)
- More pulses per session

Meta-analysis of 30 rTMS studies of MDD: Left DLPFC stimulation





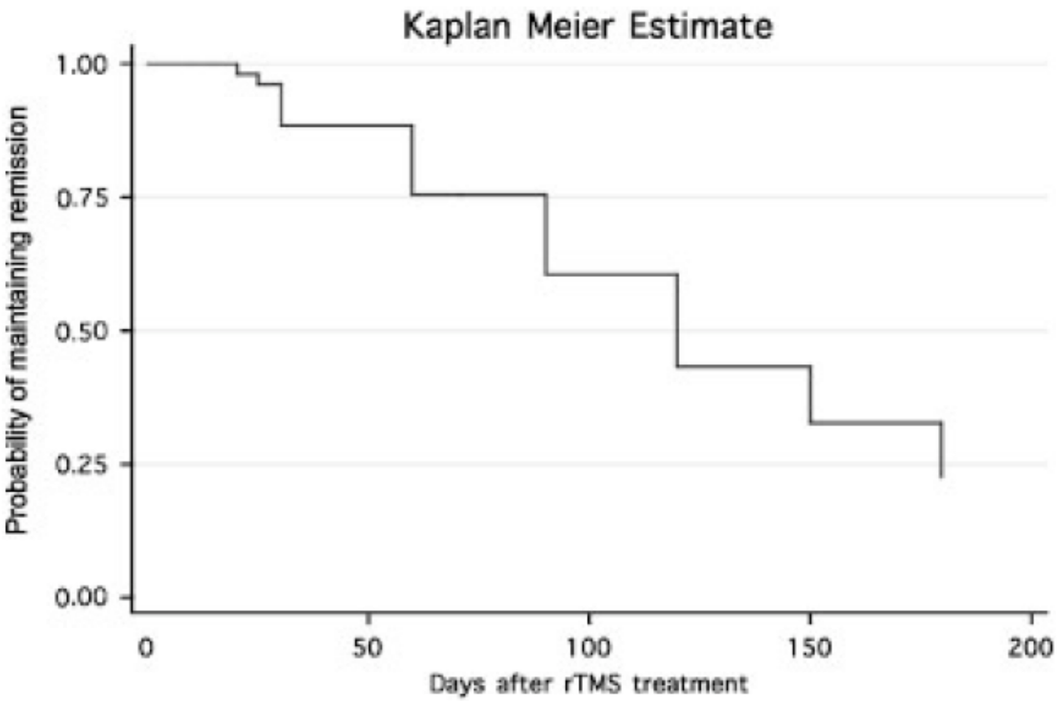
Effect size = 0.39

Schutter, 2009

Comparison of naturalistic TMS trials

Study	Type	Subjects	Δ QIDS-SR/PHQ-9	50% response	Remission
Taylor et al, 2017	Multi site	62	-5.5 @ 4 wks	50.9% CGI	17.9% CGI
Connelly et al 2012	Single site	85	-4.7 @ 4 wks	50.6% CGI	24.7% CGI
Carpenter et al 2012	Multi site	307	-8.7 @ max	58.0% CGI 41.5% IDS	37.1% CGI 26.5% IDS

rTMS in depression: How long does it last?



204 patients treated to remission

88 % R sided, 1 Hz stim

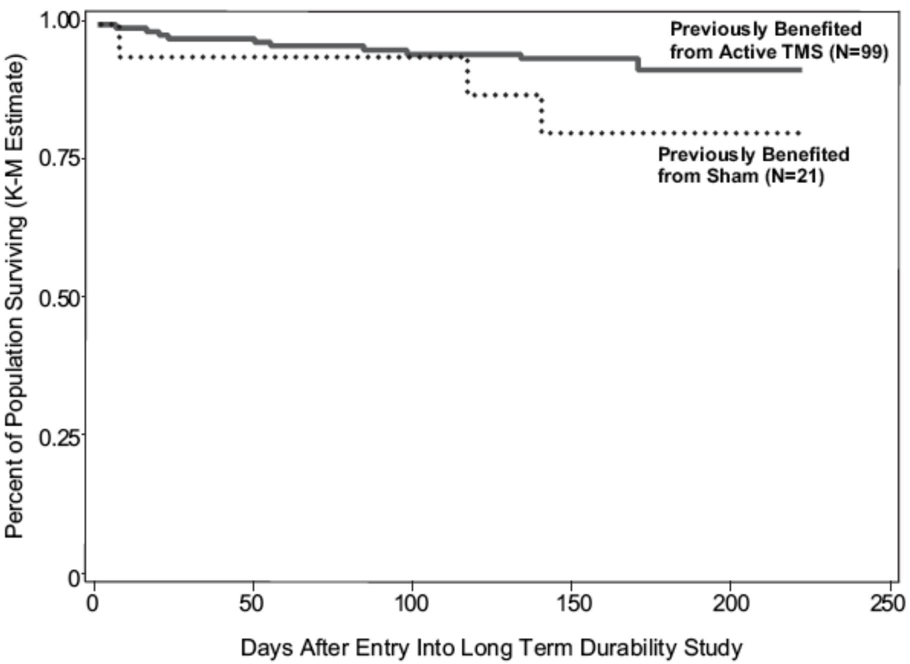
10 – 60 sessions (50 % w/ 10)

Younger age and fewer sessions predicted longer time to relapse

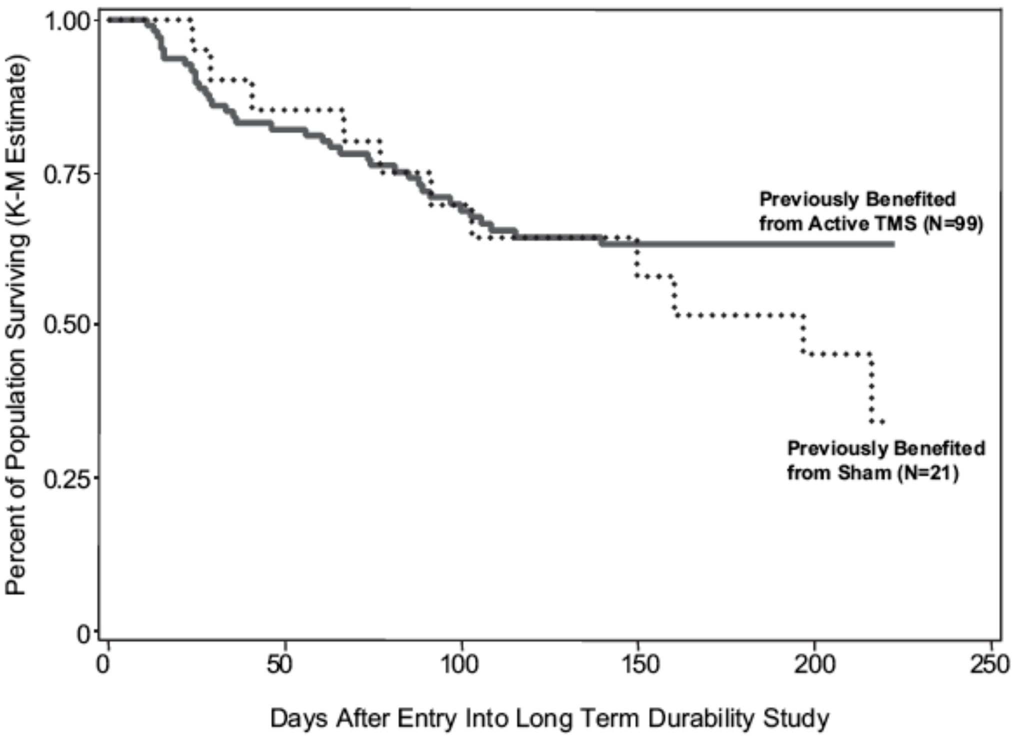
Cohen et al, 2009

Durability of TMS – from Neuronetics study

Time to replase in 99 patients agreeing to 24 week f/u

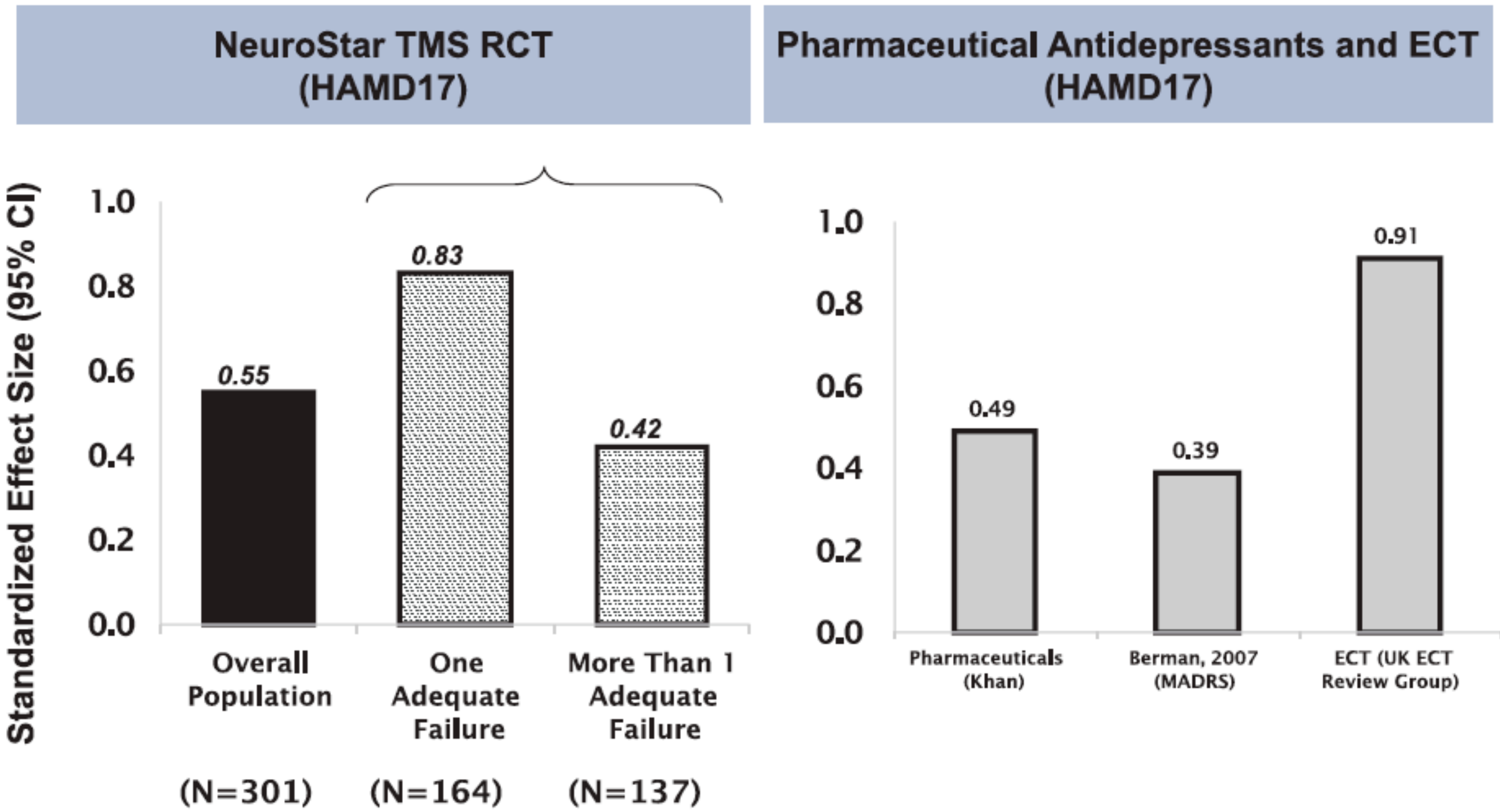


Time to re-initiation of rTMS therapy in 99 patients



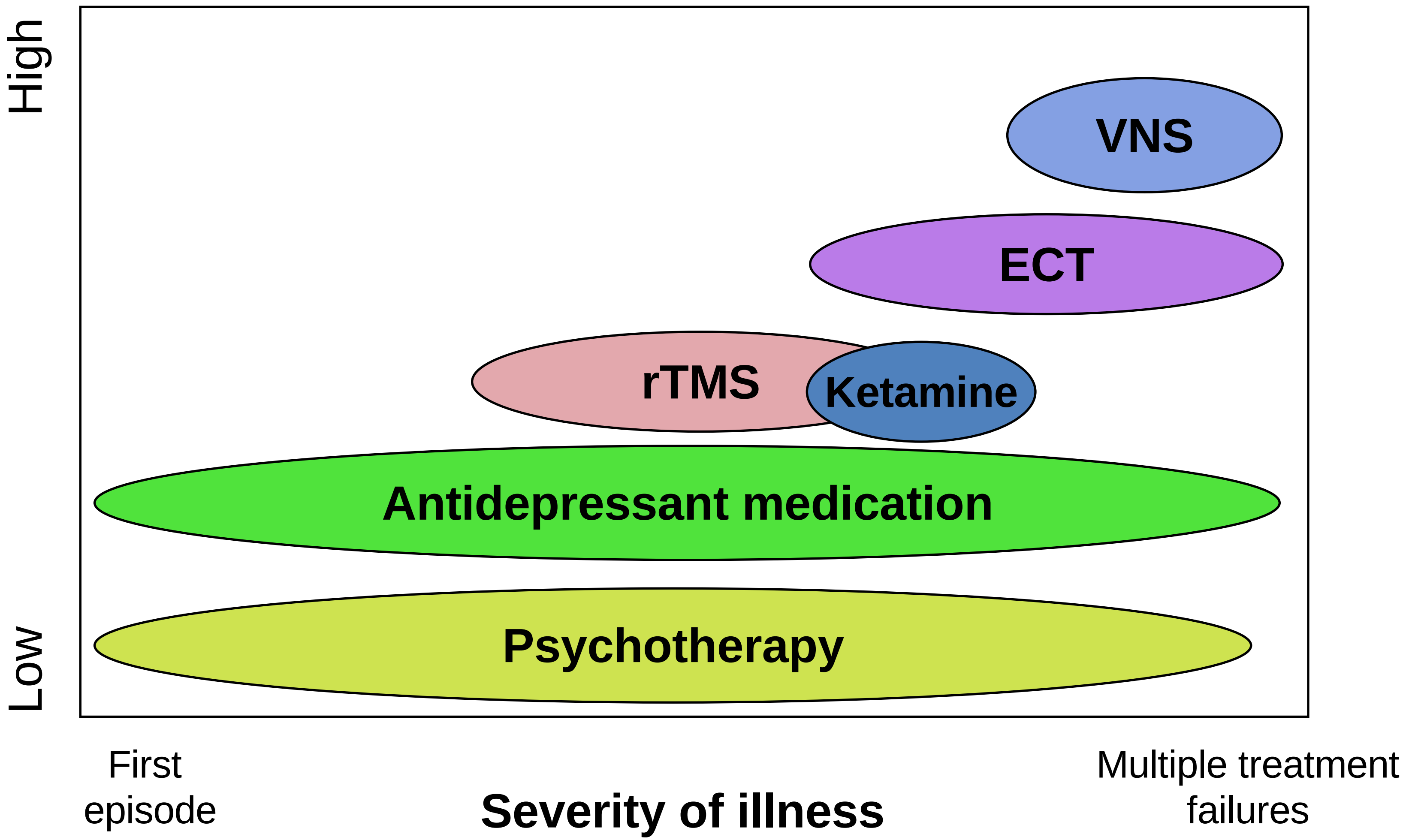
Janicak et al, 2010

Comparison of effect sizes (Cohen's d) for rTMS, pharmacotherapy and ECT



From Neuronetics trial, presented by Thase et al, 2008, Society of Biological Psychiatry

Spectrum of treatment in Depression



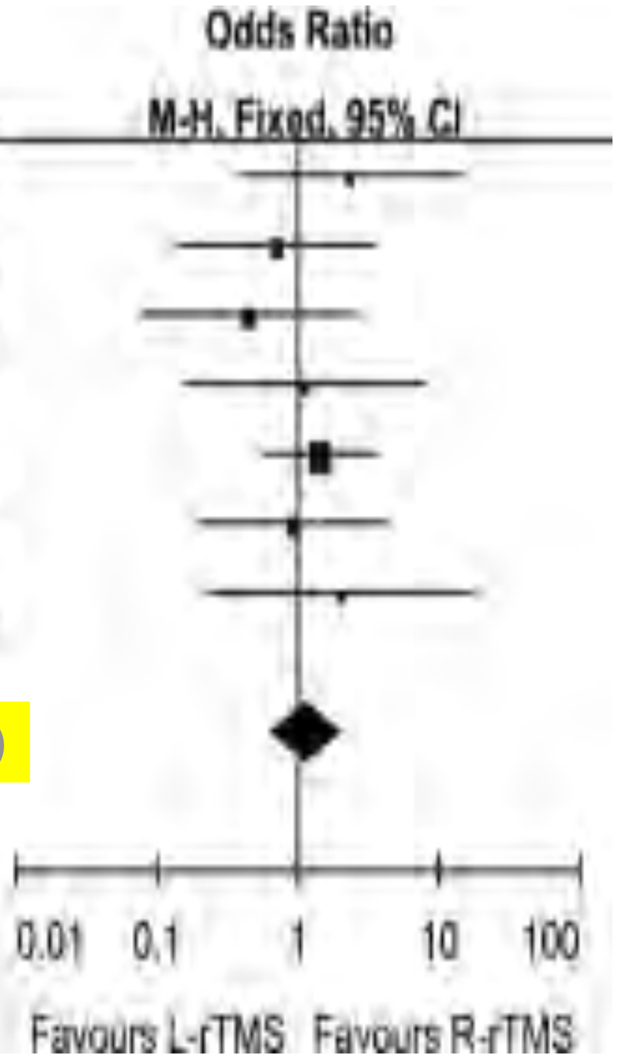
Low Frequency vs. High Frequency TMS

- High frequency (5-20 Hz, 10 Hz most common)
  - ‘Excitatory’ – potential for seizures
  - Applied to left dorsolateral prefrontal cortex
  - Typical parameter: 4 sec train, every 12-24 sec, 3000 pulses/session
  - Theory: Boost activity in left PFC
- Low frequency (1 Hz)
  - ‘Inhibitory’ – virtually no risk for seizures
  - Applied to right dorsolateral prefrontal cortex
  - Typical parameters: 1800 pulses, continuous
  - Theory: Inhibition of right PFC
- Comparison
  - High frequency has larger database (FDA approved), but much harder to tolerate than low frequency
  - Data do not support advantage of HF

	L-rTMS		R-rTMS			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
Höppner 2003	5	10	3	10	6.8%	2.33 [0.37, 14.61]	2003
Fitzgerald 2003	3	20	4	20	15.5%	0.71 [0.14, 3.66]	2003
Stern 2007	4	10	6	10	16.4%	0.44 [0.07, 2.66]	2007
Fitzgerald 2007	3	15	2	11	8.4%	1.13 [0.15, 8.21]	2007
Rossini 2008	21	32	24	42	32.5%	1.43 [0.55, 3.71]	2008
Fitzgerald 2009	7	16	5	11	15.2%	0.93 [0.20, 4.37]	2009
Eche 2012	4	6	4	8	5.2%	2.00 [0.22, 17.89]	2012
Total (95% CI)		**109**		**112**	**100.0%**	**1.15 (0.6 2.03)**	
Total events	47		46				

Heterogeneity: $Chi^2 = 2.51$, df = 6 (P = 0.87); $I^2 = 0\%$

Test for overall effect: Z = 0.47 (P = 0.64)



Chen et al 2013

Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial

Lancet, 2018

Daniel M Blumberger, Fidel Vila-Rodriguez, Kevin E Thorpe, Kfir Feffer, Yoshihiro Noda, Peter Giacobbe, Yuliya Knyahnytska, Sidney H Kennedy, Raymond W Lam, Zafiris J Daskalakis, Jonathan Downar

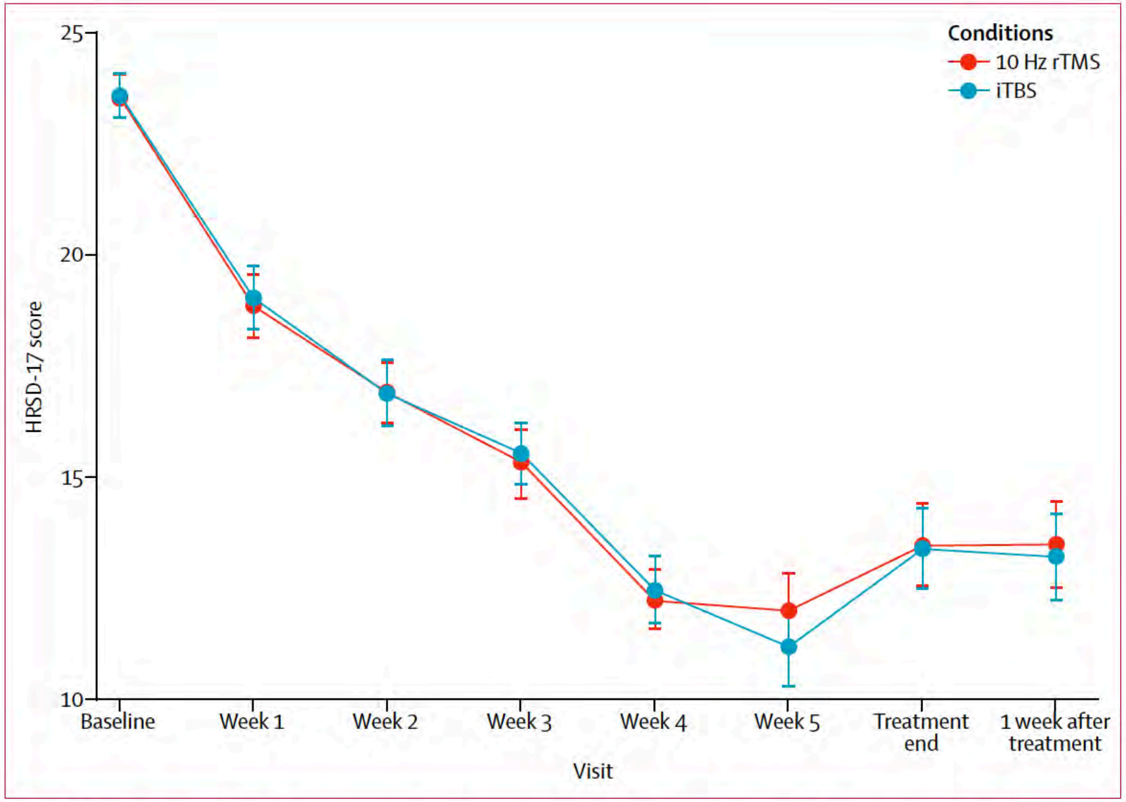


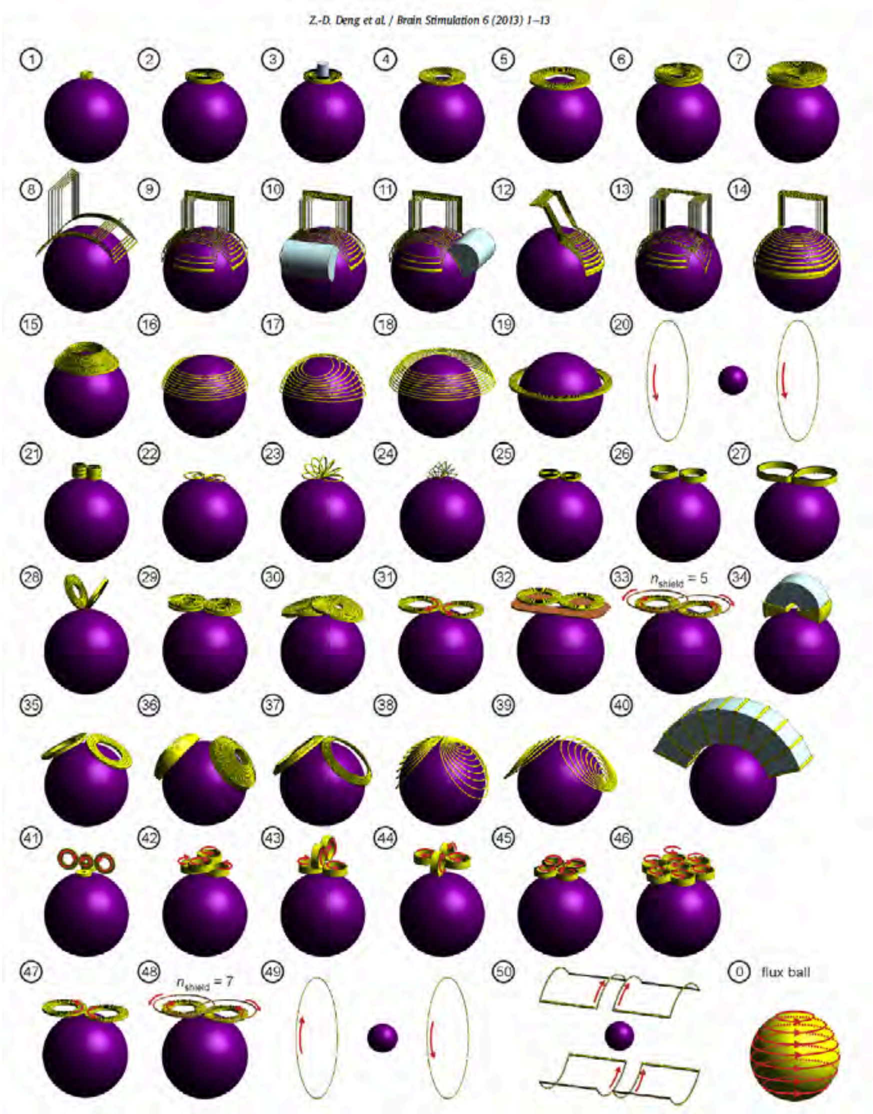
Figure 3: **Change in HRSD-17 scores over time, comparing the 10 Hz rTMS and iTBS treatment groups**
Data are mean scores with lower and upper 90% CIs.

TBS: 50 Hz triplet pulses, delivered at 5 Hz for 2 sec, repeated every 10 sec, @ 120% motor threshold, 3 min, 9 sec

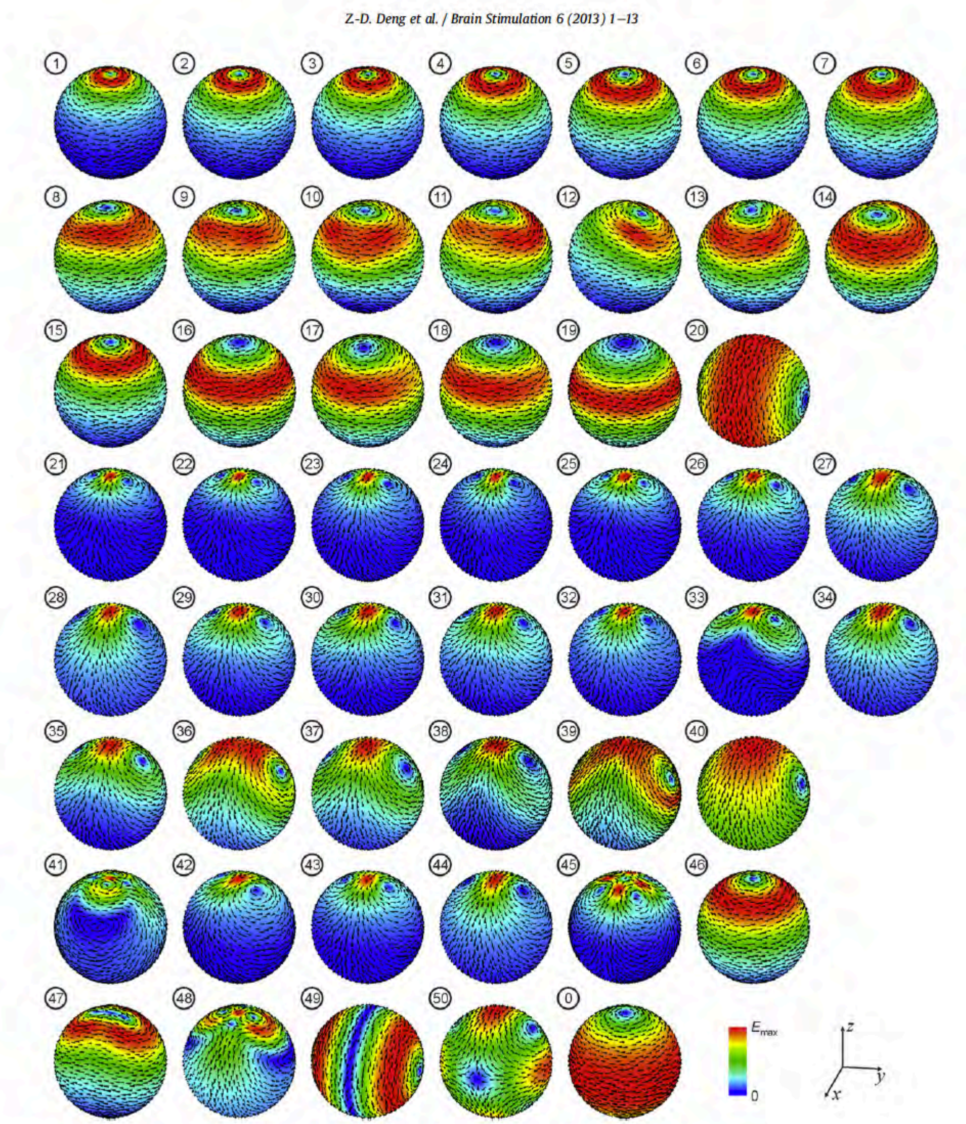
- versus -

HF rTMS: 10 Hz, for 4 sec, repeated every 30 sec, @ 120% MT, 37.5 min

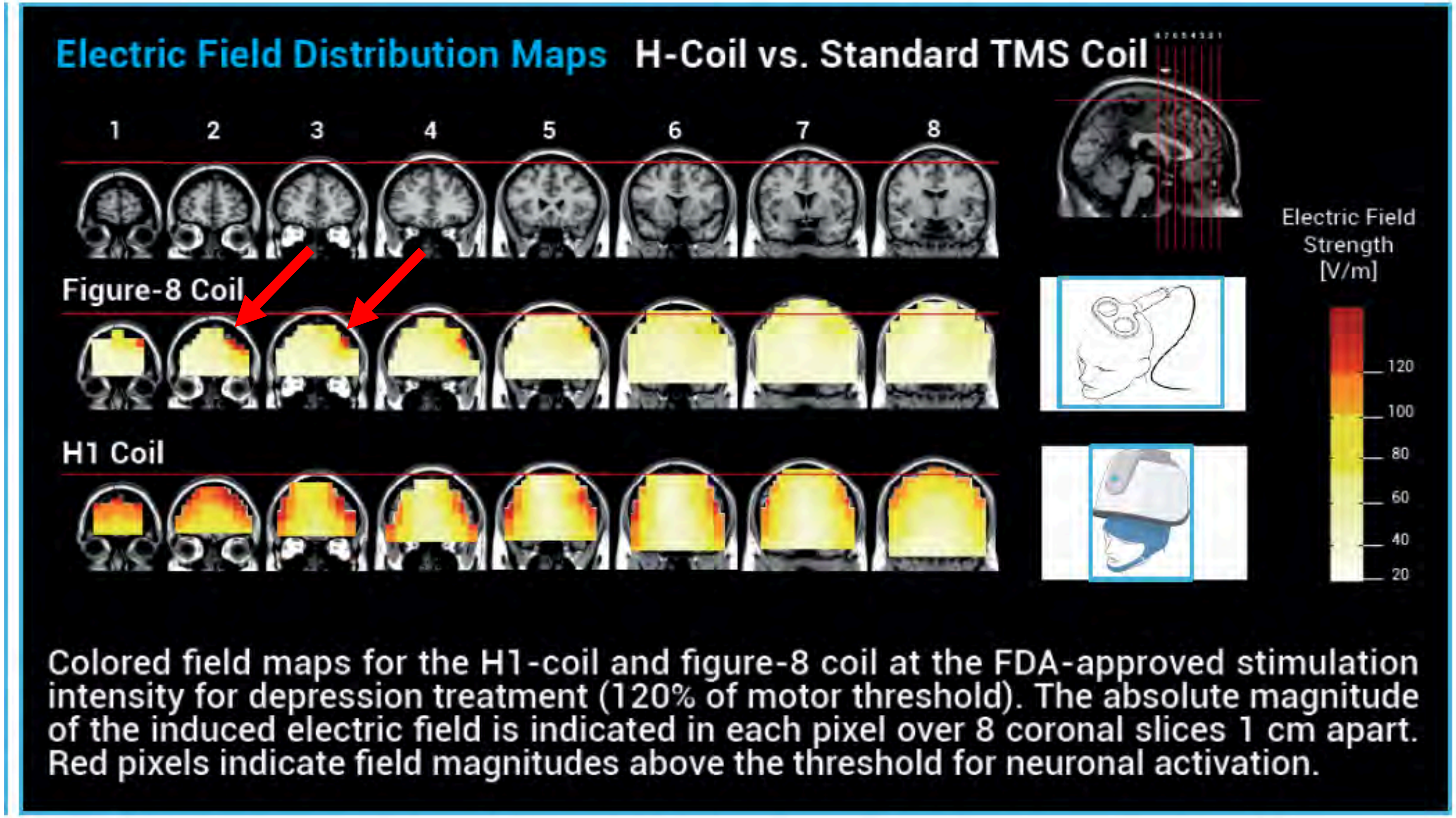
Many, many coil designs!



With diverse E-fields



Deep TMS (dTMS) – broader and deeper stimulation of prefrontal cortex

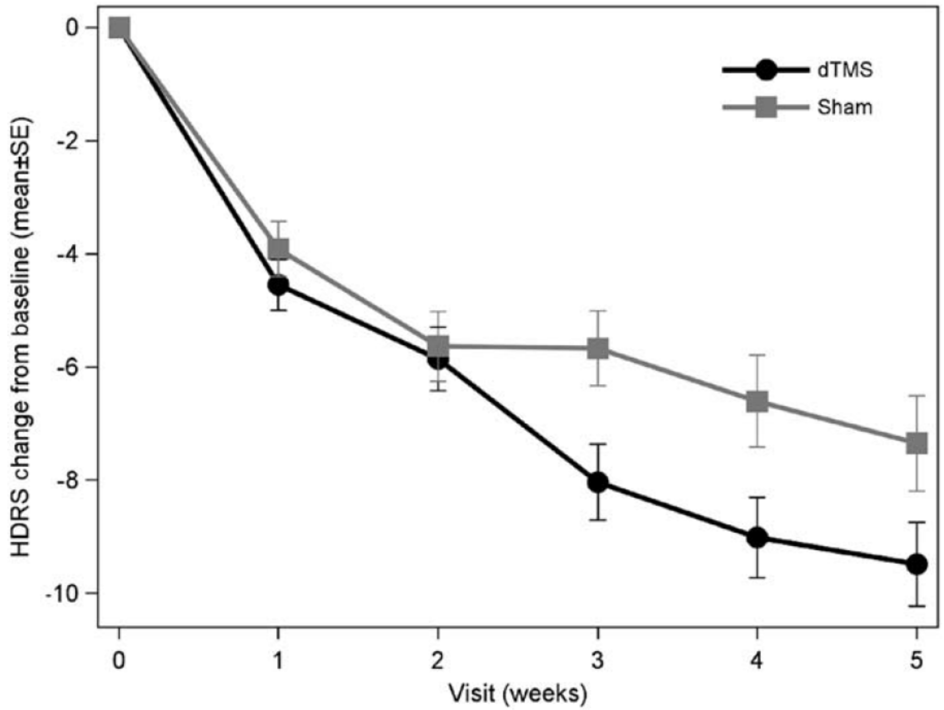


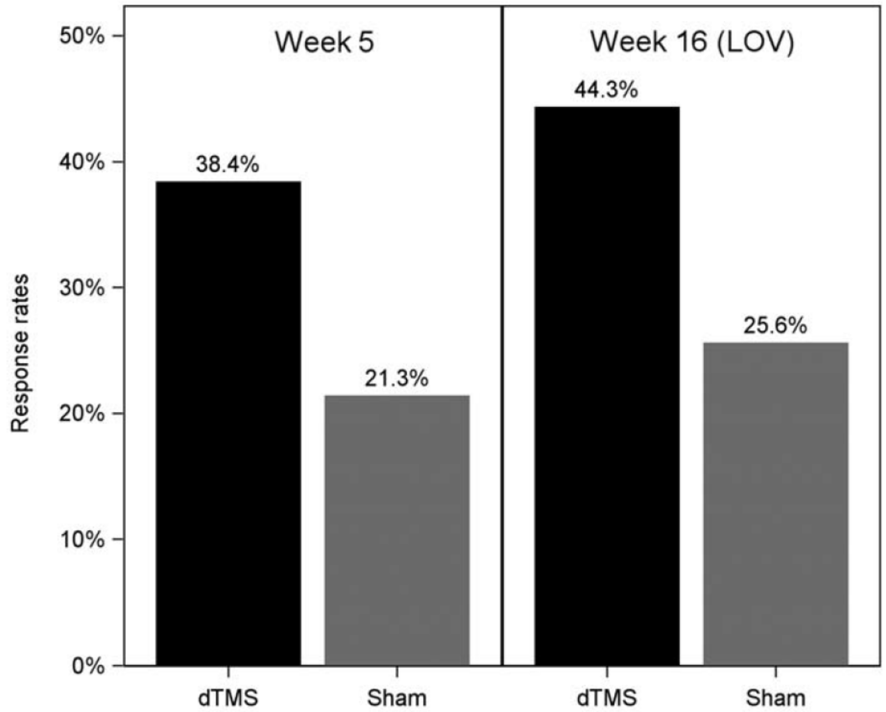
World Psychiatry, 2015

RESEARCH REPORT

Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial

Yechiel Levkovitz[1], Moshe Isserles[2], Frank Padberg[3], Sarah H. Lisanby[4], Alexander Bystritsky[5], Guohua Xia[6], Aron Tendler[7], Zafiris J. Daskalakis[8], Jaron L. Winston[9], Pinhas Dannon[10], Hisham M. Hafez[11], Irving M. Reti[12], Oscar G. Morales[13], Thomas E. Schlaepfer[14], Eric Hollander[15], Joshua A. Berman[16], Mustafa M. Husain[17], Uzi Sofer[18], Ahava Stein[19], Shmulik Adler[19], Lisa Deutsch[20], Frederic Deutsch[20], Yiftach Roth[21], Mark S. George[22], Abraham Zangen[21]





N=181

Other forms of rTMS for depression

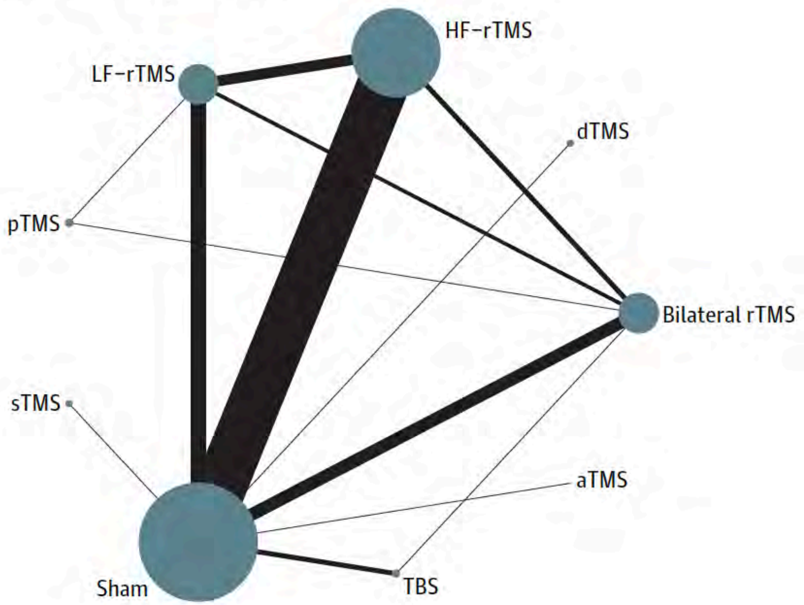
- Accelerated TMS (aTMS)
  - Multiple sessions in one day, shorten course, 15 sessions in 2 days (Holtzheimer et al, 2010; Williams et al 2018)
- Synchronized TMS (sTMS)
  - Low field stimulation with rotating magnets at patients alpha frequency (e.g. Leuchter et al, 2015)
- Priming TMS (pTMS)
  - Apply high frequency stimulation prior to low frequency stimulation (Fitzgerald et al, 2008)
- Bilateral rTMS
  - Low frequency stimulation to right, followed by high frequency to the left (Fitzgerald et al, 2016, Blumberger et al, 2011)
- Dorsomedial PFC stimulation
  - Evidence for involvement in mood regulation (Bakker et al, 2015)
- Two coil stimulation
  - dLPFC and dorsomedial PFC (Kavanaugh et al, 2018)

JAMA Psychiatry | Original Investigation | META-ANALYSIS 2016

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

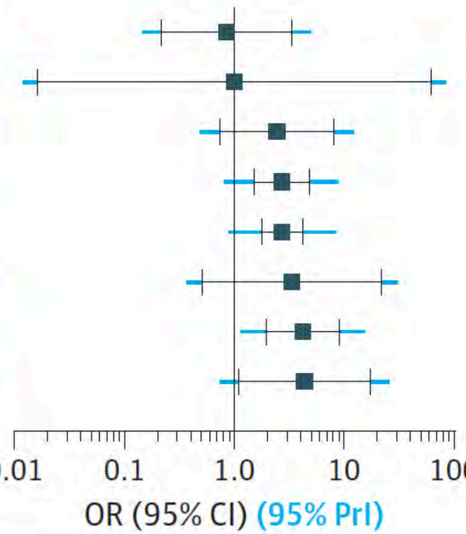
Andre R. Brunoni, MD, PhD; Anna Chaimani, PhD; Adriano H. Moffa, PsyD, MPhil; Lais B. Razza, PsyD; Wagner F. Gattaz, MD, PhD; Zafiris J. Daskalakis, MD, PhD; Andre F. Carvalho, MD, PhD

A Network diagram for response



A Response

Active Device	OR (95% CI) (95% PrI)
sTMS	0.85 (0.22-3.35) (0.15-4.94)
aTMS	1.00 (0.02-62.31) (0.01-83.19)
dTMS	2.45 (0.74-8.07) (0.49-12.28)
LF-rTMS	2.70 (1.51-4.82) (0.82-8.89)
HF-rTMS	2.73 (1.78-4.20) (0.89-8.40)
TBS	3.37 (0.52-22.05) (0.37-30.69)
Bilateral rTMS	4.22 (1.96-9.05) (1.15-15.47)
pTMS	4.37 (1.10-17.47) (0.74-25.69)



aTMS indicates accelerated TMS; dTMS, "deep" (H-coil) TMS; HF, high frequency; LF, low frequency; pTMS, priming TMS; sTMS, synchronized TMS; TBS, θ-burst stimulation. A, Response; and B, acceptability. The size of the nodes is proportional to the total number of participants allocated to each intervention and the thickness of the lines proportional to the number of studies evaluating each direct comparison.

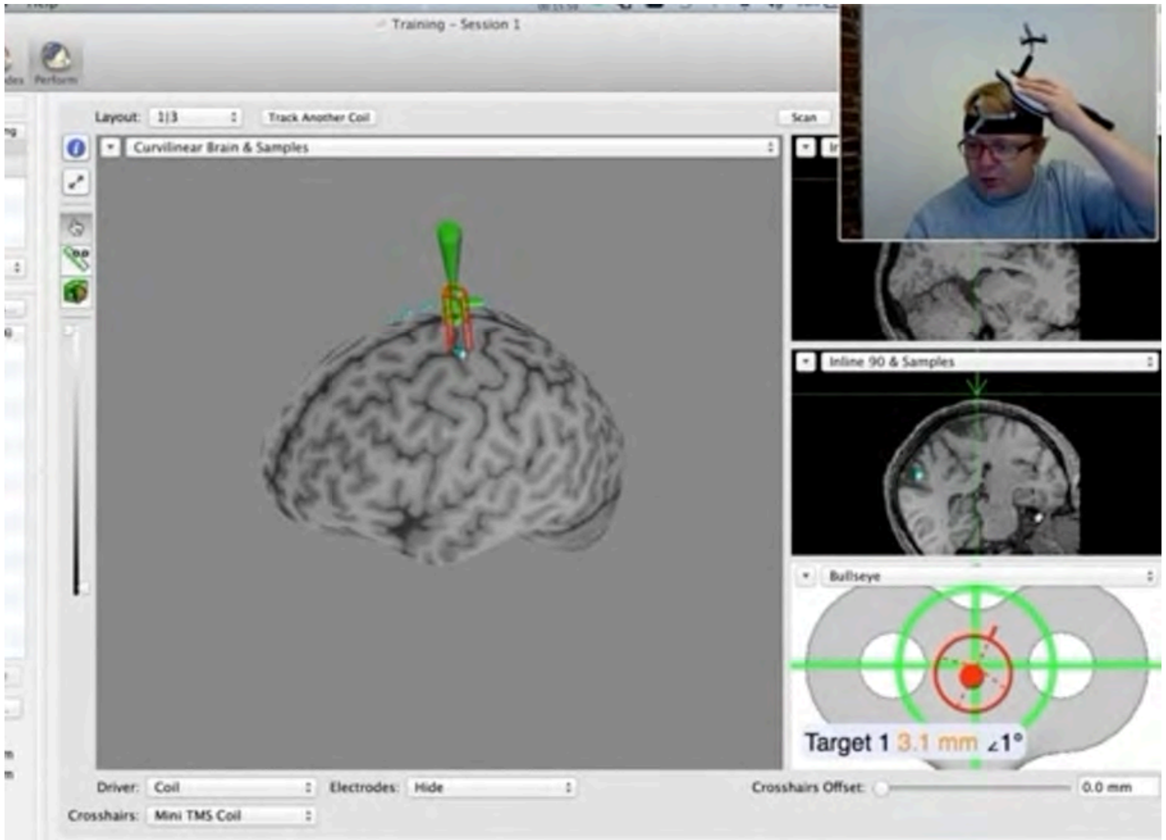
Future directions

- Targeting – optimizing site of stimulation
  - Alternative targets besides dLPFC
  - Neuronavigation with fMRI
  - Combining multiple sites
  - Deep & broad versus focal?
- Augmenting stimulation by controlling brain state
  - e.g. combine TMS with cognitive training
- Optimizing TMS pulse delivery
  - Controllable pulse stimulator
  - Patterned rTMS, e.g. TBS, quadripulse
- Patient selection
  - Matching patient biotype to type of rTMS

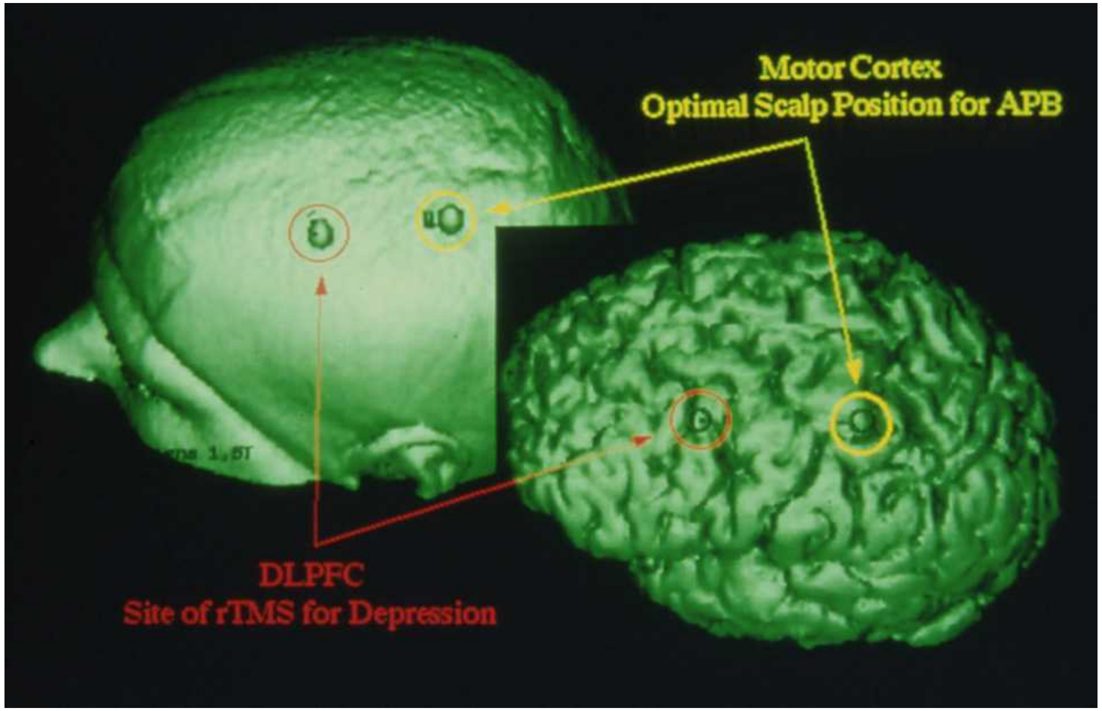
TMS targeting with frameless stereotaxy

Tracking system

Software shows position of TMS wand relative to subject's brain

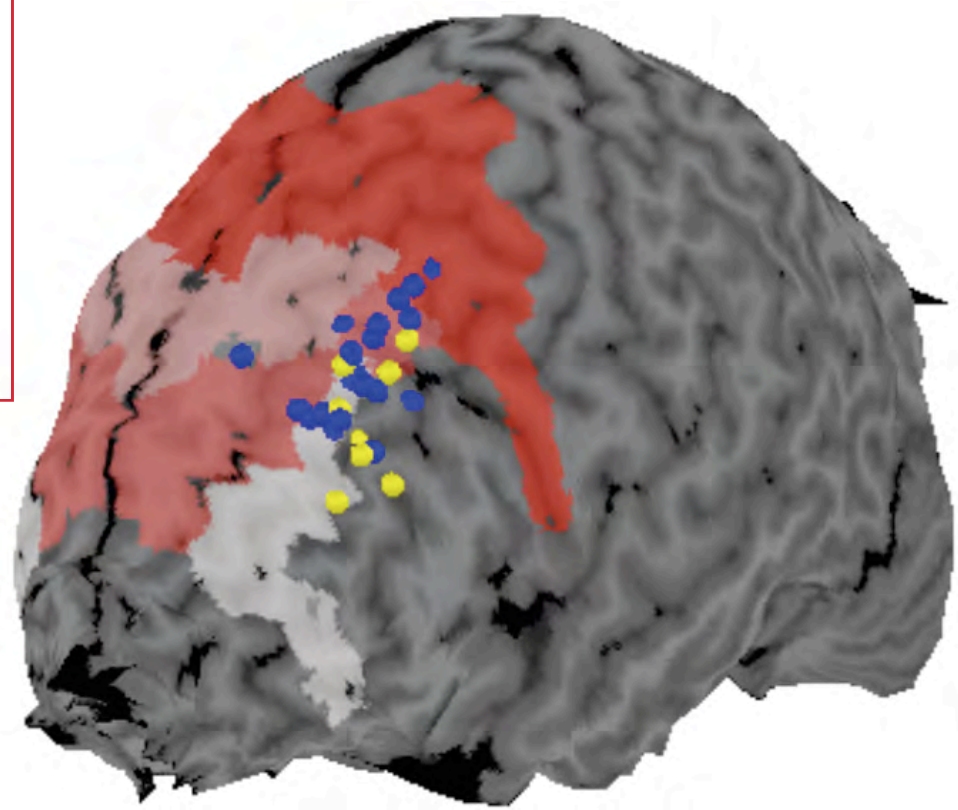


Standard positioning (ideal) - based on motor stimulation of thumb



Target: Left lateral prefrontal cortex

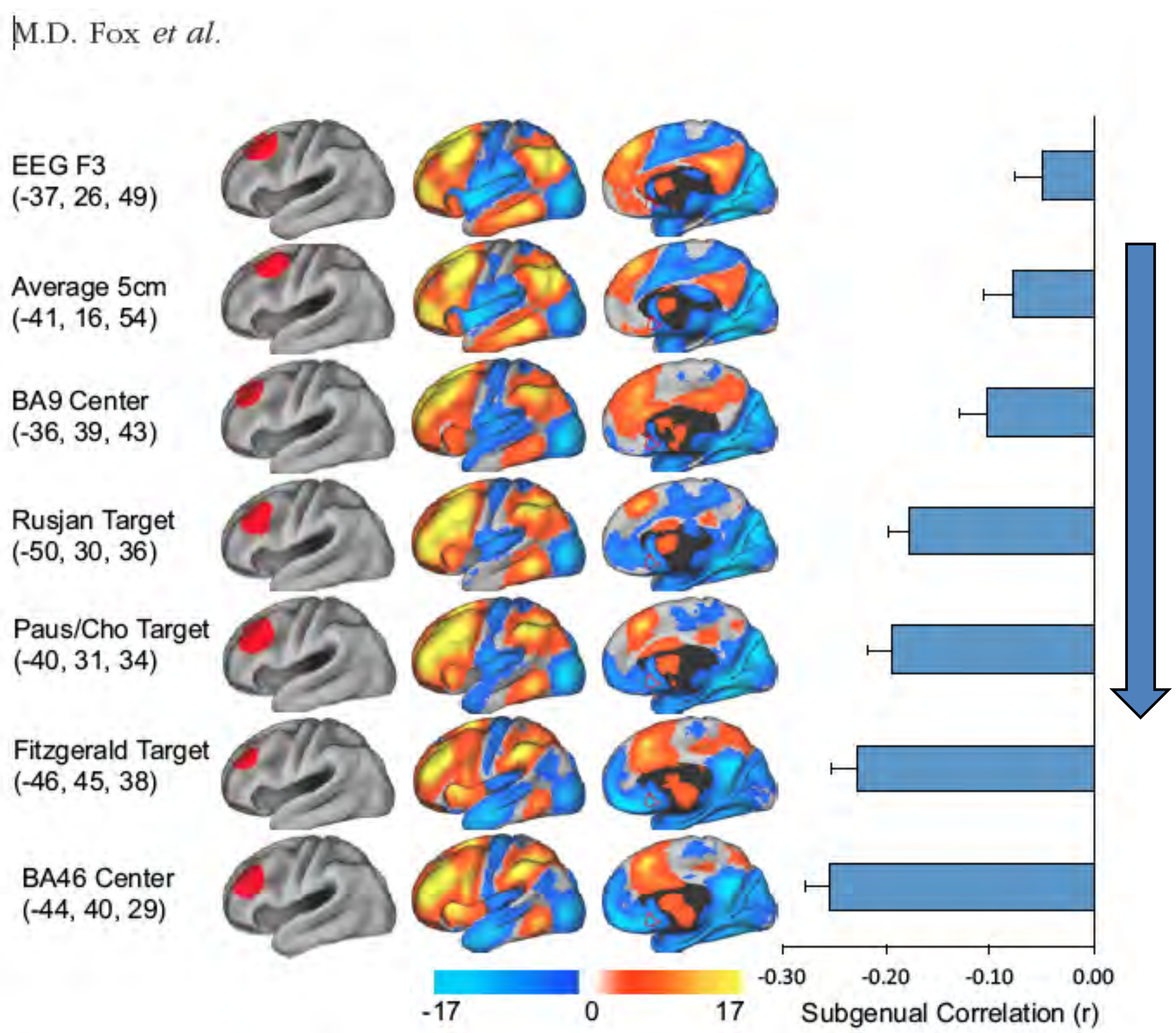
Actual positioning from 28 subjects
Blue: Non-responders
Yellow: Responders



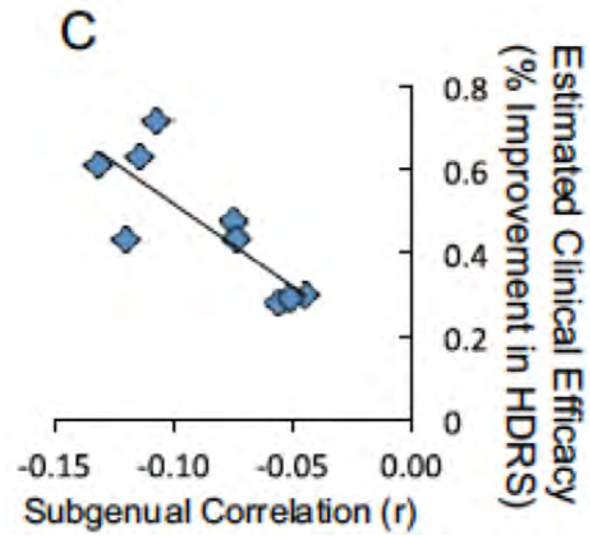
Herbsman et al, 2009

Where to target in the left dlPFC – alternative views

The more anterior the area of rTMS stimulation …

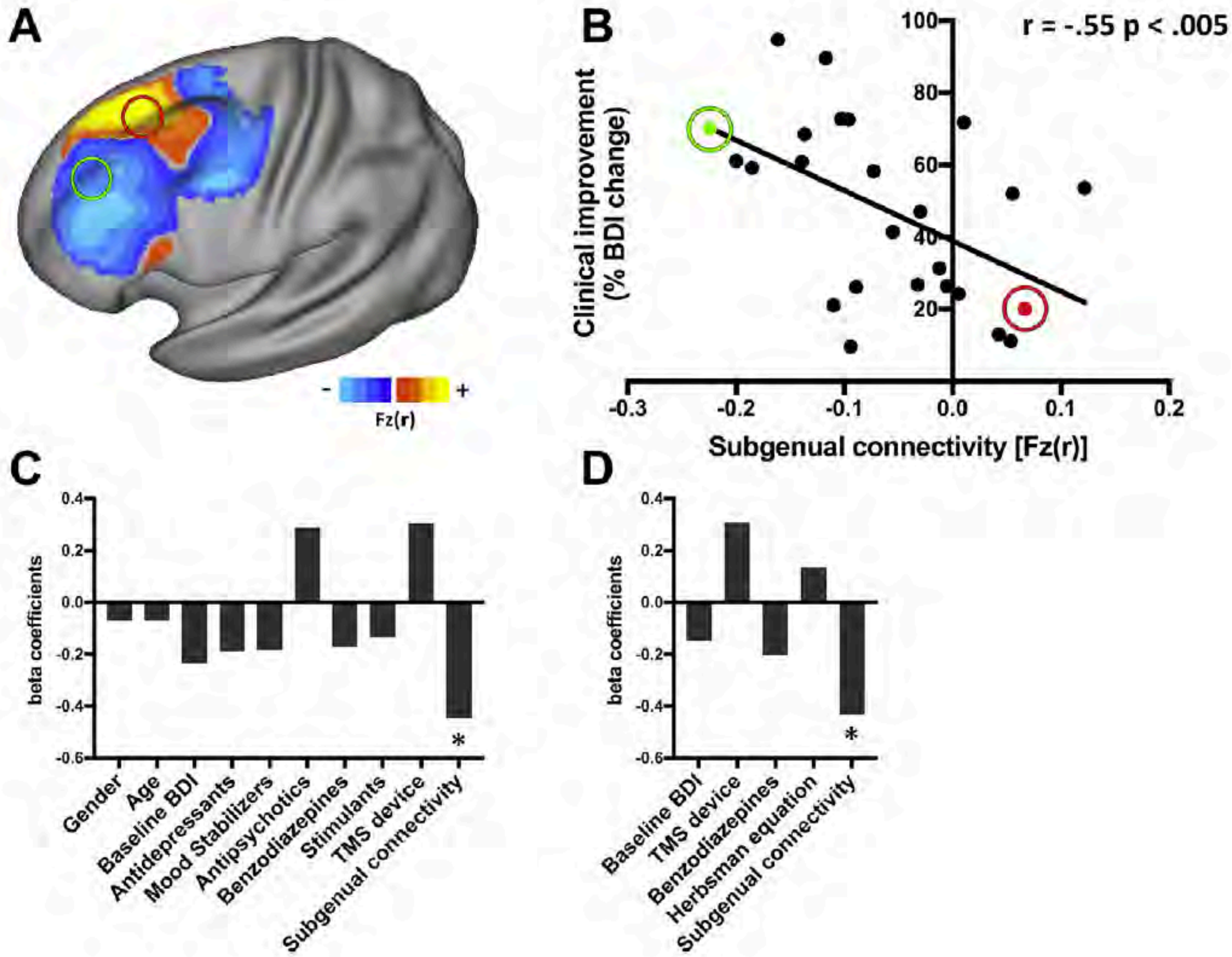


… the more negative the correlation with sgACC, and…



… the stronger the clinical effect.

Testing the hypothesis in depressed patients: sgACC negative connectivity with dlPFC predicts improvement



Weigand et al, Biological Psychiatry, 2017

TMS for MDD: Conclusions

- TMS is a powerful technique for altering neuronal function
- TMS for MDD is an effective treatment alternative
- New research to optimize and improve the therapeutic response to TMS have only begun to explore a huge parameter space
- TMS is being used in other psychiatric conditions, besides depression (FDA clearance for OCD)

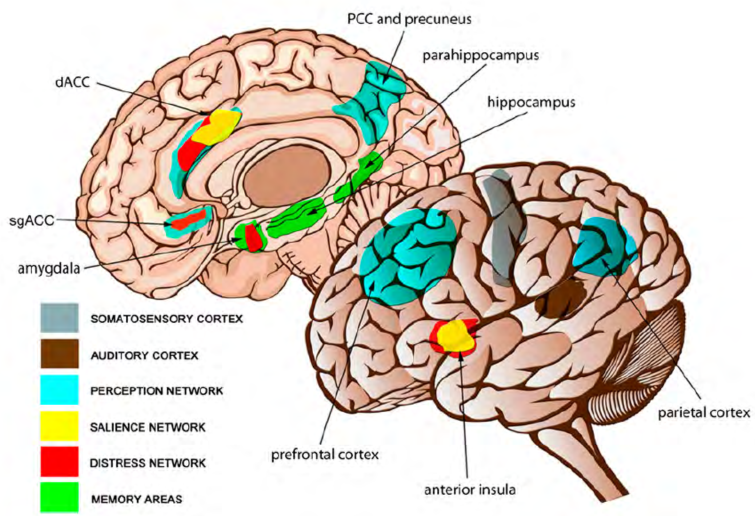
Questions?

TMS for tinnitus

Dirk De Ridder

Brain Research consortium for Advanced International, Innovative & Interdisciplinary Neuromodulation

What do Beethoven & Captain Ahab (Moby Dick) have in common ?



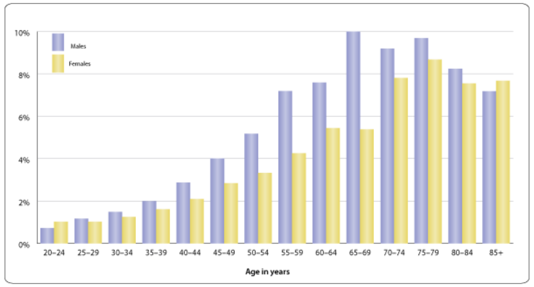
De Ridder 2011

Treatment of Tinnitus

Tinnitus

15 % of population is affected (Axelsson 1989)

- Hearing loss > normal hearing
- Increases with age
- 2.4 % of total population most severe



National Health Interview Study Disability Supplement
NIDCD 1994-1995

Most prevalent problem for war veterans

(US Department of Veterans Affairs)

Most Prevalent Service-Connected Disabilities for Veterans Receiving Compensation at the End of Fiscal Year 2011	
Tinnitus	840,865
Hearing loss	701,760
Post traumatic stress disorder	501,280
Scars, general	441,030
Diabetes mellitus	354,581
Lumbosacral or cervical strain	309,915
Limitation of motion of the knee	299,062
Hypertensive vascular disease	294,937
Traumatic arthritis	287,751
Impairment of the knee, general	268,320

1. Tinnitus = ear problem

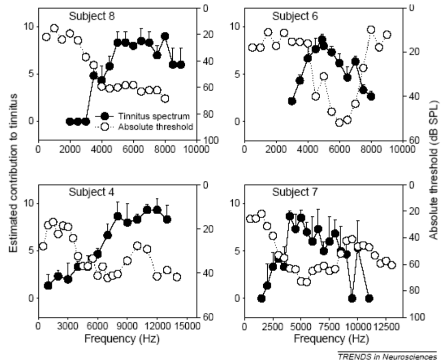
Ebers papyrus (1550 BC)

'Bewitched ear'

Pliny the Elder (23-79 AD)

'Tinnitus'

Tinnitus covers area of hearing loss (Norena 2002)



Translate to treatment

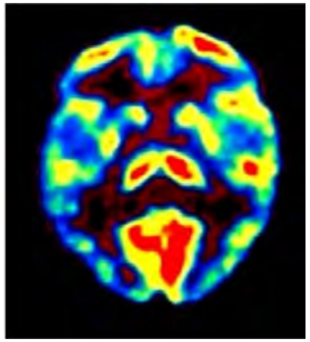
- 15-22% have major relief with hearing aids (Schleuning 1980, Von Wedel 1985, Kochkin 2008)
- Not at all in high-bandwidth amplification (Moffat 2009)
- No evidence in Cochrane meta-analysis (Hoare 2014)

Maybe it is not the ear but…

2.Tinnitus is caused by auditory cortex

Treat hyperactivity in auditory cortex…

PET

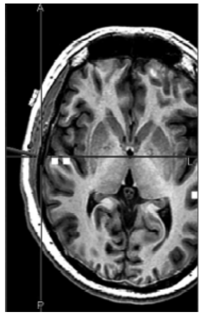


Langguth 2007

EEG

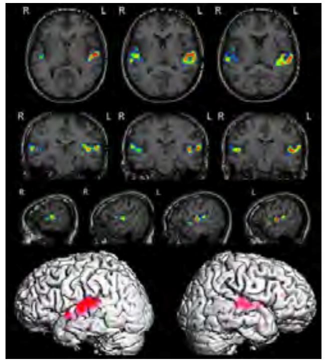
Van der Loo 2009

MEG



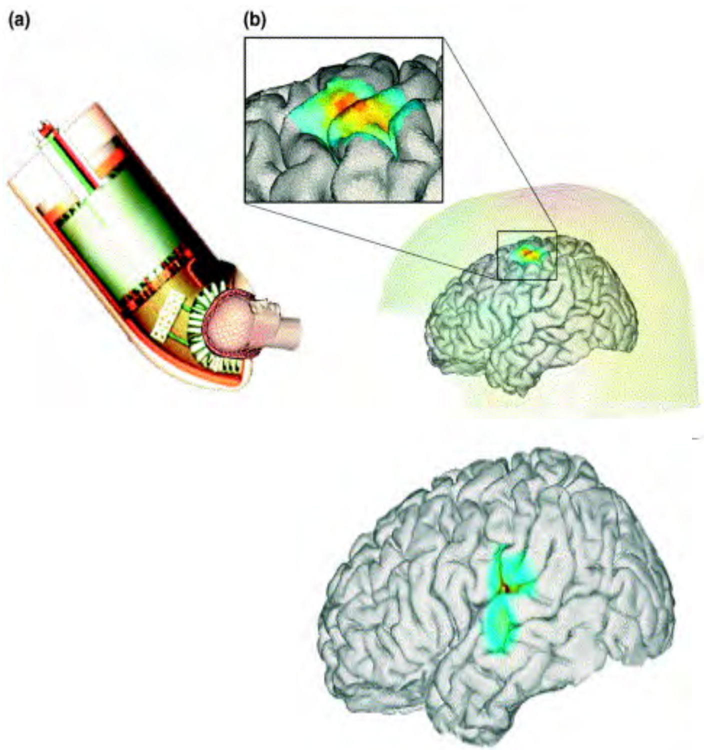
Seidman 2008

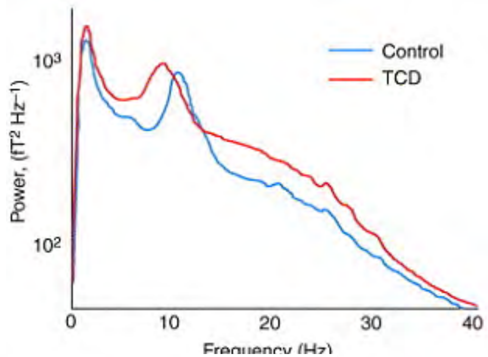
fMRI

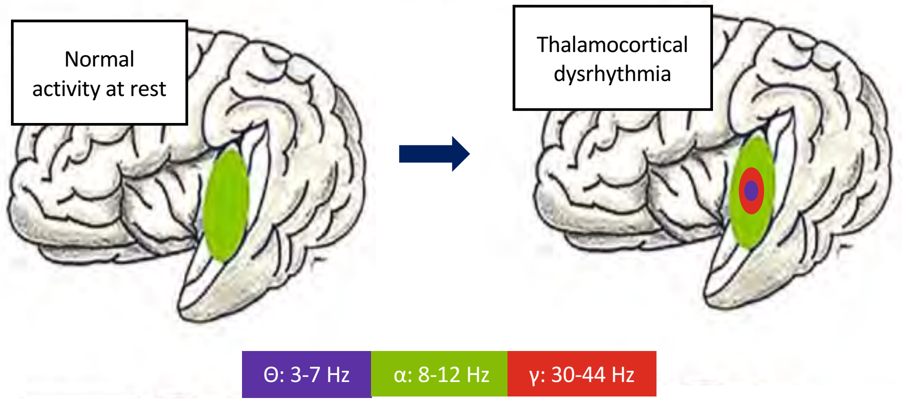


De Ridder 2004

Llinas’s thalamocortical dysrhythtmia







Llinas 1999

Thalamocortical dysrhythmia

Support vector machine learning

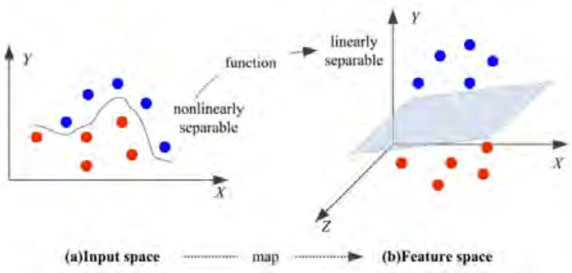
1. Select ROIs and frequency bands

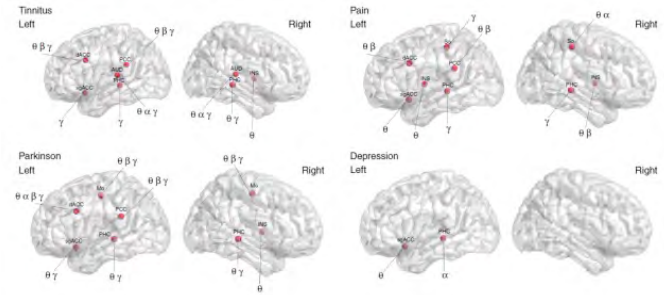
   ROIs: auditory cortex, somatosensory cortex, motor cortex, sgACC, dACC, PCC, PHC

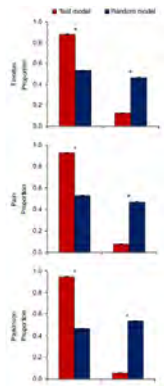
   Frequency bands: delta, theta, alpha, beta, gamma

2. Feed SVM EEGs of tinnitus patients and HC
   1. Tell SVM which are tinnitus
   2. SVM will differentiate between tinnitus and HC EEGs based on ROIs and frequency bands
   3. Will classify all pain, PD, depression as tinnitus

3. Look at CFC in tinnitus vs pain + PD + depression + HC = spatially restricted to auditory cortex
   1. Do same for pain, PD and PD



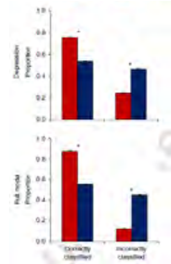




Tinnitus: 88%

Pain: 93%

Parkinson's Disease: 94%



Depression: 75%

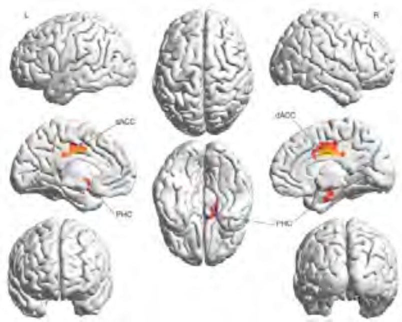
TCD: 88%

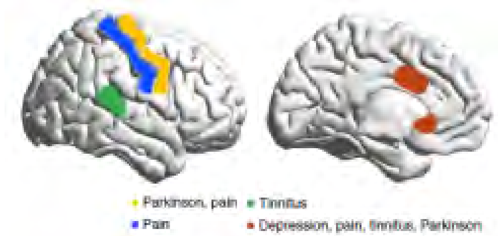
Vanneste 2018

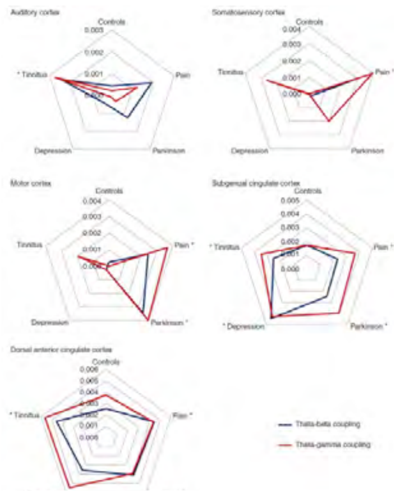
Thalamocortical dysrhythmia

Common β activity

Different θ-β & θ-γ CFC







Vanneste 2018

rTMS for tinnitus

Cochrane 2011 (Meng 2011)

Very limited support for the use of low-frequency rTMS for the treatment of patients with tinnitus

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)
(Lefaucheur 2014)

The effects of 1 Hz rTMS of Left TPC for tinnitus is level C (possible efficacy)

Meta-analysis of left TPJ TMS (Tedde deMoraes 2017)

1 Hz rTMS in contrast to HF TMS is superior to placebo (Hedges' g = 0.36; 95% CI 0.11–0.61) for chronic tinnitus, but low effect size.

TMS

Table 8
rTMS studies in tinnitus (target: temporal or temporoparietal cortex).

Articles	Number of patients	Target, coil type (placement)	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
Single sessions							
Plewnia et al. (2003)	14 (active: 14; control: 14)	Various scalp positions, F8c (10–20 EEG system)	Stimulation of non-auditory cortical areas and tilted coil	10 Hz, 120% RMT	30 pulses, 1 session	Significant tinnitus reduction (58% responders) after left temporoparietal stimulation	III
De Ridder et al. (2005)	114	Auditory cortex contralateral to tinnitus, F8c (anatomical landmarks)	Tilted coil	1.5/10/20 Hz, 90% RMT	200 pulses, 1 session	Significant tinnitus reduction (53% responders to active stimulation vs. 33% responders to sham stimulation); better results at 20 Hz for "old" tinnitus	III
Folmer et al. (2006)	15	Right or left TPC, F8c (10–20 EEG system)	"Noisy" sham coil	10 Hz, 100% RMT	150 pulses, 1 session	Significant tinnitus reduction (40% responders to active stimulation (2/3 contralateral to tinnitus; 1/3 ipsilateral) vs. 13% responders to sham stimulation)	III
De Ridder et al. (2007a)	46	Auditory cortex contralateral to tinnitus, F8c (anatomical landmarks)	Tilted coil	5/10/20 Hz 'tonic' or 'burst', 90% RMT	200 pulses, 1 session	Only 14 patients who had no response to sham rTMS were analysed: 'burst' stimulation more effective than 'tonic' stimulation on narrow band/white noise tinnitus; no difference for pure tone tinnitus	III
Meeus et al. (2009a)	64	Auditory cortex contralateral to tinnitus, F8c (anatomical landmarks)	Tilted coil	1.5/10/20 Hz 'tonic' or 'burst', 50% MSO	200 pulses, 1 session	Only 50 patients who had no response to sham rTMS were analysed: 'burst' stimulation more effective than 'tonic' stimulation on bilateral narrow band tinnitus; no difference for pure tone tinnitus; better effects in patients with lower MT; no difference for pure tone tinnitus	III
Lorenz et al. (2010), Müller et al. (2013)	10	Auditory cortex contralateral to tinnitus, F8c (10–20 EEG system)	Tilted coil	1/10 Hz, c/iTBS	1000 pulses (1/10 Hz)/600 pulses (c/iTBS), 1 session	Significant tinnitus reduction for 1 Hz rTMS and cTBS; effect correlated to the variation of alpha power, gamma power and 'auditory steady-state responses' measured on magnetoencephalography	III
Recommendation: possible effect of a single session of "burst" or LF rTMS of the auditory cortex (contralateral to the affected ear) in tinnitus (Level C)							
Repeated sessions							
Kleinjung et al. (2005)	14	Auditory cortex activation area in PET, F8c (FDG-PET-guided navigation)	Sham coil	1 Hz, 110% RMT	2000 pulses, 5 sessions	Significant tinnitus reduction (prolonged effect up to 6 months)	III
Rossi et al. (2007a)	16	Left TPC, F8c (navigation and 10–20 EEG system)	Tilted coil combined with electrical skin stimulation	1 Hz, 120% RMT	1200 pulses, 5 sessions	Significant tinnitus reduction (no prolonged effect)	III
Khedr et al. (2008, 2009c)	66 (active: 16,17,17; control: 16)	Left TPC, F8c (10–20 EEG system)	Stimulation of non-auditory cortical areas	1/10/25 Hz, 100% RMT	1500 pulses, 10 sessions	Significant tinnitus reduction for all active conditions (prolonged effect up to 12 months); less efficacious for tinnitus with longer duration	III
Anders et al. (2010)	42 (active: 22; control: 20)	Auditory cortex, F8c (10–20 EEG system)	Tilted coil	1 Hz, 110% RMT	1500 pulses, 10 sessions	Significant tinnitus reduction (not initially, but at 3-6 months after the stimulation)	II
Marcondes et al. (2010)	19 (active: 10; control: 9)	Left superior temporal cortex, F8c (10–20 EEG system)	Sham coil	1 Hz, 110% RMT	1020 pulses, 5 sessions	Significant tinnitus reduction (prolonged effect up to 6 months); effect correlated to a reduced activity of inferior temporal cortices in SPECT	III
Mennemeier et al. (2011)	21	Auditory cortex activation area in PET, F8c (FDG-PET-guided navigation)	Sham coil combined with electrical skin stimulation	1 Hz, 110% RMT	1800 pulses, 5 sessions	Significant tinnitus reduction (43% responders, 33% improvement); no correlation with activity changes in PET	II
Piccirillo et al. (2011)	14	Left TPC, F8c (navigation and 10–20 EEG system)	Sham coil	1 Hz, 110% RMT	1500 pulses, 10 sessions	Non-significant tinnitus reduction	III
Chung et al. (2012)	22 (active: 12; control: 10)	Left auditory cortex, F8c (navigation)	Sham coil	cTBS, 80% RMT	900 pulses, 10 sessions	Significant tinnitus reduction; more efficacious on emotional component of tinnitus	III
Plewnia et al. (2012)	48 (active: 16,16; control: 16)	Bilateral temporal cortex or TPC, F8c	Active stimulation	cTBS, 80% RMT	900 pulses, 20 sessions	Non-significant tinnitus reduction	III

(continued on next page)

Which factors influence outcome?

Tinnitus vs healthy controls (Wang 2017)

Lower resting motor threshold

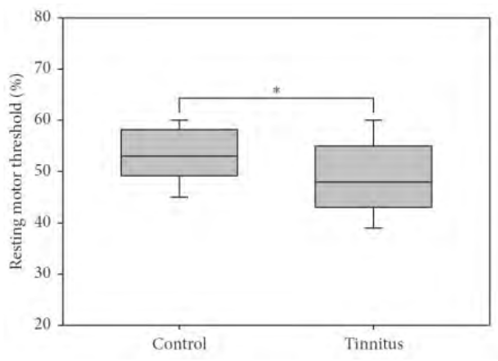
Responders have

Tinnitus of shorter duration (De Ridder 2005, Kleinjung, Wang 2017)

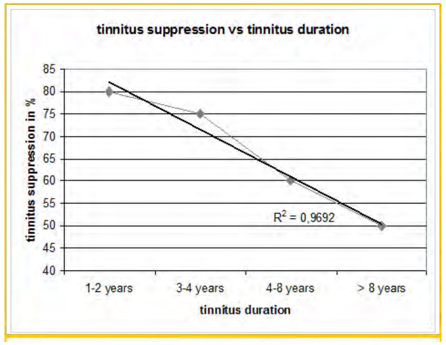
No hearing loss (Wang 2017) Why?

Less sleep problems (Wang 2017)

FC between AC and parahippocampus (De Ridder 2014) Why?



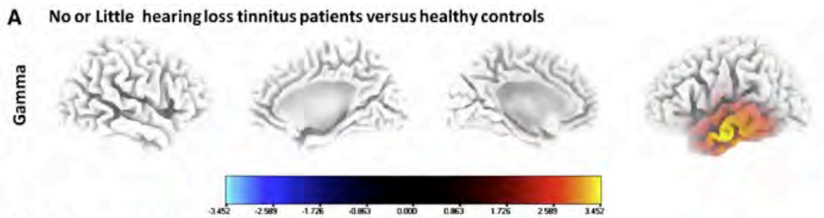
Wang 2017

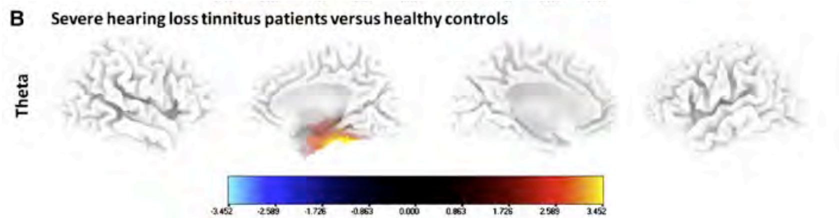


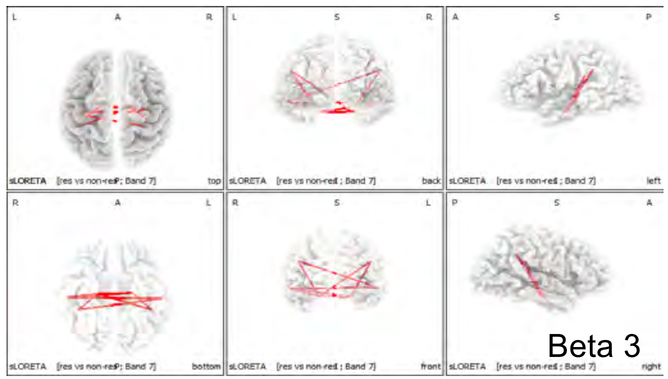
De Ridder 2005

Why is no hearing loss important?

Why is functional connectivity important?





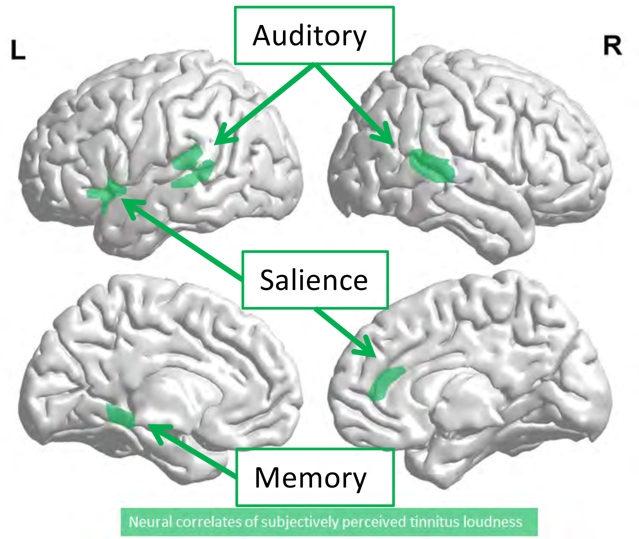


De Ridder 2014

Vanneste 2015

Activity & connectivity correlates for loudness

Activity



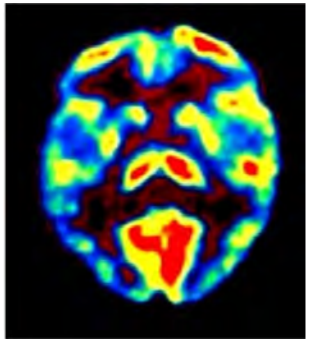
Connectivity

De Ridder, 2015

2.Tinnitus is caused by auditory cortex

Treat hyperactivity in auditory cortex…

PET

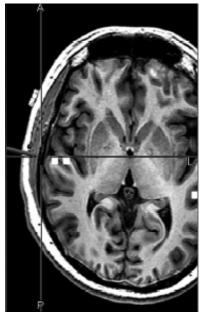


Langguth 2007

EEG

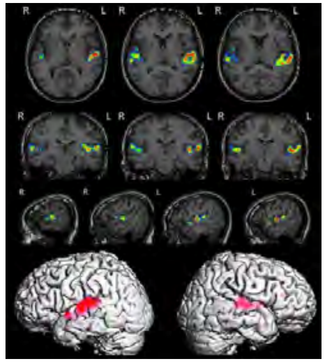
Van der Loo 2009

MEG



Seidman 2008

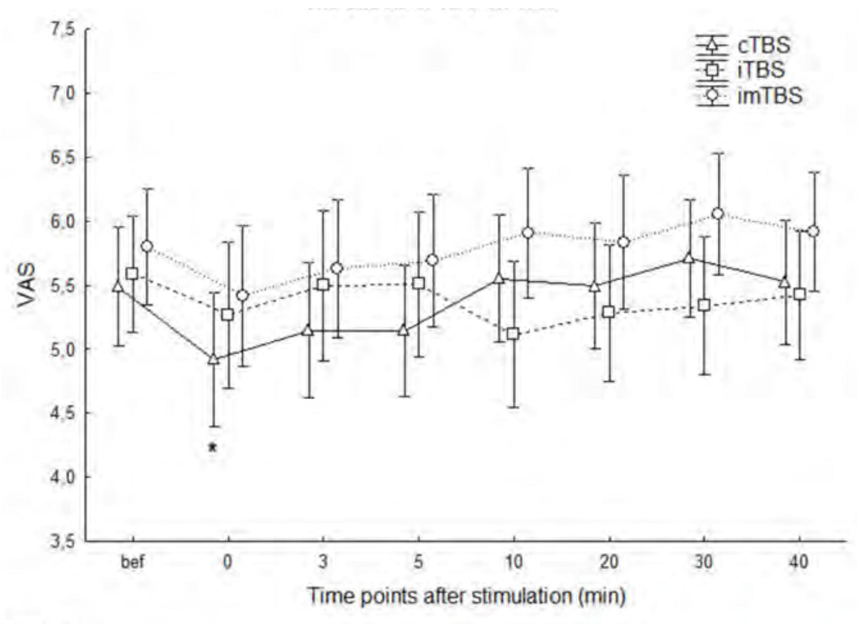
fMRI



De Ridder 2004

…and if treatment doesn’t work, change stimulation design (De Ridder 2007)

All burst stimulations seem to have similar effect: no effect



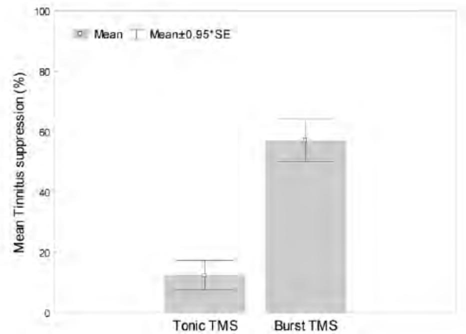
Poreisz 2009

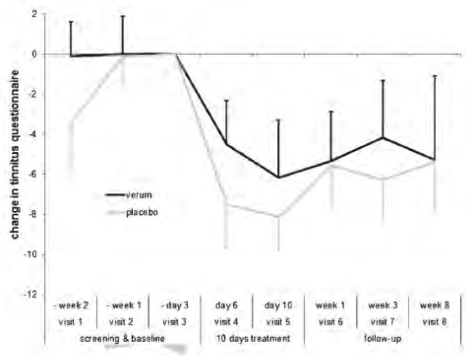
Preference doesn't mean it really works

Burst is better than tonic TMS for noise-like tinnitus (De Ridder 2007)

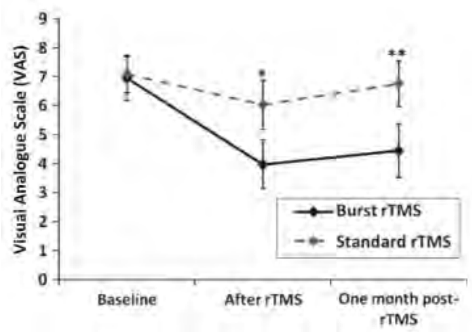
CTBS is better than HF TMS (Forogh 2014)

CTBS no better than placebo with or without neuronavigation (Schecklmann 2016, 2016, Plewnia 2012)

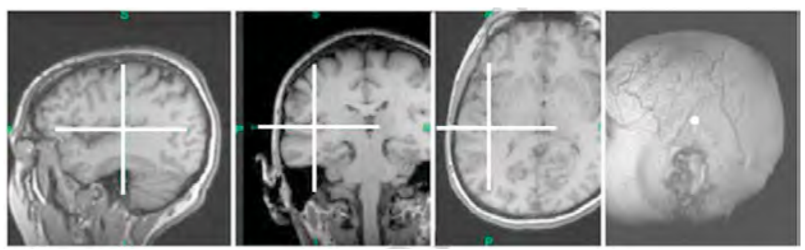




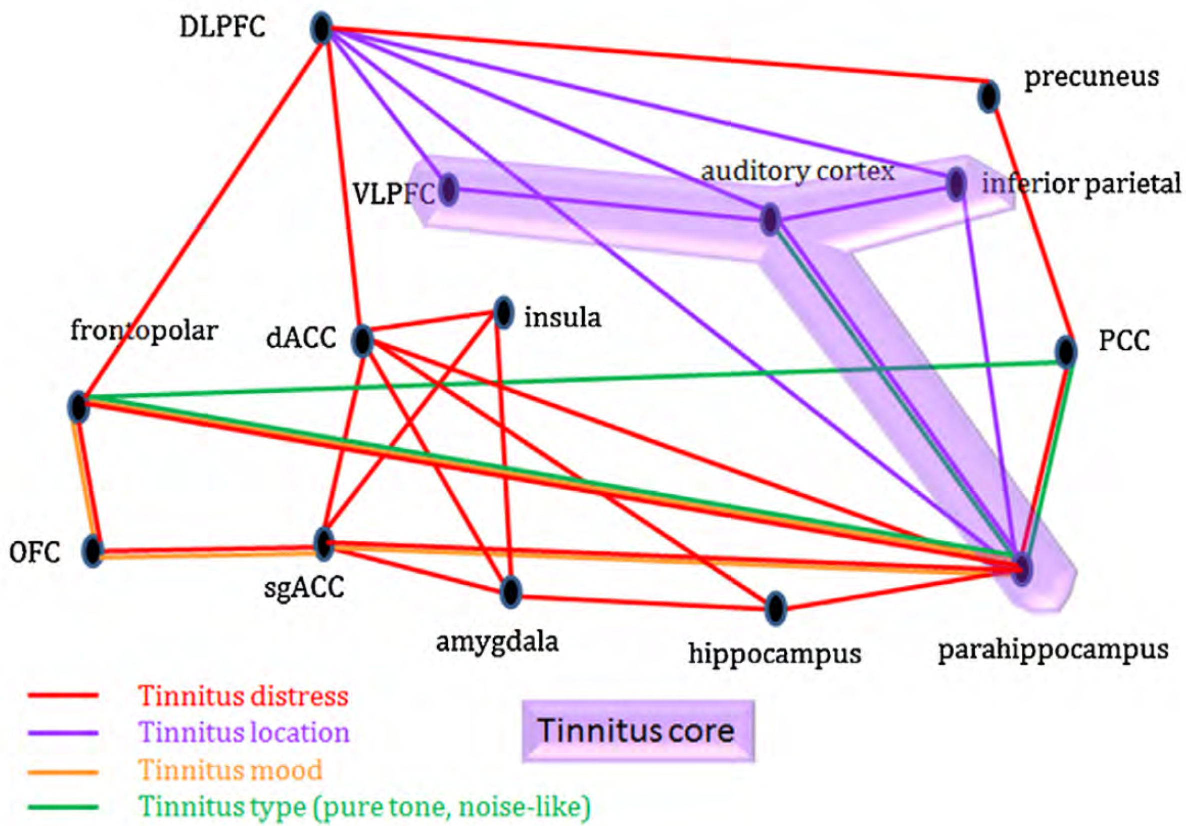
Schecklmann 2016



Forogh 2014



3. Tinnitus is emergent property of networks



De Ridder et al. Neurosci Biobehav Rev 2014

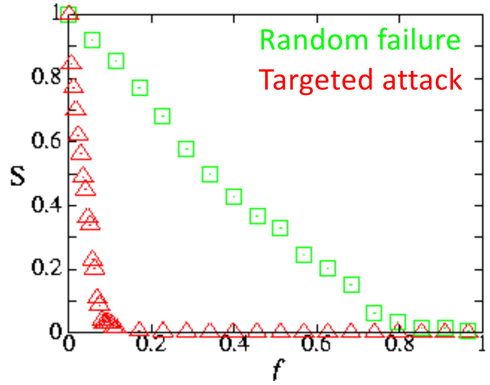
Graph theoretical analysis of brain network topology

Robustness refers to the structural integrity of the network following deletion of nodes or edges

Random failure

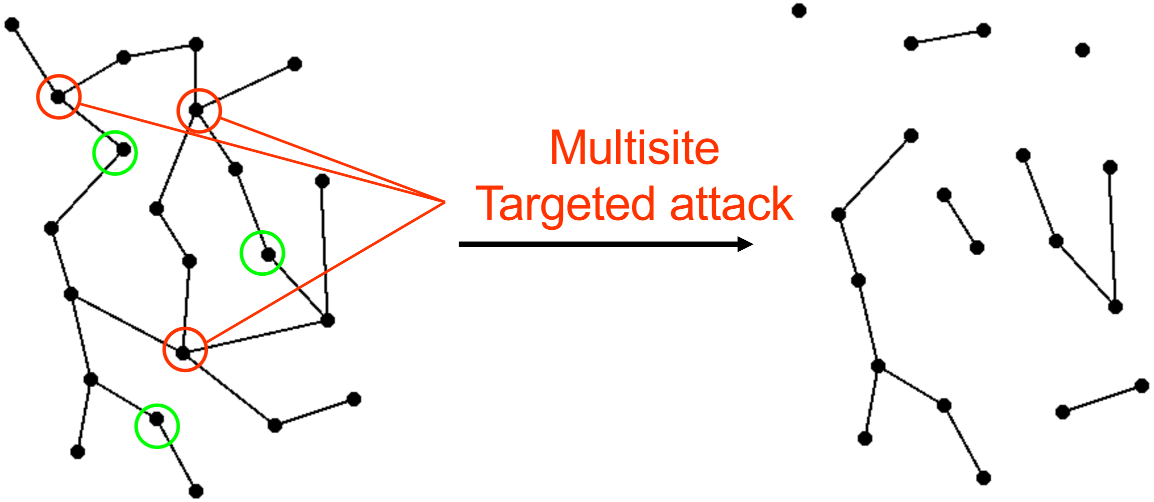
Targeted attack

Complex systems maintain their basic functions, even under errors and failures, but not targeted attacks

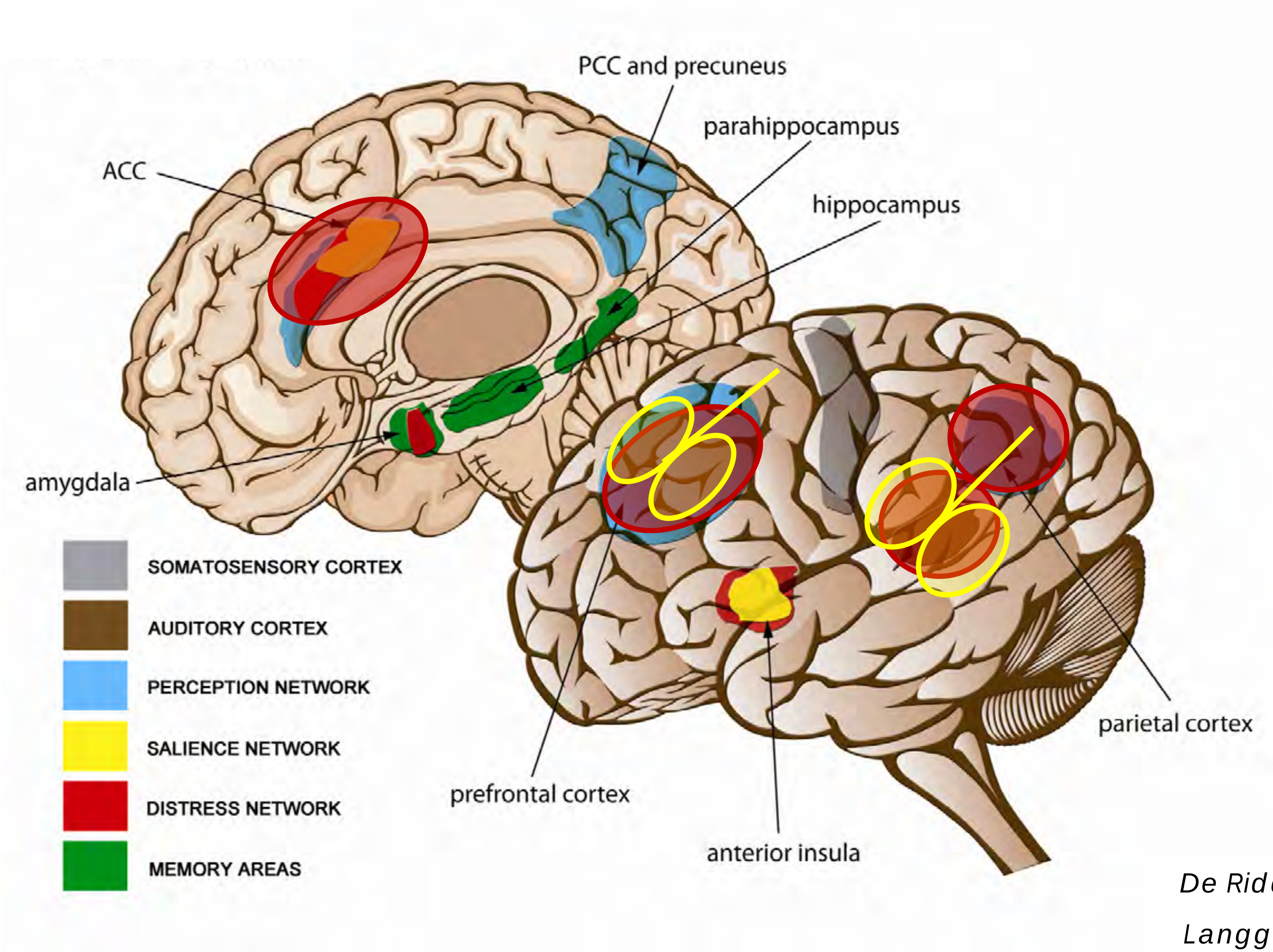


Albert 2000

Tinnitus network



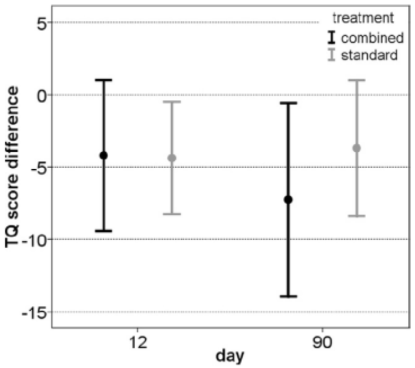
Multitarget TMS



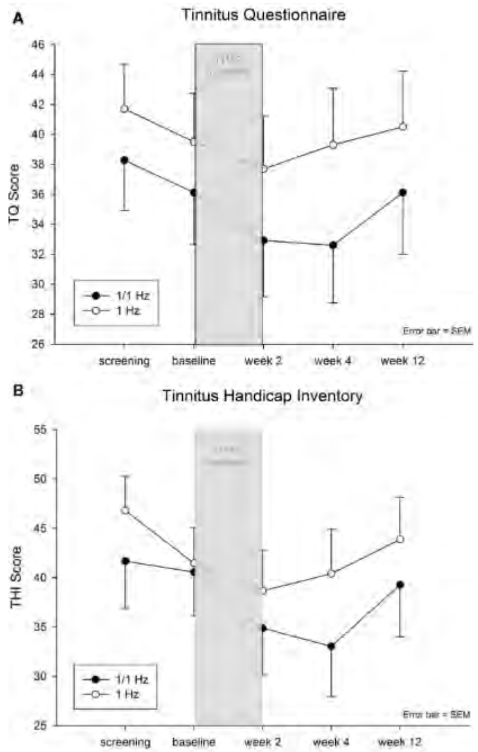
De Ridder 2011

Langguth 2013

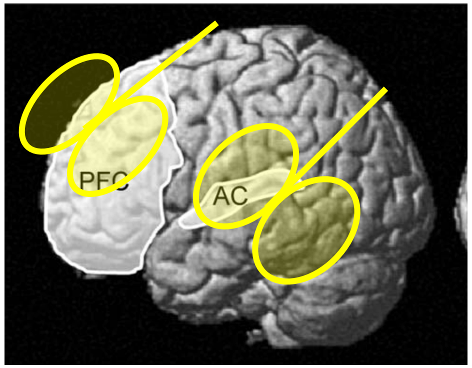
Frontal + temporal TMS



Kleinjung 2008

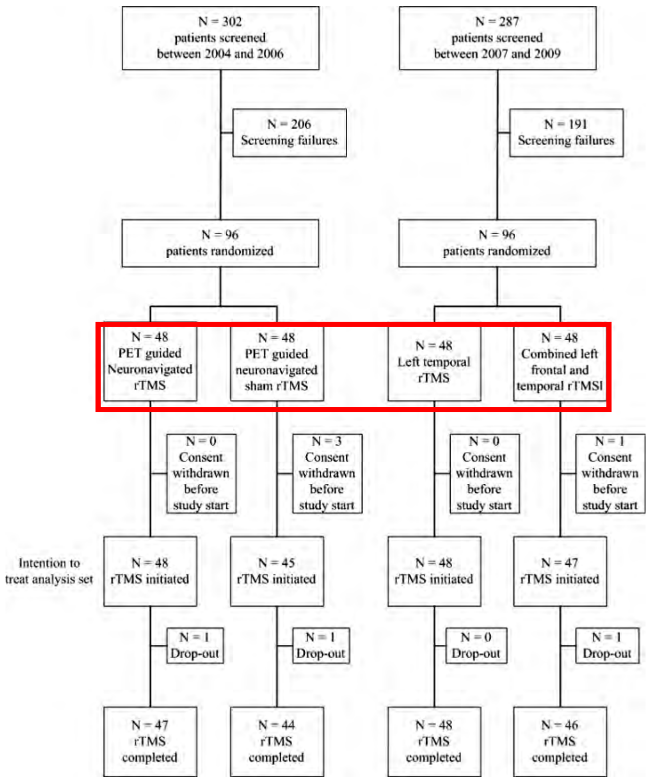


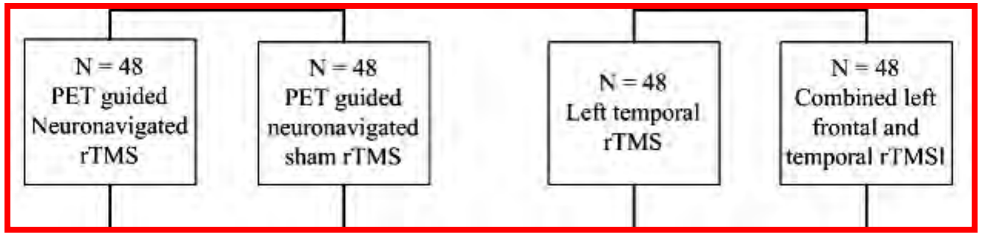
Kreuzer 2011

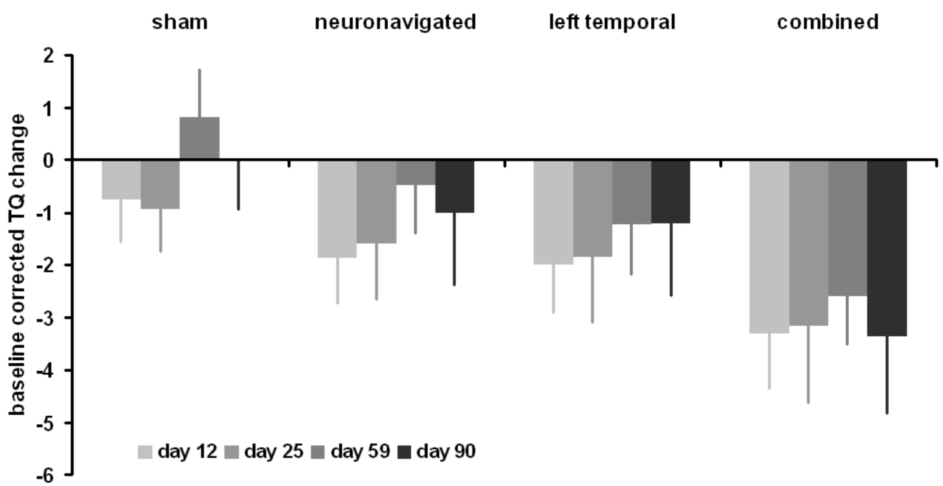


Not significantly better than standard temporal rTMS

Randomised four-armed Study (N = 192)





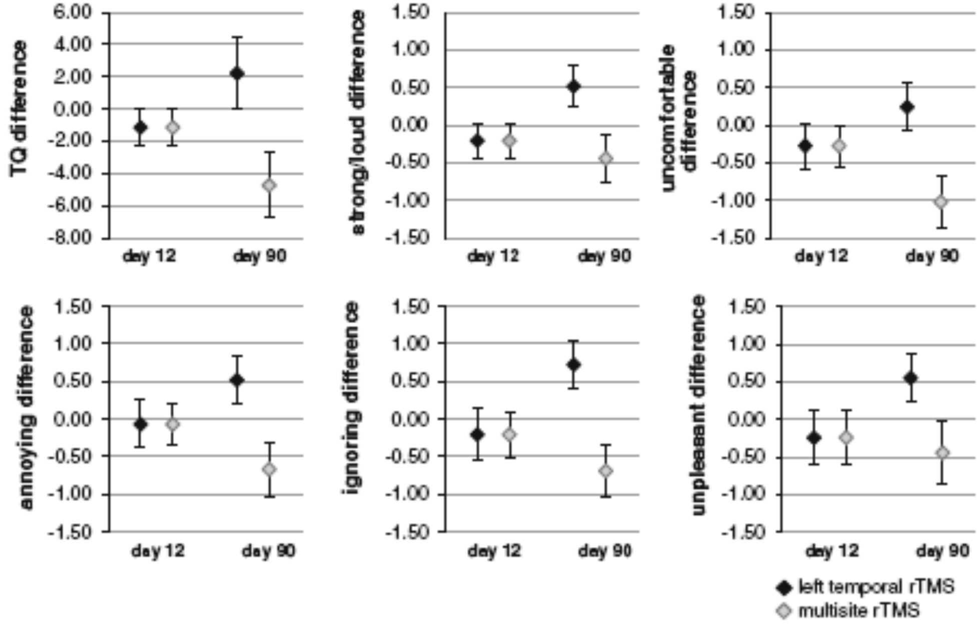


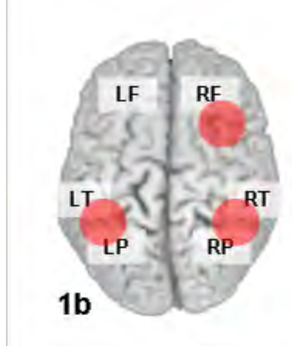
Not significantly better than sham

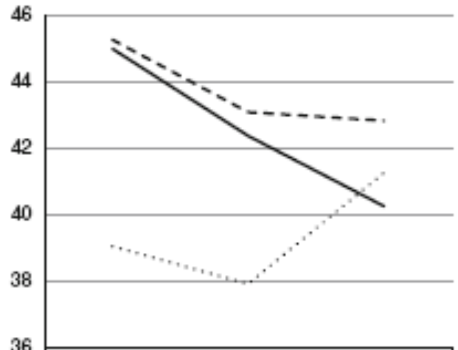
Not clinically better in relevant way (>5 points for TQ, Adamchic 2012, 6-7 points for THI, Zeman 2011)

Langguth 2012

Triple TMS







	baseline	day 12	day 90
multisite rTMS	44.98	42.36	40.24
left temporal + frontal rTMS	45.25	43.07	42.81
left temporal rTMS	39.03	37.90	41.24

No clinically better in relevant way (>5 points) than temporal or frontal + temporal rTMS *Lehner 2013*

Conclusion

Auditory cortex rTMS is no universal treatment for tinnitus
Burst TMS might be better for noise-like tinnitus
Multitarget rTMS might be superior
Depending on hearing loss or not AC or parahippocampus might be preferred target

dirk.deridder@otago.ac.nz

Brain Research consortium for Advanced International, Innovative & Interdisciplinary Neuromodulation

Transcranial Magnetic Stimulation: Applications in Autism Spectrum Disorder

Lindsay M. Oberman, PhD

Clinical Program Leader
Center for Neuroscience and Regenerative Medicine
Research Assistant Professor, Department of Medical and Clinical Psychology
Uniformed Services University of Health Sciences

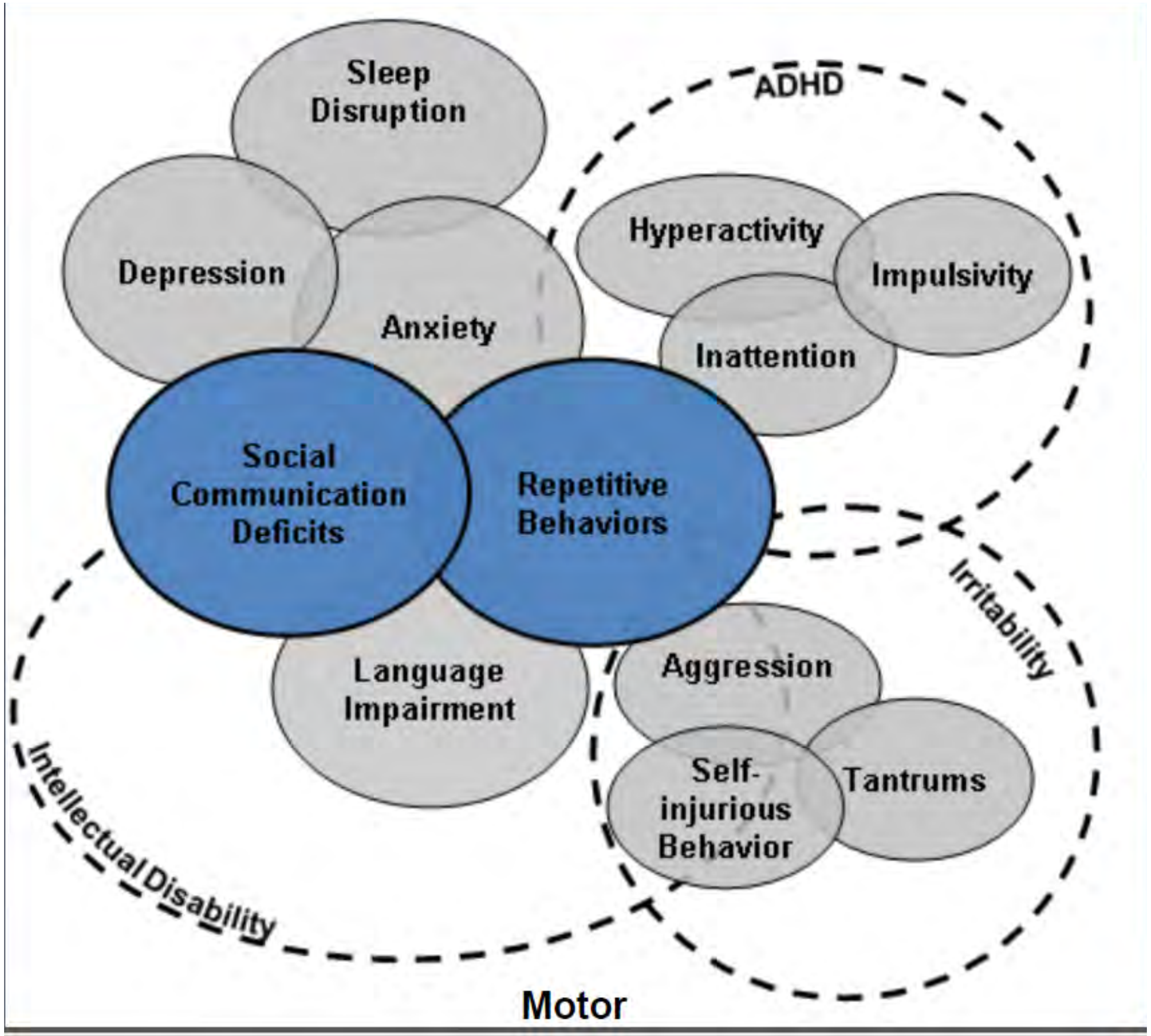
Special Volunteer, Noninvasive Neuromodulation Unit
National Institute of Mental Health, National Institutes of Health

Autism

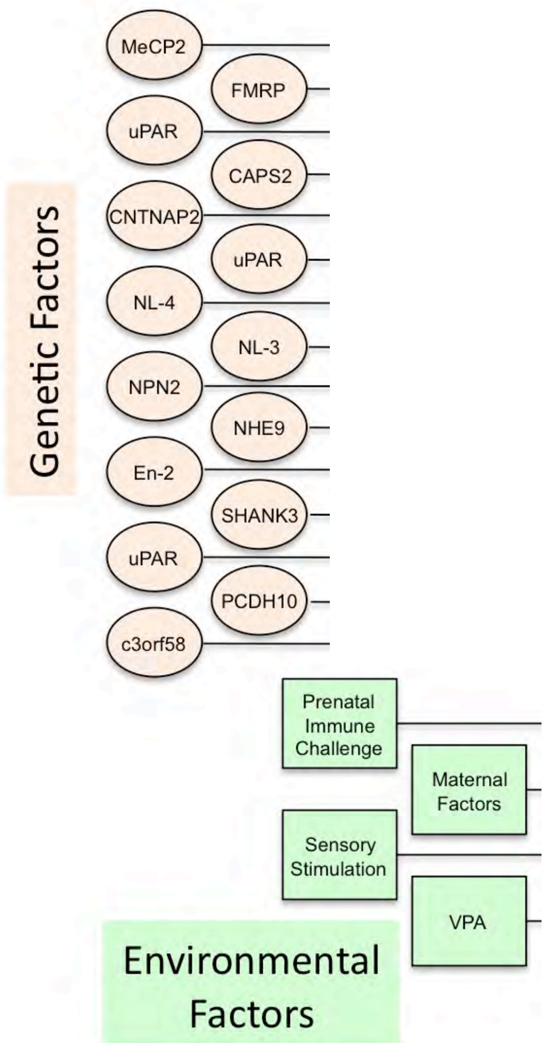
Autism: “A Behaviorally-Defined Neurodevelopmental Disorder”

-Dr. Isabelle Rapin (1928-2017)

Challenge: What Behavior?

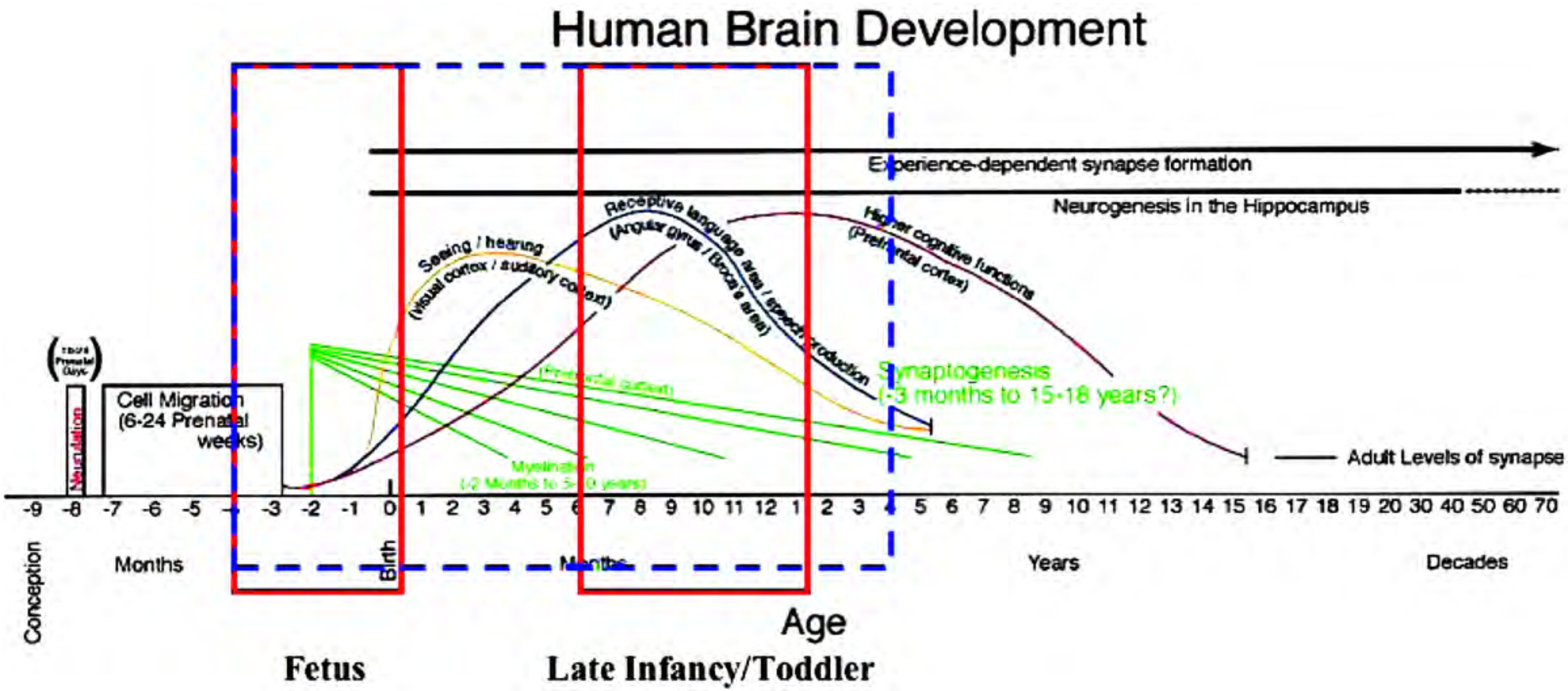


Challenge: How is Neurodevelopment Disordered?



Excitation/Inhibition Imbalance

Synaptic Plasticity

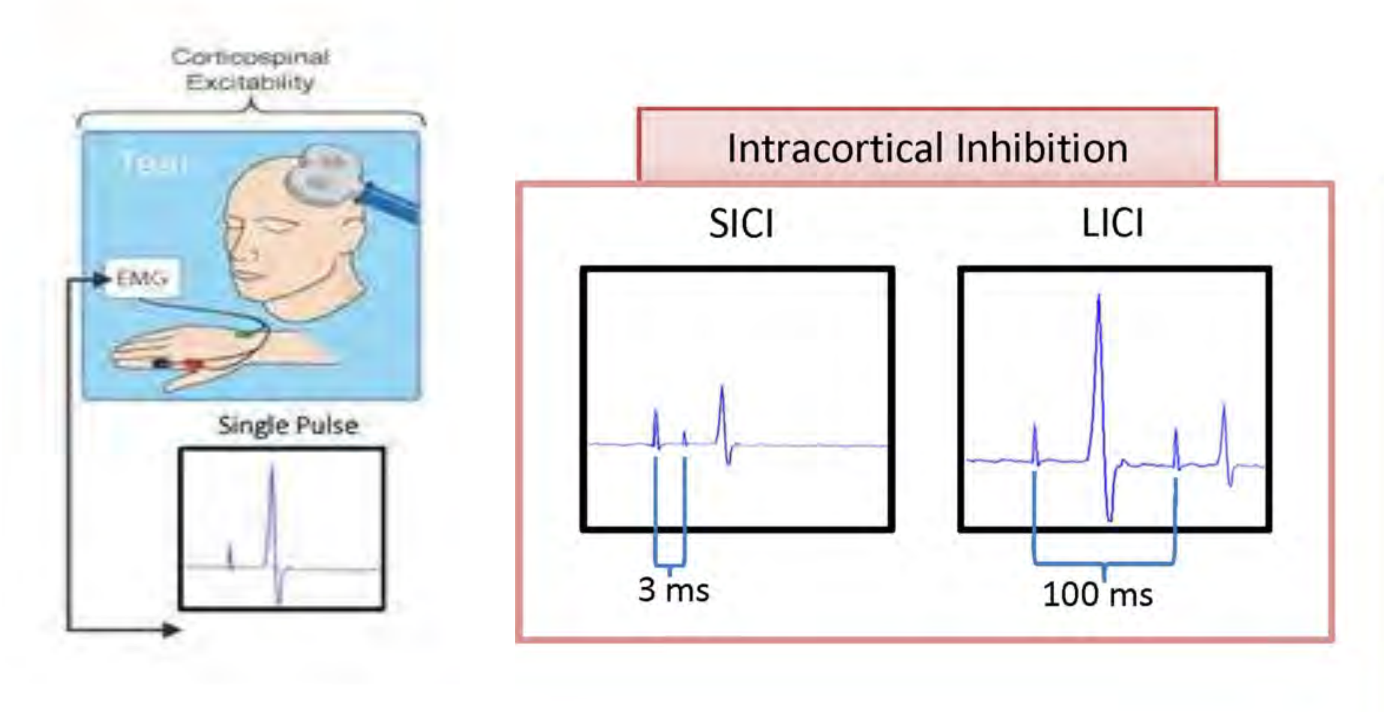


Georgieff and Innis, 2005

TMS as a Neuroscientific Probe of Brain Functioning

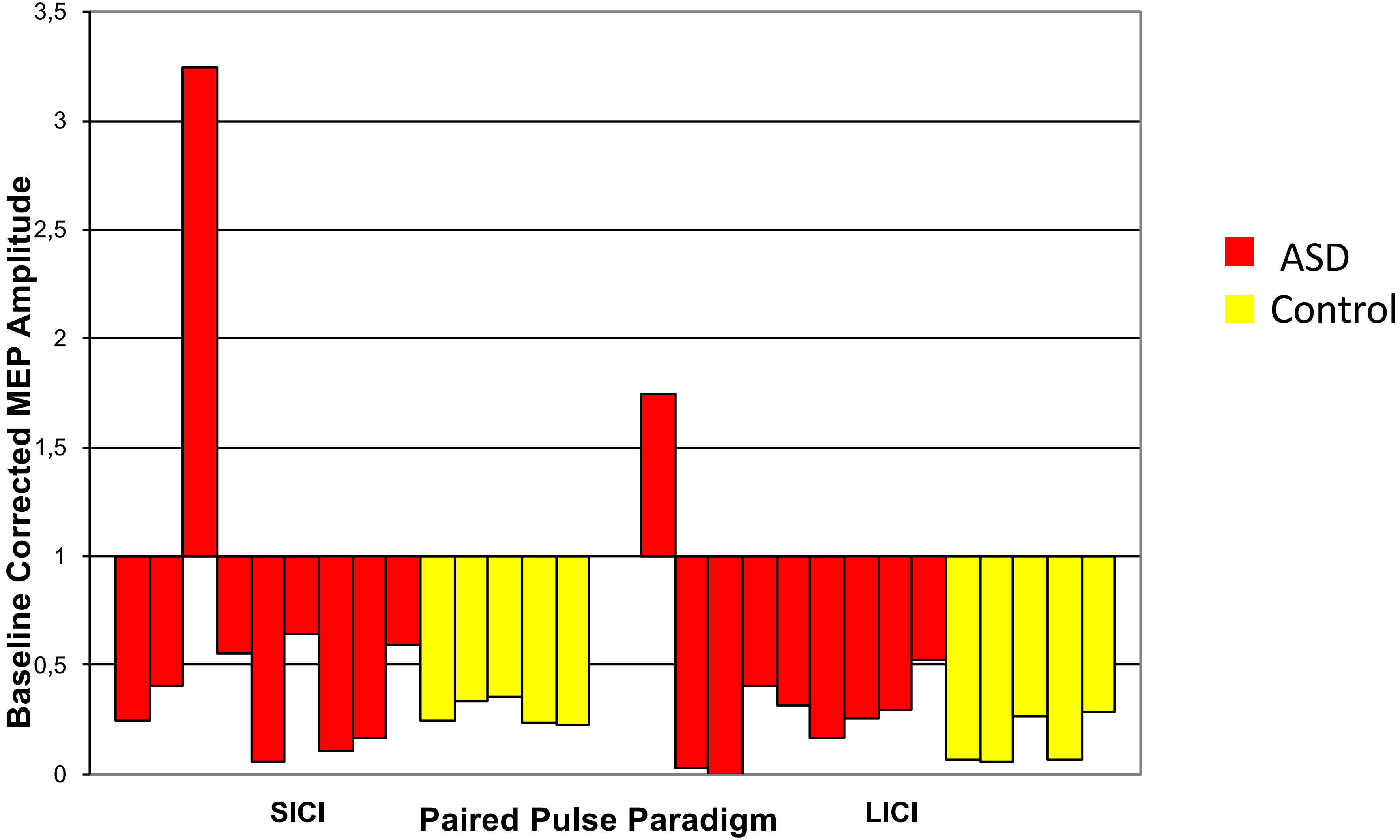
1. "Online" Single (or single burst) and Paired Pulse Paradigms
   - Effects last milliseconds-seconds (assuming no train effects)
   - Probes of Excitability and Intracortical Inhibition
     - Pathophysiology
   - Confirmation that you have "reached" your target
   - "Virtual Lesions"
     - Is activity in X region *required for* X behavior?
2. Single Sessions of rTMS: "Offline Paradigms"
   - Effects last minutes.
   - Plasticity
   - Target-engagement (modulation of target)
     - Short-term changes in physiology and/or behavior that can be measured with fMRI/EEG and/or behavioral tasks.
3. Multiple Sessions of rTMS "Offline Paradigms"
   - Effects last weeks-months
   - Therapeutic Clinical Trials

Intracortical Inhibition
Paired Pulse TMS (ppTMS)



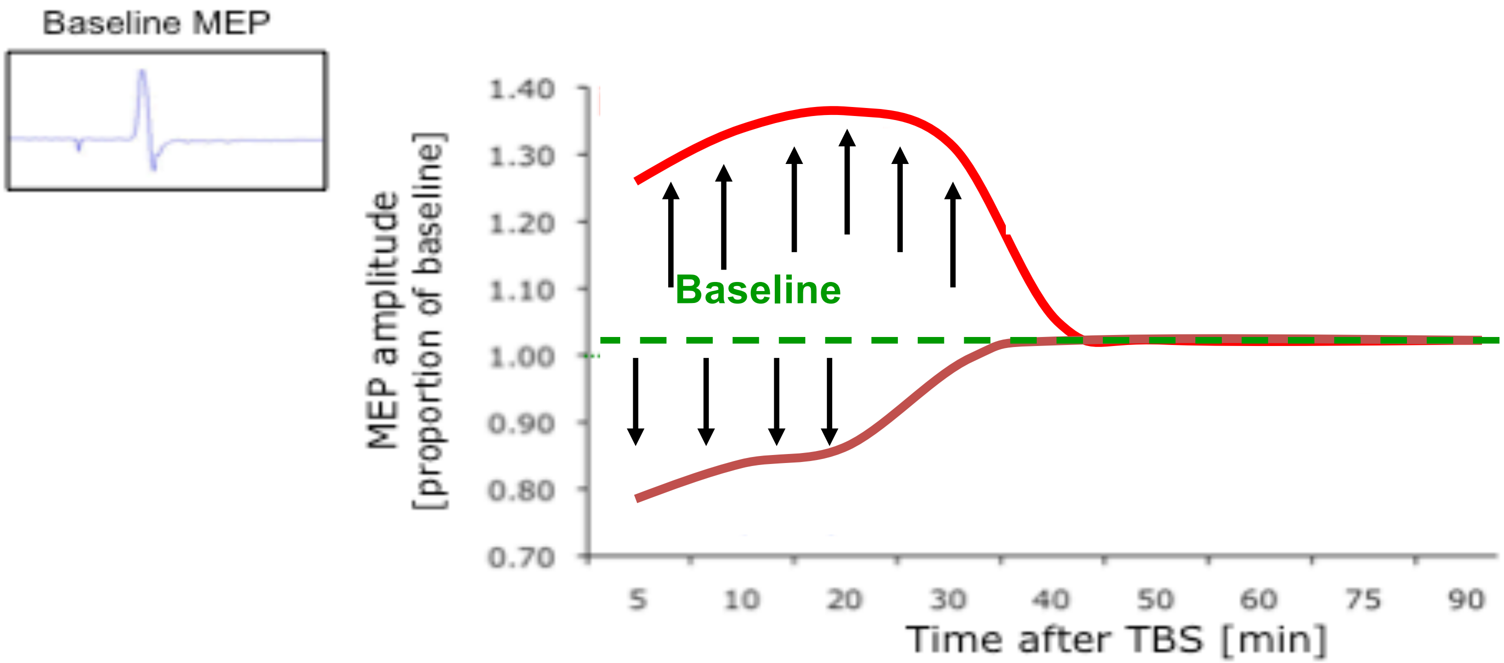
- SICI: GABA-A inhibitory mechanisms
- LICI: GABA-B inhibitory mechanisms

Intracortical Inhibition

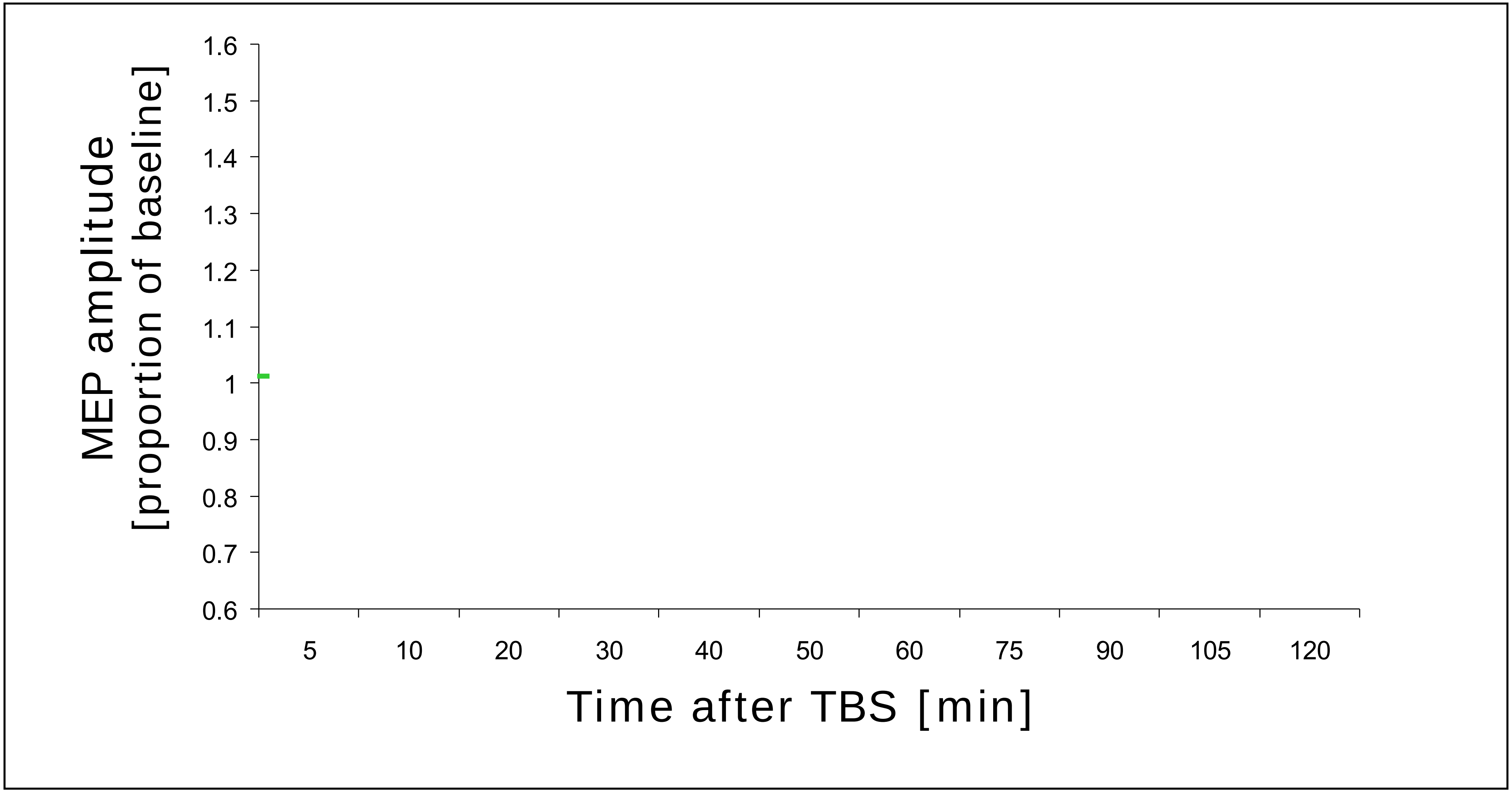


Oberman et al., 2010;
Oberman et al., in prep

Theta Burst Stimulation: rTMS modulation of GABA inhibitory control on excitatory synaptic plasticity

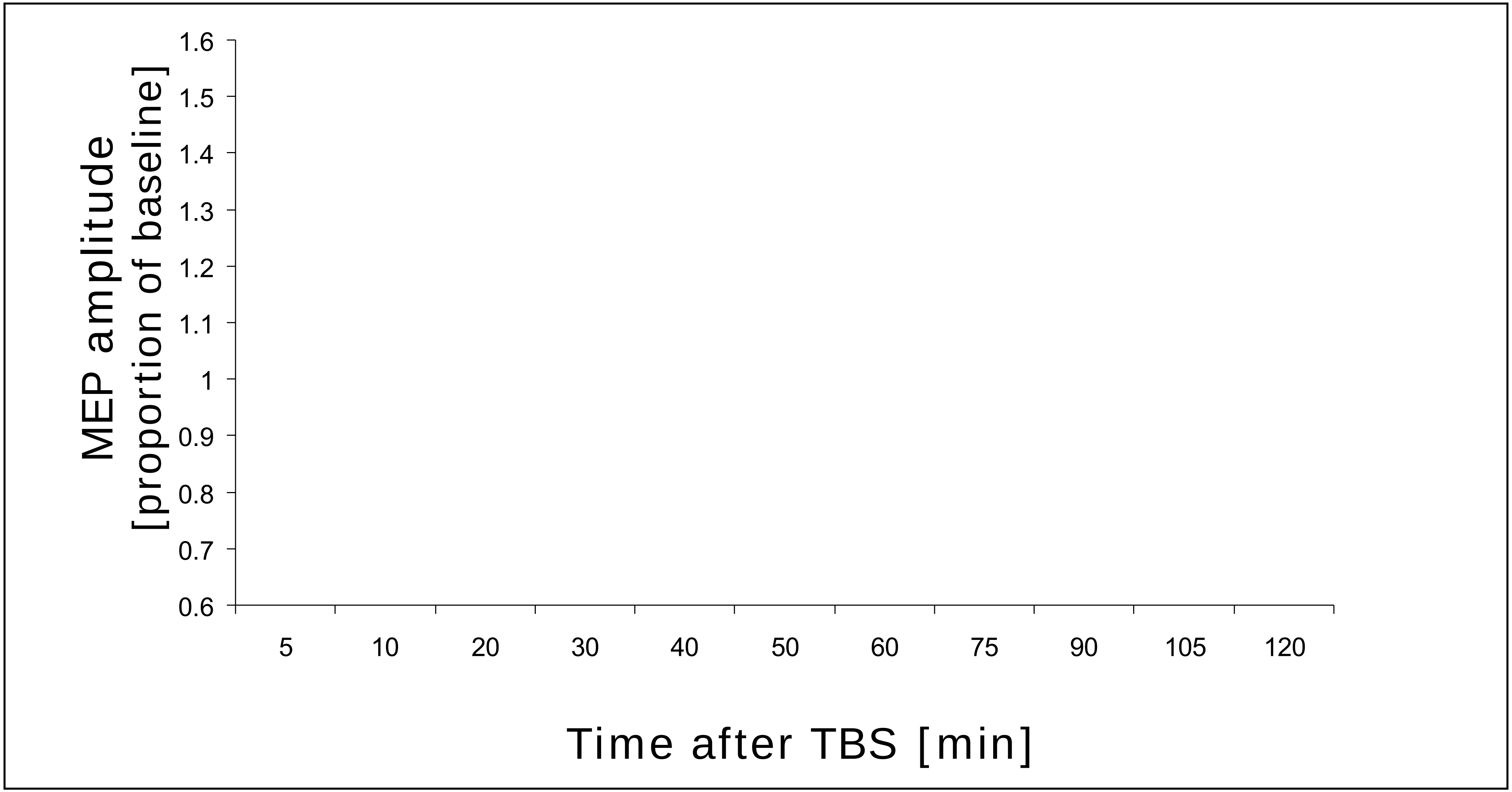


Theta Burst Results: Healthy Controls (n=20)



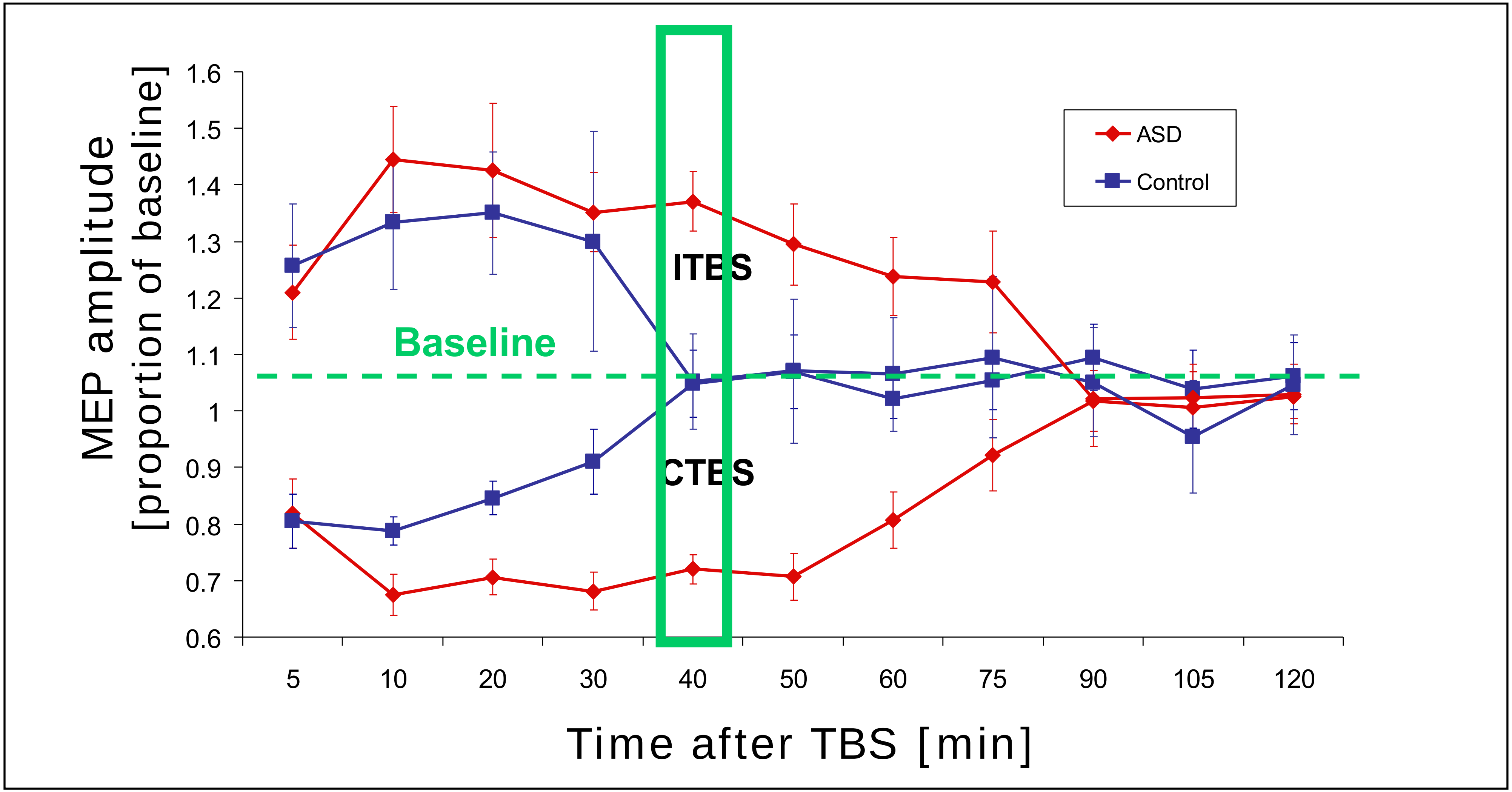
Oberman et al., 2012

Theta Burst Results: ASD (n=20)



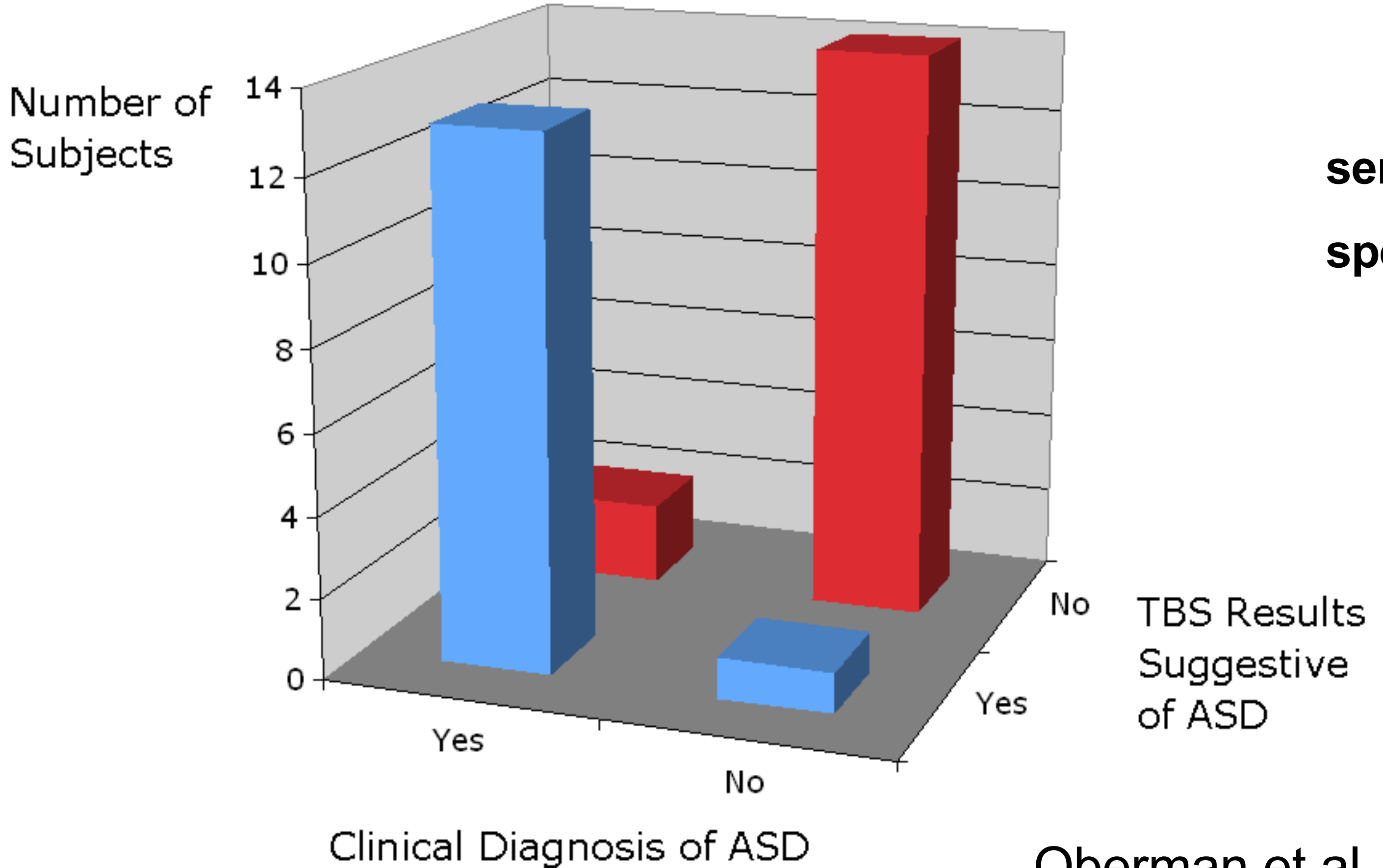
Oberman et al., 2012

Theta Burst Results: Both Groups



Oberman et al., 2012

Intersubject Reliability?



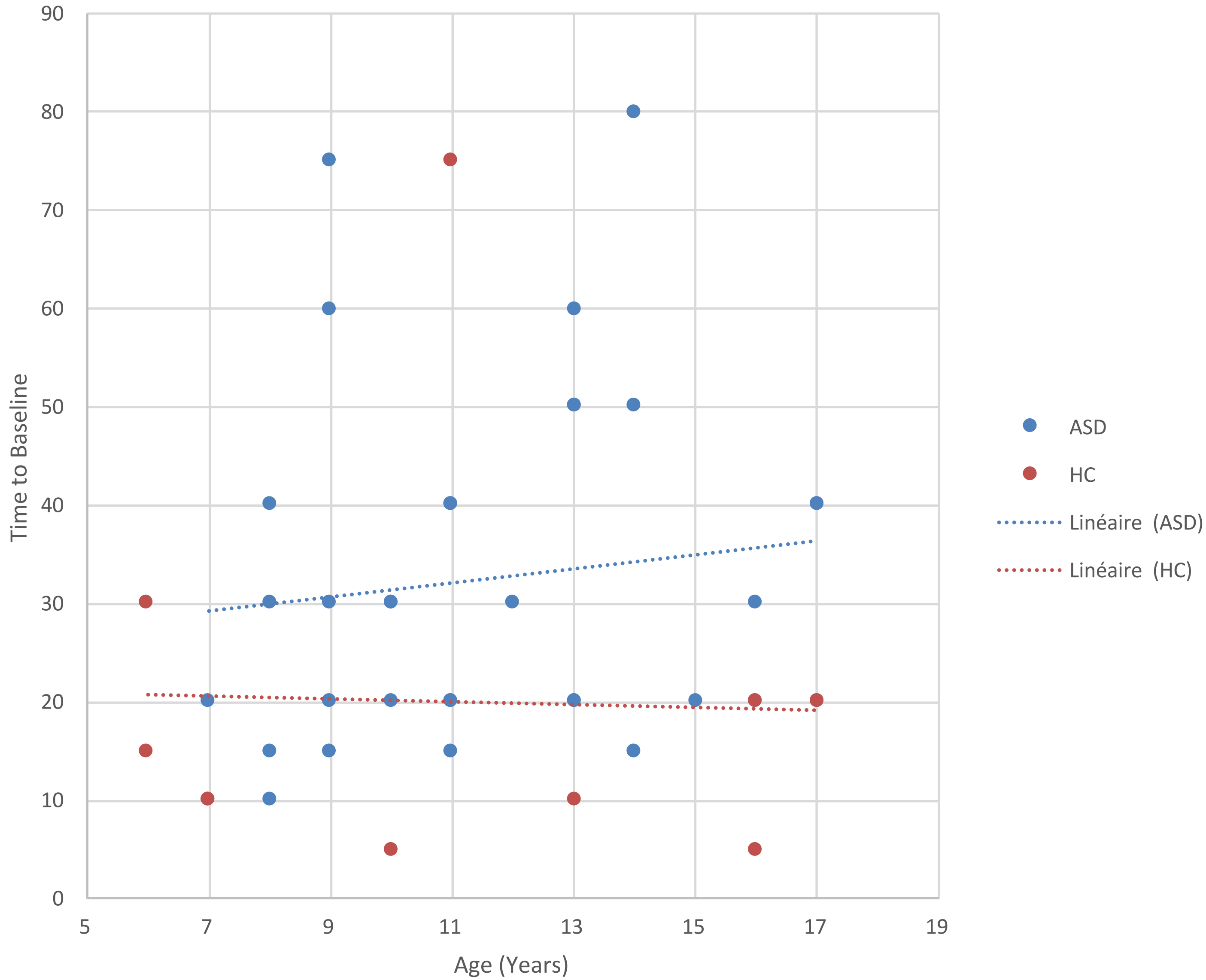
sensitivity = 0.87

specificity = 0.93

Oberman et al., 2012

n=15 in each group

Pediatric Population



Oberman et al., 2014; In Prep

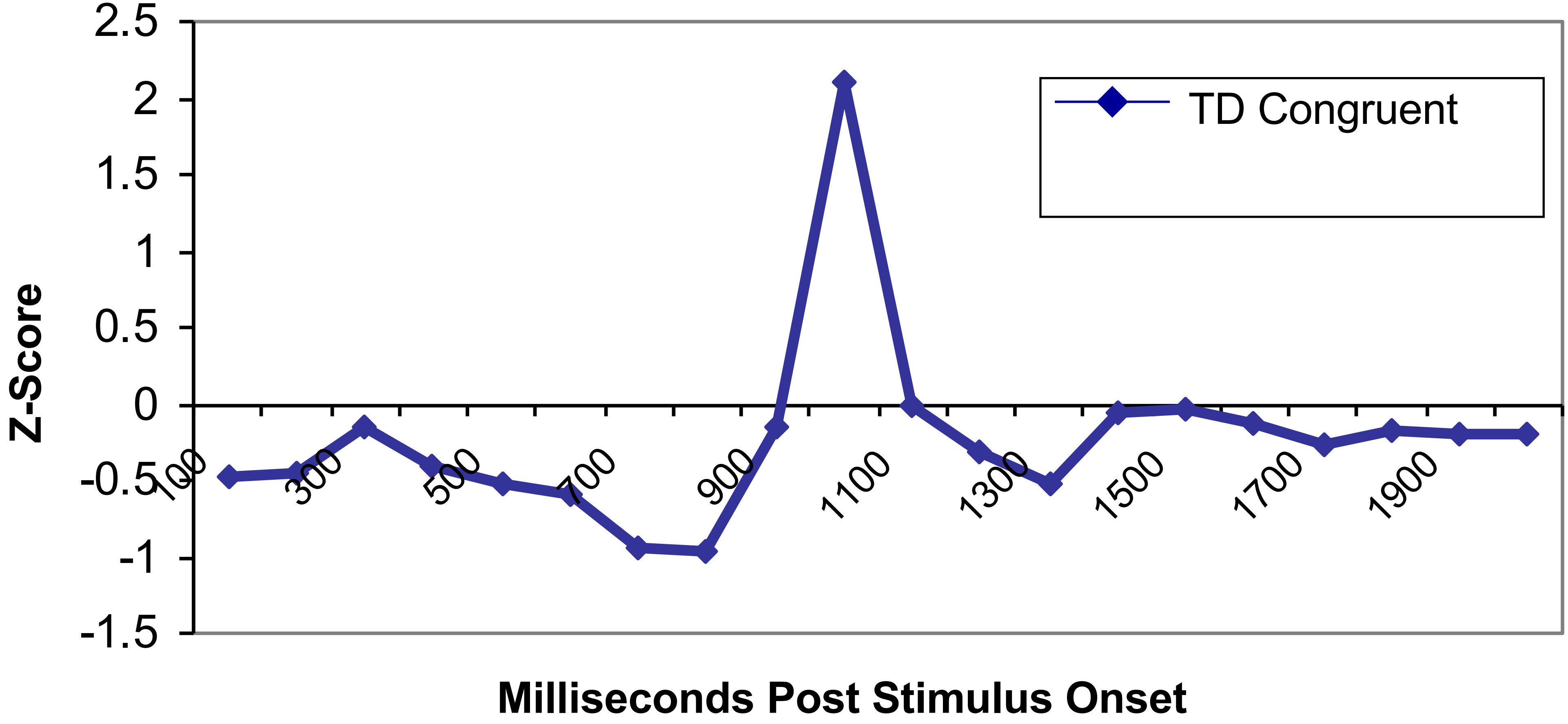
Summary of Findings from Intracortical Inhibition and Plasticity Studies in ASD

- Heterogeneity in response to ppTMS, perhaps related to underlying pathophysiology.
- Greater and Longer lasting response to cTBS in ASD with maximum group difference at 40 minutes post cTBS in adults.
- Response may increase with age in ASD group, but quite variable and limited normative data.

Development of Therapeutic rTMS Protocols in ASD

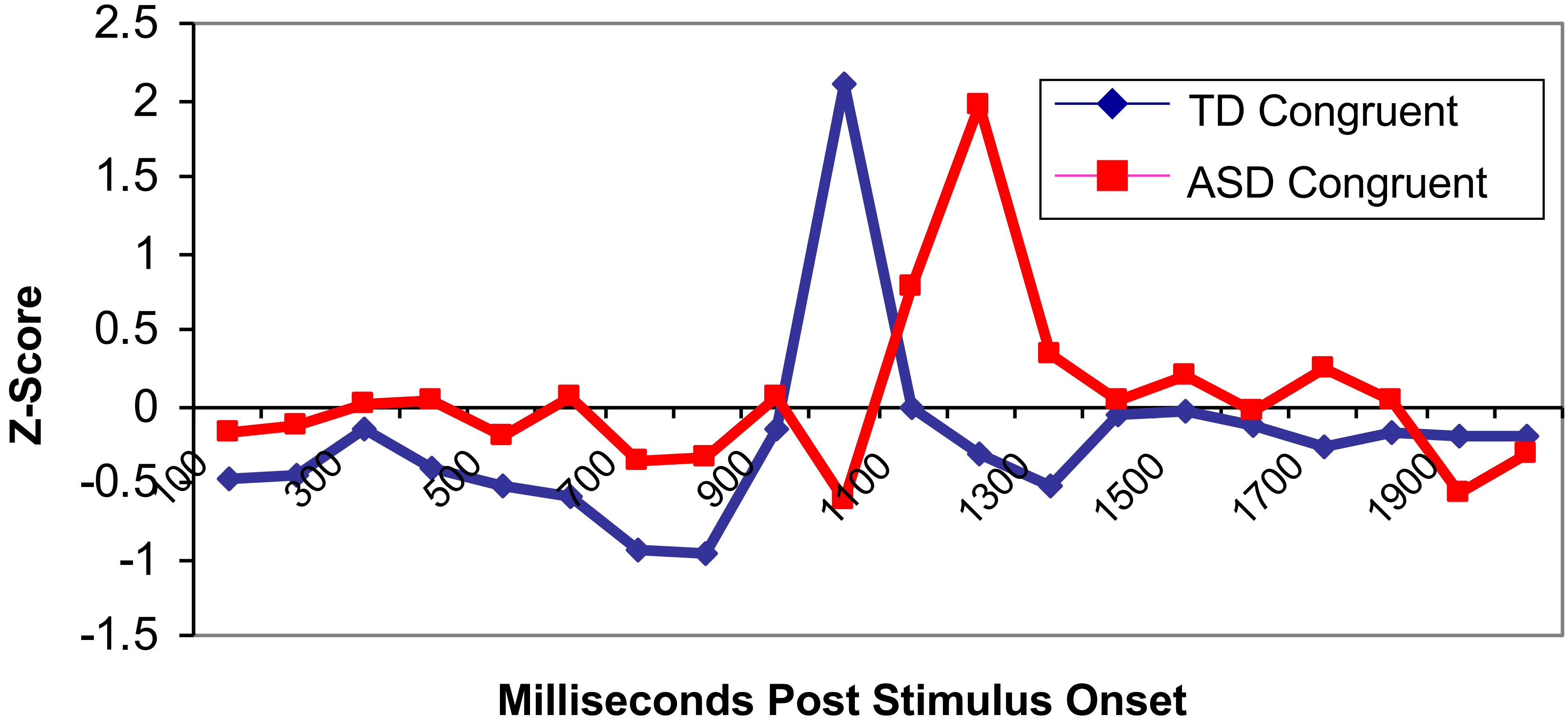
Processing of Facial Expression

Spontaneous Mimicry



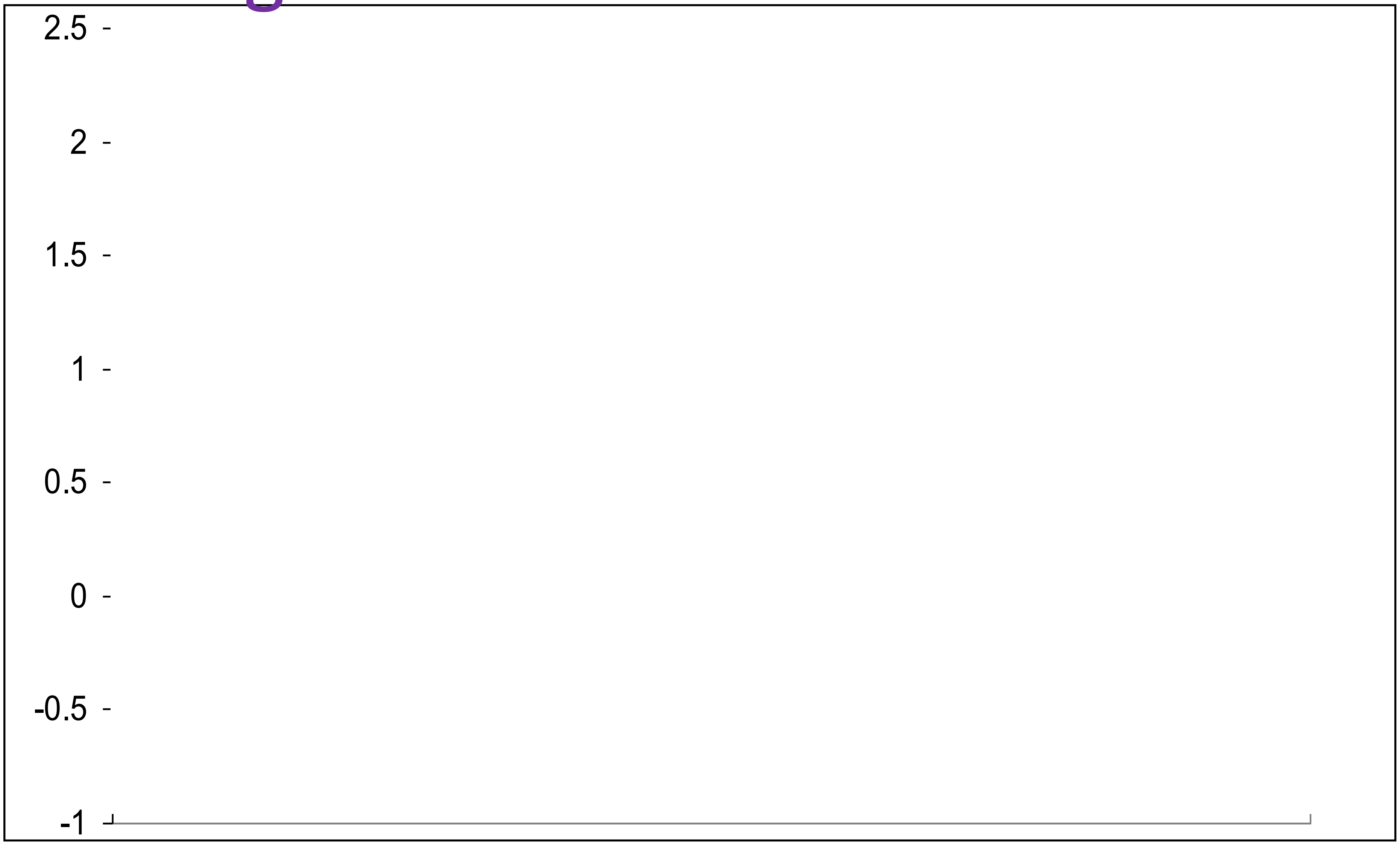
Oberman et al., 2009

Spontaneous Mimicry



Oberman et al., 2009

Spontaneous Mimicry following a single session of RH cTBS to IFG

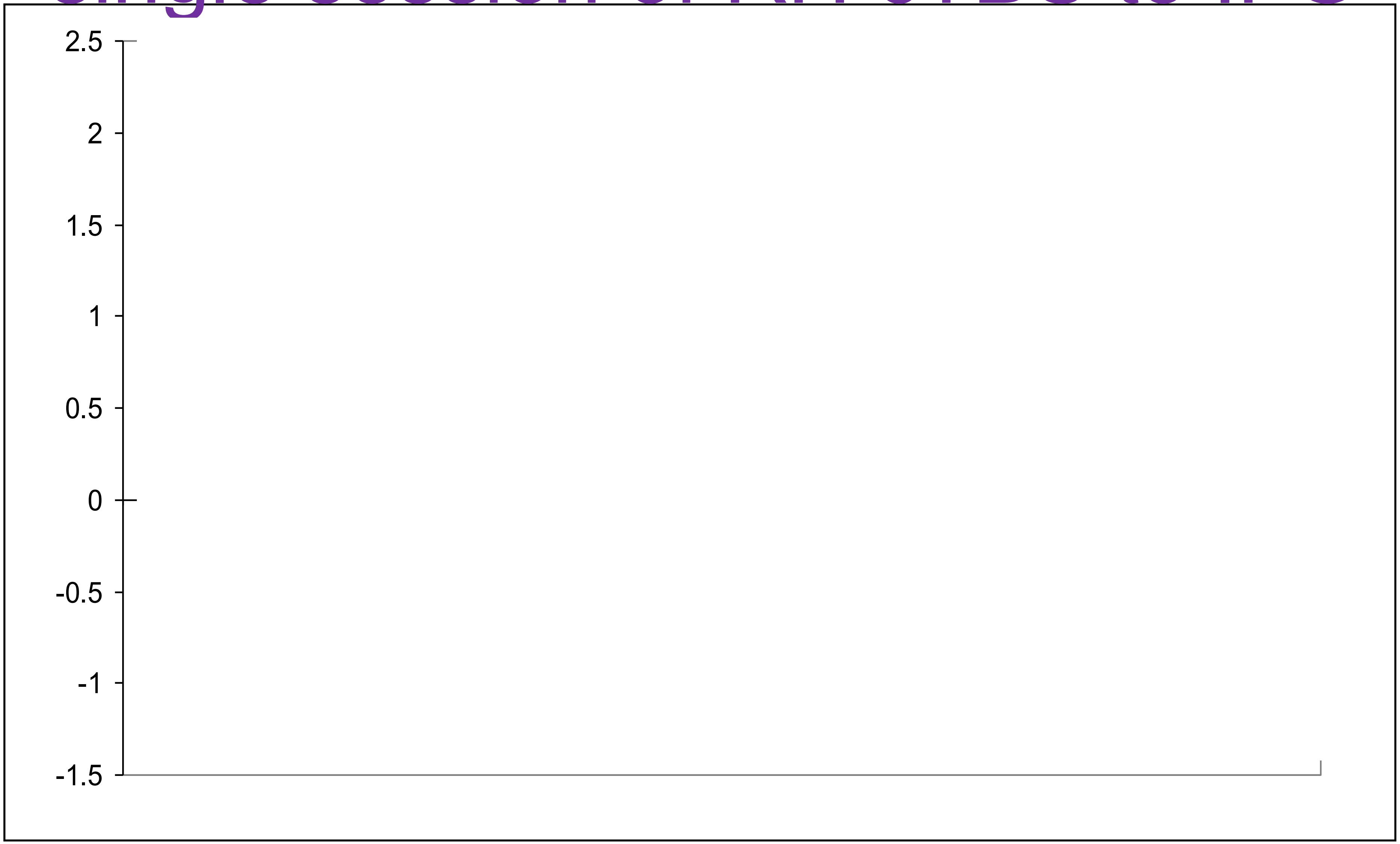


Fecteau, Oberman et al., in prep

Spontaneous Mimicry following a single session of RH cTBS to IFG

Fecteau, Oberman et al., in prep

Spontaneous Mimicry following a single session of RH cTBS to IFG



Fecteau, Oberman et al., in prep

Future Directions

- Application of rTMS to modulate task-related abnormalities in children with ASD
  - Language Processing
  - Somatosensory Hypersensitivities
- Applications of rTMS for the treatment of common Associated ASD Symptom Domains
  - Depression
  - Emotion Regulation and Irritability
  - Anxiety

Acknowledgements

The families that have participated our research

- CNRM
  - David Brody
  - Charline Simon
  - Thomas Swanson
- NIH
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  - Audrey Thurm
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  - Ellen Leibenluft
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  - Anacecilia Panameno
  - Linda Carpenter
- Children's Hospital, Boston
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- BIDMC: CNBS
  - Alvaro Pascual-Leone, MD, PhD

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Henry M. Jackson Foundation

Nancy Lurie Marks Family Foundation

COBRE Center for Central Nervous System Function

SIMONS Foundation

E.P. Bradley Hospital

Brown Institute for Brain Science (BIBS)

Questions? Concerns?
Comments?

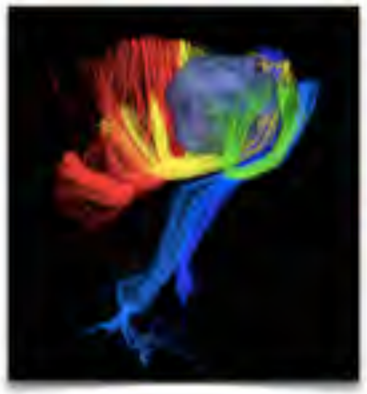
THANK YOU!

King's College Hospital
NHS Foundation Trust

TMS: Experience and use of pre-operative functional mapping in brain tumours

Mr Francesco Vergani, MD PhD, FRCS
Consultant Neurosurgeon

King's College Hospital - London, UK



NEURO-ONCOLOGY NEUROSURGERY

KING'S HEALTH PARTNERS

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An Academic Health Sciences Centre for London

Pioneering better health for all

Learning objectives

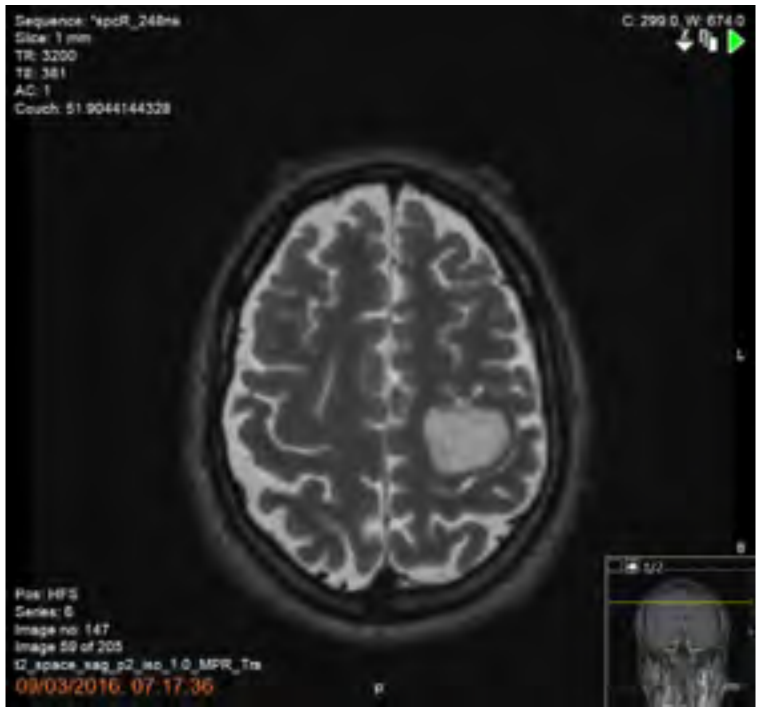
- **Case for pre surgical mapping: TMS**
- **Clinical application: pre-surgical mapping in brain tumour patients (*King's experience*)**
- **Clinical case scenarios from real life**

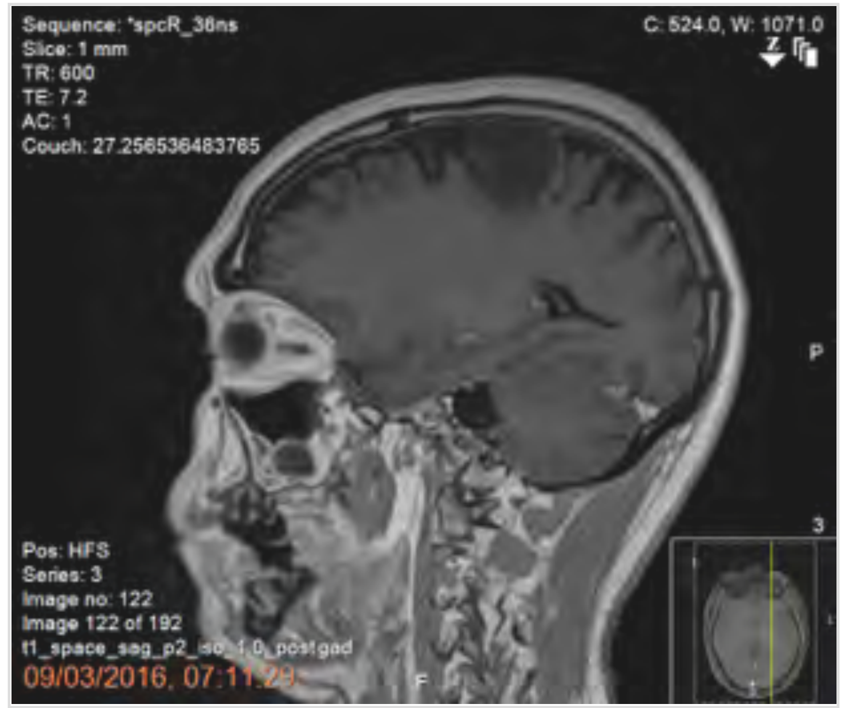
King's

Surgical challenge: eloquent areas

Gliomas have a predisposition to occur in/ near the eloquent brain particularly near the motor and speech areas

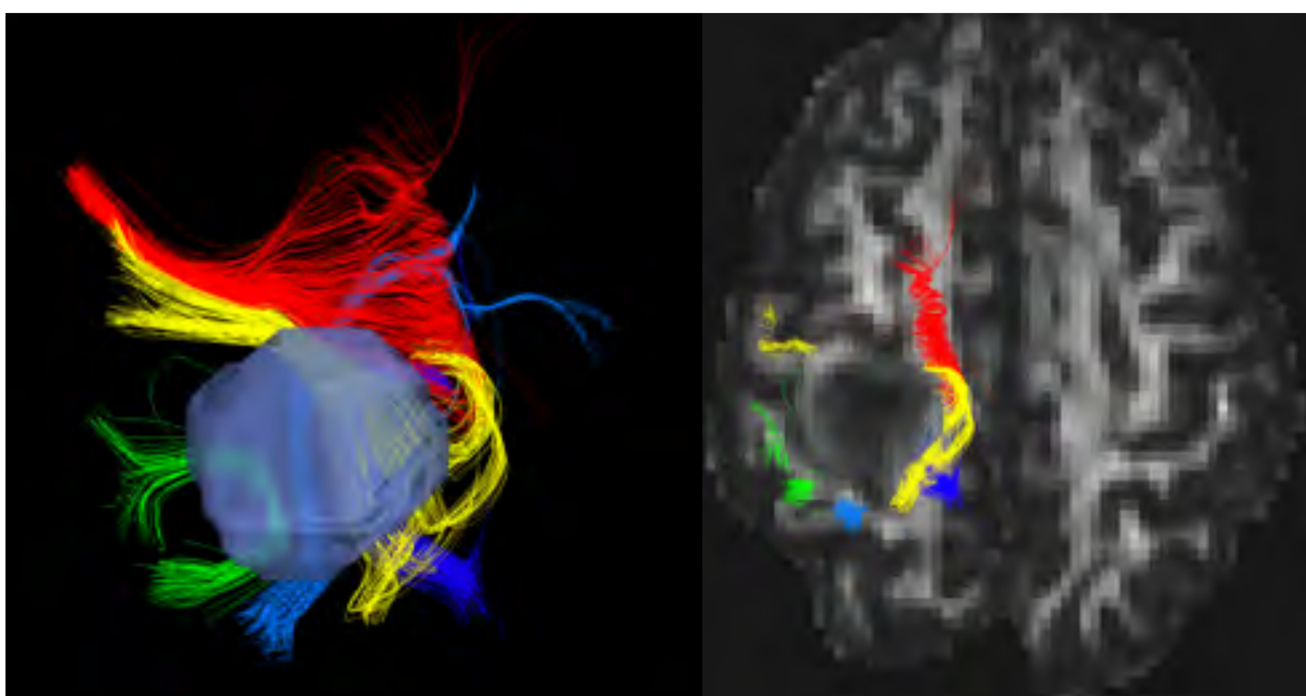
Surgical challenge: eloquent areas



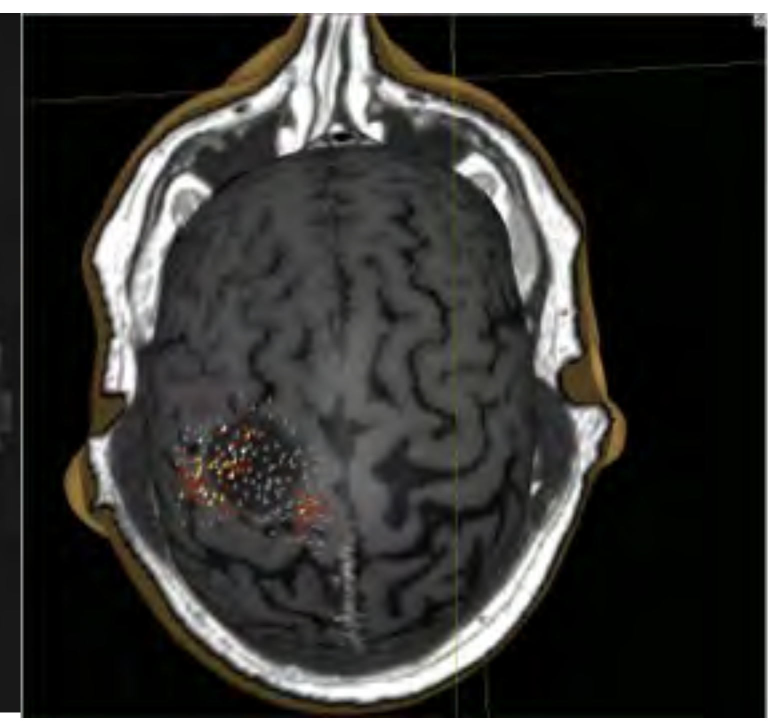


Challenge to neurosurgeons

Strategy needed to maximise the extent of resection while minimising risks

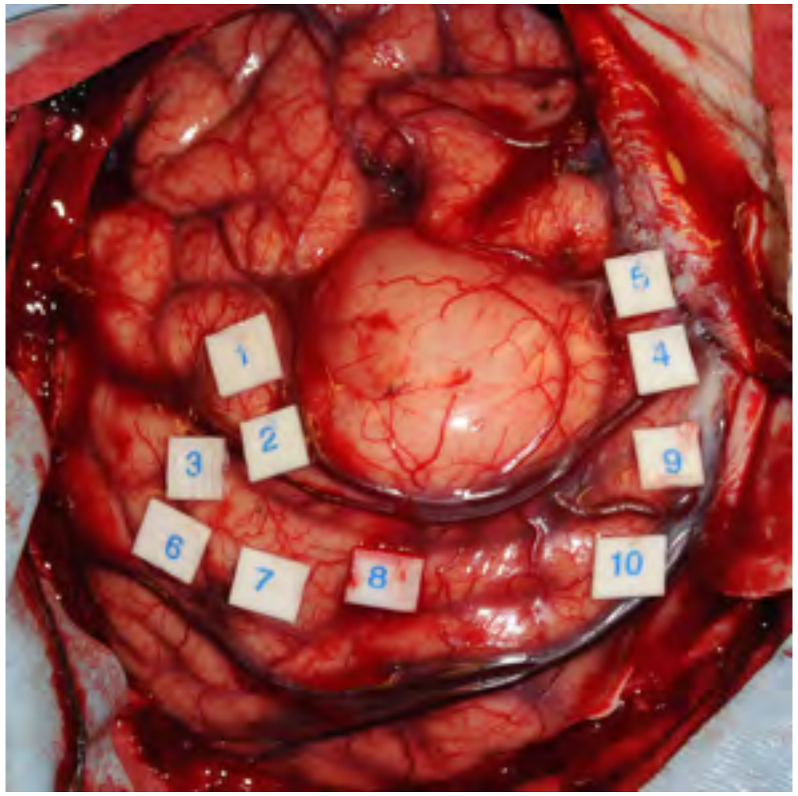


Spherical deconvolution tractography

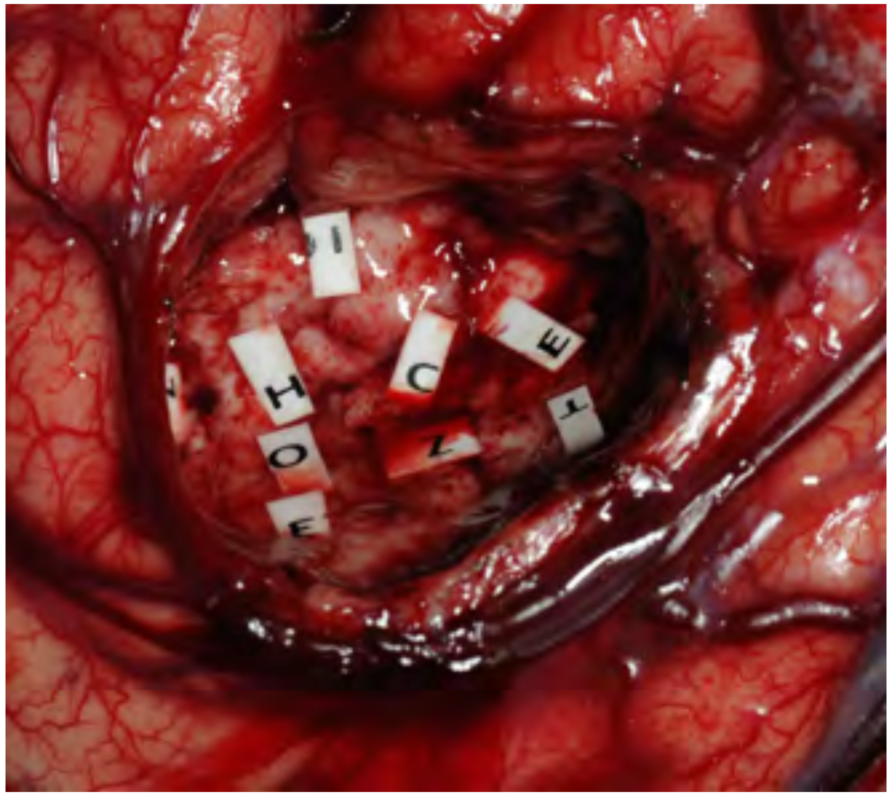


Preoperative TMS

Surgical challenge: eloquent areas



Cortical mapping before resection



Subcortical mapping at the end of resection

Surgery for gliomas: surgery of the eloquent brain

Intraoperative mapping crucial to minimise the deficits

King's

Brain Mapping

Fig. 2.—Patient, D. F., on operating table

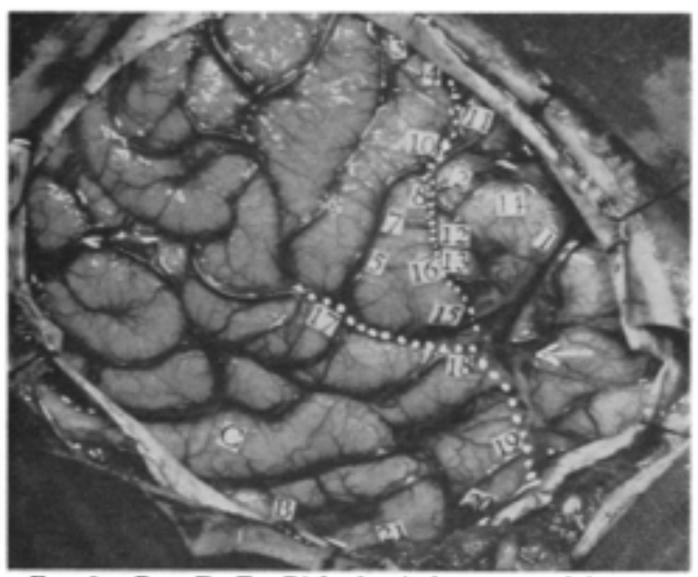
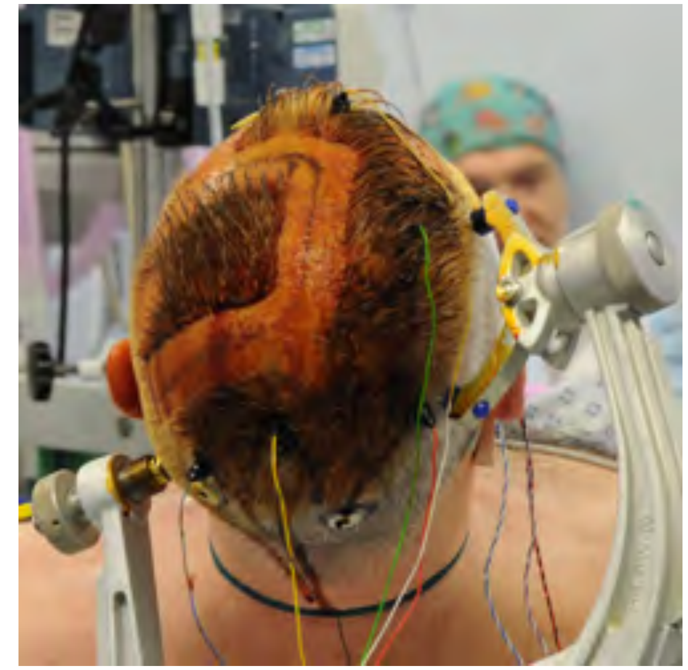
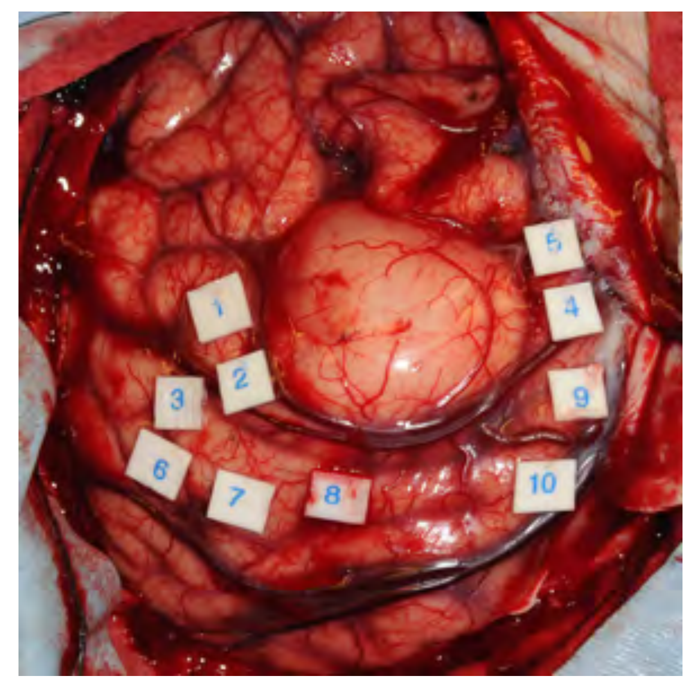


Fig. 3.—Case D. F. Right hemisphere exposed by osteoplastic craniotomy under local anesthesia. Arrow points to cortical abnormality which was more marked on the mesial surface. Numbered tickets indicate points at which electrical stimulation produced positive responses.

Wilder Penfield, 1958





King's, 2018

The case for pre-operative mapping

Understanding anatomy before surgery:

- ✓ Improved surgical planning and approach
- ✓ Better Informed consent for patients
- ✓ ? Increased surgical confidence: increasing extent of resection without added risks

King's

The case for pre-operative mapping

Anatomical/ metabolic: Tractography, fMRI

Physiological: Navigated TMS

- ➢ Physiology better correlates with functions
- ➢ More practical!

Ideally both!

The case for pre-operative mapping

Surgery for lesions in eloquent brain areas is challenging due to the risk of causing permanent neurological deficits

DES → **Gold standard for intraoperative mapping**

TMS → **Mapping tool to assist in surgical planning**

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

Optimal timing of pulse onset for language mapping with navigated repetitive transcranial magnetic stimulation

Sandro M. Krieg [a,1,2], Phiroz E. Tarapore [b,*,1], Thomas Picht [c,3], Noriko Tanigawa [d], John Houde [e], Nico Sollmann [a,2], Bernhard Meyer [a,2], Peter Vajkoczy [c,3], Mitchel S. Berger [b,4], Florian Ringel [a,1,2], Srikantan Nagarajan [e,1,5]

Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas

Clinical article

Sandro M. Krieg, M.D.,[1] Ehab Shiban, M.D.,[1] Niels Buchmann, M.D.,[1] Jens Gempt, M.D.,[1] Annette Foerschler, M.D.,[2] Bernhard Meyer, M.D.,[1] and Florian Ringel, M.D.[1]

Neuro-Oncology 2014; **0**, 1–8, doi:10.1093/neuonc/nou110

Navigated transcranial magnetic stimulation improves the treatment outcome in patients with brain tumors in motor eloquent locations

Dietmar Frey, Sarah Schilt, Valérie Strack, Anna Zdunczyk, Judith Rösler, Birat Niraula, Peter Vajkoczy, and Thomas Picht

Department of Neurosurgery, Charité University Medicine, Berlin, Germany

Contents lists available at ScienceDirect
Clinical Neurophysiology
journal homepage: www.elsevier.com/locate/clinph

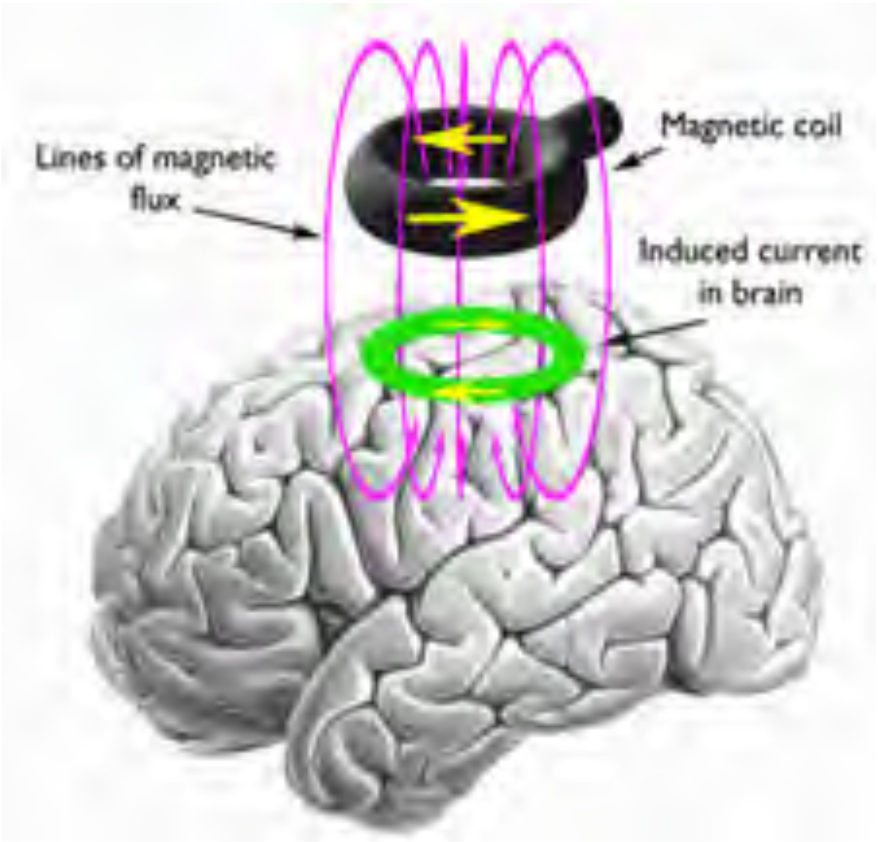
Language mapping using high gamma electrocorticography, fMRI, and TMS versus electrocortical stimulation

Abbas Babajani-Feremi [a,b,c,*], Shalini Narayana [a,b,c], Roozbeh Rezaie [a,b], Asim F. Choudhri [b,d,e], Stephen P. Fulton [b,f], Frederick A. Boop [b,e], James W. Wheless [b,f], Andrew C. Papanicolaou [a,b,c]

Clinical application

Pre-surgical mapping
Motor mapping
Language mapping

Neuropsychiatric disorders
Depression
Anorexia
Autism

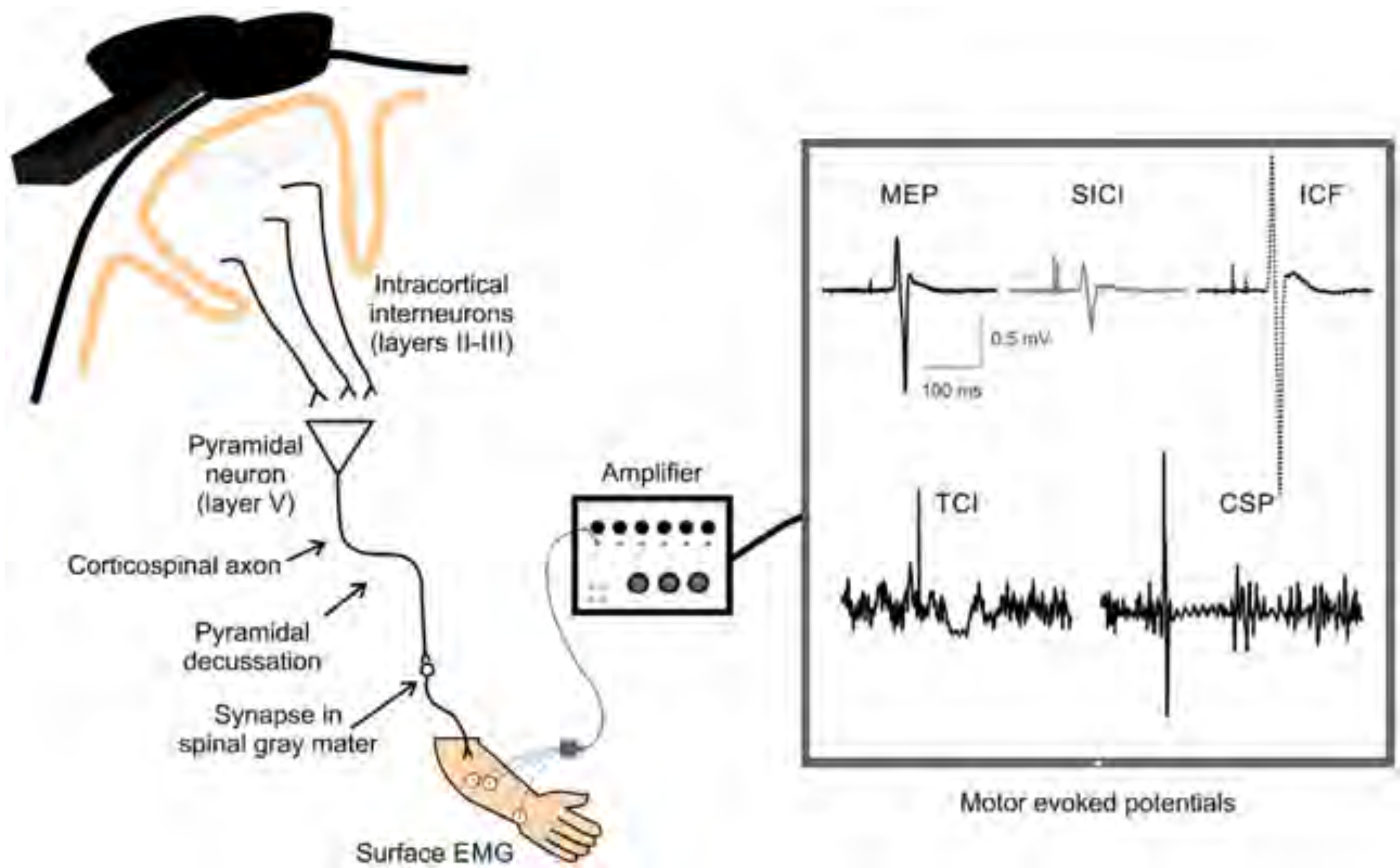


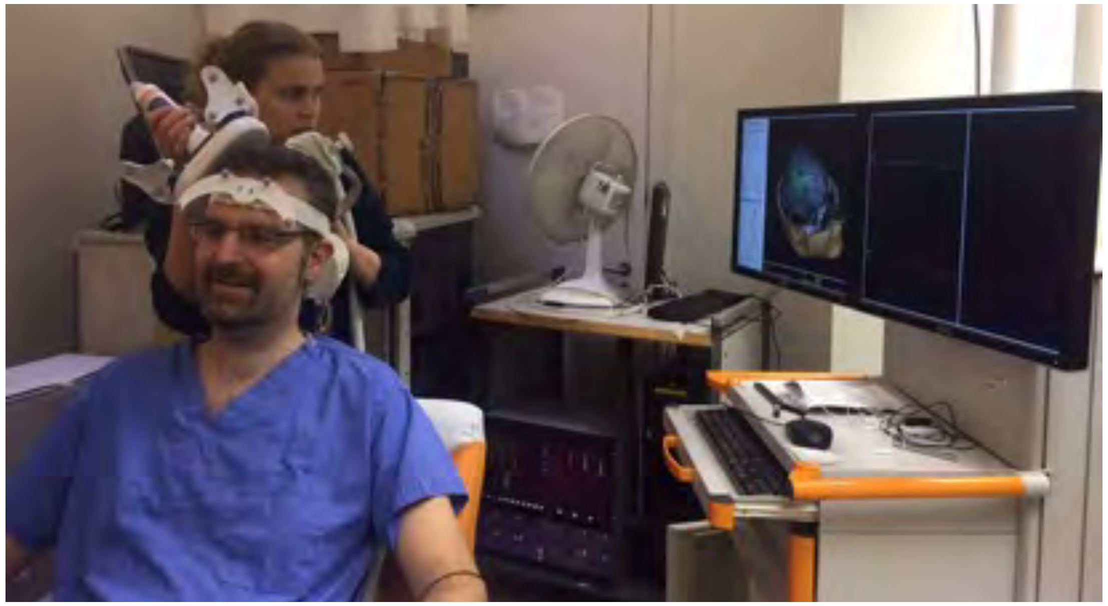
Pain
Neuropathic pain
Migraine
Phantom limb

Neuromodulation
Epilepsy
Tinnitus

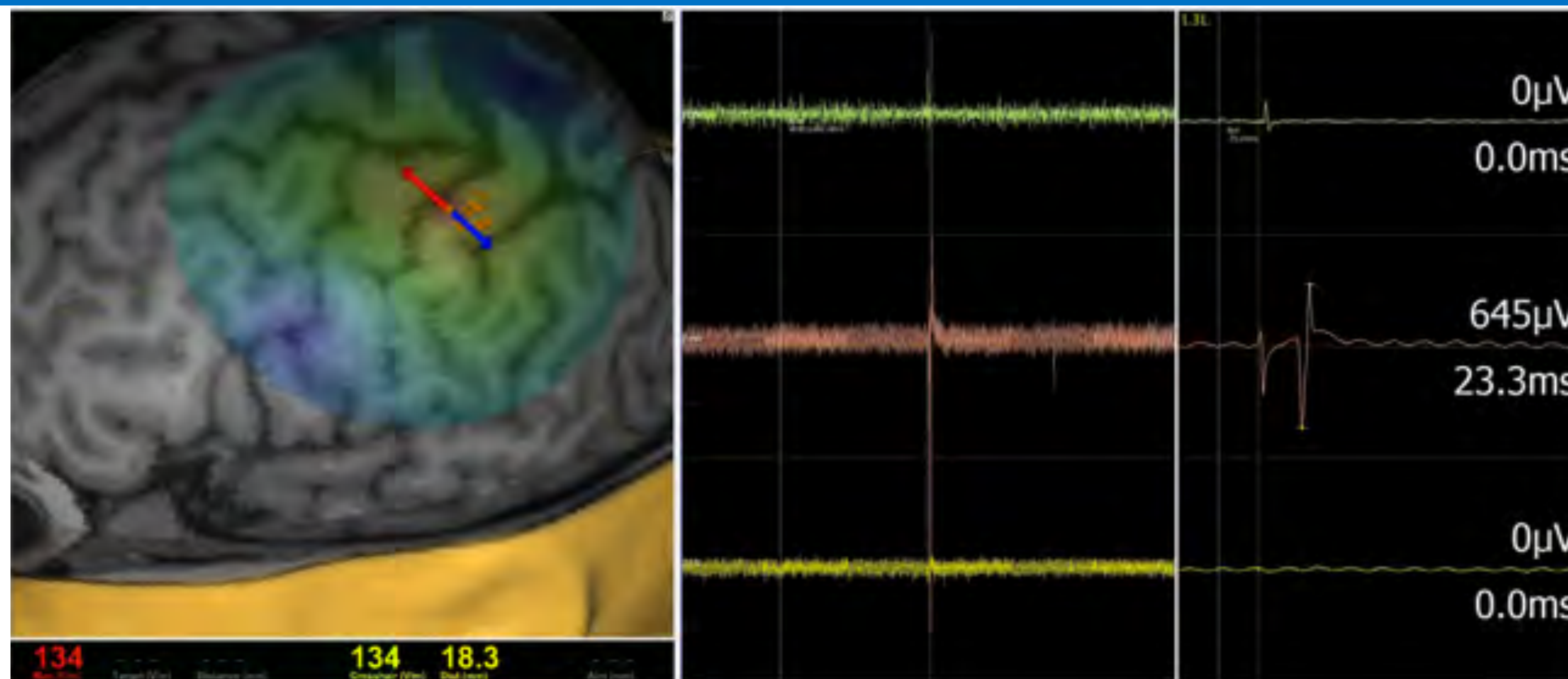
Neurorehabilitation
Stroke
Head injury

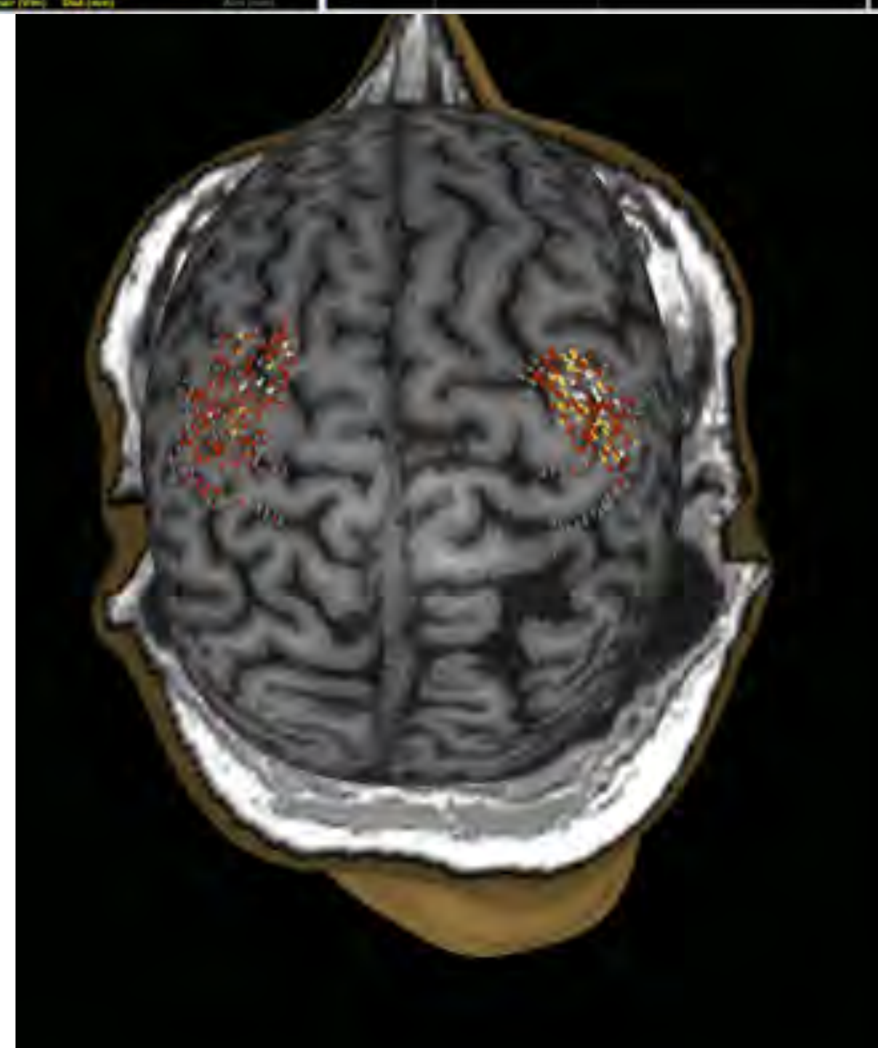
Clinical application: motor mapping





Clinical application: motor mapping





Clinical application: motor mapping

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Navigated transcranial magnetic stimulation improves the treatment outcome in patients with brain tumors in motor eloquent locations

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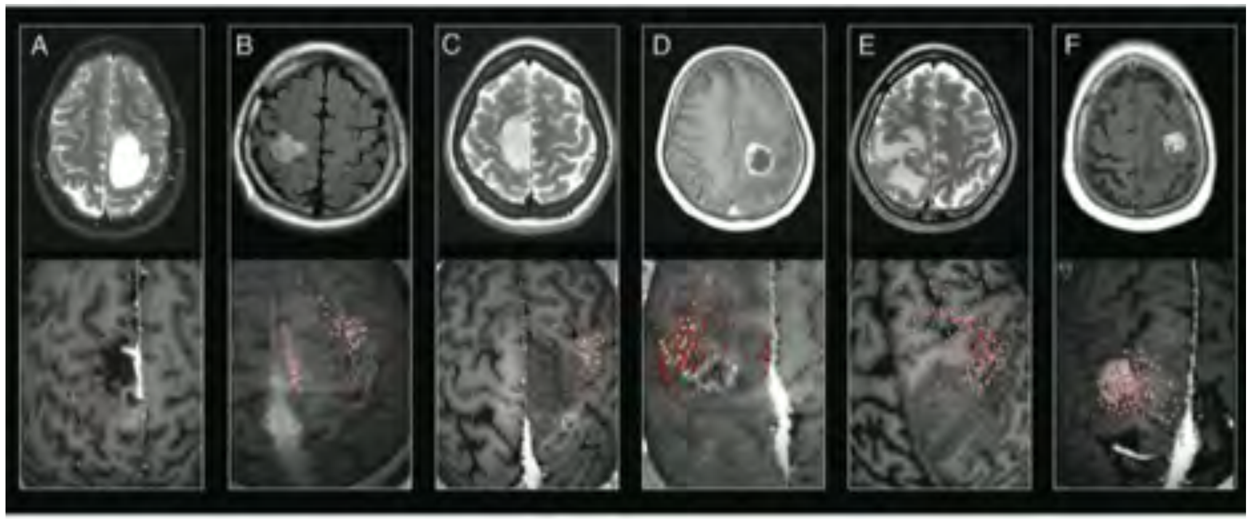

250 consecutive patients investigated with motor TMS compared to 115 matched pre-nTMS control group

TMS disproved suspected involvement of primary motor cortex in 25.1%

TMS expanded surgical indication in 14.8%, with planning of more extensive resection in 35.2% of cases

Rate of gross total resections increased significantly from 42% to 59% (P.05) in the TMS group

Nonsignificant change of postoperative deficits from 8.5% in the control group to 6.1% in the nTMS group

Clinical application: motor mapping

Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas

Clinical article

SANDRO M. KRIEG, M.D.,[1] EHAB SHIBAN, M.D.,[1] NIELS BUCHMANN, M.D.,[1] JENS GEMPT, M.D.,[1] ANNETTE FOERSCHLER, M.D.,[2] BERNHARD MEYER, M.D.,[1] AND FLORIAN RINGEL, M.D.[1]

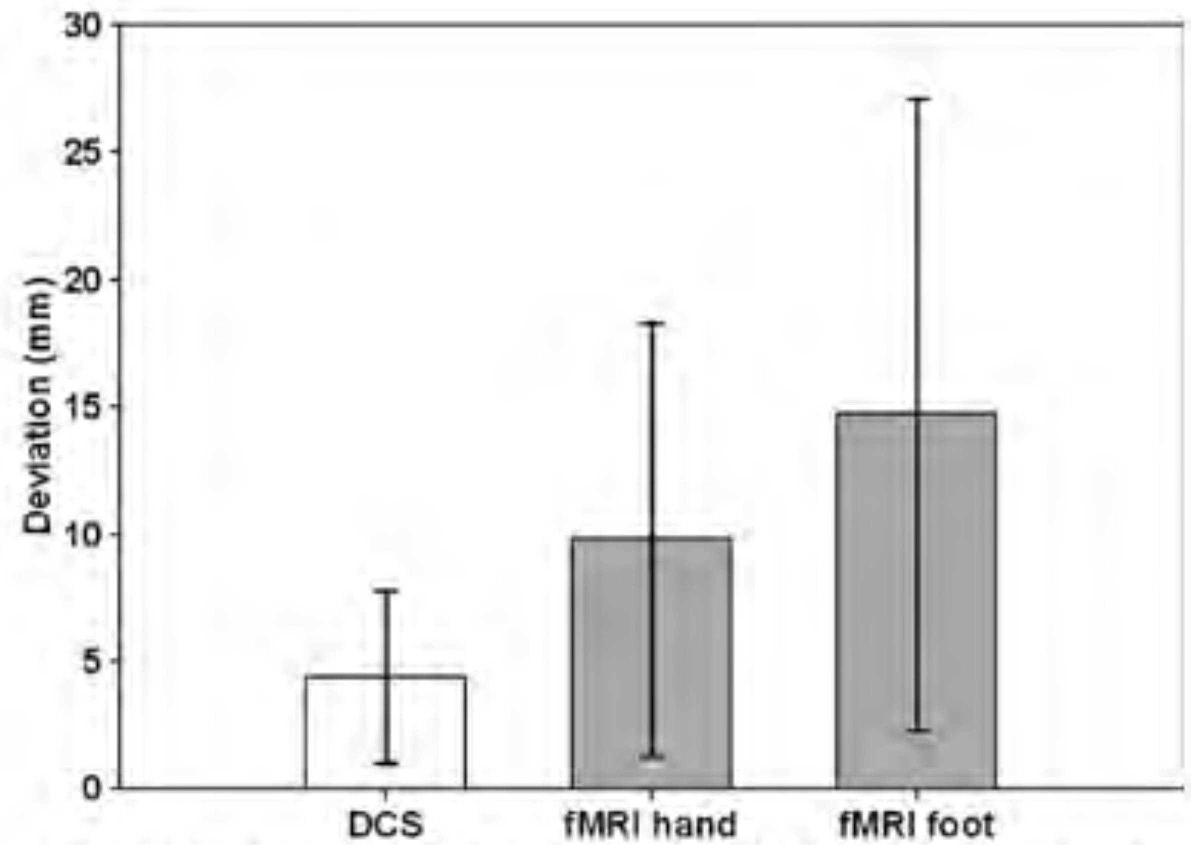

FIG. 2. Deviation of nTMS compared with DCS and fMR imaging. Bar graph showing that nTMS data correlate quite well with DCS data (4.4 ± 3.4 mm), whereas delineation of the primary motor cortex via fMR imaging differs significantly from nTMS, depending on whether the extremity is upper (9.8 ± 8.5 mm) or lower (14.7 ± 12.4 mm; $p < 0.05$).

26 patients undergoing surgery for brain tumors

nTMS compared to intraoperative direct cortical stimulation as well as fMRI.

Good accuracy of nTMS for motor mapping with mean distance between nTMS and DCS hotspots of 4.4 mm

nTMS agrees more closely with DCS than fMRI.

King's

Clinical application: language mapping

It‘s not DCS - do not aim for the speech arrest.
There are no-responders.

Strict baseline (3 x 80 images)

RMT or lower - the patient must be comfortable

5 Hz / 5 pulses (800 ms)

PPT 700 ms (adapt according to patient ability)

0 msec delay

IPI 3000 ms (adapt according to patient ability)

If no effect: 1) reduce PPT and IPI 2) 7Hz/7pulses, 10Hz/10pulses 3) increase intensity

Clinical application: language mapping

Contents lists available at ScienceDirect
NeuroImage
journal homepage: www.elsevier.com/locate/ynimg

Optimal timing of pulse onset for language mapping with navigated repetitive transcranial magnetic stimulation

Sandro M. Krieg [a,1,2], Phiroz E. Tarapore [b,*,1], Thomas Picht [c,3], Noriko Tanigawa [d], John Houde [e], Nico Sollmann [a,2], Bernhard Meyer [a,2], Peter Vajkoczy [c,3], Mitchel S. Berger [b,4], Florian Ringel [a,1,2], Srikantan Nagarajan [e,1,5]

Fig. 5. False negative. Regions of false negative rTMS mapping: left: ONSET TMS; right: DELAYED TMS.

Fig. 3. True negative. Regions of true negative rTMS mapping: left: ONSET TMS; right: DELAYED TMS.

32 patients

TMS confirmed with DCS

NPV: 100%

PPV: 55-75%

Better results with 0mS delay

King's

Clinical application: language mapping

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Clinical Neurophysiology

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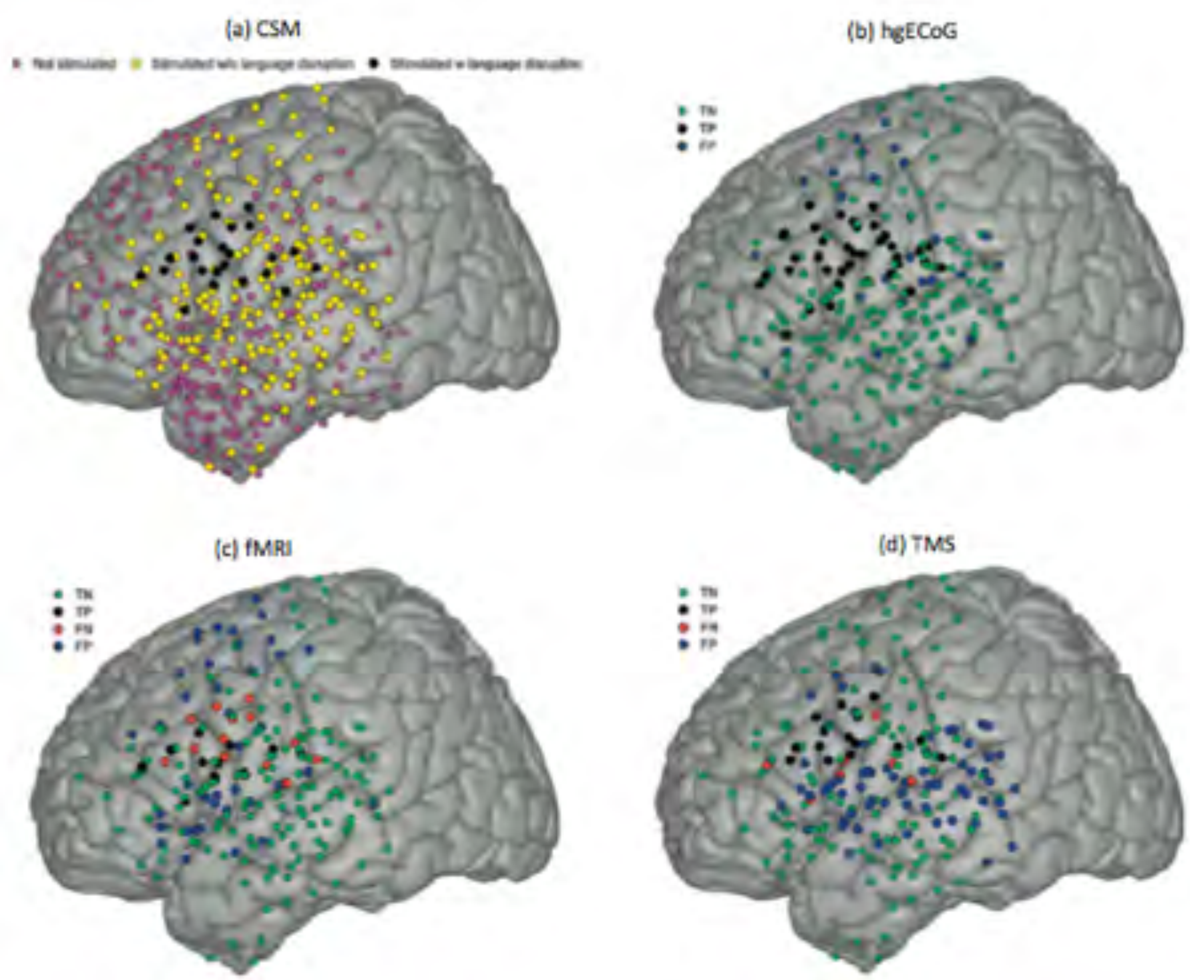
[a] Department of Pediatrics, Division of Clinical Neurosciences, University of Tennessee Health Science Center, Memphis, TN, USA
[b] Neuroscience Institute, Le Bonheur Children's Hospital, Memphis, TN, USA
[c] Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Memphis, TN, USA
[d] Department of Radiology, University of Tennessee Health Science Center, Memphis, TN, USA
[e] Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN, USA
[f] Department of Pediatrics, Division of Pediatric Neurology, University of Tennessee Health Science Center, Memphis, TN, USA



9 patients

hgEcoG, fMRI, TMS and DCS compared

NPV: 96%

PPV: 25%

Good concordance between fMRI, TMS and hg-EcoG

King's experience

ORIGINAL ARTICLE

First United Kingdom Experience of Navigated Transcranial Magnetic Stimulation in Preoperative Mapping of Brain Tumors

Josephine Jung[1,2], José-Pedro Lavrador[1], Sabina Patel[1], Anastasios Giamouriadis[1], Jordan Lam[3], Ranjeev Bhangoo[1], Keyoumars Ashkan[1,2], Francesco Vergani[1]

- Prospective data collection - King's experience (February 2017-February 2018)
- 58 patients operated for lesions in eloquent areas with DES
- **35 patients** (61%) received TMS (as an adjunct to DES)
- Data on demographics, histology, tumour location, EoR, neurological outcome

King's

King's experience

- ❑ Correlation between TMS and DES

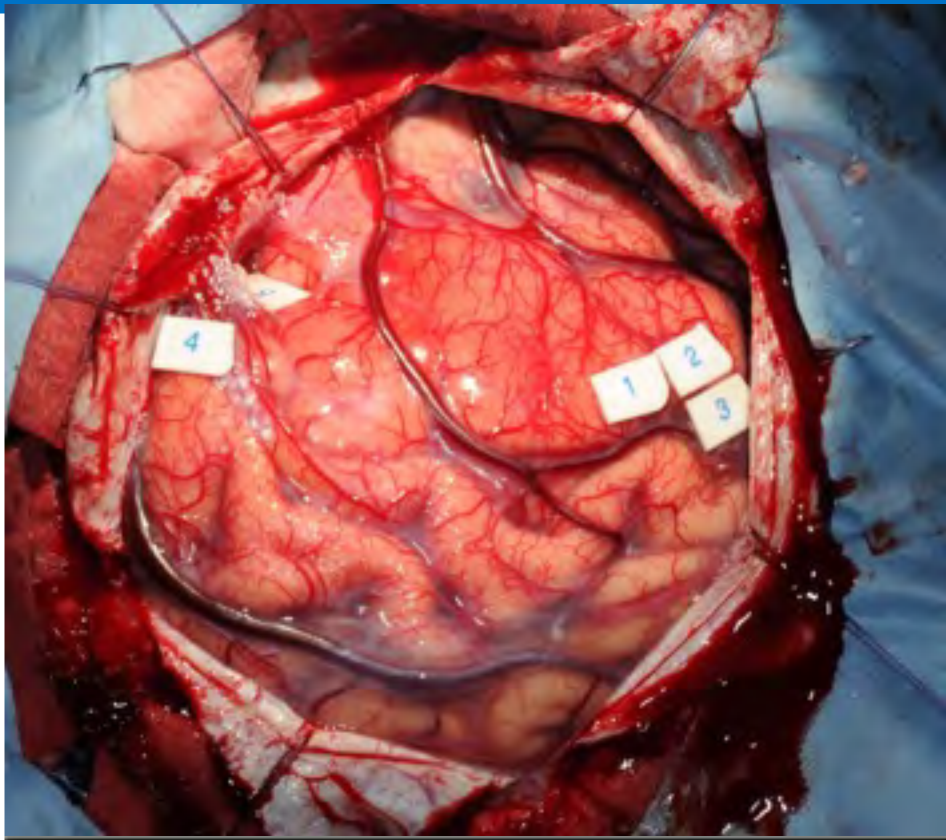
Digital pictures obtained intraoperatively - superimposed to the TMS pre-surgical mapping on 3D rendering

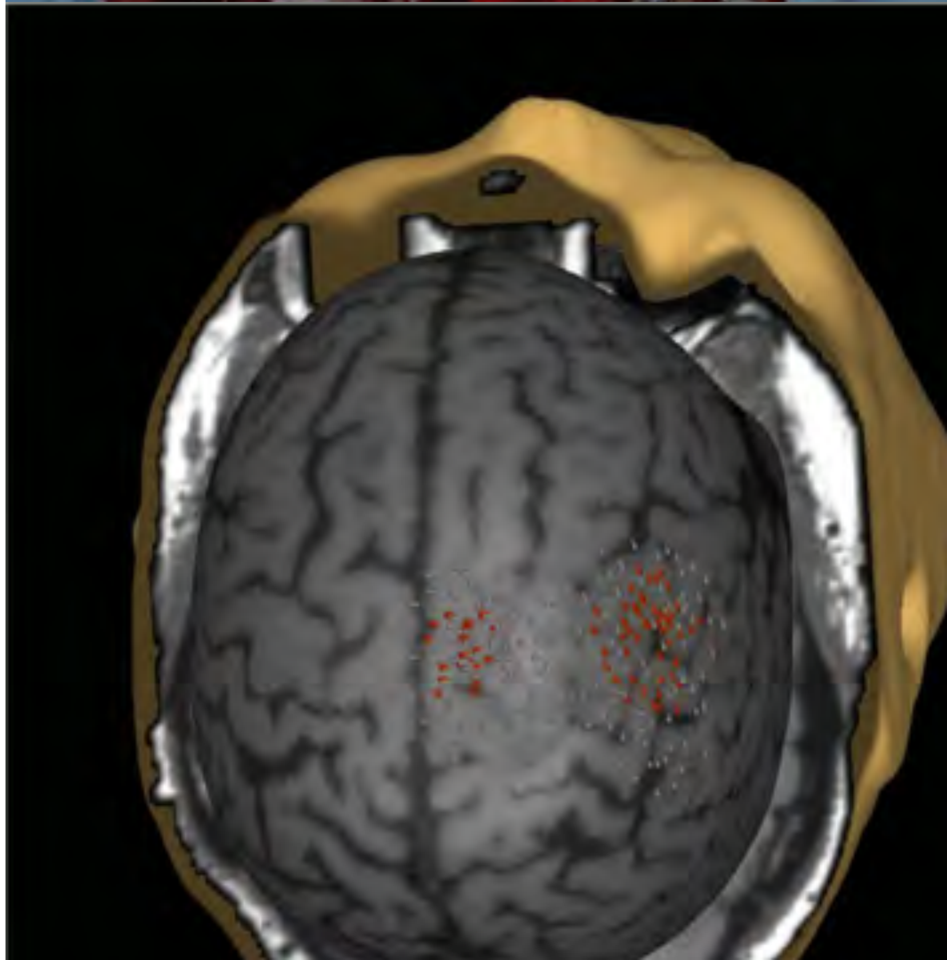
- ❑ Impact on surgical planning (independently assessed by two surgeons):

- No change
- Change:

A. indication
B. surgical approach
C. craniotomy size

Frey et al. Neuro-Oncology, 2014





King's experience

Variables	*N* (%)
Gender	
- Female	18 (51.4)
- Male	17 (48.6)
Age (years)	
- Mean ± SD	47 ± 15
- Range	19 - 67
Diagnosis	
- LGG	6 (17.1)
- HGG	24 (68.6)
- Metastasis	2 (5.7)
- Epidermoid cyst	1 (2.9)
- Cavernous haemangioma	1 (2.9)
- Glial tumour (not further specified)	1 (2.9)
Extent of resection*	
- GTR	14 (58.3)
- Subtotal	9 (37.5)
- Partial	1 (4.2)
Complications	
- Seizures	3 (8.6)
- Infection	5 (14.3)
- Haemorrhage	1 (2.9)
New neurological deficit	
- Transient (improved/ resolved)	12 (34.3)
- Permanent – expressive dysphasia	1 (2.9)

* Excluded from analysis were cavernoma (n=1) and patients without post-operative MRI within 72hrs (n=10)

85.7% Glioma

58% GTR

1 pt with permanent deficit

King's experience

24 patients (68%) - TMS for motor mapping

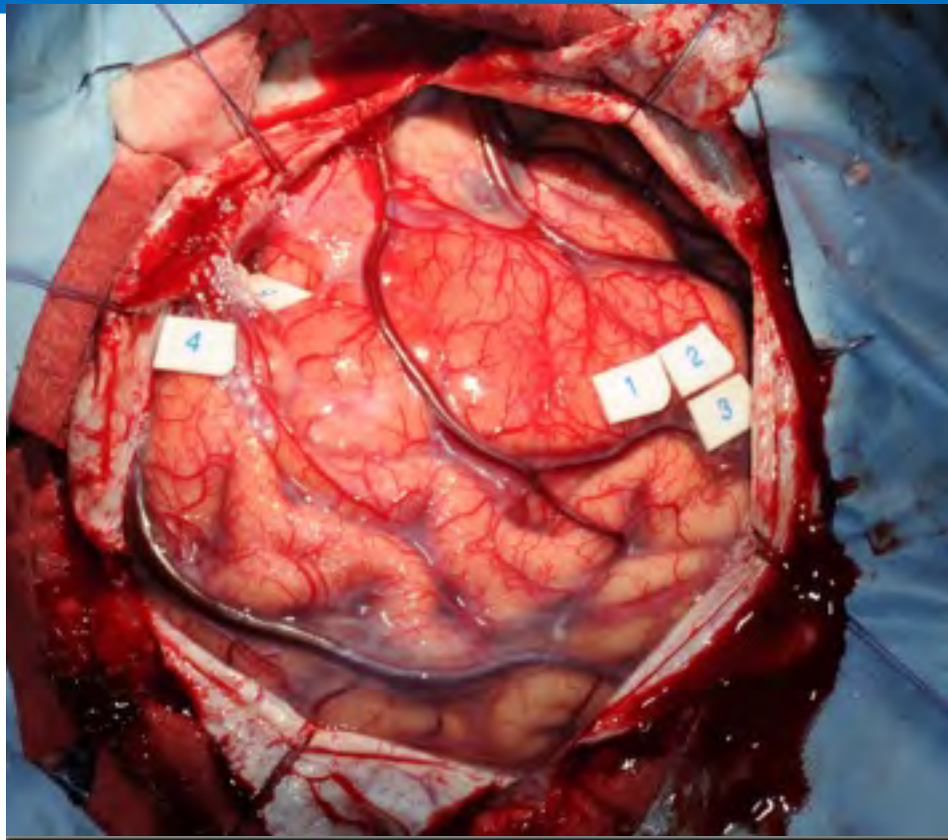
No adverse events

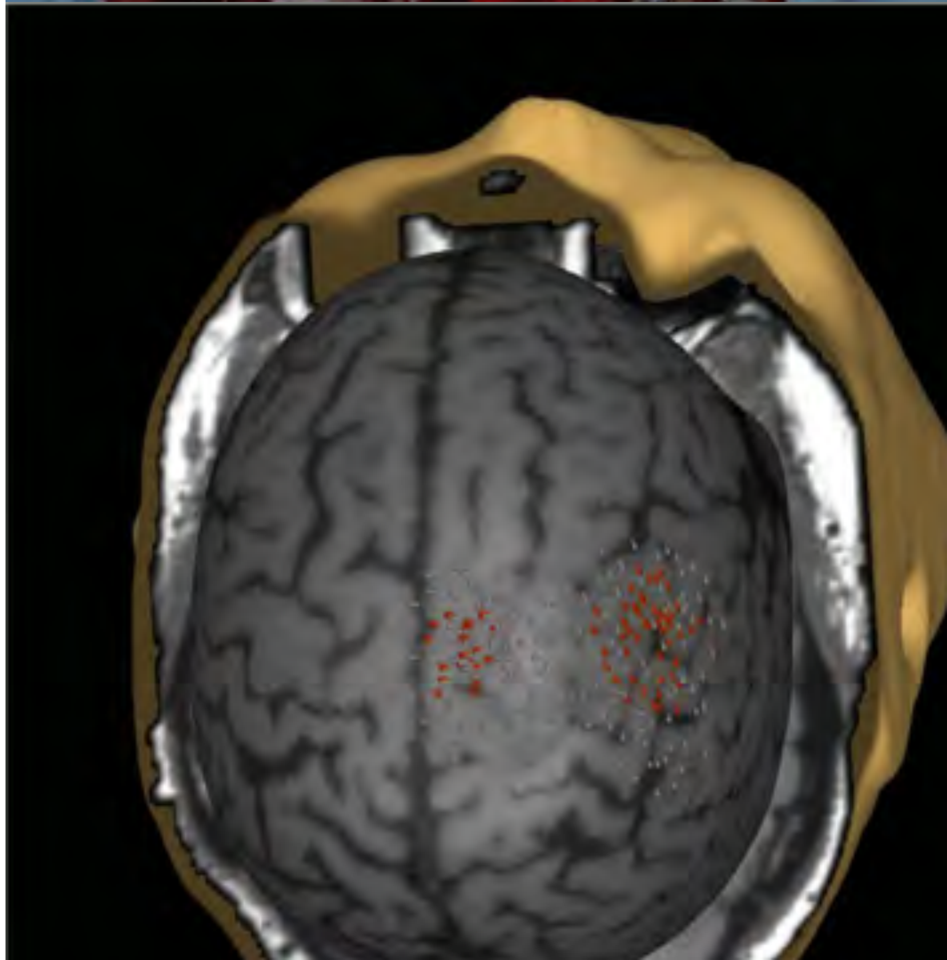
9 cases - correlation with direct cortical stimulation of the hand knob

4 cases - correlation with lower limb

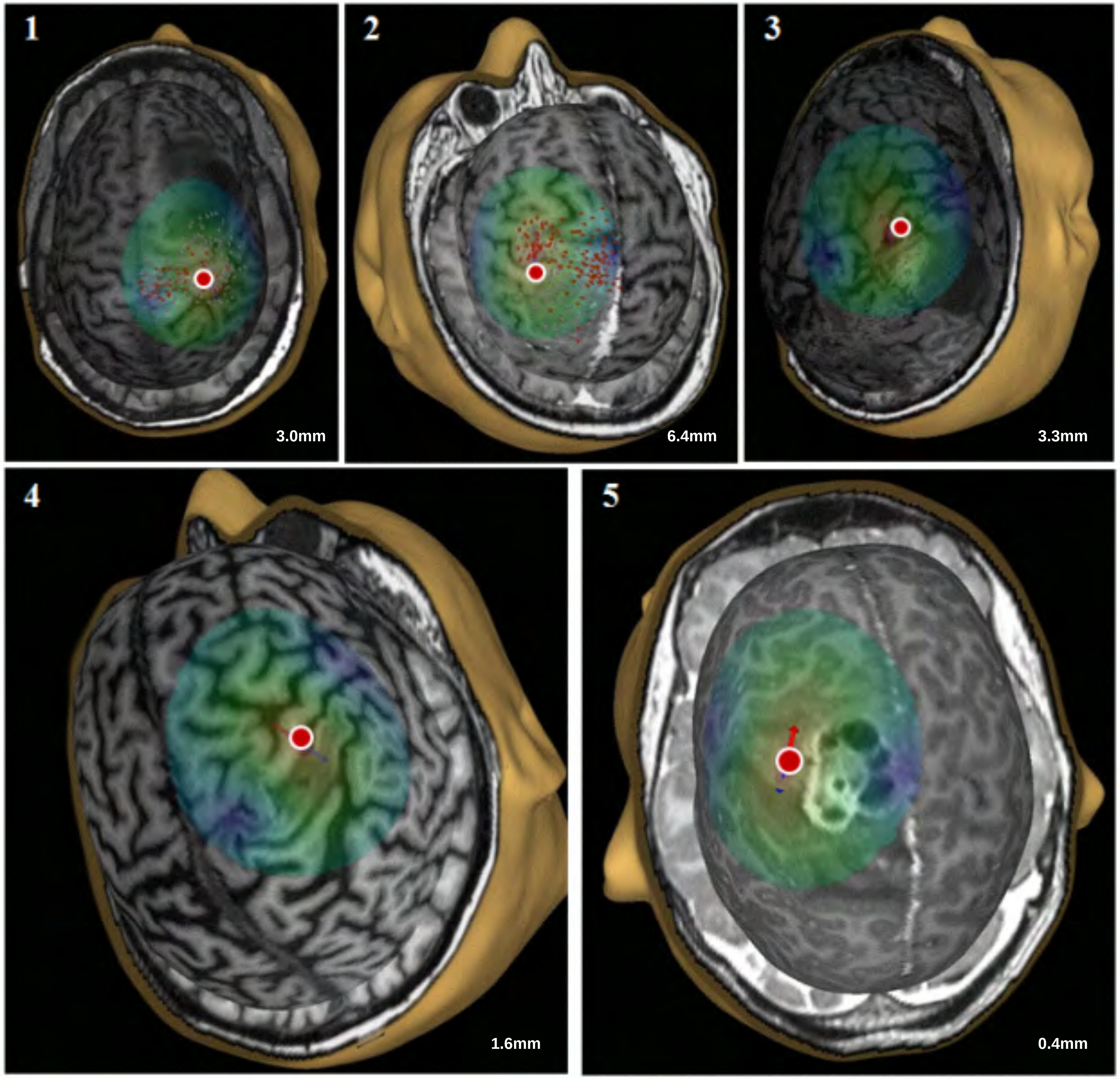
11 cases - guidance to positioning of strip electrode

0 cases - "negative" motor mapping



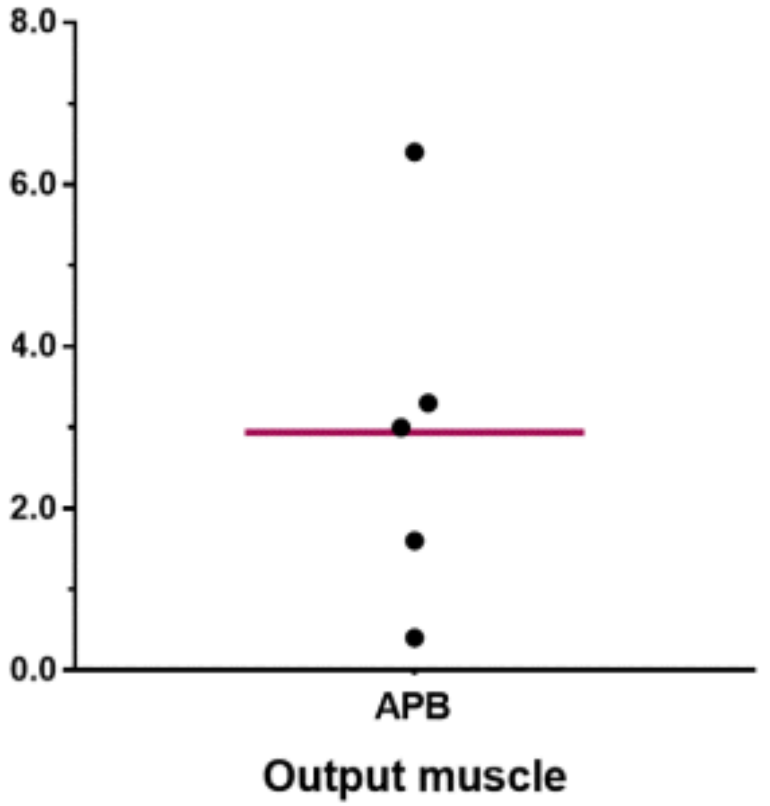


King's experience



Correspondence of nTMS with intra-operative cortical DES hot-spots for APB (5 cases)

Median distance between nTMS & DCS hotspots: 3 mm (0.4-6.4)



King's experience

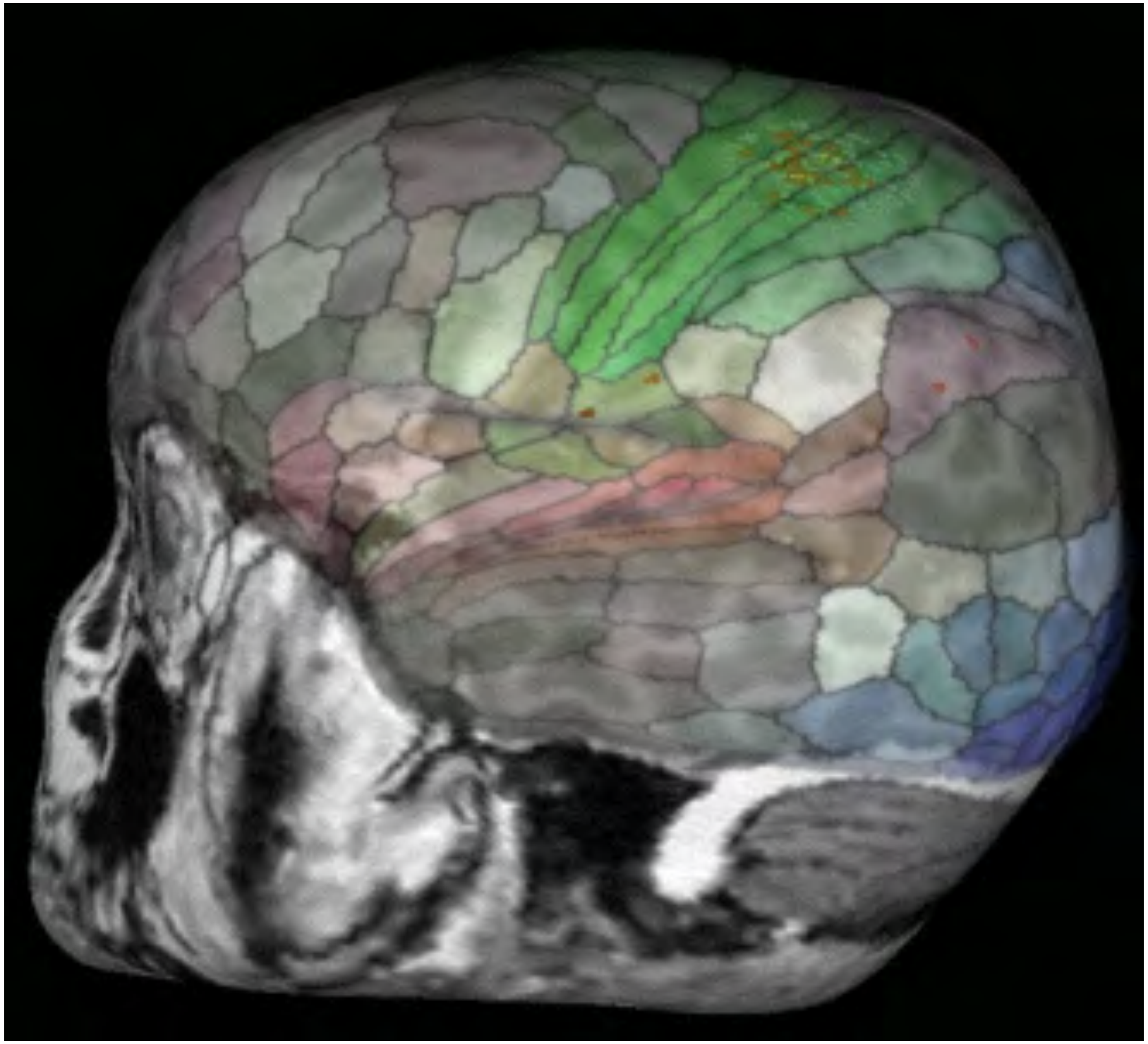
11 patients (32%) - TMS for language mapping

10 completed preop and intraop language mapping (1 pt excluded due to intraop seizures)

No adverse events after TMS
(2 cases - mild discomfort)

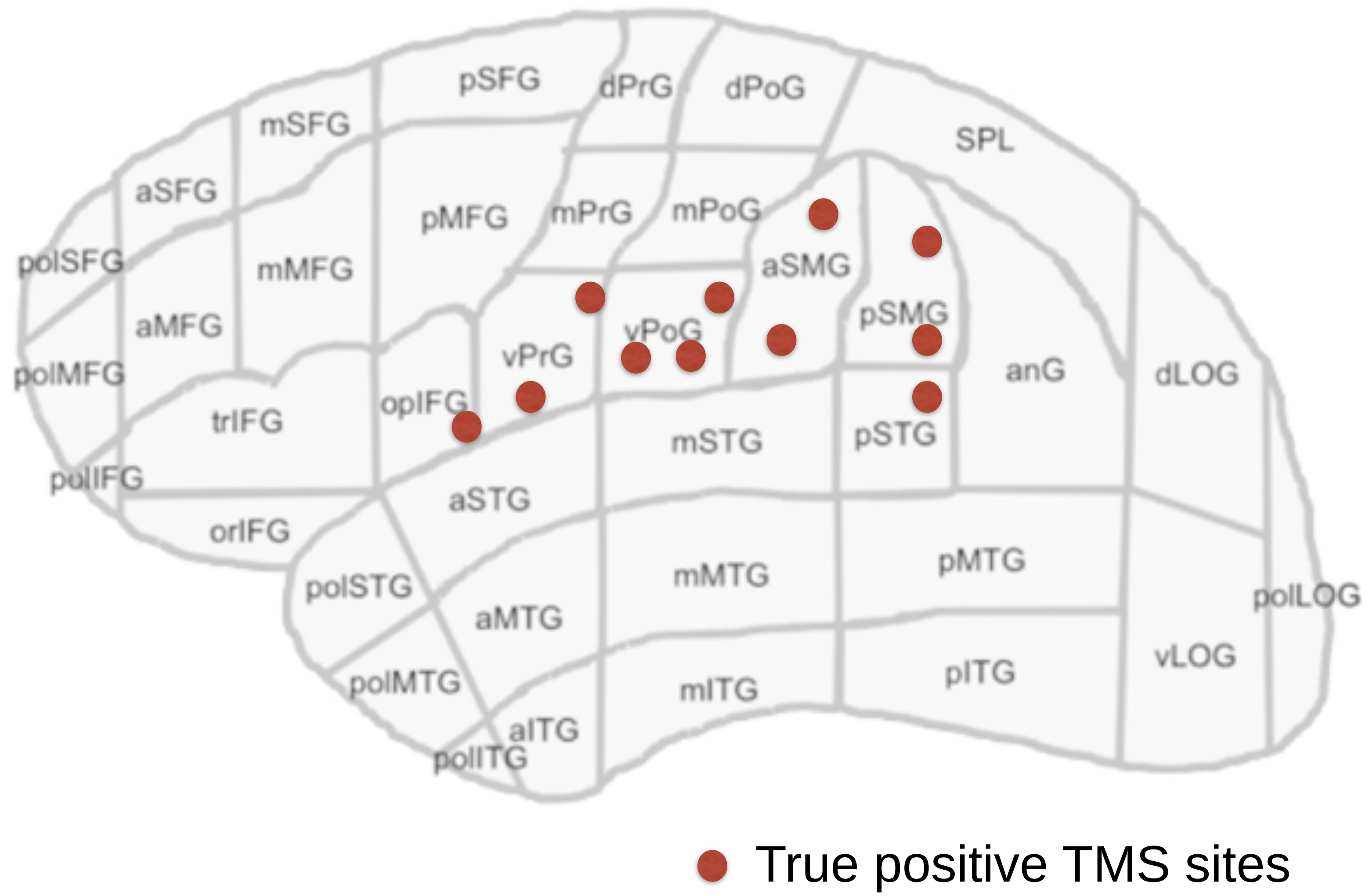
7 cases - true positive identified

2 cases - no speech disturbance observed with TMS



King's experience

Classification	DCS	TMS
True positive	+	+
True negative	-	-
False positive	-	+
False negative	+	-



	Percentage	Values
Sensitivity	63.2%	TP = 12
Specificity	66.7%	FP = 10
PPV	54.5%	FN = 7
NPV	74.1%	TN = 20

King's experience

Impact of TMS on Surgical planning	***N* (% of total)**
No change in surgical planning	**23 (65.7)**
Change in surgical planning	**10 (28.6)**
a) Indication	1 (2.9)
b) Surgical approach	3 (8.6)
c) Craniotomy size	7 (20.0)

Illustrative case: motor mapping

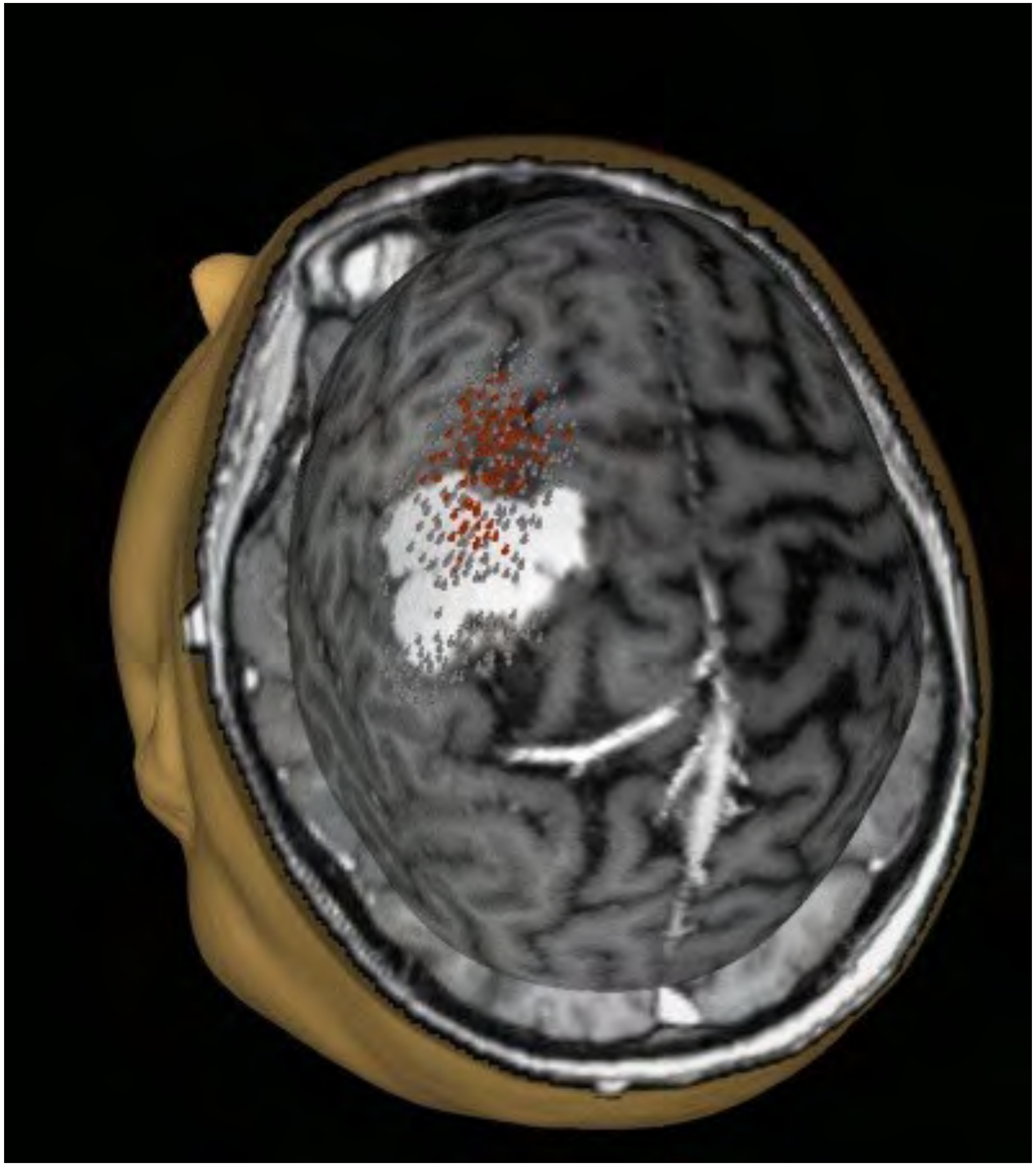
21 yrs old girl

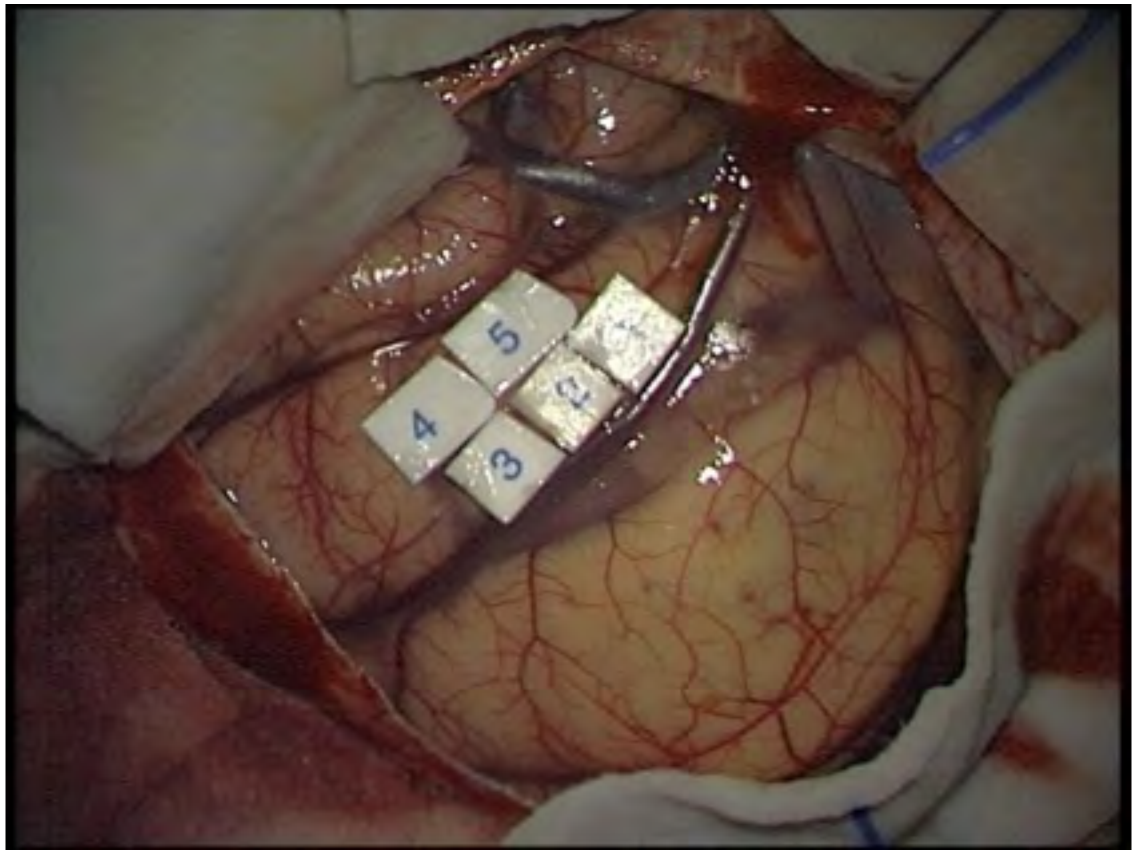
Progressive right hand weakness

Sensory-motor right upper limb seizures

?? motor cortex

Illustrative case: motor mapping



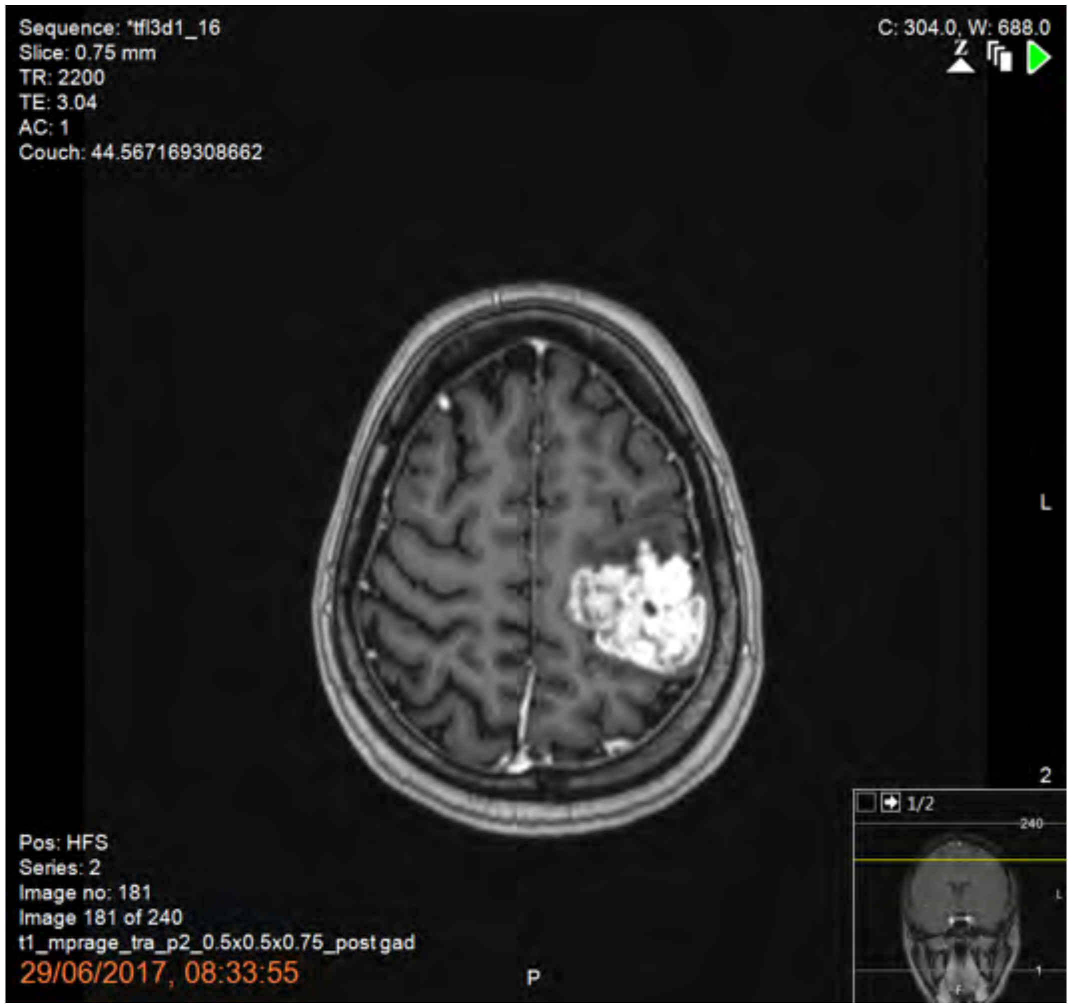


Motor cortex anterior to the tumour

Tumour embedded in the central sulcus

King's

Illustrative case: motor mapping



Complete macroscopic resection
Motor function fully recovered at 3 weeks post
2x seizures in the first week post
Histology: **ATRT**

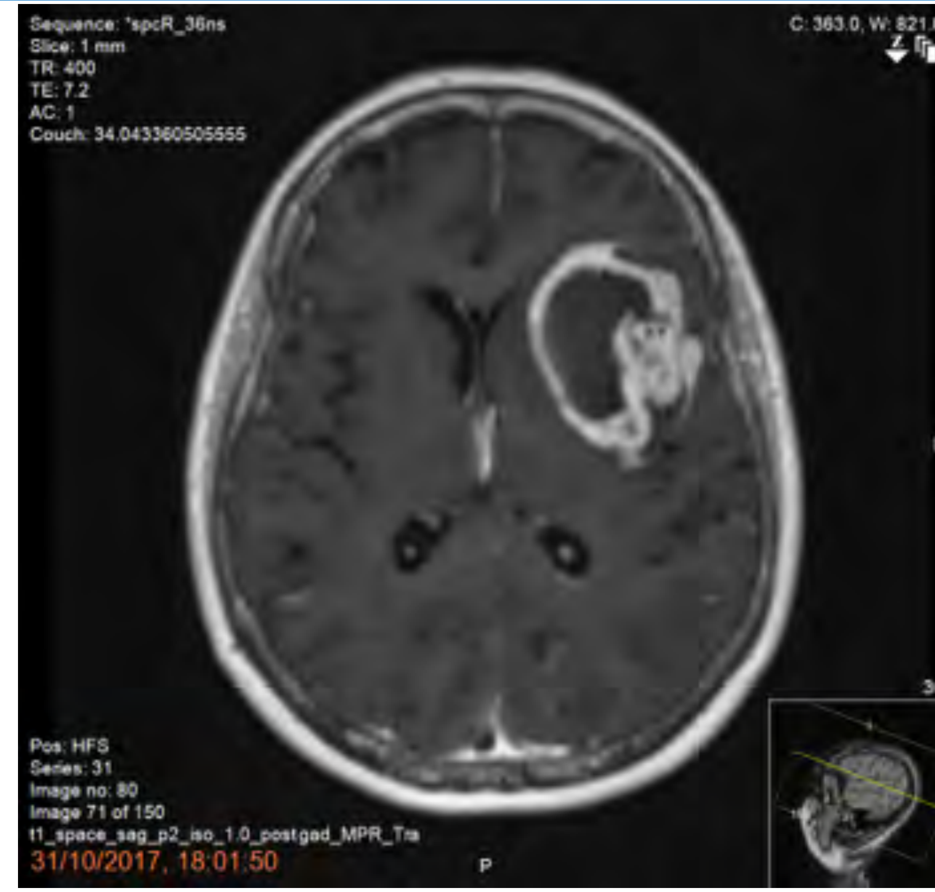
Bodi et al, Surgical Neurology International, 2018

Illustrative case: language mapping

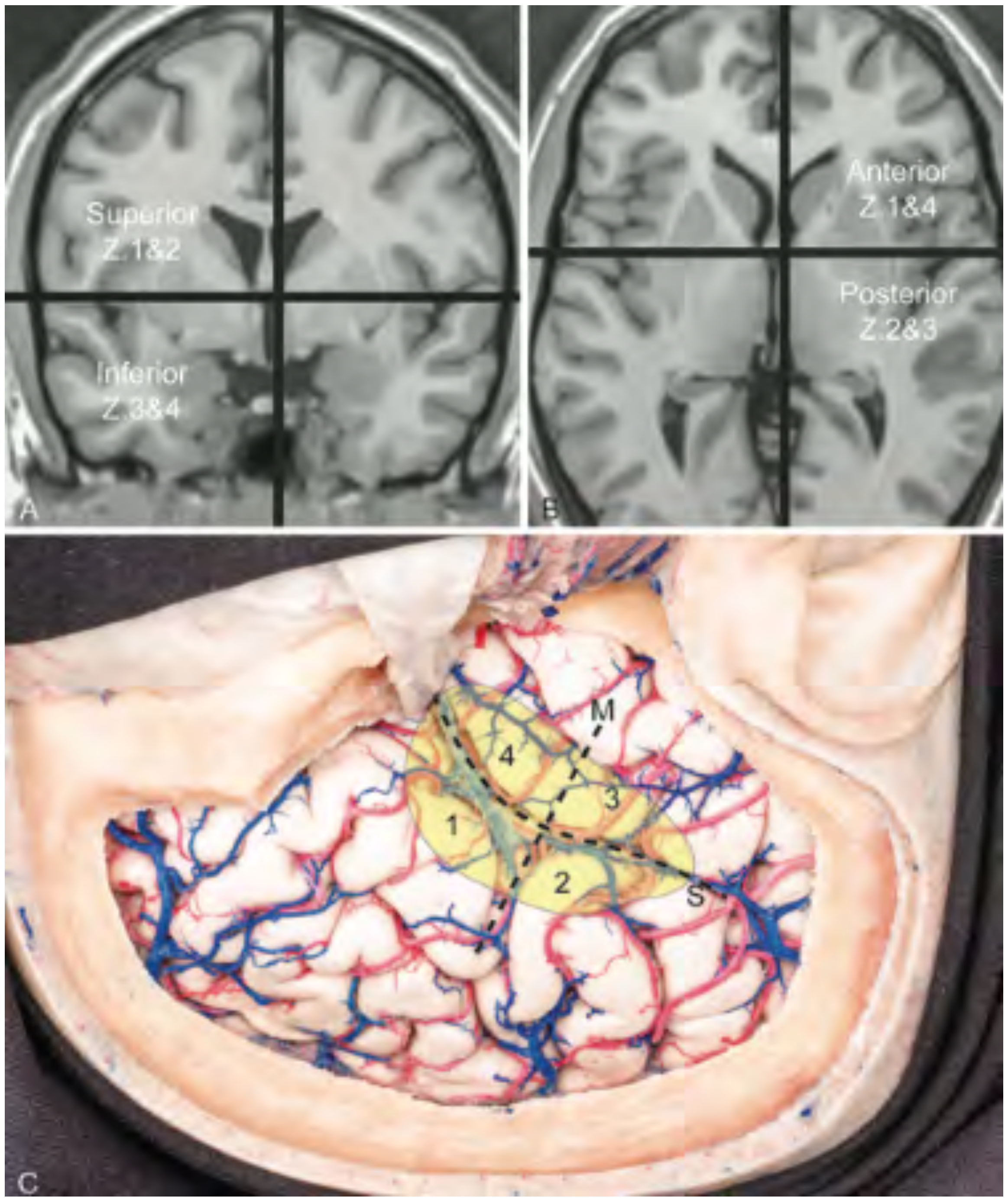
60 yrs old lady

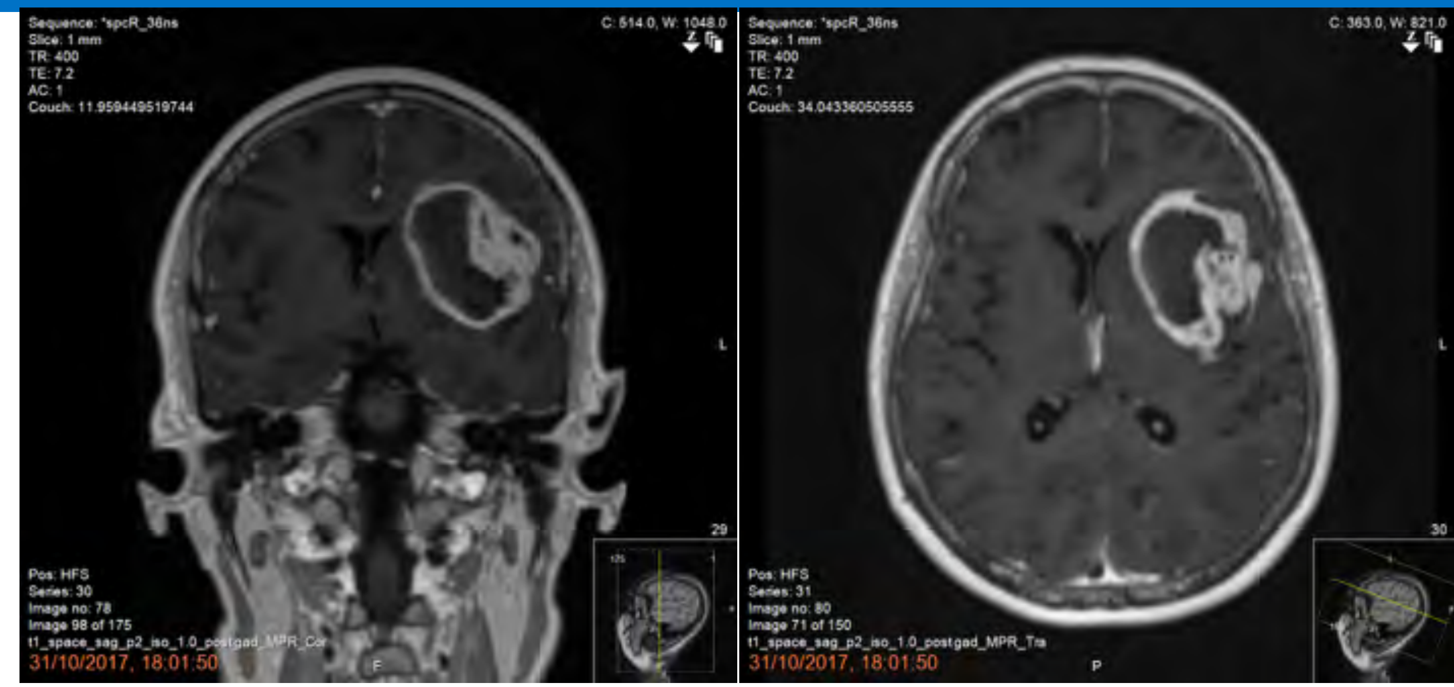
R facial droop

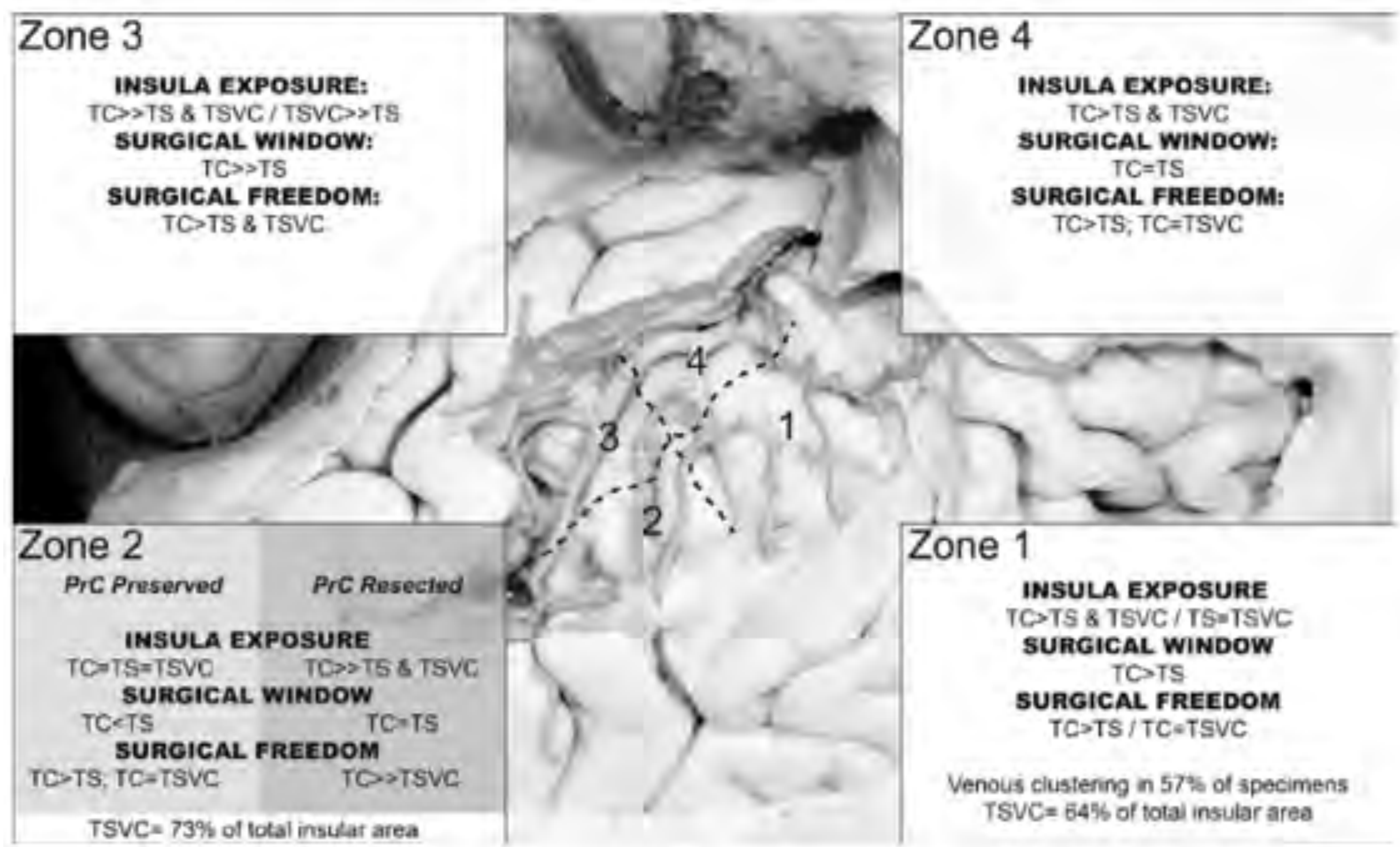
Generalised tonic-clonic seizure



Illustrative case: language mapping



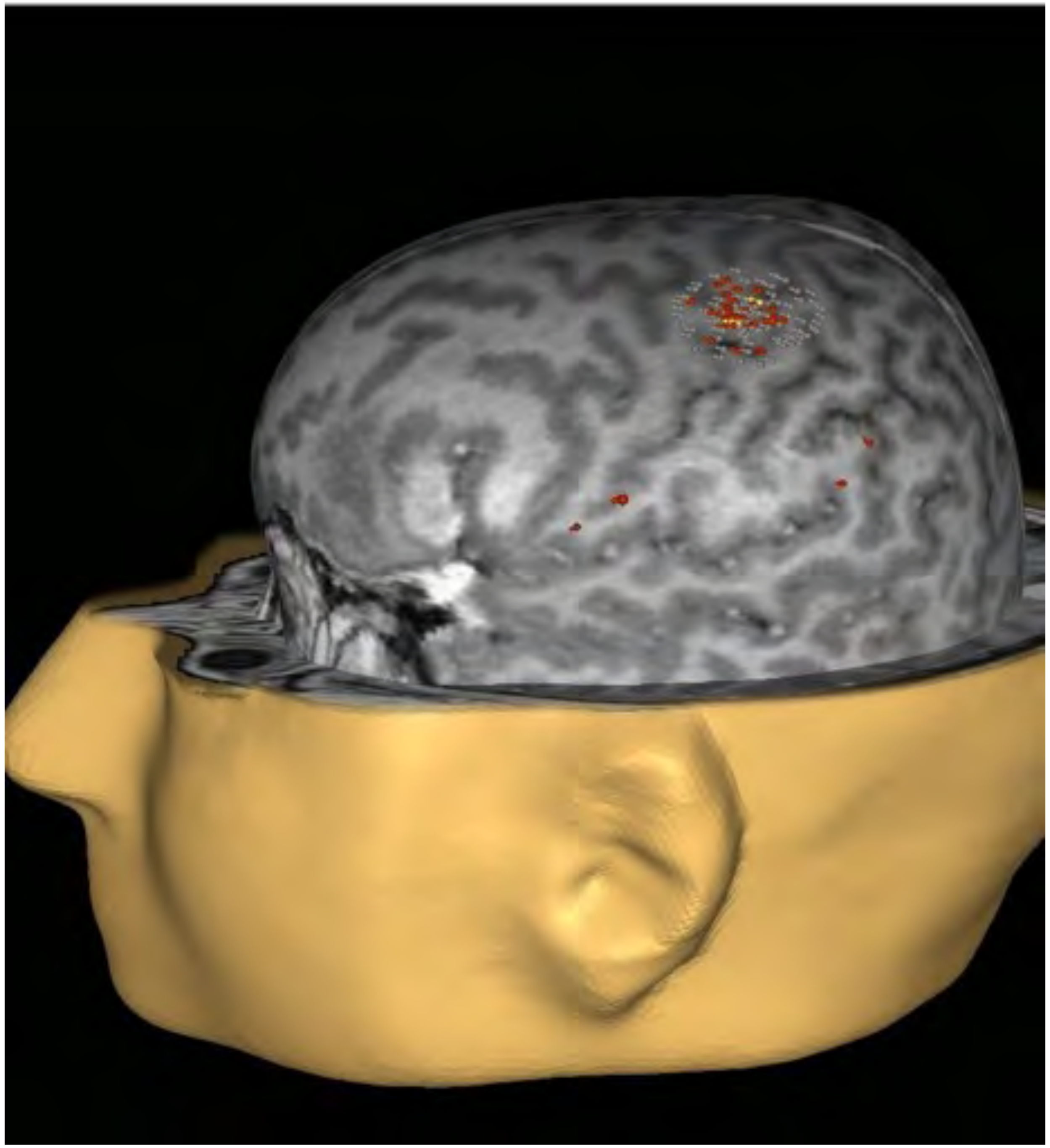


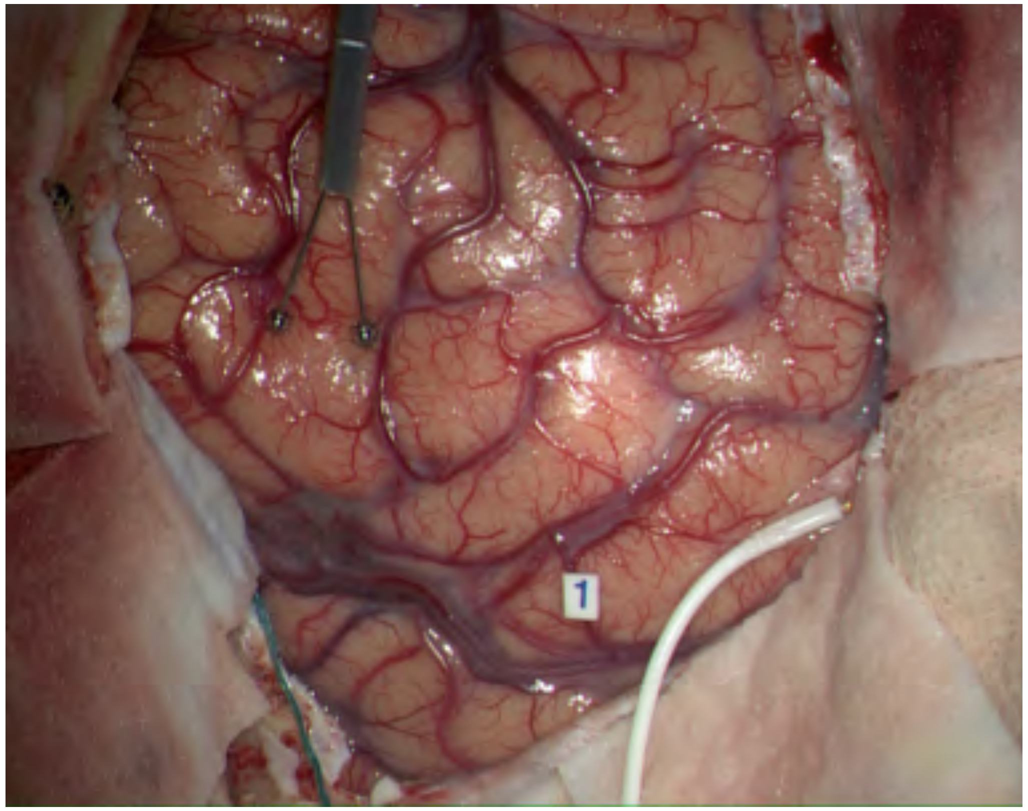


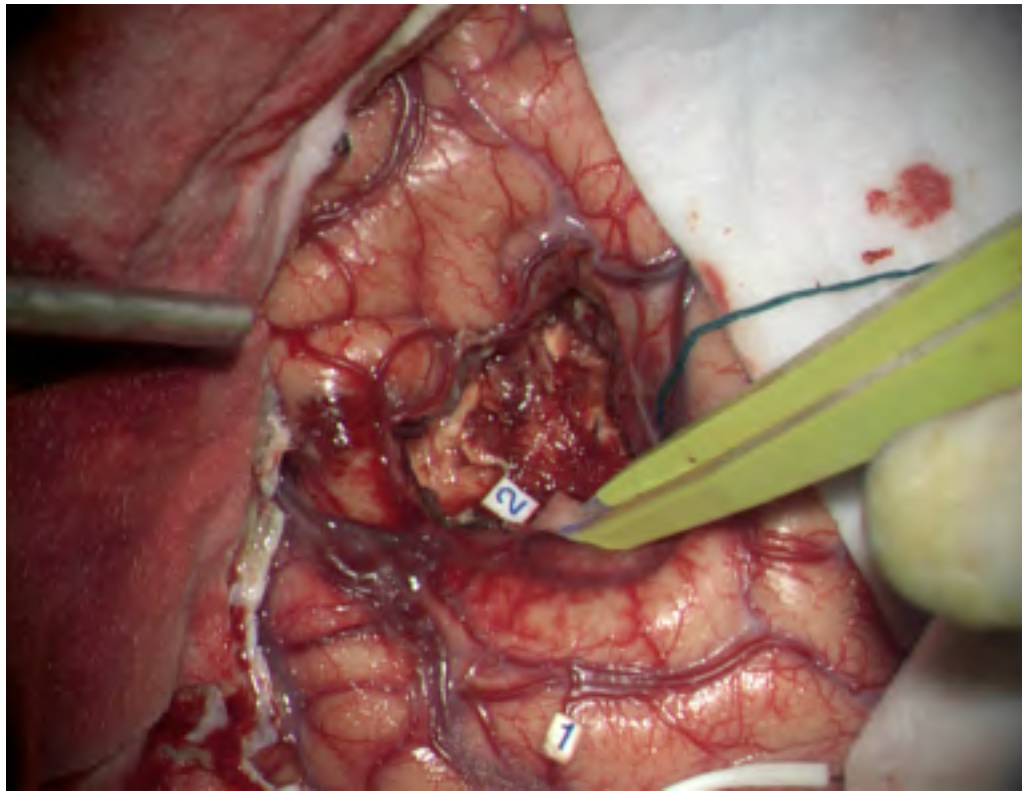
Surgical assessment of the insula. Part 1: surgical anatomy and morphometric analysis of the transsylvian and transcortical approaches to the insula

Arnau Benet, MD, Shawn L. Hervey-Jumper, MD, Jose Juan González Sánchez, MD, PhD, Michael T. Lawton, MD, and Mitchel S. Berger, MD

Illustrative case: language mapping







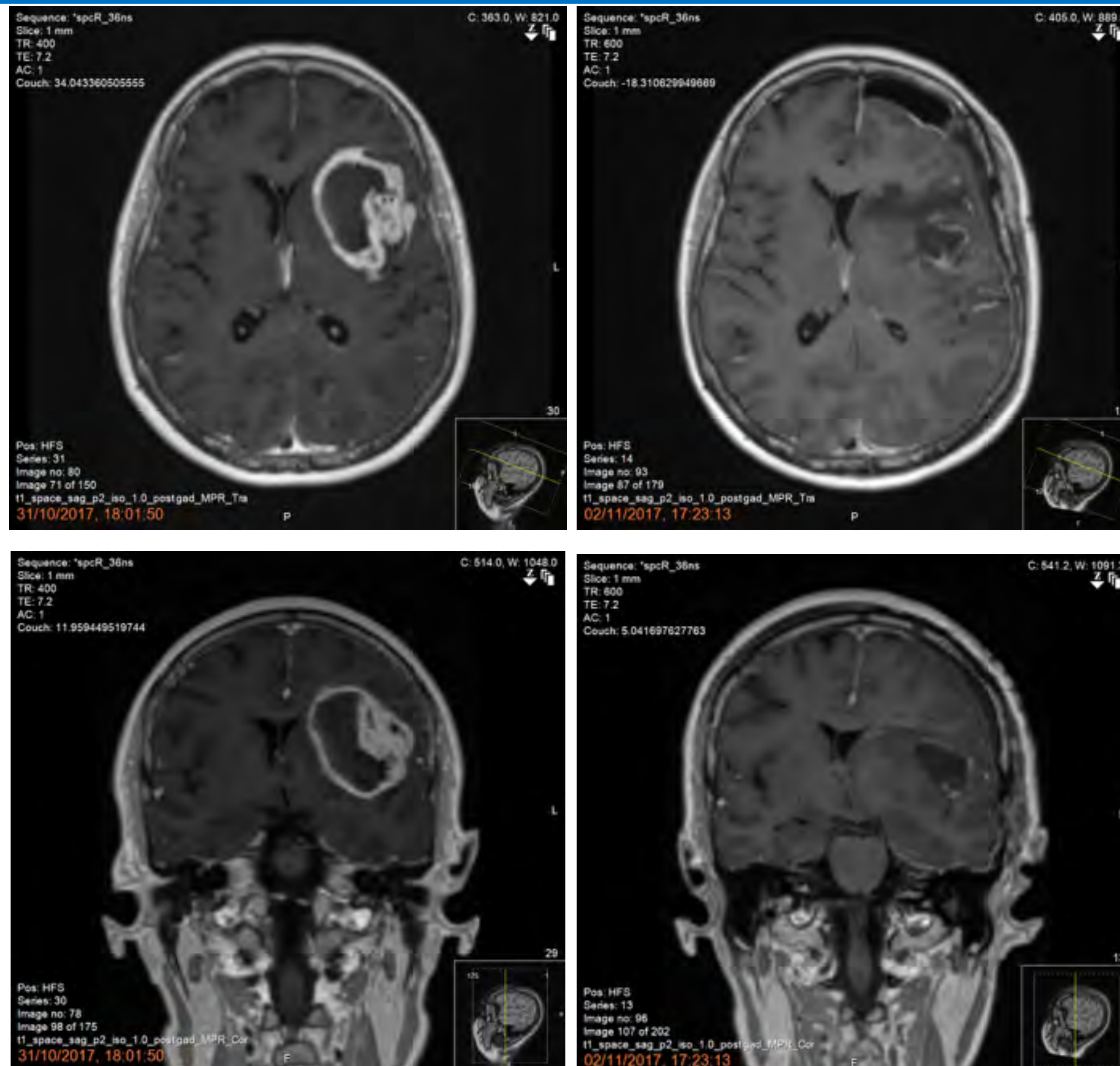
Illustrative case: language mapping

Gross total resection

No language deficit

Diagnosis:
Glioblastoma, IDH1 -, unmethylated MGMT

For Stupp regime



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Conclusions

- TMS is a **non-invasive, safe and effective** adjunct in surgical planning in eloquent brain
- It is reliable in predicting M1/motor mapping
- Promising results in language mapping
- RCTs under way

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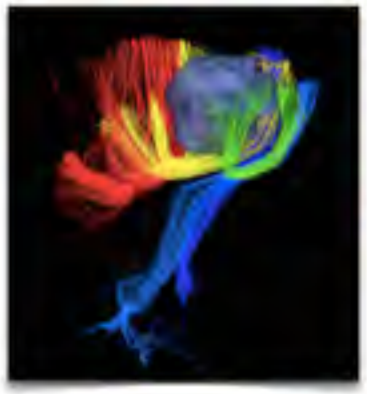
Thank you!



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https://www.elggn2019.com

The **next ELGGN (European Low Grade Glioma Network) meeting will be held in London on 14th & 15th June 2019** organised by the Consultant Neurosurgeons of King's College Hospital.

A **pre-congress course will be held on the 13th of June 2019** at the Gordon Museum of Pathology, Guy's Campus, King's College London.