NEUROLOGICAL APPLICATIONS OF TMS

MOUHSIN SHAFI, MD/PHD

BERENSON-ALLEN CENTER FOR NONINVASIVE BRAIN STIMULATION

BETH ISRAEL DEACONESS MEDICAL CENTER

HARVARD MEDICAL SCHOOL

OVERVIEW OF TALK

- FDA-Approved Indications
  - Presurgical Motor & Language Mapping
  - Migraine
- Diagnosis / Prognosis / Biomarkers
  - Motor outcome after stroke, Epilepsy, Vegetative state
- Therapeutics
  - Review of results across neurologic indications

OVERVIEW OF TALK

- FDA-Approved Indications
  - Presurgical Motor & Language Mapping
  - Migraine
- Diagnosis / Prognosis / Biomarkers / Mechanism
  - Vegetative state vs MCS; motor outcome after stroke; ezogabine in ALS; circuit hyperexcitability in epilepsy
- Therapeutics
  - Review of results across neurologic indications

US FDA-CLEARANCES FOR TMS

- Current FDA-cleared indications include
  - Major Depressive Disorder
  - **Presurgical motor and language mapping**
  - **Migraines with aura**
  - OCD
  - Smoking cessation
  - Anxiety comorbid with MDD

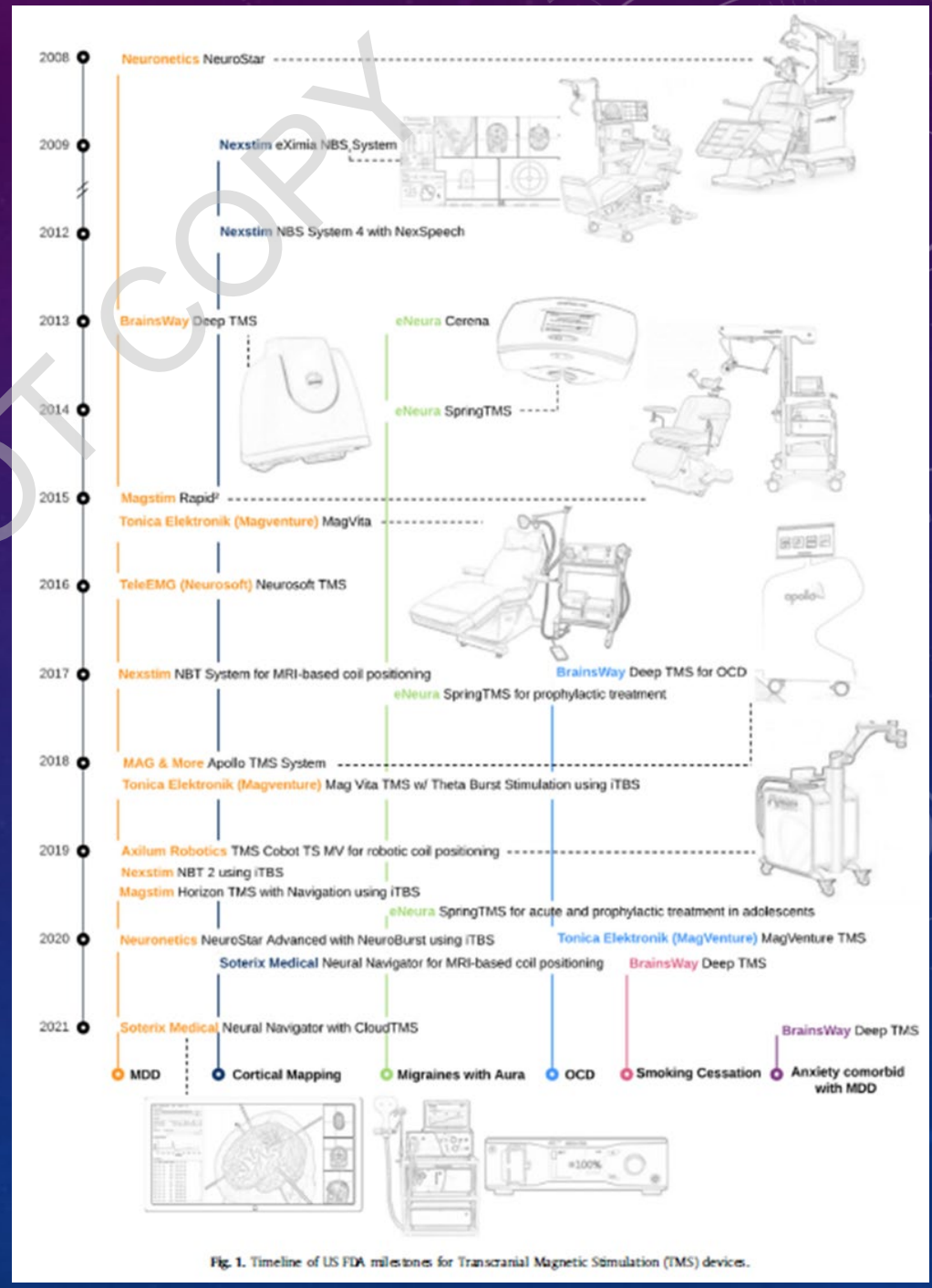
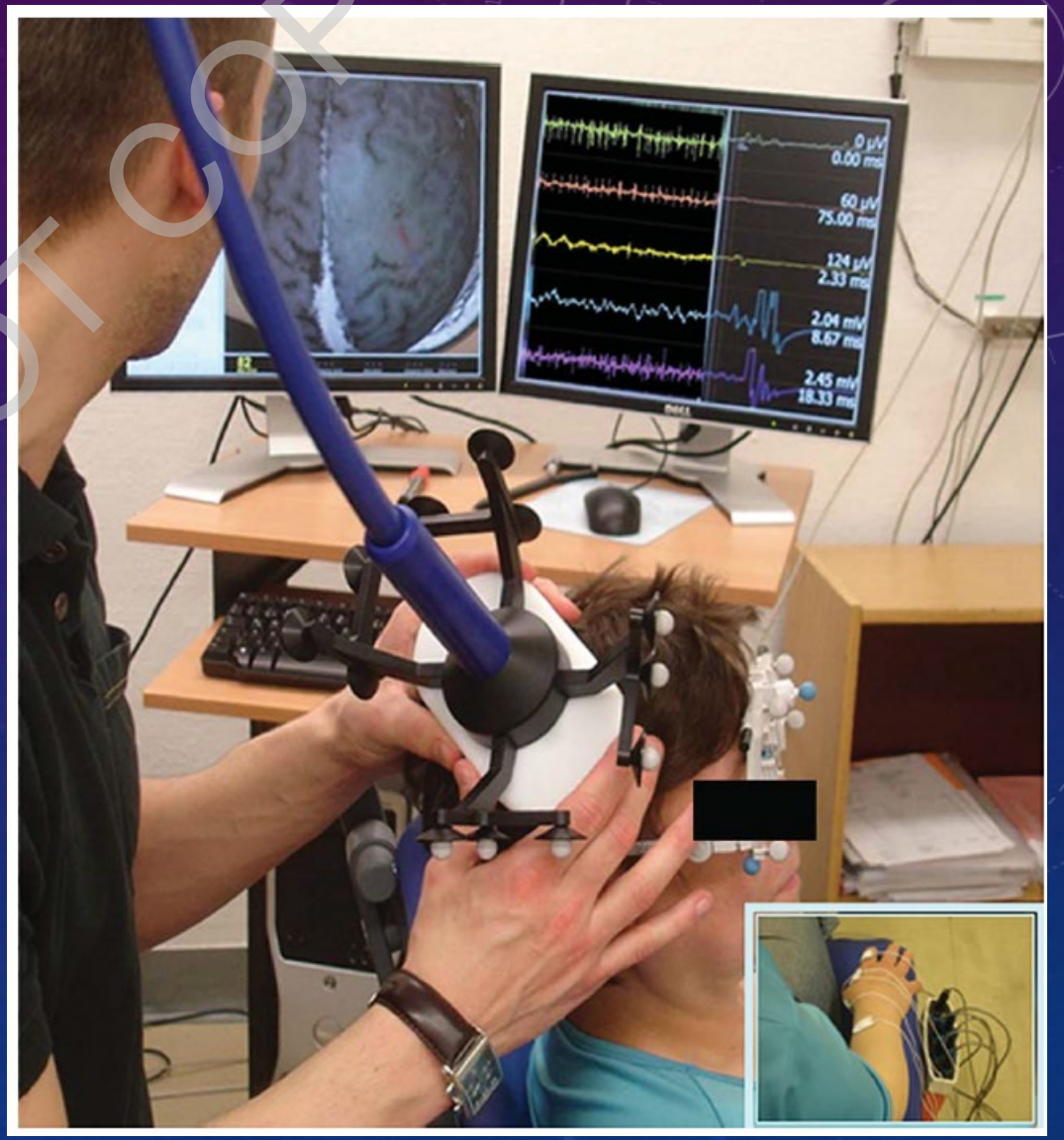


Fig. 1. Timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices.

Cohen 2022 *Brain Stimulation*

PRESURGICAL MOTOR / LANGUAGE MAPPING

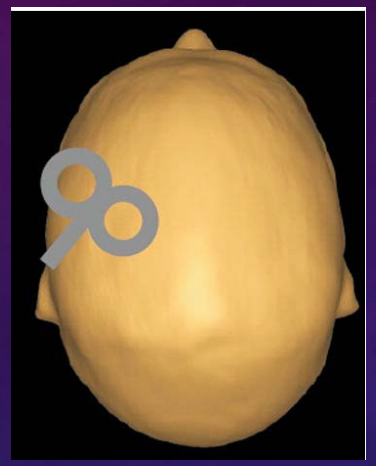
- FDA clearance of NBS device for:
  - Mapping of the primary motor cortex
  - Localization of cortical areas that do NOT contain essential speech function
  - For pre-procedural planning

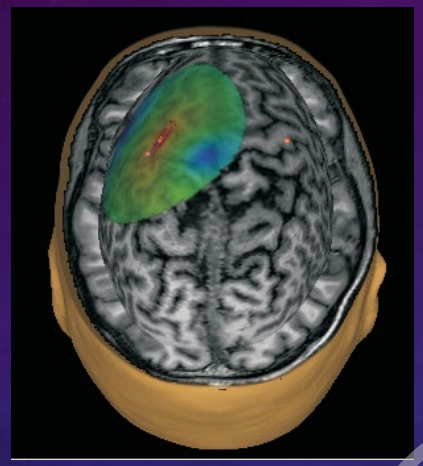


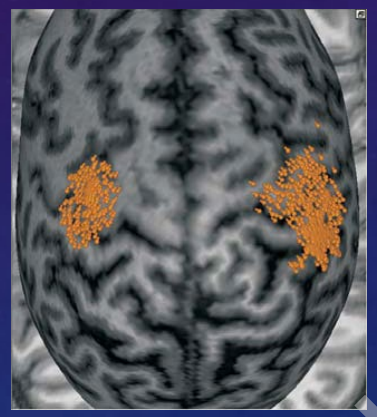
Picht 2011 *Neurosurgery*

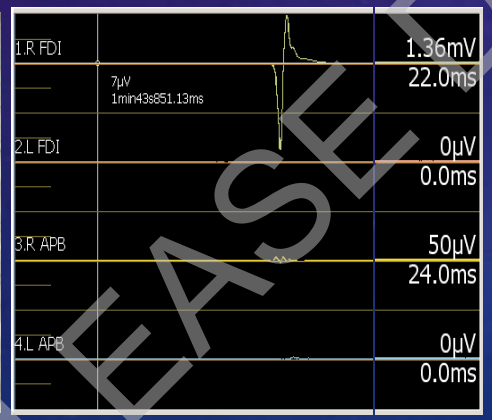
Nexstim

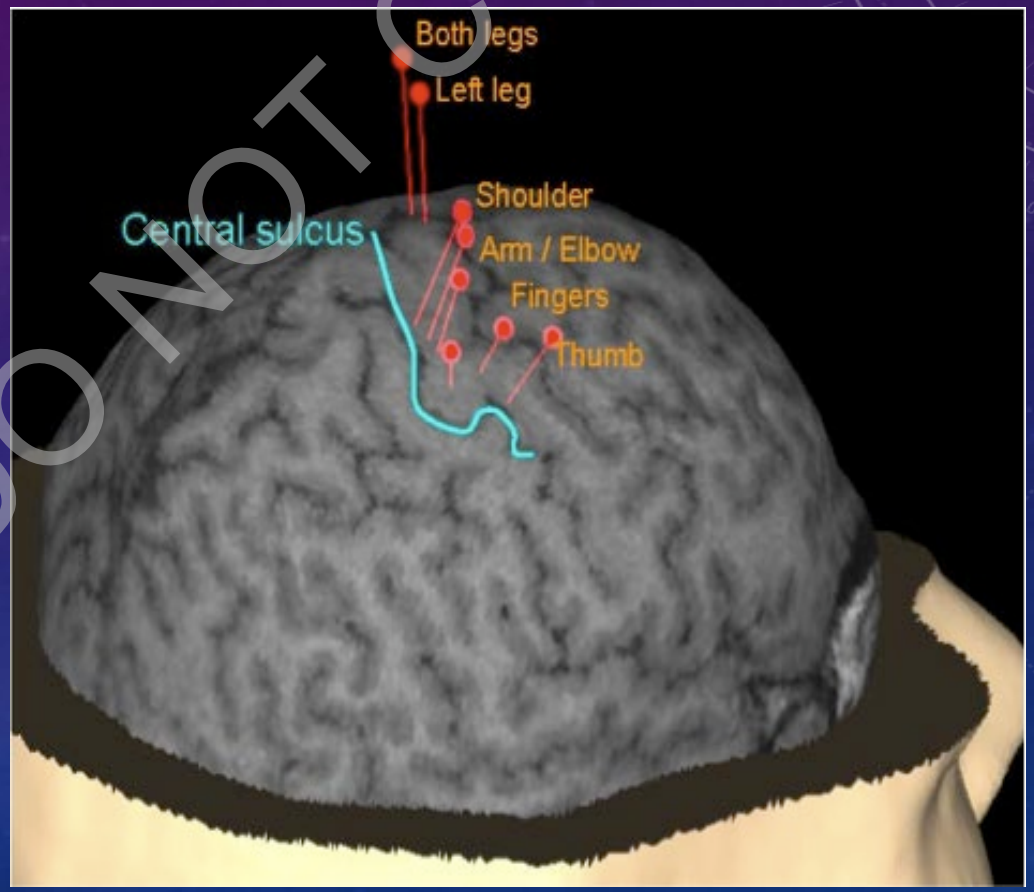
Motor Cortical Output Mapping







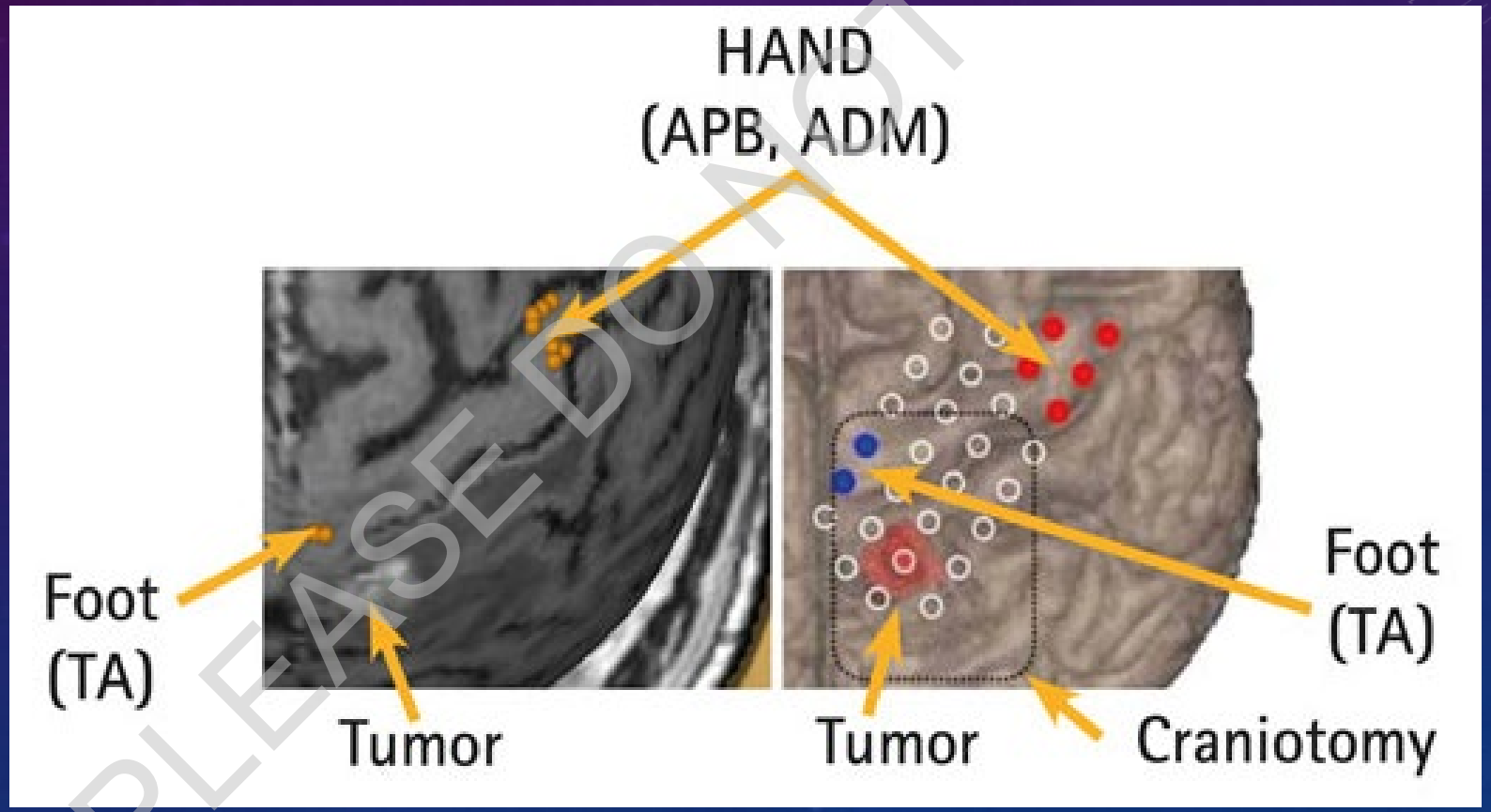




Nagib et al. *Neurosurg Clin* 2011

MOTOR CORTICAL OUTPUT MAPPING

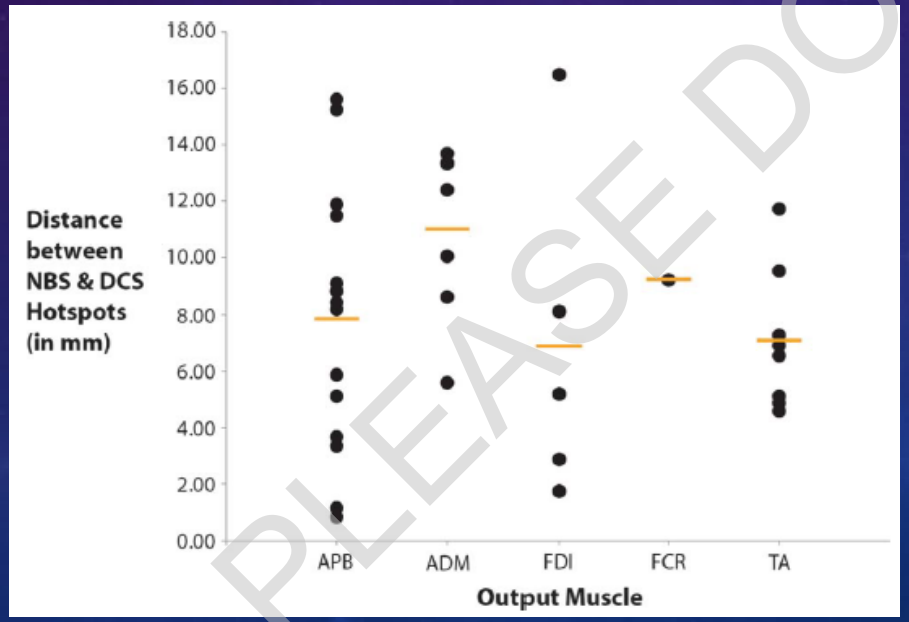
COMPARING NONINVASIVE AND INVASIVE MAPPING



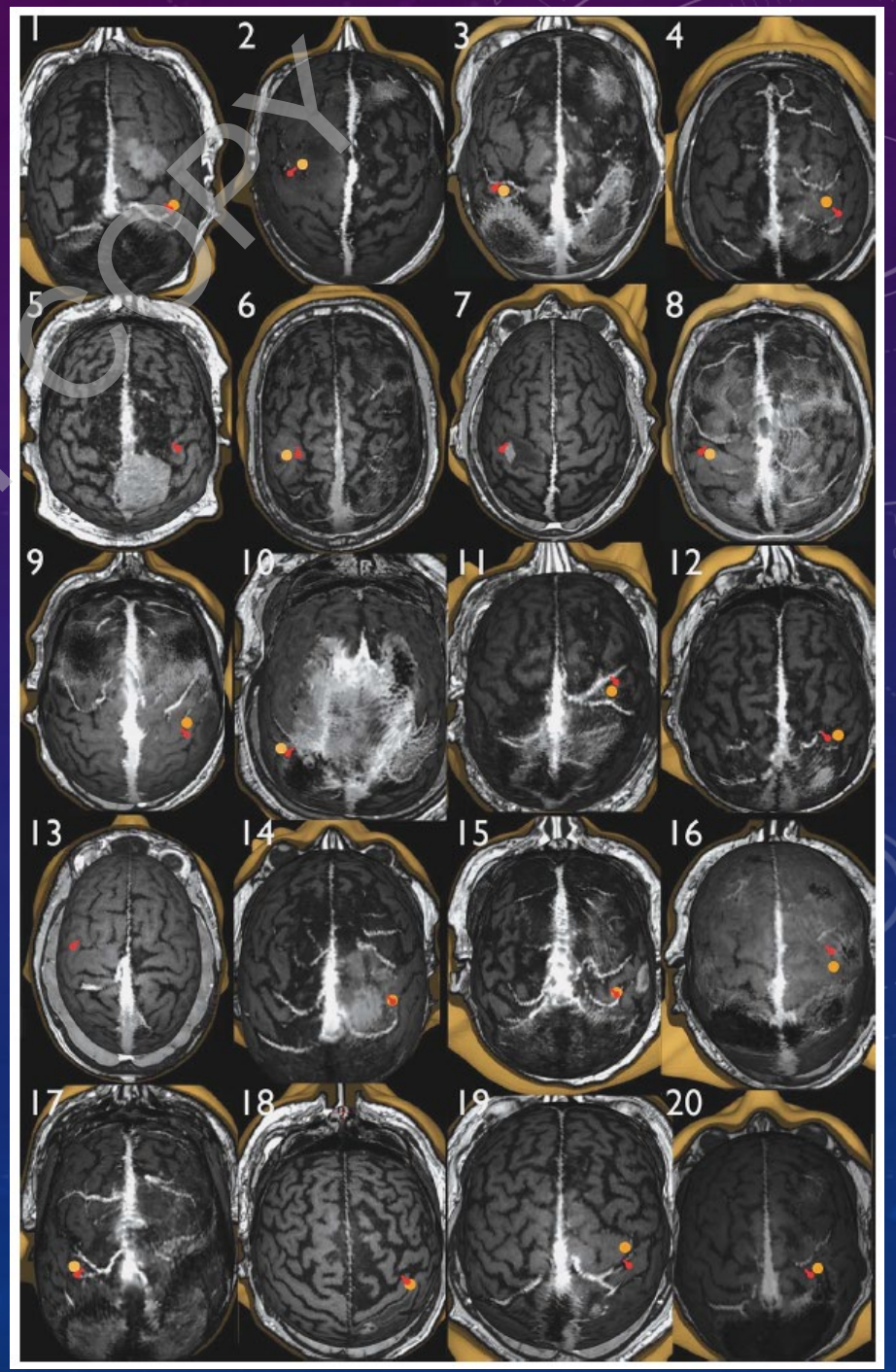
Najib et al. *Neurosurg Clin* 2011

MOTOR MAPPING

- nTMS versus Direct Cortical Stimulation (DCS):
  - Mean distance between nTMS & DCS hotspots was 7.83 +/- 1.18 mm for APB (95% CI 5.36 to 10.36 cm)
  - nTMS and DCS hotspots were in same gyrus for all patients



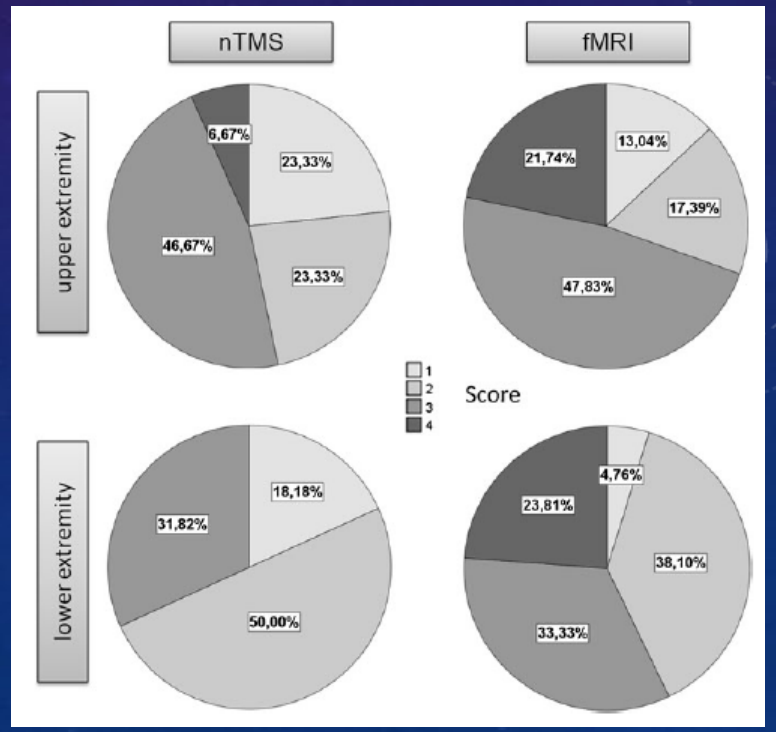
Picht 2011 *Neurosurgery*



nTMS VS fMRI

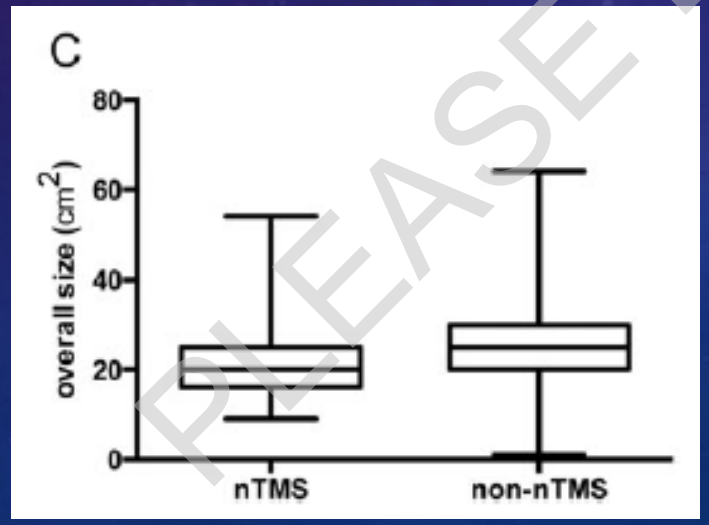
- Several studies have evaluated accuracy of motor mapping with nTMS vs fMRI (with DCS as gold standard)
  - Forster 2011, *Neurosurgery*: 10 pts, mean distance to DCS hotspot 10.5 +/- 5. 7 mm for nTMS vs 15.0 +/- 7.6 mm for fMRI
  - Mangraviti 2013, *Neurol Sci*: 7 patients, mean distance to DCS hotspot 8.5 +/- 4.6 mm for nTMS vs 12.9 +/- 5.7 mm for fMRI

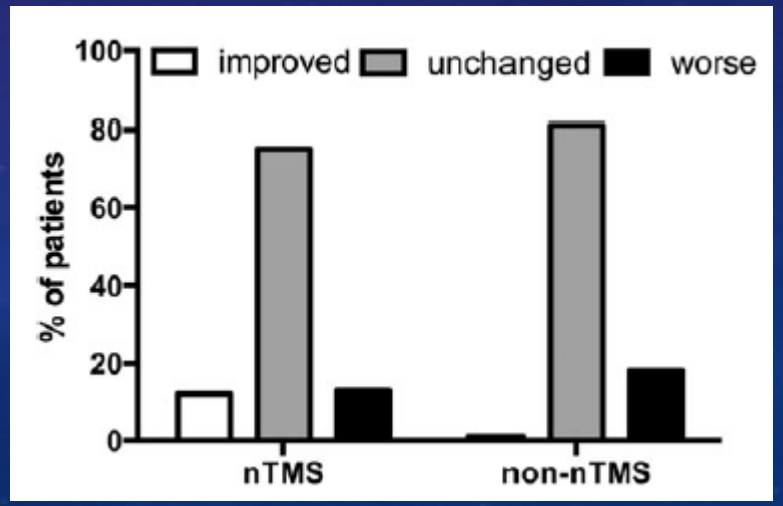
Coburger 2013, *Neurosurg Rev*: 30 patients; all 30 completed nTMS, whereas only 23 completed fMRI. Authors binned results into 4 levels, where 1 is most accurate, 4 is least accurate



MOTOR MAPPING W/ nTMS IMPROVES OUTCOME?

- Krieg 2014 *Neuro-Oncology*: Compared outcomes in 100 consecutive patients bw 2010-2013 vs 100 historical controls without nTMS from immediately prior period
  - All patients underwent intraoperative MEP monitoring as well
  - Craniotomy size significantly smaller in nTMS group
  - 12 pts in nTMS group improved, vs only 1 in control group
  - Residual tumor in 22% of nTMS group vs 42% of controls





MOTOR MAPPING W/ NTMS IMPROVES OUTCOME?

- Frey 2014 *Neurosurgery*: Compared outcomes in 250 consecutive pts from 2007 – 2012 with 115 controls from 2005-2007
  - 165 cases with intraoperative stimulation mapping, nTMS location of primary motor cortex confirmed in all cases.
  - In 82 cases with navigated intraop stim, mean distance bw nTMS and DCS hotspot was 6.2 mm (range 0.4 – 14.8 mm)
  - Gross total resection achieved in 59% of nTMS group vs only 42% of historical control, with no change in post-op deficits

Progression-free survival significantly higher in nTMS group than in control group (15.5 vs 12.4 months), although no change in overall survival

Risk stratification based on nTMS cartography	
Suspected involvement of motor cortex in 215/250 (86%) cases	
True eloquent 161 (74.9%)	False eloquent 54/215 (25.1%)
Net change biopsy/no surgery to surgery 37/54 → Conversion rate 68.5%	

MOTOR MAPPING W/ nTMS IMPROVES OUTCOME?

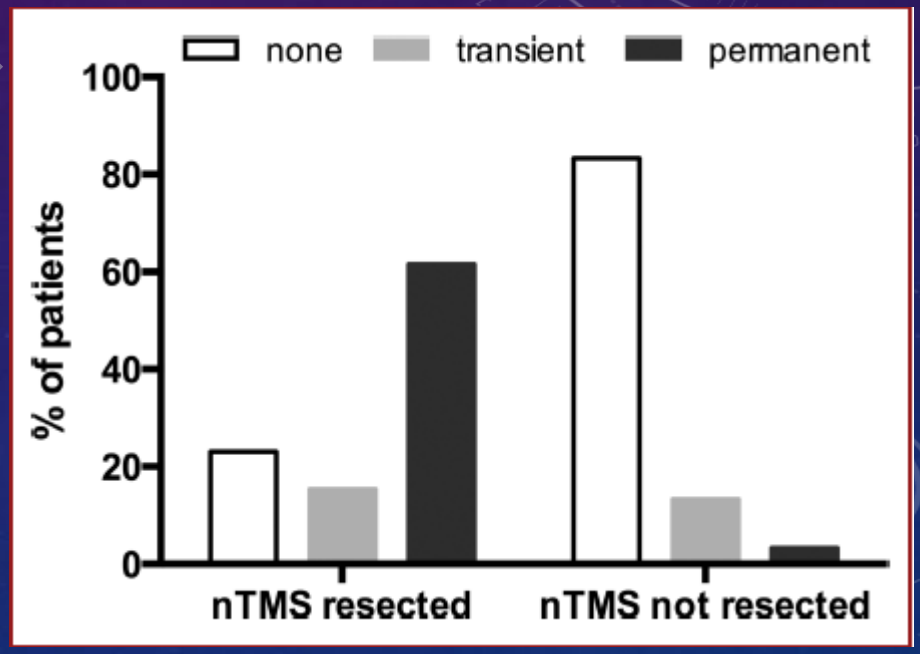
- Krieg 2015 *BMC Cancer*: Compared nTMS outcomes in 70 patients with high-grade (grade III or grade IV) glioma vs 70 historical controls
  - Trend towards decreased permanent weakness in nTMS group
  - Greater survival in grade III tumor patients in nTMS group due to greater percentage achieving gross total resection (but not present across all patients)
  - Higher survival rate at 3, 6, 9 and 12 months in nTMS group

Table 5 Survival

		nTMS	non-nTMS	p-value
All tumors	Overall survival (months)	15.7 ± 10.9	11.9 ± 10.3	0.1310
	3 months survival rate (%)	93.7	80.9	0.0298
	6 months survival rate (%)	88.5	62.7	0.0015
	9 months survival rate (%)	72.9	50.7	0.0167
	12 months survival rate (%)	58.7	40.3	0.0544

AND RESECTING nTMS MOTOR AREAS IS BAD

- Moser 2017 *Neurosurgery*: Evaluated motor outcomes in 43 patients with Rolandic or prerolandic gliomas undergoing nTMS
  - 31 patients had nTMS motor points in prerolandic regions
  - 13/43 underwent resection of nTMS-positive points; 8/13 suffered permanent paresis
  - 30/43 did not undergo any resection of nTMS-positive points; only 1/30 suffered permanent paresis



LANGUAGE MAPPING

- Picht 2013, *Neurosurgery*: Evaluated nTMS and DCS responses during language mapping in 20 patients with tumors close to left-sided language areas

TABLE 7. Sensitivity, Specificity, and Positive/Negative Predictive Values Over All Brain Regions in All Patients[a]

	All Regions			Classic Broca's Area		
	Charité Berlin (B1-B6)	TU Munich (M1-M14)	All (N = 19)	Charité Berlin (B1-B6)	TU Munich (M1-M14)	All (N = 19)
Sensitivity	0.89	0.90	0.90	1.0	1.0	1.0
Specificity	0.5	0.19	0.24	0.43	0	0.13
Positive predictive value	0.47	0.34	0.36	0.6	0.56	0.57
Negative predictive value	0.9	0.81	0.84	1.0	N/A	1.0

FIGURE 3. *Number of true positives for each region.*

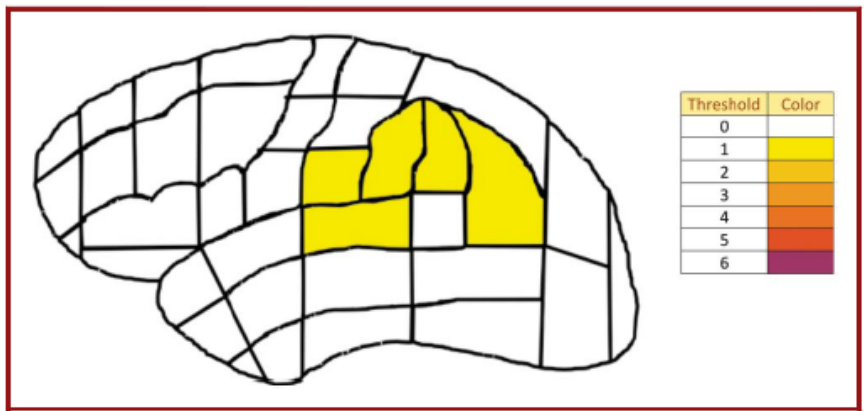
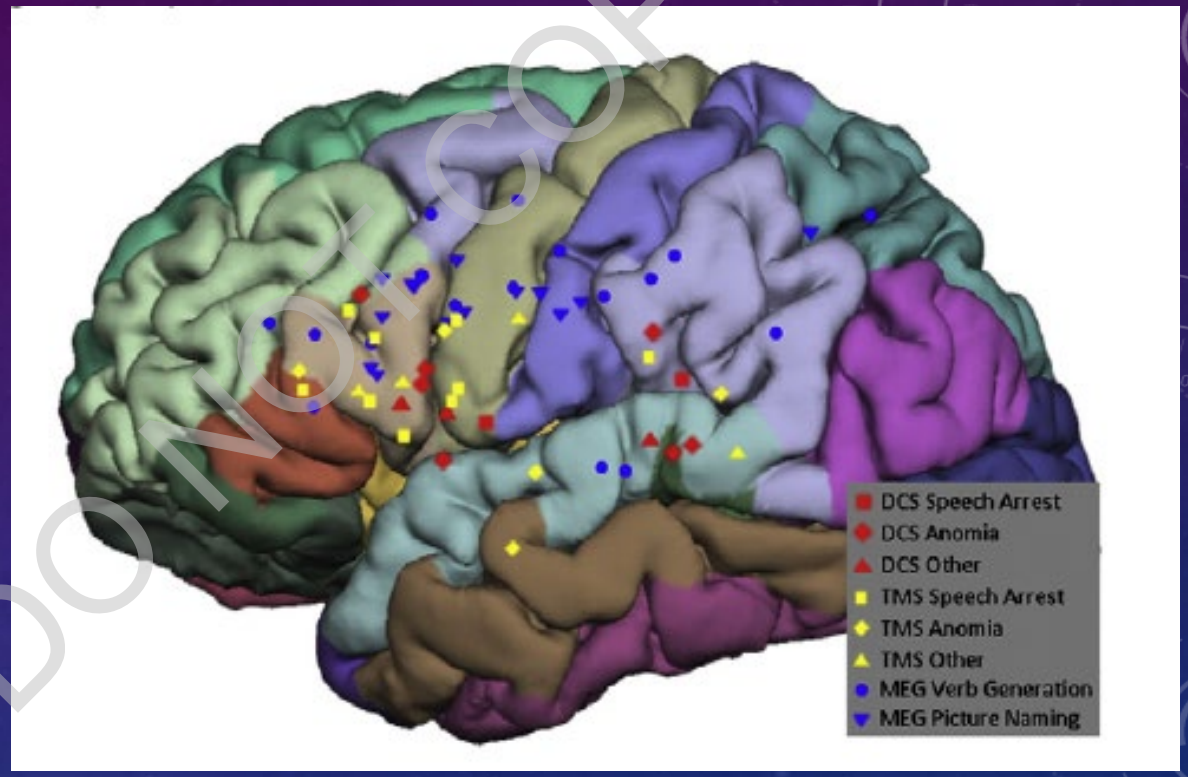


FIGURE 6. *Number of false negatives for each region.*

LANGUAGE MAPPING …

- A subsequent study (Tarapore 2013, *NeuroImage*) also demonstrated high negative predictive value, with improved specificity



	DCS+	DCS−	
nTMS+	9	4	PPV 69%
nTMS−	1	169	NPV 99%
	Sens. 90%	Spec. 98%	

COMPARED WITH FMRI AND DCS

Ille 2015a, b: Compared language mapping results from rTMS (C) and fMRI (D) with those from DCS (B)

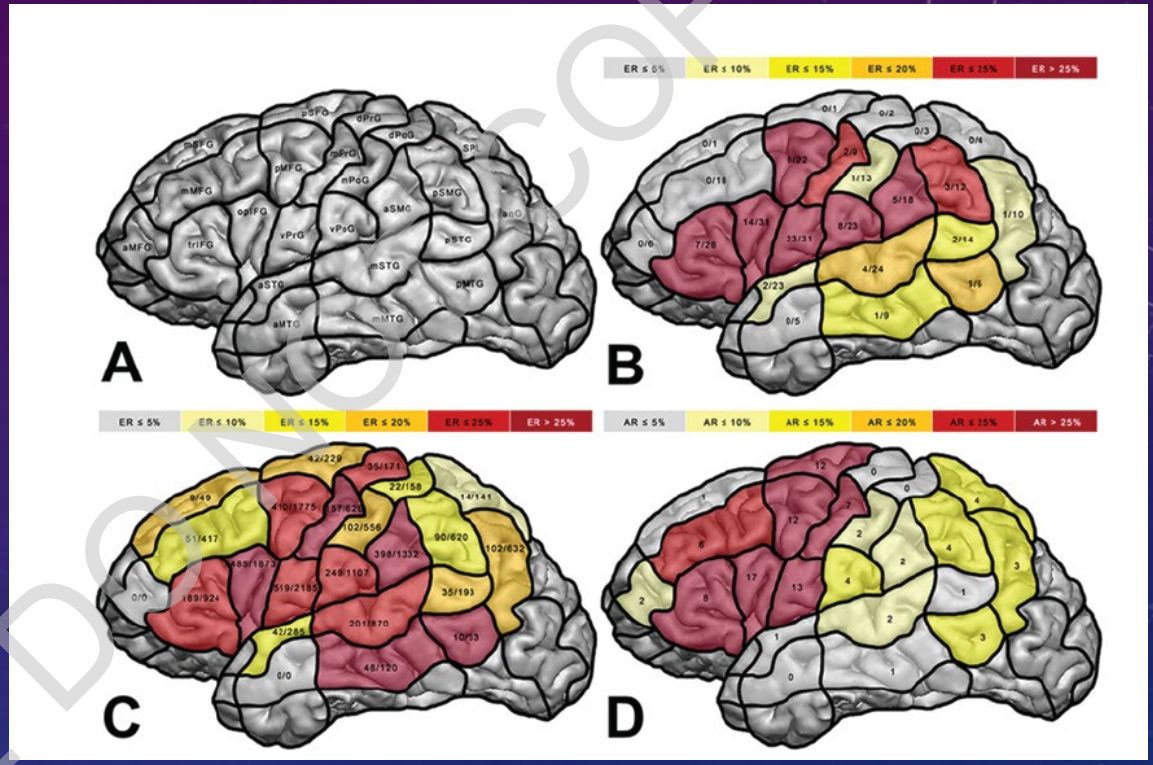


TABLE 3. Overall results without dependency on lesion location*

	rTMS vs DCS			fMRI vs DCS		
Parameter	All Mapped Regions	Anterior Regions	Posterior Regions	All Mapped Regions	Anterior Regions	Posterior Regions
PPV	34% (27–41)	56% (43–69)	22% (13–35)	48% (35–62)	61% (43–77)	33% (0–91)
NPV	91% (72–99)	100% (2–100)	100% (48–100)	79% (73–84)	53% (35–70)	79% (67–89)
Sensitivity	97% (89–100)	100% (90–100)	100% (75–100)	40% (28–52)	58% (41–74)	7% (0–34)
Specificity	15% (9–22)	4% (0–18)	10% (3–22)	84% (78–89)	56% (38–74)	96% (87–100)

AND MAY HAVE BENEFICIAL EFFECTS

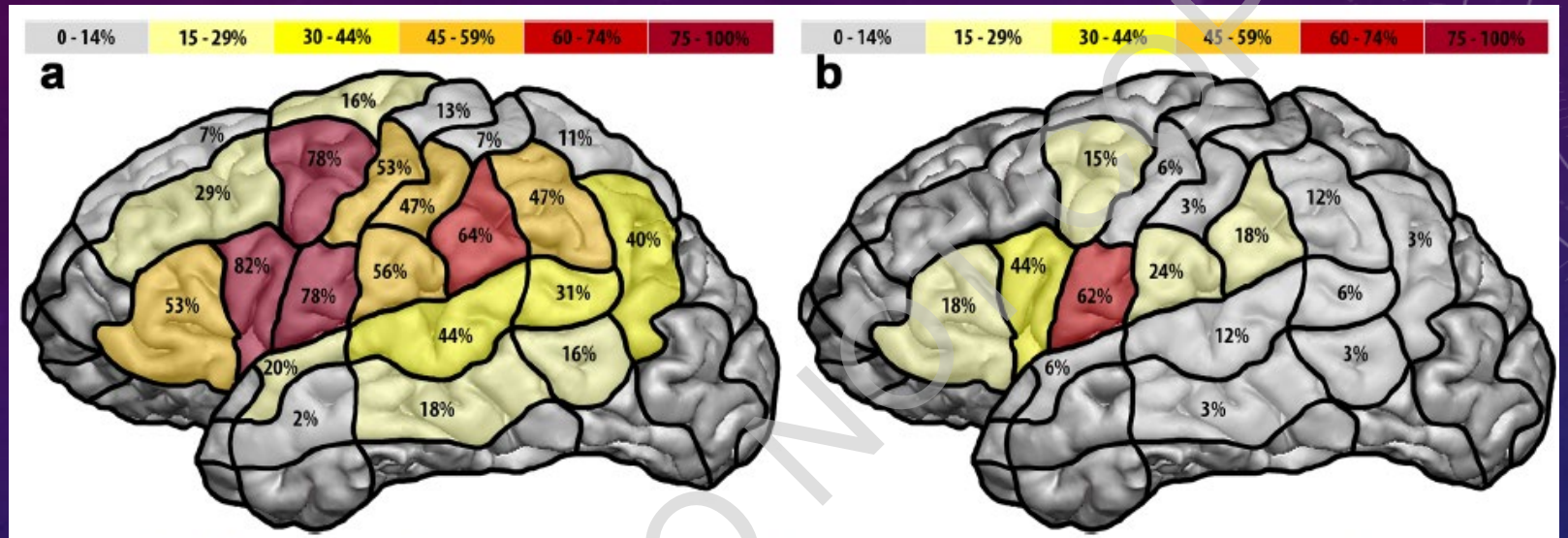
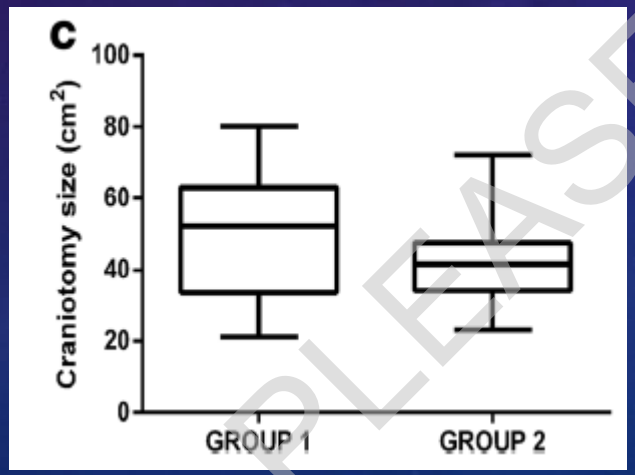
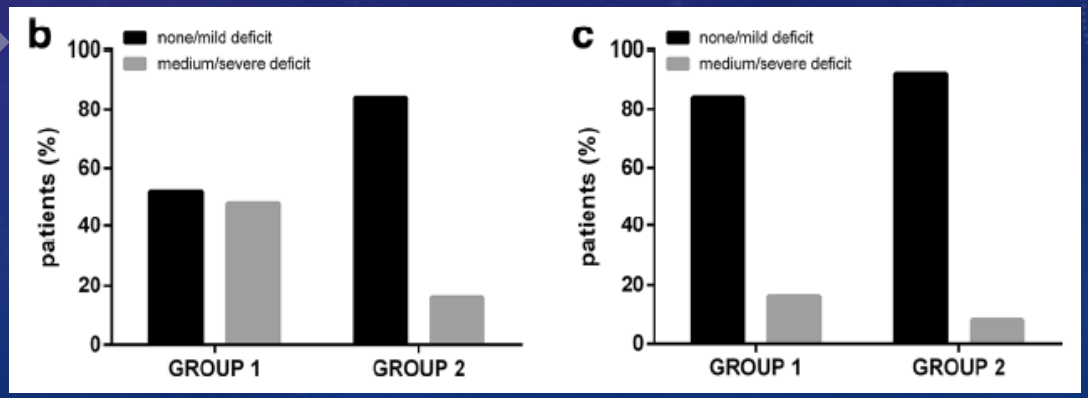


Figure 1 rTMS and DCS error maps. This figure graphically illustrates the language mapping results gained by preoperative rTMS **(a)** or intraoperative direct cortical stimulation (DCS) **(b)** for both patient cohorts together. The percentage results from the number of individuals with no-response errors per cortical parcellation system (CPS) region divided by the number of stimulated patients.



Craniotomy size smaller w/ TMS



Early language deficits decreased

Sollman 2015

PREOPERATIVE MAPPING USING NTMS

- Review paper: *Clinical Neurophysiology 2016*

The value of preoperative functional cortical mapping using navigated TMS

Intérêt de la cartographie corticale fonctionnelle préopératoire utilisant la TMS neuronaviguée

Jean-Pascal Lefaucheur [a,b,*], Thomas Picht [c]

- Operationalization and workflow: *World Neurosurgery* 2017

Implementing Functional Preoperative Mapping in the Clinical Routine of a Neurosurgical Department: Technical Note

Nico Sollmann[1,2], Bernhard Meyer[1], Sandro M. Krieg[1,2]

TMS MAPPING IN CHILDREN

Clinical Utility of Transcranial Magnetic Stimulation (TMS) in the Presurgical Evaluation of Motor, Speech, and Language Functions in Young Children With Refractory Epilepsy or Brain Tumor: Preliminary Evidence

Shalini Narayana[1,2,3], Savannah K. Gibbs[2], Stephen P. Fulton[1,2], Amy Lee McGregor[1,2], Basanagoud Mudigoudar[1,2], Sarah E. Weatherspoon[1,2], Frederick A. Boop[2,4,5] and James W. Wheless[1,2]*

epilepsy or brain tumor using TMS. All children were tested in the awake state. Motor cortices were successfully mapped in 90% of children under 3 years of age, with TMS eliciting reliable MEPs and/or CSPs. In this young cohort, we were able

Narayana 2021

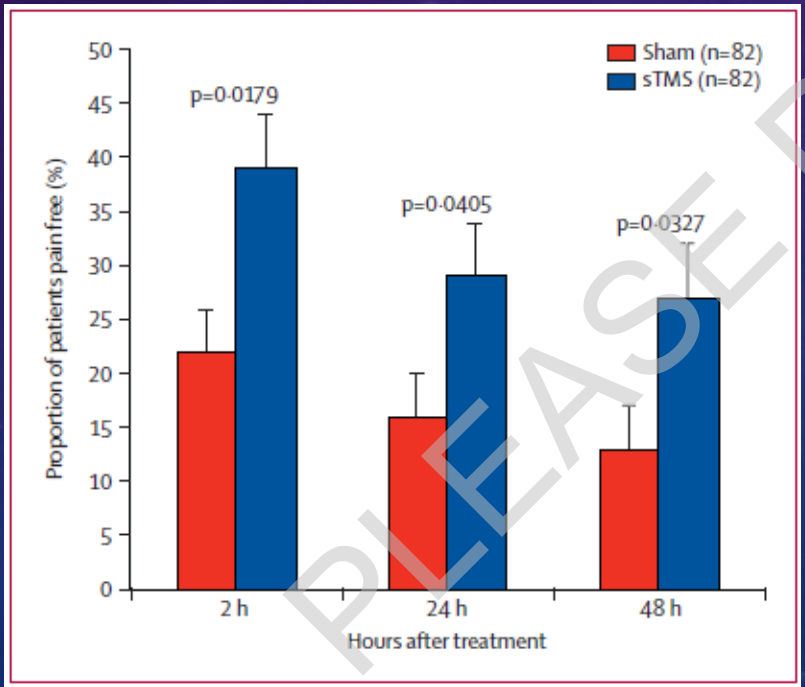
ABORTIVE THERAPY MIGRAINE

- FDA approval for the SpringTMS single-pulse portable TMS system obtained for abortive therapy of migraine with aura
  - 2 pulses of TMS administered approximately 30s apart to occipital region

Image from www.medgadget.com

EFFICACY IN ACUTE MIGRAINE

- Randomized 201 patients with migraine with aura, 1-8 episodes per month, aura for at least 30% of episodes
  - 201 randomized, 164 had migraines and treated
- Higher pain-free response rates after 2 hours (39% in verum vs 22% in sham), sustained at 24 and 48 hours



HOWEVER, a number of secondary endpoints (patients who achieved no or mild pain 2h after treatment, use of rescue drugs, consistency of pain relief, global assessment of relief) showed no significant differences

Lipton, *Lancet Neurology* 2010

PREVENTATIVE THERAPY FOR MIGRAINE

- FDA approval for the portable TMS system obtained for preventative therapy of migraine (2017).
  - The ESPOUSE Study was a multicenter, prospective, single-arm, open label, post-market observational study to evaluate sTMS for the preventive treatment of migraine with or without aura.
  - 4 pulses of TMS administered 2x per day for the prevention of migraine (and 3 pulses per day allowed for abortive therapy)
  - 263 patients enrolled. After exclusions, a full analysis set (FAS) included 132 participants
  - mean 9.06 headache days per month at baseline. After treatment, this dropped by 2.75 days, a significant decrease compared to a statistical estimate of expected placebo response ($P < .0001$).

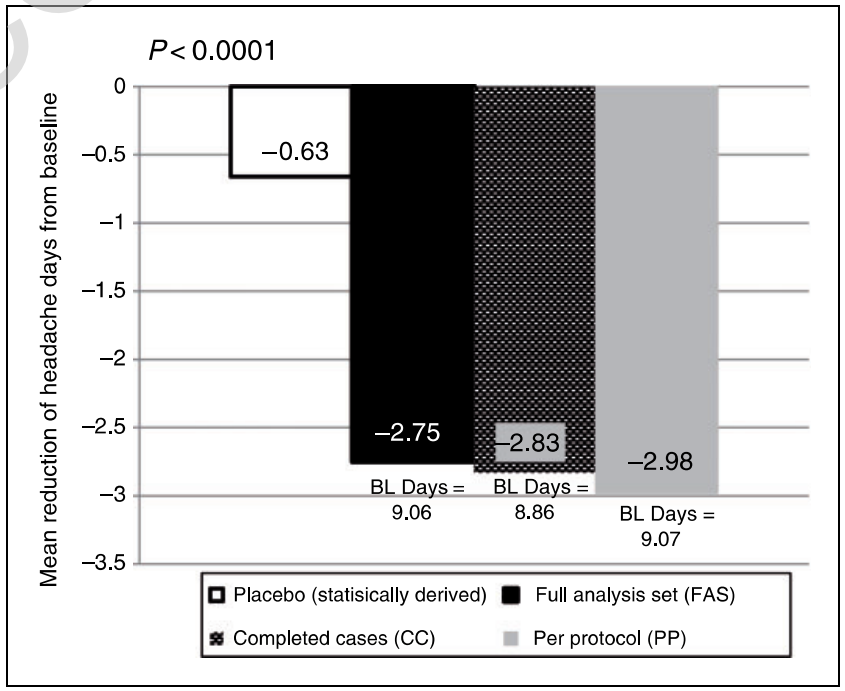


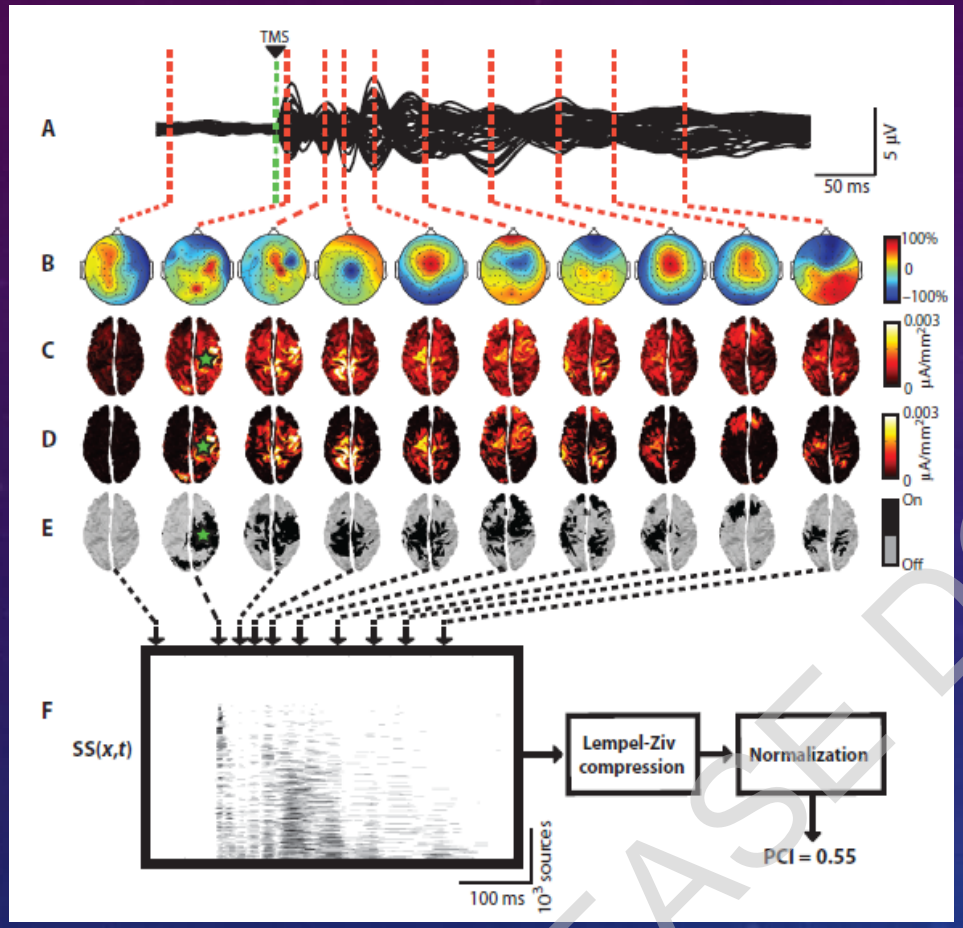
Figure 3. Primary effectiveness endpoint: Mean reduction in headache days.

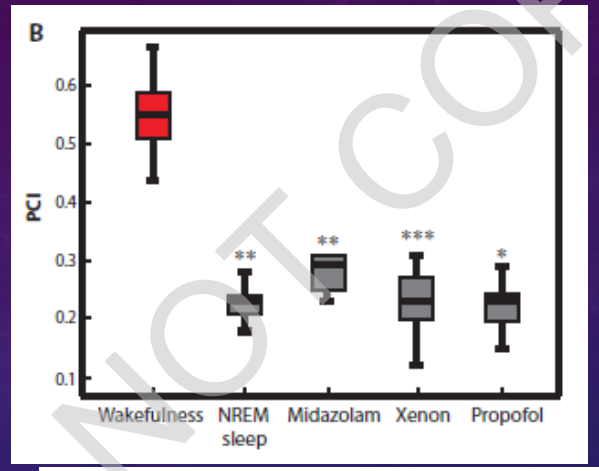
Starling *Cephalagia* 2018

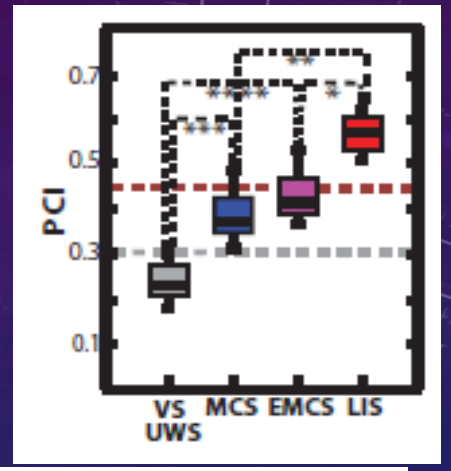
OVERVIEW OF TALK

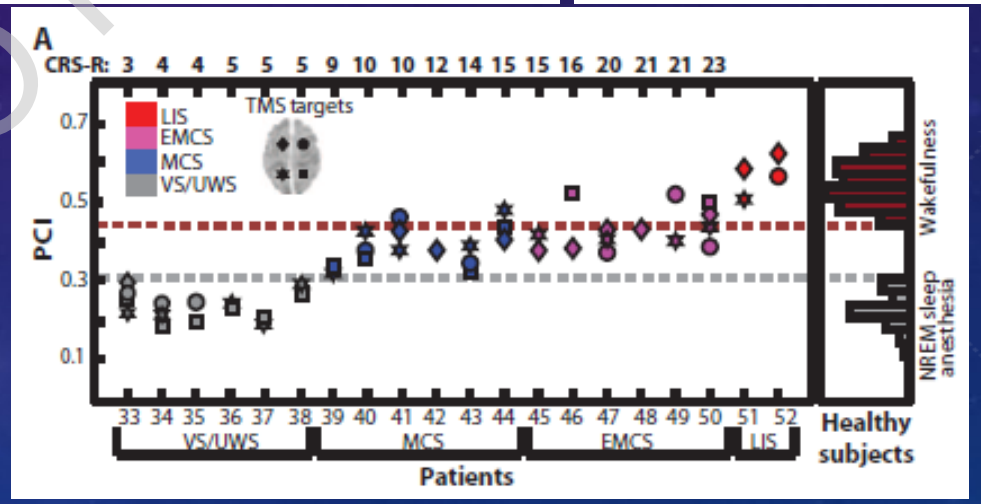
- FDA-Approved Indications
  - Presurgical Motor & Language Mapping
  - Migraine
- Diagnosis / Prognosis / Biomarkers / Mechanism
  - Vegetative state vs MCS; motor outcome after stroke; ezogabine in ALS; circuit hyperexcitability in epilepsy
- Therapeutics
  - Review of results across neurologic indications

Diagnosis of Persistent Vegetative vs Minimally Conscious State





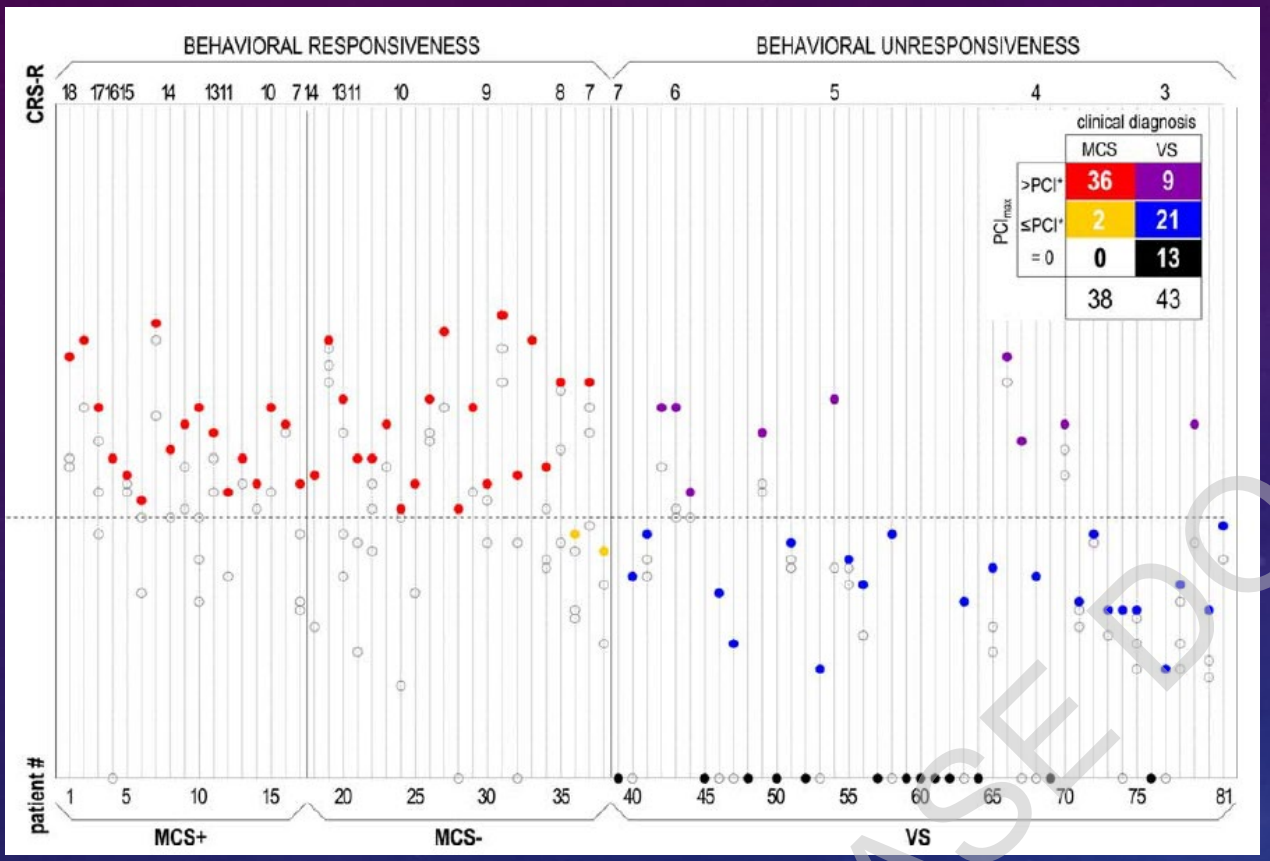


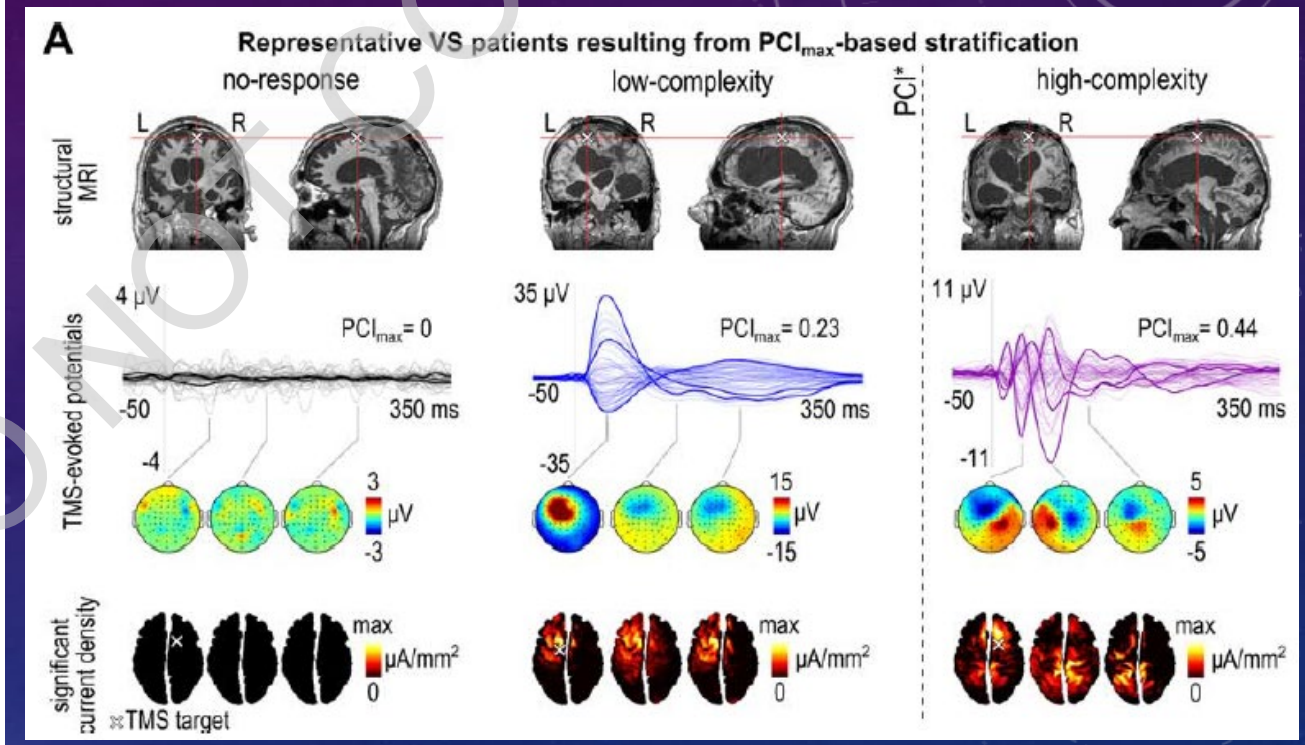


Decreased complexity of evoked response in subjects with loss of consciousness due to any etiology, and in patients with vegetative versus minimally conscious versus locked-in states

Casali 2013, *Science Trans Med*

DIAGNOSIS OF PVS VS MCS IN LARGE SAMPLES …





- PCI cutoff for consciousness developed; 36/38 MCS above cutoff, whereas only 9/43 VS above cutoff
- At 6 months, of patients initially in VS, 6/9 with highPCI had transitioned to MCS, versus 5/21 with low-complexity PCI and 0/13 with no PCI

Casarotto 2016 *Ann Neurol*

MEPS PREDICT FUNCTIONAL RECOVERY AFTER ACUTE STROKE

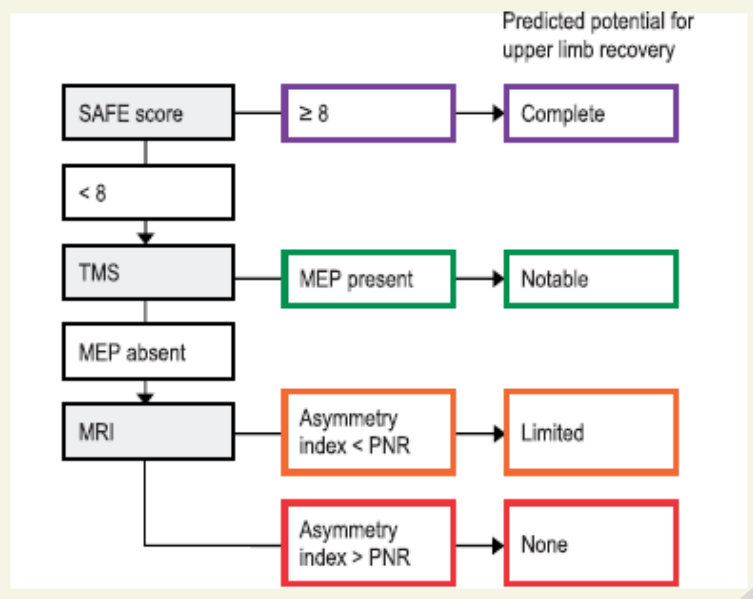
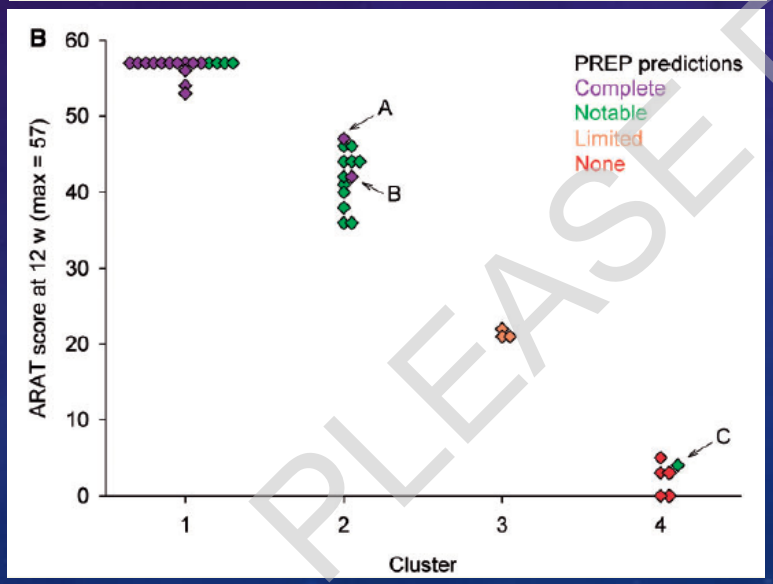
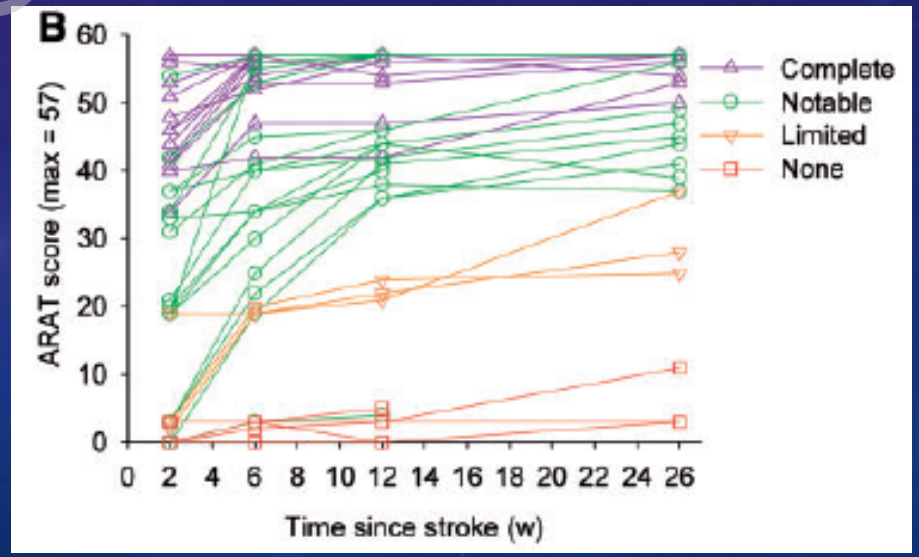


Table 1 Recovery definitions and examples of feasible

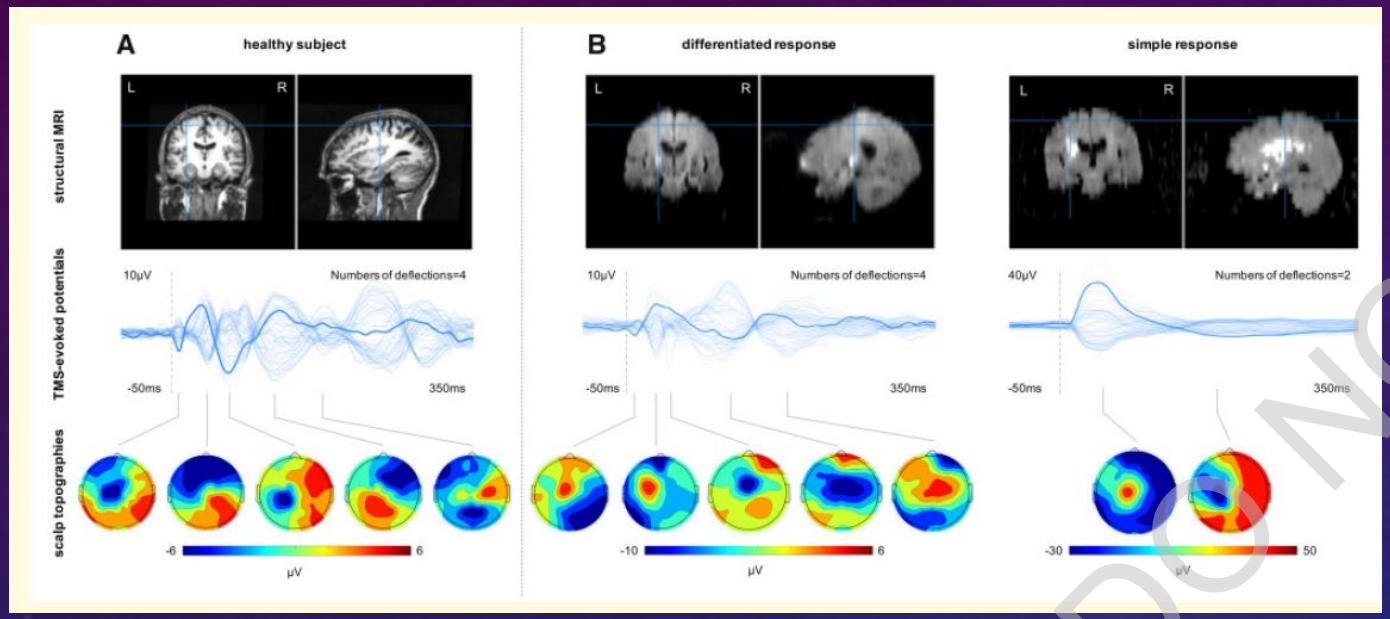
Recovery	Definition
Complete	The patient has the potential to return to normal or near-normal hand and arm function within 12 weeks.
Notable	The patient has the potential to be using their affected hand and arm in most activities of daily living within 12 weeks, though normal function is unlikely.
Limited	The patient has the potential to have some movement in their affected hand and arm within 12 weeks, but it is unlikely to be used functionally for activities of daily living.
None	The patient can expect to have minimal movement in their affected hand and arm, with little improvement at 12 weeks.

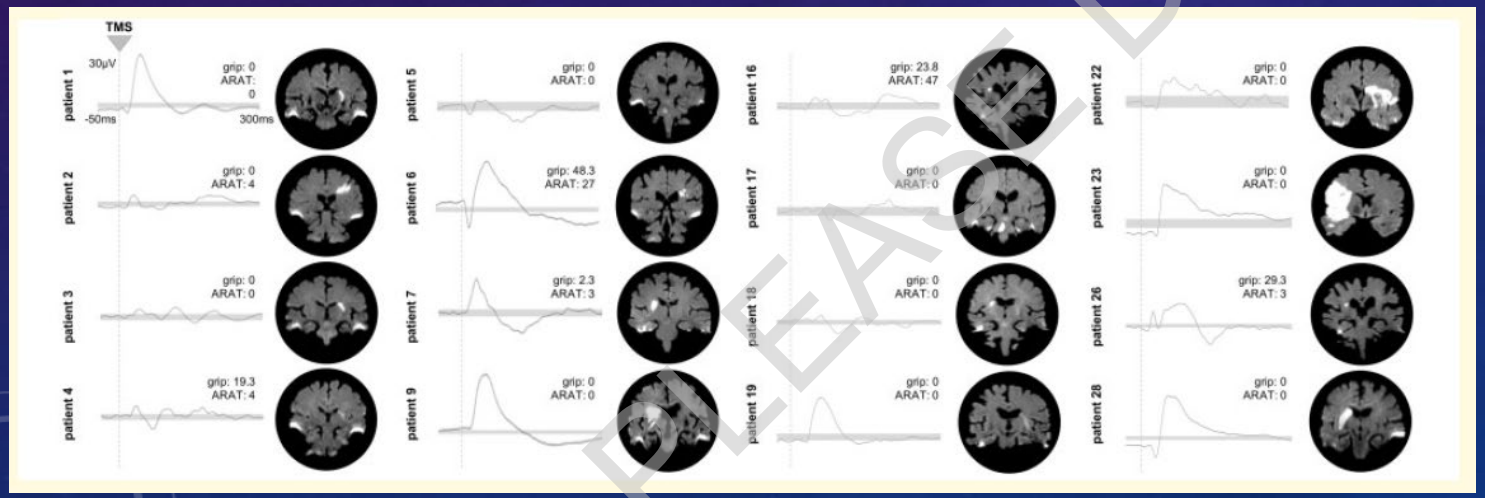


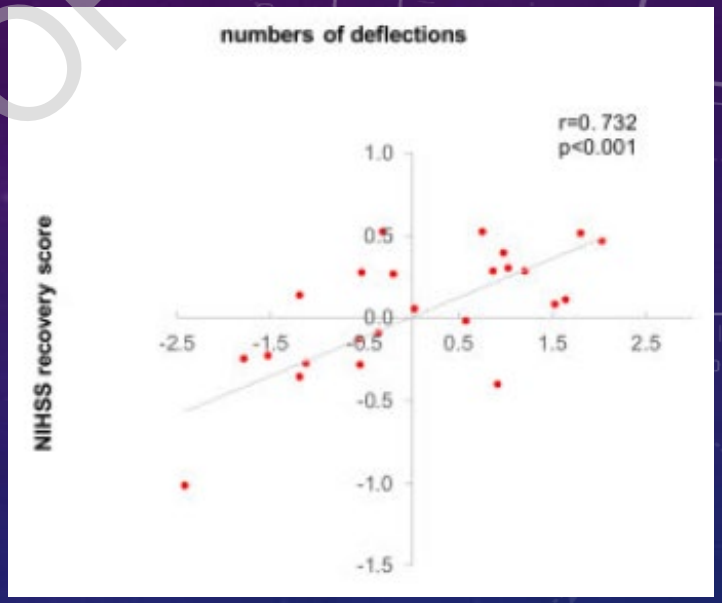


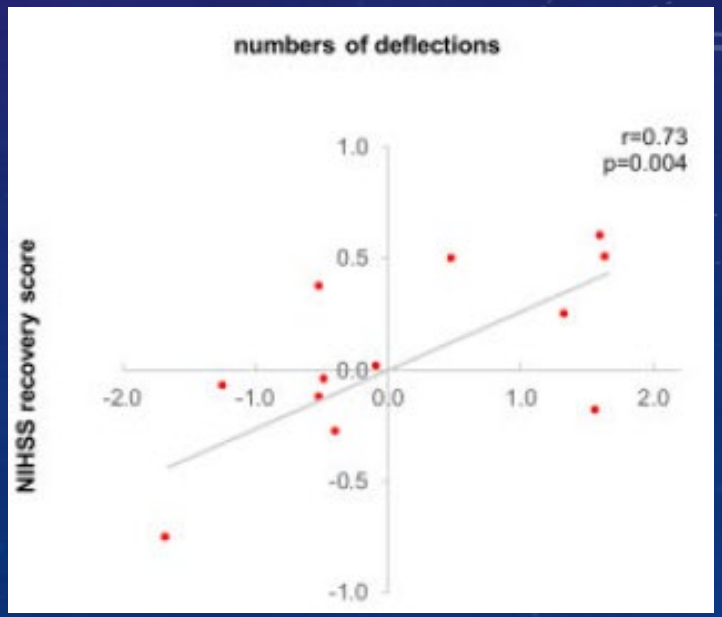
Stinear 2012, *Brain*

TMS-EEG DIFFERENCES IN STROKE PATIENTS





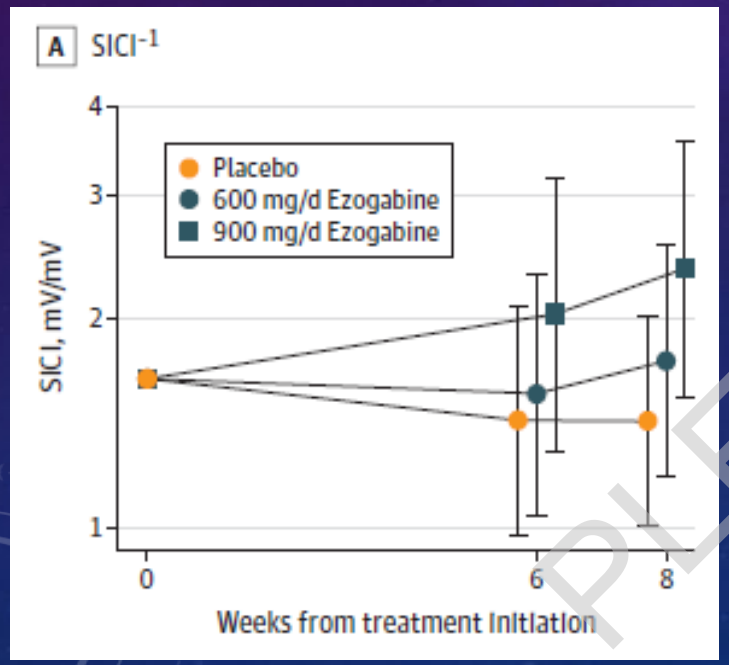


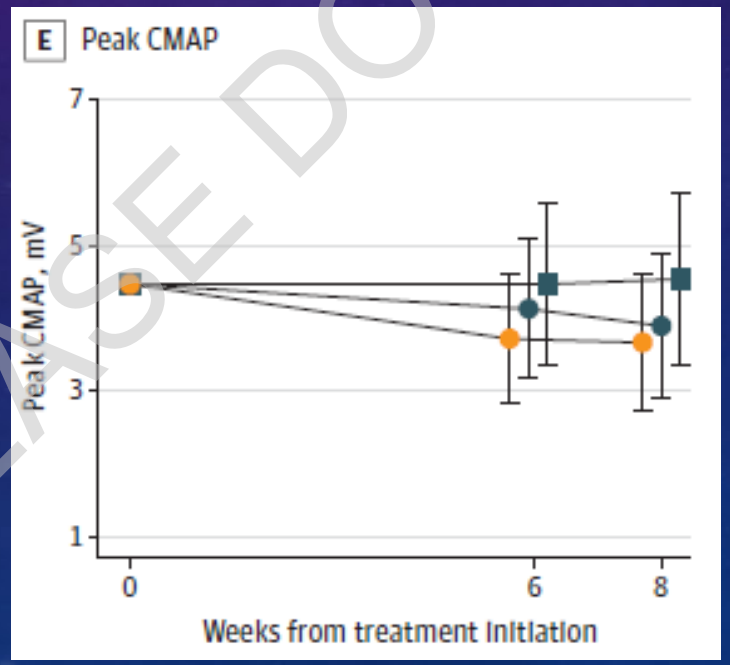


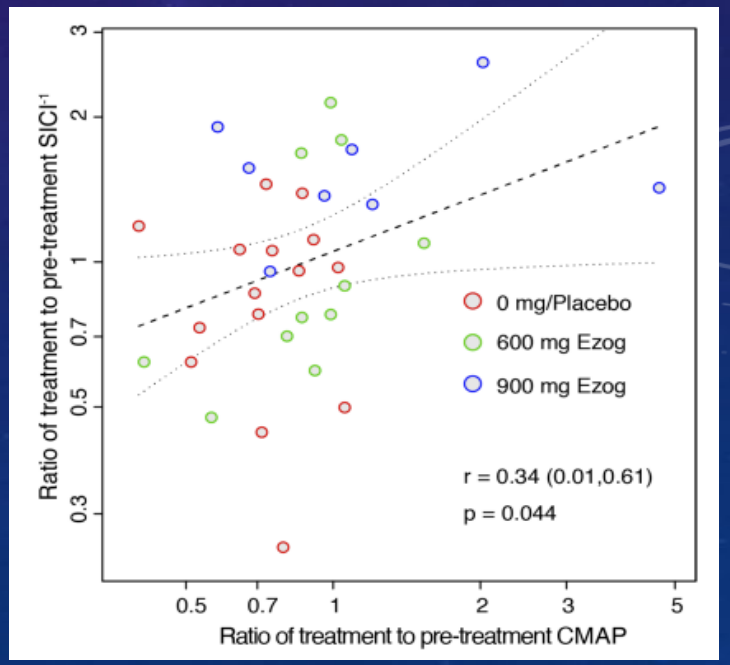
Tscherpel 2020 *Brain*

RESPONSE TO EZOGABINE IN ALS

- Wainger 2021 JAMA Neurology: Evaluated effects of 10 weeks treatment in parallel-group RCT of placebo vs ezogabine 600mg vs ezogabine 900mg on SICI and other TMS motor outcomes
  - Primary outcome: change in SICI (analyzed in paper as $SICI^{-1}$) as proxy of intracortical inhibition
  - Dose-dependent increase in SICI and preservation of CMAP
  - Increases in SICI correlated with preserved CMAP

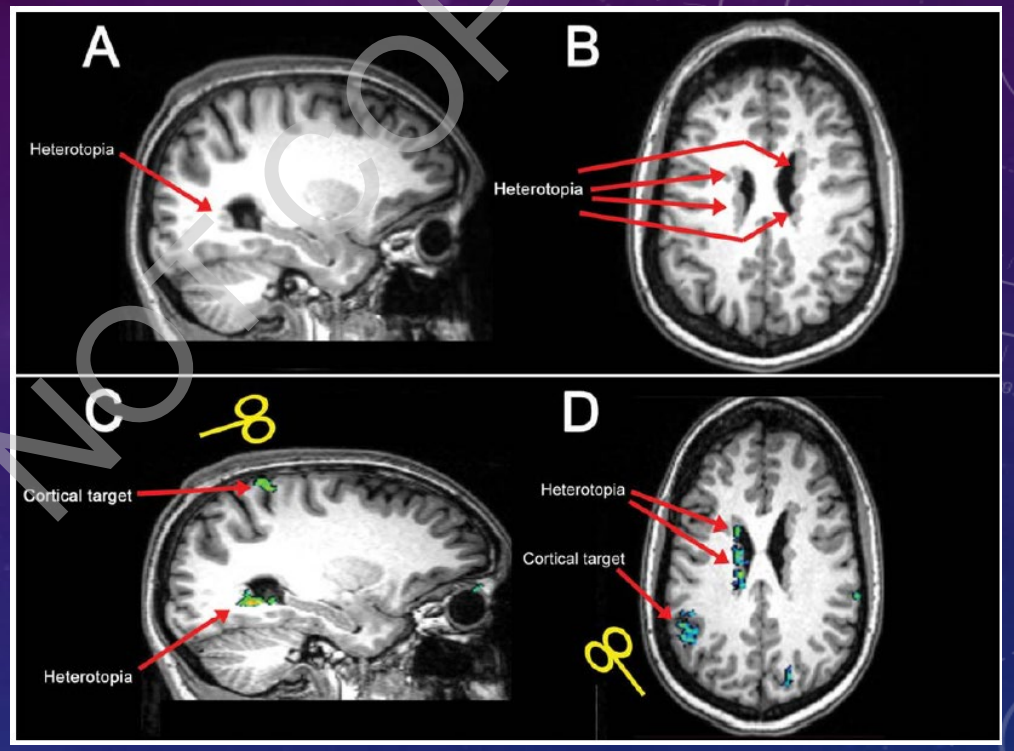


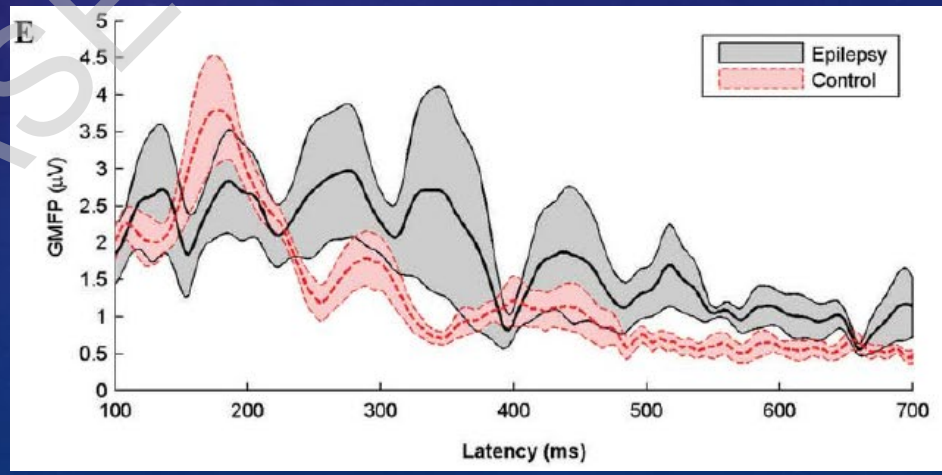


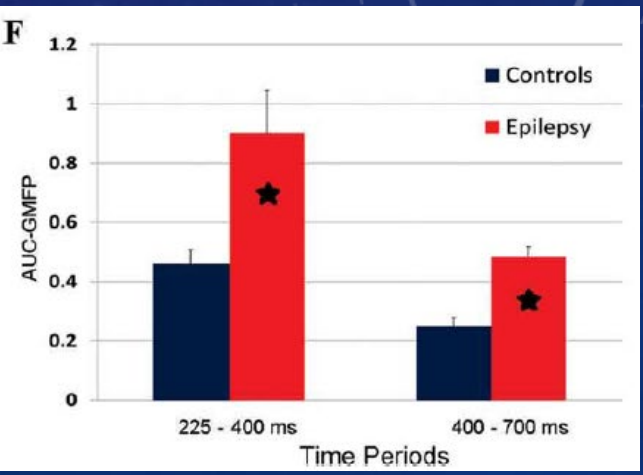


CORTICAL NETWORK HYPEREXCITABILITY IN EPILEPSY

- Shafi 2015 Annals Neurology
  - Assessed significance of abnormal resting-state connectivity in patients with epilepsy due to periventricular nodular heterotopia
  - Identified regions on cortical surface with maximal resting-state functional connectivity to heterotopic nodules, as well as control regions with minimal connectivity
  - Assessed evoked responses using TMS-EEG
  - Significantly increased delayed activity present in patients with epilepsy, more prominent at functionally connected site







OVERVIEW OF TALK

- FDA-Approved Indications
  - Presurgical Motor & Language Mapping
  - Migraine
- Diagnosis / Prognosis / Biomarkers / Mechanism
  - Vegetative state vs MCS; motor outcome after stroke; ezogabine in ALS; circuit hyperexcitability in epilepsy
- Therapeutics
  - Review of results across neurologic indications

THERAPEUTIC EFFECTS?

- rTMS has been studied as a therapeutic modality in different neurologic conditions including
  - Epilepsy
  - Migraine prevention
  - Rehabilitation for post-stroke motor deficits, neglect, and aphasia
  - Alzheimer's Disease
  - Movement Disorders (primarily Parkinson's)
  - Chronic Pain
  - Tinnitus
- However, FDA indication has not been yet obtained for any of these except migraine (multi-center trials recently completed in several disease conditions)

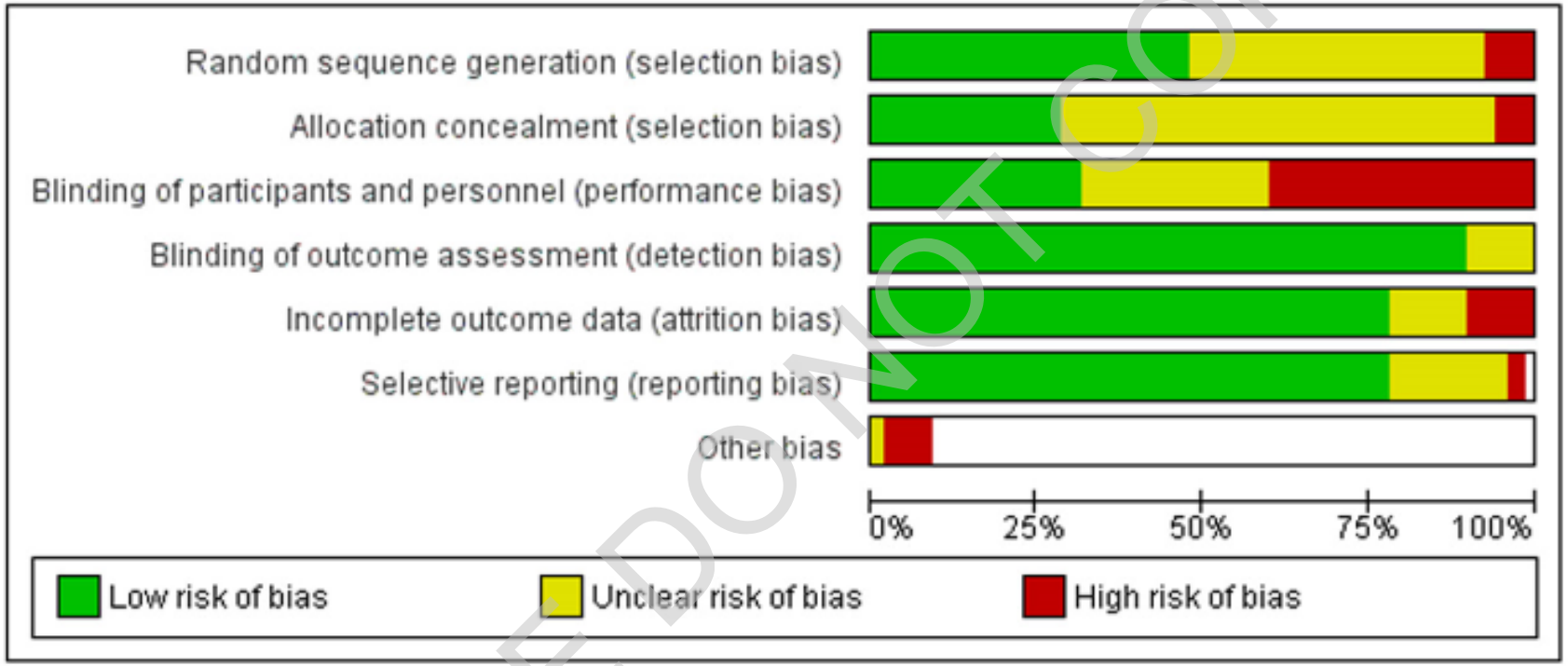
KEY REFERENCES

- Handbook of Clinical Neurology
  - Volume 116, Pages 2-763, 2013; Edited by Andres Lozano and Mark Hallett
  - Overview of Deep Brain Stimulation and Noninvasive Brain Stimulation across spectrum of neurologic diseases
- Lefaucheur et al, Clinical Neurophysiology 2014
  - Evidence-based review/guidelines on therapeutic use of rTMS in neurologic and psychiatric diseases
- Lefaucheur et al, Clinical Neurophysiology 2020
  - Recent update of the above review

BLINDING IN TMS STUDIES IS DIFFICULT

- TMS produces
  - An auditory clicking sound w/ bone conduction
  - A tapping sensation (trigeminal afferents)
  - Contraction of the temporalis and frontalis muscles
- Particularly problematic in trials in which “real” stimulation is used to determine motor threshold for titration of stimulation intensity
- Crossover trials compromised, parallel-group studies are needed!
- Placebo coils that can be preprogrammed and that use electrical stimulation to produce scalp sensations are available

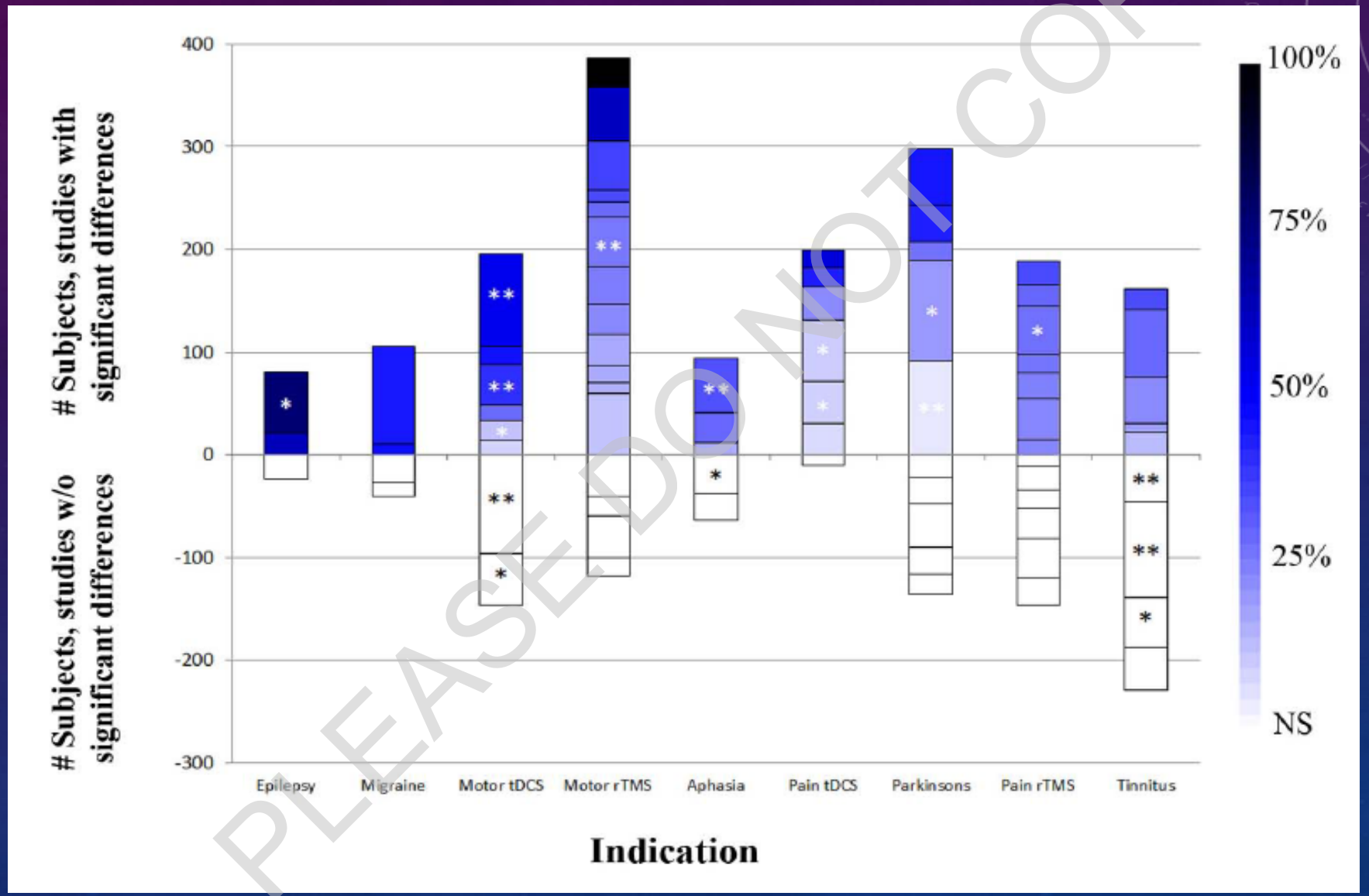
AS A RESULT STUDY QUALITY IS OFTEN POOR



Transcranial Magnetic Stimulation

Primarily due to lack of allocation concealment and inadequate blinding of participants (e.g. coil tilted away as sham stimulation group). Random sequence generation also often not specified in reports

AN OVERVIEW OF THE EVIDENCE CIRCA 2014



EPILEPSY

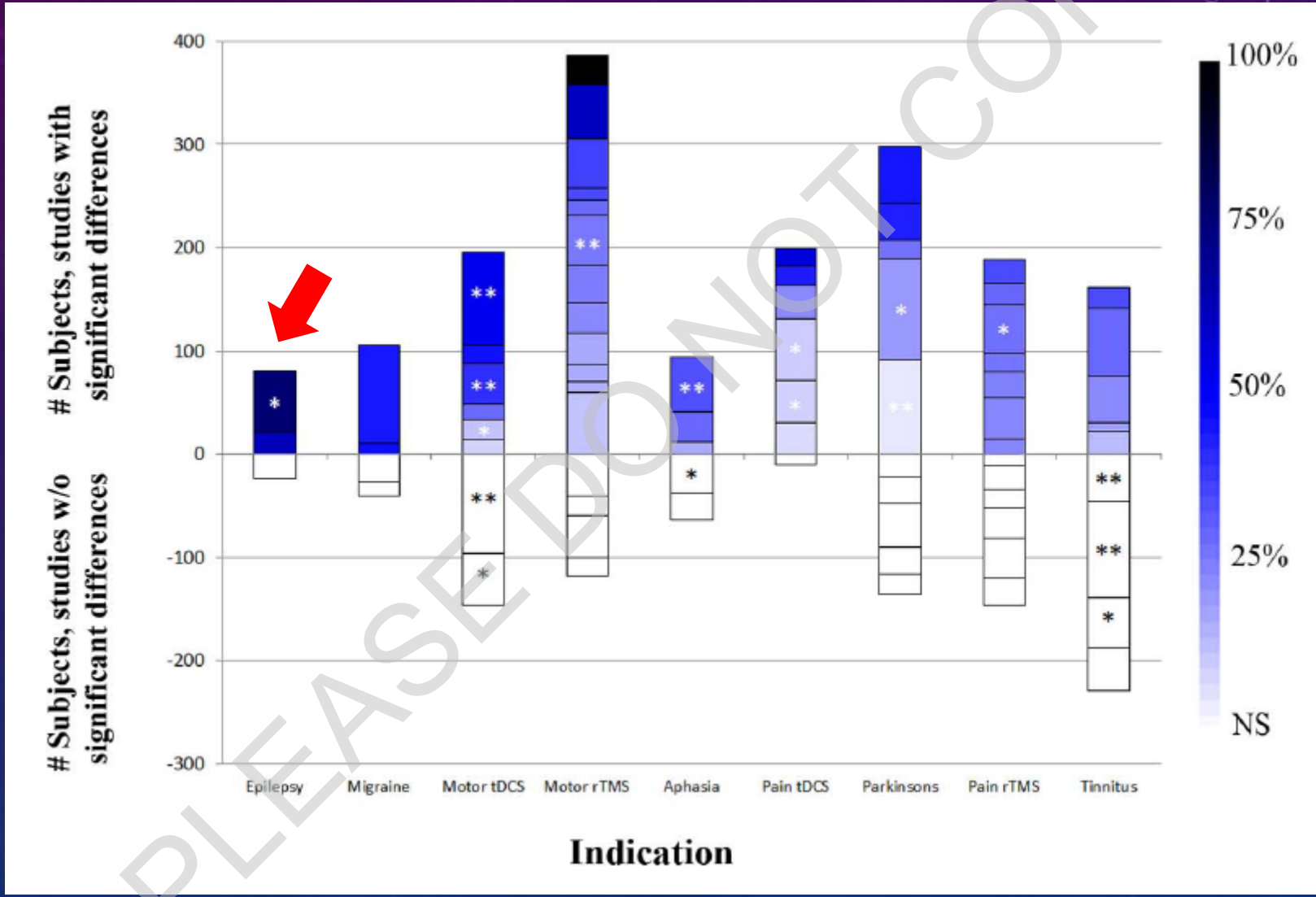
- Trials have assessed the utility of rTMS in medication-refractory epilepsy (~1/3 of patients)
  - Typically apply low-frequency rTMS to the epileptic focus or have applied to the vertex (regardless of location of epileptic focus)

Table 7
rTMS studies in epilepsy (various cortical targets).

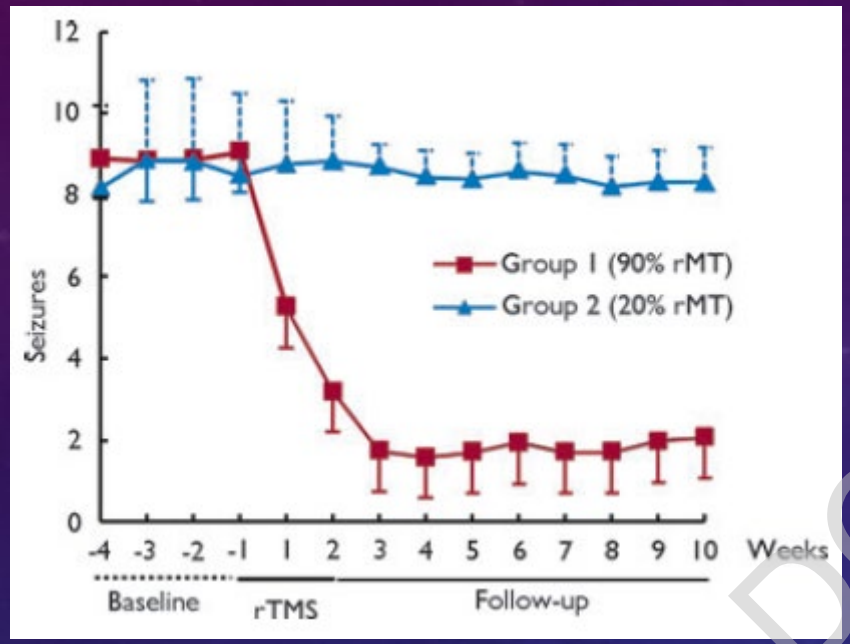
Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/ session and number of sessions	Results	Class of the study
Focal LF rTMS of epileptic focus							
Theodore et al. (2002)	24 (3 frontal, 1 parietal, 10 mesio-temporal, 10 latero-temporal) (active: 12; control: 12)	Epileptic foci, F8c	Tilted coil	1 Hz, 120% RMT	900 pulses, 14 sessions	No significant reduction of seizure frequency	III
Fregni et al. (2006c)	21 (17 partial, 4 diffuse/multifocal) (active: 12; control: 9)	Epileptic foci (n = 17) or Cz (n = 4), F8c	Sham coil	1 Hz, 70% MSO	1200 pulses, 5 sessions	Up to 72% reduction of seizure frequency, 2 weeks after rTMS; reduction of interictal EEG abnormalities	III
Sun et al. (2012)	60 (21 frontal, 3 mesio-temporal, 26 centro-parietal, 3 latero-temporal, 7 occipital) (active: 31; control: 29)	Epileptic foci, F8c	Active coil at very low stimulus intensity (20% RMT)	0.5 Hz, 90% RMT	1500 pulses, 14 sessions	Significantly greater seizure reduction rate in active vs. control group (80% vs. 2%); reduction of interictal EEG abnormalities	II
Recommendation: possible antiepileptic effect of focal LF rTMS of the epileptic focus (Level C)							
Non-focal LF rTMS at the vertex							
Tergau et al. (2003)	17 (11 extra-temporal, 2 mesio-temporal, 2 multifocal, 2 generalized)	Vertex, Cc	Sham coil	0.33–1 Hz, 100% RMT	1000 pulses, 5 sessions	30-40% reduction of seizure frequency, 2 weeks after rTMS (only for 0.33 Hz)	III
Cantello et al. (2007)	43 (41 partial, 2 generalized)	Vertex, Cc	Active coil placed over a non-connected coil	0.3 Hz, 100% RMT (n = 34), 65% MSO (n = 9)	1000 pulses, 5 sessions	No significant reduction of seizure frequency; reduction of EEG abnormalities; no change in cortical excitability	II
No recommendation for the antiepileptic effect of non-focal LF rTMS at the vertex							

Lefaucheur 2014 *Clin Neurophys*

PARALLEL-GROUP STUDIES



REMARKABLE EFFECTS SOMETIMES SEEN



Sun 2012 *Epilepsia*

Table 2. Effect of rTMS on seizures (mean ± SD)

	Baseline	Follow-up	SRR (%)
Group 1 (n = 31)	8.9 ± 11.1	1.8 ± 3.7[a]	79.8
Group 2 (n = 29)	8.6 ± 10.8	8.4 ± 10.1[b]	2.3

[a]Significantly different from baseline ($p < 0.05$).
[b]Significantly different from group 1 ($p < 0.05$).
SRR, Seizure Reduction Rate = [(Baseline seizures-Follow-up seizures)/Baseline seizures] × 100 (%).

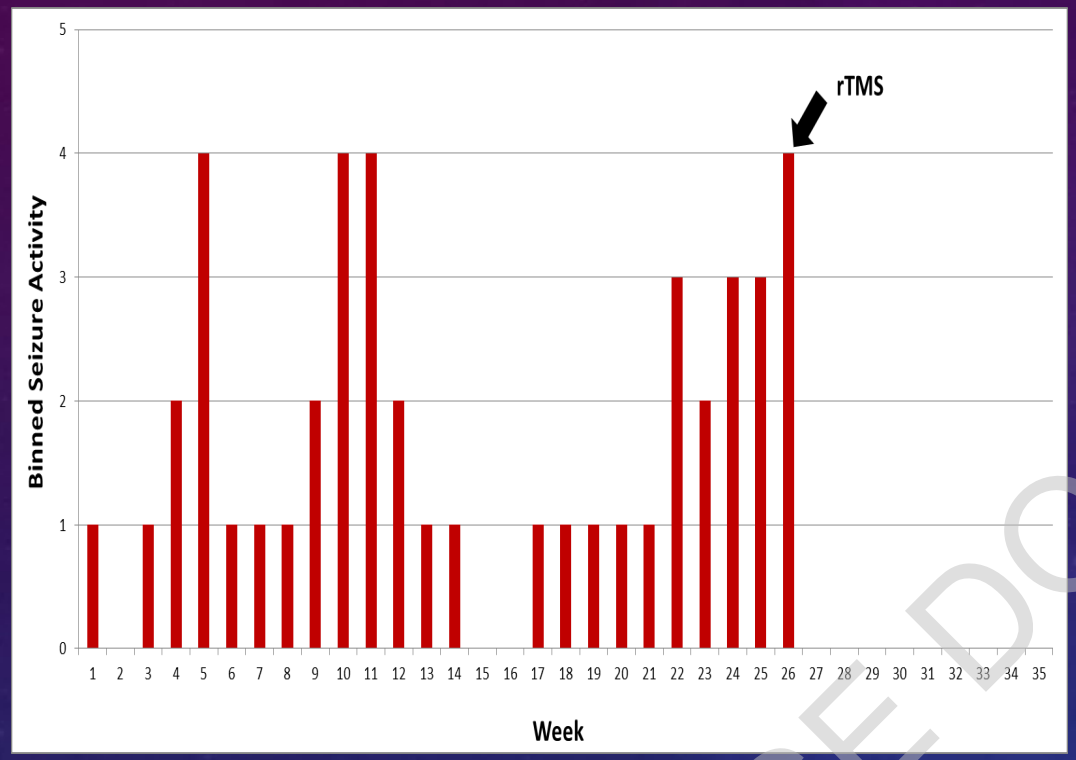
Table 3. Effect of rTMS on IED of 60 min (mean ± SD)

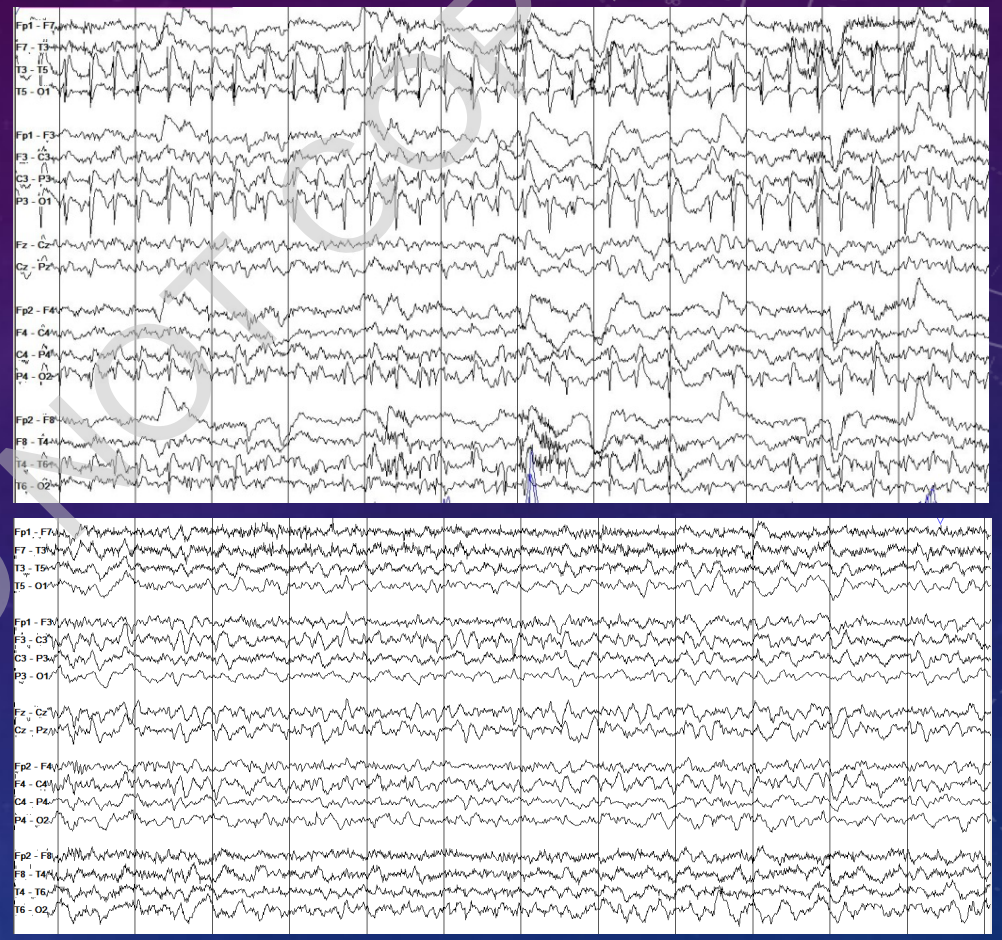
	Before rTMS	After rTMS	End of follow-up
Group 1 (n = 31)	75.1 ± 88.5	23.1 ± 48.0[a]	33.6 ± 55.6[a]
Group 2 (n = 29)	76.6 ± 72.9	71.5 ± 78.7[b]	72.3 ± 75.1[b]

[a]Significantly different from baseline ($p < 0.05$).
[b]Significantly different from group 1 ($p < 0.05$).

- Decrease in seizure frequency greater than is typically seen in pharmacologic trials
- Beneficial effects only seen when rTMS is targeted specifically to the seizure focus on the neocortical surface
- Multi-center trials needed to confirm findings!
- But but but …

BENEFICIAL EFFECTS IN STATUS EPILEPTICUS?



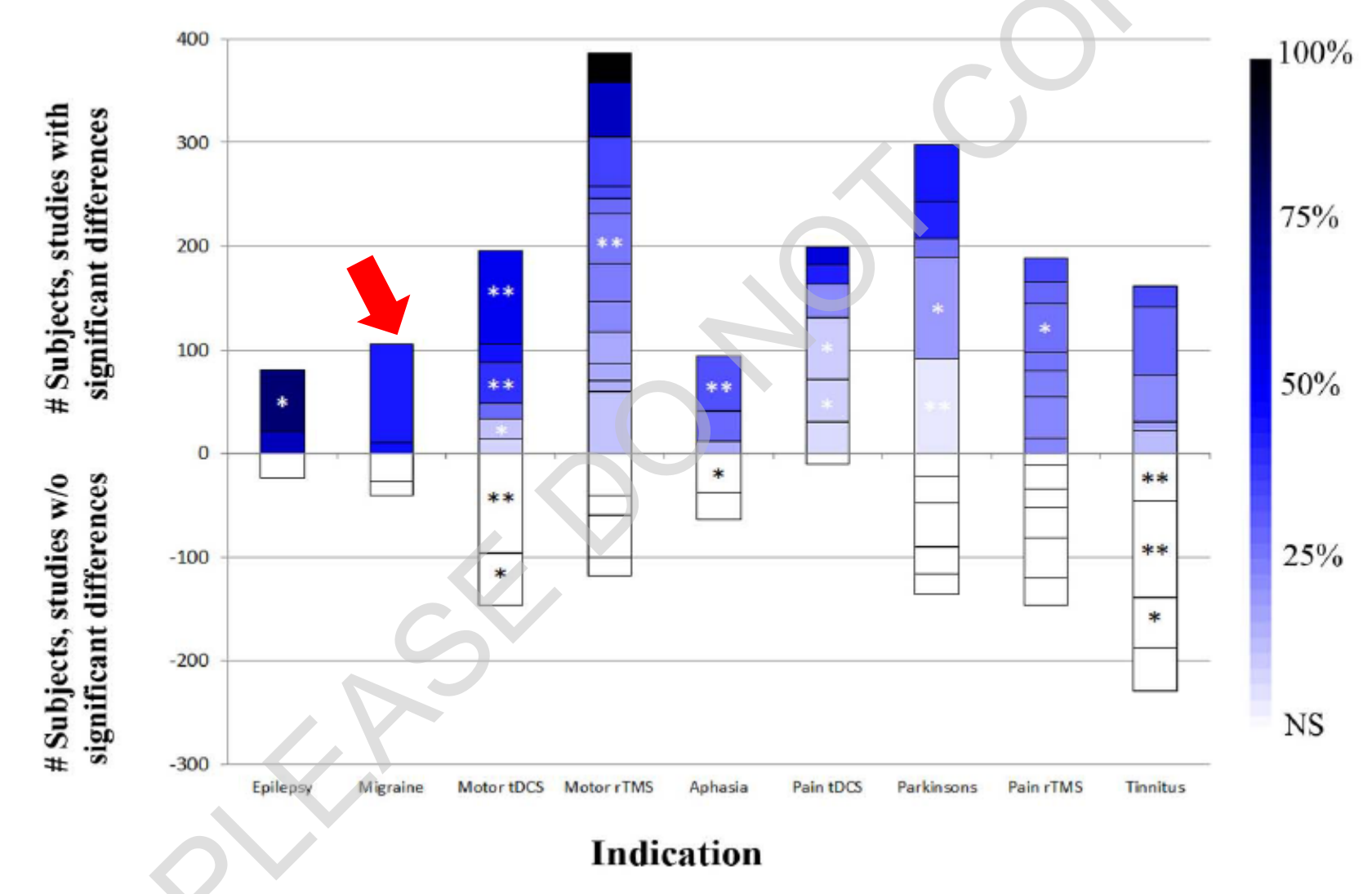


- Rotenberg (2009 *Epi & Behav*) reported sustained remission in 2/7 patients with epilepsia partialis continua
- Case reports of effectiveness of rTMS in refractory focal status epilepticus (Thordstein 2012 *Epi & Behav*; Liu 2013 *Seizure*; VanHaerents 2015, *Clinical Neurophysiology*)

MIGRAINE (CHRONIC TREATMENT)

- A total of 4 studies evaluating efficacy of rTMS for prophylactic treatment of migraine (**although FDA approved based on open-label trial with statistically-derived historical control**)
- In largest (class III) study of 95 patients, 10 Hz stimulation to L M1 resulted in more than 50% reduction in headache frequency in 79% of patients receiving real TMS, vs only 33.3% of pts receiving sham (Misra 2013 *J Neurol*)
- Small studies evaluated HF stimulation of LDPFC with mixed results; LF stimulation of vertex with no benefit.
- More recent study (Leahu 2021 *Brain Stimulation*) applied a … unique … high frequency rTMS protocol with a circular coil (active vs placebo) over 11 different brain regions in 60 patients. Reported fewer migraine days, migraine attacks and VAS improvement with real but not sham stimulation

MIGRAINE RESULTS



MOTOR REHAB AFTER STROKE

- High-frequency (“excitatory”) stimulation of ipsilesional hemisphere
- Low-frequency (“inhibitory”) stimulation of contralesional motor cortex

Edwardson 2013 *Exp Brain Res*

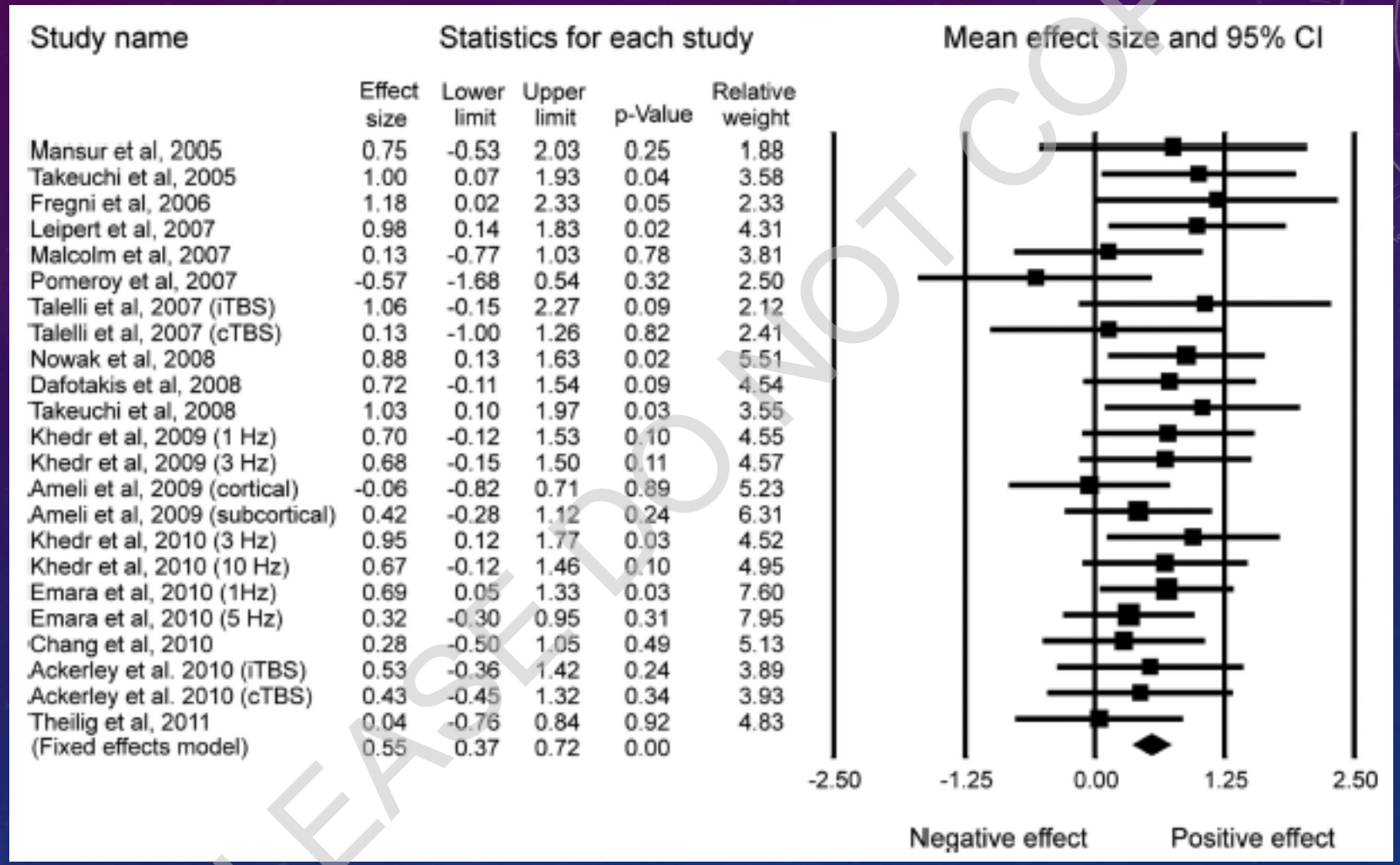
A LARGE NUMBER OF STUDIES!

Table 5
rTMS studies in motor stroke (target: primary motor cortex).

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
LF rTMS of the contralesional motor cortex: acute or post-acute stroke							
Liepert et al. (2007)	12	M1 contralesional, F8c	Sham coil	1 Hz, 90% RMT	1200 pulses, 1 session	Increase of manual dexterity (not of the force)	III
Pomeroy et al. (2007)	24 (active: 10; control: 14)	M1 contralesional, F8c	Sham coil	1 Hz, 120% RMT	200 pulses, 8 sessions (combined with motor practice in half of the patients)	No clinical changes but increased cortical excitability	III
Khedr et al. (2009a)	24 (active: 12; control: 12)	M1 contralesional, F8c	Tilted coil	1 Hz, 100% RMT	900 pulses, 5 sessions	More improvement of manual motor abilities than after ipsilesional HF rTMS at 3 months	III
Conforto et al. (2012)	29 (active: 15; control: 14)	M1 contralesional, F8c	Tilted coil	1 Hz, 90% RMT	1500 pulses, 10 sessions, followed by PT	Improvement in manual dexterity (JTT) and grip strength	III
Sasaki et al. (2013)	20 (active: 11; control: 9)	M1 contralesional, F8c	Tilted coil	1 Hz, 90% RMT	1800 pulses, 5 sessions	Improvement in grip strength and finger tapping frequency (but less beneficial than ipsilesional HF rTMS performed in 9 patients)	III
Seniów et al. (2012)	40 (active: 20; control: 20)	M1 contralesional, F8c	Sham coil	1 Hz, 90% RMT	1800 pulses, 15 sessions, followed by motor training	No differences between active and sham rTMS to improve hand motor function or the level of neurological deficit	III
Recommendation: possible effect of LF rTMS of the contralesional motor cortex in (post-)acute motor stroke (Level C)							
LF rTMS of the contralesional motor cortex: chronic stroke (>6 months after stroke)							
Mansur et al. (2005)	10	M1 contralesional, F8c	Tilted coil	1 Hz, 100% RMT	600 pulses, 1 session	Improvement of manual motor abilities, including shorter reaction and execution times	III
Takeuchi et al. (2005)	20 (active: 10; control: 10)	M1 contralesional, F8c	Tilted coil	1 Hz, 90% RMT	1500 pulses, 1 session	Improvement of manual motor abilities (movement acceleration, but not force), lasting less than 30 min	III
Fregni et al. (2006a)	15 (active: 10; control: 5)	M1 contralesional, F8c	Sham coil	1 Hz, 100% RMT	1200 pulses, 5 sessions	Improvement of manual motor abilities, lasting for 2 weeks	III
Takeuchi et al. (2008)	20 (active: 10; control: 10)	M1 contralesional, F8c	Tilted coil	1 Hz, 90% RMT	1500 pulses, 1 session	Improvement of manual motor abilities, PT efficacy, and cortical excitability, lasting for one week	III
Emara et al. (2009, 2010)	20 (active: 20; control: 20)	M1 contralesional, F8c	Tilted coil	1 Hz, 110–120% RMT	150 pulses, 10 sessions	Improvement of manual motor abilities and functional status, lasting at least 12 weeks (idem ipsilesional HF rTMS); less improvement for cortical vs. subcortical stroke	II
Theilig et al. (2011)	24 (active: 12; control: 12)	M1 contralesional, F8c	Sham coil	1 Hz, 100% RMT	900 pulses, 1 session, followed by 20 min of functional electrical stimulation	Similar improvement of motor performance with active and sham rTMS followed by functional electrical stimulation	III
Avenanti et al. (2012)	30 (active: 16; control: 14)	M1 contralesional, F8c	Tilted Cc	1 Hz, 90% RMT	1500 pulses, 10 sessions, preceded or followed by PT	Improvement in manual dexterity (9HPT, JTT, grip force); rebalance of interhemispheric excitability; clinical and neurophysiological improvements more robust and stable when rTMS was followed by PT	III
Etoh et al. (2013)	18	M1 contralesional, F8c	1 Hz rTMS 5cm posterior to M1	1 Hz, 90% RMT	240 pulses, 10 sessions, followed by repetitive motor exercises	Improvement in motor performance (ARAT); no change in spasticity	III
Recommendation: probable effect of LF rTMS of the contralesional motor cortex in chronic motor stroke (Level B)							
HF rTMS of the ipsilesional motor cortex: acute or post-acute stroke							
Khedr et al. (2005a)	52 (active: 26; control: 26)	M1 ipsilesional, F8c	Tilted coil	3 Hz, 120% RMT	300 pulses, 10 sessions	Improvement on various functional scales	II
Khedr et al. (2009a)	24 (active: 12; control: 12)	M1 ipsilesional, F8c	Tilted coil	3 Hz, 130% RMT	900 pulses, 5 sessions	Less improvement of manual motor abilities than after contralesional LF rTMS at 3 months	III
Chang et al. (2010)	28 (active: 18; control: 10)	M1 ipsilesional, F8c	Tilted coil	10 Hz, 90% RMT	1000 pulses, 10 sessions	Improvement of manual motor abilities for subcortical strokes, till 3 months after rTMS	III
Khedr et al. (2010b)	48 (active 3 Hz: 16; active 10 Hz: 16; control: 16)	M1 ipsilesional, F8c	Tilted coil	3 Hz, 130% RMT or 10 Hz, 100% RMT	750 pulses, 5 sessions	Improvement on various functional and motor scales (idem for 3 and 10 Hz). Improvement remained significant at 1 year	III
Recommendation: possible effect of HF rTMS of the ipsilesional motor cortex in (post-)acute motor stroke (Level C)							
HF rTMS of the ipsilesional motor cortex: chronic stroke (>6 months after stroke)							
Kim et al. (2006)	15	M1 ipsilesional, F8c	Tilted coil	10 Hz, 80% RMT	160 pulses, 1 session (combined with motor practice)	Improvement of cortical excitability, movement accuracy and execution time of a motor task during and immediately after stimulation	III
Emara et al. (2009, 2010)	40 (active: 20; control: 20)	M1 ipsilesional, F8c	Tilted coil	5 Hz, 80–90% RMT	750 pulses, 10 sessions	Improvement of manual motor abilities and functional status, lasting at least 12 weeks (idem contralesional LF rTMS)	II
Recommendation: possible effect of HF rTMS of the ipsilesional motor cortex in chronic motor stroke (Level C)							

Lefaucheur 2014 *Clin Neurophys*

MOST STUDIES SHOW A BENEFICIAL EFFECT

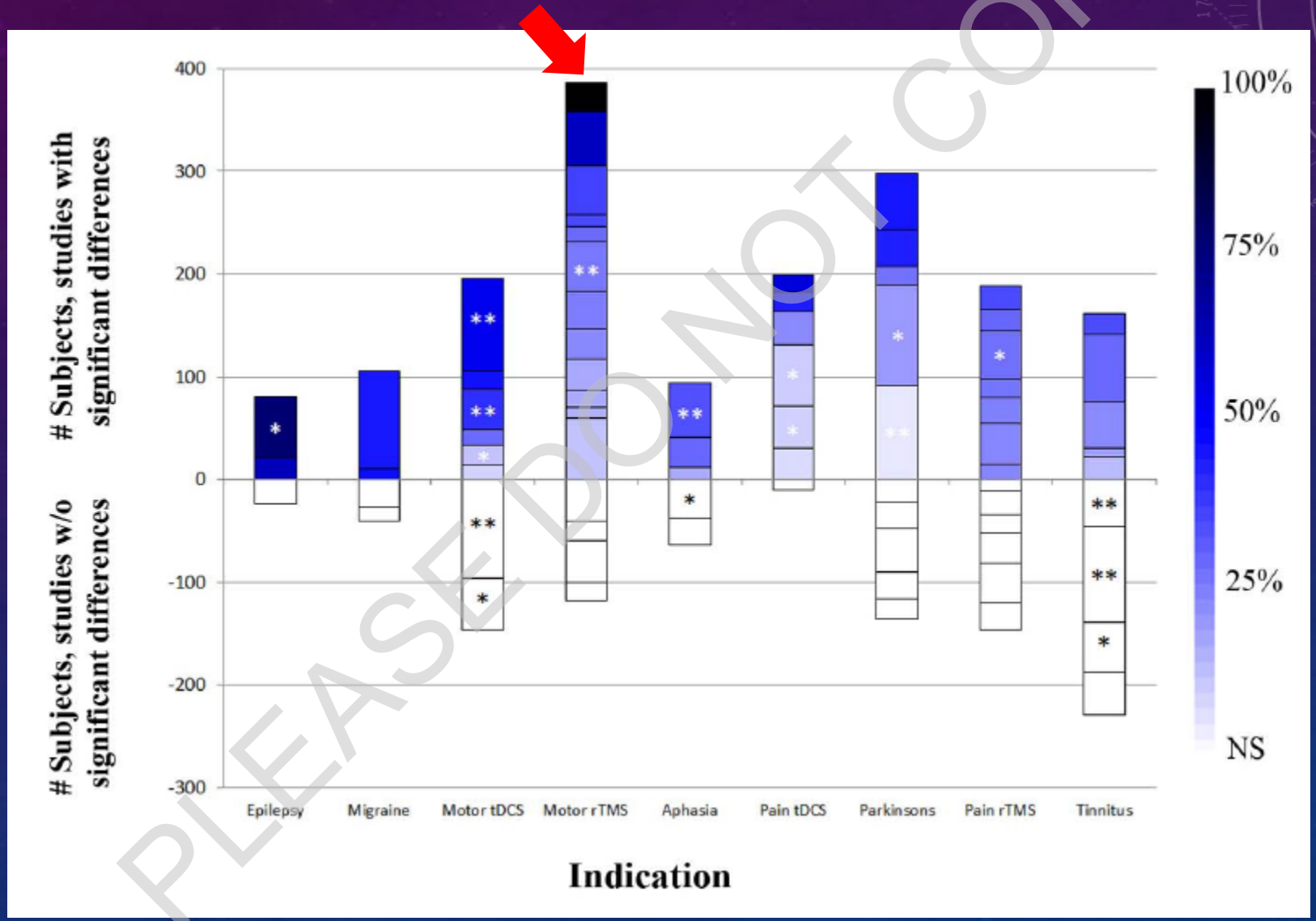


Study name	Effect size	Lower limit	Upper limit	p-Value	Relative weight
Mansur et al, 2005	0.75	-0.53	2.03	0.25	1.88
Takeuchi et al, 2005	1.00	0.07	1.93	0.04	3.58
Fregni et al, 2006	1.18	0.02	2.33	0.05	2.33
Leipert et al, 2007	0.98	0.14	1.83	0.02	4.31
Malcolm et al, 2007	0.13	-0.77	1.03	0.78	3.81
Pomeroy et al, 2007	-0.57	-1.68	0.54	0.32	2.50
Talelli et al, 2007 (iTBS)	1.06	-0.15	2.27	0.09	2.12
Talelli et al, 2007 (cTBS)	0.13	-1.00	1.26	0.82	2.41
Nowak et al, 2008	0.88	0.13	1.63	0.02	5.51
Dafotakis et al, 2008	0.72	-0.11	1.54	0.09	4.54
Takeuchi et al, 2008	1.03	0.10	1.97	0.03	3.55
Khedr et al, 2009 (1 Hz)	0.70	-0.12	1.53	0.10	4.55
Khedr et al, 2009 (3 Hz)	0.68	-0.15	1.50	0.11	4.57
Ameli et al, 2009 (cortical)	-0.06	-0.82	0.71	0.89	5.23
Ameli et al, 2009 (subcortical)	0.42	-0.28	1.12	0.24	6.31
Khedr et al, 2010 (3 Hz)	0.95	0.12	1.77	0.03	4.52
Khedr et al, 2010 (10 Hz)	0.67	-0.12	1.46	0.10	4.95
Emara et al, 2010 (1Hz)	0.69	0.05	1.33	0.03	7.60
Emara et al, 2010 (5 Hz)	0.32	-0.30	0.95	0.31	7.95
Chang et al, 2010	0.28	-0.50	1.05	0.49	5.13
Ackerley et al. 2010 (iTBS)	0.53	-0.36	1.42	0.24	3.89
Ackerley et al. 2010 (cTBS)	0.43	-0.45	1.32	0.34	3.93
Theilig et al, 2011	0.04	-0.76	0.84	0.92	4.83
(Fixed effects model)	0.55	0.37	0.72	0.00	

Hsu 2012 *Stroke*

Mean effect size of 0.55 in one recent meta-analysis

HOW ABOUT PARALLEL-GROUP STUDIES?



EFFECTS OF PARAMETERS?

SUPPLEMENTAL TABLES

Supplementary table 1: Summary of the subgrouped mean effect sizes

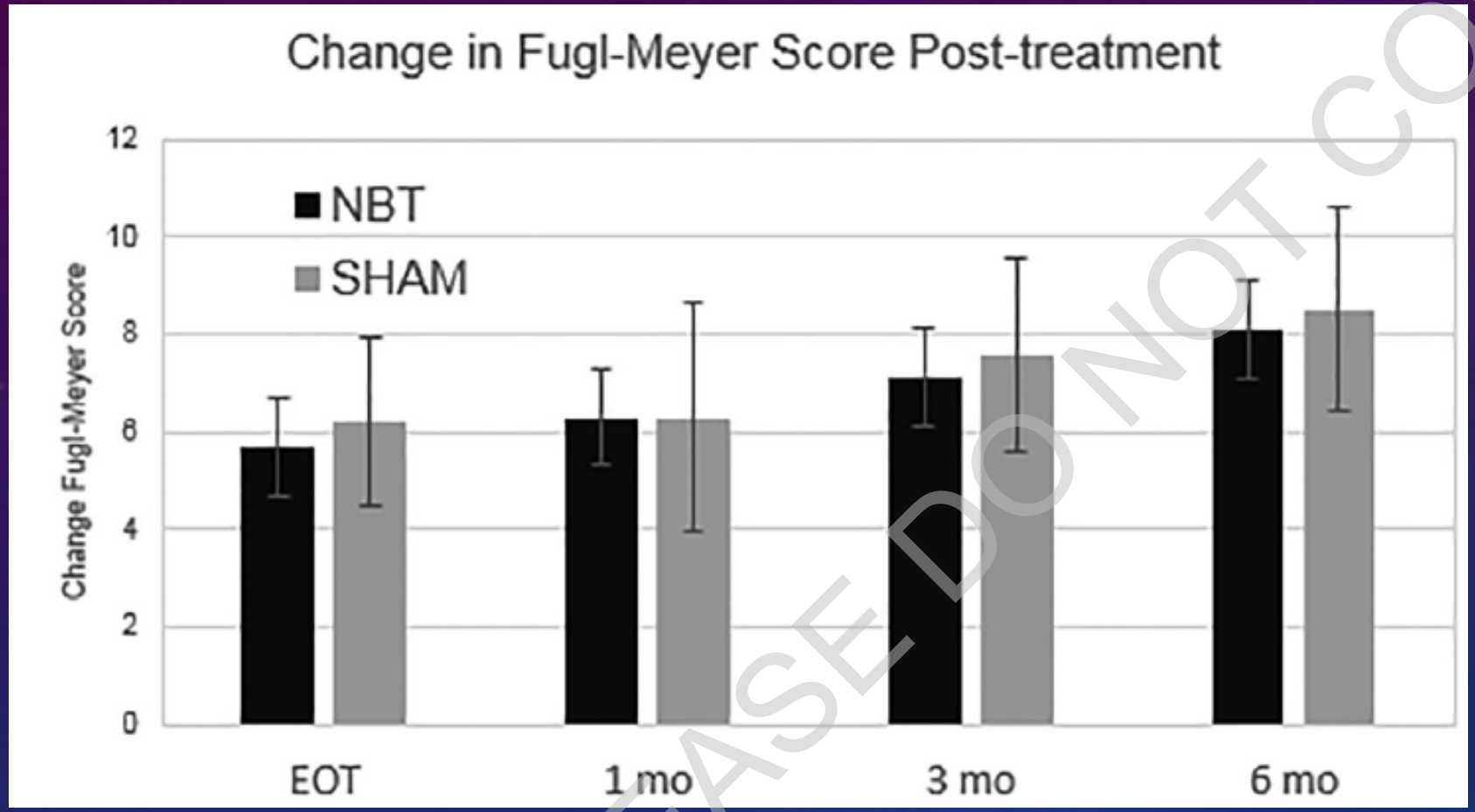
	Effect size	95% CI	p-value
Subgrouped by frequency			
Low	0.69	0.42-0.95	<0.001
High	0.41	0.14-0.68	0.003
Subgrouped by post stroke duration			
Acute	0.79	0.42-1.16	<0.001
Subacute	0.63	0.18-1.08	0.006
Chronic	0.66	0.31-1.00	<0.001
Subgrouped by lesion site			
Non-specified	0.45	0.23-0.67	<0.001
Subcortical	0.73	0.44-1.02	<0.001

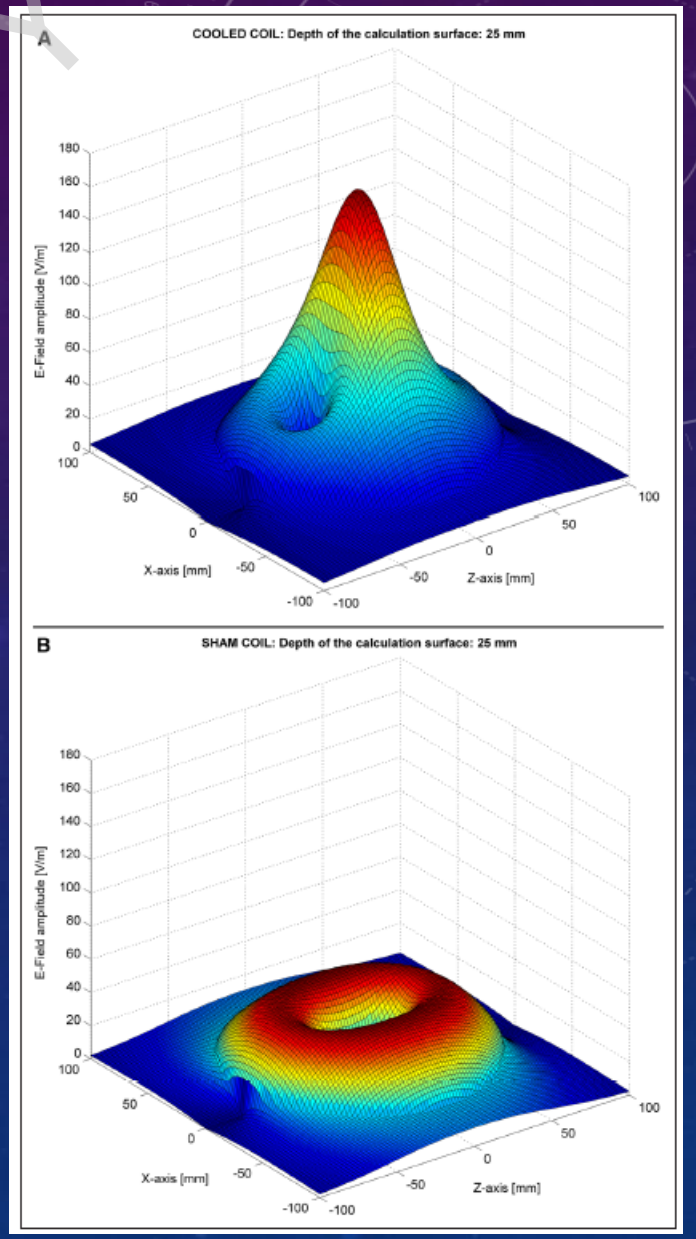
Hsu 2012, *Stroke*

NICHE TRIAL OF 1 HZ CONTRALATERAL RTMS

- **Multi-center RCT sham trial of contralesional 1 Hz rTMS**
  - **Trial of 1 Hz active or sham rTMS (2:1 allocation) to the contralesional motor cortex before eighteen 60-minute therapy sessions over a 6 week period, in patients 3 to 12 months post-stroke**
  - **Primary outcome: ≥5 point gain on upper extremity Fugl-Meyer test. Secondary outcomes performance on Action Research Arm Test and Wolf Motor Function Test**
  - **199 participants enrolled, 6-month outcome data available for 173**
  - **Mix of subcortical > cortical > cortical/subcortical > brainstem strokes**
  - **>70% were 6-12 mo post-stroke**
  - **Most were in "moderately-severe range of motor impairment)**

THE OUTCOME?



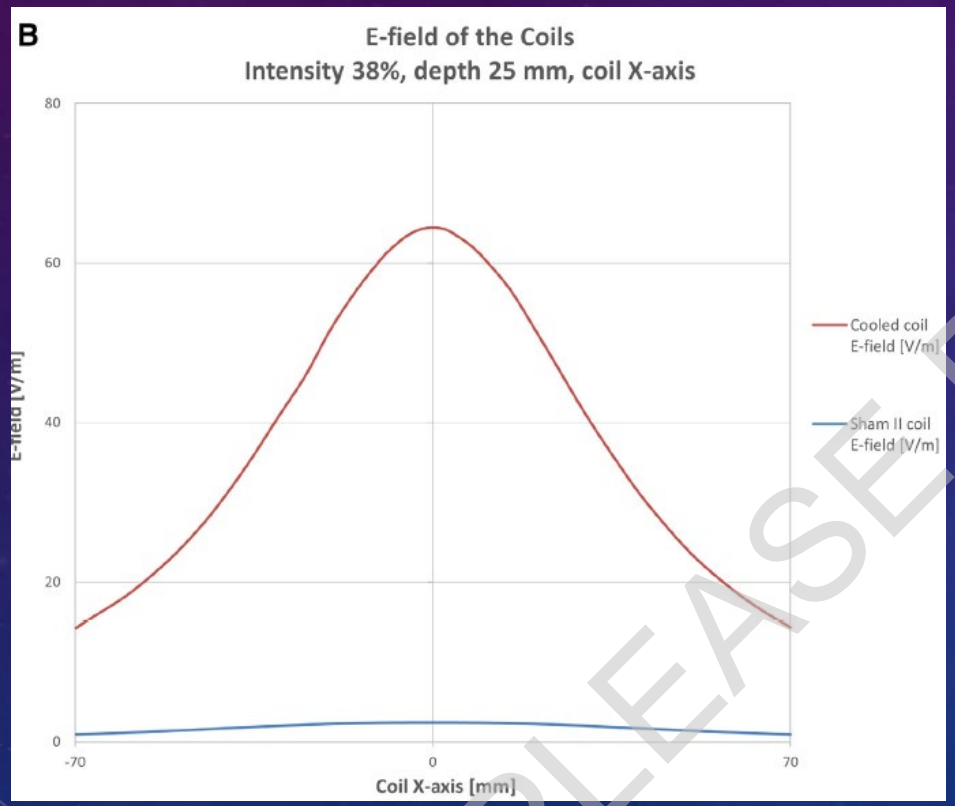


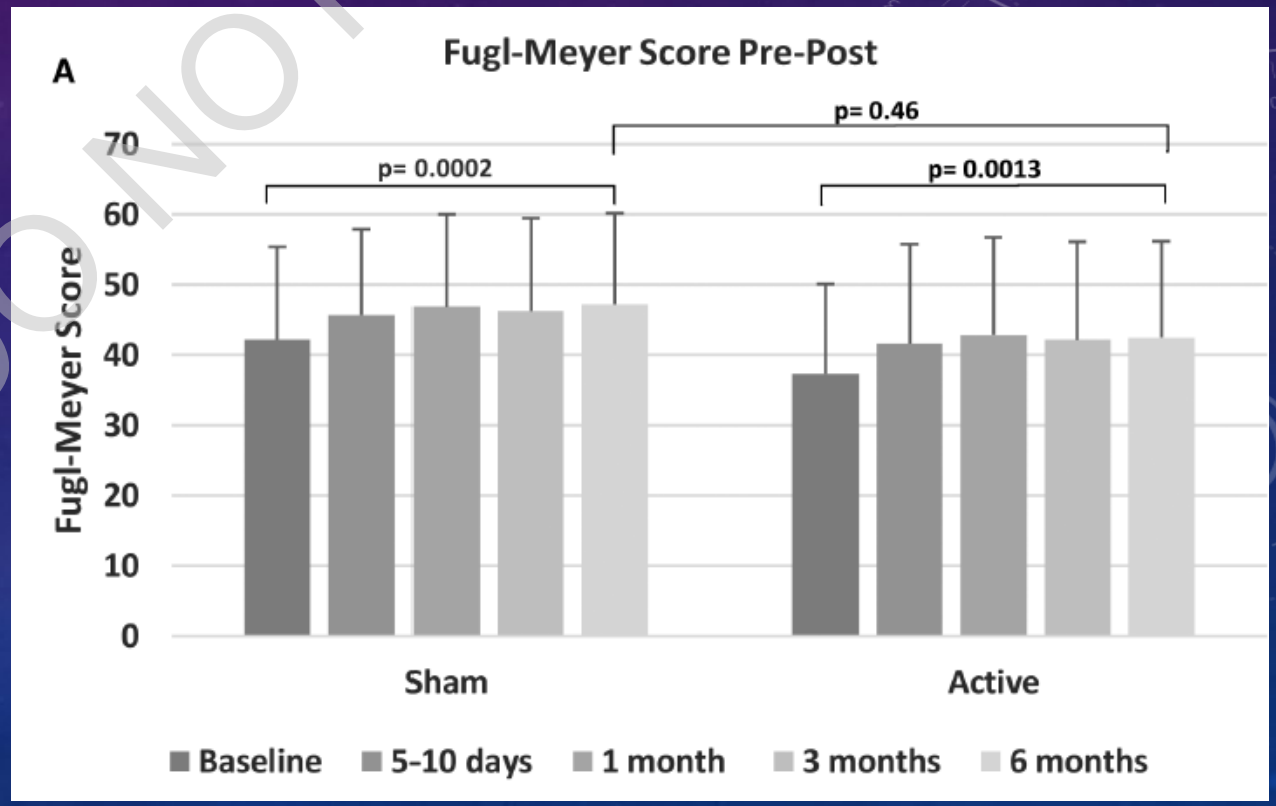
- Significant improvement in >65% of patients in BOTH groups!
- Maybe because the sham stimulation also produced weak electric fields?

Harvey 2018 *Stroke*

E-FIT TRIAL

- Repeat multi-center study comparing same 1 Hz contralesional rTMS protocol with new sham coil without the weak electric field in the NICHE study
- Randomized 60 participants 3-12 months post-stroke in 5 of the 12 NICHE centers





- 5+ point improvement in 60% of active group vs 50% sham group

Edwards 2023 *Stroke*

RESIDUAL QUESTIONS / APPROACHES

- Does stimulation in earlier phases of stroke have better effects?
- Ipsilesional high-frequency or theta-burst stimulation?
- Contralesional low-frequency plus ipsilesional theta-burst stimulation?
- “Primed” rTMS (cTBS before iTBS)
- rTMS synchronized to ongoing sensorimotor mu-oscillations? (“Personalized brain-state-dependent rTMS”)

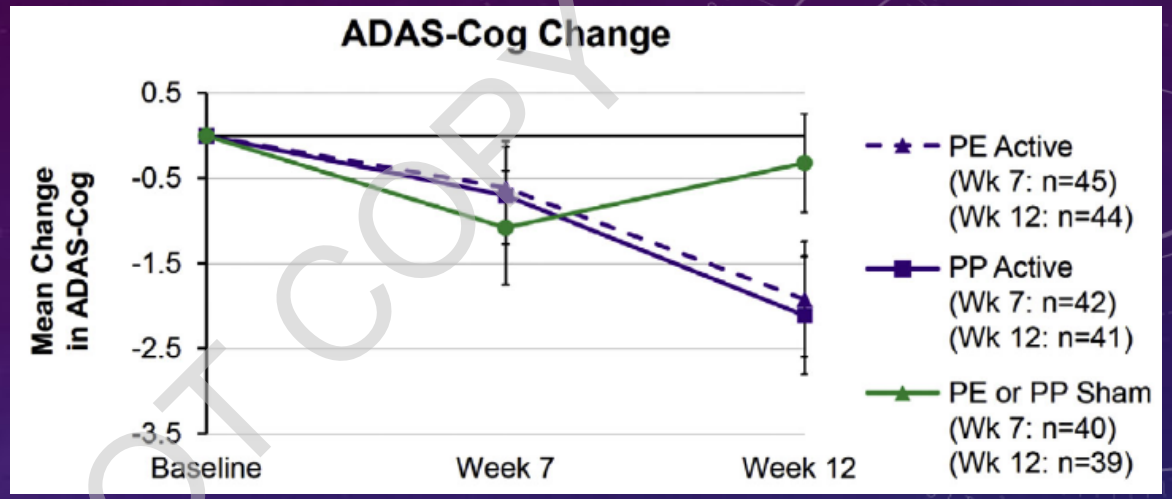
ALZHEIMER'S DISEASE

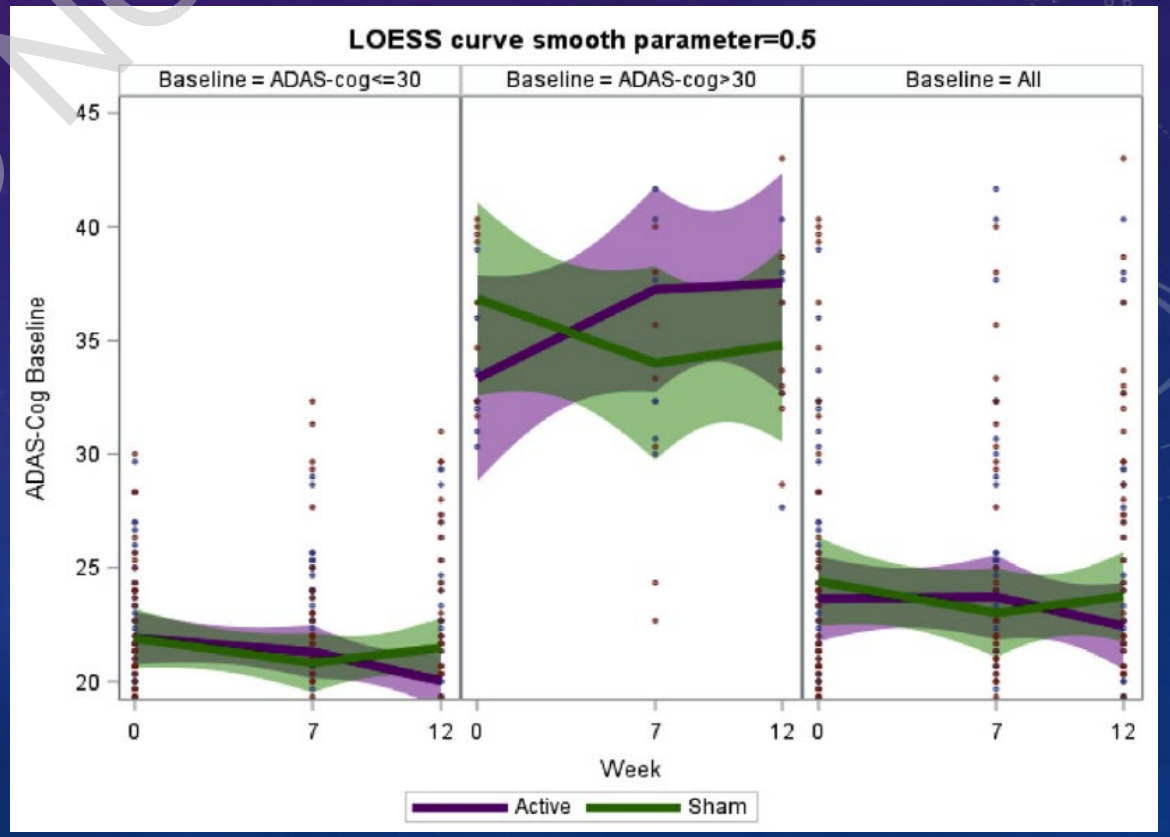
- **Neuronix trial: Multicenter study investigating combination of rTMS and cognitive training**
  - Protocol involved 2s of high frequency TMS to any of 6 brain regions (L+R DLPFC, L+R Inferior Parietal, Broca's and Wernicke's area) followed by 30s of cognitive exercise with task engaging that target
  - During each session 3 regions targeted
  - Total 1300 pulses at 10 Hz in 2s bursts of 20 pulses at 110% RMT
  - Sham coil produced same noise but no energy. Visual perception task and movies for sham
  - Enrolled 131 subjects between 60 and 90 years old
  - Treatment involved 30 sessions – 6 weeks, 5 days/week
  - Follow-up assessment 1 and 6 weeks after intervention
  - First 20 subjects "roll in" for safety. Analysis conducted on 109 subsequent participants

Sabbagh 2019 *Alz & Dementia*

NEURONIX RESULTS

- No significant difference between active and sham groups at 7 weeks, but there appeared to be a difference at 12 weeks
- In patients with baseline ADAS-cog scores ≤ 30, trend towards significant improvement in 12-week ADAS-cog (p = 0.07)
- CGI-C scores at week 12 also significantly different in favor of active treatment group. More participants worsened in the sham group (41.8% vs 16% active, p<0.01)
- However, because study did not meet its primary outcome, FDA approval was NOT obtained





Sabbagh 2019 *Alz & Dementia*

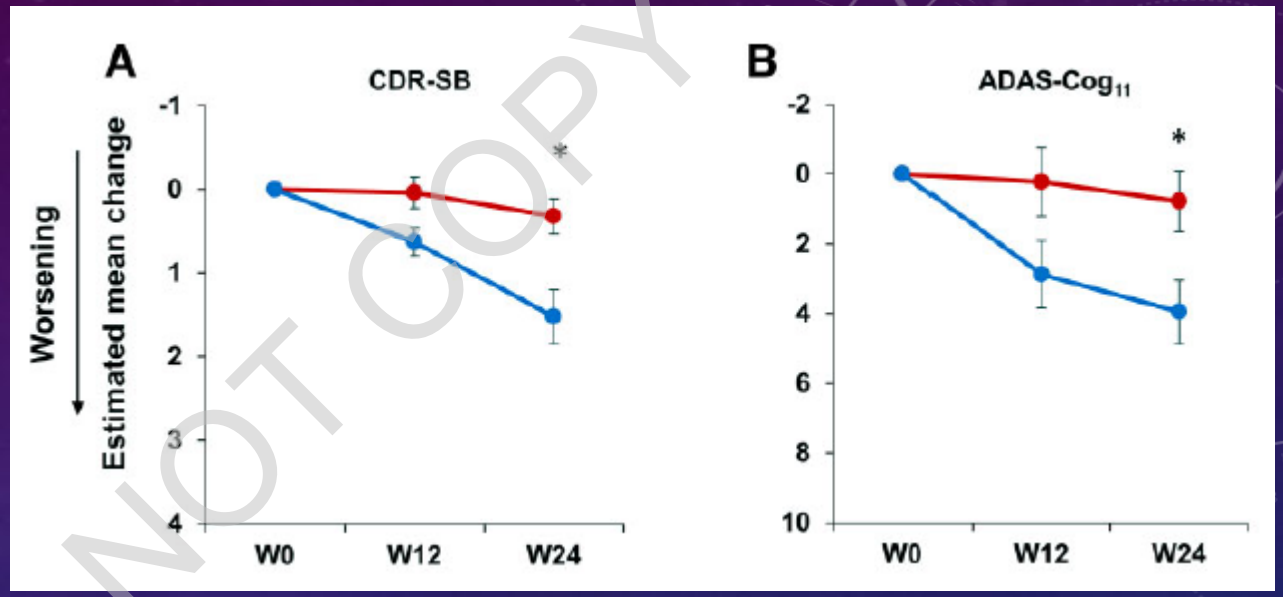
“PRECUNEUS” TMS FOR AD?

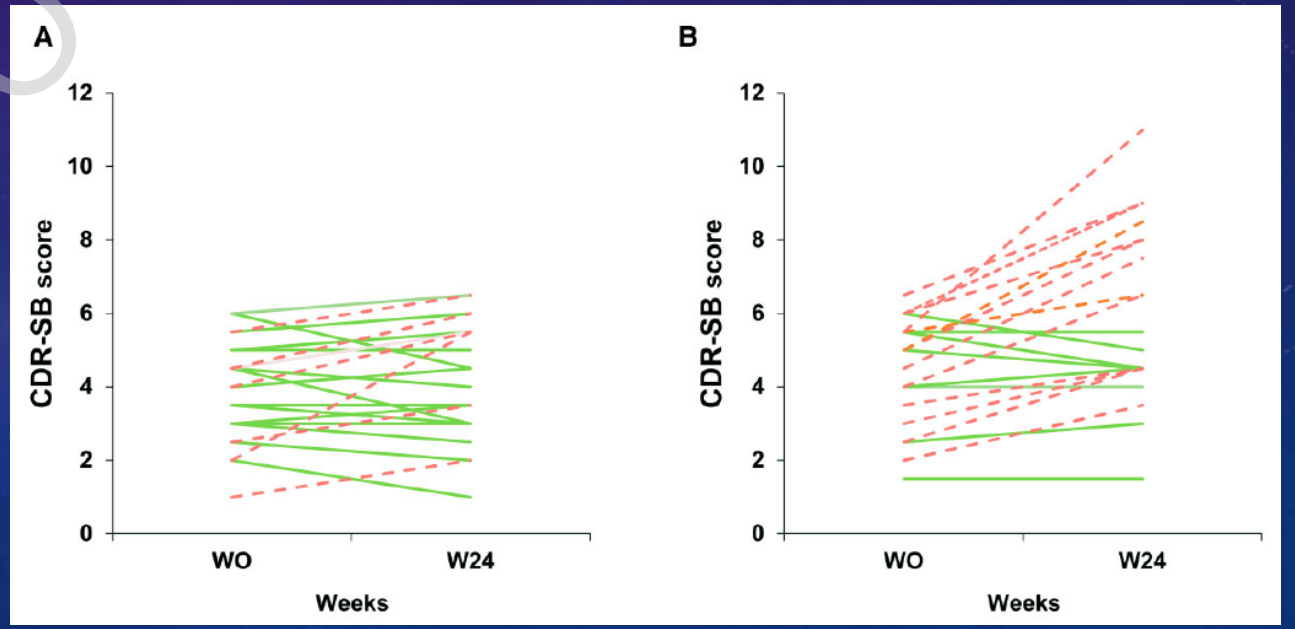
- Koch 2022 Brain: Tested 20 Hz rTMS to the “precuneus” in patients with “mild to moderate” AD
  - CDR 0.5 – 1, MMSE 18-26, CSF biomarker c/w AD
  - rTMS: 40 2s-trains at 20Hz, 28s ITI, 1600 pulses total. Applied 10 sessions over 2 weeks, followed by once weekly for 22 weeks (24 weeks total, 32 sessions). Sham was “coil positioned in correspondence to the target area, in order to preserve the same auditory and somatosensory sensations”. Magsim 70 mm figure of 8 coil.
  - 50 patients assigned (25 per group). Primary outcome measure change in CDR Sum of Boxes. Secondary outcome measures included change in ADAS-Cog
  - 45 patients completed trial

PRECUNEUS RTMS RESULTS

- Significant difference in progression between real and sham rTMS
  - Mean change in CDR-SB was -1.42 in sham group vs -0.25 in treatment group
  - 68.2% of patients in real rTMS group with minimal decline (change in CDR-SB ≤ 1) vs only 34.7% in sham group
  - ADAS-Cog similarly with only -0.67 change in real group vs -4.2 change in sham group

- BUT BUT BUT …
  - Faster rate of decline in sham group than expected
  - Magnitude of rTMS benefit (~85% slower in rTMS group) FAR greater than recent drugs





Koch 2022 *Brain*

MOVEMENT DISORDERS

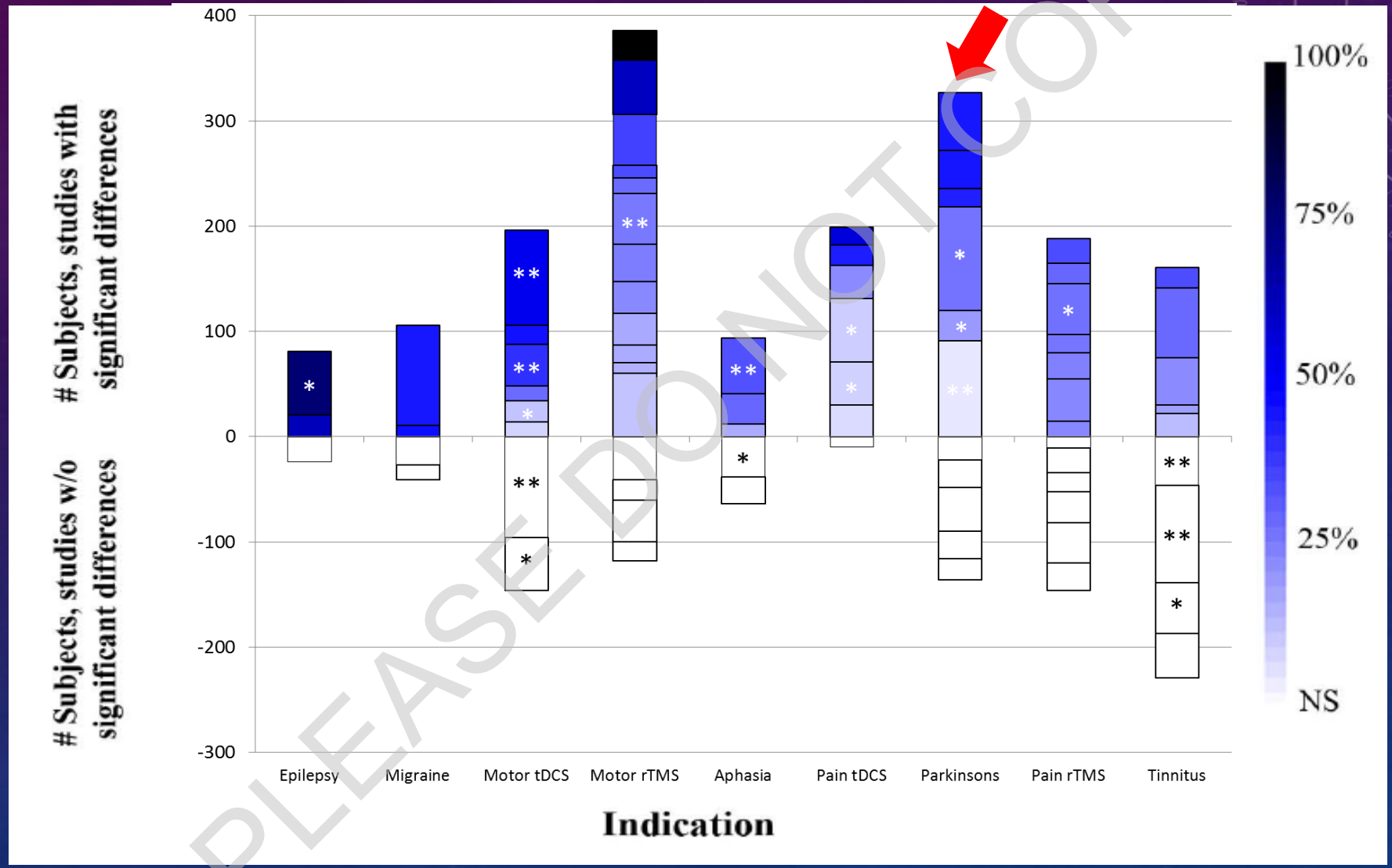
- Trials have evaluated efficacy of rTMS to unilateral M1, bilateral M1, DLPFC, SMA and cerebellum

Table 3
rTMS studies in motor symptoms of Parkinson's disease (target: (pre)motor cortex).

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
LF rTMS of M1 (unilateral stimulation of hand representation)							
Sommer et al. (2002a)	11	M1, F8c	Tilted coil	1 Hz, 120% RMT	900 pulses, 1 session	Reduction of movement time	III
Lefaucheur et al. (2004c)	12	M1, F8c	Sham coil	0.5 Hz, 80% RMT	600 pulses, 1 session	Improvement of UPDRS-III motor score (20%, with bilateral reduction of rigidity) and restoration of intracortical inhibition	III
Rothkegel et al. (2009)	22	M1, F8c	Tilted coil	0.5 Hz, 80% RMT	600 pulses, 1 session	No clinical effect	III
Filipović et al. (2010b)	10	M1, F8c	Sham coil	1 Hz, 95% AMT	1800 pulses, 4 sessions	No change in UPDRS-III motor score in either ON or OFF phase	III
No recommendation for the antiparkinsonian effect of LF rTMS of hand representation in M1							
HF rTMS of M1 (unilateral stimulation of hand representation)							
Siebner et al. (1999a)	12	M1, F8c	Tilted coil	5 Hz, 90% RMT	750 pulses, 1 session	Reduction of movement time	III
Siebner et al. (2000b)	10	M1, F8c	Tilted coil	5 Hz, 90% RMT	2250 pulses, 1 session	Improvement of UPDRS-III motor score (29%)	III
Lefaucheur et al. (2004c)	12	M1, F8c	Sham coil	10 Hz, 80% RMT	2000 pulses, 1 session	Improvement of UPDRS-III motor score (17%) and restoration of intracortical facilitation	III
Rothkegel et al. (2009)	22	M1, F8c	Tilted coil	10 Hz, 80% RMT	2000 pulses, 1 session	No clinical effect	III
No recommendation for the antiparkinsonian effect of HF rTMS of hand representation in M1							
HF rTMS of M1 (bilateral stimulation of hand and/or leg representation)							
Khedr et al. (2003)	36 (active: 19; control: 17)	Bilateral M1 (upper + lower limbs), F8c	Tilted coil	5 Hz, 120% RMT	2000 pulses, 10 sessions	Improvement of UPDRS-III motor score (49%) and walking velocity	III
Khedr et al. (2006)	20 (active: 10; control: 10)	Bilateral M1 (upper + lower limbs), F8c	Occipital stimulation	10 Hz, 100% RMT	3000 pulses, 6 sessions	Improvement of UPDRS-III motor score (15%)	III
Khedr et al. (2006)	45 (active: 35; control: 10)	Bilateral M1 (upper + lower limbs), F8c	Occipital stimulation	25 Hz, 100% RMT	3000 pulses, 6 sessions	Improvement of UPDRS-III motor score (>45%), walking velocity, and manual dexterity	II
González-García et al. (2011)	17 (active: 10; control: 7)	Bilateral M1 (upper limbs), F8c	Occipital stimulation	25 Hz, 80% RMT	1000 pulses, 15 sessions	Improvement of UPDRS-III motor score (19%) and especially bradykinesia	III
Benninger et al. (2012)	26 (active: 13; control: 13)	Bilateral M1 (upper limbs), Cc	Sham coil	50 Hz, 80% AMT	600 pulses, 8 sessions	No motor improvement, but cortical silent period lengthening	II
Maruo et al. (2013)	21	Bilateral M1 (lower limbs), F8c	Sham coil combined with electrical skin stimulation	10 Hz, 100% RMT	1000 pulses, 3 sessions	Improvement of UPDRS-III motor score (19%), pain, walking test, and finger tapping; no change in depression; repeated sessions no more effective than a single session	II
Recommendation: possible antiparkinsonian effect of HF rTMS of bilateral (multiple) sites in M1 (Level C)							
HF rTMS of the SMA							
Boylan et al. (2001)	10	Bilateral SMA, F8c	Tilted coil	10 Hz, 110% RMT	2000 pulses, 1 session	Increased reaction time and writing deterioration	III
Hamada et al. (2008b, 2009b)	98 (active: 55; control: 43)	Bilateral SMA, F8c	Sham coil	5 Hz, 110% AMT	1000 pulses, 8 sessions	Improvement of UPDRS-III motor score (20%, mainly on akinesia)	I
Shirota et al. (2013)	70 (active: 34; control: 36)	Bilateral SMA, F8c	Sham coil	10 Hz, 110% AMT	1000 pulses, 8 sessions	No significant change: only transient motor improvement similar for active and control conditions	I
No recommendation for the antiparkinsonian effect of HF rTMS of the SMA							

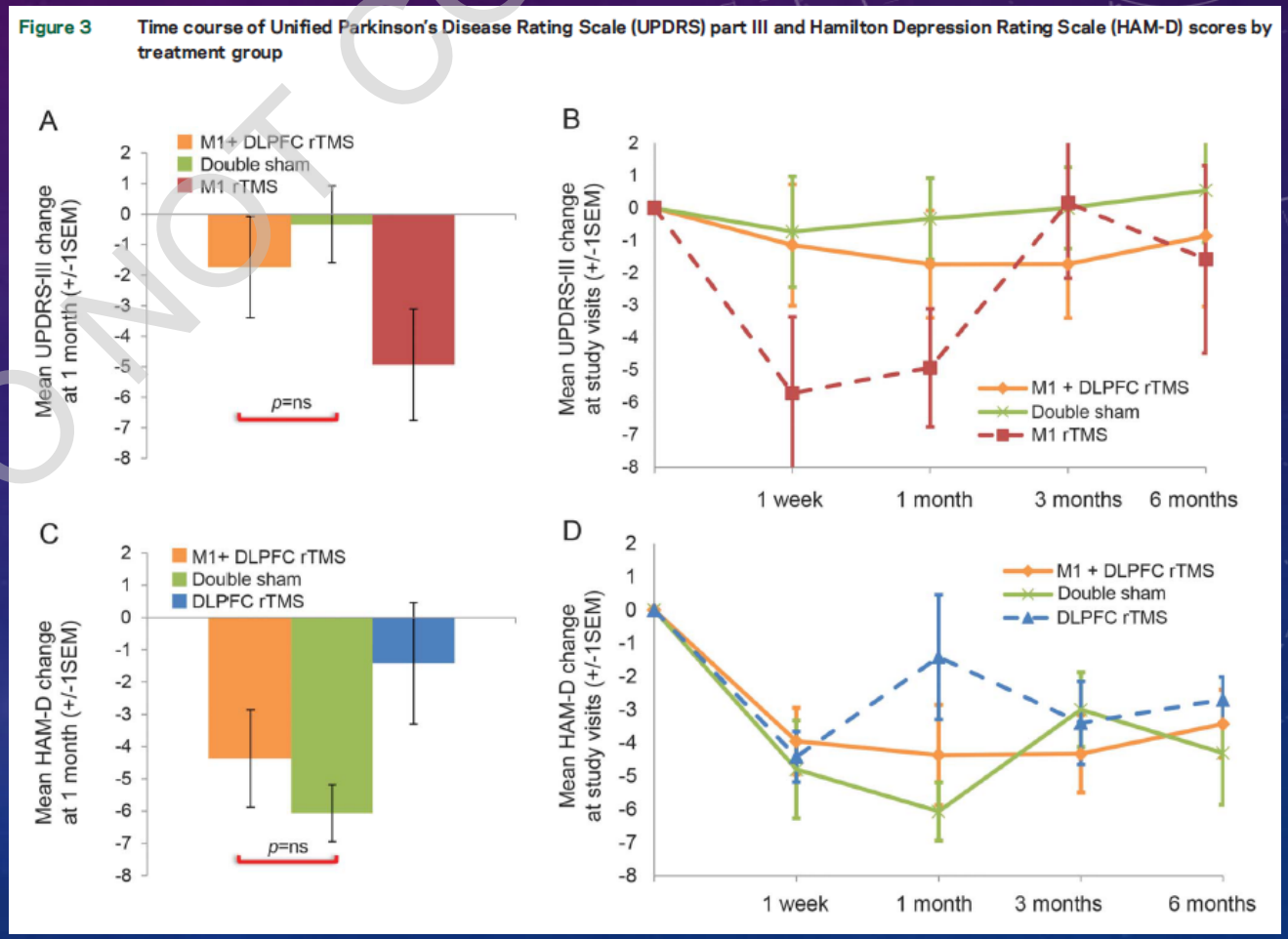
Lefaucheur 2014 *Clin Neurophys*

PARALLEL-GROUP STUDIES



RECENT UPDATES

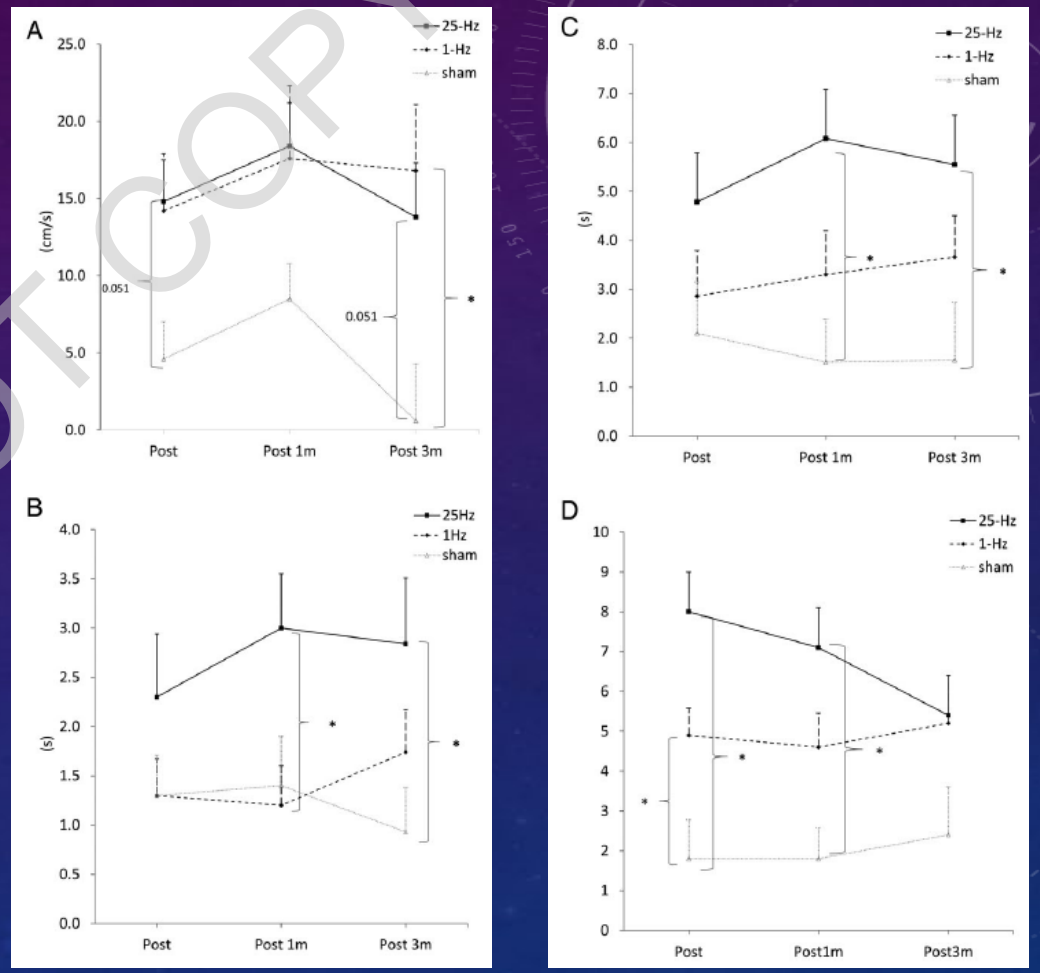
- **Brys 2016 Neurology: In a 2x2 design, compared effects of M1 and DLPFC high-frequency rTMS in 50 patients with PD and comorbid depression**
  - **Patients randomized in 1:1:1:1 fashion to receive 10 sessions of 2000 pulses (4s 10Hz trains) applied with either real or sham stimulation to left DLPFC, followed by 1000 pulses to LM1 and then RM1.**
  - **Primary outcome measures: Change in UPDRS scores and Ham-D 1 month after completion of rTMS treatment**
  - **Sham stimulation includes matched air-cooled sham coil with electrodes for skin stimulation**
  - **61 randomized, 50 completed intervention**



Primary outcome: 15% improvement in UPDRS with M1 stimulation, no improvement in HAMD

TMS FOR GAIT?

- Chung 2020 Annals Neurology: Evaluated whether priming with 25 Hz, 1 Hz, or sham rTMS followed by treadmill training improved gait in 51 patients with PD
  - 51 patients with mild to moderate PD randomized in 1:1:1 ratio, 12 sessions over 3 weeks
  - rTMS administered using 90mm double-cone coil (Magstim) to bilateral TAregion (600 pulses to each region) at 80% RMT. 25 Hz stimulation administered as 4s-ON, 50s-OFF. Sham coil disconnected with “another active coil behind participant to mimic true stimulation sound effects”
  - Immediately after rTMS, 30 minutes of treadmill training
  - Participants assessed 1 day, 1 month and 3 months after the end of intervention, “on” medication
  - Primary behavioral outcome measure: change in fastest walking speed. Secondary measures included timed-up-and-go (TUG) test, dual-task TUG, and motor UPDRS-III.



Results: Both rTMS protocols increased fastest walking speed, and led to sustained improvements in other measures. 25 Hz ?better than 1 Hz

OVERALL SUMMARY OF RESULTS

- Motor UPDRS scores can be improved by ~30% with HF rTMS to bilateral M1, although Class III studies only. ~15% improvement in Class I multi-site study conducted here
- Larger improvements tend to be seen during OFF rather than ON states
- Higher quality evidence with stimulation of SMA, where two trials have shown beneficial effects (but with smaller magnitude of benefit than is seen in M1)
- Stimulation at other sites not effective for motor UPDRS
- Potental benefits for gait with M1 rTMS followed by treadmill
- Depression may be improved with DLPFC stimulation (although study here negative), dyskinesias may improve with cerebellar stimulation

CHRONIC PAIN

- Attempt to normalize dysregulated corticothalamic pain networks
- Largest crossover study in 60 patients showed rTMS reduced pain by 22% on a VAS scale (vs 8% in sham).
- Studies suggest improvement from HF but not LF stimulation, targeting of M1 but not other regions.
- Beneficial response to rTMS may correlate with subsequent positive outcome of implanted epidural stimulator over M1

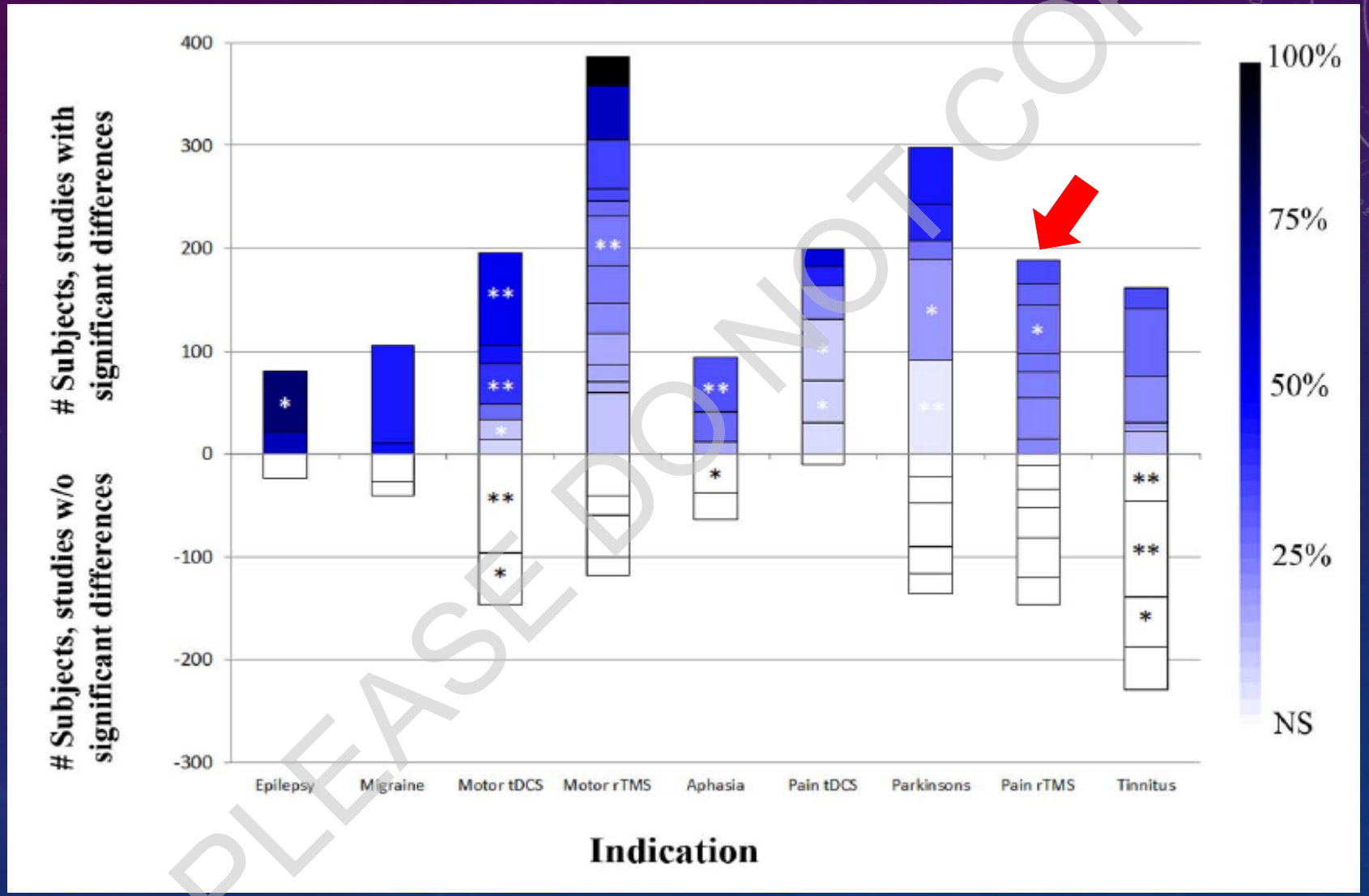
ALL PAIN TRIALS

Table 1
rTMS studies in chronic neuropathic pain (target: primary motor cortex).

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
LF rTMS of M1 contralateral to pain side							
Lefaucheur et al. (2001a)	18	M1, F8c	Sham coil	0.5 Hz, 80% RMT	1000 pulses, 1 session	Non-significant pain relief (4% responders)	III
André-Obadia et al. (2006)	12	M1, F8c	Tilted coil	1 Hz, 90% RMT	1600 pulses, 1 session	Non-significant pain relief (0% responders)	III
Irlbacher et al. (2006)	27 (active: 20; control: 18)	M1, F8c	Sham coil (2 Hz)	1 Hz, 95% RMT	500 pulses, 5 sessions	Non-significant pain relief (6% responders)	III
Lefaucheur et al. (2006a)	22	M1, F8c	Sham coil	1 Hz, 90% RMT	1200 pulses, 1 session	Non-significant pain relief (14% responders)	II
Saitoh et al. (2007)	13	M1, F8c	Tilted coil	1 Hz, 90% RMT	500 pulses, 1 session	Non-significant pain relief (unknown % responders)	III
Lefaucheur et al. (2008b)	46	M1, F8c	Sham coil	1 Hz, 90% RMT	1200 pulses, 1 session	Non-significant pain relief (9% responders)	II
Recommendation: LF rTMS of M1 contralateral to pain side is probably ineffective in neuropathic pain (Level B)							
HF rTMS of M1 contralateral to pain side							
Lefaucheur et al. (2001a)	18	M1, F8c	Sham coil	10 Hz, 80% RMT	1000 pulses, 1 session	Significant pain relief (39% responders)	III
Lefaucheur et al. (2001b)	14	M1, F8c	Sham coil	10 Hz, 80% RMT	1000 pulses, 1 session	Significant pain relief (57% responders)	III
Lefaucheur et al. (2004b)	60	M1, F8c	Sham coil	10 Hz, 80% RMT	1000 pulses, 1 session	Significant pain relief (37% responders and 23% improvement)	II
Khedr et al. (2005b)	48 (active: 28; control: 20)	M1, F8c	Tilted coil	20 Hz, 80% RMT	2000 pulses, 5 sessions	Significant pain relief (79% responders)	I
André-Obadia et al. (2006)	12	M1, F8c	Tilted coil	20 Hz, 90% RMT	1600 pulses, 1 session	Non-significant pain relief (36% responders and 11% improvement)	III
Hirayama et al. (2006)	20	M1, F8c	Tilted coil	5 Hz, 90% RMT	500 pulses, 1 session	Significant pain relief (50% responders)	II
Irlbacher et al. (2006)	27 (active: 19; control: 18)	M1, F8c	Sham coil (2 Hz)	5 Hz, 95% RMT	500 pulses, 5 sessions	Non-significant pain relief (7% responders)	III
Lefaucheur et al. (2006a)	22	M1, F8c	Sham coil	10 Hz, 90% RMT	1200 pulses, 1 session	Significant pain relief (55% responders)	II
Saitoh et al. (2007)	13	M1, F8c	Tilted coil	5–10 Hz, 90% RMT	500 pulses, 1 session	Significant pain relief (50% responders)	III
André-Obadia et al. (2008)	28	M1, F8c	Sham coil	20 Hz, 90% RMT	1600 pulses, 1 session	Significant pain relief only with posteroanterior orientation of the coil (13% improvement)	II
Lefaucheur et al. (2008b)	46	M1, F8c	Sham coil	10 Hz, 90% RMT	1200 pulses, 1 session	Significant pain relief (43% responders)	II
Kang et al. (2009)	11 (spinal cord injury)	M1, F8c	Tilted coil	10 Hz, 80% RMT	1000 pulses, 5 sessions	Non-significant pain relief (14% improvement)	III
Ahmed et al. (2011)	27 (active: 17; control: 10)	M1, F8c	Tilted coil	20 Hz, 80% RMT	2000 pulses, 5 sessions	Significant pain relief (up to 2 months after rTMS)	II
André-Obadia et al. (2011)	45	M1, F8c	Sham coil	20 Hz, 90% RMT	1600 pulses, 1 session	Significant pain relief (10% improvement)	II
Lefaucheur et al. (2011b)	59	M1, F8c	Sham coil	10 Hz, 90% RMT	2000 pulses, 1 session	Significant pain relief (36% responders and 22% improvement for "active-sham" condition)	II
Hosomi et al. (2013)	64	M1, F8c	Active coil placed over inactive coil combined with electrical scalp stimulation	5 Hz, 90% RMT	500 pulses, 10 sessions	Significant short-term pain relief (20% responders and 4% improvement for "active-sham" condition), but no significant cumulative improvement	I
Jetté et al. (2013)	16 (spinal cord injury)	M1, F8c	Sham coil	10 Hz, 90% RMT (hand area), 110% RMT (leg area)	2000 pulses, 1 session	Significant pain relief for hand or leg area stimulation for 48 h (about 15% improvement)	III
André-Obadia et al. (2014)	20	M1, F8c	Sham coil	20 Hz, 90% RMT	1600 pulses, 1 session	Significant pain relief (15% improvement), predictive of subsequent positive outcome of implanted chronic motor cortex stimulation	III
Recommendation: definite analgesic effect of HF rTMS of M1 contralateral to pain side in neuropathic pain (Level A)							

Lefaucheur 2014 *Clin Neurophys*

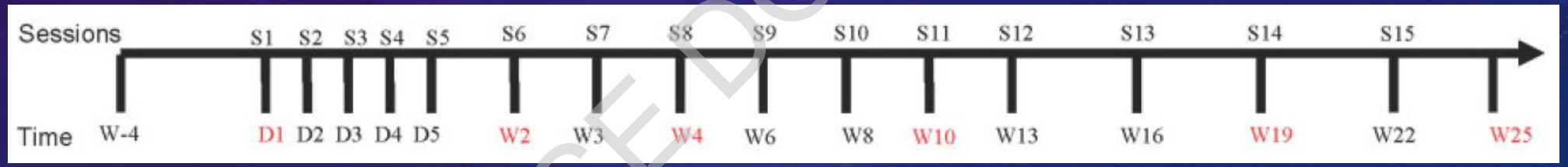
PARALLEL-GROUP RCTS HAVE VARIABLE RESULTS



And effect sizes are generally small …

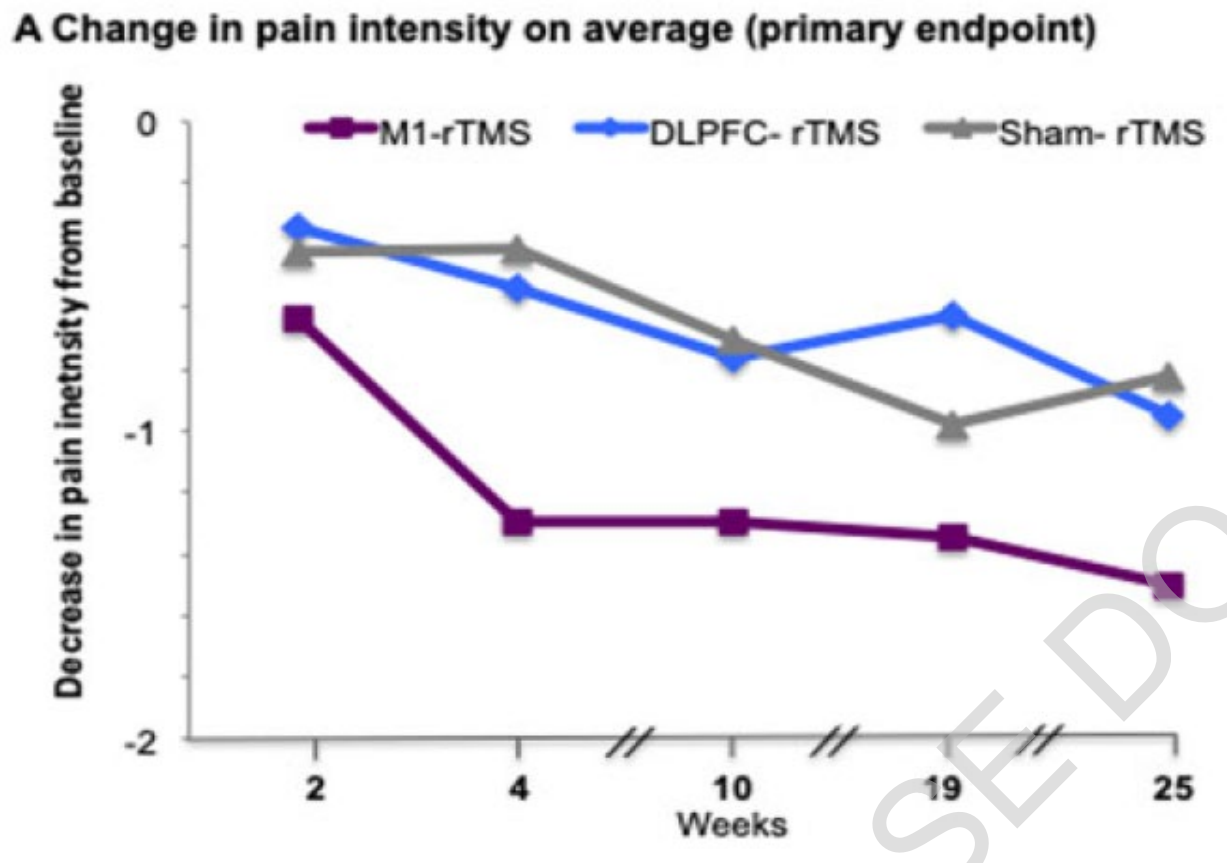
SOME RECENT WELL-DESIGNED STUDIES

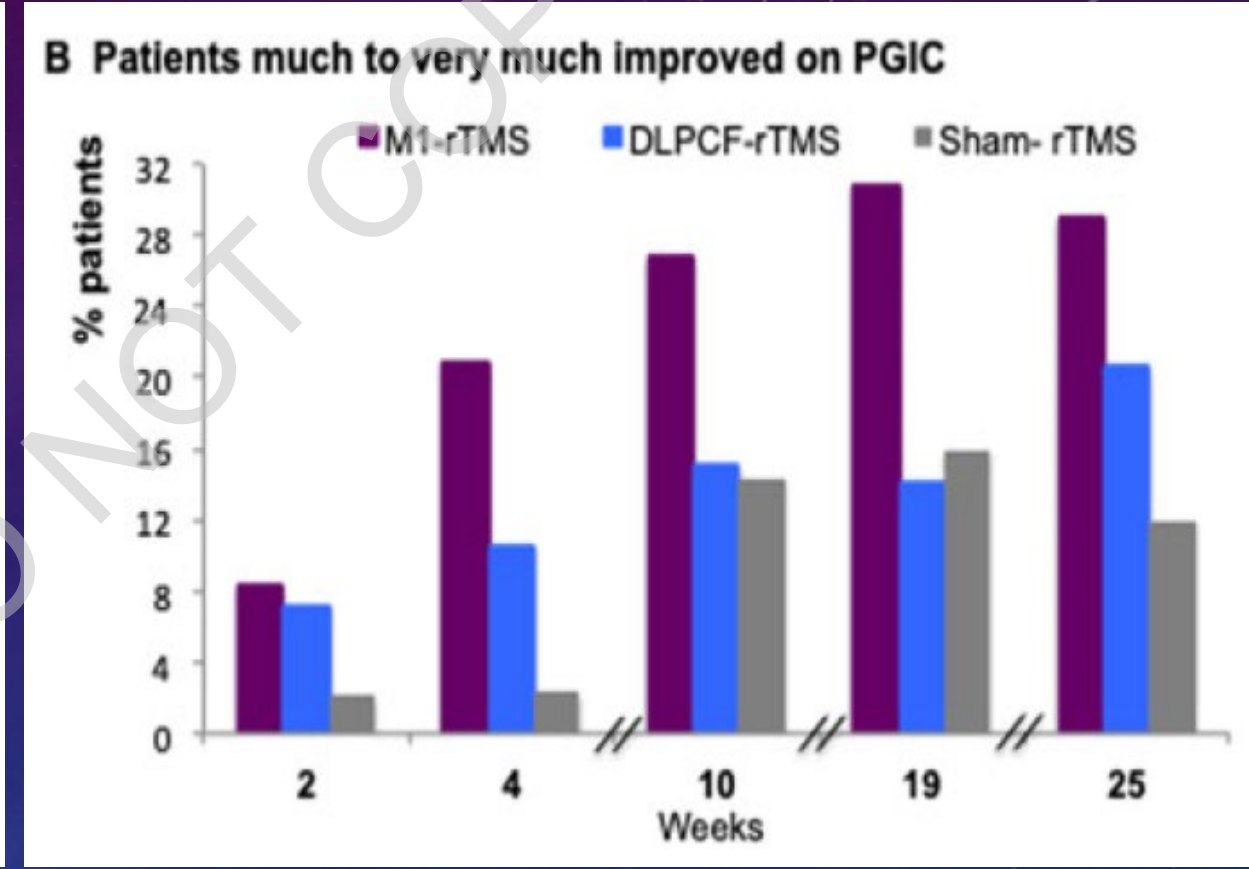
- Attal 2021 Brain: High quality multi-site RCT of M1 vs DLPFC rTMS for peripheral neuropathic pain.
  - 1:1 ratio for M1 vs DLPFC, 2:1 at each site for real or sham rTMS
  - 10 Hz rTMS w/ 10s-ON 20s-OFF for 3000 pulses per session, 80% RMT. Used MagVenture Cool-B65 A/P coil. Sham stimulation had electrical stim, which was applied during both active and placebo stimulation
  - M1 stimulation targeted “hand knob” region of M1 target. M1 target contralateral to pain, or left hemisphere for bilateral pain. DLPFC target was middle frontal gyrus between the anterior and middle thirds, left hemisphere. Robotic stimulation used.



  - Primary outcome: Mean change from baseline in average pain intensity from the brief pain inventory (0-10 NRS, 0 = no pain) over course of 25. Last measurement 3 weeks after the last TMS session. A number of secondary measures also assessed in selected visits (in red)
  - 149 patients randomized, 138 (93%) completed first 5 daily sessions, and 130 (87%) completed 8 sessions through 4 weeks. 39/49 (80%) M1 patients completed study, vs only 29/52 (55%) of DLPFC patients and 25/48 (52%) of sham patients

RESULTS





- Significantly greater improvement with M1 vs sham stimulation. No effect of DLPFC stimulation. M1 improvement of 1.5 points by week 25, vs 0.8 with sham and 0.9 with DLPFC stimulation.
- 29% of patients very much improved with M1 rTMS, vs 12% for sham rTMS.
- Pain relief 40.5% with M1 rTMS, 24.4% for sham rTMS.
- >50% pain relief 44.7% with M1, 12% with sham. NNT for >50% pain relief 3.1

TINNITUS

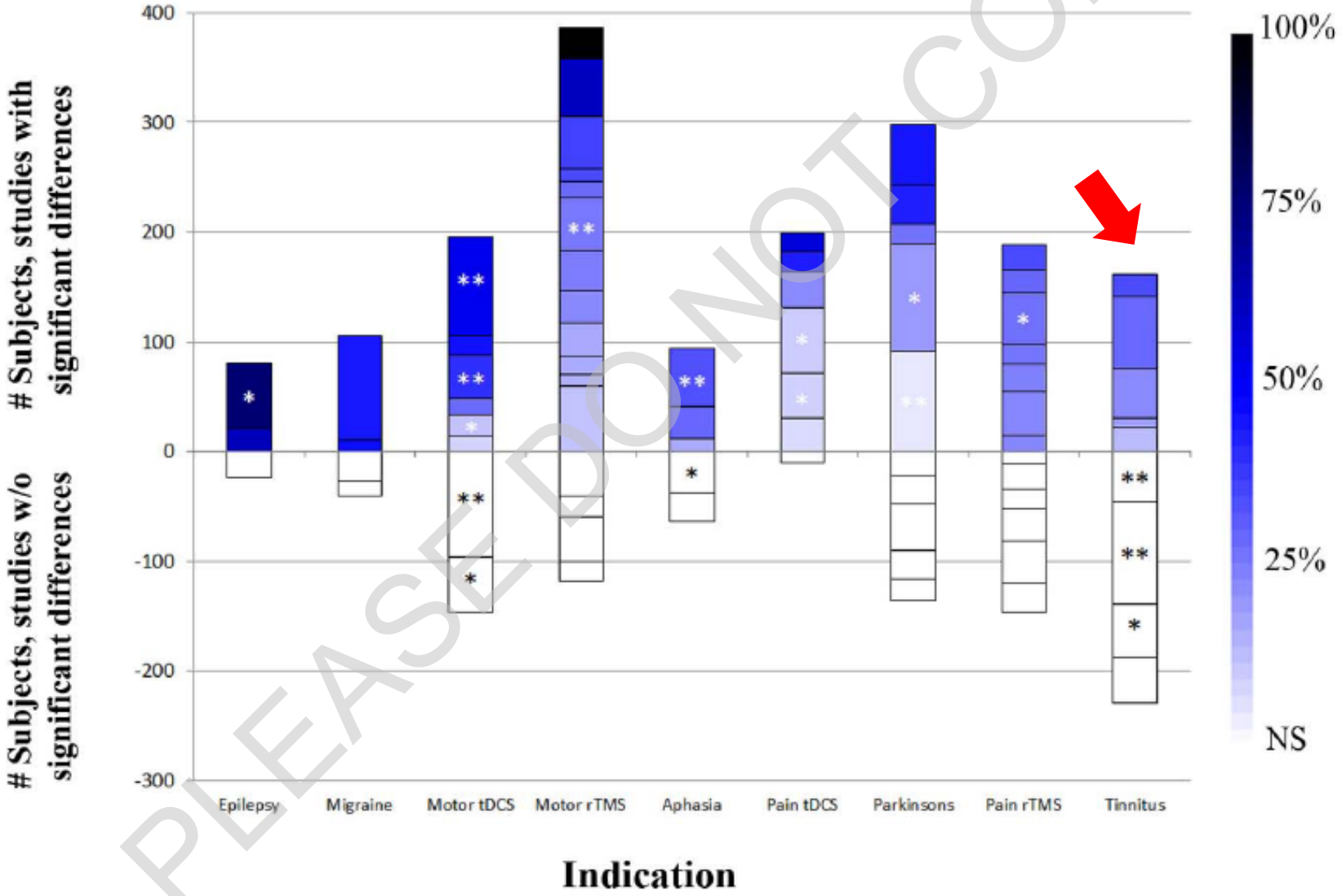
- The phantom perception of sound or noise in the absence of an acoustic stimulus
  - fMRI/PET studies have demonstrated alterations in both the auditory system (left temporoparietal ctx) and non-auditory regions in limbic and frontal areas
- Initial single-session studies suggested at least transient decreases in tinnitus, but all poor quality studies (class III)
- Subsequent multi-session studies, especially well-designed parallel group ones (Landgrebe 2017 Brain Stimulation) , have reported less impressive results (**although see Folmer 2015 JAMA Otolaryngol Head Neck Surg for an exception**)

MULTI SESSION TINNITUS TRIALS

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 behind the mastoid	cTBS, 80% RMT	900 pulses, 20 sessions	Non-significant tinnitus reduction	III
Hoekstra et al. (2013)	50 (active: 25; control: 25)	Bilateral primary auditory cortex, F8c (navigation)	Sham coil	1 Hz, 110% RMT	4000 pulses (2000 left, 2000 right), 5 sessions	Non-significant tinnitus reduction	I
Lee et al. (2013)	15	Left temporal cortex, F8c (10–20 EEG system)	Tilted coil	1 Hz, 100% RMT	1200 pulses, 10 sessions	Significant tinnitus reduction, negatively correlated to the duration of tinnitus	III
Piccirillo et al. (2013)	14	Left temporoparietal junction, F8c	Sham coil	1 Hz, 110% RMT	1500 pulses, 20 sessions	Non-significant tinnitus reduction	III
Bilici et al. (2014)	75 (active 30, 15; control 30)	Left TPC, Cc	Sham coil	1/10 Hz, 110% RMT	900 pulses (1 Hz) or 600 pulses (10 Hz), 10 sessions	Significant tinnitus reduction for all active conditions, less pronounced in combination with paroxetine	III
Langguth et al. (2014)	185 (active: 47,48,46; control: 44)	PET-guided temporal cortex, left temporal cortex, combined left temporal + prefrontal cortices, F8c (navigation and 10–20 EEG system)	Sham coil	1 Hz (temporal cortex), 20 Hz (prefrontal cortex), 110% RMT	2000 or 4000 pulses, 10 sessions	Significant tinnitus reduction for all 3 active conditions, but no statistical significant difference in comparison to sham; better effects on a descriptive level for combined frontal and temporal rTMS	I
Recommendation: possible effect of repeated sessions of LF rTMS of the TPC (on the left hemisphere or contralateral to the affected ear) in tinnitus (Level C)							

Lefaucheur 2014 *Clin Neurophys*

RESULTS IN PARALLEL-GROUP NOT IMPRESSIVE



THE LESSONS FROM TINNITUS?

- Known neural target that is hyperactive
- Target can be reached with TMS
- Yet…trials to date have been negative
- Possible reasons:
  - limbic involvement, like central pain?
  - Bilateral treatments necessary?
  - Multi-site stimulation?
  - rTMS protocols not doing what they are supposed to do?
  - rTMS itself is noisy?

CONCLUSIONS

- TMS is FDA-approved and beneficial in presurgical motor and language mapping
- TMS is FDA approved for abortive therapy AND prophylactic therapy of migraine … but ?efficacy for prophylaxis
- Studies suggest that TMS biomarkers may be helpful in diagnosis, prognosis and understanding mechanisms across a variety of neuropsychiatric disease
  - But still early!
- TMS has shown promising results for treatment of a broad array of neurologic indications, BUT large multisite RCTs have shown disappointing results (with the notable exception of chronic neuropathic pain)
  - Lots of room for bias to creep in
  - Strong placebo effects
  - Be skeptical!!!