# Neurological Applications of Transcranial Magnetic Stimulation

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# Overview of Talk

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

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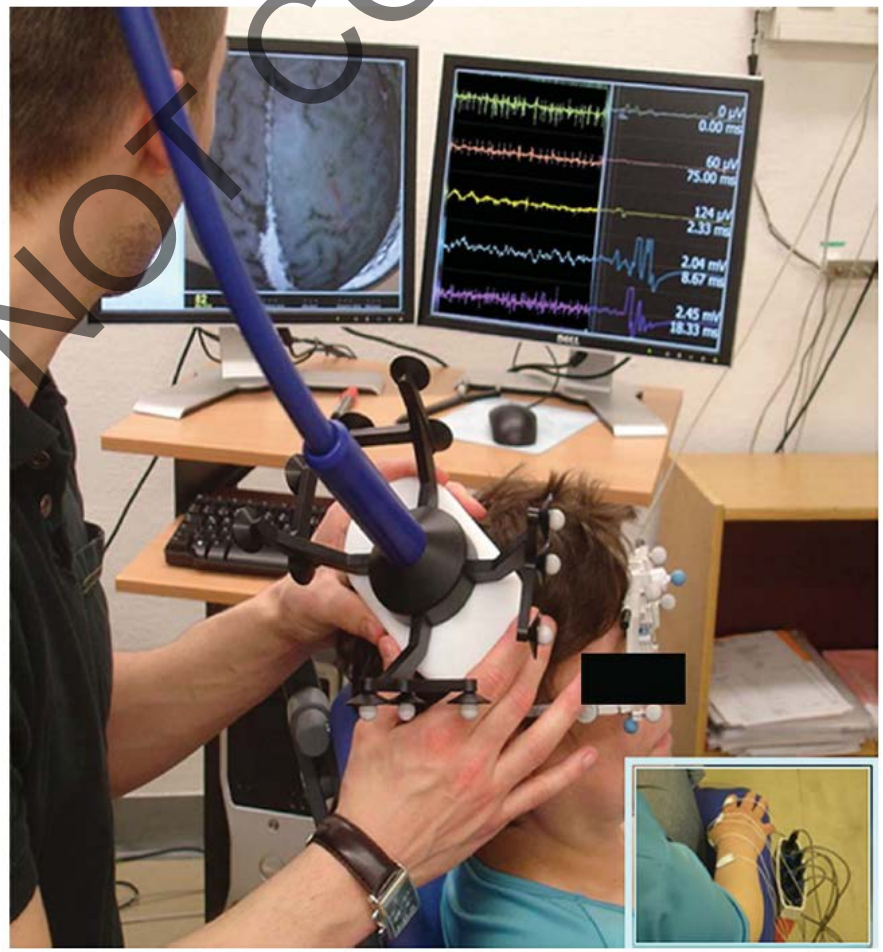
# Motor / Language Mapping

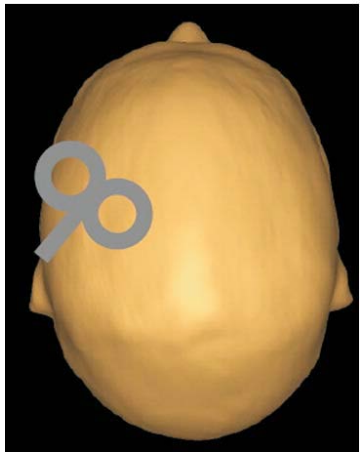
- FDA approval of Nexstim NBS device for:
  - Mapping of the primary motor cortex
  - Localization of cortical areas that do NOT contain essential speech function
  - For pre-procedural planning

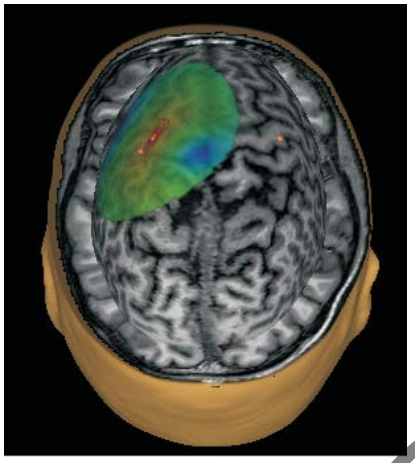


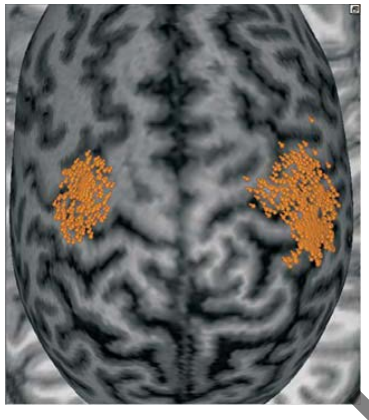
Picht 2011 *Neurosurgery*

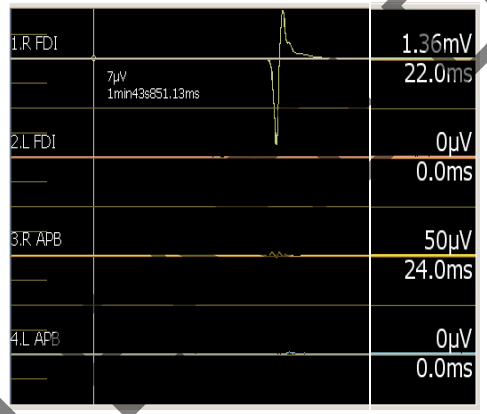


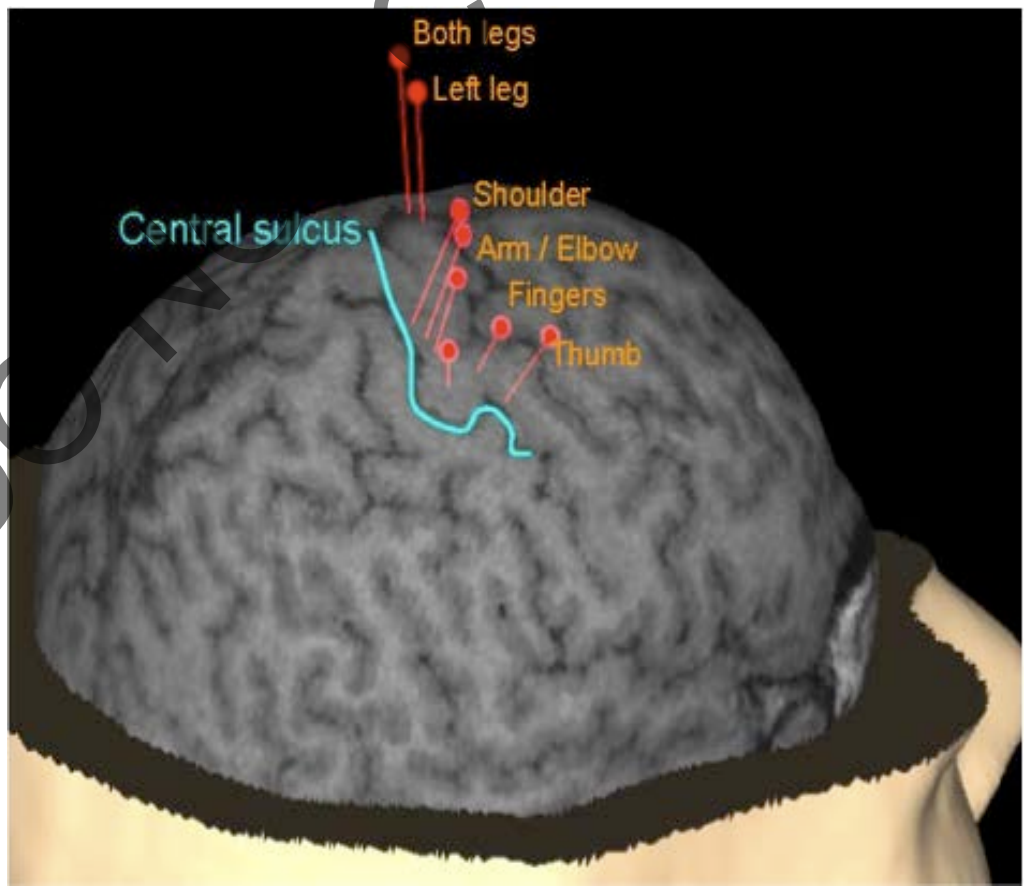
# Motor Cortical Output Mapping









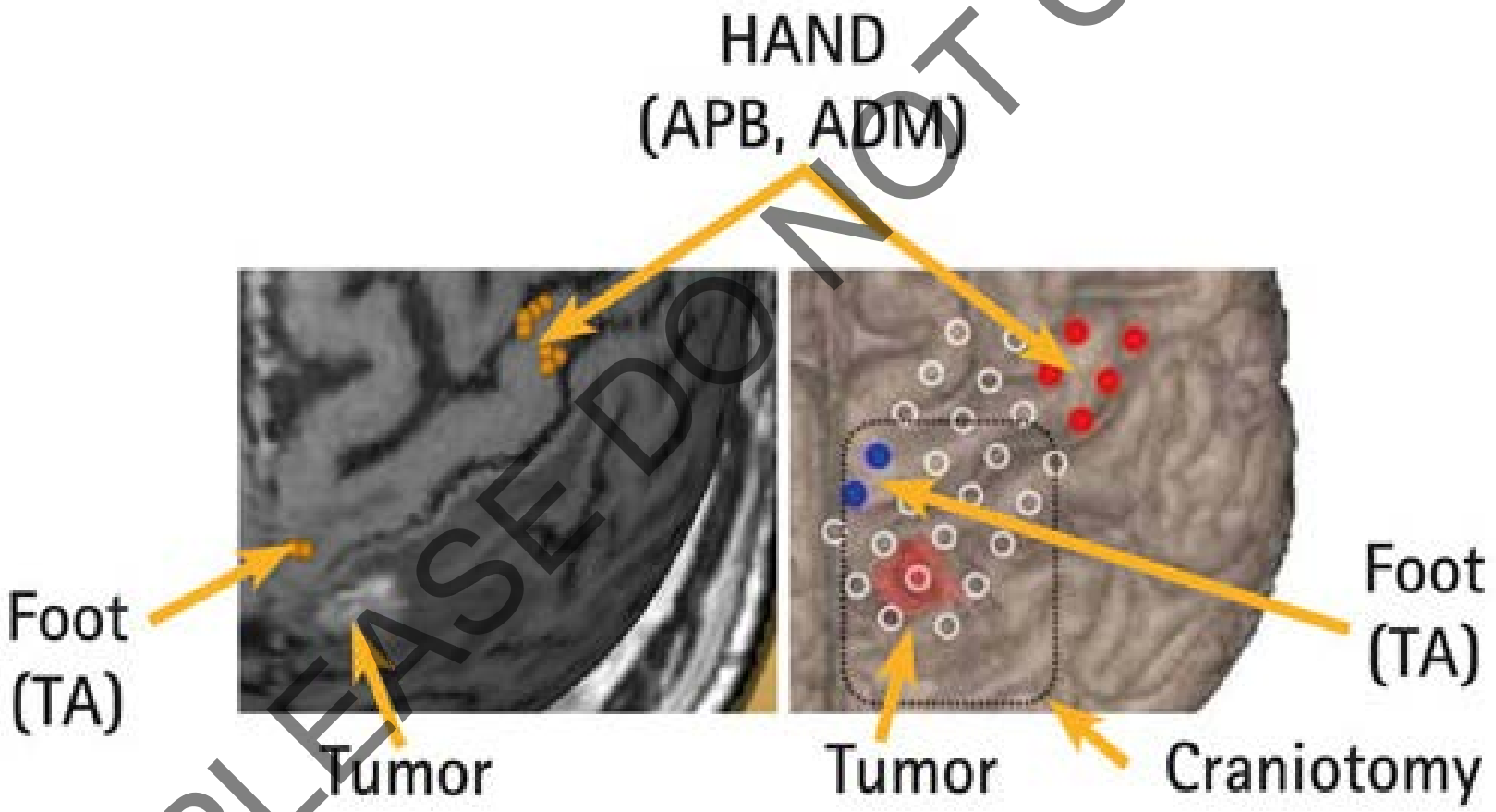



Nagib et al. *Neurosurg Clin* 2011



# Motor Cortical Output Mapping

## Comparing Noninvasive and Invasive Mapping

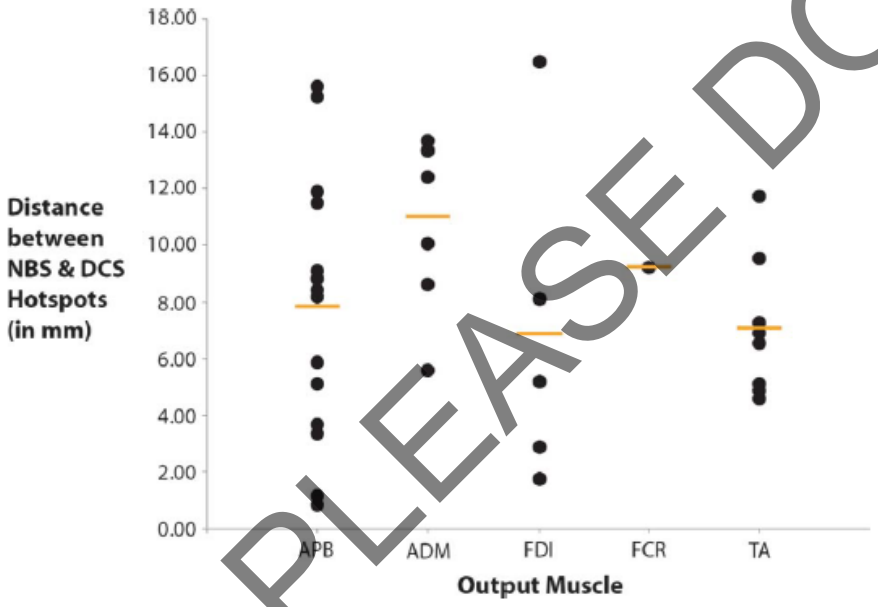




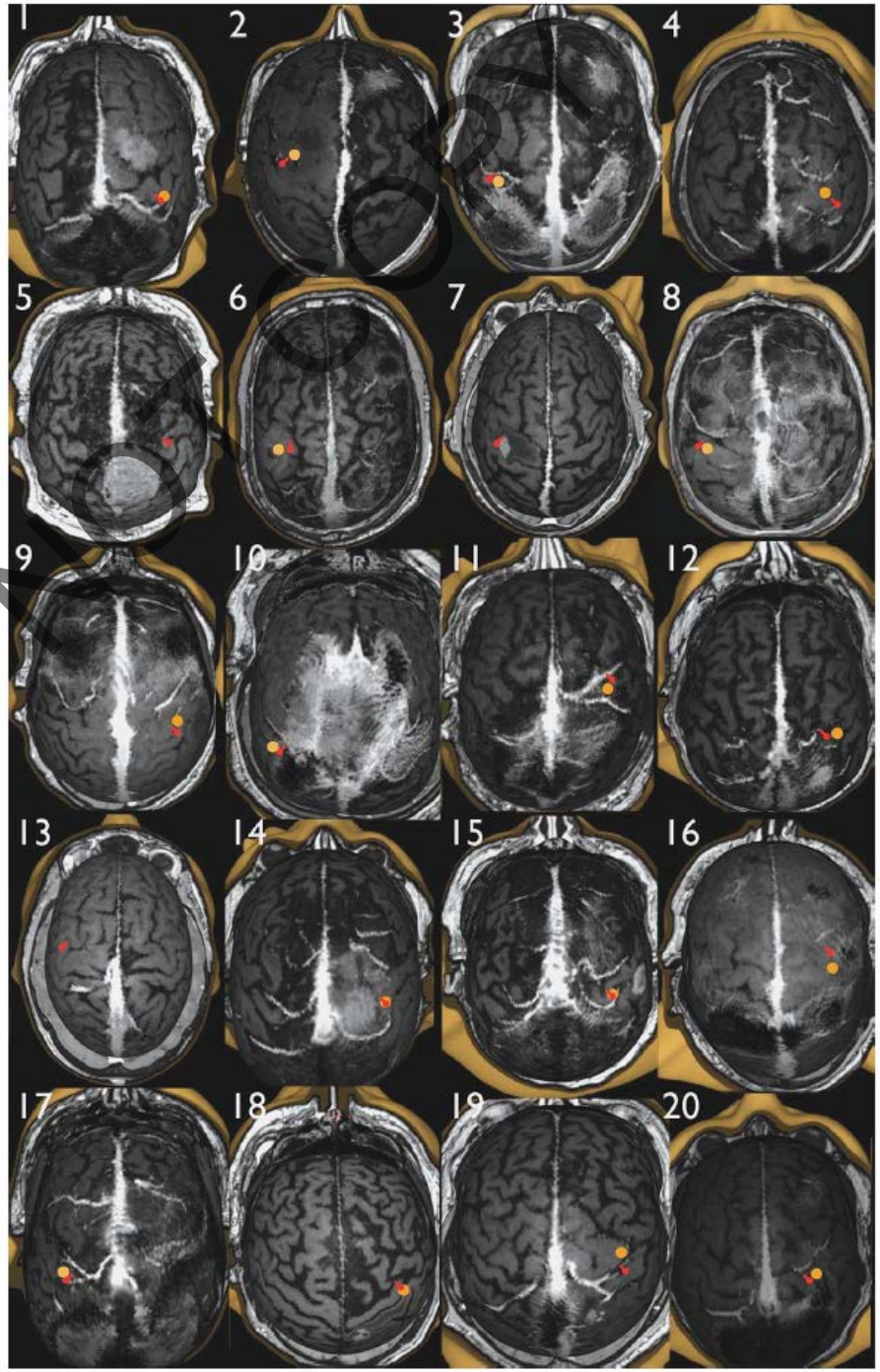

Najib et al. *Neurosurg Clin* 2011

# Motor mapping

- Comparing nTMS to 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



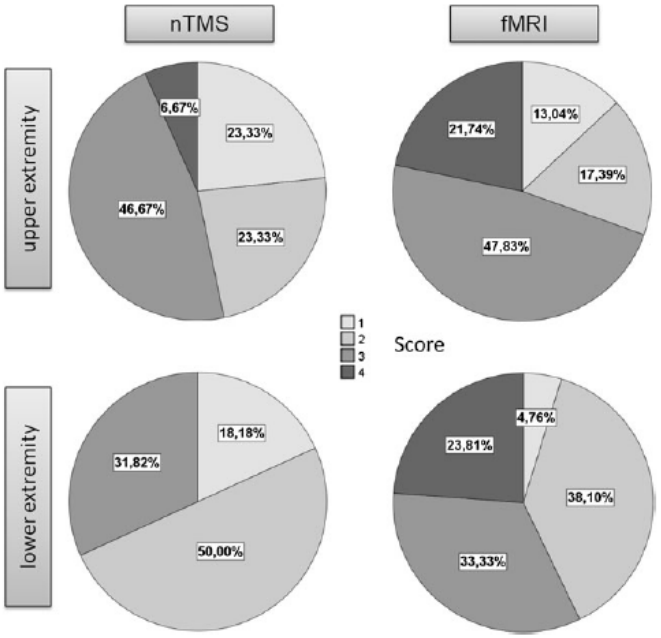

Picht 2011 *Neurosurgery*



# nTMS vs fMRI

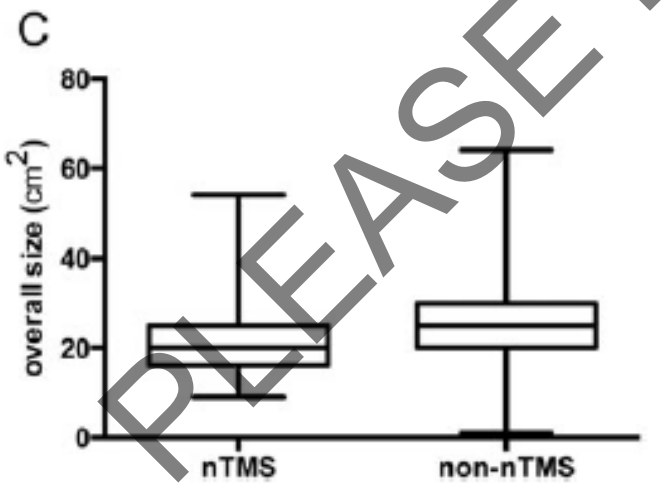
- Several studies have evaluated accuracy of motor mapping with nTMS vs fMRI (with DCS as gold standard)
  - Forster 2011, *Neurosurgery*: 10 pts, mean distance to DCS hotspot 10.5 +/- 5. 7 mm for nTMS vs 15.0 +/- 7.6 mm for fMRI
  - Mangraviti 2013, *Neurol Sci*: 7 patients, mean distance to DCS hotspot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

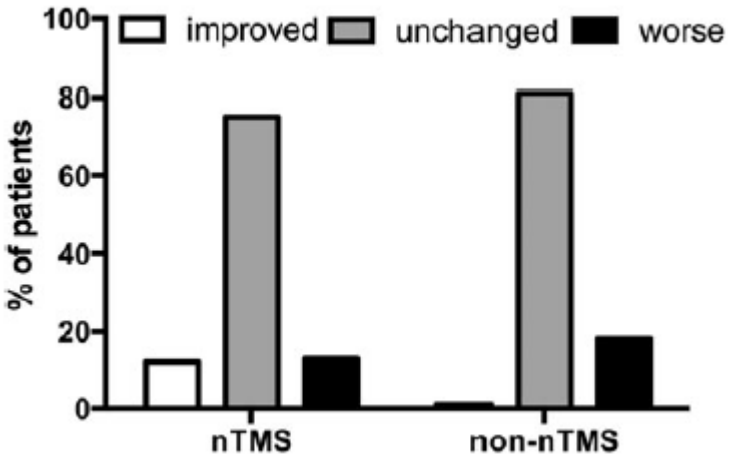
Coburger 2013, *Neurosurg Rev*: 30 patients; all 30 completed nTMS, whereas only 23 completed fMRI. Authors binned results into 4 levels, where 1 is most accurate, 4 is least accurate



# Motor mapping w/ nTMS improves outcome?

- Krieg 2014 *Neurosurgery*: 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% | |

# 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 |

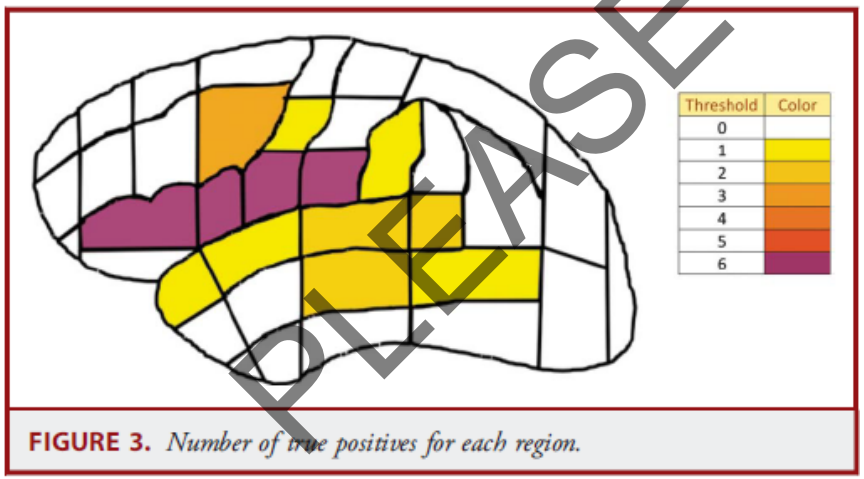



**FIGURE 3.** *Number of true positives for each region.*

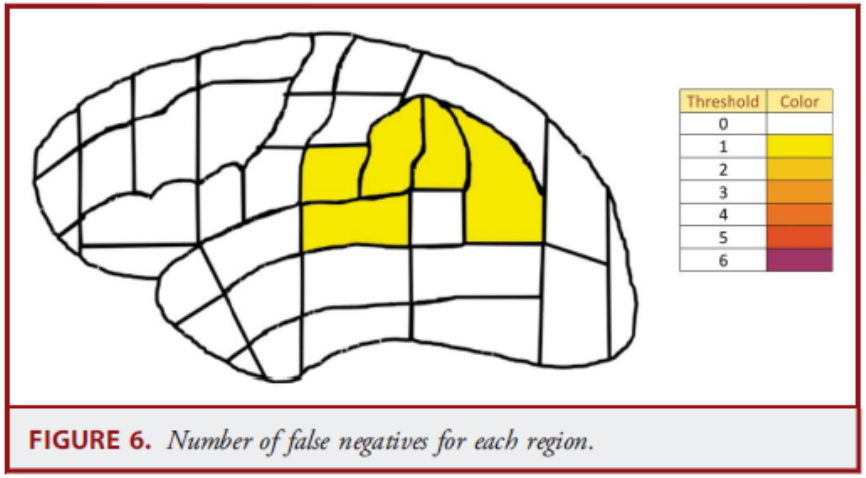
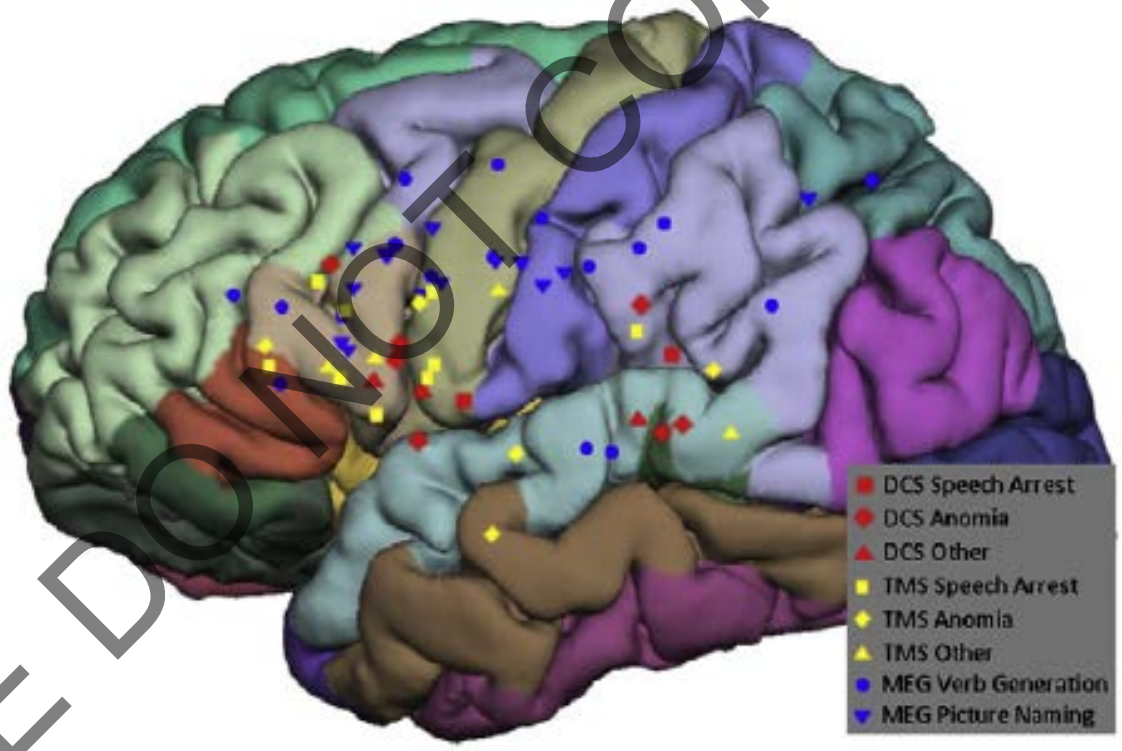



**FIGURE 6.** *Number of false negatives for each region.*

# 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)

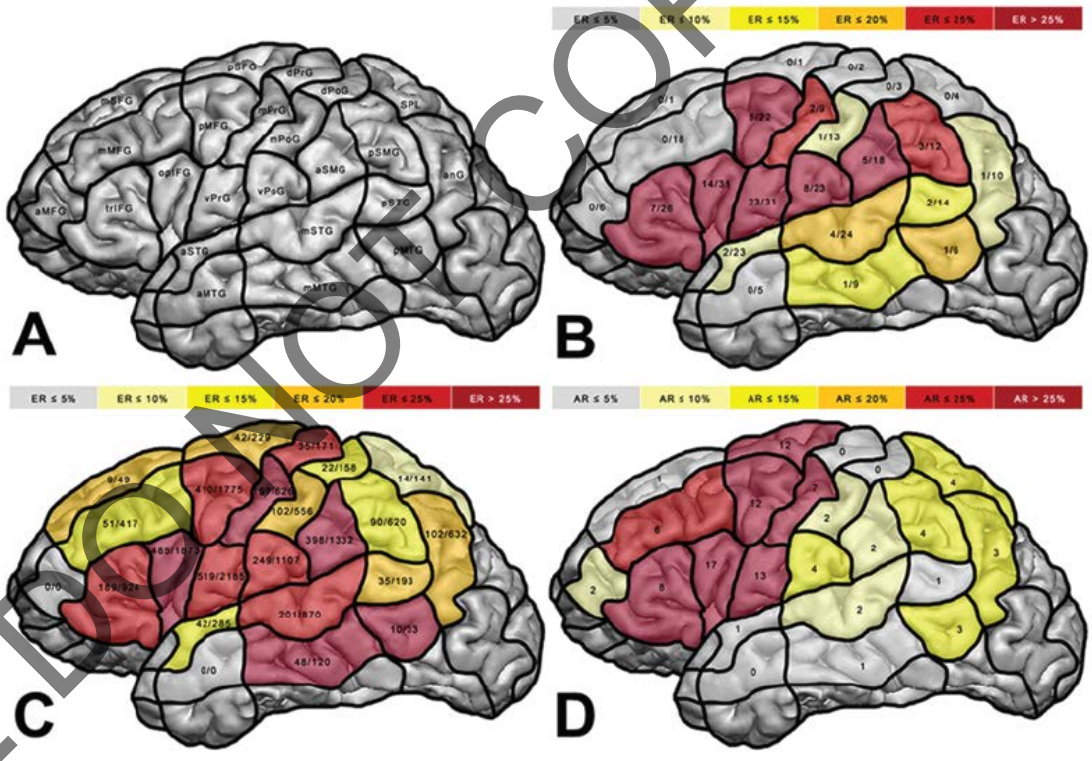





**TABLE 3. Overall results without dependency on lesion location***

| Parameter | rTMS vs DCS | | | fMRI vs DCS | | |
|---|---|---|---|---|---|---|
| | 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

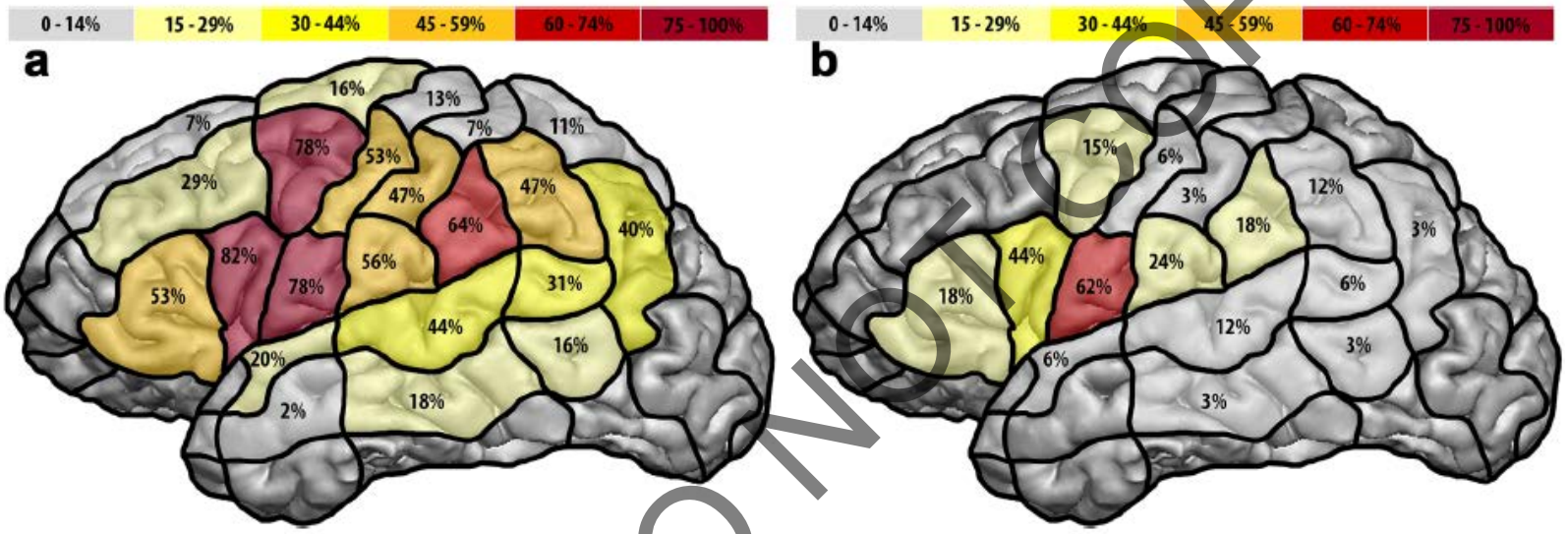
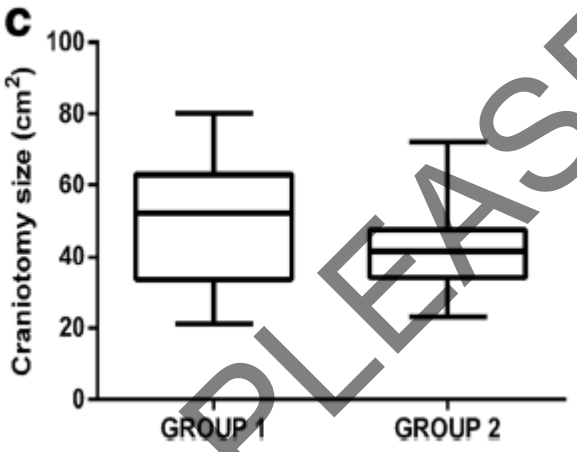
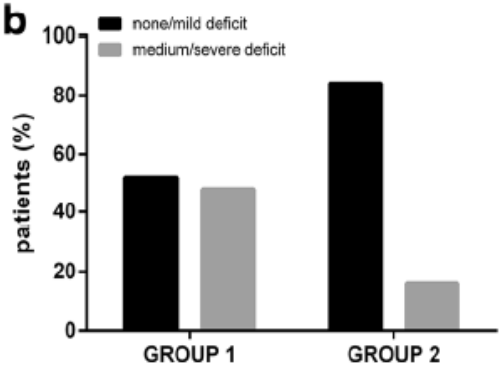
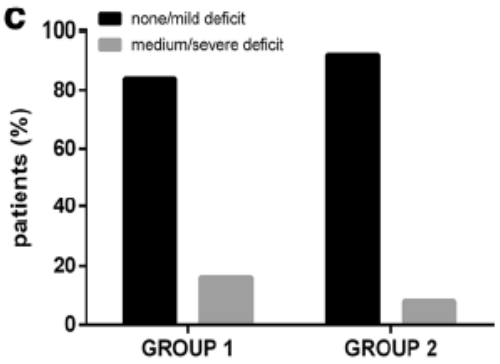



**Figure 1** rTMS and DCS error maps. This figure graphically illustrates the language mapping results gained by preoperative rTMS **(a)** or intraoperative direct cortical stimulation (DCS) **(b)** for both patient cohorts together. The percentage results from the number of individuals with no-response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

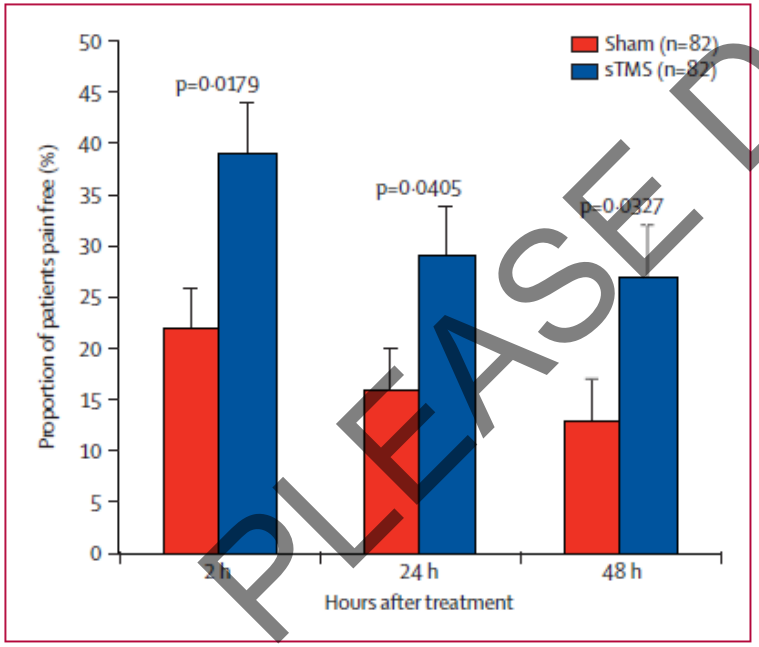
# Abortive therapy migraine

- 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

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# MEPs predict functional recovery after acute stroke

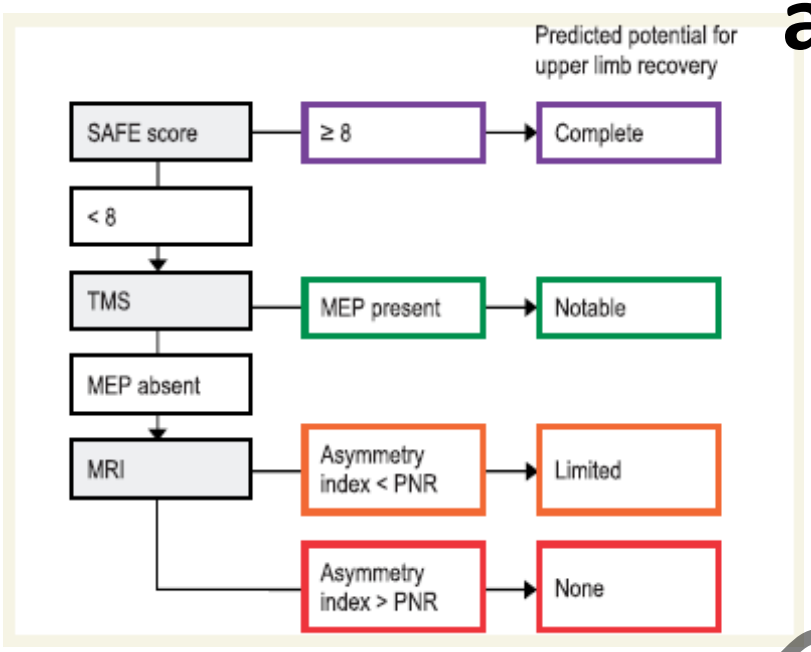
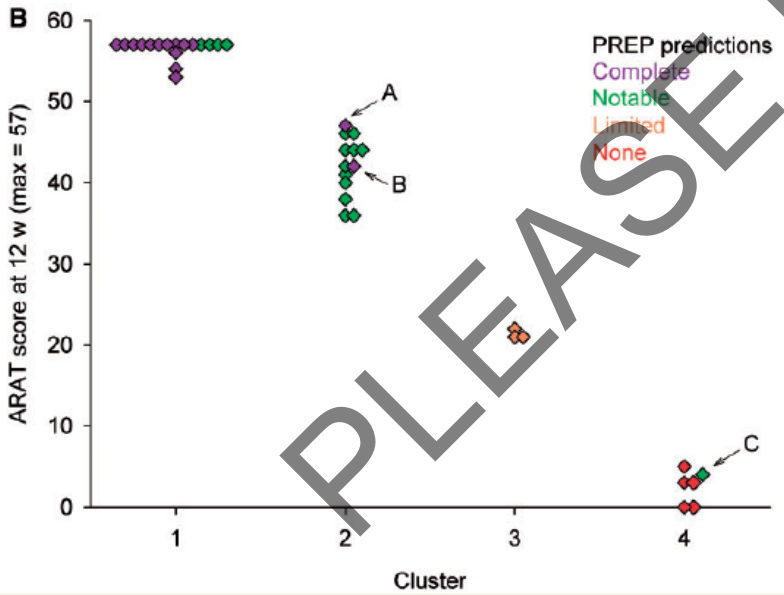
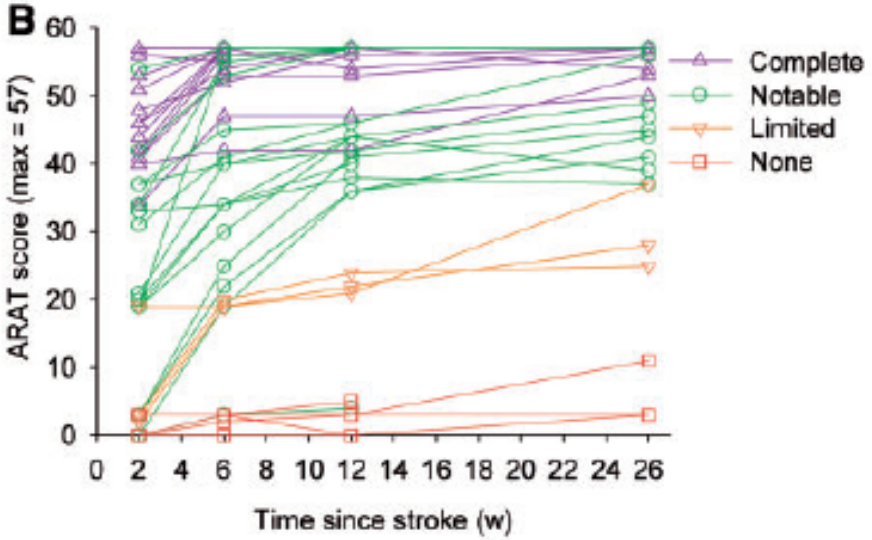



Table 1 Recovery definitions and examples of feasible

| 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. |

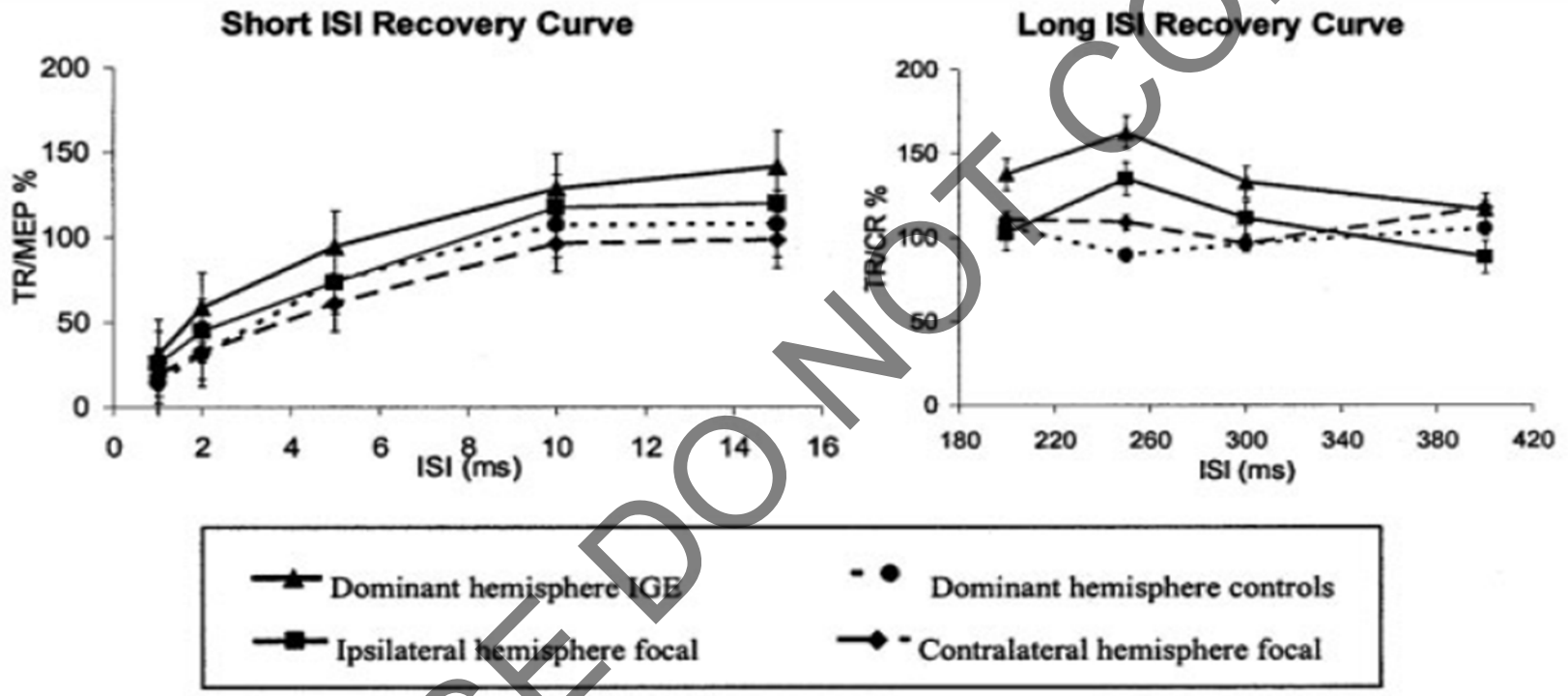





Stinear 2012, *Brain*

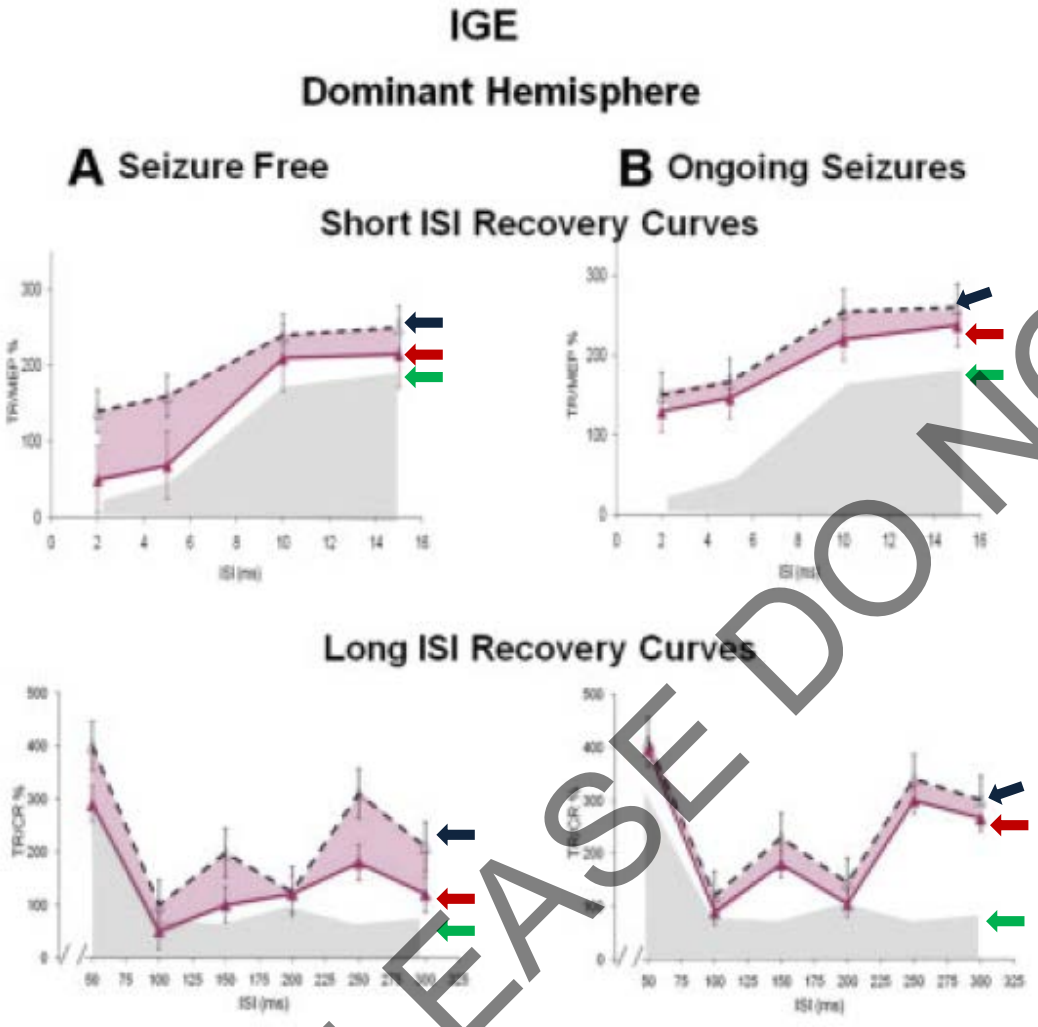
# Paired-pulse measures identify cortical hyperexcitability in Epilepsy




Paired-pulse measures suggest altered excitation / inhibition balance in patients with newly-diagnosed epilepsy compared to healthy controls

Badawy 2007 *Ann Neurol*

# And predict response to medications




TMS-EMG paired-pulse measures normalize in patients who respond to meds; no such changes seen those with ongoing seizures

TABLE 4: Sensitivity, Specificity, and Predictive Values (with 95% Confidence Interval) of More Than 100% Reduction in Recovery Ratios at the 250-Millisecond Interstimulus Interval for Predicting Seizure Freedom after Medication

| Diagnosis | IGE | Focal Epilepsy |
|---|---|---|
| Sensitivity | 0.65 (0.49–0.79) | 0.35 (0.17–0.56) |
| Specificity | 0.92 (0.62–0.99) | 0.78 (0.52–0.94) |
| Positive Predictive Value | 0.97 (0.82–0.99) | 0.69 (0.39–0.91) |
| Negative Predictive Value | 0.42 (0.23–0.63) | 0.45 (0.27–0.64) |

IGE = idiopathic generalized epilepsy.

Epilepsy patients, before meds

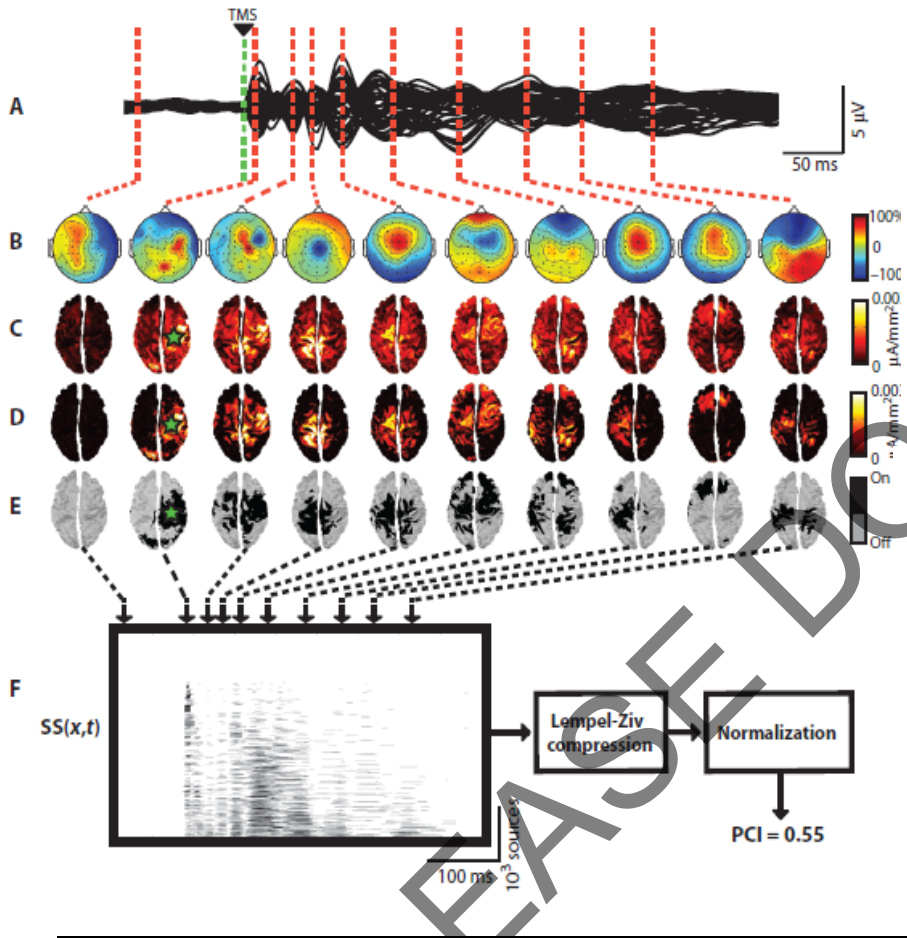
Epilepsy patients, after meds

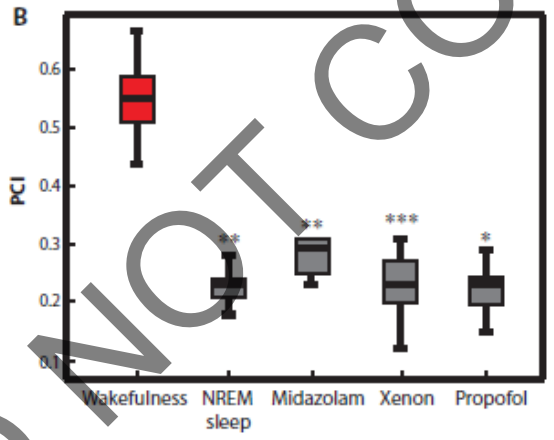
Normal controls

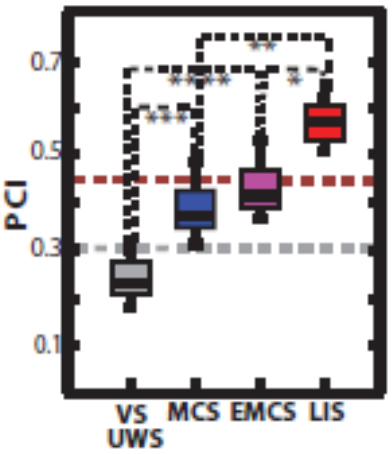
Badawy 2010, *Ann Neurol*

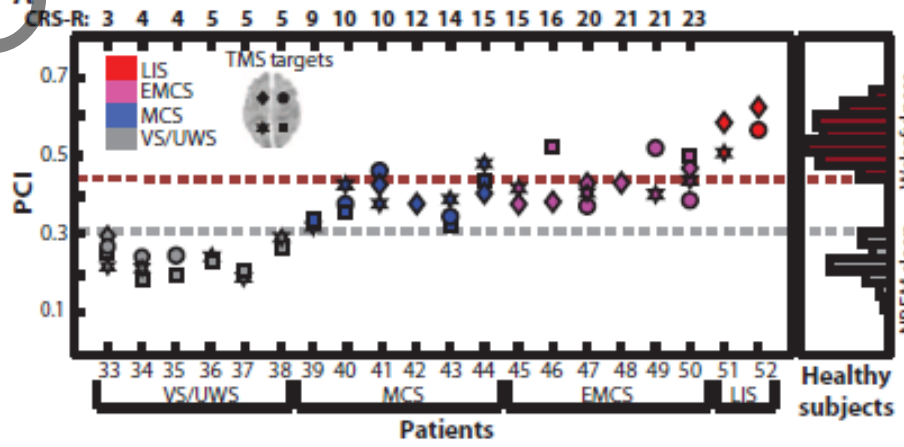
# Diagnosis of Persistent Vegetative vs Minimally Conscious State

**Casali 2013, *Science Trans Med***




**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**



M/F

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# Theraputic effects?

- rTMS has been studied as a therapeutic modality in different neurologic conditions including
  - Epilepsy
  - Migraine prevention
  - Motor rehabilitation after stroke
  - Cognitive rehabilitation in post-stroke aphasia, post-stroke neglect and Alzheimer's Disease
  - Movement Disorders (primarily Parkinson's)
  - Chronic Pain
  - Tinnitus
- However, FDA indication has not been yet obtained for any of these (multi-center trials currently underway 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
  - Recent evidence-based review/guidelines on therapeutic use of rTMS in neurologic and psychiatric diseases

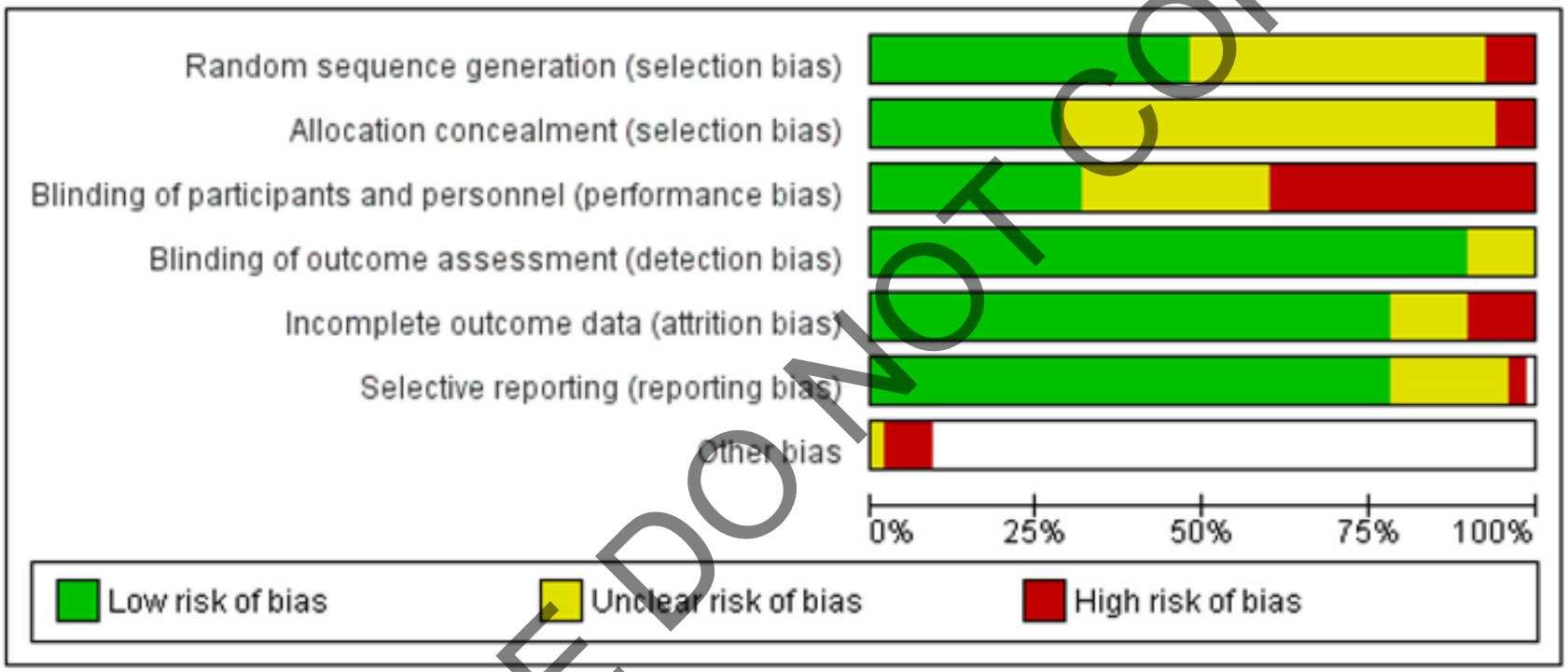
# Principles for successful intervention with TMS/tDCS

- Known brain region or network
- Known goal to enhance or decrease activity of that network
- Target can be engaged by stimulation intervention

# 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!
- Recently, placebo coils that can be preprogrammed and that use electrical stimulation to produce scalp sensations have become commercially available

# As a result study quality is often poor

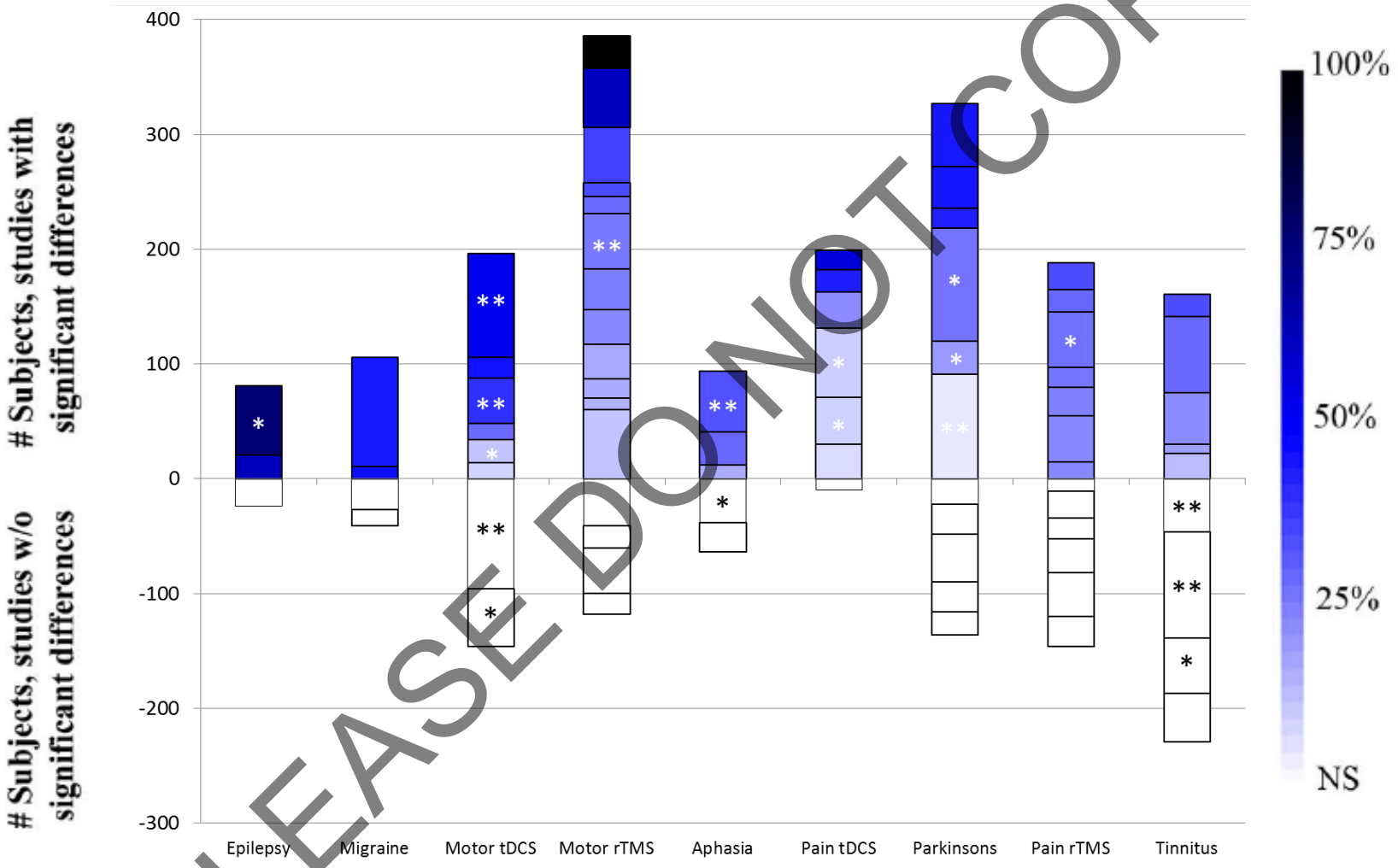



## Transcranial Magnetic Stimulation

- 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

Shafi et al, *in preparation*

# An overview of the current evidence






Shafi et al, *in preparation*

# TMS and tDCS for Neurological indications

# 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)

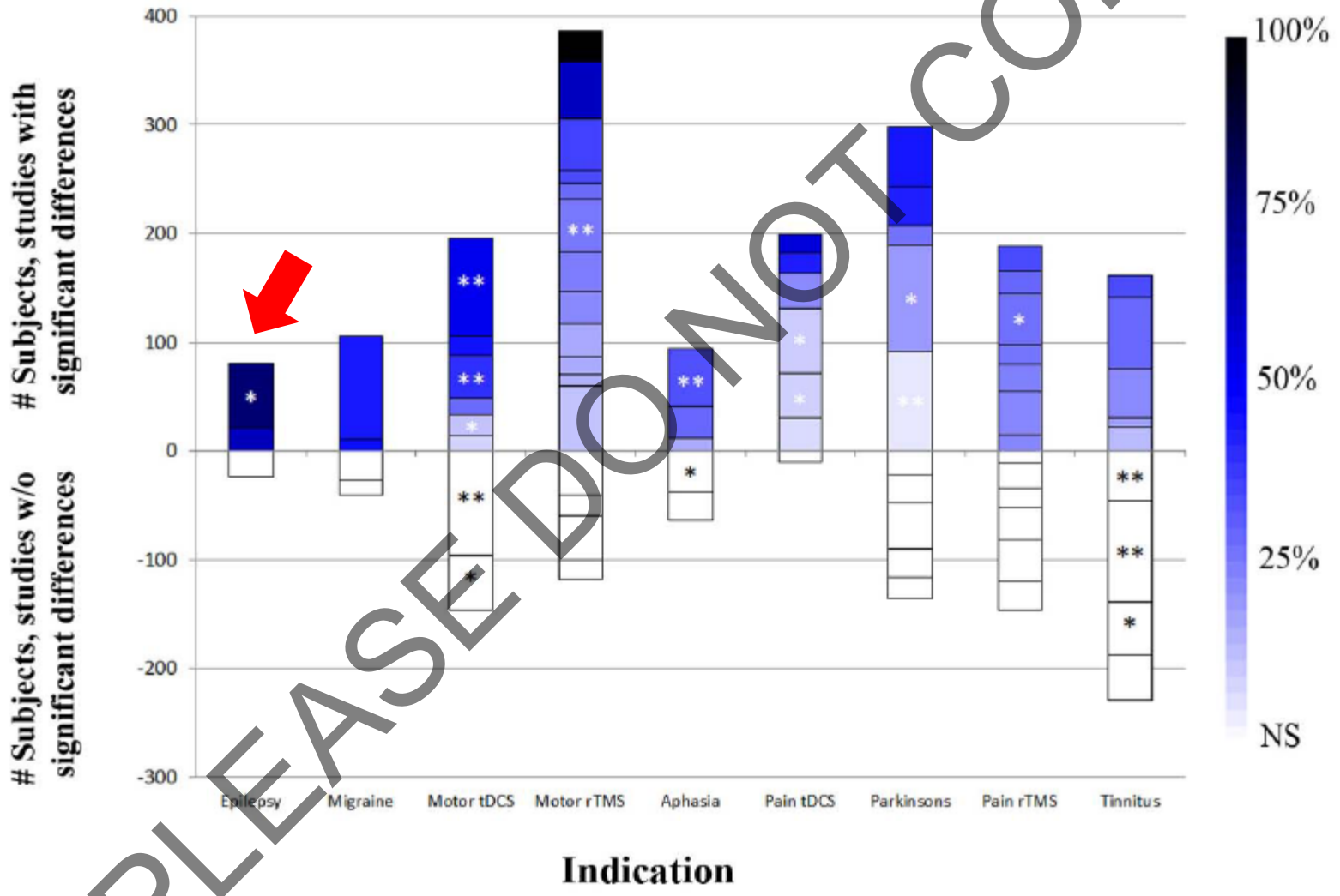


**Table 7**
rTMS studies in epilepsy (various cortical targets).

| 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*

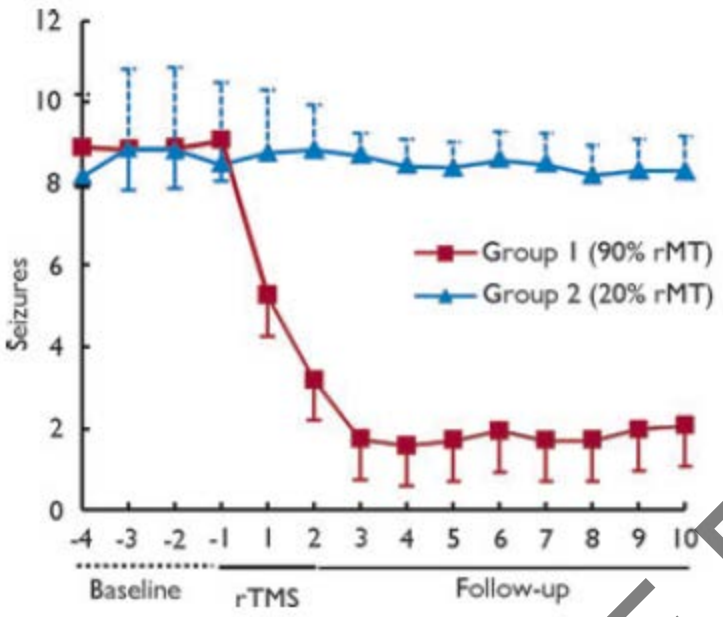
# Parallel-group studies






Shafi et al, *in preparation*

# 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 (%).

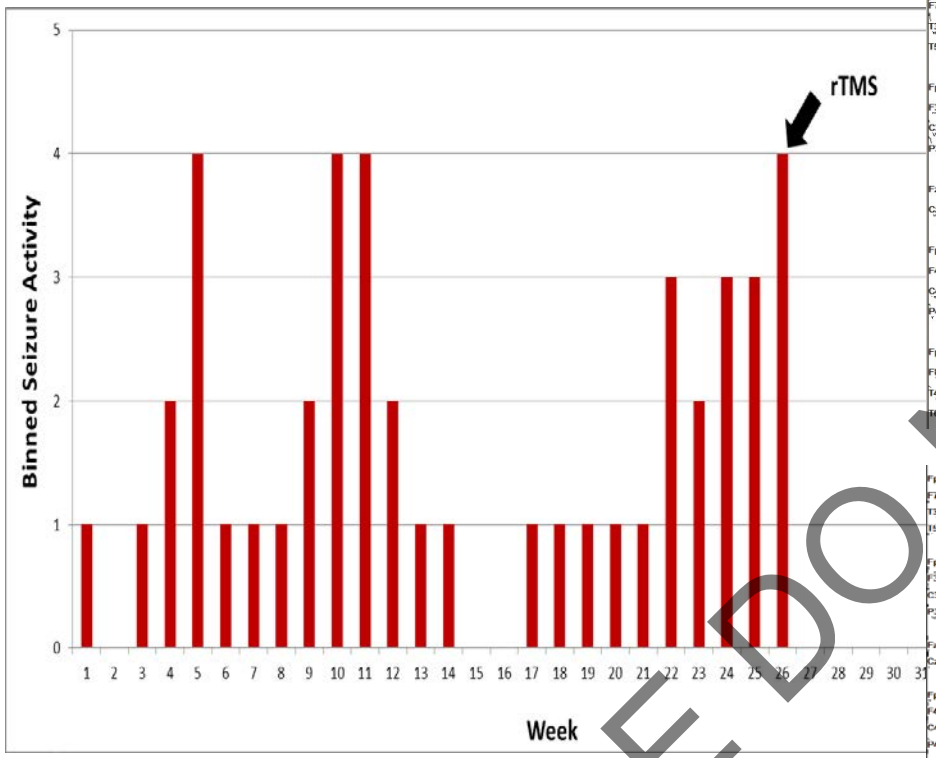
**Table 3. Effect of rTMS on IED of 60 min (mean ± SD)**

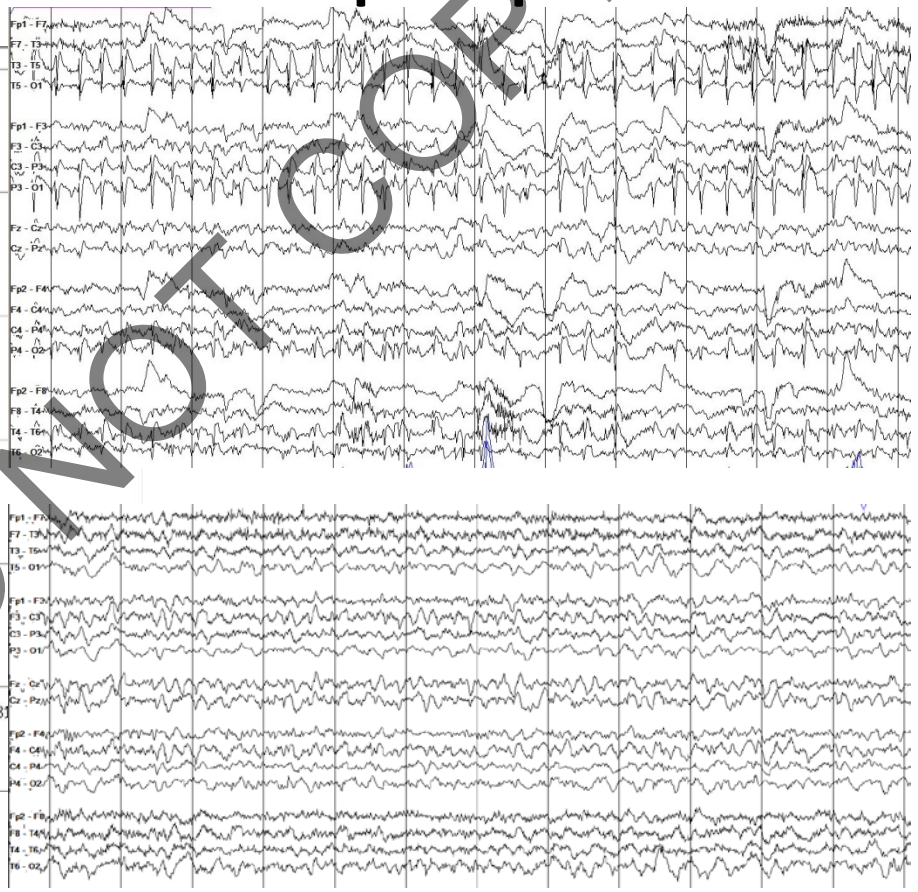
| | Before rTMS | After rTMS | End of follow-up |
|---|---|---|---|
| Group 1 (n = 31) | 75.1 ± 88.5 | 23.1 ± 48.0[a] | 33.6 ± 55.6[a] |
| Group 2 (n = 29) | 76.6 ± 72.9 | 71.5 ± 78.7[b] | 72.3 ± 75.1[b] |

[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
- But beneficial effects only seen when rTMS is targeted specifically to the seizure focus on the neocortical surface
- Multi-center trials needed to confirm findings!

# Beneficial effects in status epilepticus?



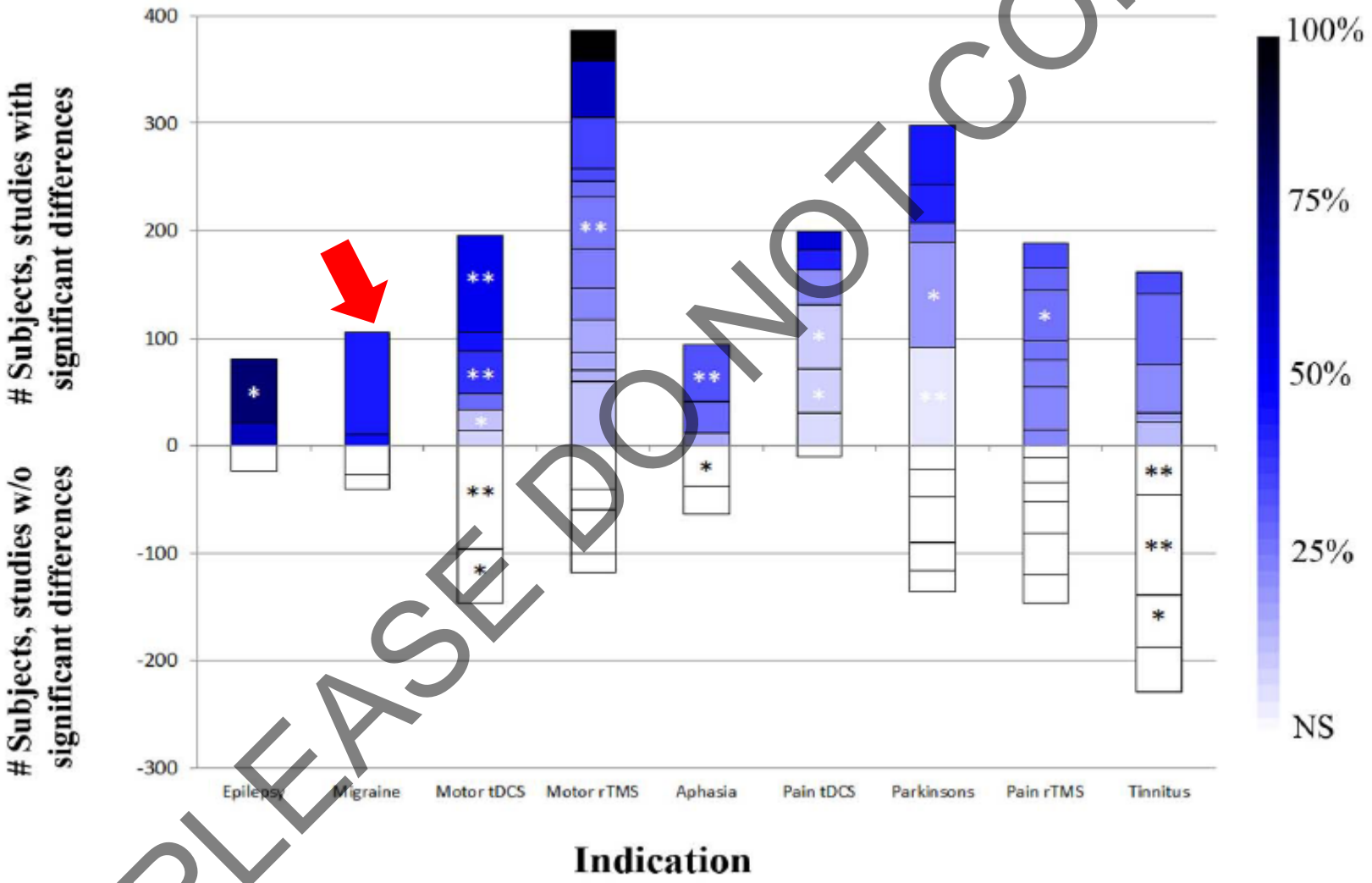


- Rotenberg (2009 *Epi & Behav*) reported sustained remission in 2/7 patients with epilepsia partialis continua
- Case reports of effectiveness of rTMS in refractory focal status epilepticus (Thordstein 2012 *Epi & Behav*; Liu 2013 *Seizure*; VanHaerents 2015, *Clinical Neurophysiology*)

# Migraine (chronic treatment)

- A total of 4 studies evaluating efficacy of rTMS for prophylactic treatment of migraine
- 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.

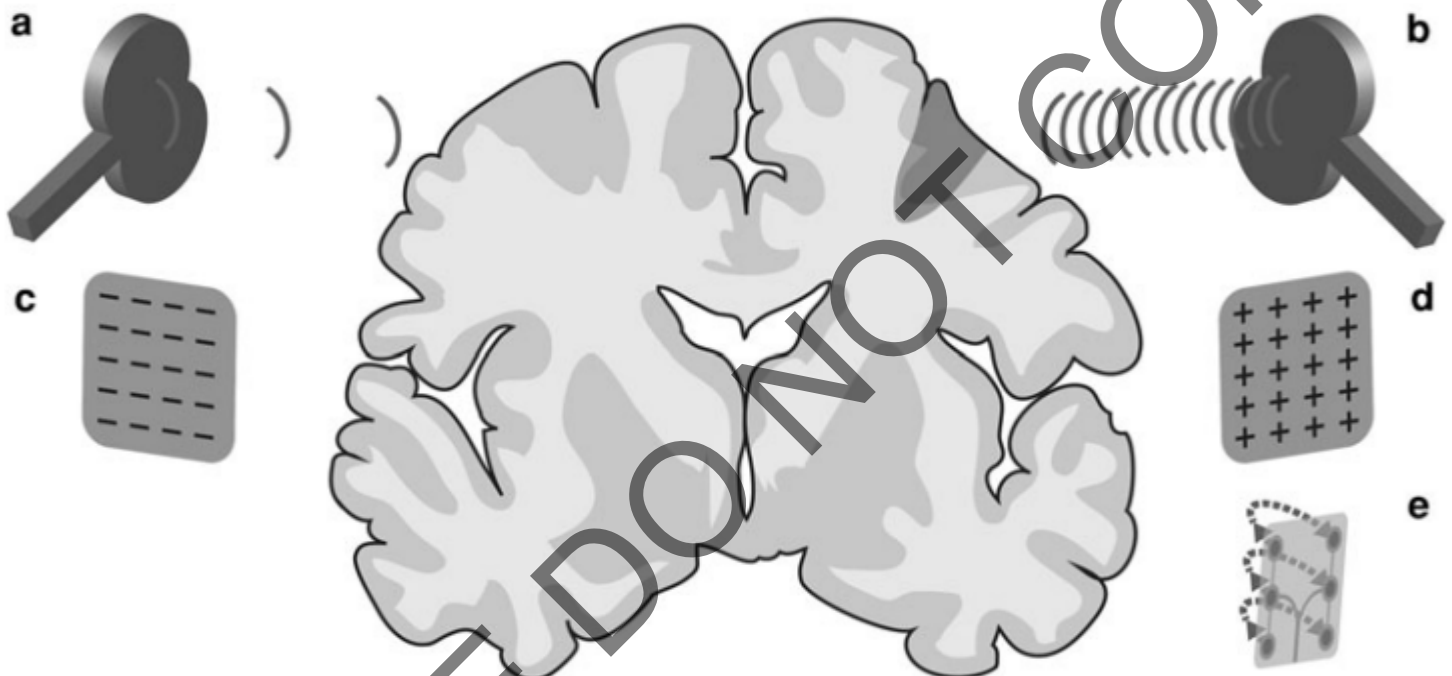
# Migraine results






Shafi et al, *in preparation*

# 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)** | | | | | | | |



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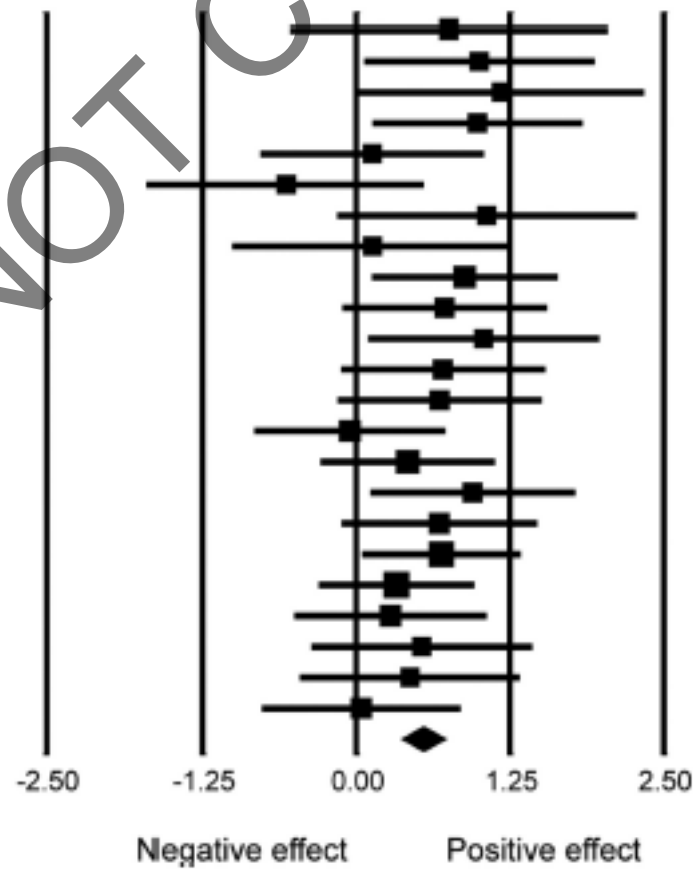
# Most studies show a beneficial effect

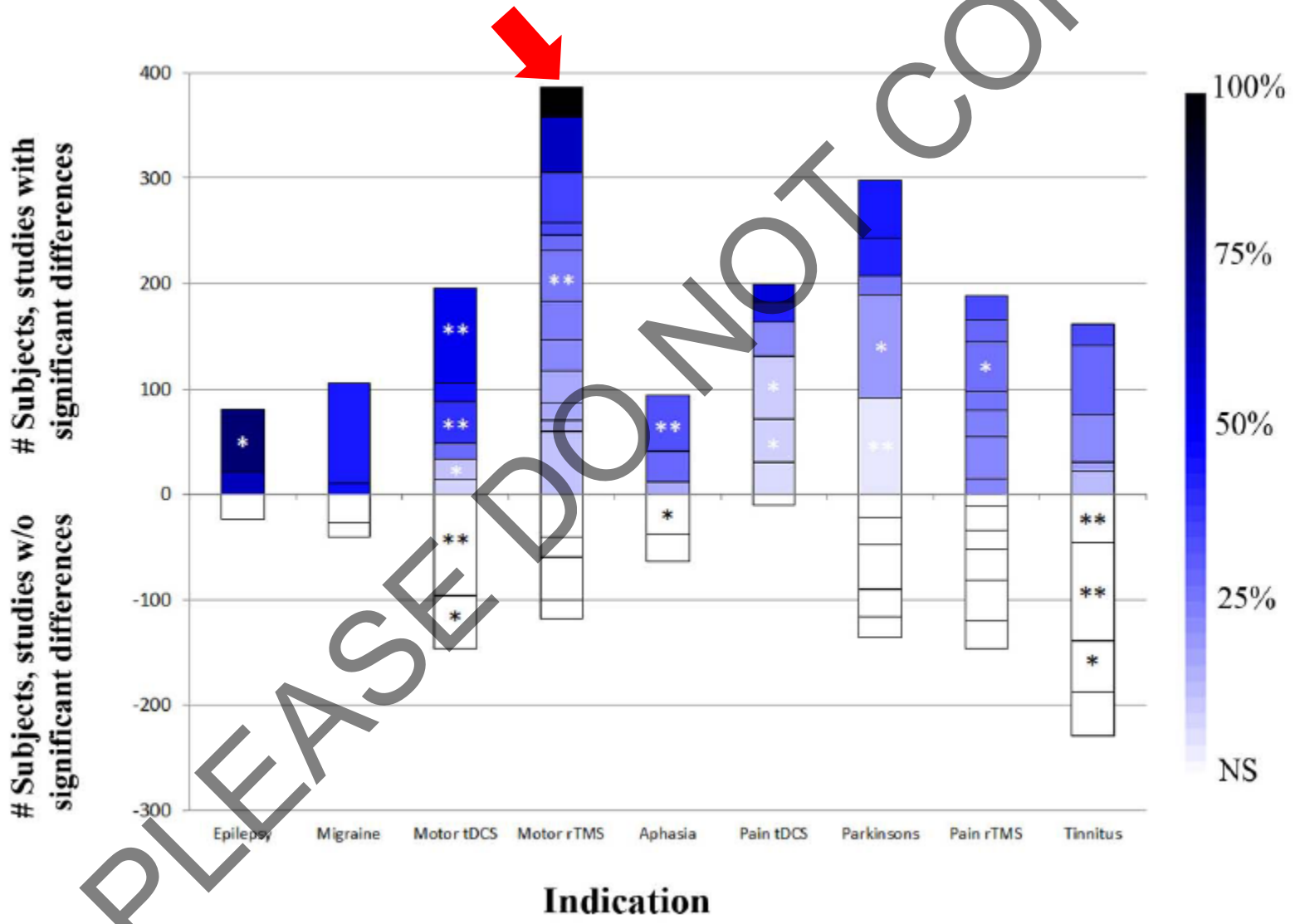
| Study name | Effect size | Lower limit | Upper limit | p-Value | Relative weight |
|---|---|---|---|---|---|
| Mansur et al, 2005 | 0.75 | -0.53 | 2.03 | 0.25 | 1.88 |
| Takeuchi et al, 2005 | 1.00 | 0.07 | 1.93 | 0.04 | 3.58 |
| Fregni et al, 2006 | 1.18 | 0.02 | 2.33 | 0.05 | 2.33 |
| Leipert et 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?






Shafi et al, *in preparation*

# 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*

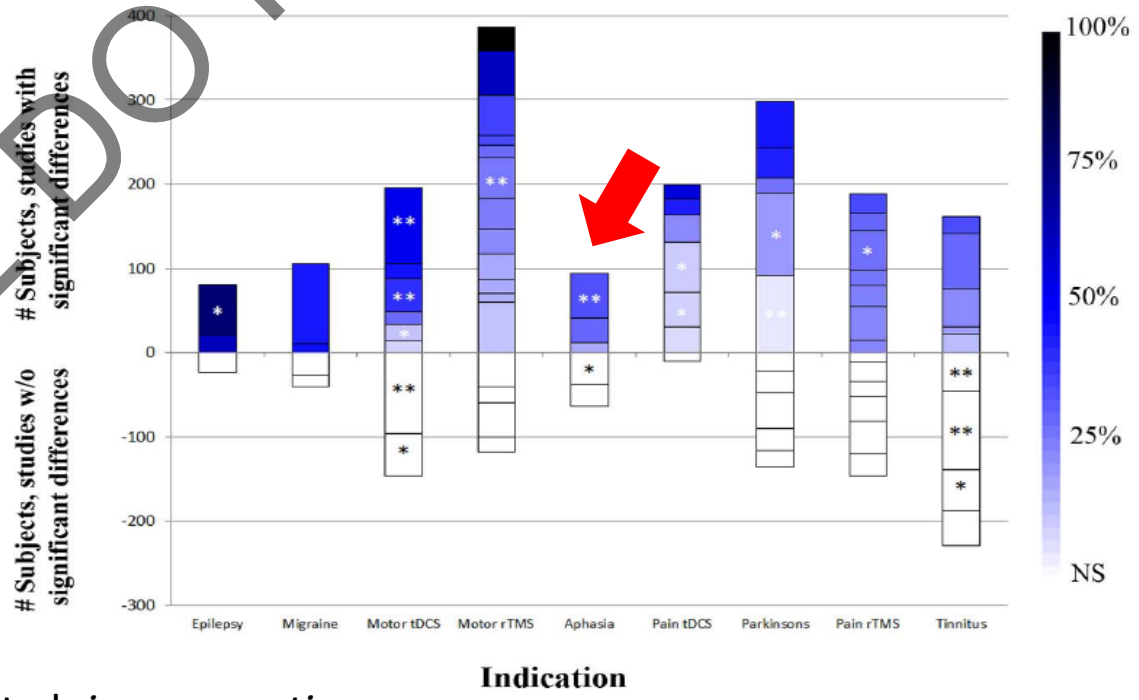
# Open questions

- Does benefit actually exist?
  - Multi-center study of “inhibitory” contralesional navigated rTMS currently underway (NICHE trial)
- Optimal type of stimulation
  - High-frequency ipsilesional vs low-frequency contralesional vs both?
  - Acute, subacute or chronic?
- Combining brain stimulation with physical therapy beneficial? Timing?
- **Current multi-center RCT completed**
  - **No beneficial result of contralesional 1 Hz stimulation relative to sham**

# rTMS for aphasia

- Trials have focused on primarily the right hemispheric analog of Broca's area (pars triangularis)
  - MRI neuronavigation is critical! Stimulation of nearby pars opercularis has no benefit, and leads to worsening on some measures (Naeser 2011 *Brain & Lang*).

- Beneficial effects on naming and language only seen in trials with MRI-neuronavigation, but absent in 2/3 trials with stimulation based on scalp/EEG coordinates




Shafi et al, *in preparation*

# Visuospatial neglect

- Studies again based on framework of pathophysiologic interhemispheric balance
- Most studies to date have applied continuous theta burst stimulation to the contralesional left posterior parietal cortex

**Table 6**
rTMS (cTBS) studies in hemispatial neglect (target: left posterior parietal 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 |
|---|---|---|---|---|---|---|---|
| Nyffeler et al. (2009) | 11 (12–1080 days after stroke) | P3, Cc | Sham coil | cTBS, 100% RMT | 2–4 cTBS trains, 1 session | Improvement in a visuospatial task for 8 h after two TBS trains and for 32 h after 4 TBS trains | III |
| Cazzoli et al. (2012) | 24 (mean 27 days after stroke) | P3, Cc | Sham coil | cTBS, 100% RMT | 4 cTBS trains, 2 sessions | Improvement (37%) on various tasks and scales for at least 3 weeks after the stimulation | III |
| Koch et al. (2012) | 20 (24–102 days after stroke) (active: 10, control: 10) | P3, F8c | Sham coil | cTBS, 80% AMT | 2 cTBS trains, 10 sessions | Improvement (23%) in the Behavioral Attention Test at 1 month after the stimulation | III |
| **Recommendation: possible effect of cTBS of the contralesional left posterior parietal cortex in hemispatial neglect (Level C)** | | | | | | | |

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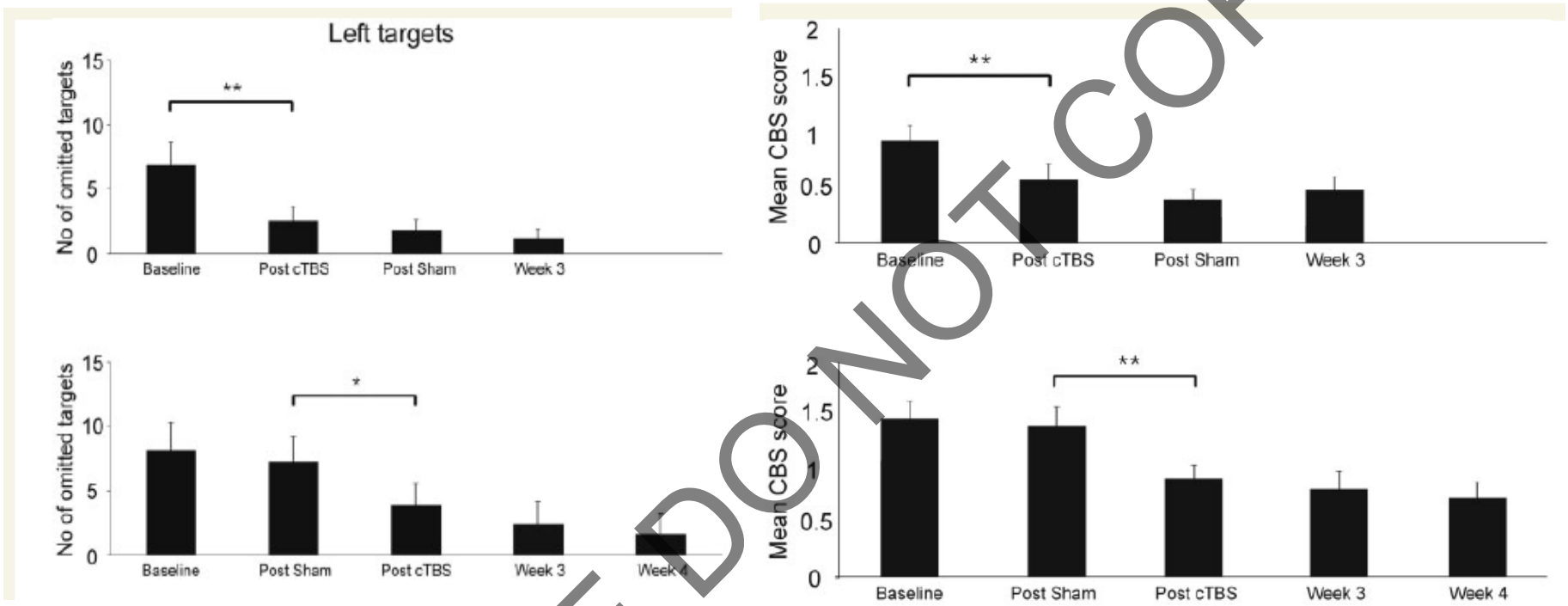
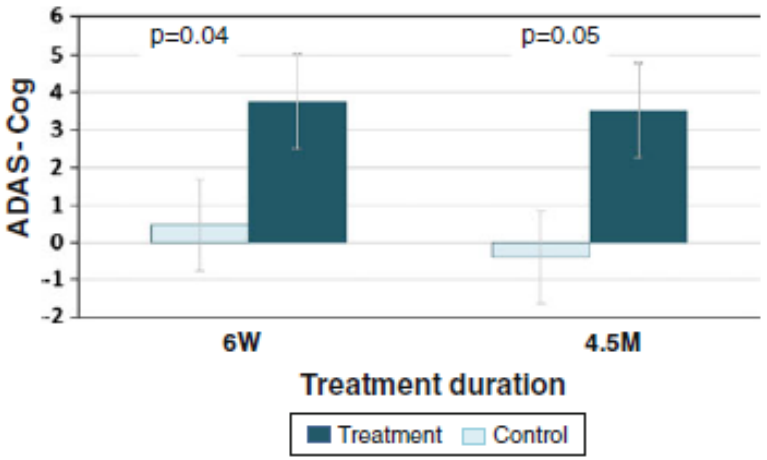
# Improvement in neglect and ADLs




- cTBS to left PPC improved detection of left-sided targets and activities of daily living in one class III trial (Cazzoli 2012 *Brain*)
- Benefits sustained at least two weeks in another class III trial (Koch 2012 *Neurology*)

# Alzheimer's

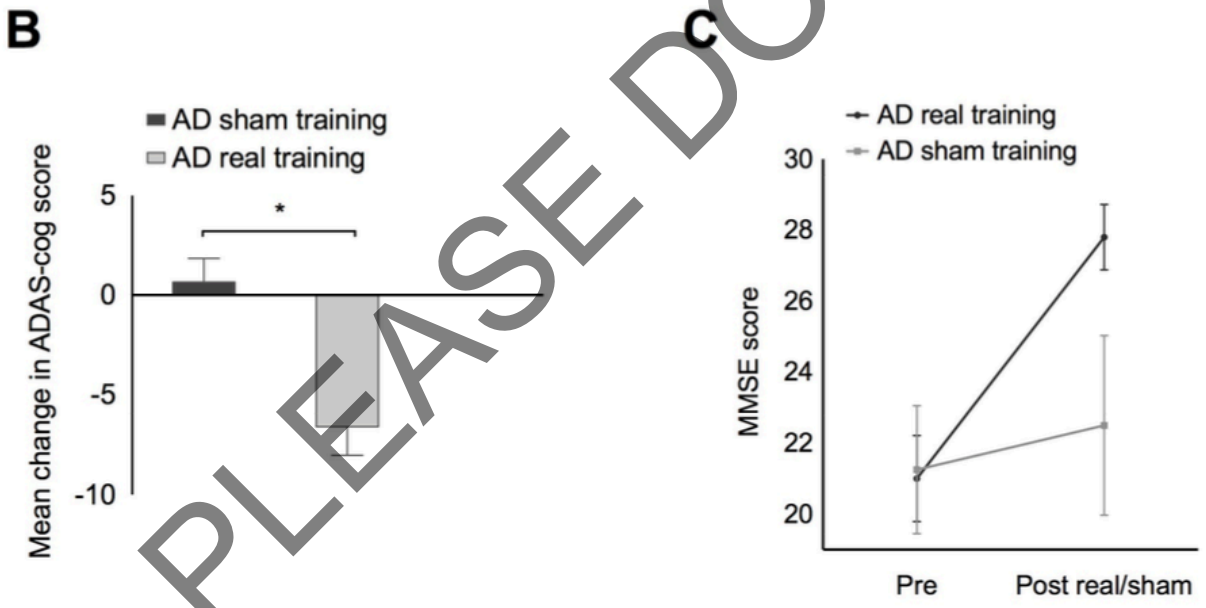
- Early crossover studies: improvement in naming after HF-rTMS of either L or R DLPFC (Cotelli 2006 *Arch Neurol*, Cotelli 2008 *Eur J Neurol*)
- Recent class III randomized trial: bilateral HF but not LF rTMS improved cognition (~20% on MMSE), ADLs and depression scores in pts with mild-moderate (but not severe) dementia (Ahmed 2012 *J Neurol*)
- Rabey 2012 *J Neural Transm:* Small pilot study of multi-site HF stimulation in combination with cognitive training. A follow-up multi-site RCT launched.



# TMS for AD

- One open-label trial and two small double-blind trials of TMS + cognitive exercises, all showing a benefit on the ADAS-cog.
- Protocol involves 2s of high frequency TMS to any of 6 brain regions (L+R DLPFC, L+R Parietal, Broca's and Wernicke's area) followed by 30s of cognitive exercise with task engaging that target

# BIDMC Neuronix Trial (n=12)

# 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** | | | | | | | |



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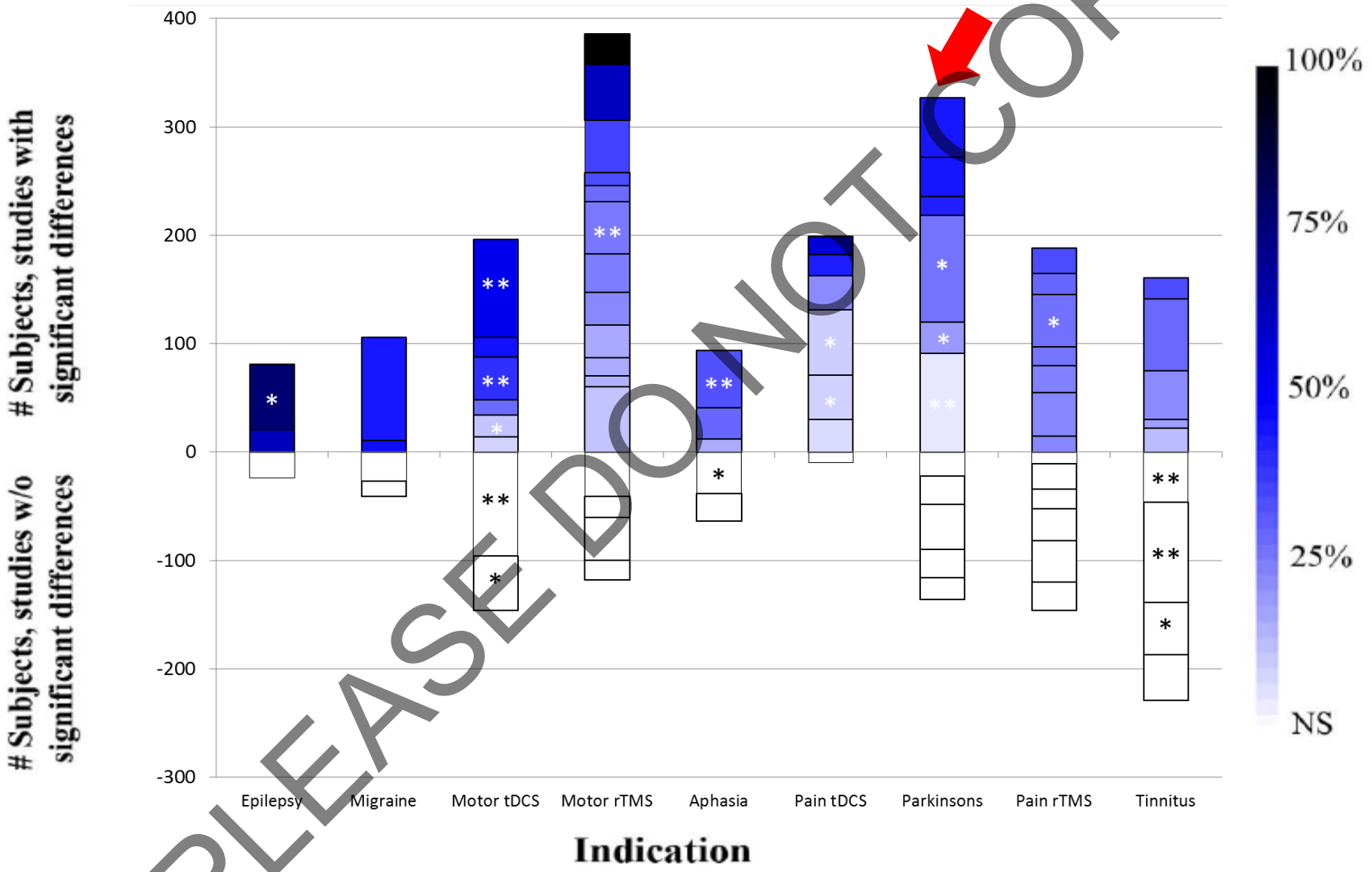
# Parallel-group studies



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# Overall summary of results

- Motor UPDRS scores can be improved by ~30% with HF rTMS to bilateral M1, although Class III studies only. More recent Class I study run here showed about 15% improvement in UPDRS
- 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
- Depression may be improved with DLPFC stimulation, 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)** | | | | | | | |



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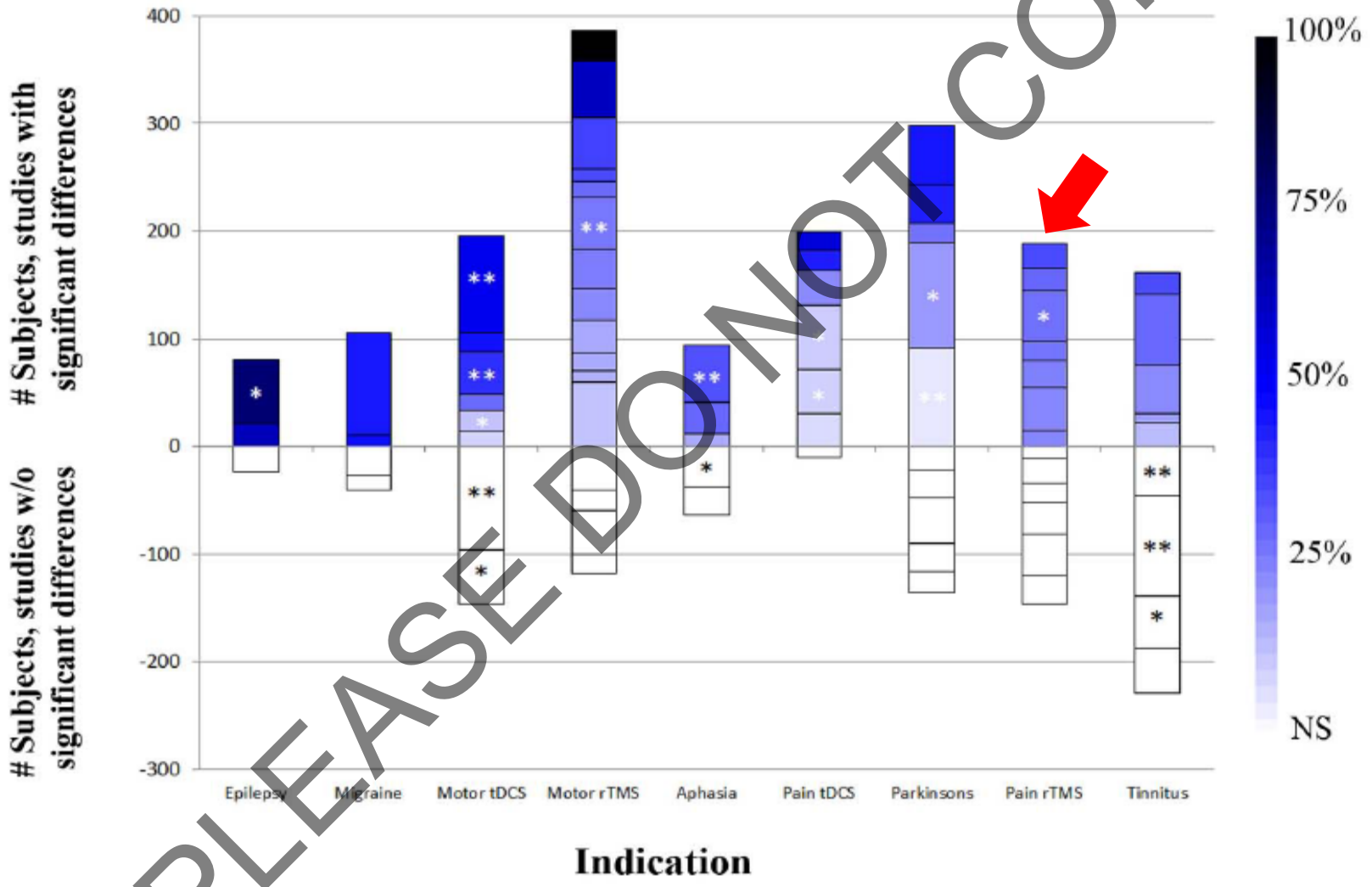
# Parallel-group RCTs have variable results






And effect sizes are generally small …

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# 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, have reported less impressive results

# 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)**



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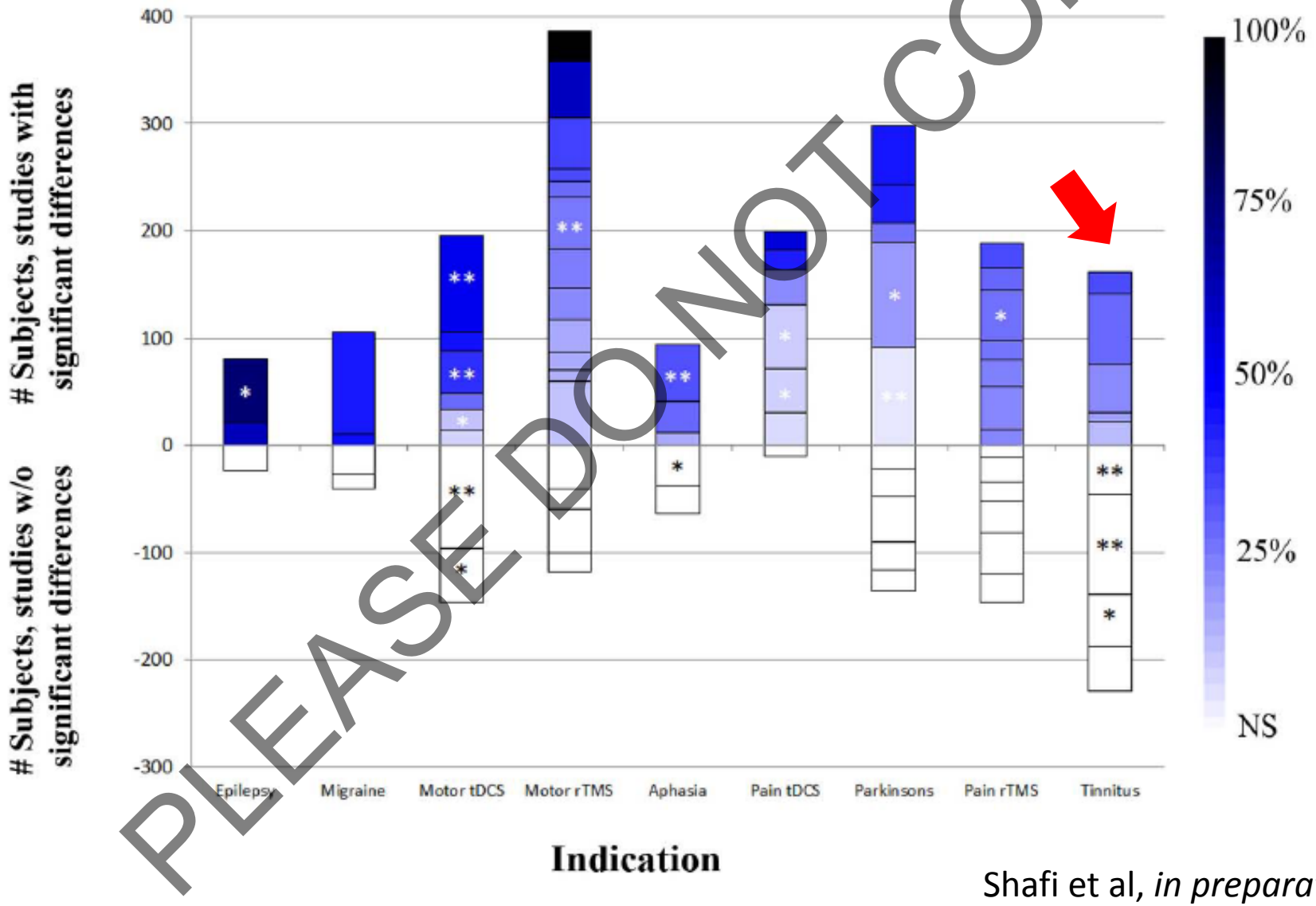
# Results in parallel-group not impressive



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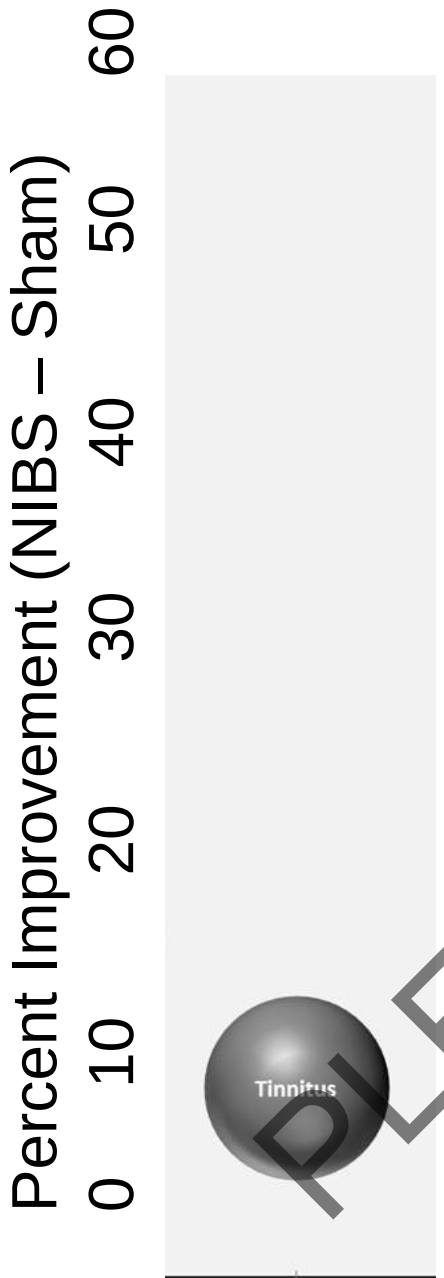
# The Lesson from Tinnitus…




- 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?

# Overall effects in parallel-group RCTs

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# Conclusions

- Currently, TMS is FDA approved for motor / language mapping, and for abortive treatment of migraine
- Early studies suggest that TMS metrics may have an important role as diagnostic and prognostic biomarkers in a number of disease states
- rTMS shows promise as a therapeutic modality in a number of disease states, although well-designed multi-center parallel-group randomized trials are necessary