NEUROLOGICAL APPLICATIONS OF TMS

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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

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
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?

  
  • 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
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>
<thead>
<tr>
<th>Table 5 Survival</th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>All tumors</td>
</tr>
<tr>
<td>3 months survival rate (%)</td>
</tr>
<tr>
<td>6 months survival rate (%)</td>
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<tr>
<td>9 months survival rate (%)</td>
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<tr>
<td>12 months survival rate (%)</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>TABLE 7. Sensitivity, Specificity, and Positive/Negative Predictive Values Over All Brain Regions in All Patients*</th>
<th>All Regions</th>
<th>Classic Broca’s Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Charité Berlin (B1-B6)</td>
<td>TUM Munich (M1-M14)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.89</td>
<td>0.90</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.47</td>
<td>0.34</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>0.9</td>
<td>0.81</td>
</tr>
</tbody>
</table>

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

**FIGURE 6.** Number of false negatives for each region.
A subsequent study (Tarapore 2013, NeuroImage) also demonstrated high negative predictive value, with improved specificity.
Ille 2015a, b: Compared language mapping results from rTMS (C) and fMRI (D) with those from DCS (B)

<table>
<thead>
<tr>
<th>TABLE 3. Overall results without dependency on lesion location*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
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<tr>
<td></td>
</tr>
<tr>
<td>PPV</td>
</tr>
<tr>
<td>NPV</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
</tbody>
</table>
AND MAY HAVE BENEFICIAL EFFECTS

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
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, Savannah K. Gibbs, Stephen P. Fulton, Amy Lee McGregor, Basanagoud Mudigoudar, Sarah E. Weatherspoon, Frederick A. Boop, and James W. Wheless

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
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
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.
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• Therapeutics
  • Review of results across neurologic indications
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*
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
MEPS PREDICT FUNCTIONAL RECOVERY AFTER ACUTE STROKE

Table 1 Recovery definitions and examples of feasible

<table>
<thead>
<tr>
<th>Recovery</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>The patient has the potential to return to normal or near-normal hand and arm function within 12 weeks.</td>
</tr>
<tr>
<td>Notable</td>
<td>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.</td>
</tr>
<tr>
<td>Limited</td>
<td>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.</td>
</tr>
<tr>
<td>None</td>
<td>The patient can expect to have minimal movement in their affected hand and arm, with little improvement at 12 weeks.</td>
</tr>
</tbody>
</table>

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
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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.

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

<table>
<thead>
<tr>
<th>Target, coil type</th>
<th>Control condition</th>
<th>Number of pulses/sessions</th>
<th>Results</th>
<th>Class of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epileptic foci, FBC</td>
<td>Tilted coil</td>
<td>1 Hz, 120% RMT</td>
<td>900 pulses, 14 sessions</td>
<td>No significant reduction of seizure frequency</td>
</tr>
<tr>
<td>Epileptic foci (n=17)</td>
<td>Sham coil</td>
<td>1 Hz, 70% M50</td>
<td>1200 pulses, 5 sessions</td>
<td>Up to 72% reduction of seizure frequency, 2 weeks after rTMS; reduction of interictal EEG abnormalities</td>
</tr>
<tr>
<td>Epileptic foci, FBC</td>
<td>Active coil at very low stimulus intensity (20% RMT)</td>
<td>0.5 Hz, 50% RMT</td>
<td>1500 pulses, 14 sessions</td>
<td>Significantly greater seizure reduction rate in active vs. control group (85% vs. 25% reduction of interictal EEG abnormalities)</td>
</tr>
</tbody>
</table>

**Recommendation:** possible antiepileptic effect of focal LF rTMS of the epileptic focus (Level C)

<table>
<thead>
<tr>
<th>Target, coil type</th>
<th>Control condition</th>
<th>Number of pulses/sessions</th>
<th>Results</th>
<th>Class of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertex, Cc</td>
<td>Sham coil</td>
<td>0.33–1 Hz, 100% RMT</td>
<td>1000 pulses, 5 sessions</td>
<td>30–40% reduction of seizure frequency, 2 weeks after rTMS (only for 0.33 Hz)</td>
</tr>
<tr>
<td>Vertex, Cc</td>
<td>Active coil placed over a non-connected coil</td>
<td>0.1 Hz, 100%, 50% RMT (n = 34), 6% M50 (n = 9)</td>
<td>1000 pulses, 5 sessions</td>
<td>No significant reduction of seizure frequency; reduction of EEG abnormalities; no change in cortical excitability</td>
</tr>
</tbody>
</table>

Lefaucheur 2014 Clin Neurophys
PARALLEL-GROUP STUDIES
REMARKABLE EFFECTS SOMETIMES SEEN

• 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 …

Sun 2012 Epilepsia
• 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
• 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 9: rTMS studies in motor stroke (target: primary motor cortex).

<table>
<thead>
<tr>
<th>Articles</th>
<th>Number of patients</th>
<th>Target, coil type</th>
<th>Control condition</th>
<th>Stimulation frequency and intensity</th>
<th>Number of pulses/duration and number of sessions</th>
<th>Results</th>
<th>Class of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefaucheur et al. (2014)</td>
<td>12</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 80% RMT</td>
<td>300 pulses, 1 session</td>
<td>Increase of motor intensity (not of the face)</td>
<td>II</td>
</tr>
<tr>
<td>Beers et al. (2007)</td>
<td>24 (active: 12; control: 12)</td>
<td>M1 contralateral, F1c</td>
<td>Sham coil</td>
<td>1 Hz, 120% RMT</td>
<td>200 pulses, 8 sessions (combined with motor practice)</td>
<td>No clinical changes but increased cortical excitability</td>
<td>II</td>
</tr>
<tr>
<td>Shibata et al. (2009a)</td>
<td>24 (active: 12; control: 12)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 100% RMT</td>
<td>100 pulses, 4 sessions</td>
<td>More improvement of motor power than after ipsilateral LF rTMS at 3 months</td>
<td>II</td>
</tr>
<tr>
<td>Contreras et al. (2012)</td>
<td>20 (active: 10; control: 10)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 80% RMT</td>
<td>1500 pulses, 10 sessions, followed by PT</td>
<td>Improvement in manual dexterity (FTT) and grip strength</td>
<td>II</td>
</tr>
<tr>
<td>Sasaki et al. (2011)</td>
<td>20 (active: 10; control: 10)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 80% RMT</td>
<td>1000 pulses, 5 sessions</td>
<td>Improvement in grip strength and finger tapping frequency (but less beneficial than ipsilateral LF rTMS performed in 5 patients)</td>
<td>II</td>
</tr>
<tr>
<td>Sambhi et al. (2012)</td>
<td>20 (active: 10; control: 10)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 80% RMT</td>
<td>1000 pulses, 1 session, followed by motor training</td>
<td>No differences between active and sham rTMS in improving hand motor function or the level of neurological deficit</td>
<td>II</td>
</tr>
</tbody>
</table>

Recommendations: possible effect of LF rTMS of the contralateral motor cortex in post-stroke motor stroke (Level II)

<table>
<thead>
<tr>
<th>Articles</th>
<th>Number of patients</th>
<th>Target, coil type</th>
<th>Control condition</th>
<th>Stimulation frequency and intensity</th>
<th>Number of pulses/duration and number of sessions</th>
<th>Results</th>
<th>Class of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moro et al. (2005)</td>
<td>10</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 100% RMT</td>
<td>500 pulses, 1 session</td>
<td>Improvement of manual motor abilities, including shorter reaction and execution times</td>
<td>II</td>
</tr>
<tr>
<td>Takahashi et al. (2005)</td>
<td>20 (active: 10; control: 10)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 100% RMT</td>
<td>1500 pulses, 1 session</td>
<td>Improvement of manual motor abilities (movement acceleration, but not force) lasting less than 30min</td>
<td>II</td>
</tr>
<tr>
<td>Pernughi et al. (2006a)</td>
<td>15 (active: 10; control: 5)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 100% RMT</td>
<td>1200 pulses, 5 sessions</td>
<td>Improvement of manual motor abilities, lasting for 2 weeks</td>
<td>II</td>
</tr>
<tr>
<td>Shibata et al. (2008)</td>
<td>20 (active: 10; control: 10)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 80% RMT</td>
<td>1500 pulses, 1 session</td>
<td>Improvement of manual motor abilities, PT efficacy, and cortical excitability, lasting for 4 months</td>
<td>II</td>
</tr>
<tr>
<td>Emura et al. (2009, 2010)</td>
<td>20 (active: 10; control: 10)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 100% RMT</td>
<td>1200 pulses, 10 sessions</td>
<td>Improvement of manual motor abilities and functional status, lasting II at least 12 weeks (silent ipsilateral LF rTMS): less improvement for control vs. unilaterally stroke</td>
<td>II</td>
</tr>
<tr>
<td>Thelen et al. (2011)</td>
<td>24 (active: 12; control: 12)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 100% RMT</td>
<td>1000 pulses, 1 session, followed by 20min of functional electrical stimulation</td>
<td>Similar improvement of motor performance with active and sham rTMS (followed by functional electrical stimulation)</td>
<td>II</td>
</tr>
<tr>
<td>Asamatsu et al. (2011)</td>
<td>30 (active: 10; control: 10)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 100% RMT</td>
<td>1500 pulses, 15 sessions, preceded or followed by PT</td>
<td>Improvement in manual dexterity (FTT, grip force, relaxation): relevance of interhemispheric excitability, clinical and neurophysiological improvements more robust and stable when (TMS) was followed by PT Improvement in motor performance (FARMT): no change in spasticity</td>
<td>II</td>
</tr>
<tr>
<td>Bals et al. (2015)</td>
<td>18</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 80% RMT</td>
<td>240 pulses, 10 sessions, followed by repetitive motor exercise</td>
<td>Improvement on various functional scales</td>
<td>II</td>
</tr>
</tbody>
</table>

Recommendations: possible effect of LF rTMS of the contralateral motor cortex in chronic stroke (Level II)

<table>
<thead>
<tr>
<th>Articles</th>
<th>Number of patients</th>
<th>Target, coil type</th>
<th>Control condition</th>
<th>Stimulation frequency and intensity</th>
<th>Number of pulses/duration and number of sessions</th>
<th>Results</th>
<th>Class of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shibata et al. (2009a)</td>
<td>52 (active: 26; control: 26)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 120% RMT</td>
<td>300 pulses, 1 session</td>
<td>Improvement on various functional scales</td>
<td>II</td>
</tr>
<tr>
<td>Shibata et al. (2009a)</td>
<td>24 (active: 12; control: 12)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 100% RMT</td>
<td>500 pulses, 5 sessions</td>
<td>Less improvement of manual motor abilities than after contralateral LF rTMS at 3 months</td>
<td>II</td>
</tr>
<tr>
<td>Chung et al. (2010)</td>
<td>10 (active: 5; control: 5)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 100% RMT</td>
<td>1000 pulses, 10 sessions</td>
<td>Improvement of manual motor abilities for subchronic strokes, till 3 months after TMS Improvement on various functional and motor scales (ident for 3 and 11-16): improvement remained significant at 1 year</td>
<td>II</td>
</tr>
<tr>
<td>Shibata et al. (2010b)</td>
<td>48 (active: 24; control: 24)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 120% RMT</td>
<td>750 pulses, 5 sessions</td>
<td>Improvement of cortical excitability, movement accuracy and execution time of a motor task during and immediately after stimulation</td>
<td>II</td>
</tr>
</tbody>
</table>

Recommendations: possible effect of LF rTMS of the ipsilateral motor cortex in post-stroke motor stroke (Level II)

<table>
<thead>
<tr>
<th>Articles</th>
<th>Number of patients</th>
<th>Target, coil type</th>
<th>Control condition</th>
<th>Stimulation frequency and intensity</th>
<th>Number of pulses/duration and number of sessions</th>
<th>Results</th>
<th>Class of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (2006)</td>
<td>15</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 80% RMT</td>
<td>160 pulses, 1 session (combined with motor practice)</td>
<td>Improvement of cortical excitability, movement accuracy and execution time of a motor task during and immediately after stimulation</td>
<td>II</td>
</tr>
<tr>
<td>Emura et al. (2009, 2010)</td>
<td>40 (active: 20; control: 20)</td>
<td>M1 contralateral, F1c, T1 coil</td>
<td>Sham coil</td>
<td>1 Hz, 80-95% RMT</td>
<td>750 pulses, 10 sessions</td>
<td>Improvement of manual motor abilities and functional status, lasting at least 12 weeks (silent contralateral LF rTMS)</td>
<td>II</td>
</tr>
</tbody>
</table>

Recommendations: possible effect of LF rTMS of the ipsilateral motor cortex in chronic stroke (Level II)
MOST STUDIES SHOW A BENEFICIAL EFFECT

Mean effect size of 0.55 in one recent meta-analysis

Hsu 2012 *Stroke*
HOW ABOUT PARALLEL-GROUP STUDIES?
### SUPPLEMENTAL TABLES

**Supplementary table 1: Summary of the subgrouped mean effect sizes**

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

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”)

PLEASE DO NOT COPY
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

<table>
<thead>
<tr>
<th>TMS studies in motor symptoms of Parkinson’s disease (lateral pre/motor cortex)</th>
<th>Articles</th>
<th>Number of patients</th>
<th>Target and site type</th>
<th>Control condition</th>
<th>Stimulation Frequency and intensity</th>
<th>Number of pulse/session and number of sessions</th>
<th>Results</th>
<th>Class of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF rTMS of M1 (unilateral stimulation of hand representation)</td>
<td>Summerer et al. (2002a)</td>
<td>11</td>
<td>M1, F3c</td>
<td>Tilted coil</td>
<td>1 Hz, 1200 RMS, 500 pulses, 1 session</td>
<td>Reduction of movement time</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Lefaucheur et al. (2004c)</td>
<td>12</td>
<td>M1, F3c, M1</td>
<td>Sham coil</td>
<td>0.5 Hz, BEM, 600 pulses, 1 session</td>
<td>Improvement of UPDRS-III motor score (20%), with bilateral reduction of rigidity and restoration of intracortical inhibition</td>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rothkegel et al. (2009)</td>
<td>12</td>
<td>M1, F3c, M1</td>
<td>Tilted coil</td>
<td>0.5 Hz, BEM, 600 pulses, 1 session</td>
<td>No clinical effect</td>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filippova et al. (2010b)</td>
<td>10</td>
<td>M1, F3c</td>
<td>Tilted coil</td>
<td>0.5 Hz, BEM, 1000 pulses, 1 session</td>
<td>No change in UPDRS-III motor score in either ON or OFF phase</td>
<td>III</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No recommendation for the anti-parkinsonian effect of LF rTMS of hand representation in M1

<table>
<thead>
<tr>
<th>HF rTMS of M1 (unilateral stimulation of hand and/or leg representation)</th>
<th>Articles</th>
<th>Number of patients</th>
<th>Target and site type</th>
<th>Control condition</th>
<th>Stimulation Frequency and intensity</th>
<th>Number of pulse/session and number of sessions</th>
<th>Results</th>
<th>Class of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefaucheur et al. (2004c)</td>
<td>12</td>
<td>M1, F3c, M1</td>
<td>Tilted coil</td>
<td>0.5 Hz, BEM, 600 pulses, 1 session</td>
<td>Reduction of movement time</td>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovet et al. (2004b)</td>
<td>20 (active: 18; control: 19)</td>
<td>M1, F3c</td>
<td>Tilted coil</td>
<td>0.5 Hz, BEM, 600 pulses, 1 session</td>
<td>Improvement of UPDRS-III motor score (20%), mainly on akinesia</td>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khaliq et al. (2009)</td>
<td>21 (active: 16; control: 16)</td>
<td>M1, F3c</td>
<td>Sham coil</td>
<td>10 Hz, BEM, 600 pulses, 1 session</td>
<td>No significant change; only transient motor improvement similar for active and control conditions</td>
<td>I</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No recommendation for the anti-parkinsonian effect of HF rTMS of hand and/or leg representation in M1
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 TA region (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

• Potential 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
### Table 1

<table>
<thead>
<tr>
<th>Articles</th>
<th>Number of patients</th>
<th>Target coil type</th>
<th>Control condition</th>
<th>Stimulation frequency and intensity</th>
<th>Number of pulses/session and number of sessions</th>
<th>Results</th>
<th>Class of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefaucheur et al. (2013a)</td>
<td>18</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>0.5 Hz, 80% RMT</td>
<td>3000 pulses, 1 session</td>
<td>Non-significant pain relief (45 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Lefaucheur et al. (2006)</td>
<td>12</td>
<td>MI, Rcc</td>
<td>Tiled coil</td>
<td>1 Hz, 95% RMT</td>
<td>3000 pulses, 1 session</td>
<td>Non-significant pain relief (55 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Lefaucheur et al. (2007)</td>
<td>20</td>
<td>MI, Rcc</td>
<td>Sham coil (2 Hz)</td>
<td>1 Hz, 95% RMT</td>
<td>3000 pulses, 5 sessions</td>
<td>Non-significant pain relief (64 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Lefaucheur et al. (2006a)</td>
<td>22</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>1 Hz, 95% RMT</td>
<td>1200 pulses, 1 session</td>
<td>Non-significant pain relief (145 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Lefaucheur et al. (2006b)</td>
<td>19</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>1 Hz, 95% RMT</td>
<td>1200 pulses, 5 sessions</td>
<td>Non-significant pain relief (95 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Lefaucheur et al. (2007a)</td>
<td>20</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>1 Hz, 95% RMT</td>
<td>1200 pulses, 1 session</td>
<td>Non-significant pain relief (217 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Lefaucheur et al. (2007b)</td>
<td>20</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>1 Hz, 95% RMT</td>
<td>1200 pulses, 5 sessions</td>
<td>Non-significant pain relief (217 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Khedr et al. (2006a)</td>
<td>46 (active: 39; control: 19)</td>
<td>MI, Rcc</td>
<td>Tiled coil</td>
<td>20 Hz, 90% RMT</td>
<td>2000 pulses, 5 sessions</td>
<td>Significant pain relief (796 responders)</td>
<td>I</td>
</tr>
<tr>
<td>Andri-Obaida et al. (2006)</td>
<td>12</td>
<td>MI, Rcc</td>
<td>Tiled coil</td>
<td>20 Hz, 90% RMT</td>
<td>5000 pulses, 1 session</td>
<td>Non-significant pain relief (265 responders and 113 improvement)</td>
<td>III</td>
</tr>
<tr>
<td>Higuchi et al. (2005)</td>
<td>20</td>
<td>MI, Rcc</td>
<td>Tiled coil</td>
<td>20 Hz, 90% RMT</td>
<td>5000 pulses, 1 session</td>
<td>Non-significant pain relief (565 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Irlacher et al. (2000)</td>
<td>27 (active: 19; control: 8)</td>
<td>MI, Rcc</td>
<td>Tiled coil</td>
<td>20 Hz, 90% RMT</td>
<td>5000 pulses, 5 sessions</td>
<td>Non-significant pain relief (75 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Lefaucheur et al. (2006a)</td>
<td>22</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>20 Hz, 90% RMT</td>
<td>1200 pulses, 1 session</td>
<td>Significant pain relief (555 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Satoh et al. (2007)</td>
<td>13</td>
<td>MI, Rcc</td>
<td>Tiled coil</td>
<td>20 Hz, 90% RMT</td>
<td>5000 pulses, 1 session</td>
<td>Non-significant pain relief (305 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Andri-Obaida et al. (2008)</td>
<td>14</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>20 Hz, 90% RMT</td>
<td>1200 pulses, 5 sessions</td>
<td>Non-significant pain relief (95 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Lefaucheur et al. (2009)</td>
<td>46</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>20 Hz, 90% RMT</td>
<td>1200 pulses, 5 sessions</td>
<td>Non-significant pain relief (95 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Kang et al. (2009)</td>
<td>11 (ipsilateral cord injury)</td>
<td>MI, Rcc</td>
<td>Tiled coil</td>
<td>20 Hz, 90% RMT</td>
<td>2000 pulses, 5 sessions</td>
<td>Significant pain relief (up to 2 months after rTMS)</td>
<td>III</td>
</tr>
<tr>
<td>Alomar et al. (2011)</td>
<td>27 (active: 19; control: 8)</td>
<td>MI, Rcc</td>
<td>Tiled coil</td>
<td>20 Hz, 90% RMT</td>
<td>2000 pulses, 5 sessions</td>
<td>Significant pain relief (15 responders)</td>
<td>III</td>
</tr>
<tr>
<td>Andri-Obaida et al. (2011)</td>
<td>45</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>20 Hz, 90% RMT</td>
<td>3000 pulses, 1 session</td>
<td>Significant pain relief (60 responses and 22 improvement for “active-sham” condition)</td>
<td>III</td>
</tr>
<tr>
<td>Lefaucheur et al. (2011b)</td>
<td>39</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>20 Hz, 90% RMT</td>
<td>3000 pulses, 1 session</td>
<td>Significant pain relief (60 responders and 44 improvement for “active-sham” condition)</td>
<td>III</td>
</tr>
<tr>
<td>Hessami et al. (2013)</td>
<td>64</td>
<td>MI, Rcc</td>
<td>Active coil placed over trigger point combined with electrical scalp stimulation</td>
<td>5 Hz, 90% RMT</td>
<td>500 pulses, 10 sessions</td>
<td>Significant short-term pain relief (265 responders and 4% improvement for “active-sham” condition)</td>
<td>I</td>
</tr>
<tr>
<td>Jerit et al. (2013)</td>
<td>16 (ipsilateral cord injury)</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>20 Hz, 90% RMT (hand area)</td>
<td>2000 pulses, 1 session</td>
<td>Significant pain relief for hand or leg area stimulation for 48 h (about 15% improvement)</td>
<td>III</td>
</tr>
<tr>
<td>Andri-Obaida et al. (2014)</td>
<td>20</td>
<td>MI, Rcc</td>
<td>Sham coil</td>
<td>20 Hz, 90% RMT</td>
<td>3000 pulses, 1 session</td>
<td>Significant pain relief (15 responders), predictive of subsequent positive outcome of implanted chronic motor cortex stimulation</td>
<td>III</td>
</tr>
</tbody>
</table>

**Recommendation:** definite analgesic effect of HF rTMS of M1 contralateral to pain side in neuropathic pain (Level A)
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

<table>
<thead>
<tr>
<th>Repeated sessions</th>
<th>Numbers</th>
<th>Intervention Details</th>
<th>sham coil</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kleinjung et al. (2005)</strong></td>
<td>14</td>
<td>Auditory cortex activation area in PET, Fk8 (FGD-PET-guided navigation)</td>
<td>1 Hz, 110% RMT</td>
<td>2000 pulses, 5 sessions</td>
</tr>
<tr>
<td><strong>Rossi et al. (2007a)</strong></td>
<td>16</td>
<td>Left TPC, Fk8 (navigation and 10-20 EEG system)</td>
<td>1 Hz, 120% RMT</td>
<td>1200 pulses, 5 sessions</td>
</tr>
<tr>
<td><strong>Khedr et al. (2008, 2009a)</strong></td>
<td>66 (active: 16, 17, 17; control: 16)</td>
<td>Left TPC, Fk8 (10-20 EEG system)</td>
<td>1/10/25 Hz, 100% RMT</td>
<td>1500 pulses, 10 sessions</td>
</tr>
<tr>
<td><strong>Anders et al. (2010)</strong></td>
<td>42 (active: 22; control: 20)</td>
<td>Auditory cortex, Fk8 (10-20 EEG system)</td>
<td>1 Hz, 110% RMT</td>
<td>1500 pulses, 10 sessions</td>
</tr>
<tr>
<td><strong>Marcoula et al. (2010)</strong></td>
<td>19 (active: 10; control: 9)</td>
<td>Left superior temporal cortex, Fk8 (10-20 EEG system)</td>
<td>1 Hz, 110% RMT</td>
<td>1020 pulses, 5 sessions</td>
</tr>
<tr>
<td><strong>Menemel et al. (2011)</strong></td>
<td>21</td>
<td>Auditory cortex activation area in PET, Fk8 (FGD-PET-guided navigation)</td>
<td>1 Hz, 110% RMT</td>
<td>1800 pulses, 5 sessions</td>
</tr>
<tr>
<td><strong>Piccirillo et al. (2011)</strong></td>
<td>14</td>
<td>Left TPC, Fk8 (navigation and 10-20 EEG system)</td>
<td>1 Hz, 110% RMT</td>
<td>1500 pulses, 10 sessions</td>
</tr>
<tr>
<td><strong>Chung et al. (2012)</strong></td>
<td>22 (active: 12; control: 10)</td>
<td>Left auditory cortex, Fk8 (navigation)</td>
<td>cTBS, 80% RMT</td>
<td>900 pulses, 10 sessions</td>
</tr>
<tr>
<td><strong>Plesnja et al. (2012)</strong></td>
<td>48 (active: 16; control: 16)</td>
<td>Bilateral temporal cortex or TPC, Fk8</td>
<td>cTBS, 80% RMT</td>
<td>900 pulses, 20 sessions</td>
</tr>
<tr>
<td><strong>Hoelestra et al. (2013)</strong></td>
<td>50 (active: 25; control: 25)</td>
<td>Bilateral primary auditory cortex, Fk8 (navigation)</td>
<td>1 Hz, 110% RMT</td>
<td>4000 pulses (2000 left, 2000 right, 5 sessions)</td>
</tr>
<tr>
<td><strong>Lee et al. (2013)</strong></td>
<td>15</td>
<td>Left temporal cortex, Fk8 (10-20 EEG system)</td>
<td>1 Hz, 100% RMT</td>
<td>1200 pulses, 10 sessions</td>
</tr>
<tr>
<td><strong>Piccirillo et al. (2013)</strong></td>
<td>14</td>
<td>Left temporoauditory junction, Fk8</td>
<td>1 Hz, 110% RMT</td>
<td>1500 pulses, 20 sessions</td>
</tr>
<tr>
<td><strong>Bilici et al. (2014)</strong></td>
<td>75 (active 30, 15; control 30)</td>
<td>Left TPC, Cc</td>
<td>1/10 Hz, 110% RMT</td>
<td>600 pulses (1 Hz) or 600 pulses (10 Hz), 10 sessions</td>
</tr>
<tr>
<td><strong>Langguth et al. (2014)</strong></td>
<td>185 (active: 47, 48, 46; control: 44)</td>
<td>PET-guided temporal cortex, left temporal cortex, combined left temporal + prefrontal cortex, Fk8 (navigation and 10-20 EEG system)</td>
<td>1 Hz (temporal cortex), 20 Hz (prefrontal cortex), 110% RMT</td>
<td>2000 or 4000 pulses, 10 sessions</td>
</tr>
</tbody>
</table>

**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)
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!!!