NACT 2026
20th Nordic Experience Meeting
Building Competence in Neurostimulation Therapies: from Evidence into Action

EFFICACY OF SUB-THRESHOLD TMS IN TREATMENT-RESISTANT DEPRESSION

Gustav Bizik, MD, PhD

Aalborg University Hospital

Aalborg University

I have no relevant disclosures related to this topic.

WHAT is subthreshold TMS?

WHY does it matter?

WHAT is the focus of this lecture?

WHAT is subthreshold TMS?

No consensus in terminology:

- ”Low field TMS”
- ”Low intensity TMS”
- ”Pulsed (/Pulseting) Electromagnetic Fields”

In common: delivered in intensity below the individual’s resting motor threshold → **SUBTHRESHOLD TMS**

Supposed to modulate the excitability and brain network activity (among other effects)

WHY does it matter?

Effect

- At least 30% patients suffering from depression meet definition of TRD (McIntyre, 2023)
- 50-70% of this population fail to respond to TMS (Marwaha, 2023)
- 20-40% fail to respond to ECT (Espinoza & Kellner, 2022)

Tolerability

- 6% discontinue antidepressant medication at 2 months, 12% at 12 months (De Crescenzo, 2024) specifically due to side effects

Accessibility

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Review evidence on efficacy and safety in treatment-resistant depression, based on RCTs

Present research and clinical experience using T-PEMF technology from Denmark

Discuss the potential clinical applications of subthreshold TMS

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NIHR | National Institute for Health and Care Research

PROSPERO
International prospective register of systematic reviews

The use of transcranial pulsed electromagnetic fields (T-PEMF) in depression: A systematic review and meta-analysis comparing effects of low-intensity TMS

Nana Brandborg Sørensen, Gustav Bizik, Klaus Martiny, Poul Videbech, Martin Balslev Jorgensen, Kamilla Miskowiak, Anders Jorgensen

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REVIEW

Efficacy and Tolerability of Low-Field Magnetic Stimulation for Treatment of Depressive Disorder

A Systematic Review and Meta-Analysis of Randomized Sham-Controlled Studies

*Dhiman R. Bharadwaj, MBBS, DPM, MD, DNB,**
Suresh Aaditya, MBBS, MD,† Shailja Singh, MBBS, MD,‡
Neha Sharma, MBBS, MD, DNB, MRCPsych,§
Jyothirmayi Kotipalli, MBBS, MD, MRCPsych,‖
Arogya Nadhudu Dovari, MBBS, MD,¶ Swarndeep Singh, MBBS, MD,#
*Brijesh Sathian, MD[AM], MPH, PhD,** and*
Sai Krishna Tikka, MBBS, DPM, MD††

Four categories of subthreshold TMS approaches

EP-MRSI (Echo Planar Magnetic Resonance Spectroscopic Imaging)

PEMF (Pulsed Electromagnetic Fields)

Head Coil LFMS (Low-Field Magnetic Stimulation)

sTMS (Synchronized Transcranial Magnetic Stimulation)

EP-MRSI (Echo Planar Magnetic Resonance Spectroscopic Imaging)

Rationale: Clinical observation at McLean Hospital Brain Imaging Center

Stimulation sequence: conventional double-echo spin-echo T2 scan - **EP-MRSI scans totaling 20.5 minutes** - T1 anatomic scan - echo-planar T2 imaging acquisition

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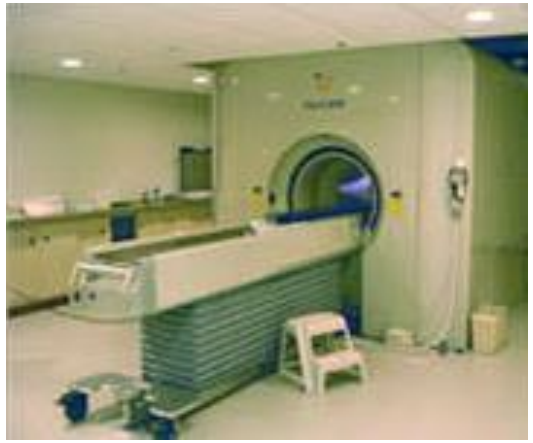

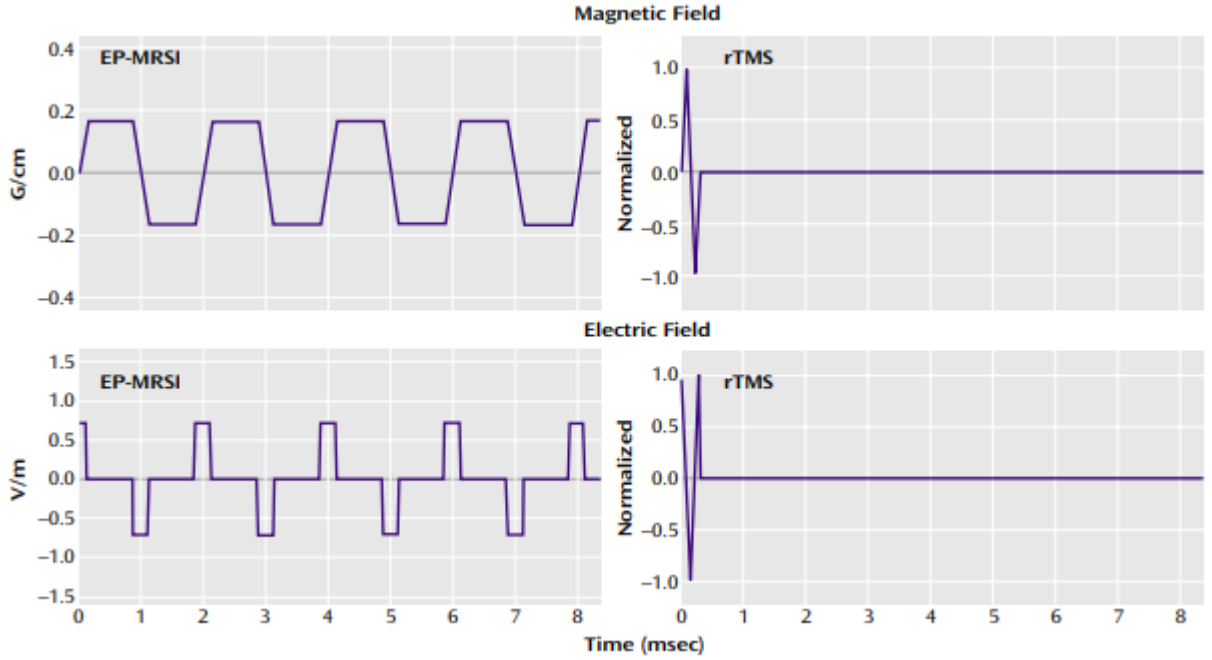

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MARTINY, 2010

VAN BELKUM, 2021

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Rationale: One of the dynamic components of the gradient field in the MRSI protocol is suggested to mediate the (rapid) antidepressant effect

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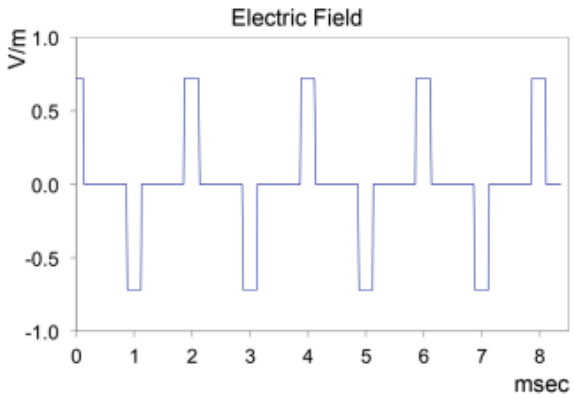

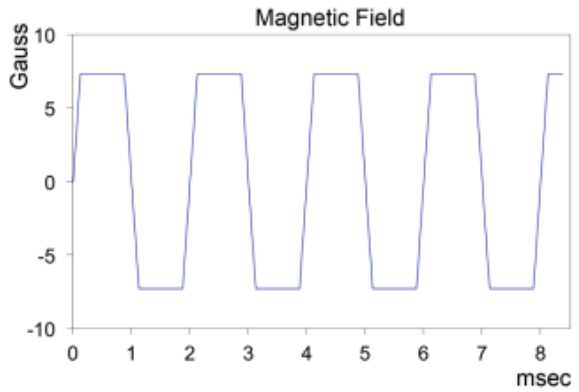

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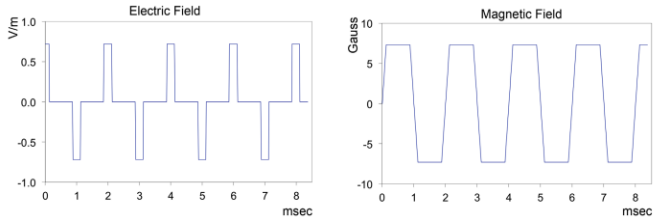

	Method	Field	Pulse	Frequency
ECT	Electrode	>200 V/m	1 msec	60 Hz
DBS	Implant	100 V/m	60 µsec	120 Hz
rTMS	Coil	100 V/m	500 µsec	10 Hz
LFMS	Coil	1 V/m	256 µsec	1 kHz

sTMS (Synchronized Transcranial Magnetic Stimulation)

Rationale: resetting cortical oscillators by synchronizing the TMS pulses to the frequency of the patient's individual alpha frequency

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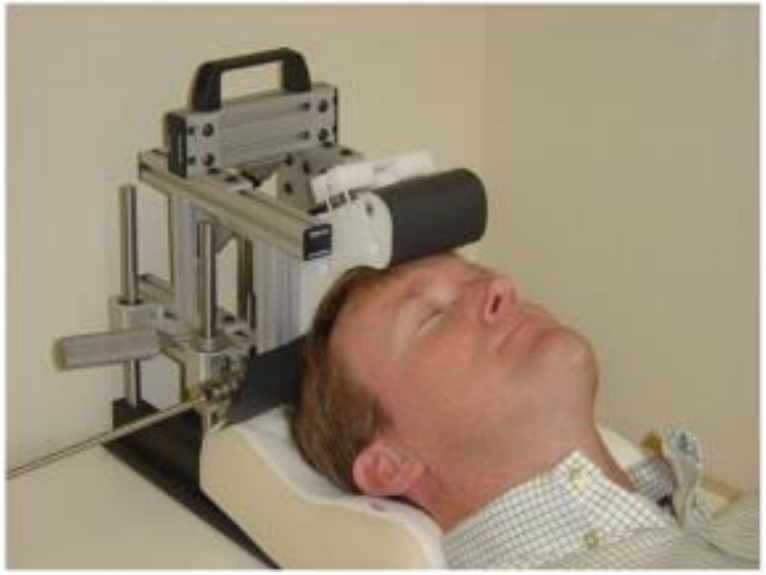
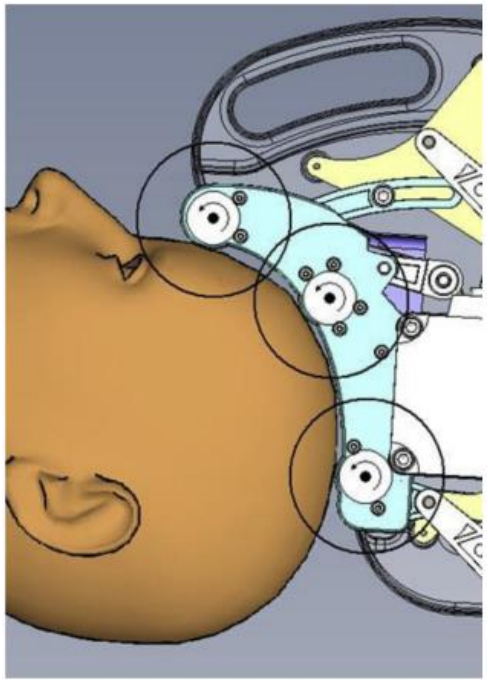
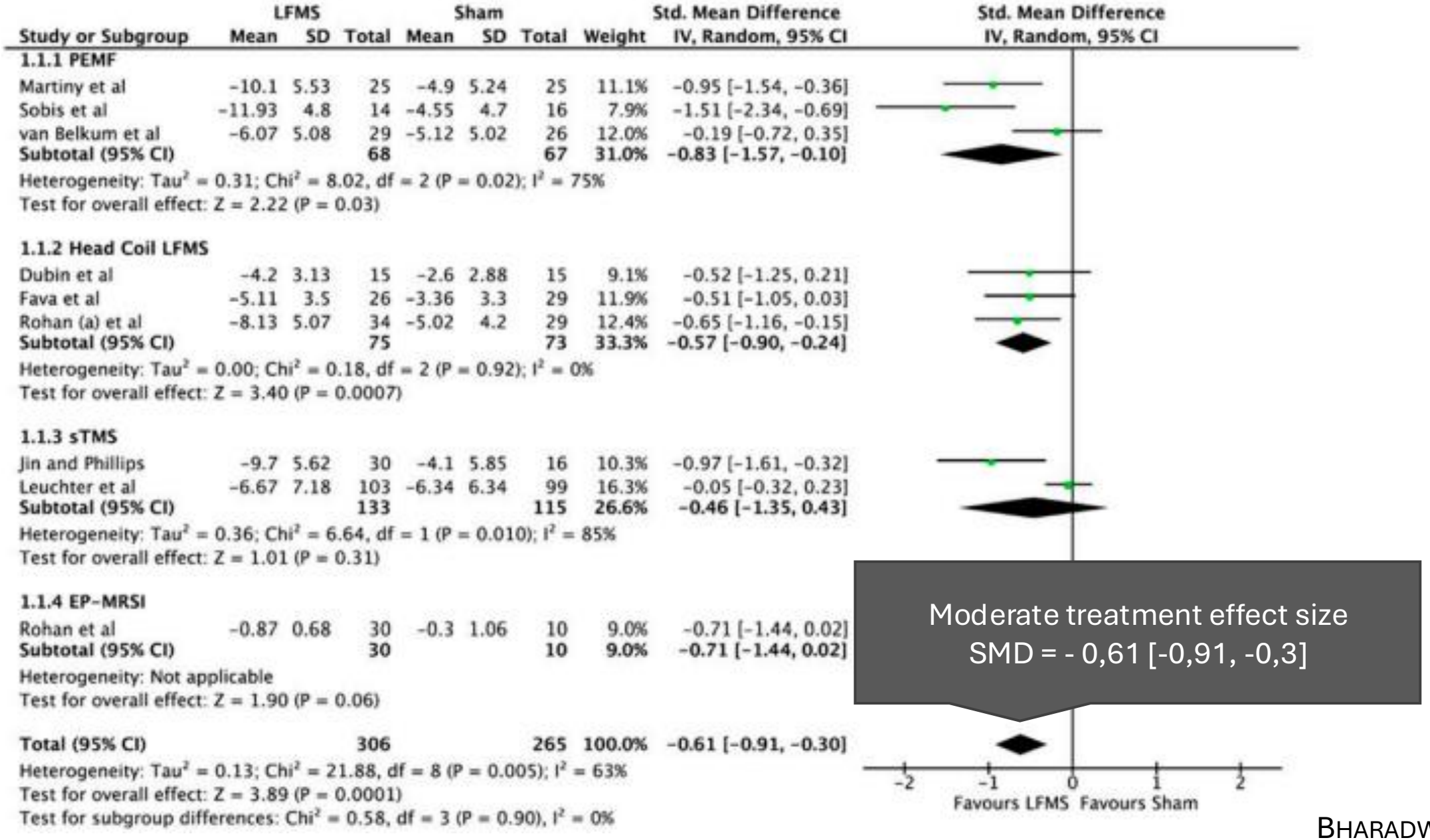




Study	Country	Sample size, n	Diagnosis	Definition of Treatment Resistance	Proportion of Patiens Drug Free	Outcomes
Rohan et al. 2004	USA	54	BPD	NA	Active: 11/30 Sham: 2/10	BAS
Martiny et al., 2010	Denmark	50	TRD-MDD/BPD	≥3 on Sackheim criteria	Nil	HDRS, MED, VAS
Sobiś et al., 2010	Poland	30	TRD-MDD	Two unsuccessful courses of antidepressive therapy, with at least 2 antidepressive drugs from different groups, administered in relatively high doses for at least 6 weeks	Nil	HDRS, MADRS
Jin & Phillips, 2014	China and USA	46	MDD	NA	Nil	HDRS
Rohan et al., 2014	USA	63	BPD/MDD	NA	Nil	HDRS, VAS
Leuchter et al., 2015	USA	202	MDD	NA	All	HDRS, MADRS, CGI
Fava et al., 2018	USA	84	TRD-MDD	Failure to respond to 1 or more trials of an adequate dose of an antidepressant for at least 8 weeks	Nil	HDRS, MADRS, SDQ
Dubin et al., 2019	USA	30	TRD-MDD	Failure to respond to 1 or more trials of an adequate dose of an antidepressant for at least 8 weeks	Nil	HDRS, PANAS, VAS
Van Belkum et al., 2021	Netherlands	55	TRD-MDD	> 17 on HDRS-17, nonresponsiveness to one or more antidepressants, given for at least 4 weeks and in an adequate dose	NA	HDRS

Study	Modality	Frequency	Intensity	Field Strength	Target Region	Duration
Rohan et al.	EP-MRSI	1 kHz	0.7 V/m	NA	Diffuse	Single session (1 h)
Martiny et al.	t-PEMF	<333 Hz	2.2 mV/cm	19 Gauss	Bilateral temporal/parietal, occipital	Daily ×5/week, 5 weeks
Sobiś et al.	PEMF	180–195 Hz	NA	15 μT	NA	12 min, 5×/week, 3 weeks
Jin & Phillips	sTMS	IAF ± 1Hz	NA	0.64 T	Midline frontal–parietal	30 min ×5/week, 4 weeks
Leuchter et al.	sTMS	IAF ± 1Hz	NA	0.64 T	Midline frontal–parietal	Daily ×5/week, 6 weeks
Rohan et al.	LFMS	1 kHz	≤1.43 V/m	20 Gauss	Diffuse	Single session (20 min)
Fava et al. (2018)	LFMS	500 Hz	0.5 V/m	< 50 Gauss	Diffuse	20 min ×4 days
Dubin et al.	LFMS	NA	0.7 V/m	NA	Diffuse	20 min ×3 days
Van Belkum et al.	t-PEMF	NA	NA	100 μT	10-20 EEG system	5 weeks



Moderate treatment effect size
SMD = - 0,61 [-0,91, -0,3]

BHARADWAJ, 2026

BHARADWAJ, 2026

Pooled OR (responders): **3,39** (95% CI = 1,31 – 8,87, p=0,01)

Pooled OR (remitters): **2.68** (95% CI = 0,63 – 11,39, p=0,18)

Post-intervention follow-up data only for 2 studies

Tolerability: overall well-tolerated

musculoskeletal pain (OR=2,69, 95% CI: 1,14-6,31)

Experience from Denmark

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Re5 Neuro Tretment System

Several research trials

Integrated into treatment algorithms in several psychiatric centers

Re5 T-PEMF

Brain Stimulation 19 (2026) 103074

Contents lists available at ScienceDirect

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

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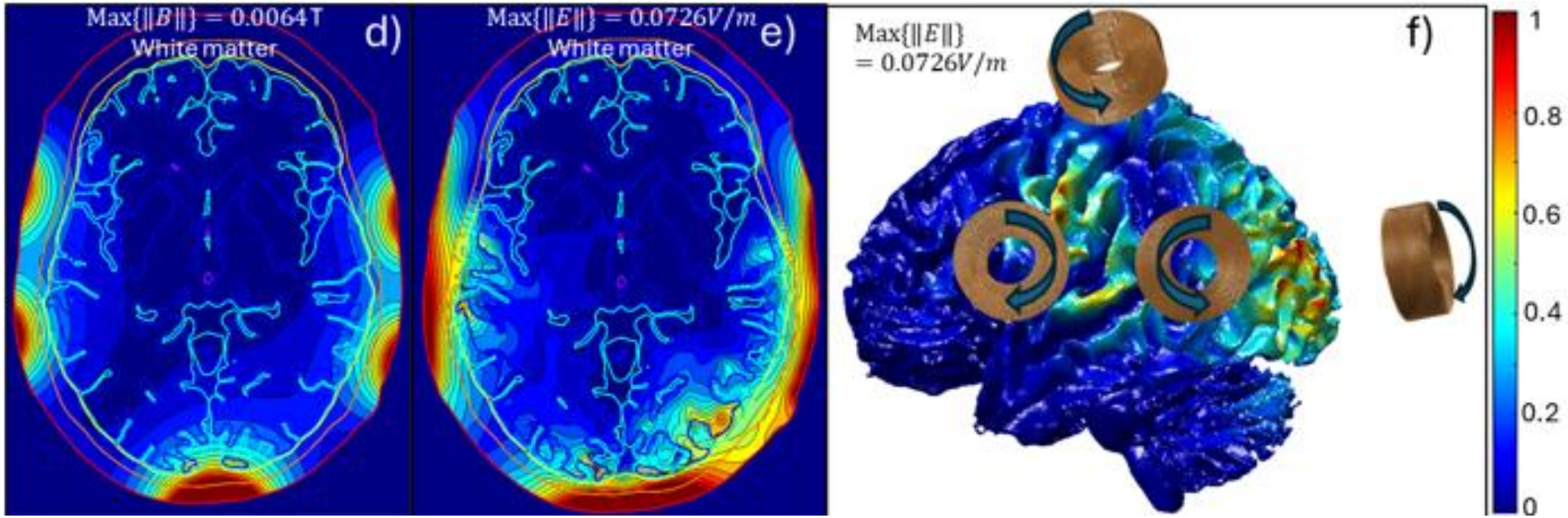

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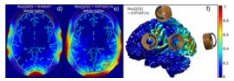

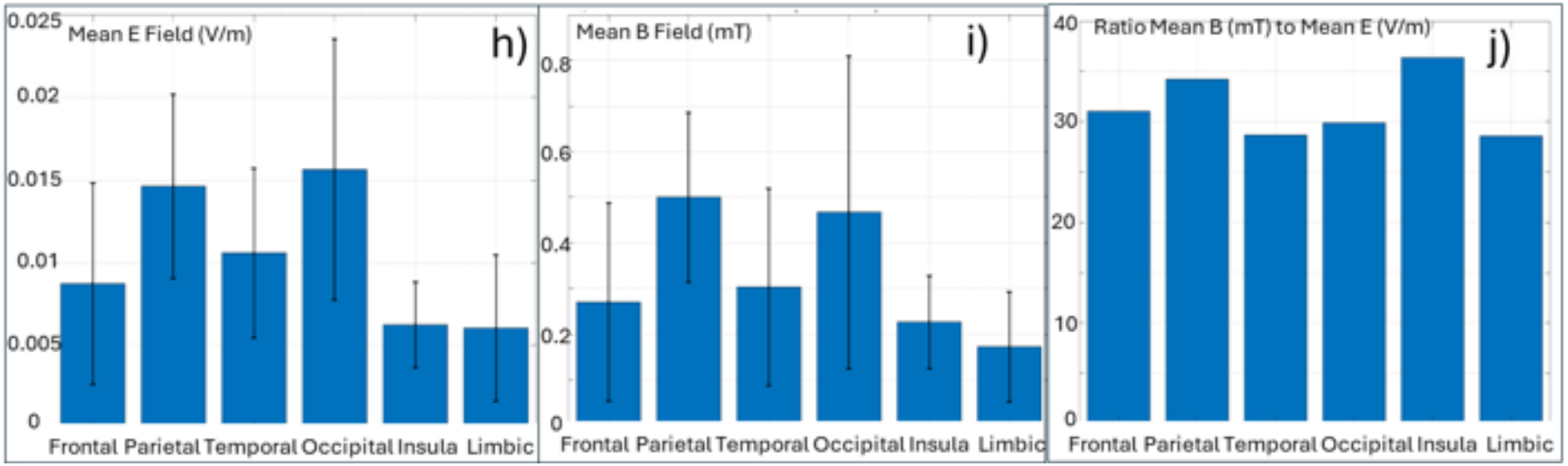

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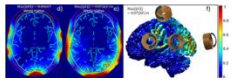

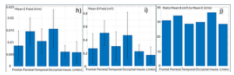

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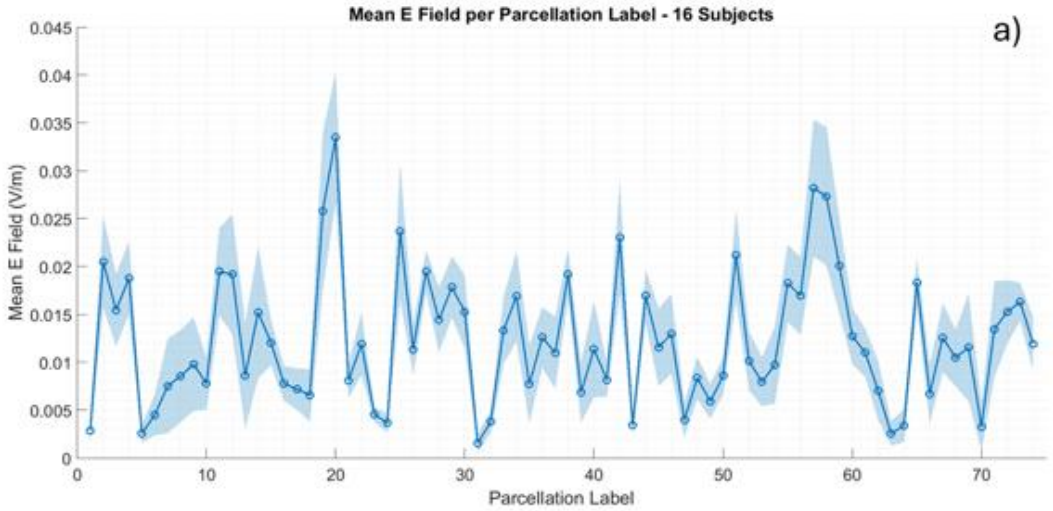

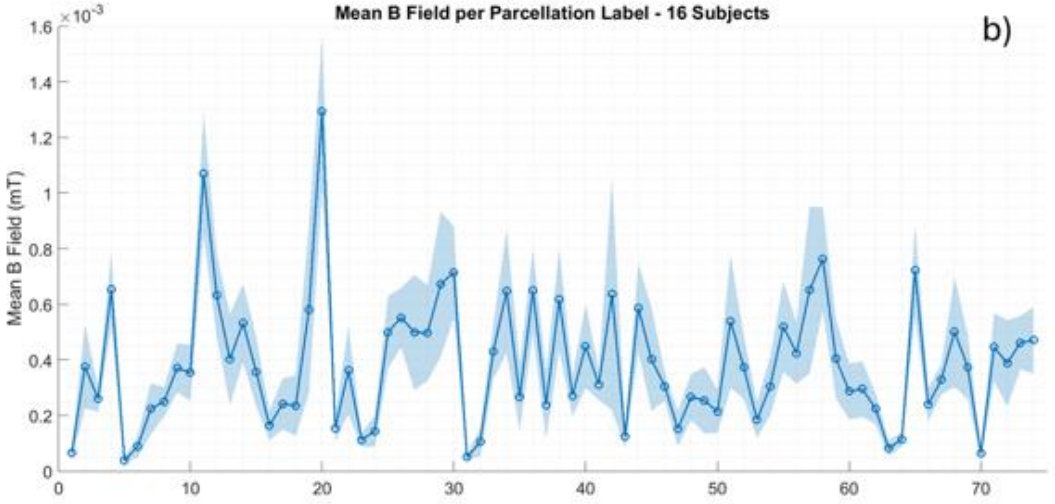

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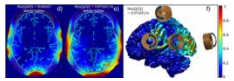

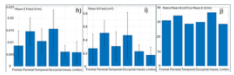

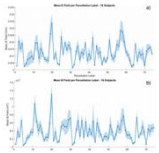

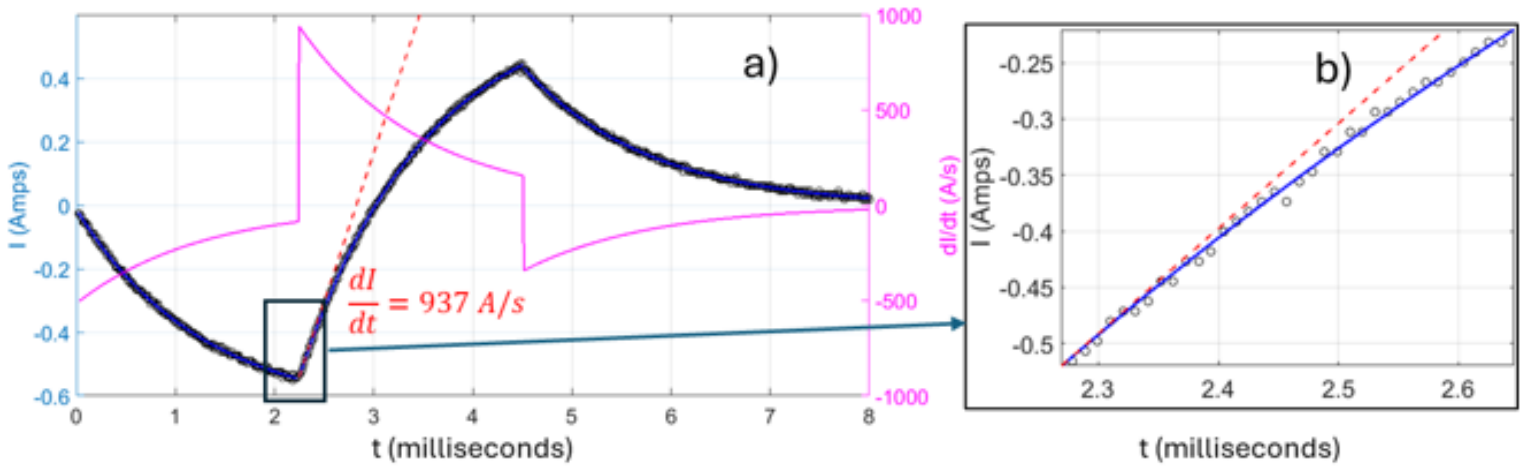

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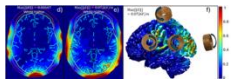
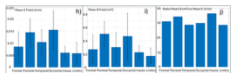
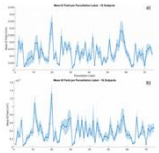
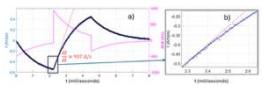








Stimulation modality	Typical pulse duration	Typical peak cortical electric field (V/m)	Typical peak cortical magnetic field (mT)	Ratio of magnetic to electric field (mT/(V/m))
Re5 – NTS (present study)	4.5 ms biphasic pulse, 50 Hz	0.18 (present study)	5.5 (present study)	30
rTMS	200–500 μs bi- or monophasic pulse, 1 to 10 Hz	114 (present participant #1)	161 (present participant #1)	1.4
tES	DC or sinusoidal	0.1–1	N/A	N/A

Martiny, 2010

RCT, Active (n=25) vs. Sham (n=25)

Straasø, 2014

RT, One session/d (n=34) vs. Two sessions/d (n=31)

5 weeks vs. 8 weeks

Bech, 2015

Two years follow-up of Straasø cohort, re-treatment in relaps (n=13)

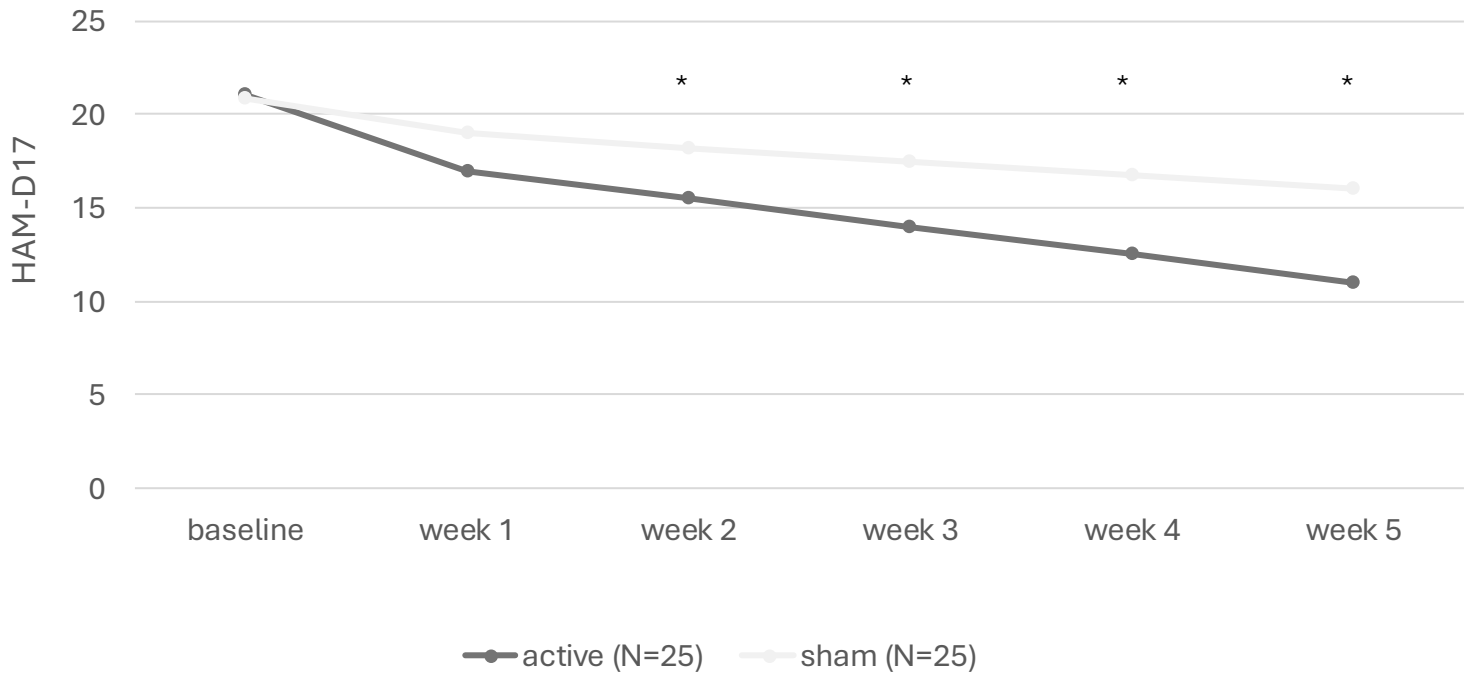
Larsen, 2020

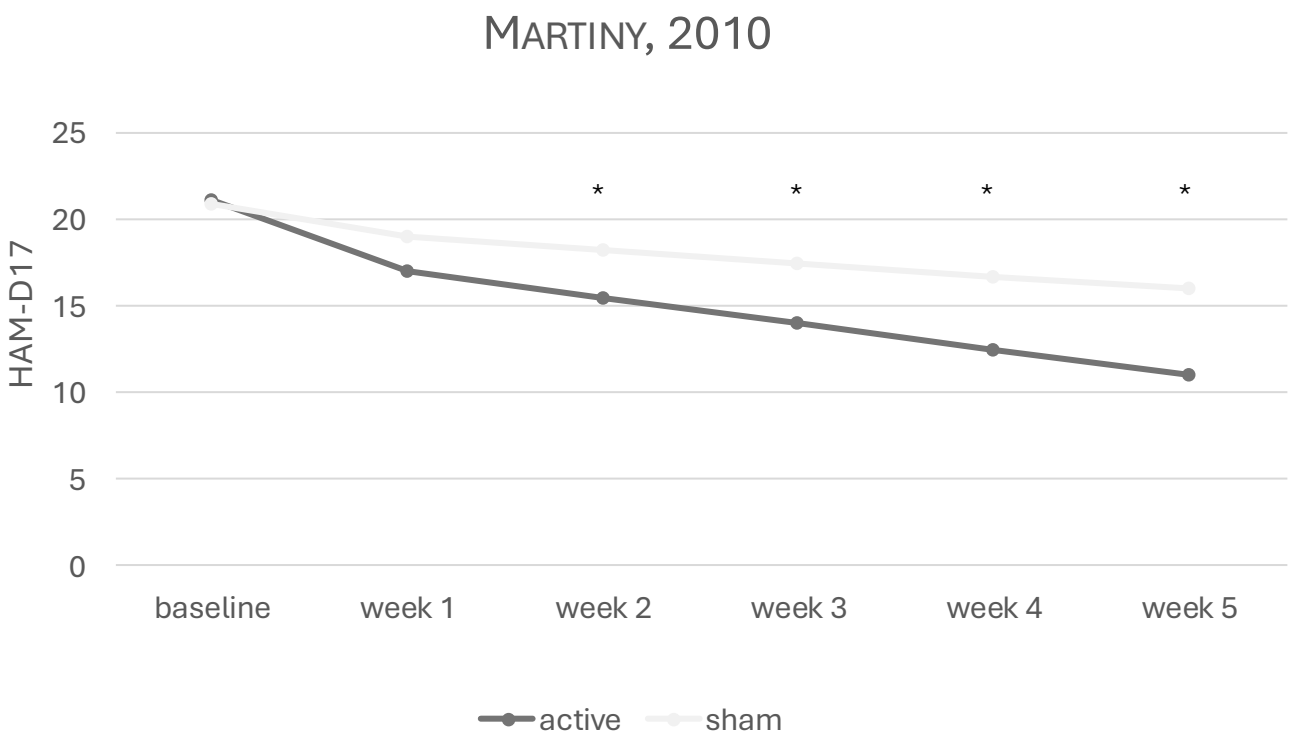
Five sites, prospective single-arm cohort (n=52)

Jensen, 2025

Real-world retrospective cohort (n=40)

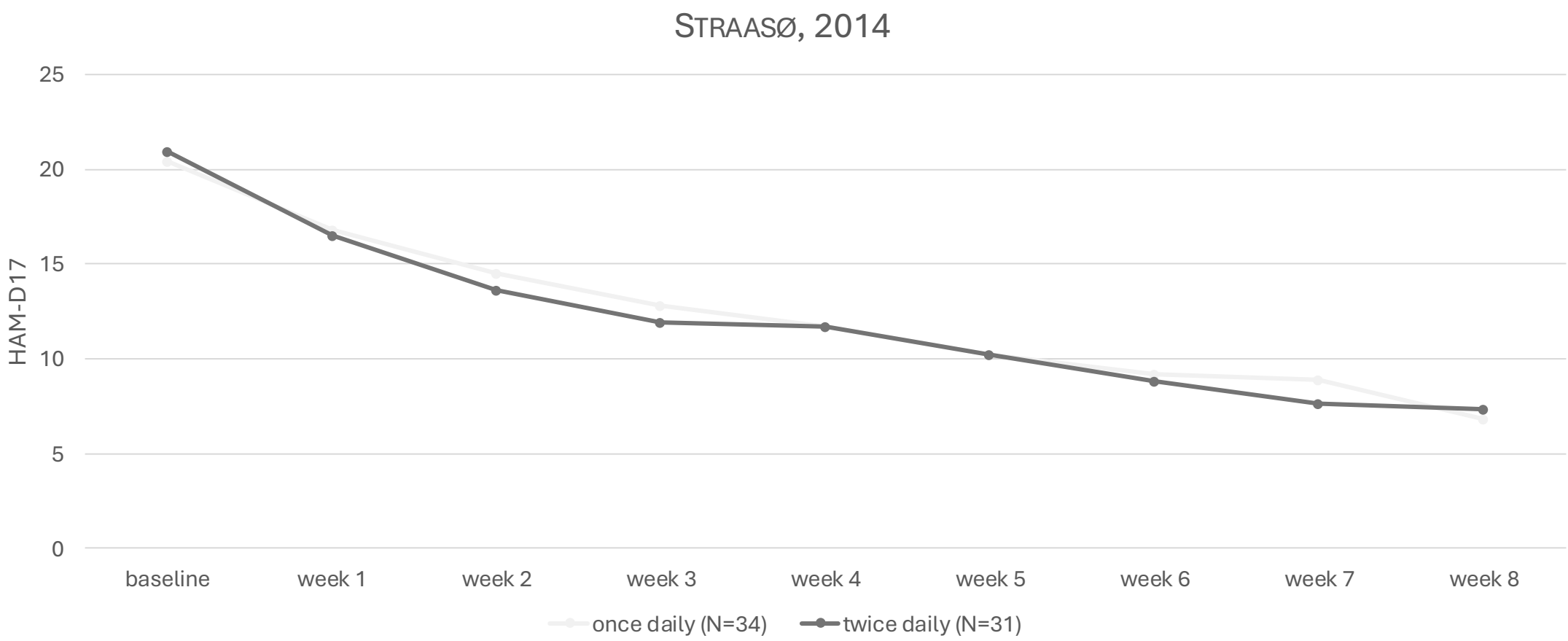
MARTINY, 2010



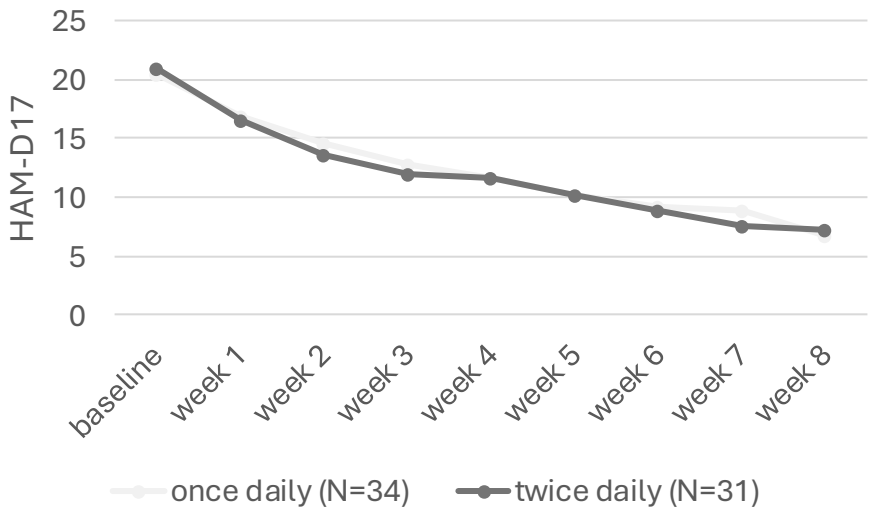


NNT=2 (response)

NNT=3 (remission)

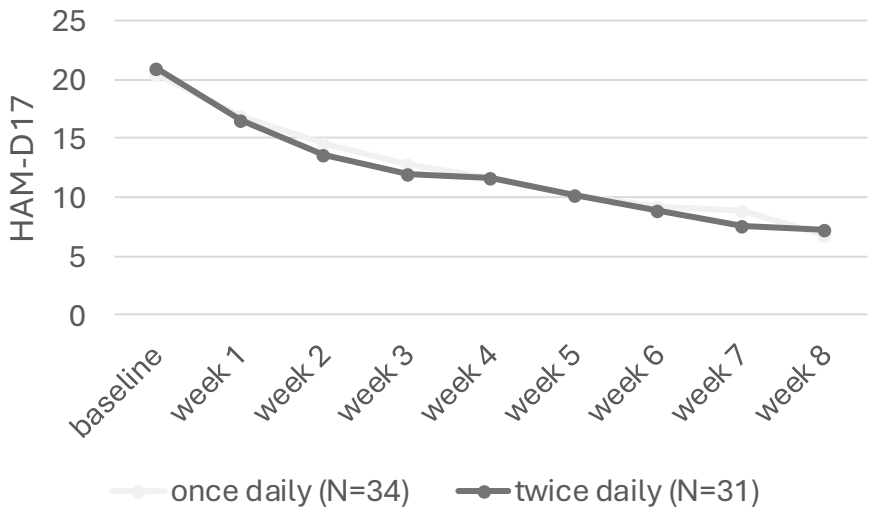

STRAASØ, 2014
HAM-D17
25
20
15
10
5
0
baseline
week 1
week 2
week 3
week 4
week 5
week 6
week 7
week 8
once daily (N=34)
twice daily (N=31)

STRAASØ, 2014



	One dose daily ($n = 34$)	Two doses daily ($n = 31$)	p
$HAM\text{-}D_{17}<8$			
After 5 weeks	26.5%	32.3%	0.79
After 8 weeks	73.5%	67.7%	0.79
$HAM\text{-}D_{6}<5$			
After 5 weeks	11.8%	12.9%	1.00
After 8 weeks	52.9%	61.3%	0.62

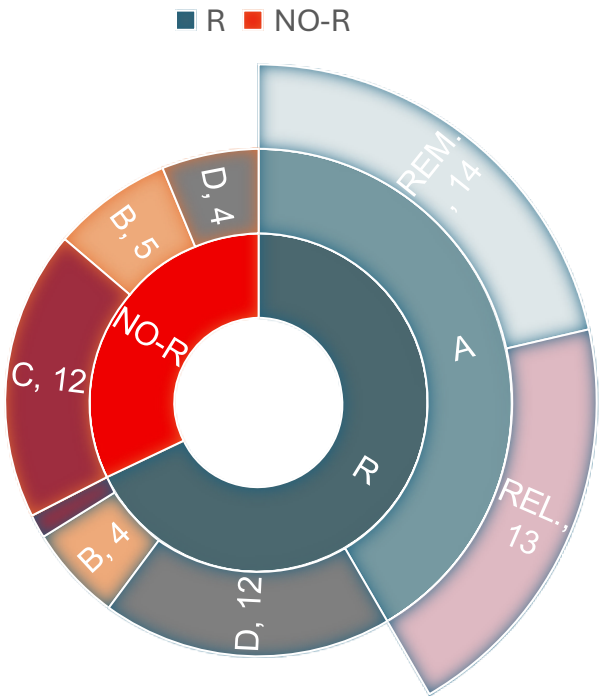
STRAASØ, 2014



	One dose daily ($n = 34$)	Two doses daily ($n = 31$)	p
HAM-D_{17}<8			
After 5 weeks	26.5%	32.3%	0.79
After 8 weeks	73.5%	67.7%	0.79
HAM-D_6<5			
After 5 weeks	11.8%	12.9%	1.00
After 8 weeks	52.9%	61.3%	0.62

Better toleration of the antidepressive medication in both treatment groups

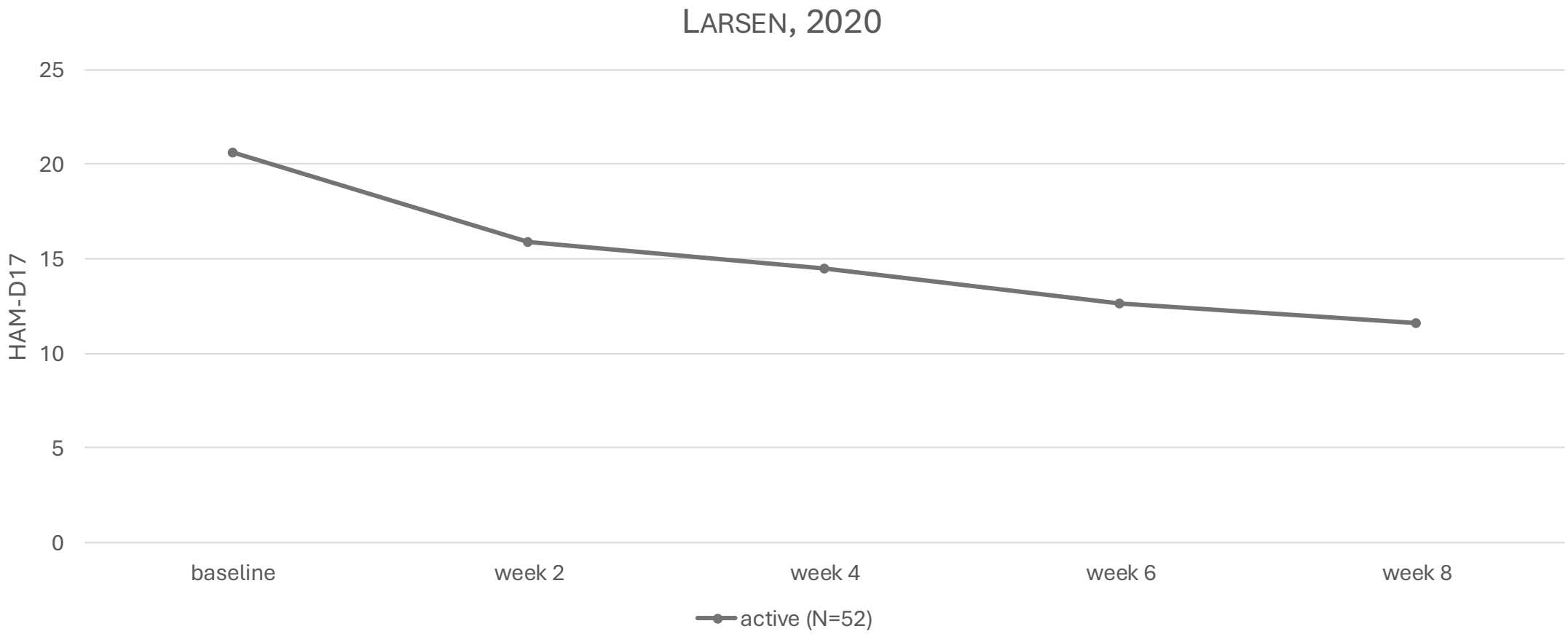
TWO YEARS FOLLOW-UP, BECH, 2015

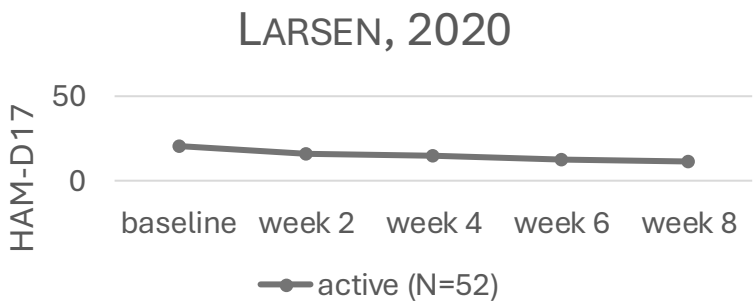


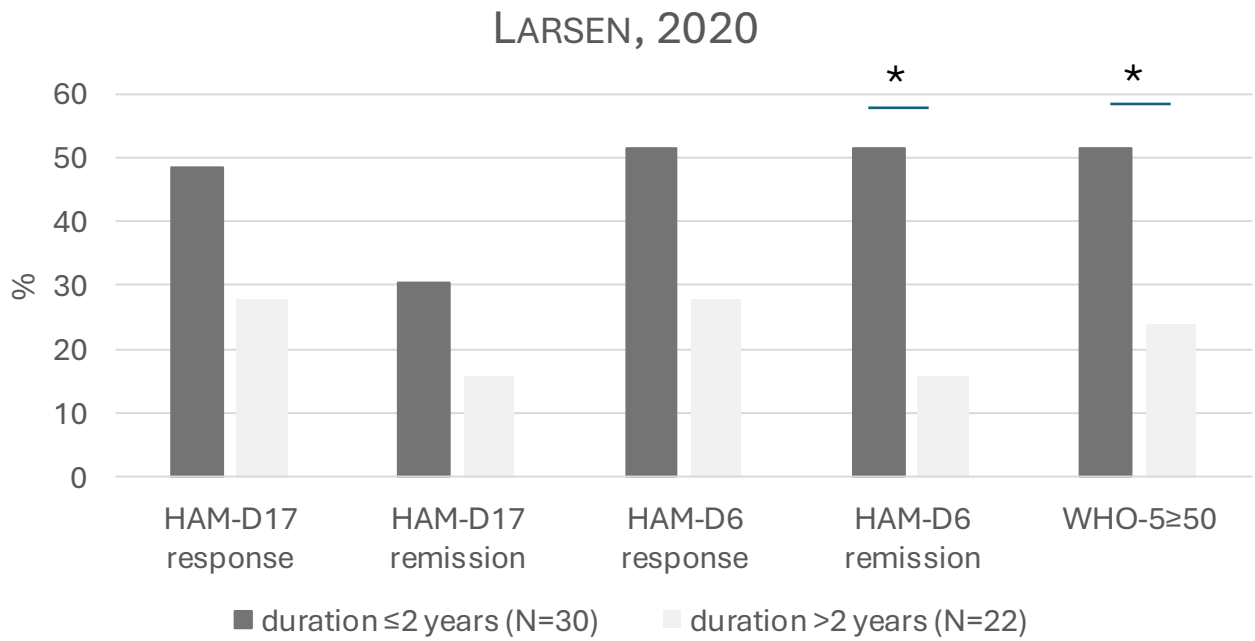
R – remission, NO-R – no remission (STRAASØ, 2014)

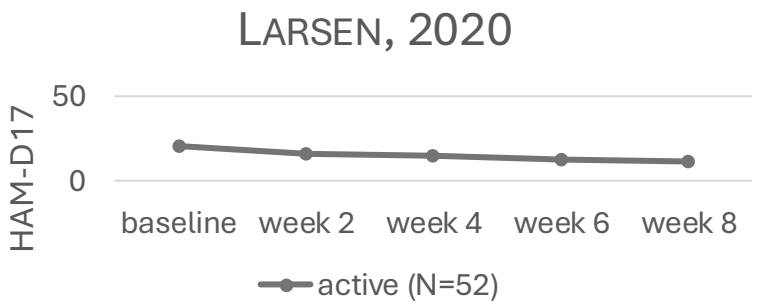
Two years follow-up – patients ´ retrospective assessement
A- good effect of T-PEMF
B- partial effect of T-PEMF
C- no effect of T-PEMF
D- do not remember

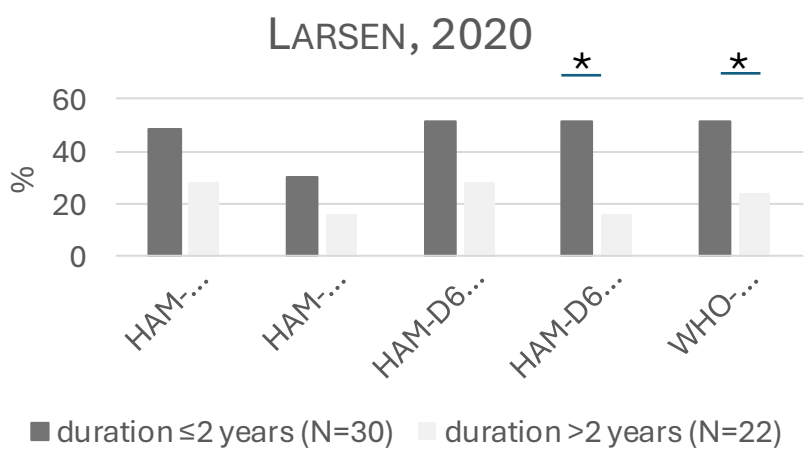
relaps 4-16 måneder after T-PEMF (median 8)
100% remission after T-PEMF re-treatment

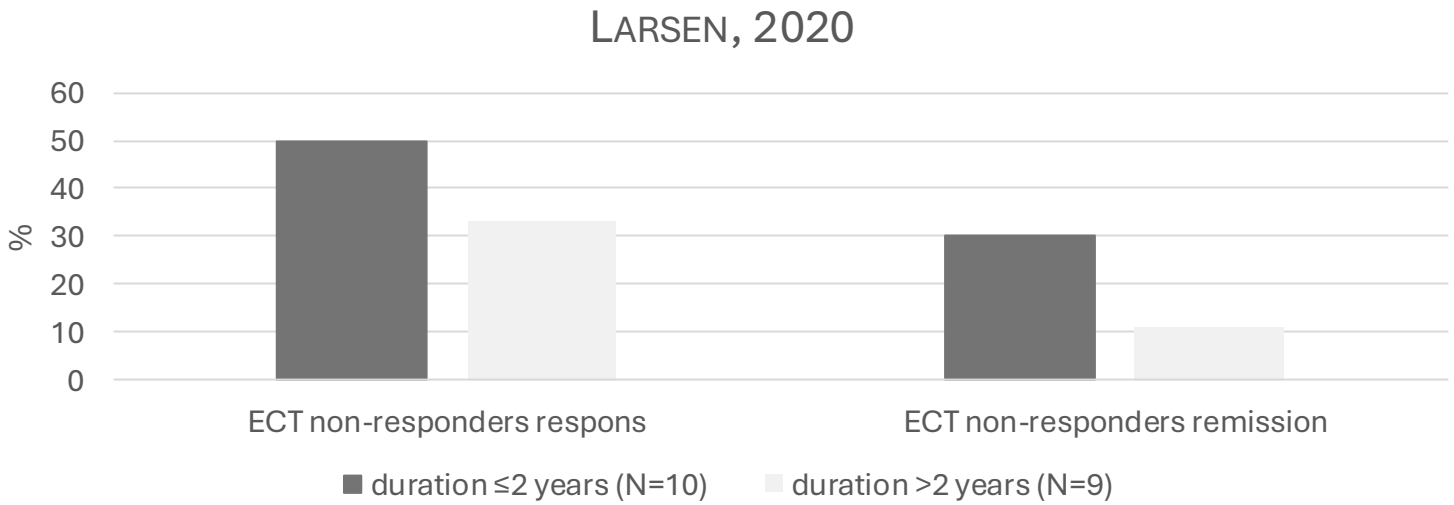

LARSEN, 2020
25
20
15
10
5
0
HAM-D17
baseline
week 2
week 4
week 6
week 8
active (N=52)


LARSEN, 2020
HAM-D17
50
0
baseline
week 2
week 4
week 6
week 8
active (N=52)


LARSEN, 2020
%
60
50
40
30
20
10
0
*
*
HAM-D17 response
HAM-D17 remission
HAM-D6 response
HAM-D6 remission
WHO-5≥50
duration ≤2 years (N=30)
duration >2 years (N=22)


LARSEN, 2020
HAM-D17
50
0
baseline
week 2
week 4
week 6
week 8
active (N=52)


LARSEN, 2020
*
*
%
60
40
20
0
HAM-...
HAM-...
HAM-D6...
HAM-D6...
WHO-...
duration ≤2 years (N=30)
duration >2 years (N=22)


LARSEN, 2020
%
60
50
40
30
20
10
0
ECT non-responders respons
ECT non-responders remission
duration ≤2 years (N=10)
duration >2 years (N=9)

Journal of Affective Disorders 368 (2025) 487–492

Contents lists available at ScienceDirect

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

Research paper

Real-world treatment outcomes of transcranial pulsating electromagnetic fields as augmentation therapy for treatment-resistant depression

Rikke Hedegaard Jensen [a], René Ernst Nielsen [b,c], Gustav Bizik [b,c,*]

[a] Department of Health Science and Technology, Aalborg University, Aalborg, Denmark
[b] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
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40 TRD patients, mean age 48 (14), median MSM score 9 (IQR 8- 10)

	N	Baseline	Week 8	*p*
HAM-D_{17}	40	20.8 (3.3)	14.5 (6.2)	<.001[a]
HAM-D_6	36	10.0 (9.0; 12.0)	7.5 (5.0; 9.8)	<.001[b]
Self-rated HAM-D_6	29	14.0 (12.0; 16.0)	12.0 (6.5; 14.5)	< 0.01[b]
WHO-5	29	20.0 (12.0; 28.0)	28.0 (16.0; 50.0)	<.001[b]

HAM-D_{17}: Hamilton Rating Scale for Depression 17-item version; HAM—D_6: Hamilton Rating Scale for Depression 6-item version; Q1: Lower quartile; Q3: Upper quartile; SD: Standard deviation; WHO-5: WHO-5 Well-Being Index.

[a] Paired t-test.

[b] Wilcoxon signed rank test.

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[a] Paired t-test.
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	Unadjusted		Adjusted	
	OR (95 % CI)	p^a	OR (95 % CI)	p^a
HAM-D_{17} ($n = 40$)				
Age	1.02 (0.97; 1.07)	0.543	1.02 (0.97; 1.07)	0.481
Duration: 2–5 years - < 2 years	0.35 (0.07; 1.76)	0.201	0.34 (0.07; 1.73)	0.191
Duration: > 5 years - < 2 years	0.75 (0.13; 4.22)	0.744	0.80 (0.14; 4.61)	0.803
HAM-D_6 (n = 36)				
Age	0.99 (0.94; 1.04)	0.752	1.00 (0.95; 1.06)	0.993
Duration: 2–5 years - < 2 years	0.15 (0.03; 0.95)	0.044	0.15 (0.03; 0.96)	0.045
Duration: > 5 years - < 2 years	0.75 (0.12; 4.66)	0.758	0.75 (0.12; 4.75)	0.761
Self-rated HAM-D_6 ($n = 29$)				
Age	1.03 (0.96; 1.09)	0.439	1.03 (0.96; 1.11)	0.350
Duration: 2–5 years - < 2 years	0.10 (0.01; 1.06)	0.056	0.09 (0.01; 0.99)	0.049
Duration: > 5 years - < 2 years	0.30 (0.03; 3.63)	0.344	0.34 (0.03; 4.33)	0.404

CI: Confidence interval; HAM—D_{17}: Hamilton Rating Scale for Depression 17-item version; HAM—D_6: Hamilton Rating Scale for Depression 6-item version; OR: Odds ratio.
[a] Binary logistic regression.

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WHO-5	29	20.0 (12.0; 28.0)	28.0 (16.0; 50.0)	<.001 [b]

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Duration: 2–5 years - < 2 years	0.35 (0.07; 1.76)	0.201	0.34 (0.07; 1.73)	0.191
Duration: > 5 years - < 2 years	0.75 (0.13; 4.22)	0.744	0.80 (0.14; 4.61)	0.803
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Age	0.99 (0.94; 1.04)	0.752	1.00 (0.95; 1.06)	0.993
Duration: 2–5 years - < 2 years	0.15 (0.03; 0.95)	0.044	0.15 (0.03; 0.96)	0.045
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CI: Confidence interval; HAM—D_{17}: Hamilton Rating Scale for Depression 17-item version; HAM—D_6: Hamilton Rating Scale for Depression 6-item version; OR: Odds ratio.
[a] Binary logistic regression.

	n	All	n	Unipolar depression	n	Bipolar disorder	p [a]
Response							
HAM-D_{17}	40	30.0 % (12)	37	29.7 % (11)	3	33.3 % (1)	1.000
HAM-D_6	36	33.3 % (12)	33	33.3 % (11)	3	33.3 % (1)	1.000
Self-rated HAM-D_6	29	24.1 % (7)	26	23.1 % (6)	3	33.3 % (1)	1.000
Remission							
HAM-D_{17}	40	15.0 % (6)	37	13.5 % (5)	3	33.3 % (1)	0.394
HAM-D_6	40	20.0 % (8)	37	18.9 % (7)	3	33.3 % (1)	0.498
Self-rated HAM-D_6	31	16.1 % (5)	28	14.3 % (4)	3	33.3 % (1)	0.422

HAM-D_{17}: Hamilton Rating Scale for Depression 17-item version; HAM—D_6: Hamilton Rating Scale for Depression 6item version.
[a] Fisher's exact test comparing unipolar depression and bipolar disorder groups.

Naturalistic bipolar cohort (unpublished)

15 patients with **difficult-to-treat bipolar depression**

Results

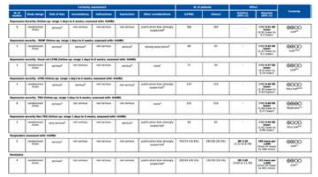
- 52 years (9.3), 6(40%) bipolar I, 8 (53%) bipolar II
- Highly treatment-resistant
- HDRS-17 (**21.1** (SD 3.1) to **15.5** (SD 7.2), p=0.025)
- WHO-5 (**14** (IQR 10–19.5) to **32** (IQR 12–40), p=0.015)
- **Three of 15 patients** initiating T-PEMF both **response and remission**
- Mild adverse effects reported (headache 27%, nausea 13%, fatigue 7%) and high adherence
- One patient discontinued due to emergent **hypomanic/manic** symptoms

Does subthreshold TMS have a clinical potential ?

Does subthreshold TMS have a clinical potential ?

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[LFMS]	[Sham]	Relative (95% CI)	Absolute (95% CI)	
Depression Severity (follow-up: range 1 days to 6 weeks; assessed with: HAMD)											
9	randomised trials	serious[a]	not serious	not serious	not serious	publication bias strongly suspected[b]	306	265	-	SMD **0.61 SD lower** (0.91 lower to 0.3 lower)	⨁⨁◯◯ Low[a,b]
Depression severity - PEMF (follow-up: range 1 days to 6 weeks; assessed with: HAMD)											
3	randomised trials	serious[c]	serious[d]	not serious	serious[e]	strong association[f]	68	67	-	SMD **0.83 SD lower** (1.57 lower to 0.1 lower)	⨁⨁◯◯ Low[c,d,e,f]
Depression severity- Head coil LFMS (follow-up: range 1 days to 6 weeks; assessed with: HAMD)											
3	randomised trials	serious[g]	not serious	not serious	serious[h]	none[i]	71	54	-	SMD **0.57 SD lower** (0.9 lower to 0.24 lower)	⨁⨁◯◯ Low[g,h,i]
Depression severity- sTMS (follow-up: range 1 days to 6 weeks; assessed with: HAMD)											
2	randomised trials	serious[j]	serious[k]	not serious	not serious[l]	publication bias strongly suspected[m]	133	115	-	SMD **0.46 SD lower** (1.35 lower to 0.43 higher)	⨁◯◯◯ Very low[j,k,l,m]
Depression severity- TRD (follow-up: range 1 days to 6 weeks; assessed with: HAMD)											
6	randomised trials	serious[n]	not serious	not serious	not serious	none[o]	212	210	-	SMD **0.68 SD lower** (1.09 lower to 0.27 lower)	⨁⨁⨁◯ Moderate[n,o]
Depression severity Non TRD (follow-up: range 1 days to 6 weeks; assessed with: HAMD)											
3	randomised trials	very serious[p]	not serious	not serious	serious[q]	publication bias strongly suspected[r]	94	61	-	SMD **0.54 SD lower** (1.01 lower to 0.06 lower)	⨁◯◯◯ Very low[p,q,r]
Responders (assessed with: HAMD)											
5	randomised trials	serious[s]	not serious	not serious	not serious	publication bias strongly suspected[t]	74/173 (42.8%)	28/138 (20.3%)	**OR 3.39** (1.31 to 8.78)	**260 more per 1,000** (from 47 more to 488 more)	⨁⨁◯◯ Low[s,t]
Remission											
4	randomised trials	serious[u]	not serious	not serious	not serious	publication bias strongly suspected[v]	29/143 (20.3%)	13/128 (10.2%)	**OR 2.68** (0.63 to 11.39)	**131 more per 1,000** (from 35 fewer to 461 more)	⨁⨁◯◯ Low[u,v]

BHARADWAJ, 2026



On the one hand…

Different technologies, heterogenous protocols

Few sham-controled trials

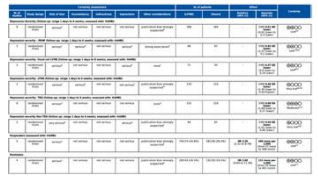
Limited data on long-term treatment outcomes

On the other hand…

Effective in a subgroup of TRD patients, high sucess rate efter re-treatment

Few and mild side effects, few contraindications

Can be used at home



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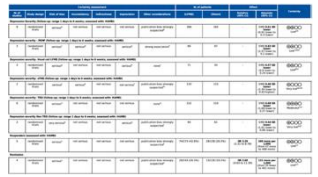

Pragmatic approach (Aalborg)

Response rates lower that those reported in initial studies

T-PEMF systematically included when treatment options are discussed with patients

… potentially even earlier in the course of the illness

Thank you for your attention

g.bizik@rn.dk