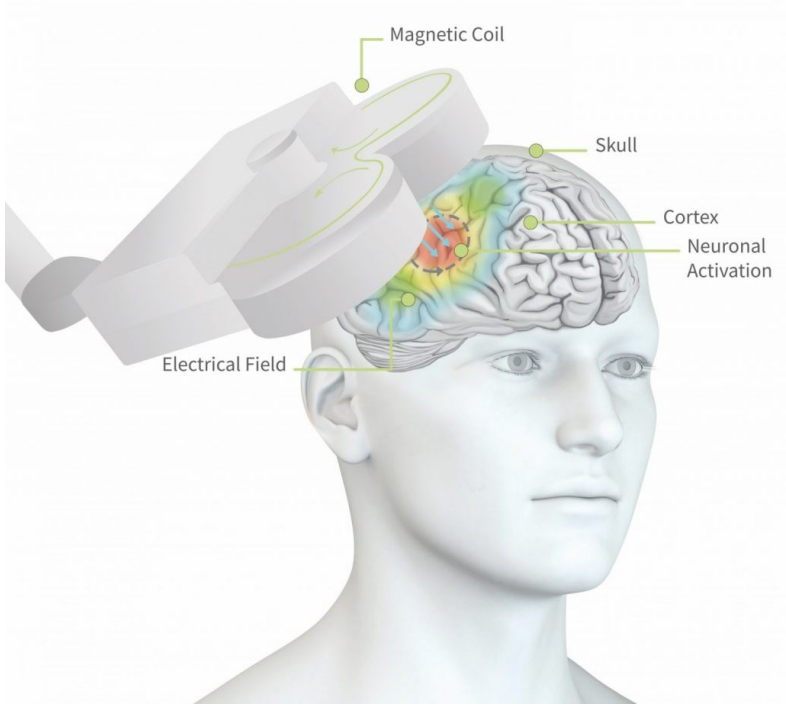
REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

rTMS



Ana Lisa Carmo
TMS-ansvarlig overlæge
Afdeling for Depression og Angst, Psykiatrien Aarhus Universitetshospital
Regionspsykiatrien Midt (Viborg)

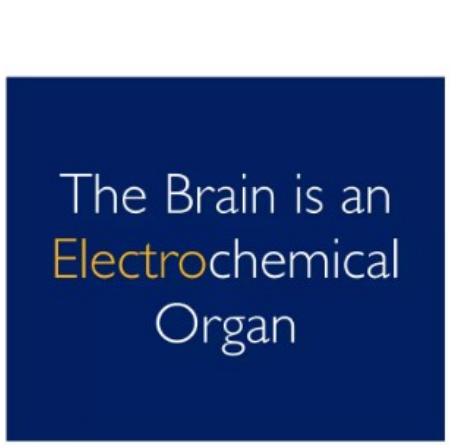
- Neuromodulation – hvorfor?
- Hvad er rTMS
- Evidensgrundlaget
- Målgruppe
- Sikkerhed: kontraindikationer/risikofaktorer, bivirkninger
- TMS-forløb
- Perspektiver...

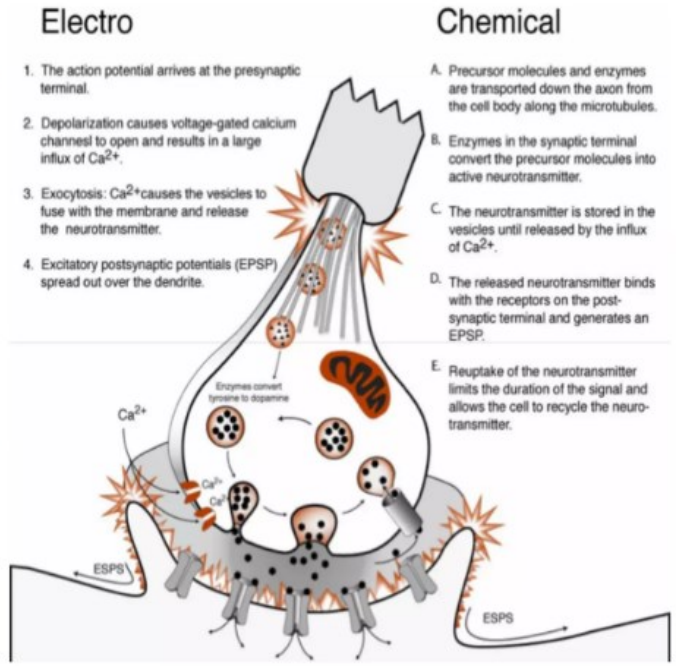
DEPRESSION
Behandling med antidepressiva

- På trods af flere farmakologiske behandlingsmuligheder opnår en del af patienterne fortsat ikke fuld remission
- Remissionsraten med den nuværende standardbehandling med antidepressiva hos patienter, som tidligere har svigtet på to behandlinger er 13-14% (Warden et al. Curr Psychiatry Rep, 2007)
- Dropout rates – bivirkninger
- Somatisk komorbiditet kan begrænse valg af antidepressiva
- **Stort behov for andre behandlingsmuligheder**

NEUROMODULATION

- **Ikke invasiv:**
  - Electroconvulsive therapy (ECT)
  - **Repetitive transcranial magnetic stimulation (rTMS)**
  - Transcranial direct current stimulation (tDCS)
  - Transcranial pulsed electromagnetic fields (T-PEMF)
  - Magnetic seizure therapy (MST)
  - Transcranial pulsed ultrasound
  - Transcutaneous vagus nerve stimulation
  - ……
- **Invasiv:**
  - Vagus Nerve Stimulation
  - Deep brain stimulation
  - Direct cortical stimulation
  - ….





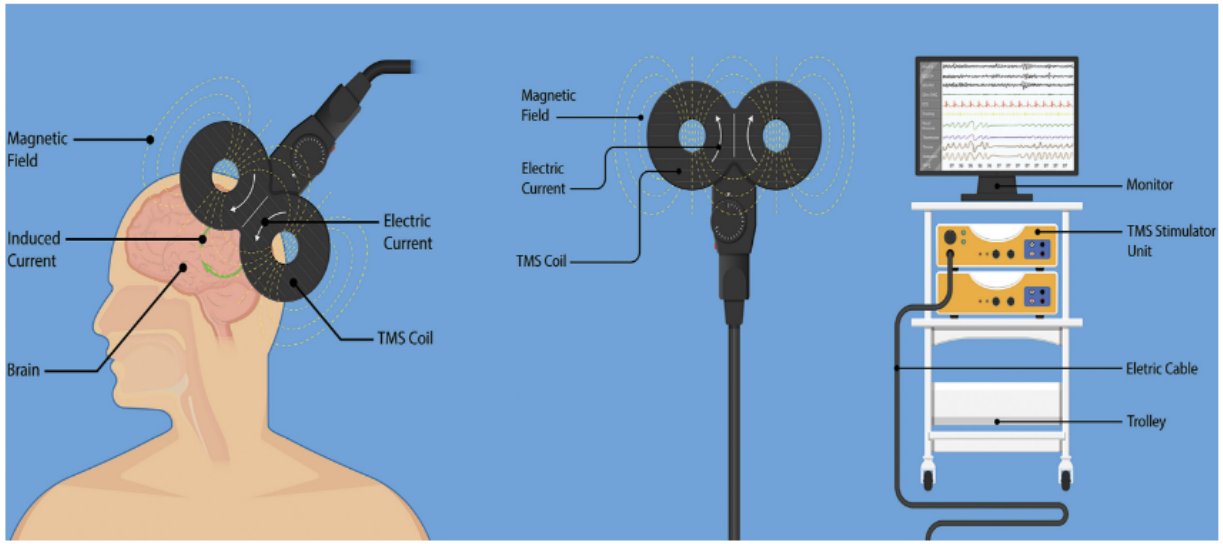
From Higgins and George, Neuroscience for Clinicians, 2007, Lippincott

rTMS – repetitiv transkraniel magnetisk stimulation

Ikke-invasiv hjernestimuleringsteknik

Fokal stimulering af udvalgte områder af centralnervesystem.

Bygger i princippet på elektromagnetisk induktion og indebærer, at hjernevævet noninvasivt udsættes for en strømpåvirkning via et dynamisk varierende magnetfelt.

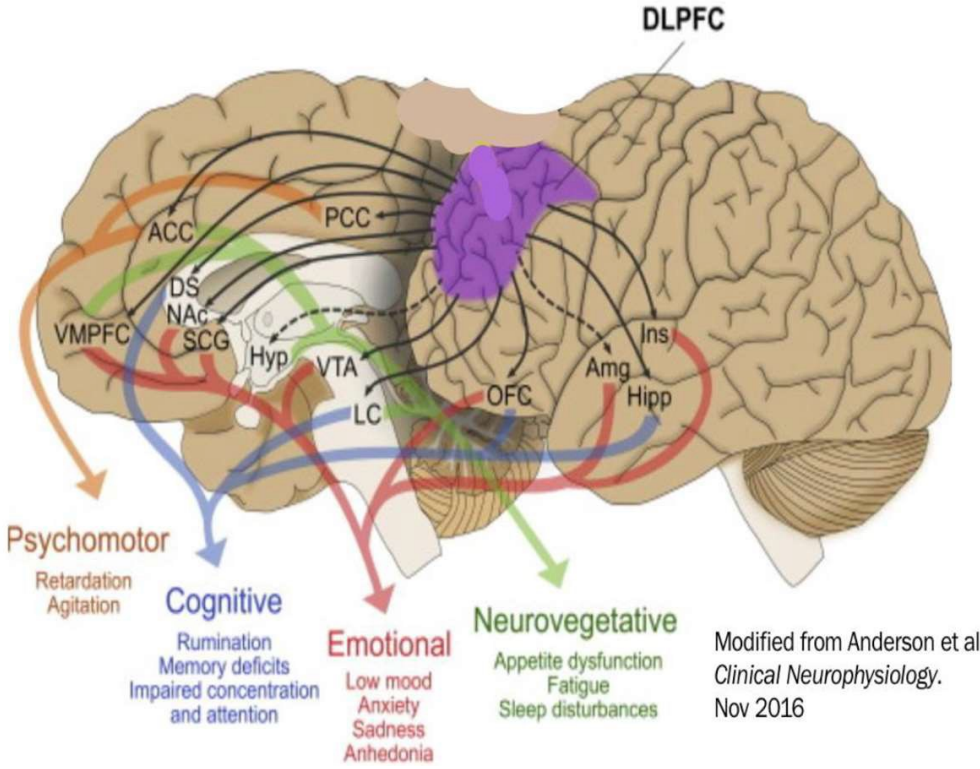


While the shape of the TMS coil and the target areas on the skull have changed somewhat in recent years, the basic approach remains roughly the same. Clinicians apply a painless magnetic pulse to the skull by means of a coil. The flux induces an electric field that modifies neuronal activity. Image credit: Shutterstock/Pepermpron.

rTMS – repetitiv transkraniel magnetisk stimulation

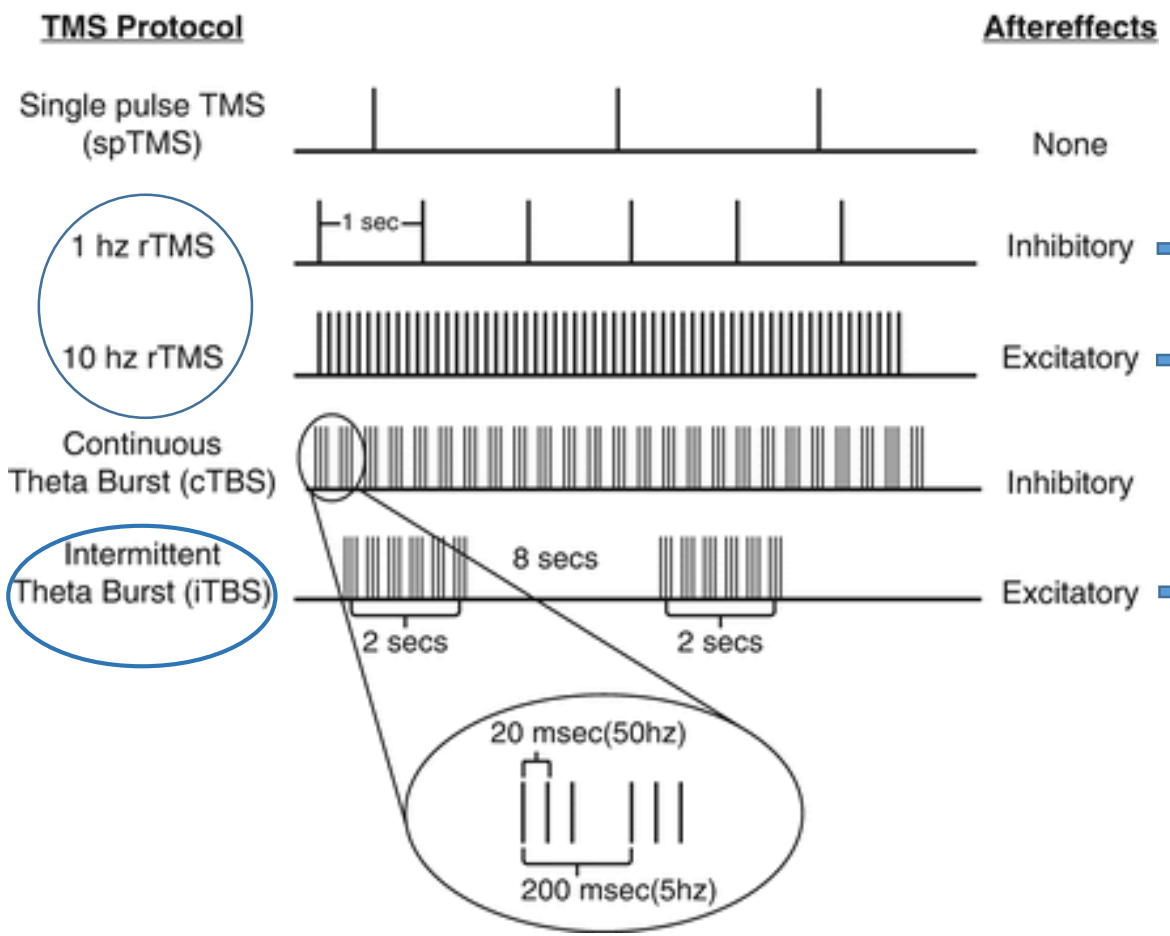
- Det magnetiske felt inducerer svage elektriske strømme, som påvirker signaloverførelsen mellem nervecellerne i hjernebarkens øverste lag og bevirker, via interneurale forbindelser, ændringer i subkortikale områder, som indgår i depressionens sygdomsmekanisme.

- Hvis behandlingen gentages, kan der skabes varige funktionsændringer i de neurale netværk.



Modified from Anderson et al. *Clinical Neurophysiology.* Nov 2016

rTMS-protokoller

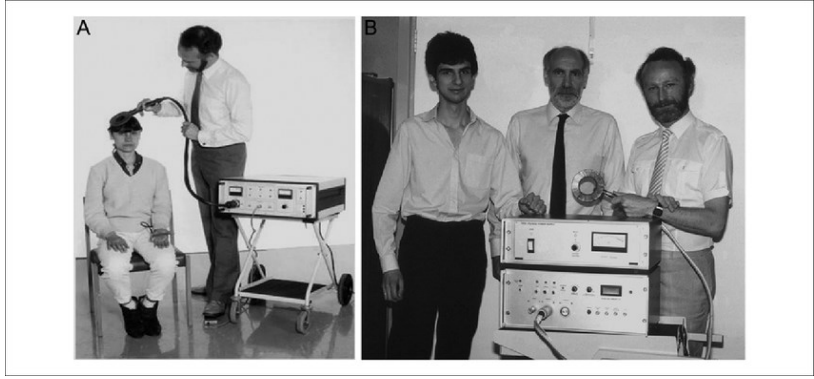


Højre DLPFC: sænker aktivitet i det underliggende hjernevæv (25 min)

Venstre DLPFC: øger aktivitet i det underliggende hjernevæv (19 min)

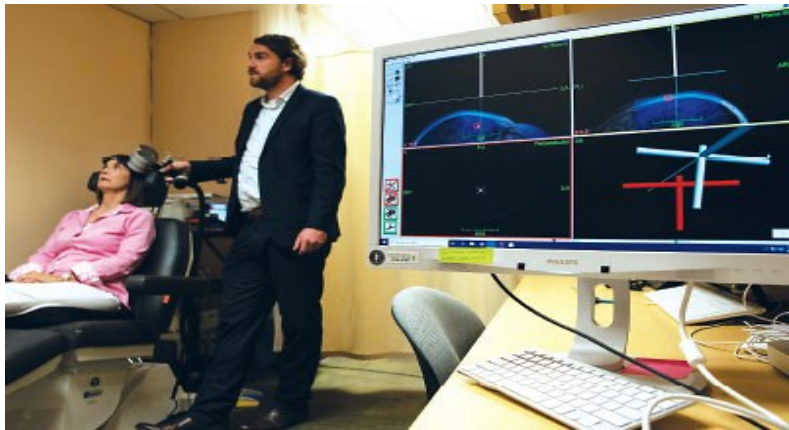
Venstre DLPFC: øger aktivitet i det underliggende hjernevæv (3 min)

Historie…



- **1985-** første TMS udstyr – Anthony Barker, Sheffield Universitet
- **1990- ….:** forskning, optimering af teknologien og protokoller

- **2008 –** rTMS FDA-godkendt - TRD
- **2018 –** iTBS FDA-godkendt - TRD



- **2018 –** rTMS FDA-godkendt – TR-OCD
- **2022 –**SAINT Neuromodulation System FDA-godkendt - TRD

rTMS – Evidensbaseret behandling

- **2007:** Første multicentriske dobbeltblindet randomiseret design (RCT) (O´Reardon et al., 2007)

large multi-center trial led to initial FDA approval in USA

301 patients (active 155; sham 146)

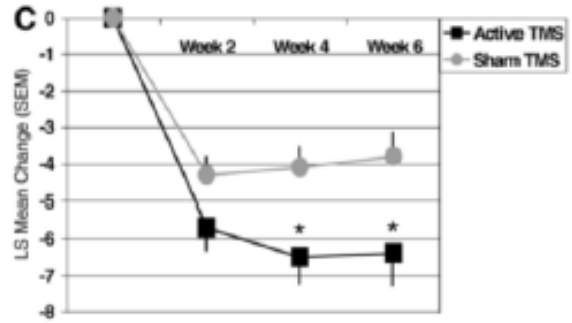
treatment-resistant (1.6 failed attempts)

medication-free

adequate sham control

→ mimicking both auditory and somato-sensory side effects of TMS

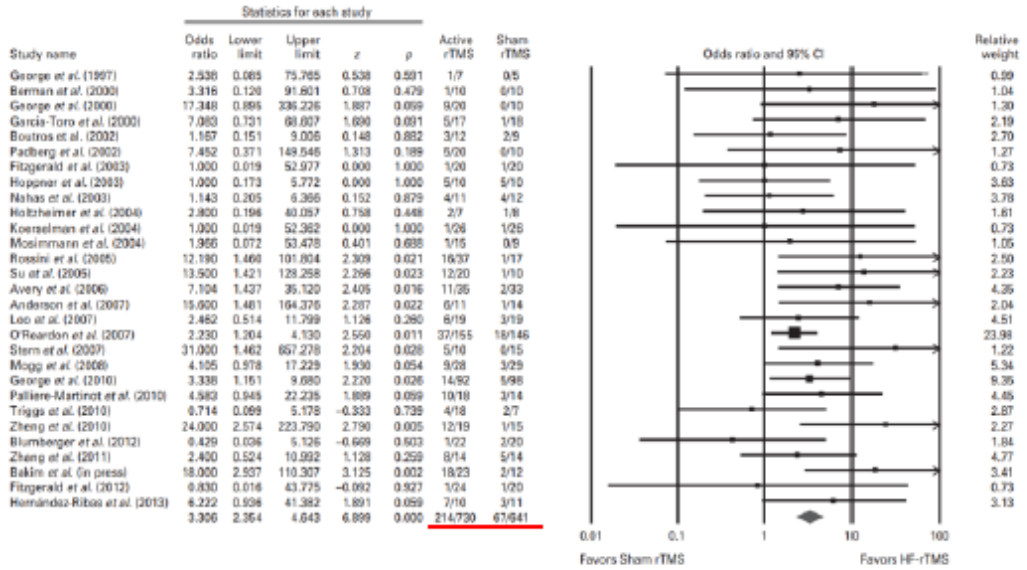
→ successful blinding



reduction of depression score

O'Reardon et al. (2007). Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression. Biological Psychiatry

Response rate



Study name	Odds ratio	Lower limit	Upper limit	z	p	Active rTMS	Sham rTMS	Relative weight
George et al. (1997)	2.538	0.085	75.765	0.538	0.591	1/7	0/5	0.99
Berman et al. (2000)	3.316	0.120	91.601	0.708	0.479	1/10	0/10	1.04
George et al. (2000)	17.348	0.895	336.226	1.887	0.059	9/20	0/10	1.30
Garcia-Toro et al. (2000)	7.083	0.731	68.607	1.690	0.091	5/17	1/18	2.19
Boutros et al. (2002)	1.167	0.151	9.006	0.148	0.882	3/12	2/9	2.70
Padberg et al. (2002)	7.452	0.371	149.646	1.313	0.189	5/20	0/10	1.27
Fitzgerald et al. (2003)	1.000	0.019	52.977	0.000	1.000	1/20	1/20	0.73
Hoppner et al. (2003)	1.000	0.173	5.772	0.000	1.000	5/10	5/10	3.63
Nahas et al. (2003)	1.143	0.205	6.366	0.152	0.879	4/11	4/12	3.78
Holtzheimer et al. (2004)	2.800	0.196	40.057	0.758	0.448	2/7	1/8	1.61
Koerselman et al. (2004)	1.000	0.019	52.362	0.000	1.000	1/26	1/26	0.73
Mosimmann et al. (2004)	1.966	0.072	53.478	0.401	0.688	1/15	0/9	1.05
Rossini et al. (2005)	12.190	1.466	101.804	2.309	0.021	16/37	1/17	2.50
Su et al. (2005)	13.500	1.421	128.258	2.266	0.023	12/20	1/10	2.23
Avery et al. (2006)	7.104	1.437	35.120	2.405	0.016	11/35	2/33	4.35
Anderson et al. (2007)	15.000	1.481	164.376	2.287	0.022	6/11	1/14	2.04
Loo et al. (2007)	2.462	0.514	11.799	1.126	0.260	6/19	3/19	4.51
O'Reardon et al. (2007)	2.230	1.204	4.130	2.550	0.011	37/155	16/146	23.98
Stern et al. (2007)	31.000	1.462	657.278	2.204	0.028	5/10	0/15	1.22
Mogg et al. (2008)	4.105	0.978	17.229	1.930	0.054	9/28	3/29	5.34
George et al. (2010)	3.338	1.151	9.680	2.220	0.026	14/92	5/98	9.35
Palliere-Martinot et al. (2010)	4.583	0.945	22.235	1.889	0.059	10/18	3/14	4.45
Trigg et al. (2010)	0.714	0.099	5.178	-0.333	0.739	4/18	2/7	2.87
Zheng et al. (2010)	24.000	2.574	223.790	2.790	0.005	12/19	1/15	2.27
Blumberger et al. (2012)	0.429	0.036	5.126	-0.669	0.503	1/22	2/20	1.84
Zheng et al. (2011)	2.400	0.524	10.992	1.128	0.259	8/14	5/14	4.77
Baklim et al. (in press)	18.000	2.537	110.307	3.125	0.002	18/23	2/12	3.41
Fitzgerald et al. (2012)	0.830	0.016	43.775	-0.092	0.927	1/24	1/20	0.73
Hernández-Ribas et al. (2013)	6.222	0.936	41.382	1.891	0.059	7/10	3/11	3.13
	3.306	2.354	4.643	6.899	0.000	214/730	67/641	

Statistics for each study

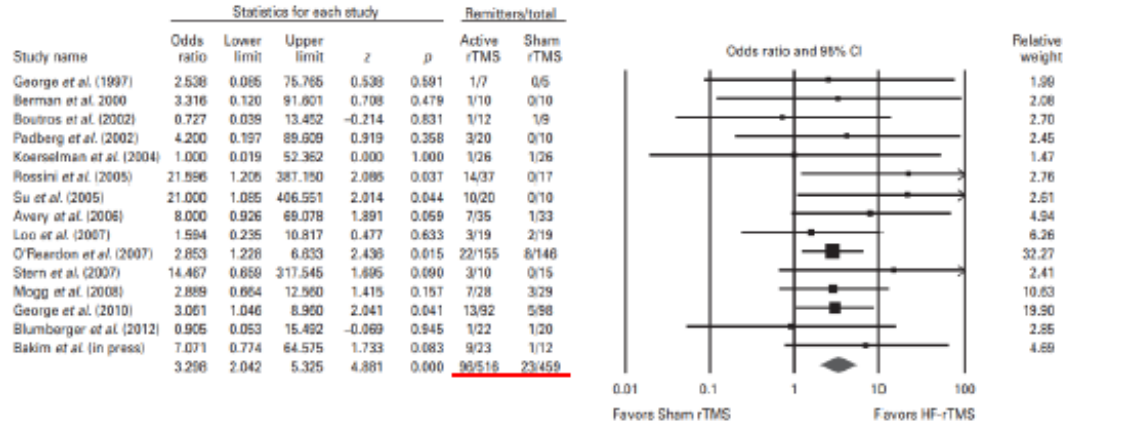
Odds ratio and 95% CI

0.01 0.1 1 10 100

Favors Sham rTMS Favors HF-rTMS

Berlim et al. (2014)

Remission rate



Study name	Odds ratio	Lower limit	Upper limit	z	p	Remitters/total Active rTMS	Remitters/total Sham rTMS	Relative weight
George et al. (1997)	2.538	0.085	75.765	0.538	0.591	1/7	0/5	1.99
Berman et al. 2000	3.316	0.120	91.601	0.708	0.479	1/10	0/10	2.08
Boutros et al. (2002)	0.727	0.039	13.452	-0.214	0.831	1/12	1/9	2.70
Padberg et al. (2002)	4.200	0.197	89.609	0.919	0.358	3/20	0/10	2.45
Koerselman et al. (2004)	1.000	0.019	52.362	0.000	1.000	1/26	1/26	1.47
Rossini et al. (2005)	21.596	1.205	387.150	2.085	0.037	14/37	0/17	2.76
Su et al. (2005)	21.000	1.085	406.551	2.014	0.044	10/20	0/10	2.61
Avery et al. (2006)	8.000	0.926	69.078	1.891	0.059	7/35	1/33	4.94
Loo et al. (2007)	1.594	0.235	10.817	0.477	0.633	3/19	2/19	6.26
O'Reardon et al. (2007)	2.853	1.226	6.633	2.436	0.015	22/155	8/146	32.27
Stern et al. (2007)	14.467	0.859	317.545	1.695	0.090	3/10	0/15	2.41
Mogg et al. (2008)	2.889	0.664	12.560	1.415	0.157	7/28	3/29	10.63
George et al. (2010)	3.061	1.046	8.960	2.041	0.041	13/92	5/98	19.90
Blumberger et al. (2012)	0.905	0.053	15.492	-0.069	0.945	1/22	1/20	2.85
Baklim et al. (in press)	7.071	0.774	64.575	1.733	0.083	9/23	1/12	4.69
	3.298	2.042	5.325	4.881	0.000	96/516	23/459	

Odds ratio and 95% CI

0.01 0.1 1 10 100

Favors Sham rTMS Favors HF-rTMS

Berlim et al. (2014)

RCT-undersøgelser samt meta-analyser - understøtter effekten af TMS på vanskeligt behandlelig depression (Gaynes et al., 2014, Mutz et al., 2018, Blumberger et al., 2018, Sehatzadeh et al., 2019)

Real-world outcomes

Conolly et al, 2012: responsrate 50% (100 patienter)

Fitzgerald et al, 2016: responsrate 45% (1100 patienter)

Griffths et al, 2019: responsrate 40% (73 patienter)

Donse et al, 2018: responsrate 66% rTMS+psykoterapi (196 patienter)

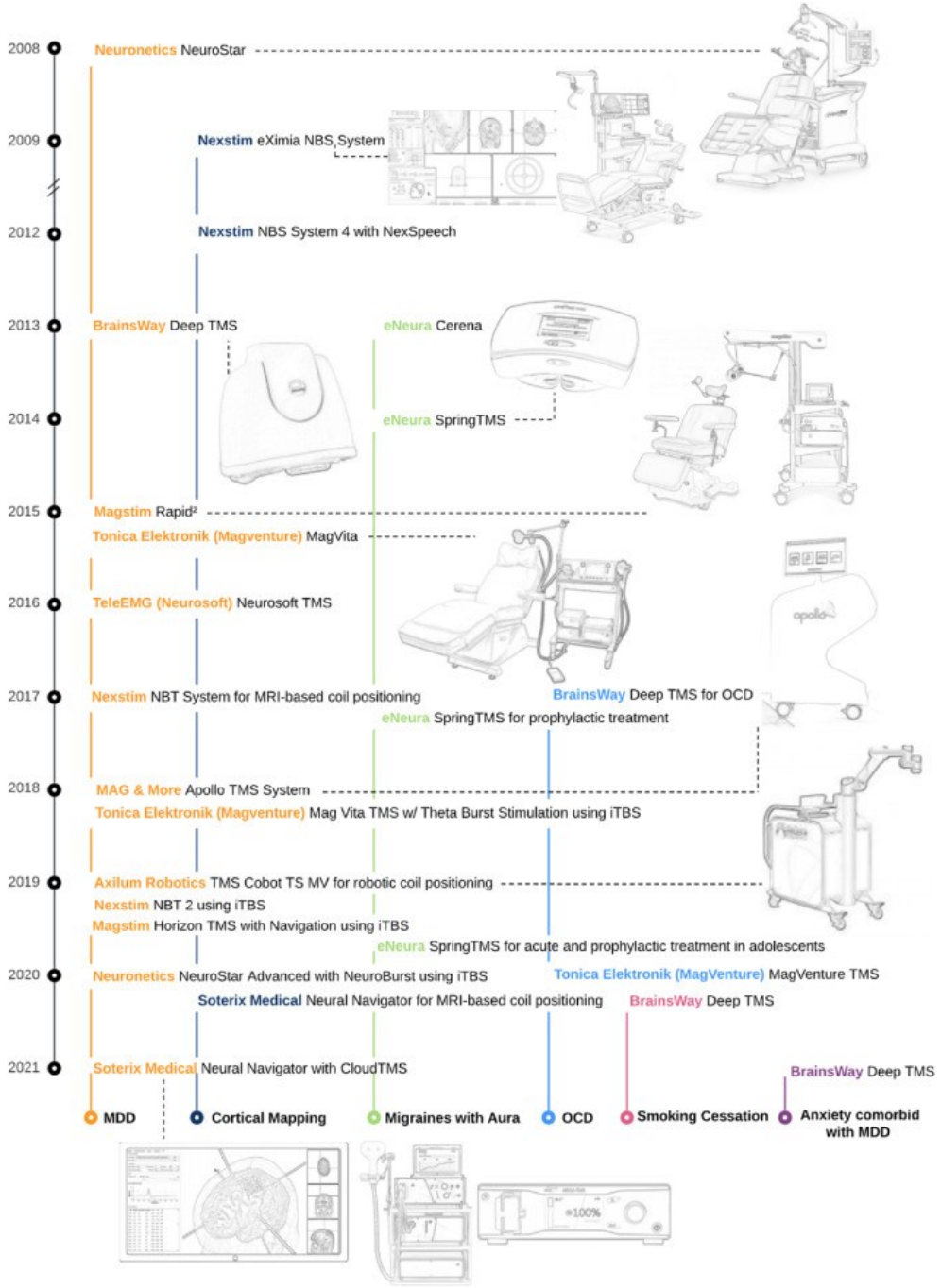
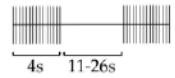
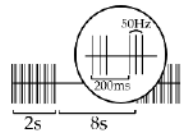
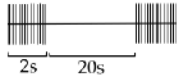
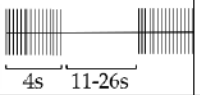
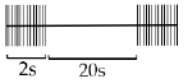
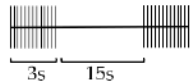


Table 1. Description of FDA-cleared transcranial magnetic stimulation protocols to treat psychiatric disorders.

Disorder	Frequency	Ses. Pulses (Duration)	Schedule (No Ses.)	Target Region	Examples of TMS Manufacturers (Coils)
Major Depressive Episode	10Hz rTMS 	3000 (18′ 48″ to 37′ 30″)	1/d (20–30d)	L-DLPFC	NeuroStar 
				L-DLPFC	Magstim (e.g., HORIZON® Coils) 
				BL-DLPFC (L-DLPFC)	Brainsway (H1 coil) 
				L-DLPFC	Magventure (e.g., B65 coil) 
	Intermittent Theta Burst 	600 (3′ 9″)	1/d (20–30 d)	L-DLPFC	NeuroStar  Magstim  Magventure 
		18000 (9′ 27″)	Accelerated: 10/d (5 d)	L-DLPFC	Magventure (B65 coil) 
With Comorbid Anxiety	20Hz rTMS 	1980 (20′ 12″)	1st: 1/d (20 d) 2nd: 2/w (12 w)	BL-DLPFC (L-DLPFC)	Brainsway (H1 coil) 
	10Hz rTMS 	3000 (18′ 48″)	1st: 1/d (30 d) 2nd: ~2/w (3 w)	L-DLPFC	NeuroStar 
Obsessive Compulsive Disorder	20Hz rTMS 	2000 (18′)	1/day (29 d)	ACC/mPFC	Brainsway (H7 coil) 
				ACC/mPFC	Magventure (DB-80 coil) 
Smoking Cessation	10Hz rTMS 	1800 (17′ 48″)	1st: 1/d (15d) 2nd: 1/w (3 w)	BL-lPFC BL-Insula	Brainsway (H4 coil) 

′—minutes; ″—seconds; ACC—anterior cingulate cortex; BL—bilateral; CE—Conformitè Europëenne; d—day; DLPFC—dorsolateral prefrontal cortex; FDA—Food and Drug Administration; Hz—Hertz; L—left; lPFC—lateral

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)

Jean-Pascal Lefaucheur [a,b,*], André Aleman [c], Chris Baeken [d,e,f], David H. Benninger [g], Jérôme Brunelin [h], Vincenzo Di Lazzaro [i], Saša R. Filipović [j], Christian Grefkes [k,l], Alkomiet Hasan [m], Friedhelm C. Hummel [n,o,p], Satu K. Jääskeläinen [q], Berthold Langguth [r], Letizia Leocani [s], Alain Londero [t], Raffaele Nardone [u,v,w], Jean-Paul Nguyen [x,y], Thomas Nyffeler [z,aa,ab], Albino J. Oliveira-Maia [ac,ad,ae], Antonio Oliviero [af], Frank Padberg [m], Ulrich Palm [m,ag], Walter Paulus [ah], Emmanuel Poulet [h,ai], Angelo Quartarone [aj], Fady Rachid [ak], Irena Rektorová [al,am], Simone Rossi [an], Hanna Sahlsten [ao], Martin Schecklmann [r], David Szekely [ap], Ulf Ziemann [aq]

Table 2. Summary of recommendations of TMS in psychiatric disorders.

Major Depressive Episode	Definite antidepressant effect of HF-TMS of the left DLPFC (Level A)
	Probable antidepressant effect of LF-TMS of the right DLPFC (Level B) and probably no differential antidepressant effect between right LF-TMS and left HF-TMS (Level B)
	Definite antidepressant effect of rTMS of the DLPFC in unipolar depression (Level A), but no recommendation for bipolar depression
	Antidepressant effect of rTMS of the DLPFC is probably additive to the efficacy of antidepressant drugs (Level B) and possibly potentiating (Level C)
PTSD	Possible effect of HF-TMS of the right DLPFC (Level C)
Auditory hallucinations	Possible effect of LF-TMS of the left TPC (Level C)
Negative symptoms of schizophrenia	Probable effect of HF-TMS of the left DLPFC (Level B)
Addiction and craving	Possible effect of HF-rTMS of the left DLPFC on cigarette craving and consumption (Level C)

HF—high-frequency; LF—low-frequency; TMS—transcranial magnetic stimulation; DLPFC—dorsolateral prefrontal cortex; TPC—temporoparietal cortex; PTSD—post-traumatic stress disorder. Level A ("definitely effective or ineffective") required at least two Class I studies or one Class I study and at least two Class II studies; Level B ("probably effective or ineffective") required at least two Class II studies or the combination of one Class I or II study and at least two Class III studies; and Level C ("possibly effective or ineffective") required at least two Class III studies or any combination of two studies of different Classes I, II, or III. Table adapted from Lefaucheur J-P et al. (2020) [40] "Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)." Clinical Neurophysiology 131 (2020) 474–528.

MÅLGRUPPE I REGION MIDT

Voksne patienter med moderat til svær depression, hvor et af følgende kriterier er opfyldt:

- Persisterende depression på trods af behandling med antidepressiv medicin fra minimum to forskellige farmakologiske klasser givet i tilstrækkelig dosering i mindst 4-6 uger
- Persisterende depression, hvor man har afprøvet antidepressiv medicin fra minimum to forskellige farmakologiske klasser, men måtte seponere på grund af uacceptable bivirkninger

OBS

TMS er ikke egnet til behandling af patienter med svær depression med psykotiske symptomer, svær agitation eller akut øget selvmordsrisiko.

Der er ikke tilstrækkelig evidens for effektivitet af TMS i denne patientgruppe

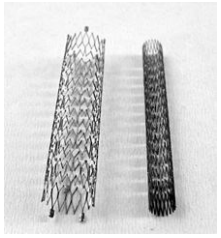
SIKKERHED - Kontraindikationer

• **Implanteret elektronisk/medicinsk udstyr** i hovedet eller inden for 30 cm af behandlingsspolen kan påvirkes af det inducerede magnetiske felt (f.eks. cochlear-implantater eller pacemaker).

• **Ledende ferromagnetiske eller andre magnetfølsomme metaller** implanteret i hovedet eller inden for 30 cm af behandlingsspolen (aneurismeklips, stents, fragmenter fra projektiler, cerebrale shunts, m.m.)

• **Aktuelt misbrug/overforbrug af stoffer eller benzodiazepiner**.

• **Moderate til svære elektrolytforstyrrelser**



SIKKERHED- Risikofaktorer

- Følgende tilstande kan øge risikoen for krampeanfald, og patienten kan derfor ikke henvises til TMS, uden at der først drøftes med TMS-ansvarlig overlæge, og risikovurdering dokumenteres:

    - Epilepsi eller anamnese med krampeanfald.

    - Andre organiske hjernelidelser, f.eks: hjerneinfarkt, hjerneblødning, hjernetumor, intrakraniel hypertension, tidligere svært hovedtraume, tidligere neurokirurgiske intervention.

BIVIRKNINGER

- Som regel milde, og nogle patienter oplever slet ingen bivirkninger.
- Mange års forskning i metoden viser, at behandlingen ikke medfører langsigtede bivirkninger, herunder kognitive bivirkninger

Oftest oplevede bivirkninger:

- **Lokalt ubehag** i forbindelse med behandlingen i form af trækninger i ansigtsmuskulaturen og oplevelsen af stød
- **Hovedpine** efter behandlingen er almindeligt forekommende, især i de første behandlingssessioner, og vil forventelig aftage.
- Svimmelhed
- Træthed

Rossi et al. Clin Neurophysiol, 2021

BIVIRKNINGER

Sjældne bivirkninger:

- **Forbigående hørenedsættelse** kan forekomme meget sjældent, især i de tilfælde, hvor patienter afviser anvendelse af øreppropper under behandling.

- **Synkope-** Vasovagal respons ifm. eksempelvis øget angst, hypoglycemi, hyperventilation og dehydrering.

- **Krampeanfald -** Risikoen er meget lav (1 per 10.000), og krampeanfaldet er som regel af kort varighed og giver ikke yderligere komplikationer.

Rossi et al. Clin Neurophysiol, 2021

rTMS-forløb

- **TMS-serie:** en daglig behandlingssession, på alle hverdage i 6 uger; 30 behandlinger.

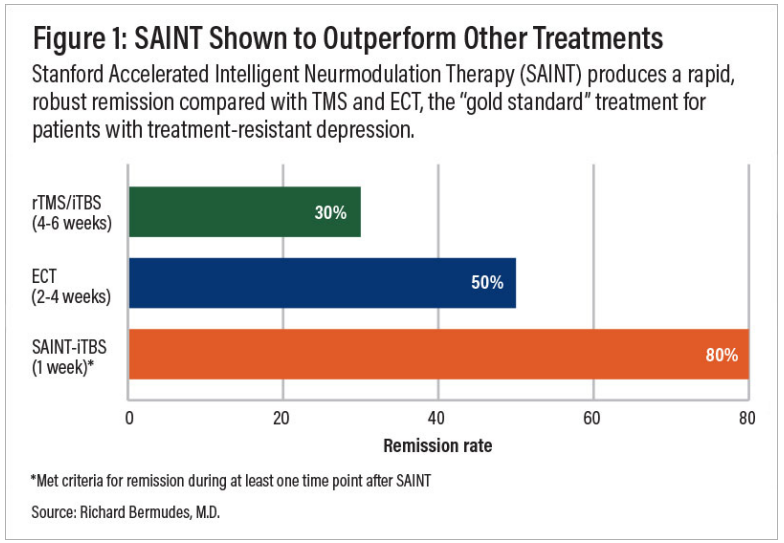
- Remission eller respons: **udtrapningsfase**

- Evt **vedligeholdelses TMS**

Hvor bevæger vi os hen?

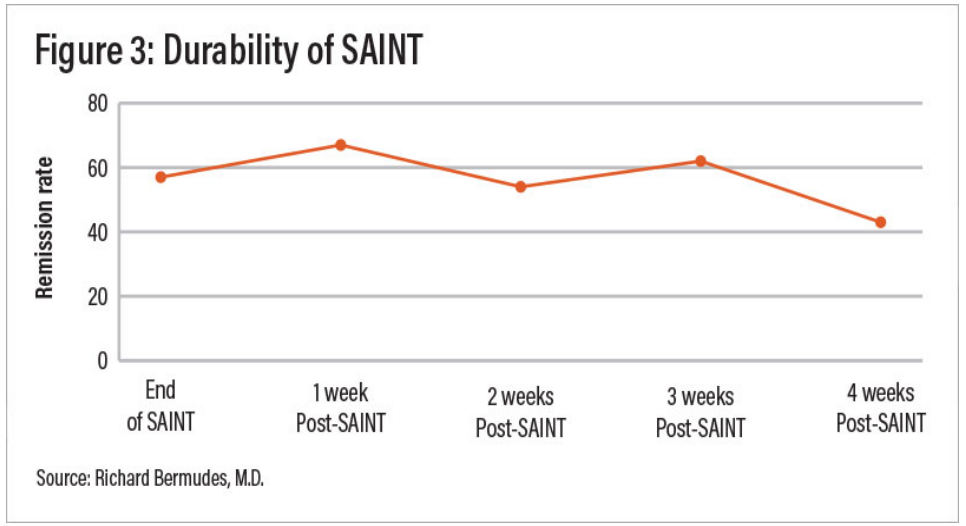
Stanford Neuromodulation Therapy (SNT)

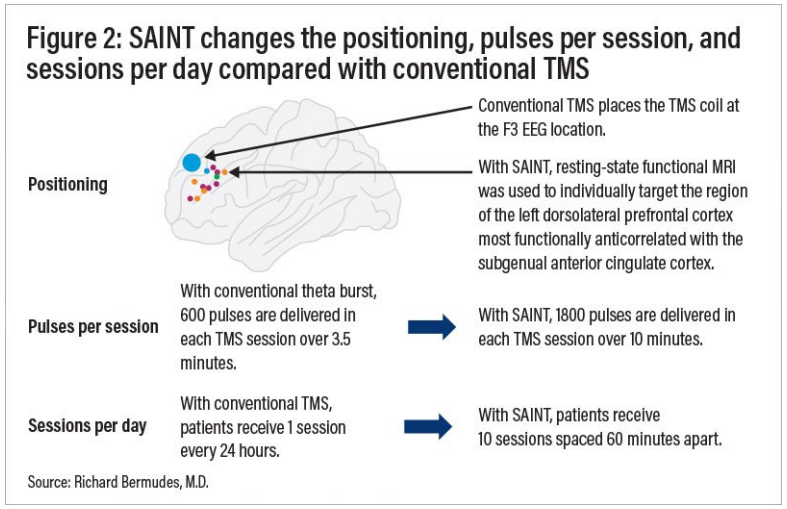
- A Double-Blind Randomized Controled Trial (2021)



- **29 patienter med TRD**
- **10 iTBS behandlinger om dagen i 5 dage**
- **14 iTBS / 15 sham (placebo)**
- **Remission:** 79% iTBS vs 13,3% sham

2022: FDA-godkendelse, men....





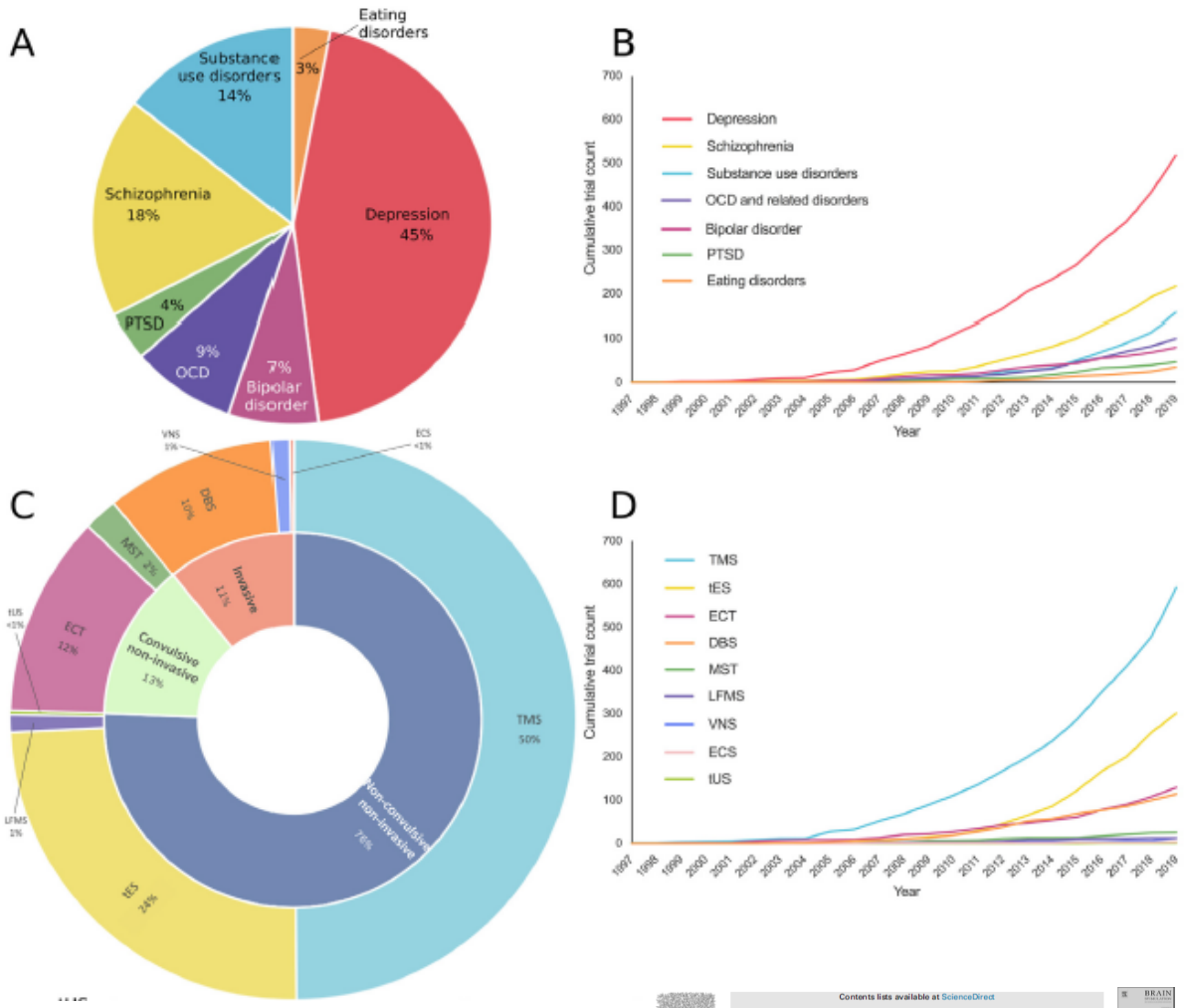
Hvorfor virkede det?

- Placering af spolen – fMRI?
- Antal af impulser? (600 vs 1800)
- Antal af daglige behandlinger? (1 vs 10)

Lovende perspektiver ....

- **Neuromodulation**
  - stigende udvikling internationalt
  - stort forskningspotentiale.

- Mere effektive rTMS protokoller til behandling af depression – accelerated protocols, neuroimaging..
- rTMS til behandlingsrefraktær OCD
- rTMS til behandling af andre psykiske lidelser? (PTSD, negative symptomer ved skizofreni,...)



Contents lists available at ScienceDirect
Brain Stimulation
journal homepage: http://www.journals.elsevier.com/brain-stimulation

Neuromodulatory treatments for psychiatric disease: A comprehensive survey of the clinical trial landscape

Gavin J.B. Elias [a, b, 1], Alexandre Boutet [a, b, c, 1], Roohie Parmar [a], Emily H.Y. Wong [a], Jürgen Germann [a, b], Aaron Loh [a, b], Michelle Paff [a], Aditya Pancholi [a], Dave Gwun [a], Clement T. Chow [a], Flavia Venetucci Gouveia [d], Irene E. Harmsen [a, b], Michelle E. Beyn [a], Emiliano Santarnecchi [e], Alfonso Fasano [b, f, g], Daniel M. Blumberger [h, i], Sidney H. Kennedy [b, i, j], Andres M. Lozano [a, b], Venkat Bhat [a, i, k, *]

TAK!

anamar@rm.dk

This amazing wave of brain stimulation methods continues to swell and grow.

Brain stimulation methods are helping psychiatrists to treat our patients, decrease patients' distress, battle stigma, and discover how the brain works in health and disease.

What a wonderful ride it has been and will continue to be!

Mark George, MD. *From Heretical Idea to Mainstream Psychiatry: Brain Stimulation Has Ridden a Wave*. American Psychiatry Association, October 2021. https://doi.org/10.1176/appi.pn.2021.11.26