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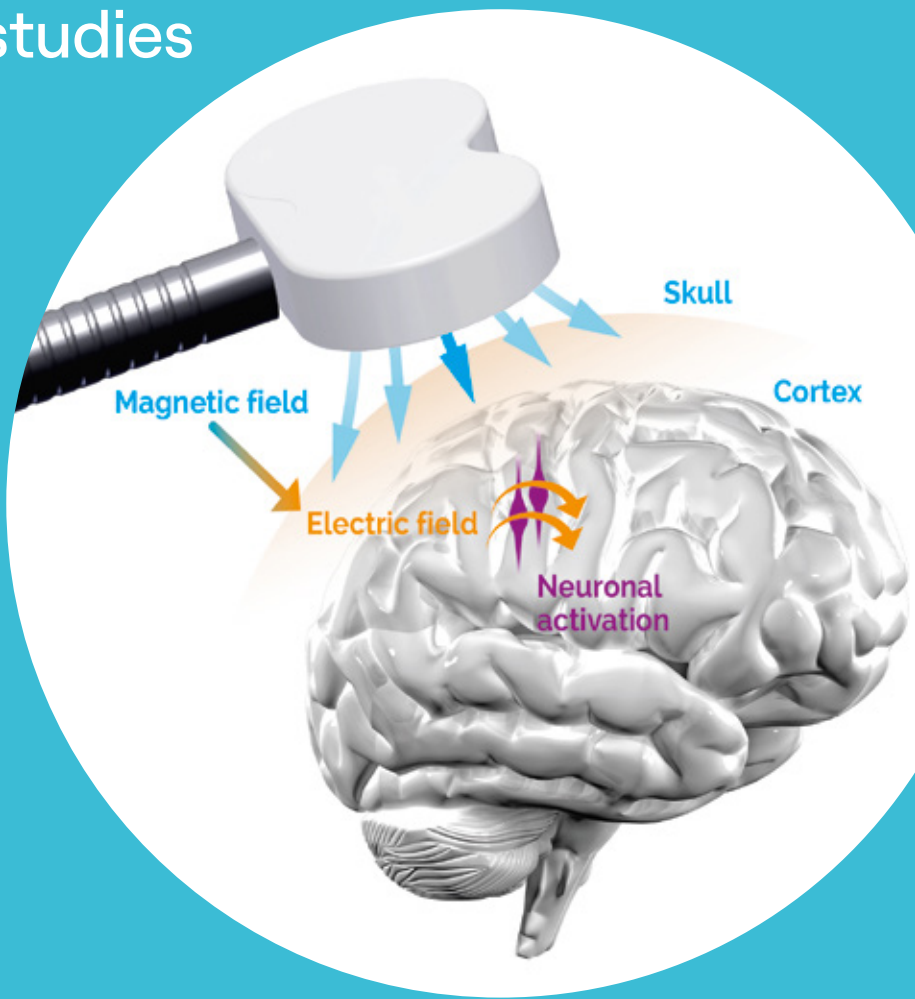
Transcranial Magnetic Stimulation TMS

Effectiveness in studies



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Content

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TMS: Overview – evidence-based guidelines

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

Authors

Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipovic SR, Grefkes C, Hasan A, Hummel FC, Jääskeläinen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen JP, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorová I, Rossi S, Sahlsten H, Schecklmann M, Szekely D, Ziemann U

Source

Clinical Neurophysiology, 131 (2020), pp 474–528

Objective

overview of the latest research results on the therapeutic use of rTMS and evaluation of the scientific evidence.

Methodology

classification of studies in terms of criteria randomized/controlled, number of patients, clear statements on procedure, primary outcome, exclusion criteria, statistical analysis, patient groups. Summary of outcomes

Results

Level A	depression (high-frequency rTMS) • neuropathic pain • post-stroke contralateral hand motor recovery in post-acute stage
Level B	depression (low-frequency rTMS, bilateral rTMS • post-traumatic stress disorder • fibromyalgia • Parkinson's disease: depressive symptoms • Parkinson's disease: motor symptoms • post-stroke ipsilateral hand motor recovery in post-acute stage • post-stroke nonfluent aphasia in chronic stage • lower limb spasticity in multiple sclerosis
Level C	obsessive compulsive disorder • addiction/craving • schizophrenia: auditory hallucinations & negative symptoms • tinnitus • hemispatial neglect in post-acute stage after stroke • pilepsy • Alzheimer's disease: cognitive function • complex regional pain syndrome - type I

Conclusions

A review of hundreds of scientific studies has shown that rTMS can provide significant improvement in various neurological and psychiatric disorders. rTMS is scientifically proven to be definitely effective in the treatment of neuropathic pain and depression as well as in the hand motor recovery from stroke. Furthermore, scientific studies show that rTMS is probably effective for patients with motor impairment, Parkinson's disease, multiple sclerosis, post-traumatic stress disorder or aphasia.

Depression

Simultaneous rTMS and psychotherapy in major depressive disorder: Clinical outcomes and predictors from a large naturalistic study.

Authors

Donse L, Padberg F, Sack AT, Rush AJ, Arns M

Source

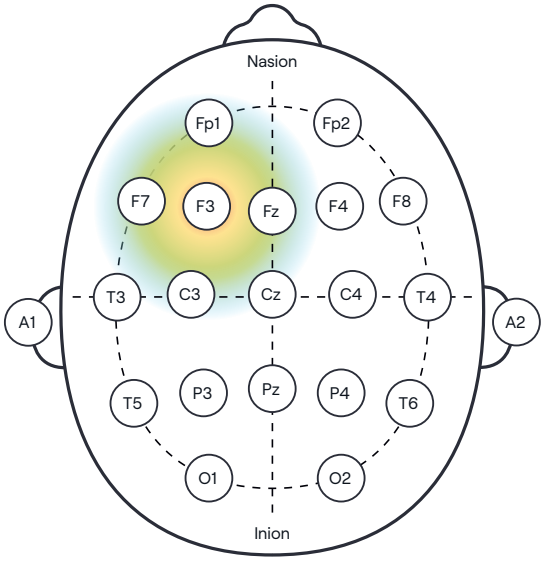
Brain Stimulation 11 (2018) 337-345

Objective

evaluation of feasibility and clinical outcome of rTMS in combination with psychotherapy in major depressive disorder. Identification of clinical predictors of response and remission

Methodology

naturalistic study including 196 patients with depression, rTMS treatment with simultaneous psychotherapy. 97% had been unsuccessfully treated with medication at least once before.



Protocol

target area	left DLPFC / right DLPFC
stim. frequency	10 Hz / 1 Hz
stim. intensity	110 - 120 % RMT
number of pulses per session	1,500 / 1,200
treatment	2 - 10 times per week
scope	21 treatments on average
assessment	BDI, DASS, Reaktion defined as ≥ 50 % reduction in BDI score

Results

assessment	
response rate	**66,3 %**
remission	**56,0 %**
BDI	baseline 31.3 / Last session 14.1 / 55.9 % reduction, $p < 0.001$
DASS D **DASS A** **DASS S**	baseline 28.6 / last session 12.1 baseline 13.7 / last session 5.6 baseline 22.4 / last session 10.1
follow-up 6 months	group of responders
BDI **DASS depression** **DASS anxiety** **DASS stress**	baseline 29.4 / last session 8.0 / follow-up 13.8 baseline 27.0 / last session 6.5 / follow-up 11.8 baseline 14.1 / last session 4.0 / follow-up 7.2 baseline 22.3 / last session 7.3 / follow-up 12.5

Conclusions

The combined therapy rTMS + psychotherapy led to high response and remission rates. In addition, the effect also showed good stability in the follow-up. Considering the high proportion of treatment resistance against antidepressants in the sample, the result is of clinical relevance.

Depression

Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial.

Authors

O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, Demitrack MA, George MS, Sackheim HA

Source

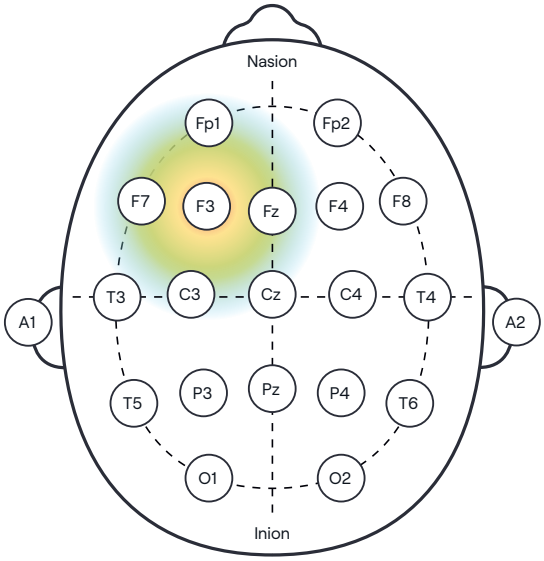
Brain Stimulation 11 (2018) 337-345

Objective

effectiveness and safety of TMS over left DLPFC in the acute treatment of major depression

Methodology

double-blind, placebo-controlled study with 301 patients with depression (155 active rTMS, 146 placebo stimulation). Patients were medication-free and had shown medication resistance prior to rTMS treatment.



Protocol

target area	left DLPFC using 5 cm rule
stim. frequency	10 Hz
stim. intensity	120 % RMT
number of pulses per session	3,000
treatment	every day, 5 times per week
scope	max. 30 treatments
assessment	MADRS, HAMD17, HAMD24

Results

assessment	significance active vs. placebo	active stimulation	placebo stimulation
MADRS response rate*	**P < 0.01**	23.9 %	12.3 %
HAMD24 response rate	**P < 0.05**	23.9 %	15.1 %
MADRS remission rate**	**P < 0.05**	14.2 %	5.5 %
HAMD24 remission rate***	**P < 0.05**	17.4 %	8.2 %
adverse events			
scalp discomfort/ pain reported as mild to moderate		35.8 %; diminished after first 5 sessions	3.8 %
increase in suicidality		**1 event**	**10 events**

* 50 % improvement from baselinee. ** total score < 10 *** total score < 8 **** total score < 11

Conclusions

TMS administered over the left DLPFC using the parameters reported here for a period of up to 6 weeks was effective in treating major depression with a good tolerability profile. These results indicate that rTMS offers clinicians a novel alternative in the treatment of this disorder.

Depression

Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized placebo-controlled study.

Authors

Li CT, Chen MH, Juan CH, Huang HH, Chen LF, Hsieh JC, Tu PC, Bai YM, Tsai SJ, Lee YC, Su TP

Source

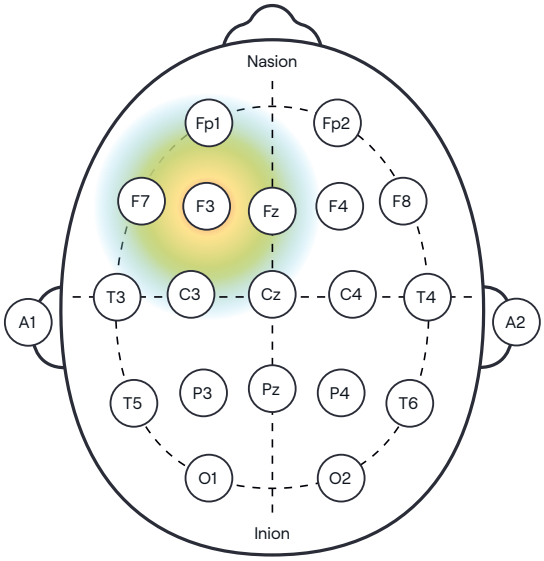
Brain 137 (2014) 2088–2098

Objective

antidepressant effect of right pre-frontal continuous, left-prefrontal intermittent and combined theta-burst stimulation compared to placebo group of patients showing different levels of antidepressant treatment resistance

Methodology

double-blind, placebo-controlled study with 60 patients with treatment-resistant depression (right-sided cTBS, left-sided iTBS, combined cTBS+iTBS, placebo: 15 subjects per group)



Protocol

target area	left/right DLPFC defined as navigated BA9/BA46
stim. frequency	3-pulse 50 Hz bursts applied at frequency of 5 Hz: (1) right-sided cTBS (1 train of 120 s), (2) left-sided iTBS (trains of 2 s with 10 s pause), (3) combination of both
stim. intensity	80 % RMT
number of pulses per session	1,800 pulses per side
treatment	every day, 5 times per week
scope	10 treatments
assessment	HDRS-17

Results

	right-sided cTBS	left-sided iTBS	combination	placebo stimulation
rate of change of HDRS scores	-22.5 %	-42.3 %	-52.5 %	-17.4 %
responders	25 %	**40 %**	**66.7 %**	13.3 %
patients with moderate treatment resistance				
change in HDRS scores	-9.8	-8.6	-15.0	-4.0
patients with high treatment resistance				
change in HDRS scores	-1.4	-8.4	-10.6	0.1

Conclusions

Active theta-burst stimulation is safe, well-tolerated and effective in the treatment of therapy-resistant depression. The number of sessions needed for reduction in HDRS scores seems to be higher in case of greater treatment resistance. Left-sided iTBS and combined cTBS + iTBS are more effective than cTBS in highly refractory depression.

Obsessive-compulsive disorder (OCD)

Repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorders: Double blind randomized clinical trial.

Authors

Elbeh KA, Elserogy YM, Khalifa HE, Ahmed MA, Hafez MH, Khedr EM

Source

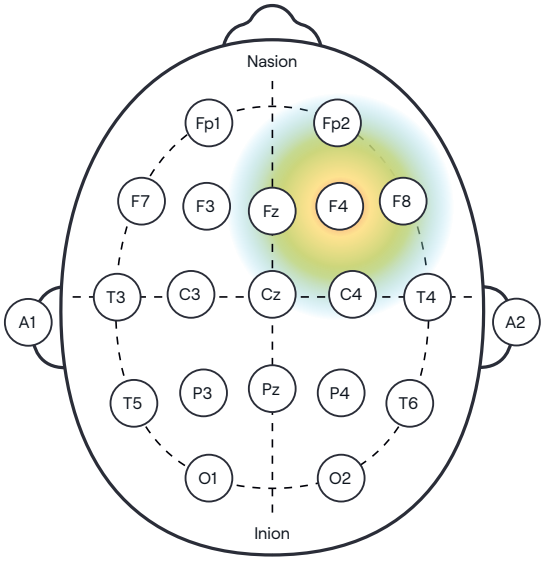
Psychiatry Res 238 (2016) 264–269

Objective

effectiveness of 1 Hz and 10 Hz rTMS compared to placebo in patients with OCD

Methodology

double-blind, placebo-controlled study with 45 patients (1 Hz, 10 Hz, placebo: 15 subjects per group)



Protocol

target area	right DLPFC (5 cm rule)
stim. frequency	1 Hz / 10 Hz
stim. intensity	100 % RMT
number of pulses per session	2,000
treatment	every day, 5 time per week
scope	10 treatments
assessment	Y-BOCS, HAM-A, CGI-S

Results

		1 Hz	10 Hz	placebo stimulation
Y-BOCS	post-treatment	**-12.0***	-6.8*	-1.4***
	3 month follow-up	**-11.0***	-2.5***	-2.1***
HAM-A	post-treatment	-12.3*	-7.3*	-1.6***
	3 month follow-up	-11.9*	-3.6***	-3.0***
CGI-S	post-treatment	-2.2*	-1.1**	-0.4***
	3 month follow-up	-2.0*	-0.5***	-0.5***

* $p<0.01$ ** $p<0.05$ *** $p>0.05$

Conclusions

1 Hz rTMS over the right DLPFC shows significant reduction of OCD symptoms after 10 sessions. The improvement is evident in obsessions and compulsions as well as in anxiety. The effect was maintained in the follow-up after 3 months. In conclusion, low frequency rTMS over the right DLPFC is a promising tool for the treatment of OCD.

Anxiety

Repetitive transcranial magnetic stimulation of the right dorsal lateral prefrontal cortex in the treatment of generalized anxiety disorder: A randomized, double-blind placebo controlled clinical trial.

Authors
Dilkov D, Hawken ER, Kaludiev E, Milev R

Source

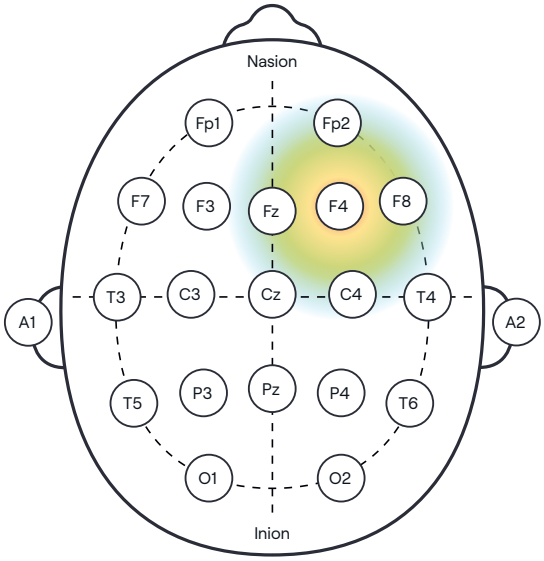
Prog Neuropsychopharmacol Biol
Psychiatry 78 (2017) 61–65

Objective

effectiveness of 20 Hz rTMS compared to placebo in patients with generalized anxiety disorder (GAD)

Methodology

single-blind, placebo-controlled study with 40 patients (15 active rTMS, 25 placebo stimulation)



Protocol

target area	right DLPFC (5 cm rule)
stim. frequency	20 Hz
stim. intensity	110 % RMT
number of pulses per session	3,600
treatment	5 treatments in week 1 - 4 3 treatments in week 5 2 treatments in week 6
scope	25 treatments
assessment	HARS, HDRS-21, CGI

Results

reductions in scores		active stimulation	placebo stimulation	significance
HARS	post-treatment	-25	-1	**p<0.001**
	6 week follow-up	-26	-1	
HDRS-21	post-treatment	-11	0	**p<0.001**
	6 week follow-up	-11	1	
CGI	post-treatment	-2	0	**p<0.001**
	6 week follow-up	-3	0	
responders*	-1.4	**100 %**	8 %	

* HARS score reduction >= 50 %

Conclusions

High-frequency stimulation of the right DLPFC showed clinically significant improvement in anxiety and depression scores in patients with GAD. Follow-up data demonstrate a sustained effect of the response. Considering 50 % of patients do not have a satisfactory response to pharmacotherapies, the treatment successes with rTMS suggest this method is a viable alternative for patients with GAD.

Post-traumatic stress disorder (PTBS)

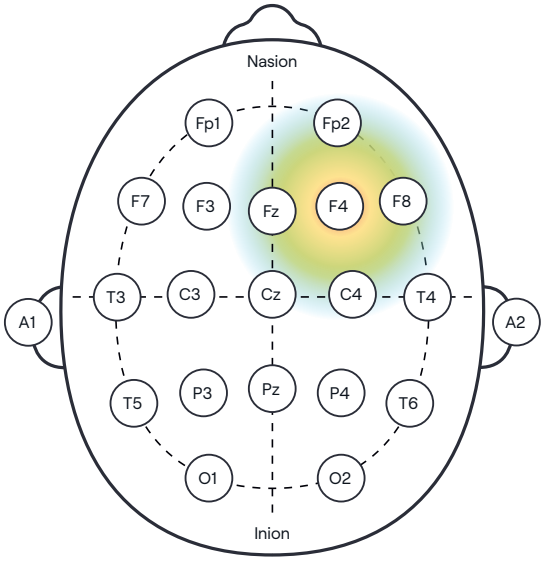
Unilateral right and bilateral dorsolateral prefrontal cortex transcranial magnetic stimulation in treatment post-traumatic stress disorder: A randomized controlled study.

Authors
Ahmadizadeh MJ, Rezaei M

Source
Brain Res Bull 140 (2018) 334–340

Objective
efficacy of bilateral rTMS and unilateral right rTMS compared to placebo in patients with PTSD

Methodology
single-blind, placebo-controlled study with 65 patients (21 unilateral, 22 bilateral, 22 placebo)



Protocol

target area	bilateral / right DLPFC (Beam F3)
stim. frequency	20 Hz
stim. intensity	100 % of RMT
number of pulses per session	2,400
treatment	3 treatments per week for 2 weeks, twice per week for another 2 weeks
scope	10 treatments
assessment	PCL-M

Results

change in PCL-M scores	unilateral	bilateral	placebo stimulation
...after 5 sessions	-2.36	-11.16	-1.8
...after 10 sessions	-21.16	-25.45	-3.62
responders*	**41 %**	**62 %**	

Conclusions

Bilateral and unilateral right high-frequency rTMS leads to significant reductions of PTSD symptoms. The improvement occurs faster with bilateral stimulation. However, there is no significant difference after 10 sessions. The treatment is safe and well tolerated.

Malignant neuropathic pain

Repetitive transcranial magnetic stimulation in neuropathic pain secondary to malignancy: a randomized clinical trial.

Authors

Khedr EM, Kotb HI, Mostafa MG, Mohamad MF, Amr SA, Ahmed MA, Karim AA, Kamal SMM

Source

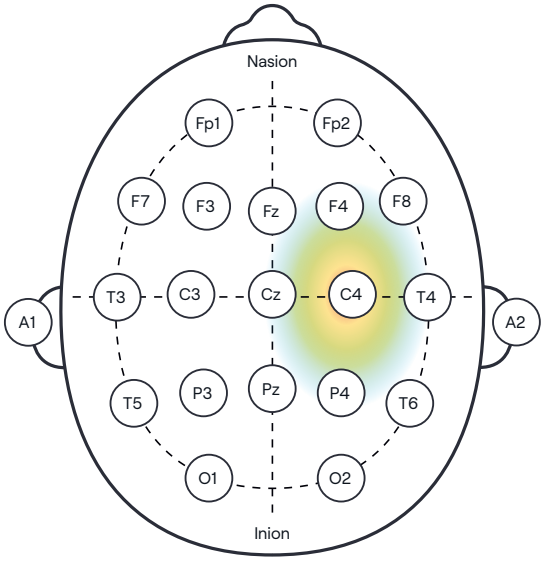
Eur J Pain 19 (2015) 519–527

Objective

efficacy of rTMS over the primary motor cortex (M1) in patients with malignant neuropathic pain

Methodology

randomized, placebo-controlled trial including 34 patients (17 active, 17 placebo) suffering from malignant neuropathic pain



Protocol

target area	hand: M1 contralateral to side of pain
stim. frequency	20 Hz
stim. intensity	80 % RMT
number of pulses per session	2,000
treatment	every day, 5 times per week
scope	10 treatments
assessment	VDS, VAS, LANSS, HAM-D

Results

	active stimulation	placebo stimulation
VDS, VAS	significant difference in pain relief in favor of active rTMS after 10 sessions and 15 days follow-up	
LANSS, HAM-D	significant difference in pain relief in favor of active rTMS after 10 sessions and 15 days and 1 month follow-up	
response rate*:		
after sessions	**86.6 %**	6.6 %
follow-up 15 days	**80 %**	6.6 %
follow-up 1 month	**26.6 %**	6.6 %

* > 30 % pain relief

Conclusions

The results demonstrate that 10 rTMS sessions over the M1 can induce pain relief in malignant neuropathic pain. A high proportion of patients in the active group responded to HF rTMS with lasting effect up to 15 days. In about one quarter of patients the effect remained stable 1 month after treatment.

Chronic neuropathic pain

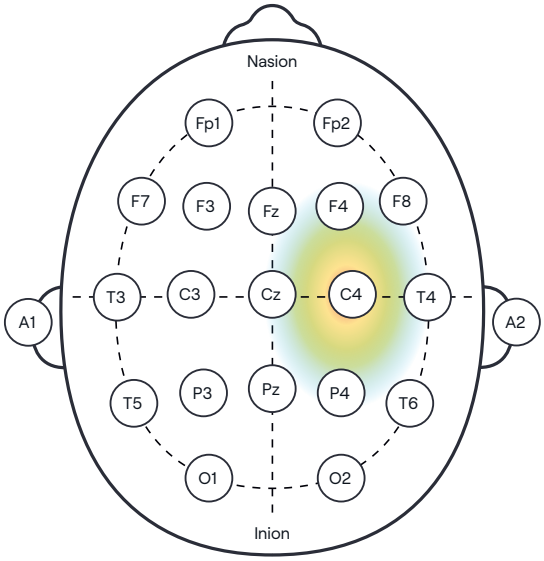
Time course of the response to navigated repetitive transcranial magnetic stimulation at 10 Hz in chronic neuropathic pain

Authors
Lawson McLean A, Frank S, Zafar N, Waschke A, Kalff R, Reichart R

Source
Neurol Res 40 (2018) 564–572

Objective
evaluation of the time to response and effectiveness of navigated rTMS at a frequency of 10 Hz in patients with chronic neuropathic pain

Methodology
prospective study including 48 patients with unilateral chronic neuropathic pain



Protocol

target area	contralateral motor cortex (atypical facial, upper limb and torso pain: hand area; lower limb pain: lower limb area)
stim. frequency	10 Hz
stim. intensity	80 % of RMT
number of pulses per session	1,000
treatment	daily, 4 - 5 times per week
scope	9 treatments
assessment	VAS, German Pain Questionnaire

Results

response rate **responders in 6 weeks follow-up**	**58.3 %** **41.6 %**
VAS **post stimulation** **6 weeks follow-up**	**significant pain reduction in the responder group (p<0.001)**
pain reduction in the responder group:	
atypical facial pain	54.8 %
central post-stroke pain	66.3 %
neuropathic lower limb pain	42.9 %
others	35.5 %
pain relief onset	after 3 - 41 days

Conclusions

Clinical benefit of navigated rTMS in treatment of chronic pain has been demonstrated. In particular, patients with chronic painful post-traumatic trigeminal neuropathy responded well to high-frequency stimulation. Patients with a mean pain history of less than five years benefited significantly from this treatment, so early treatment with repetitive TMS should be encouraged.

Motor disorders – stroke

Daily repetitive transcranial magnetic stimulation for poststroke upper limb paresis in the subacute period.

Authors

Hosomi K, Morris S, Sakamoto T, Taguchi J, Maruo T, Kageyama Y, Kinoshita Y, Goto Y, Shimokawa T, Komaya T, Saitoh Y

Source

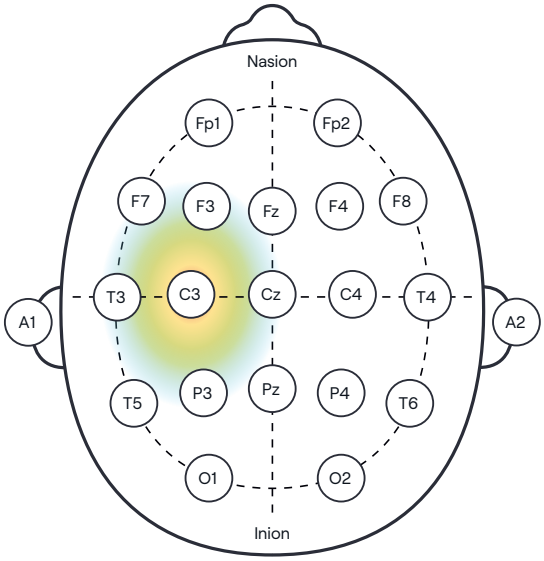
J Stroke Cerebrovasc Dis 25 (2016) 1655–1664

Objective

efficacy and safety of daily rTMS in motor recovery of subacute stroke patients

Methodology

double-blind, placebo-controlled study with 41 patients (20 active, 21 placebo); rTMS accompanied a regular rehab-ilitation program; daily rehabilitation consisted of 8 sessions a 20 min including physical and occupational therapy



Protocol

target area	hand M1 (C3)
stim. frequency	5 Hz
stim. intensity	90 % RMT
number of pulses per session	500
treatment	every day, 5 time per week
scope	10 treatments
assessment	BS, FMA, handgrip strength, NIHSS, FIM

Results

	active stimulation	placebo stimulation
BS	significant improvement in hand score, significant difference between active and placebo for hand score, significant improvement in arm score, improvement in lower limb score	improvement in arm and lower limb score
FMA, NIHSS, FM	significant improvement compared to baseline	
hand grip strength	significant improvement no significant group difference	improvement
adverse events	no serious adverse events	

Conclusions

Daily HF rTMS of the ipsilesional M1 is tolerable and facilitates motor recovery in the paralytic hand of subacute stroke patients. The effectiveness of physical and occupational therapy in the framework of an intense rehabilitation program in the subacute stage after stroke can be increased by accompanying rTMS.

Motor disorders – stroke

Effect of combined low-frequency repetitive transcranial magnetic stimulation and virtual reality training on upper limb function in subacute stroke: a double-blind randomized controlled trial.

Authors

Zheng C, Liao W, Xia W

Source

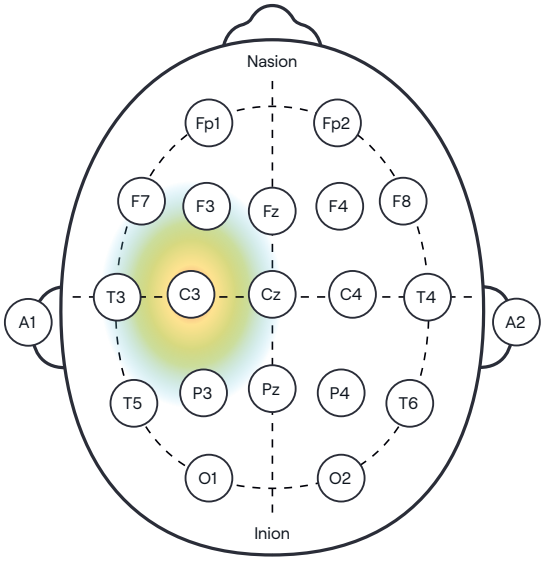
J Huazhong Univ Sci Technolog
Med Sci 35 (2015) 248–254

Objective

effect of combined low-frequency rTMS and virtual reality training in stroke patients

Methodology

double-blind, placebo-controlled trial including 108 patients with hemiplegia after stroke (55 active, 53 placebo) on average 19 days poststroke. The rTMS treatment was combined with a rehabilitation program which included VR training, occupational therapy and physiotherapy



Protocol

target area	hand M1 (C3)
stim. frequency	1 Hz
stim. intensity	90 % RMT
number of pulses per session	1,800
treatment	every day, 6 times per week
scope	24 treatments
assessment	U-FMA, WMFT, MBI, SF-36

Results

	active stimulation			placebo stimulation		
	before treatment	four weeks after treatment	dif.	before treatment	four weeks after treatment	dif.
WMFT scores	32.4	51.8	**25.7**	31.6	44.7	**13.1**
MBI scores	52.6	87.2	**34.6**	53.4	71.6	**18.2**
SF-36 scores (PF)	34.4	65.6	**31.2**	33.6	47.4	**13.8**

Conclusions

LF rTMS combined with intensive rehabilitation programs (physio-therapy, occupational therapy, VR training) can effectively improve the upper limb function, the living activity, and the quality of life in patients with hemiplegia following stroke. The VR training seems to be particularly boosted by LF rTMS finished only a few minutes before starting the VR training.

Aphasia – stroke

The persistent and broadly modulating effect of inhibitory rTMS in nonfluent aphasic patients: a placebo-controlled, double-blind study.

Authors

Tsai PY, Wang CP, Ko JS, Chung YM, Chang YW, Wang JX

Source

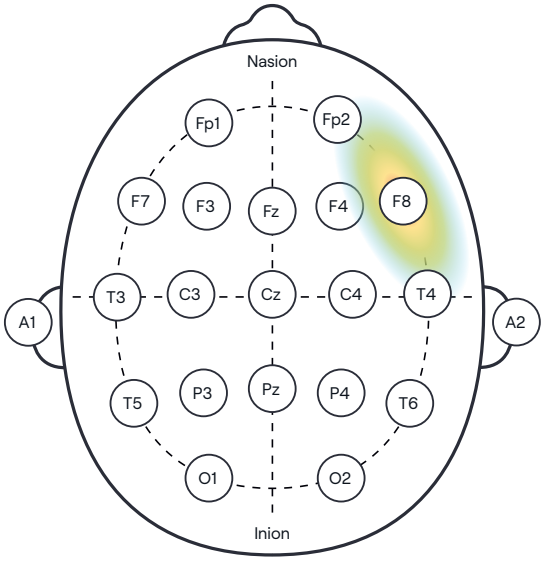
Neurorehabil Neural Repair 28 (2014) 779–787

Objective

effectiveness of rTMS on language performance in stroke patients with nonfluent aphasia; identification of charater-istics of patients predisposed to benefit most

Methodology

randomized, placebo-controlled study with 56 patients with nonfluent aphasia 18 months poststroke on average (33 LF rTMS, 23 placebo) combined with 1 hour of speech therapy



Protocol

target area	contralesional pars triangularis
stim. frequency	1 Hz
stim. intensity	90 % RMT
number of pulses per session	600
treatment	every day, 5 times per week
scope	10 treatments
assessment	CCAT, picture naming test

Results

overall CCAT score after 10 sessions	significant improvement compared to baseline, p<0.001
	significant improvement compared to placebo, p<0.001
subscores of CCAT after 10 sessions	**significant improvement compared to placebo in conversation** in conversion; ip<0.032, description, p<0.024, expression, p<0.002, repetition, p<0.023
overall CCAT score in follow-up 3 month	**significant improvement compared to baseline, p<0.008**
subscores of CCAT in follow-up 3 month	significant improvement compared to baseline in description, p<0.031 expression, p<0.026, repetition, p<0.013
impact on therapeutic outcome	**- outcome independent of severity of non-fluent aphasia** **- outcome independent of time post-stroke** - history of diabetes mellitus: negative impact on improvement, p<0.024 - high contralesional corticomotor excitability: better outcome of inhibitory rTMS, p<0.006

Conclusions

Down-regulating the circuitry of the right pars triangularis (PTr) through inhibitory rTMS, achieves a persistent and broadly modulating effect, irrespective of aphasia severity and subtype. Patients with lower RMT in the right motor system seem to benefit the most.

Multiple Sclerosis

High-frequency repetitive transcranial magnetic stimulation and intermittent thetaburst stimulation for spasticity management in secondary progressive multiple sclerosis.

Authors

Korzhova J, Bakulin I, Sinitsyn D, Poydasheva A, Suponeva N, Zakharova M, Piradov M

Source

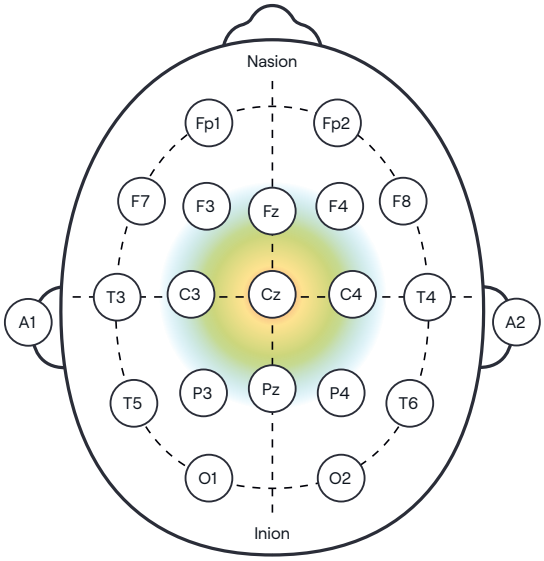
Eur J Neurol 26 (2019) 680-686

Objective

comparison of HF-rTMS (20 Hz) and iTBS on the level of spasticity and concomitant symptoms in patients with secondary progressive multiple sclerosis

Methodology

randomized, placebo controlled study with 34 patients (12 HF-rTMS, 12 iTBS, 10 placebo, each combined with physical therapy)



Protocol

target area	bilateral leg M1
stim. frequency	20 Hz / iTBS*
stim. intensity	80 % MSO**
number of pulses per session	1,600 / 1,200
treatment	every day, 5 times per week
scope	10 treatments
assessment	MAS, NAS, SESS, MFIS

* bursts at 5 Hz containing 3 pulses at 35 Hz

** **maximum stimulant power

Results

	20 Hz	iTBS	placebo stimulation
MAS, SESS, NAS after 10 session	significant reduction of spasticity in MAS, NAS, not significant in SESS	significant reduction of spasticity	no significant reduction of spasticity
NAS, SESS follow-up 2 weeks	significant reduction of spasticity	significant reduction of spasticity	no significant reduction of spasticity
NAS, SESS follow-up 12 week	no significant reduction of spasticity	**significant reduction of spasticity**	no significant reduction of spasticity
pain level (spasticity related)	**significant reduction of pain** at end of sessions and in follow-up 2 weeks, not significant in follow-up 12 weeks	no significant reduction	no significant reduction
fatigue (MFIS)	**significant reduction of fatigue** at end of sessions and in follow-up 2 weeks, gradual increase until follow-up 12 week	no significant reduction	no significant reduction

Conclusions

The results show that HF-rTMS and iTBS significantly reduce spasticity, in contrast to placebo stimulation. Some evidence was found in favor of a longer-lasting effect of iTBS. A reduction in pain and fatigue could be achieved by HF-rTMS but did not result from iTBS.

Abbreviations

BS Brunnstrom stages
CCAT Concise Chinese Aphasia Test
CGI-S Clinical Global Impression-Severity scale
DASS Depressions-Angst-Stress-Skala
DLPFC dorsolateral prefrontal cortex
FIM Functional Independence Measure
FMA Fugl-Meyer Assessment
GAD general anxiety disorder
HAM-A Hamilton Anxiety Rating Scale
HAM-D Hamilton Rating Scale for Depression
HF-rTMS high-frequency rTMS
iTBS intermitting theta-burst stimulation
LANSS Leeds Assessment of Neuropathic Symptoms and Signs
MADR Montgomery–Asberg Depression Rating Scale
MAS Modified Ashworth Scale
MBI Modified Barthel Index
MFIS Modified Fatigue Impact Scale
MSO Maximum Stimulant Output
NAS Numerical Analog Scale
NIHSS National Institutes of Health Stroke Scale
OCD obsessive compulsive disorder
SESS Subjective Evaluating Spasticity Scale
SF-36 Short Form Health Survey Questionnaire
TPC Temporopolar Cortex
U-FMA Fugl-Meyer Assessment for upper limb
VAS Visual Analogue Scale
VDS Verbal Descriptor Scale
WMFT Wolf Motor Function Test
Y-BOCS Yale-Brown obsessive compulsive scale

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