Approccio terapeutico non farmacologico al dolore cronico neuropatico

Stimolazione Cerebrale Non Invasiva - NIBS

Dr med Paolo Rossi

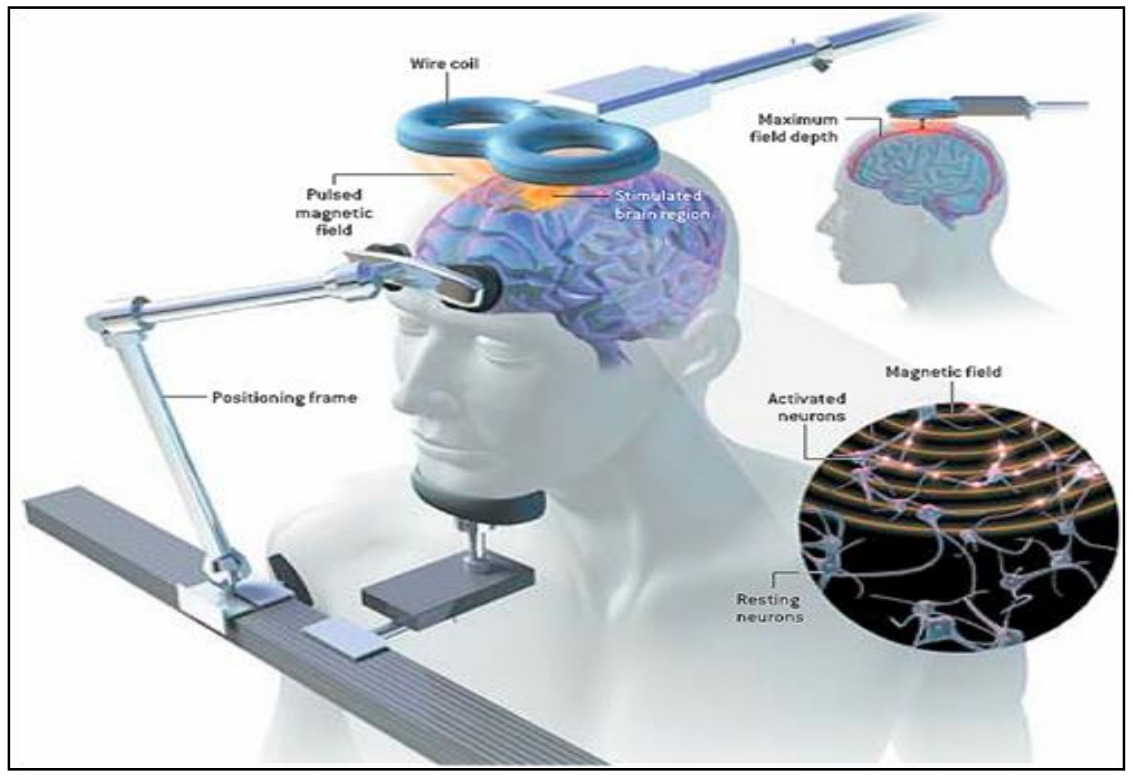
9 maggio 2025

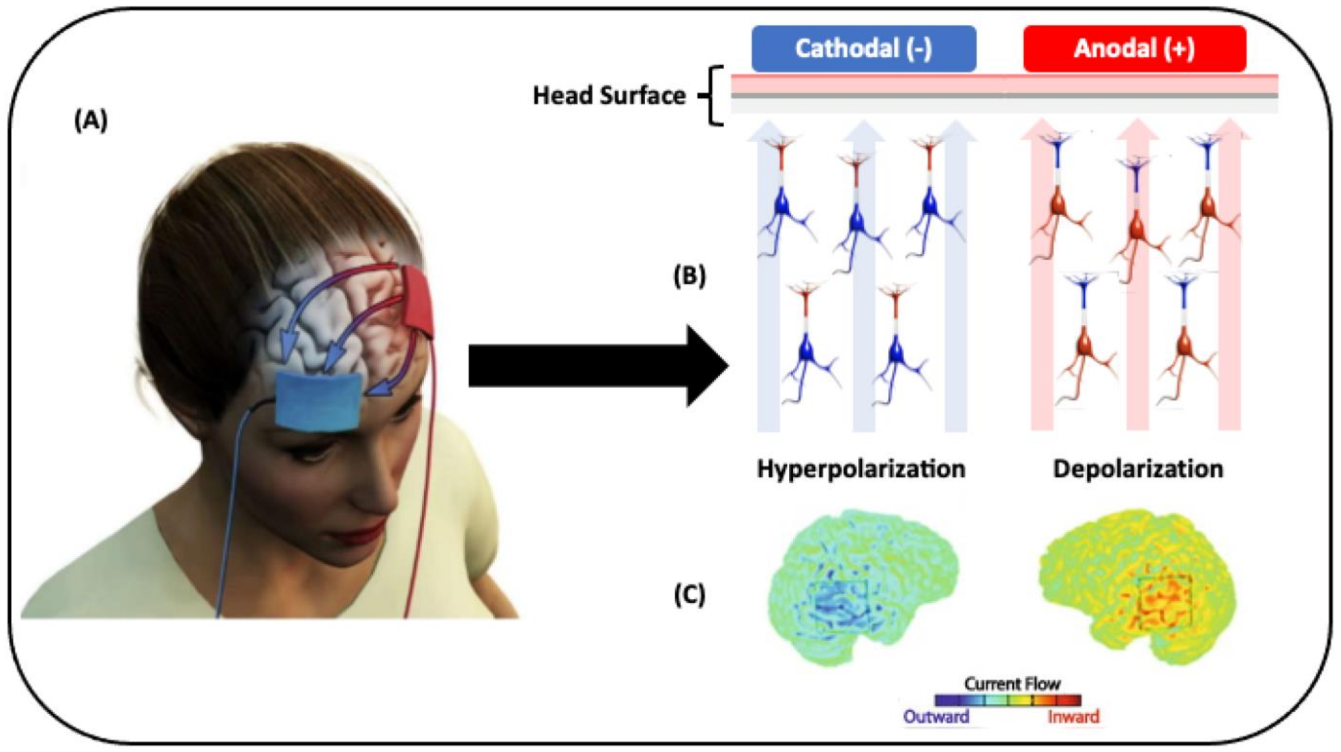
Non Invasive Brain Stimulation

La **NIBS** (*Non-Invasive Brain Stimulation*, ovvero *Stimolazione Cerebrale Non Invasiva*) è un insieme di tecniche utilizzate per modulare l'attività neuronale del cervello senza la necessità di interventi chirurgici o impianti.

TMS (Transcranial Magnetic Stimulation)

utilizza campi magnetici generati da una bobina posizionata sul cuoio capelluto per indurre correnti elettriche nei tessuti cerebrali sottostanti, influenzando l'attività neuronale.


Wire coil
Maximum field depth
Pulsed magnetic field
Stimulated brain region
Positioning frame
Magnetic field
Activated neurons
Resting neurons


Cathodal (-)
Anodal (+)
Head Surface
(A)
(B)
Hyperpolarization
Depolarization
(C)
Current Flow
Outward
Inward

tDCS (Transcranial Direct Current Stimulation)

applica una debole corrente elettrica continua attraverso elettrodi posizionati sullo scalpo per modulare l’eccitabilità corticale (aumentandola o riducendola).

TMS - Stimolazione Magnetica Transcranica

- Single-Pulse TMS – Singolo impulso magnetico
- Paired-Pulse TMS – Coppia di impulsi
- Repetitive TMS (rTMS) – “treni” di impulsi applicati a bassa od alta frequenza

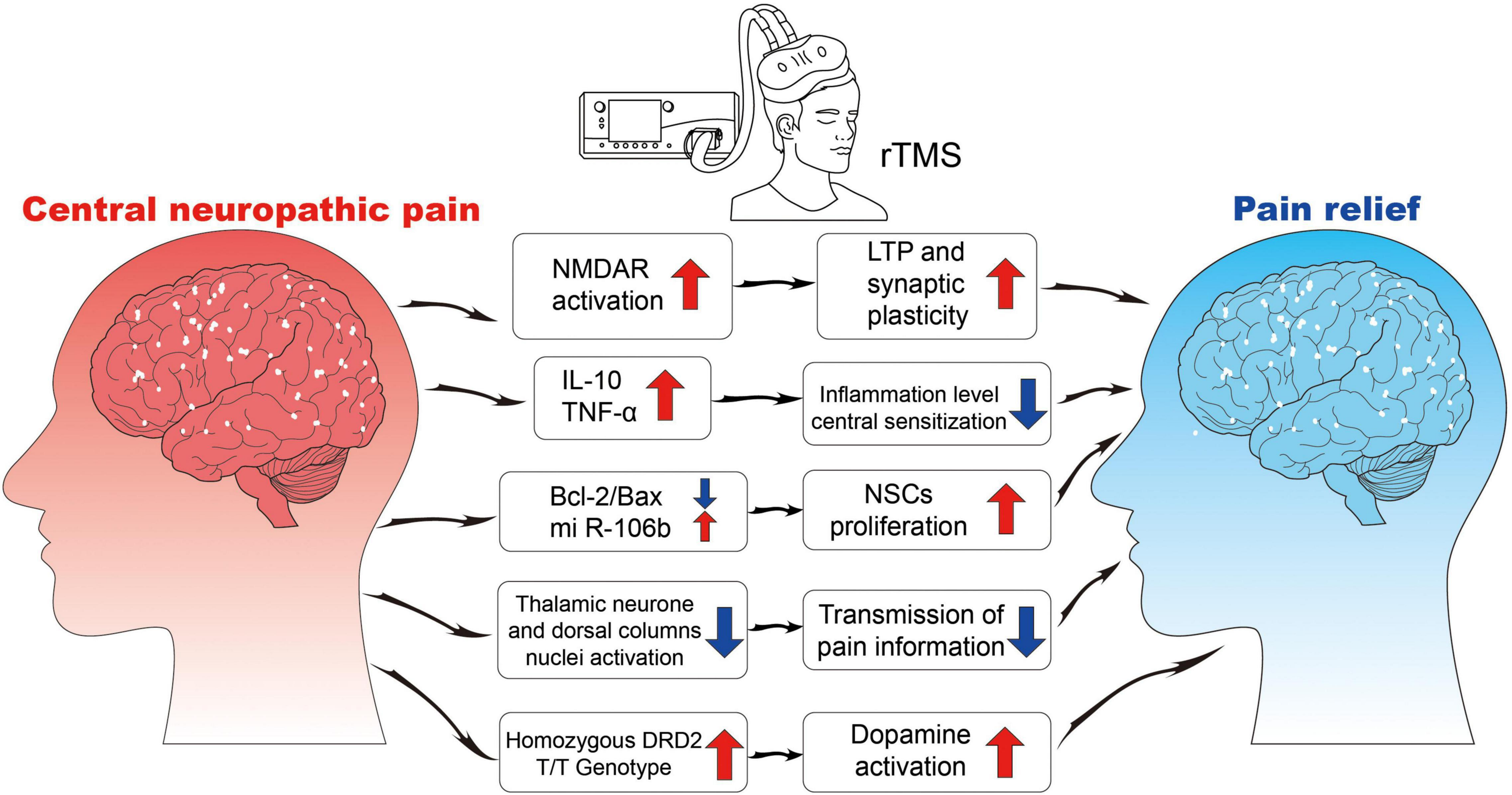
TMS - Stimolazione Magnetica Transcranica

La applicazione di stimoli ripetuti di TMS (rTMS) è in grado di detrminare modificazioni della eccitabilità corticale

≤ 1Hz ⬇ eccitabilità corticale

≥ 5Hz: ⬆ eccitabilità corticale

rTMS - Meccanismo d'azione



rTMS

Central neuropathic pain

Pain relief

NMDAR activation ↑

LTP and synaptic plasticity ↑

IL-10 TNF-α ↑

Inflammation level central sensitization ↓

Bcl-2/Bax ↓ mi R-106b ↑

NSCs proliferation ↑

Thalamic neurone and dorsal columns nuclei activation ↓

Transmission of pain information ↓

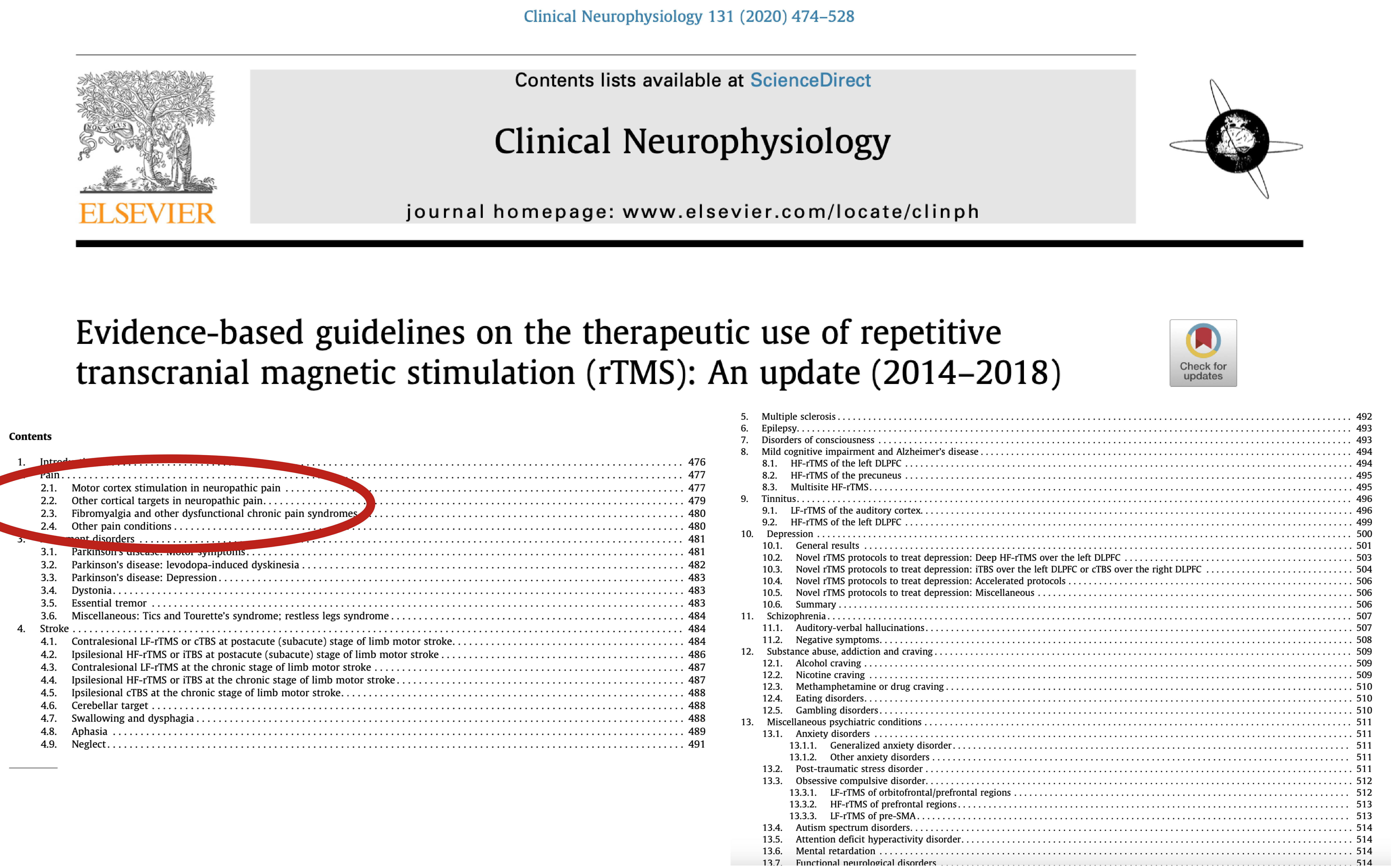
Homozygous DRD2 T/T Genotype ↑

Dopamine activation ↑

rTMS - Protocolli di Stimolazione

- Area motoria M1 controlaterale alla sede del dolore (se bilaterale, emisfero dominante)
- Stimolazione eccitatoria - frequenza 10-20Hz
- Sessioni quotidiane per 5-10 giorni consecutivi

- Responder: pain relief >30%



Clinical Neurophysiology 131 (2020) 474–528

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)

Contents

1. Introduction . . . 476
2. Pain . . . 477
    - 2.1. Motor cortex stimulation in neuropathic pain . . . 477
    - 2.2. Other cortical targets in neuropathic pain . . . 479
    - 2.3. Fibromyalgia and other dysfunctional chronic pain syndromes . . . 480
    - 2.4. Other pain conditions . . . 480
3. Movement disorders . . . 481
    - 3.1. Parkinson's disease: Motor symptoms . . . 481
    - 3.2. Parkinson's disease: levodopa-induced dyskinesia . . . 482
    - 3.3. Parkinson's disease: Depression . . . 483
    - 3.4. Dystonia . . . 483
    - 3.5. Essential tremor . . . 483
    - 3.6. Miscellaneous: Tics and Tourette's syndrome; restless legs syndrome . . . 484
4. Stroke . . . 484
    - 4.1. Contralesional LF-rTMS or cTBS at postacute (subacute) stage of limb motor stroke . . . 484
    - 4.2. Ipsilesional HF-rTMS or iTBS at postacute (subacute) stage of limb motor stroke . . . 486
    - 4.3. Contralesional LF-rTMS at the chronic stage of limb motor stroke . . . 487
    - 4.4. Ipsilesional HF-rTMS or iTBS at the chronic stage of limb motor stroke . . . 487
    - 4.5. Ipsilesional cTBS at the chronic stage of limb motor stroke . . . 488
    - 4.6. Cerebellar target . . . 488
    - 4.7. Swallowing and dysphagia . . . 488
    - 4.8. Aphasia . . . 489
    - 4.9. Neglect . . . 491
5. Multiple sclerosis . . . 492
6. Epilepsy . . . 493
7. Disorders of consciousness . . . 493
8. Mild cognitive impairment and Alzheimer's disease . . . 494
    - 8.1. HF-rTMS of the left DLPFC . . . 494
    - 8.2. HF-rTMS of the precuneus . . . 495
    - 8.3. Multisite HF-rTMS . . . 495
9. Tinnitus . . . 496
    - 9.1. LF-rTMS of the auditory cortex . . . 496
    - 9.2. HF-rTMS of the left DLPFC . . . 499
10. Depression . . . 500
    - 10.1. General results . . . 501
    - 10.2. Novel rTMS protocols to treat depression: Deep HF-rTMS over the left DLPFC . . . 503
    - 10.3. Novel rTMS protocols to treat depression: iTBS over the left DLPFC or cTBS over the right DLPFC . . . 504
    - 10.4. Novel rTMS protocols to treat depression: Accelerated protocols . . . 506
    - 10.5. Novel rTMS protocols to treat depression: Miscellaneous . . . 506
    - 10.6. Summary . . . 506
11. Schizophrenia . . . 507
    - 11.1. Auditory-verbal hallucinations . . . 507
    - 11.2. Negative symptoms . . . 508
12. Substance abuse, addiction and craving . . . 509
    - 12.1. Alcohol craving . . . 509
    - 12.2. Nicotine craving . . . 509
    - 12.3. Methamphetamine or drug craving . . . 510
    - 12.4. Eating disorders . . . 510
    - 12.5. Gambling disorders . . . 510
13. Miscellaneous psychiatric conditions . . . 511
    - 13.1. Anxiety disorders . . . 511
        - 13.1.1. Generalized anxiety disorder . . . 511
        - 13.1.2. Other anxiety disorders . . . 511
    - 13.2. Post-traumatic stress disorder . . . 511
    - 13.3. Obsessive compulsive disorder . . . 512
        - 13.3.1. LF-rTMS of orbitofrontal/prefrontal regions . . . 512
        - 13.3.2. HF-rTMS of prefrontal regions . . . 513
        - 13.3.3. LF-rTMS of pre-SMA . . . 513
    - 13.4. Autism spectrum disorders . . . 514
    - 13.5. Attention deficit hyperactivity disorder . . . 514
    - 13.6. Mental retardation . . . 514
    - 13.7. Functional neurological disorders . . . 514

Clinical Neurophysiology 131 (2020) 474–528

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

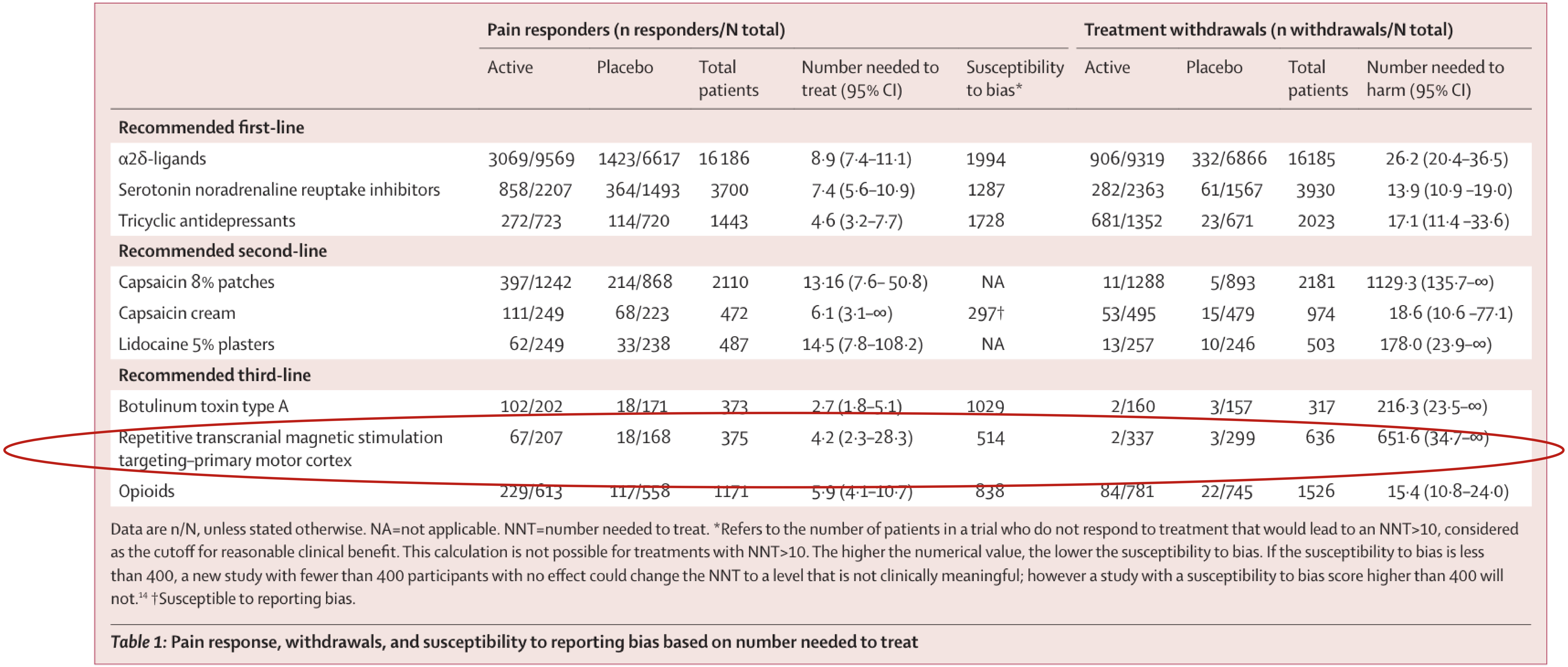
Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018)

Table 1
HF-rTMS of M1 contralateral to pain region in neuropathic pain.

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/ session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Khedr et al. (2015)	30 patients with malignant neuropathic pain (real: 15; sham: 15)	Hand M1 contralateral to pain, F8c (anteroposterior orientation)	Tilted coil	20 Hz, 80% RMT	2000 pulses, 10 sessions	Reduction of pain score at the end of rTMS protocol (49% on VRS and 37% on VAS), up to 2 weeks after the last session (46% on VRS and 36% on VAS); 87–80% responders (>30% pain relief)	II
Ma et al. (2015)	40 patients with postherpetic neuralgia (real: 20; sham: 20)	Homotopic M1 contralateral to pain region, F8c (anteroposterior orientation)	Tilted coil	10 Hz, 80% RMT	1500 pulses, 10 sessions	Reduction of pain score (17% on VAS), up to 3 months after the last session; 50% responders (>50% pain relief)	II
Attal et al., 2016	32 patients with neuropathic lumbar radicular pain (real: 21; sham: 11)	Hand M1 contralateral to pain, F8c (anteroposterior orientation)	Sham coil	10 Hz, 80% RMT	3000 pulses, 3 sessions	Reduction of pain score at the end of rTMS protocol (#60% on VAS), up to 5 days after the last session (#25% on VAS); 43% responders (>30% pain relief)	II
Nurmikko et al. (2016)	27 patients with neuropathic pain of various origins (crossover)	Homotopic M1 contralateral to pain region or an adjacent motor region, F8c (perpendicular to central sulcus)	Occipital stimulation	10 Hz, 90% RMT	2000 pulses, 5 sessions	Reduction of pain score compared to control condition one week after the last session (9–11% on VAS); 30% responders (>30% pain relief)	II

Pharmacotherapy and non-invasive neuromodulation for neuropathic pain: a systematic review and meta-analysis

Nadia Soliman*, Xavier Moisset*, Michael C Ferraro, Daniel Ciampi de Andrade, Ralf Baron, Joletta Belton†, David L H Bennett, Margarita Calvo, Patrick Dougherty, Ian Gilron, Aki J Hietaharju, Koichi Hosomi, Peter R Kamerman, Harriet Kemp, Elena K Enax-Krumova, Ewan McNicol, Theodore J Price, Srinivasa N Raja, Andrew S C Rice, Blair H Smith, Fiona Talkington†, Andrea Truini, Jan Vollert, Nadine Attal*, Nanna B Finnerup*, Simon Haroutounian*, NeuPSIG Review Update Study Group



	Pain responders (n responders/N total)					Treatment withdrawals (n withdrawals/N total)			
	Active	Placebo	Total patients	Number needed to treat (95% CI)	Susceptibility to bias*	Active	Placebo	Total patients	Number needed to harm (95% CI)
Recommended first-line									
α2δ-ligands	3069/9569	1423/6617	16 186	8·9 (7·4–11·1)	1994	906/9319	332/6866	16185	26·2 (20·4–36·5)
Serotonin noradrenaline reuptake inhibitors	858/2207	364/1493	3700	7·4 (5·6–10·9)	1287	282/2363	61/1567	3930	13·9 (10·9 –19·0)
Tricyclic antidepressants	272/723	114/720	1443	4·6 (3·2–7·7)	1728	681/1352	23/671	2023	17·1 (11·4 –33·6)
Recommended second-line									
Capsaicin 8% patches	397/1242	214/868	2110	13·16 (7·6– 50·8)	NA	11/1288	5/893	2181	1129·3 (135·7–∞)
Capsaicin cream	111/249	68/223	472	6·1 (3·1–∞)	297†	53/495	15/479	974	18·6 (10·6 –77·1)
Lidocaine 5% plasters	62/249	33/238	487	14·5 (7·8–108·2)	NA	13/257	10/246	503	178·0 (23·9–∞)
Recommended third-line									
Botulinum toxin type A	102/202	18/171	373	2·7 (1·8–5·1)	1029	2/160	3/157	317	216·3 (23·5–∞)
Repetitive transcranial magnetic stimulation targeting–primary motor cortex	67/207	18/168	375	4·2 (2·3–28·3)	514	2/337	3/299	636	651·6 (34·7–∞)
Opioids	229/613	117/558	1171	5·9 (4·1–10·7)	838	84/781	22/745	1526	15·4 (10·8–24·0)

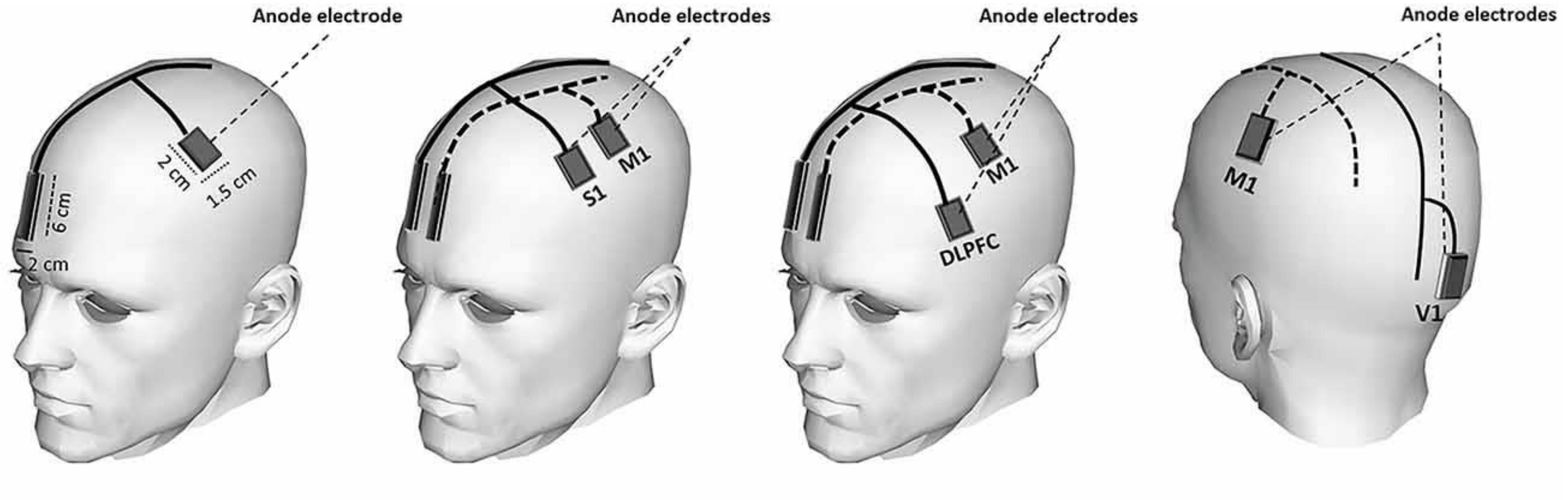
Data are n/N, unless stated otherwise. NA=not applicable. NNT=number needed to treat. *Refers to the number of patients in a trial who do not respond to treatment that would lead to an NNT>10, considered as the cutoff for reasonable clinical benefit. This calculation is not possible for treatments with NNT>10. The higher the numerical value, the lower the susceptibility to bias. If the susceptibility to bias is less than 400, a new study with fewer than 400 participants with no effect could change the NNT to a level that is not clinically meaningful; however a study with a susceptibility to bias score higher than 400 will not.[14] †Susceptible to reporting bias.

Table 1: **Pain response, withdrawals, and susceptibility to reporting bias based on number needed to treat**

Lancet Neurol 2025; 24: 413–28

tDCS - Protocolli di stimolazione

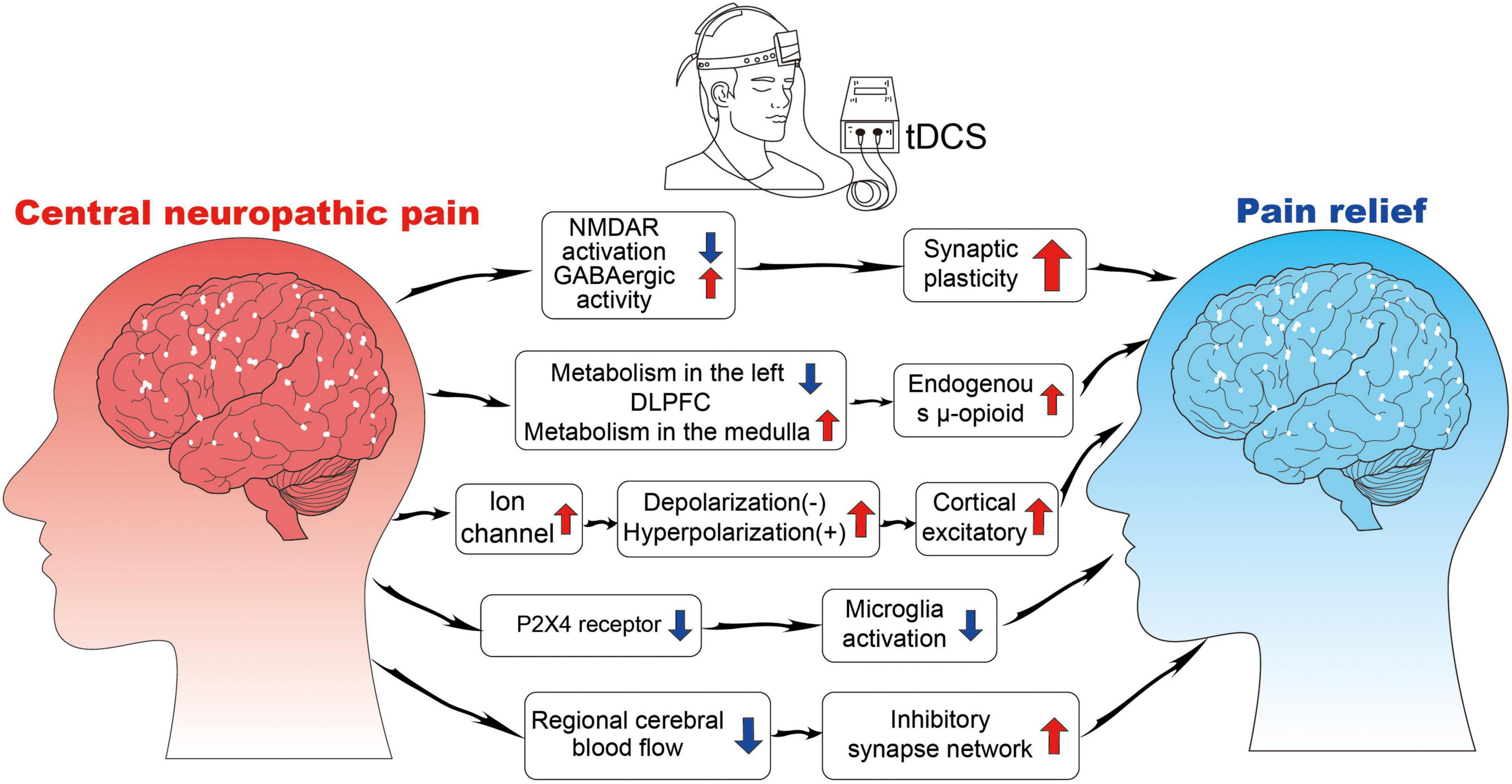
- **Elettrodi**: due elettrodi (anodo e catodo) collegati a un generatore di corrente continua.
- **Montaggio**: l'anodo (positivo) aumenta l'eccitabilità neurale, mentre il catodo (negativo) la riduce.
- **Sede Stimolazione:** M1 o Corteccia Pre-Frontale Dorso-Laterale (DLPFC)
- **Corrente**: tipicamente tra **1 e 2 mA**.
- **Durata**: usualmente **20 minuti** per sessione.
- **Frequenza**: di solito **una seduta al giorno per 5–10 giorni consecutivi**.



Anode electrode
2 cm
1.5 cm
6 cm
2 cm
Anode electrodes
M1
S1
Anode electrodes
M1
DLPFC
Anode electrodes
M1
V1

a-tDCS of M1 a-tDCS$_{UHDS}$ of M1-S1 a-tDCS$_{UHDS}$ of M1-DLPFC a-tDCS$_{UHDS}$ of M1-V1*

tDCS - Meccanismo d’azione



tDCS

Central neuropathic pain

Pain relief

NMDAR activation ↓
GABAergic activity ↑

Synaptic plasticity ↑

Metabolism in the left DLPFC ↓
Metabolism in the medulla ↑

Endogenous μ-opioid ↑

Ion channel ↑

Depolarization(-) Hyperpolarization(+) ↑

Cortical excitatory ↑

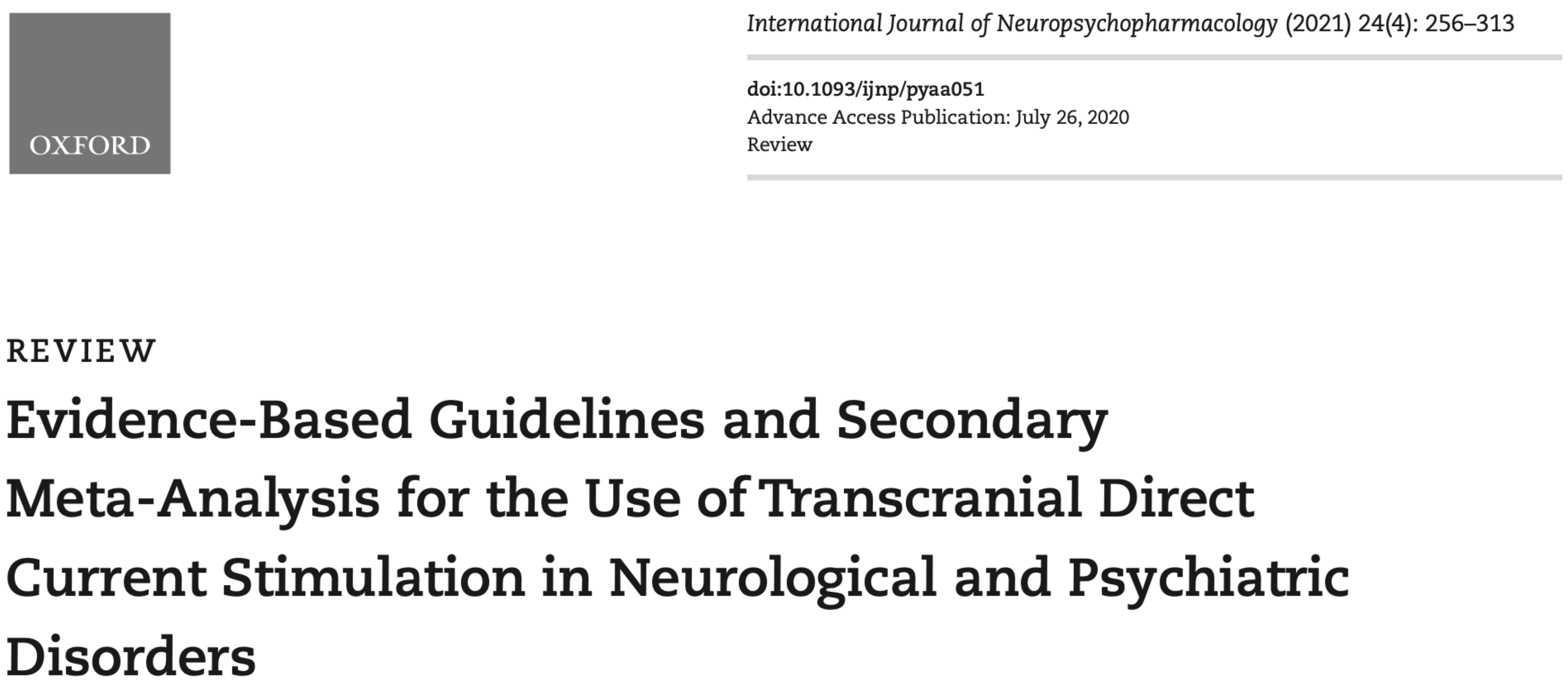
P2X4 receptor ↓

Microglia activation ↓

Regional cerebral blood flow ↓

Inhibitory synapse network ↑

REHA TICINO



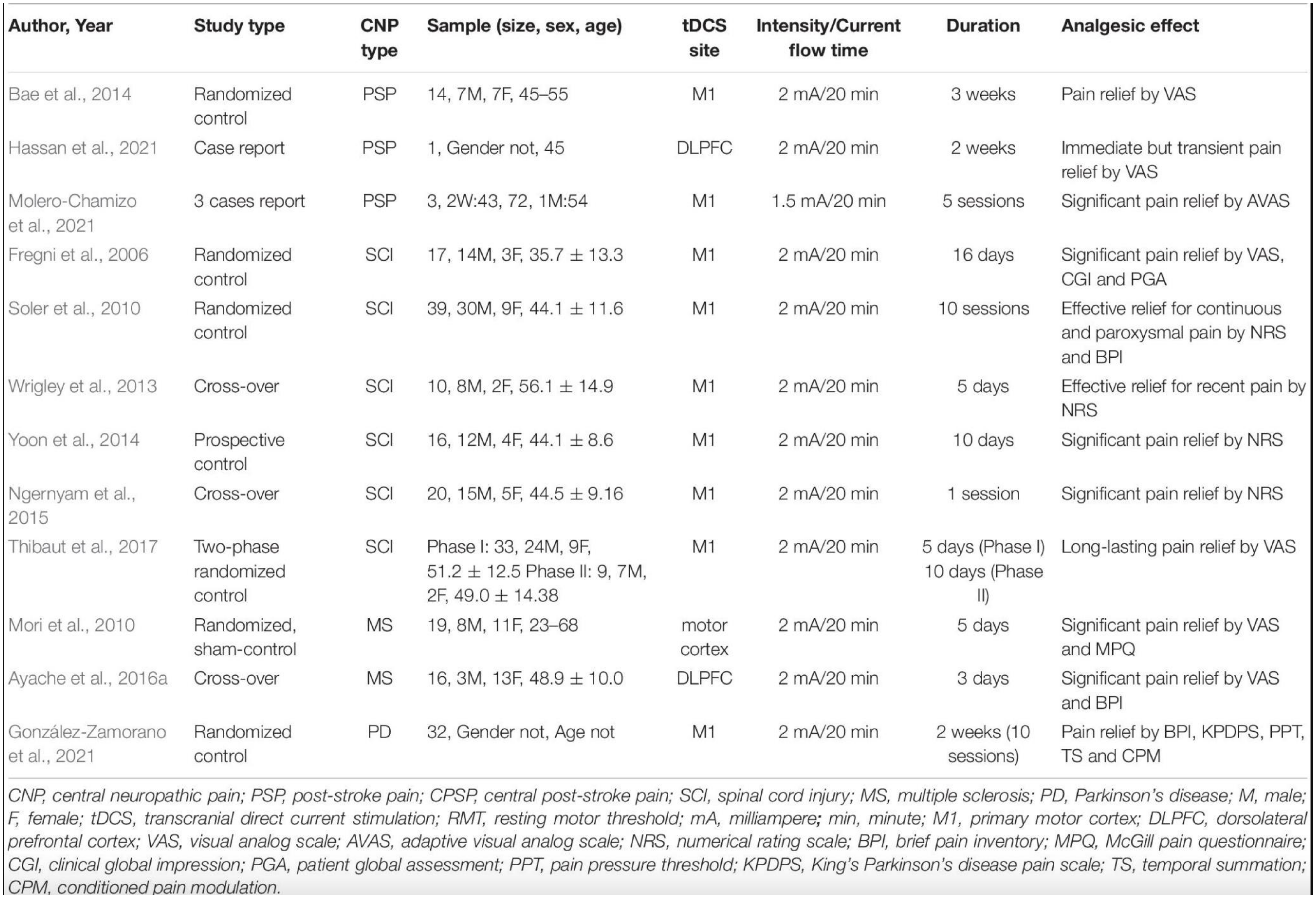
OXFORD

International Journal of Neuropsychopharmacology (2021) 24(4): 256–313

doi:10.1093/ijnp/pyaa051
Advance Access Publication: July 26, 2020
Review

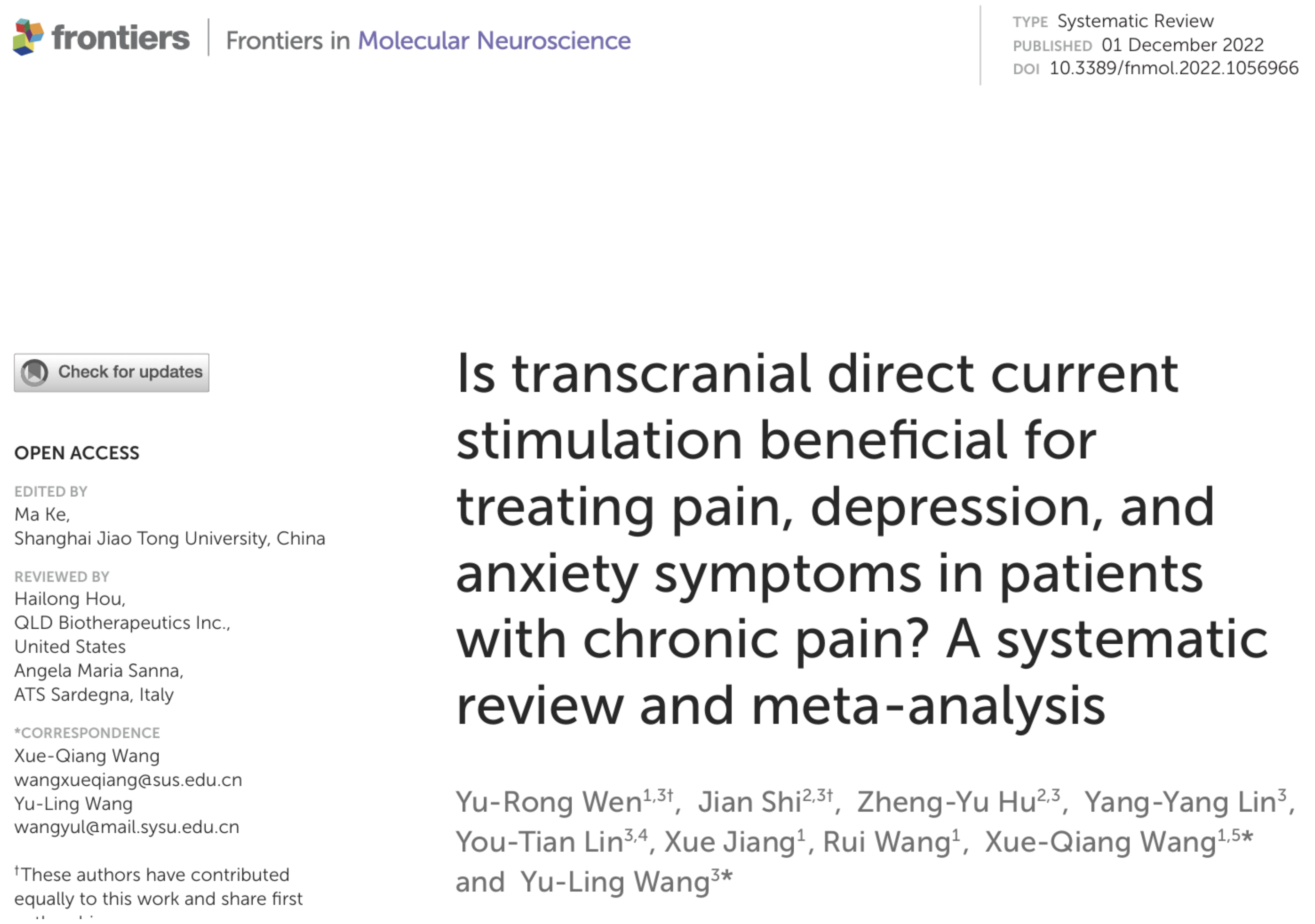
REVIEW

Evidence-Based Guidelines and Secondary Meta-Analysis for the Use of Transcranial Direct Current Stimulation in Neurological and Psychiatric Disorders



Author, Year	Study type	CNP type	Sample (size, sex, age)	tDCS site	Intensity/Current flow time	Duration	Analgesic effect
Bae et al., 2014	Randomized control	PSP	14, 7M, 7F, 45–55	M1	2 mA/20 min	3 weeks	Pain relief by VAS
Hassan et al., 2021	Case report	PSP	1, Gender not, 45	DLPFC	2 mA/20 min	2 weeks	Immediate but transient pain relief by VAS
Molero-Chamizo et al., 2021	3 cases report	PSP	3, 2W:43, 72, 1M:54	M1	1.5 mA/20 min	5 sessions	Significant pain relief by AVAS
Fregni et al., 2006	Randomized control	SCI	17, 14M, 3F, 35.7 ± 13.3	M1	2 mA/20 min	16 days	Significant pain relief by VAS, CGI and PGA
Soler et al., 2010	Randomized control	SCI	39, 30M, 9F, 44.1 ± 11.6	M1	2 mA/20 min	10 sessions	Effective relief for continuous and paroxysmal pain by NRS and BPI
Wrigley et al., 2013	Cross-over	SCI	10, 8M, 2F, 56.1 ± 14.9	M1	2 mA/20 min	5 days	Effective relief for recent pain by NRS
Yoon et al., 2014	Prospective control	SCI	16, 12M, 4F, 44.1 ± 8.6	M1	2 mA/20 min	10 days	Significant pain relief by NRS
Ngernyam et al., 2015	Cross-over	SCI	20, 15M, 5F, 44.5 ± 9.16	M1	2 mA/20 min	1 session	Significant pain relief by NRS
Thibaut et al., 2017	Two-phase randomized control	SCI	Phase I: 33, 24M, 9F, 51.2 ± 12.5 Phase II: 9, 7M, 2F, 49.0 ± 14.38	M1	2 mA/20 min	5 days (Phase I) 10 days (Phase II)	Long-lasting pain relief by VAS
Mori et al., 2010	Randomized, sham-control	MS	19, 8M, 11F, 23–68	motor cortex	2 mA/20 min	5 days	Significant pain relief by VAS and MPQ
Ayache et al., 2016a	Cross-over	MS	16, 3M, 13F, 48.9 ± 10.0	DLPFC	2 mA/20 min	3 days	Significant pain relief by VAS and BPI
González-Zamorano et al., 2021	Randomized control	PD	32, Gender not, Age not	M1	2 mA/20 min	2 weeks (10 sessions)	Pain relief by BPI, KPDPS, PPT, TS and CPM

CNP, central neuropathic pain; PSP, post-stroke pain; CPSP, central post-stroke pain; SCI, spinal cord injury; MS, multiple sclerosis; PD, Parkinson's disease; M, male; F, female; tDCS, transcranial direct current stimulation; RMT, resting motor threshold; mA, milliampere; min, minute; M1, primary motor cortex; DLPFC, dorsolateral prefrontal cortex; VAS, visual analog scale; AVAS, adaptive visual analog scale; NRS, numerical rating scale; BPI, brief pain inventory; MPQ, McGill pain questionnaire; CGI, clinical global impression; PGA, patient global assessment; PPT, pain pressure threshold; KPDPS, King's Parkinson's disease pain scale; TS, temporal summation; CPM, conditioned pain modulation.



frontiers | Frontiers in Molecular Neuroscience

TYPE Systematic Review
PUBLISHED 01 December 2022
DOI 10.3389/fnmol.2022.1056966

Check for updates

OPEN ACCESS

EDITED BY
Ma Ke,
Shanghai Jiao Tong University, China

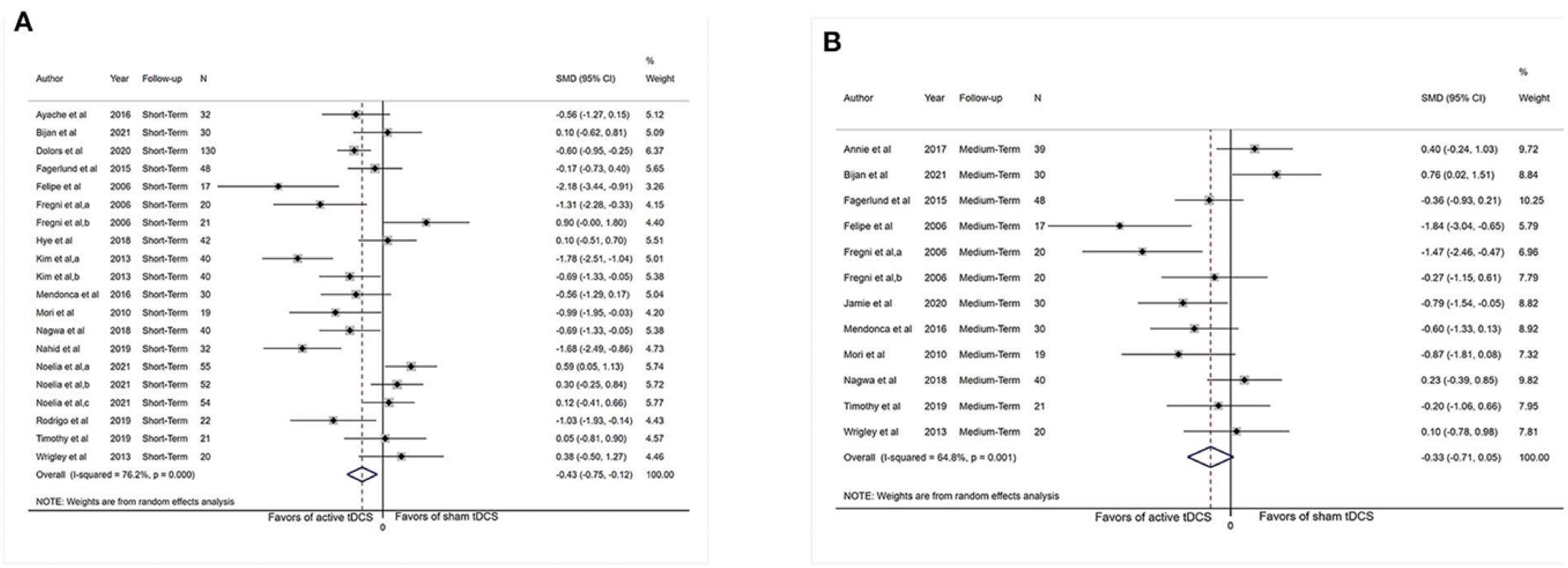
REVIEWED BY
Hailong Hou,
QLD Biotherapeutics Inc.,
United States
Angela Maria Sanna,
ATS Sardegna, Italy

*CORRESPONDENCE
Xue-Qiang Wang
wangxueqiang@sus.edu.cn
Yu-Ling Wang
wangyul@mail.sysu.edu.cn

[†]These authors have contributed equally to this work and share first

Is transcranial direct current stimulation beneficial for treating pain, depression, and anxiety symptoms in patients with chronic pain? A systematic review and meta-analysis

Yu-Rong Wen[1,3†], Jian Shi[2,3†], Zheng-Yu Hu[2,3], Yang-Yang Lin[3], You-Tian Lin[3,4], Xue Jiang[1], Rui Wang[1], Xue-Qiang Wang[1,5*] and Yu-Ling Wang[3*]



A

Author	Year	Follow-up	N	SMD (95% CI)	% Weight
Ayache et al	2016	Short-Term	32	-0.56 (-1.27, 0.15)	5.12
Bijan et al	2021	Short-Term	30	0.10 (-0.62, 0.81)	5.09
Dolors et al	2020	Short-Term	130	-0.60 (-0.95, -0.25)	6.37
Fagerlund et al	2015	Short-Term	48	-0.17 (-0.73, 0.40)	5.65
Felipe et al	2006	Short-Term	17	-2.18 (-3.44, -0.91)	3.26
Fregni et al,a	2006	Short-Term	20	-1.31 (-2.28, -0.33)	4.15
Fregni et al,b	2006	Short-Term	21	0.90 (-0.00, 1.80)	4.40
Hye et al	2018	Short-Term	42	0.10 (-0.51, 0.70)	5.51
Kim et al,a	2013	Short-Term	40	-1.78 (-2.51, -1.04)	5.01
Kim et al,b	2013	Short-Term	40	-0.69 (-1.33, -0.05)	5.38
Mendonca et al	2016	Short-Term	30	-0.56 (-1.29, 0.17)	5.04
Mori et al	2010	Short-Term	19	-0.99 (-1.95, -0.03)	4.20
Nagwa et al	2018	Short-Term	40	-0.69 (-1.33, -0.05)	5.38
Nahid et al	2019	Short-Term	32	-1.68 (-2.49, -0.86)	4.73
Noelia et al,a	2021	Short-Term	55	0.59 (0.05, 1.13)	5.74
Noelia et al,b	2021	Short-Term	52	0.30 (-0.25, 0.84)	5.72
Noelia et al,c	2021	Short-Term	54	0.12 (-0.41, 0.66)	5.77
Rodrigo et al	2019	Short-Term	22	-1.03 (-1.93, -0.14)	4.43
Timothy et al	2019	Short-Term	21	0.05 (-0.81, 0.90)	4.57
Wrigley et al	2013	Short-Term	20	0.38 (-0.50, 1.27)	4.46
Overall (I-squared = 76.2%, p = 0.000)				-0.43 (-0.75, -0.12)	100.00

NOTE: Weights are from random effects analysis

B

Author	Year	Follow-up	N	SMD (95% CI)	% Weight
Annie et al	2017	Medium-Term	39	0.40 (-0.24, 1.03)	9.72
Bijan et al	2021	Medium-Term	30	0.76 (0.02, 1.51)	8.84
Fagerlund et al	2015	Medium-Term	48	-0.36 (-0.93, 0.21)	10.25
Felipe et al	2006	Medium-Term	17	-1.84 (-3.04, -0.65)	5.79
Fregni et al,a	2006	Medium-Term	20	-1.47 (-2.46, -0.47)	6.96
Fregni et al,b	2006	Medium-Term	20	-0.27 (-1.15, 0.61)	7.79
Jamie et al	2020	Medium-Term	30	-0.79 (-1.54, -0.05)	8.82
Mendonca et al	2016	Medium-Term	30	-0.60 (-1.33, 0.13)	8.92
Mori et al	2010	Medium-Term	19	-0.87 (-1.81, 0.08)	7.32
Nagwa et al	2018	Medium-Term	40	0.23 (-0.39, 0.85)	9.82
Timothy et al	2019	Medium-Term	21	-0.20 (-1.06, 0.66)	7.95
Wrigley et al	2013	Medium-Term	20	0.10 (-0.78, 0.98)	7.81
Overall (I-squared = 64.8%, p = 0.001)				-0.33 (-0.71, 0.05)	100.00

NOTE: Weights are from random effects analysis

FIGURE 2

Forest plot showing overall effect sizes (Hedges' g) of real tDCS on pain intensity within studies. These plots show the pooled SMD (large diamond shape) and I^2 resulting from the meta-analysis. **(A)** Pain scores from short-term data. **(B)** Pain scores from medium-term data. CI, confidence interval; SMD, standard mean difference; tDCS, transcranial direct current stimulation; a, motor cortex; b, dorsolateral prefrontal cortex; c, operculo-insular cortex.

Warnings

rTMS

- Epilessia non controllata
- Pacemaker, neurostimolatori
- Clip Metalliche
- Epilessia

tDCS

- Epilessia non controllata
- lesioni cutanee nella sede degli elettrodi
- pacemaker, neurostimolatori

rTMS vs tDCS

	rTMS	**tDCS**
Facilità uso	±	+
Tollerabilità	+	++
Costi	$$	$
Rimborsabilità	❌	❌

Conclusioni

- rTMS e TDCS sono in grado di rimodulare l'eccitabilità corticale mediando plasticità corticale, neurotrasmettitori SNC e regolando il rilascio di citochine pro-infiammatorie
- Efficacia sul dolore neuropatico più definita per rTMS
- Profilo di sicurezza alto
  - CAVE: epilessia, device impiantabili, clips metalliche (psicosi attive?)
- Costi Device

Grazie per l'ascolto!

CLINICA HILDEBRAND
Centro di riabilitazione Brissago

REHA TICINO

eoc
Ente Ospedaliero Cantonale

www.rehaticino.ch