Transcranial Magnetic Stimulation of the Primary Motor Cortex

Subjects: Clinical Neurology | Neurosciences

Contributor: Abdulhameed Tomeh, Abdul Hanif Khan Yusof Khan, Hamidon Basri, Wan Aliaa Wan Sulaiman

Transcranial magnetic stimulation (TMS) has emerged as a novel technique to stimulate the human brain through the scalp. Over the years, identifying the optimal brain region and stimulation parameters has been a subject of debate in the literature on therapeutic uses of repetitive TMS (rTMS). Nevertheless, the primary motor cortex (M1) has been a conventional target for rTMS to treat motor symptoms, such as hemiplegia and spasticity, as it controls the voluntary movement of the body. However, with an expanding knowledge base of the M1 cortical and subcortical connections, M1-rTMS has shown a therapeutic efficacy that goes beyond the conventional motor rehabilitation to involve pain, headache, fatigue, dysphagia, speech and voice impairments, sleep disorders, cognitive dysfunction, disorders of consciousness, anxiety, depression, and bladder dysfunction.

Keywords: transcranial magnetic stimulation ; therapeutic use ; primary motor cortex ; non-motor symptoms

1. Introduction

The primary motor cortex (M1) consists of a population of neurons that play a crucial role in the voluntary regulation of movement [1]. Transcranial magnetic stimulation (TMS) was introduced to study the human M1 in 1985 as a novel, painless technique that can be delivered non-invasively [2]. Application of TMS in a repetitive manner can induce neuroplastic effects in the targeted region and its functionally connected networks and thus alter neuronal excitability beyond the period of stimulation [3]. Conventional repetitive TMS (rTMS) protocols in research and clinical practice include high-frequency (HF)-rTMS (5–20 Hz) and low-frequency (LF)-rTMS (≤1 Hz), which can increase or decrease M1 excitability, respectively, for several minutes after stimulation [4][5]. Another rTMS protocol, known as theta-burst stimulation (TBS), was developed later with reduced administration duration. The TBS protocol consists of extremely high-frequency (50 Hz) stimulation in the pattern of three bursts at the theta range (5 Hz) [6]. This protocol can be applied as intermittent TBS (iTBS) or continuous TBS (cTBS), which have comparable efficacy to HF-rTMS and LF-rTMS, respectively [6]. The impact of HF-rTMS/iTBS on enhancing M1 excitability and LF-rTMS/cTBS on reducing M1 excitability is thought to rely on principles of long-term potentiation (LTP) and long-term depression (LTD) plasticity, respectively [7]. At the cellular level, LTP/LTD plasticity results from a prolonged strengthening/inhibition of synaptic transmission following synchronous/asynchronous presynaptic and postsynaptic activity [8].

To localize the primary motor cortex (M1), a single-pulse TMS is applied away from the vertex towards the right or left M1 to activate the motor neurons and induce a muscle twitch. This twitch can be measured by electromyography (EMG) to record the motor evoked potential (MEP). Originally, a “motor hotspot” was defined as the optimal TMS coil position over M1 that evokes MEPs of maximum amplitude and shortest latency in a target muscle [9]. However, due to practical issues, the motor hotspot is more commonly localized as the TMS coil position over M1 that evokes the largest and most consistent MEP amplitude from a target muscle, regardless of its latency [10][11]. In some cases, because of stroke or corticospinal tract injury, MEPs might be absent upon M1 stimulation. Still, the motor hotspot can be targeted using the mirror image of the unaffected hemisphere [12]. Another method to localize the M1 in TMS studies is by magnetic resonance imaging (MRI) based on specific anatomical landmarks of the M1, i.e., hand knob [13], or by functional MRI (fMRI) while performing a specific motor task [14]. However, the motor hotspot method is more commonly employed in the TMS literature [15].

Afterward, the motor threshold is measured to personalize the TMS intensity for each individual. Resting motor threshold (RMT) is defined as the lowest TMS intensity needed to evoke an MEP of ≥50 μV in 5 of 10 consecutive trials in the relaxed muscle. In comparison, active motor threshold (AMT) is the lowest TMS intensity required to elicit MEP ≥200 μV in 5 of 10 consecutive trials during an isometric contraction of the target muscle of 10–20% of its maximal strength [3]. In therapeutic applications, the TMS intensity is usually reported as a percentage of the RMT in conventional rTMS paradigms, and AMT in studies that employ TBS paradigms [15].

Following localization of the motor hotspot and determining the TMS intensity, the TMS coil is fixed over the M1 for the whole treatment session. Jung et al. found that marking the hotspot with a felt-tip pen yielded similar consistency of MEPs compared with using a neuronavigation system with MRI guidance [16]. Nonetheless, expert panels advise using a neuronavigation system to ensure higher accuracy while applying the TMS coil over the M1 [15]. Concerning the types of the TMS coils, a figure-of-eight coil is most commonly applied at the hand and face regions of the M1 as it produces focal and superficial stimulation. While non-focal coils, such as H-coils and double-cone coils, are used preferably to target the lower limb and pelvic representation of the M1 as it produces deeper stimulation [17].

2. Pain

Over the years, various brain stimulation techniques at M1 have been trialed with a promising analgesic efficacy, including invasive epidural motor cortex stimulation [18] and non-invasive techniques such as transcranial direct current stimulation (tDCS) [19] and rTMS [20].

The rationale behind the analgesic efficacy of M1 stimulation relies mainly, but not exclusively, on its interconnections with the endogenous opioid system. Positron emission tomography (PET) scans demonstrated that M1 stimulation directly potentiated the top-down opioid-mediated inhibition system [21][22]. In addition, blocking μ-opioid receptors with the drug naloxone significantly reduced the analgesic efficacy of M1 stimulation [23], further supporting the relation between M1-rTMS stimulation and the release of endogenous opioids. Therefore, recent evidence highlights the potential role of blood β-endorphin measurement as an objective response biomarker in treating chronic pain with rTMS [24][25].

Another putative mechanism pertains to the glutamate receptor, N-methyl-D-aspartate (NMDA). The drug ketamine, an NMDA receptor antagonist, significantly reduced the analgesic efficacy of high-frequency rTMS over M1, suggesting a shared pathway with the LTP-like plasticity mechanisms [26]. In addition, a disruption in the γ-aminobutyric acid (GABA)-mediated intracortical inhibition was noticeable in both acute [27] and chronic pain conditions [28]. In turn, high-frequency M1-rTMS was shown to restore the defective intracortical inhibition with a direct correlation between the analgesic effect and cortical excitability [29][30][31]. This notion highlights the principle of state dependency of TMS, where the facilitatory effect of high-frequency rTMS is reversed and the cortical excitability decreases if the high-frequency rTMS is applied during a state of enhanced cortical excitability [32][33].

On the neural network level, neuroimaging studies have shown that M1 stimulation modulated the excitability of other cortical and subcortical areas related to sensory, cognitive, and emotional components of pain, such as the thalamus, insular cortex, and anterior cingulate gyrus [34][35].

3. Fatigue

Fatigue is a frequent and disabling symptom experienced in various diseases and cannot be completely explained by conventional structural damage [36]. With the lack of effective treatments, M1-rTMS has been applied to relieve fatigue in patients with fibromyalgia syndrome [37], multiple sclerosis [38], amyotrophic lateral sclerosis [39], and chronic neuropathic pain [40]. The mechanism of action of rTMS in fatigue management remains unknown. However, applying rTMS at M1 might modulate the functional connectivity between the impaired neural networks in these patients, resulting in reduced fatigue perception [38].

4. Dysphagia

The rationale behind employing M1-rTMS in dysphagia management relies mainly on its effect on the corticobulbar projections to swallowing muscles [41]. Applying rTMS over the swallowing musculature hotspot at M1 has been trialed with promising results in dysphagia after stroke [42], Parkinson's disease [43], and in the context of aging, aka presbydysphagia [44].

5. Speech and Voice Impairments

As M1 receives input from Broca's area and projects through corticobulbar tracts to the muscles responsible for speech production [45], several clinical studies have investigated the potential to increase or decrease excitability in these tracts through rTMS protocols. These studies involved post-stroke aphasia [46] and dysarthria [47], Parkinson's disease-related hypokinetic dysarthria [48], Tourette syndrome [49], and adductor laryngeal dystonia [50].

6. Sleep Disorders

The therapeutic application of M1-rTMS in sleep disorders has been investigated in restless legs syndrome [51], sleep bruxism [52], obstructive sleep apnea [53], and sleep disturbances associated with neurological conditions, in particular Parkinson's disease and chronic pain [54].

Restless legs syndrome (RLS) is characterized by M1 disinhibition and CNS dopaminergic dysfunction [51]. In turn, high-frequency rTMS at M1 was shown to restore the intracortical inhibition since its mechanism is state-dependent on the cortical excitability prior to TMS stimulation [32][33]. In addition, M1-rTMS activates the corticostriatal projections leading to the endogenous release of dopamine [55].

On the other hand, reducing the nocturnal recurrence of motor symptoms and pain in PD and chronic pain conditions, respectively, can result in indirect improvement in sleep quality. In addition, inducing LTP-like plasticity in the M1 during wakefulness was found to modulate the slow-wave activity during sleep and could thereby regulate the sleep need [56][57].

7. Cognitive Dysfunction

The application of M1-rTMS has been investigated in a few studies of affected cognition in Parkinson's disease [58], stroke [59], and fibromyalgia syndrome [60]. The procognitive effect of M1 stimulation in these conditions can be rationalized by the increasingly identified roles of M1 in higher cognitive processes, such as attention, memory, motor imagery, and language comprehension, and the functional connectivity between M1 and parietal cortex that supports the planning and execution of goal-oriented movements [61][62][63][64][65].

8. Disorders of Consciousness

The mechanistic rationale for the therapeutic use of M1-rTMS in disorders of consciousness is related in part to EEG findings showing that high-frequency rTMS at M1 transiently increased neuronal oscillations in the α and β frequency [66]. In addition, fMRI studies demonstrated that high-frequency rTMS at M1 induced blood-oxygenation-level-dependent (BOLD) changes both locally and in remote brain regions, including the supplementary motor area, dorsal premotor area, putamen, cingulate motor area, and crucially, the thalamus [67]. The application of M1-rTMS was safe and utilized without any adverse effects in patients with disorders of consciousness, including minimally conscious state (MCS) and vegetative state/unresponsive wakefulness syndrome, and improved the coma recovery scale in a subset of comatose patients [68].

9. Anxiety and Depression

The mechanistic rationale behind the improvement in anxiety and depression following M1-rTMS might stem from its effect on the concomitant symptoms and consequently emotional improvement in mood and general behavior. On the other hand, a recent meta-analysis combined with resting-state fMRI reported a positive correlation between M1 and depressive disorders-regions of interest (ROI), hence proposing M1 as a potential therapeutic target in depressive disorders [69]. In addition, M1-rTMS stimulation was found to alter the serum levels of kynurenine [70][71], a tryptophan metabolite and one culprit in the pathophysiology of depression [72]. Preliminary evidence of antidepressant efficacy of M1-rTMS has been reported in patients with Parkinson's disease [73], stroke [70], and chronic pain [74].

10. Bladder Dysfunction

The mechanistic rationale for the use of M1-rTMS in this condition relies on its influence on the corticospinal tract excitability and consequently detrusor/urethral sphincter functionality [75]. In addition, recent evidence has revealed an essential role of certain M1 neuronal subpopulations in issuing the "order" to initiate voiding via their projections to the pontine micturition center [76][77]. Preliminary evidence on the therapeutic potential of M1-rTMS on urinary symptoms has been reported in multiple sclerosis [75], Parkinson's disease [78], and bladder pain syndrome/interstitial cystitis [79].

This entry is adapted from 10.3390/brainsci12060761

References

1. Cathy M. Stinear; James Coxon; Winston Byblow; Primary motor cortex and movement prevention: Where Stop meets Go. *Neuroscience & Biobehavioral Reviews* **2009**, *33*, 662-673, 10.1016/j.neubiorev.2008.08.013.
2. A.T. Barker; R. Jalinous; I.L. Freeston; NON-INVASIVE MAGNETIC STIMULATION OF HUMAN MOTOR CORTEX. *The Lancet* **1985**, *325*, 1106-1107, 10.1016/s0140-6736(85)92413-4.
3. P.M. Rossini; D. Burke; R. Chen; L.G. Cohen; Z. Daskalakis; R. Di Iorio; Vincenzo Di Lazzaro; Florinda Ferreri; P.B. Fitzgerald; M.S. George; et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clinical Neurophysiology* **2015**, *126*, 1071-1107, 10.1016/j.clinph.2015.02.001.
4. Alvaro Pascual-Leone; Josep Valls-Solé; Eric M. Wassermann; Mark Hallett; Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* **1994**, *117*, 847-858, 10.1093/brain/117.4.847.
5. R. Chen; J. Classen; C. Gerloff; P. Celnik; E. M. Wassermann; M. Hallett; L. G. Cohen; Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology* **1997**, *48*, 1398-1403, 10.1212/wnl.48.5.1398.
6. Ying-Zu Huang; Mark J. Edwards; Elisabeth Rounis; Kailash P. Bhatia; John C. Rothwell; Theta Burst Stimulation of the Human Motor Cortex. *Neuron* **2005**, *45*, 201-206, 10.1016/j.neuron.2004.12.033.
7. Ying-Zu Huang; Ming-Kue Lu; Andrea Antal; Joseph Classen; Michael Nitsche; Ulf Ziemann; Michael Ridding; Masashi Hamada; Yoshikazu Ugawa; Shapour Jaberzadeh; et al. Plasticity induced by non-invasive transcranial brain stimulation: A position paper. *Clinical Neurophysiology* **2017**, *128*, 2318-2329, 10.1016/j.clinph.2017.09.007.
8. Marc Forrest; Euan Parnell; Peter Penzes; Dendritic structural plasticity and neuropsychiatric disease. *Nature Reviews Neuroscience* **2018**, *19*, 215-234, 10.1038/nrn.2018.16.
9. P.M. Rossini; A.T. Barker; Alfredo Berardelli; M.D. Caramia; G. Caruso; R.Q. Cracco; M.R. Dimitrijević; M. Hallett; Y. Katayama; C.H. Lücking; et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology* **1994**, *91*, 79-92, 10.1016/0013-4694(94)90029-9.
10. H.R. Siebner; U. Ziemann; What is the threshold for developing and applying optimized procedures to determine the corticomotor threshold?. *Clinical Neurophysiology* **2014**, *125*, 1-2, 10.1016/j.clinph.2013.07.012.
11. Charalambos C. Charalambous; Jing Nong Liang; Steve A. Kautz; Mark S. George; Mark G. Bowden; Bilateral Assessment of the Corticospinal Pathways of the Ankle Muscles Using Navigated Transcranial Magnetic Stimulation. *Journal of Visualized Experiments* **2019**, *x*, e58944, 10.3791/58944.
12. Yh Kim; Wh Chang; Oy Bang; St Kim; Yh Park; Pkw Lee; Long-term effects of rTMS on motor recovery in patients after subacute stroke. *Journal of Rehabilitation Medicine* **2010**, *42*, 758-764, 10.2340/16501977-0590.
13. Heegoo Kim; Jinuk Kim; Hwang-Jae Lee; Jungsoo Lee; YoonJu Na; Won Hyuk Chang; Yun-Hee Kim; Optimal stimulation site for rTMS to improve motor function: Anatomical hand knob vs. hand motor hotspot. *Neuroscience Letters* **2020**, *740*, 135424, 10.1016/j.neulet.2020.135424.
14. B Boroojerdi; H Foltys; T Krings; U Spetzger; A Thron; R Töpper; Localization of the motor hand area using transcranial magnetic stimulation and functional magnetic resonance imaging. *Clinical Neurophysiology* **1999**, *110*, 699-704, .
15. Jean-Pascal Lefaucheur; André Aleman; Chris Baeken; David H. Benninger; Jerome Brunelin; Vincenzo Di Lazzaro; Saša R. Filipović; Christian Grefkes; Alkomiet Hasan; Friedhelm C. Hummel; et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). *Clinical Neurophysiology* **2020**, *131*, 474-528, 10.1016/j.clinph.2019.11.002.
16. Nikolai H. Jung; Igor Delvendahl; Nicola G. Kuhnke; Dieter Hauschke; Sabine Stolle; Volker Mall; Navigated transcranial magnetic stimulation does not decrease the variability of motor-evoked potentials. *Brain Stimulation* **2010**, *3*, 87-94, 10.1016/j.brs.2009.10.003.
17. Simone Rossi; Andrea Antal; Sven Bestmann; Marom Bikson; Carmen Brewer; Jürgen Brockmöller; Linda L. Carpenter; Massimo Cincotta; Robert Chen; Jeff D. Daskalakis; et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clinical Neurophysiology* **2020**, *132*, 269-306, 10.1016/j.clinph.2020.10.003.
18. Takashi Tsubokawa; Yoichi Katayama; Takamitsu Yamamoto; Teruyasu Hirayama; Seigou Koyama; Chronic motor cortex stimulation in patients with thalamic pain. *Journal of Neurosurgery* **1993**, *78*, 393-401, 10.3171/jns.1993.78.3.0393.

19. Felipe Fregni; Paulo Boggio; Moisés Lima; Merari J.L. Ferreira; Tim Wagner; Sergio P. Rigonatti; Anita W. Castro; Daniel R. Souza; Marcelo Riberto; Steven D. Freedman; et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* **2006**, *122*, 197-209, 10.1016/j.pain.2006.02.023.

20. Jean-Pascal Lefaucheur; Xavier Drouot; Yves Keravel; Jean-Paul Nguyen; Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. *NeuroReport* **2001**, *12*, 2963-2965, 10.1097/00001756-200109170-00041.

21. Joseph Maarrawi; Roland Peyron; P. Mertens; Nicolas Costes; M. Magnin; M. Sindou; B. Laurent; Luis Garcia-Larrea; Motor cortex stimulation for pain control induces changes in the endogenous opioid system. *Neurology* **2007**, *69*, 827-834, 10.1212/01.wnl.0000269783.86997.37.

22. S. Lamusuo; J. Hirvonen; P. Lindholm; I. K. Martikainen; N. Hagelberg; R. Parkkola; T. Taiminen; Jarmo Hietala; S. Helin; A. Virtanen; et al. Neurotransmitters behind pain relief with transcranial magnetic stimulation - positron emission tomography evidence for release of endogenous opioids. *European Journal of Pain* **2017**, *21*, 1505-1515, 10.1002/ejp.1052.

23. Daniel Ciampi De Andrade; Alaa Mhalla; Frédéric Adam; Manoel Jacobsen Texeira; Didier Bouhassira; Neuropharmacological basis of rTMS-induced analgesia: The role of endogenous opioids. *Pain* **2011**, *152*, 320-326, 10.1016/j.pain.2010.10.032.

24. Erickson Bonifácio de Assis; Carolina Dias de Carvalho; Clarice Martins; Suellen Andrade; Beta-Endorphin as a Biomarker in the Treatment of Chronic Pain with Non-Invasive Brain Stimulation: A Systematic Scoping Review. *Journal of Pain Research* **2021**, *ume 14*, 2191-2200, 10.2147/jpr.s301447.

25. Helena K. Kim; Daniel M. Blumberger; Jonathan Downar; Zafiris J. Daskalakis; Systematic review of biological markers of therapeutic repetitive transcranial magnetic stimulation in neurological and psychiatric disorders. *Clinical Neurophysiology* **2020**, *132*, 429-448, 10.1016/j.clinph.2020.11.025.

26. Daniel Ciampi de Andrade; Alaa Mhalla; Frédéric Adam; Manoel Jacobsen Texeira; Didier Bouhassira; Repetitive transcranial magnetic stimulation induced analgesia depends on N-methyl-d-aspartate glutamate receptors. *Pain* **2014**, *155*, 598-605, 10.1016/j.pain.2013.12.022.

27. Marianne Jodoin; Dominique M. Rouleau; Audrey Bellemare; Catherine Provost; Camille Larson-Dupuis; Émilie Sandman; Georges-Yves Laflamme; Benoit Benoit; Stéphane LeDuc; Martine Levesque; et al. Moderate to severe acute pain disturbs motor cortex intracortical inhibition and facilitation in orthopedic trauma patients: A TMS study. *PLOS ONE* **2020**, *15*, e0226452, 10.1371/journal.pone.0226452.

28. Rosalind S. Parker; Gwyn N. Lewis; David A. Rice; Peter J. McNair; Is Motor Cortical Excitability Altered in People with Chronic Pain? A Systematic Review and Meta-Analysis. *Brain Stimulation* **2016**, *9*, 488-500, 10.1016/j.brs.2016.03.020.

29. Alaa Mhalla; Sophie Baudic; Daniel Ciampi de Andrade; Michele Gautron; Serge Perrot; Manoel Jacobson Teixeira; Nadine Attal; Didier Bouhassira; Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. *Pain* **2011**, *152*, 1478-1485, 10.1016/j.pain.2011.01.034.

30. J. P. Lefaucheur; Xavier Drouot; I. Menard-Lefaucheur; Y. Keravel; J. P. Nguyen; Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. *Neurology* **2006**, *67*, 1568-1574, 10.1212/01.wnl.0000242731.10074.3c.

31. Koichi Hosomi; Haruhiko Kishima; Satoru Oshino; Masayuki Hirata; Naoki Tani; Tomoyuki Maruo; Shiro Yorifuji; Toshiki Yoshimine; Youichi Saitoh; Cortical excitability changes after high-frequency repetitive transcranial magnetic stimulation for central poststroke pain. *Pain* **2013**, *154*, 1352-1357, 10.1016/j.pain.2013.04.017.

32. Juha Silvanto; Alvaro Pascual-Leone; State-Dependency of Transcranial Magnetic Stimulation. *Brain Topography* **2008**, *21*, 1-10, 10.1007/s10548-008-0067-0.

33. Nicolas Lang; Hartwig R. Siebner; Diana Ernst; Michael A. Nitsche; Walter Paulus; Roger N. Lemon; John Rothwell; Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. *Biological Psychiatry* **2004**, *56*, 634-639, 10.1016/j.biopsych.2004.07.017.

34. Luis Garcia-Larrea; Roland Peyron; P Mertens; C M. Gregoire; F Lavenne; D Le Bars; Philippe Convers; Francois Mauguiere; M Sindou; B Laurent; et al. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. *Pain* **1999**, *83*, 259-273, 10.1016/s0304-3959(99)00114-1.

35. Duncan J. Hodkinson; Andreas Bungert; Richard William Bowtell; Stephen R. Jackson; Jeyoung Jung; Operculo-insular and anterior cingulate plasticity induced by transcranial magnetic stimulation in the human motor cortex: a dynamic casual modeling study. *Journal of Neurophysiology* **2021**, *125*, 1180-1190, 10.1152/jn.00670.2020.

36. Mario Stampanoni Bassi; Fabio Buttari; Luana Gilio; Nicla De Paolis; Diego Fresegna; Diego Centonze; Ennio Iezzi; Inflammation and Corticospinal Functioning in Multiple Sclerosis: A TMS Perspective. *Frontiers in Neurology* **2020**, *11*, 566, 10.3389/fneur.2020.00566.

37. Wen-Hsuan Hou; Tzu-Ya Wang; Jiunn-Horng Kang; The effects of add-on non-invasive brain stimulation in fibromyalgia: a meta-analysis and meta-regression of randomized controlled trials. *Rheumatology* **2016**, *55*, 1507-1517, 10.1093/rheumatology/kew205.

38. Gunnar Gaede; Marina Tiede; Ina Lorenz; Alexander U. Brandt; Caspar Pfueller; Jan Dörr; Judith Bellmann-Strobl; Sophie K. Piper; Yiftach Roth; Abraham Zangen; et al. Safety and preliminary efficacy of deep transcranial magnetic stimulation in MS-related fatigue. *Neurology - Neuroimmunology Neuroinflammation* **2017**, *5*, e423, 10.1212/nxi.0000000000000423.

39. Giampietro Zanette; Antonio Forgione; Paolo Manganotti; Antonio Fiaschi; Stefano Tamburin; The effect of repetitive transcranial magnetic stimulation on motor performance, fatigue and quality of life in amyotrophic lateral sclerosis. *Journal of the Neurological Sciences* **2008**, *270*, 18-22, 10.1016/j.jns.2008.01.011.

40. N. André-Obadia; M. Magnin; L. Garcia-Larrea; Theta-burst versus 20 Hz repetitive transcranial magnetic stimulation in neuropathic pain: A head-to-head comparison. *Clinical Neurophysiology* **2021**, *132*, 2702-2710, 10.1016/j.clinph.2021.05.022.

41. David Gow; John Rothwell; Anthony Hobson; David Thompson; Shaheen Hamdy; Induction of long-term plasticity in human swallowing motor cortex following repetitive cortical stimulation. *Clinical Neurophysiology* **2004**, *115*, 1044-1051, 10.1016/j.clinph.2003.12.001.

42. Ivy Cheng; Ayodele Sasegbon; Shaheen Hamdy; Effects of Neurostimulation on Poststroke Dysphagia: A Synthesis of Current Evidence From Randomized Controlled Trials. *Neuromodulation: Technology at the Neural Interface* **2020**, *24*, 1388-1401, 10.1111/ner.13327.

43. Eman M. Khedr; Khaled Mohamed; Radwa Kamel Soliman; Asmaa M. M. Hassan; John C. Rothwell; The Effect of High-Frequency Repetitive Transcranial Magnetic Stimulation on Advancing Parkinson’s Disease With Dysphagia: Double Blind Randomized Clinical Trial. *Neurorehabilitation and Neural Repair* **2019**, *33*, 442-452, 10.1177/1545968319847968.

44. Giuseppe Cosentino; Cristina Tassorelli; Paolo Prunetti; Giulia Bertino; Roberto De Icco; Massimiliano Todisco; Salvatore Di Marco; Filippo Brighina; Antonio Schindler; Mariangela Rondanelli; et al. Anodal transcranial direct current stimulation and intermittent theta-burst stimulation improve deglutition and swallowing reproducibility in elderly patients with dysphagia. *Neurogastroenterology & Motility* **2020**, *32*, e13791, 10.1111/nmo.13791.

45. Gert Holstege; Hari H. Subramanian; Two different motor systems are needed to generate human speech. *Journal of Comparative Neurology* **2015**, *524*, 1558-1577, 10.1002/cne.23898.

46. Shuo Xu; Qing Yang; Mengye Chen; Panmo Deng; Ren Zhuang; Zengchun Sun; Chong Li; Zhijie Yan; Yongli Zhang; Jie Jia; et al. Capturing Neuroplastic Changes after iTBS in Patients with Post-Stroke Aphasia: A Pilot fMRI Study. *Brain Sciences* **2021**, *11*, 1451, 10.3390/brainsci11111451.

47. Yong Gyu Kwon; Kyung Hee Do; Sung Jong Park; Min Cheol Chang; Min Ho Chun; Effect of Repetitive Transcranial Magnetic Stimulation on Patients With Dysarthria After Subacute Stroke. *Annals of Rehabilitation Medicine* **2015**, *39*, 793-799, 10.5535/arm.2015.39.5.793.

48. Alice Estevo Dias; Egberto Reis Barbosa; K. Coracini; F. Maia; M. A. Marcolin; F. Fregni; Effects of repetitive transcranial magnetic stimulation on voice and speech in Parkinson's disease. *Acta Neurologica Scandinavica* **2006**, *113*, 92-99, 10.1111/j.1600-0404.2005.00558.x.

49. Katherine Dyke; Georgina Jackson; Stephen Jackson; Non-invasive brain stimulation as therapy: systematic review and recommendations with a focus on the treatment of Tourette syndrome. *Experimental Brain Research* **2021**, *240*, 341-363, 10.1007/s00221-021-06229-y.

50. Cecília N. Prudente; Mo Chen; Kaila L. Stipancic; Katherine L. Marks; Sharyl Samargia-Grivette; George S. Goding; Jordan R. Green; Teresa J. Kimberley; Effects of low-frequency repetitive transcranial magnetic stimulation in adductor laryngeal dystonia: a safety, feasibility, and pilot study. *Experimental Brain Research* **2021**, *240*, 561-574, 10.1007/s00221-021-06277-4.

51. Raffaele Nardone; Luca Sebastianelli; Viviana Versace; Francesco Brigo; Stefan Golaszewski; Elke Pucks-Faes; Leopold Saltuari; Eugen Trinka; Contribution of transcranial magnetic stimulation in restless legs syndrome: pathophysiological insights and therapeutical approaches. *Sleep Medicine* **2019**, *71*, 124-134, 10.1016/j.sleep.2019.12.009.

52. Wei-Na Zhou; Hai-Yang Fu; Yi-Fei Du; Jian-Hua Sun; Jing-Lu Zhang; Chen Wang; Peter Svensson; Ke-Lun Wang; Short-term effects of repetitive transcranial magnetic stimulation on sleep bruxism - a pilot study.. *International Journal*

of Oral Science **2015**, *8*, 61-5, 10.1038/ijos.2015.35.

53. Raffaele Nardone; Luca Sebastianelli; Viviana Versace; Francesco Brigo; Stefan Golaszewski; Elke Pucks-Faes; Leopold Saltuari; Eugen Trinka; Effects of repetitive transcranial magnetic stimulation in subjects with sleep disorders. *Sleep Medicine* **2020**, *71*, 113-121, 10.1016/j.sleep.2020.01.028.

54. Alberto Herrero Babiloni; Audrey Bellemare; Gabrielle Beetz; Sophie-A. Vinet; Marc O. Martel; Gilles J. Lavigne; Louis De Beaumont; The effects of non-invasive brain stimulation on sleep disturbances among different neurological and neuropsychiatric conditions: A systematic review. *Sleep Medicine Reviews* **2020**, *55*, 101381, 10.1016/j.smrv.2020.101381.

55. Antonio P. Strafella; Tomáš Paus; Maria Fraraccio; Alain Dagher; Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. *Brain* **2003**, *126*, 2609-2615, 10.1093/brain/awg268.

56. Reto Huber; Steve K. Esser; Fabio Ferrarelli; Marcello Massimini; Michael J. Peterson; Giulio Tononi; TMS-Induced Cortical Potentiation during Wakefulness Locally Increases Slow Wave Activity during Sleep. *PLOS ONE* **2007**, *2*, e276-e276, 10.1371/journal.pone.0000276.

57. Luigi De Gennaro; Fabiana Fratello; Cristina Marzano; Fabio Moroni; Giuseppe Curcio; Daniela Tempesta; Maria Concetta Pellicciari; Cornelia Pirulli; Michele Ferrara; Paolo Maria Rossini; et al. Cortical Plasticity Induced by Transcranial Magnetic Stimulation during Wakefulness Affects Electroencephalogram Activity during Sleep. *PLOS ONE* **2008**, *3*, e2483, 10.1371/journal.pone.0002483.

58. Eman M. Khedr; Khaled O. Mohamed; Anwar M. Ali; Asmaa M. Hasan; The effect of repetitive transcranial magnetic stimulation on cognitive impairment in Parkinson’s disease with dementia: Pilot study. *Restorative Neurology and Neuroscience* **2020**, *38*, 55-66, 10.3233/RNN-190956.

59. Ayhan Aşkın; Aliye Tosun; Ümit Seçil Demirdal; Effects of low-frequency repetitive transcranial magnetic stimulation on upper extremity motor recovery and functional outcomes in chronic stroke patients: A randomized controlled trial. *Somatosensory & Motor Research* **2017**, *34*, 102-107, 10.1080/08990220.2017.1316254.

60. Sophie Baudic; Nadine Attal; Alaa Mhalla; Daniel Ciampi de Andrade; Serge Perrot; Didier Bouhassira; Unilateral repetitive transcranial magnetic stimulation of the motor cortex does not affect cognition in patients with fibromyalgia. *Journal of Psychiatric Research* **2013**, *47*, 72-77, 10.1016/j.jpsychires.2012.09.003.

61. Sagarika Bhattacharjee; Rajan Kashyap; Turki Abualait; Sh Annabel Chen; Woo-Kyoung Yoo; Shahid Bashir; The Role of Primary Motor Cortex: More Than Movement Execution. *Journal of Motor Behavior* **2020**, *53*, 258-274, 10.1080/00222895.2020.1738992.

62. Francesca Vitale; Iván Padrón; Alessio Avenanti; Manuel de Vega; Enhancing Motor Brain Activity Improves Memory for Action Language: A tDCS Study. *Cerebral Cortex* **2020**, *31*, 1569-1581, 10.1093/cercor/bhaa309.

63. Barbara Tomasino; Michele Gremese; The Cognitive Side of M1. *Frontiers in Human Neuroscience* **2016**, *10*, 298, 10.3389/fnhum.2016.00298.

64. Nikola Vukovic; Matteo Feurra; Anna Shpektor; Andriy Myachykov; Yury Shtyrov; Primary motor cortex functionally contributes to language comprehension: An online rTMS study. *Neuropsychologia* **2017**, *96*, 222-229, 10.1016/j.neuropsychologia.2017.01.025.

65. Rossella Breveglieri; Sara Borgomaneri; Matteo Filippini; Marina De Vitis; Alessia Tessari; Patrizia Fattori; Functional Connectivity at Rest between the Human Medial Posterior Parietal Cortex and the Primary Motor Cortex Detected by Paired-Pulse Transcranial Magnetic Stimulation. *Brain Sciences* **2021**, *11*, 1357, 10.3390/brainsci11101357.

66. Giorgio Fuggetta; Enea F. Pavone; Antonio Fiaschi; Paolo Manganotti; Acute modulation of cortical oscillatory activities during short trains of high-frequency repetitive transcranial magnetic stimulation of the human motor cortex: A combined EEG and TMS study. *Human Brain Mapping* **2007**, *29*, 1-13, 10.1002/hbm.20371.

67. Sven Bestmann; Jurgen Baudewig; Hartwig R. Siebner; John Rothwell; Jens Frahm; Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *European Journal of Neuroscience* **2004**, *19*, 1950-1962, 10.1111/j.1460-9568.2004.03277.x.

68. Christen M. O'Neal; Lindsey N. Schroeder; Allison A. Wells; Sixia Chen; Tressie M. Stephens; Chad A. Glenn; Andrew K. Conner; Patient Outcomes in Disorders of Consciousness Following Transcranial Magnetic Stimulation: A Systematic Review and Meta-Analysis of Individual Patient Data. *Frontiers in Neurology* **2021**, *12*, 694970, 10.3389/fneur.2021.694970.

69. Binlong Zhang; Jiao Liu; Tuya Bao; Georgia Wilson; Joel Park; Bingcong Zhao; Jian Kong; Locations for noninvasive brain stimulation in treating depressive disorders: A combination of meta-analysis and resting-state functional connectivity analysis. *Australian & New Zealand Journal of Psychiatry* **2020**, *54*, 582-590, 10.1177/0004867420920372.

70. Masachika Niimi; Tamaki Ishima; Kenji Hashimoto; Takatoshi Hara; Naoki Yamada; Masahiro Abo; Effect of repetitive transcranial magnetic stimulation on the kynurenine pathway in stroke patients. *NeuroReport* **2020**, *31*, 629-636, 10.1097/wnr.0000000000001438.
71. Berthold Kepplinger; Stroke Patients after repetitive Transcranial Magnetic Stimulation (rTMS)–Alterations of Tryptophan Metabolites in the Serum. *International Journal of Neurorehabilitation* **2014**, *01*, 1-11, 10.4172/2376-0281.1000128.
72. Kamiyu Ogyu; Kaoruhiko Kubo; Yoshihiro Noda; Yusuke Iwata; Sakiko Tsugawa; Yuki Omura; Masataka Wada; Ryosuke Tarumi; Eric Plitman; Sho Moriguchi; et al. Kynurenine pathway in depression: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews* **2018**, *90*, 16-25, 10.1016/j.neubiorev.2018.03.023.
73. Attila Makkos; Endre Pal; Zsuzsanna Aschermann; József Janszky; Éva Balázs; Katalin Takács; Kázmér Karádi; Sámuel Komoly; Norbert Kovacs; High-Frequency Repetitive Transcranial Magnetic Stimulation Can Improve Depression in Parkinson's Disease: A Randomized, Double-Blind, Placebo-Controlled Study. *Neuropsychobiology* **2016**, *73*, 169-177, 10.1159/000445296.
74. Xue Jiang; Wangwang Yan; Ruihan Wan; Yangyang Lin; Xiaoxia Zhu; Ge Song; Kangyong Zheng; Yuling Wang; Xueqiang Wang; Effects of repetitive transcranial magnetic stimulation on neuropathic pain: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews* **2021**, *132*, 130-141, 10.1016/j.neubiorev.2021.11.037.
75. D Centonze; F Petta; Viviana Versace; Silvia Rossi; F Torelli; C Prosperetti; Ga Marfia; G Bernardi; Giacomo Koch; Roberto Miano; et al. Effects of motor cortex rTMS on lower urinary tract dysfunction in multiple sclerosis. *Multiple Sclerosis Journal* **2007**, *13*, 269-271, 10.1177/1352458506070729.
76. Jiwei Yao; Quanchao Zhang; Xiang Liao; Qianwei Li; Shanshan Liang; Xianping Li; Yalun Zhang; Xiangning Li; Haoyu Wang; Han Qin; et al. A corticopontine circuit for initiation of urination. *Nature Neuroscience* **2018**, *21*, 1541-1550, 10.1038/s41593-018-0256-4.
77. Zheyi Ni; Hailan Hu; Let it go: central neural control of urination.. *Nature Neuroscience* **2018**, *21*, 1499-1501, 10.1038/s41593-018-0259-1.
78. Livia Brusa; Enrico Finazzi Agrò; Filomena Petta; Francesco Sciobica; Sara Torriero; Emanuele Lo Gerfo; Cesare Iani; Paolo Stanzione; Giacomo Koch; Effects of inhibitory rTMS on bladder function in Parkinson's disease patients. *Movement Disorders* **2009**, *24*, 445-447, 10.1002/mds.22434.
79. Mauro Cervigni; Emanuela Onesti; Marco Ceccanti; Maria C. Gori; Giorgio Tartaglia; Giuseppe Campagna; Giovanni Panico; Lorenzo Vacca; Chiara Cambieri; Laura Libonati; et al. Repetitive transcranial magnetic stimulation for chronic neuropathic pain in patients with bladder pain syndrome/interstitial cystitis. *Neurourology and Urodynamics* **2018**, *37*, 2678-2687, 10.1002/nau.23718.