Application of Repetitive Transcranial Magnetic Stimulation in Tourette Syndrome

10

Antonio Mantovani

Tic disorders have been the subject of etiological speculation for at least the past 300 years. Over the past 35 years, Tourette syndrome (TS) has come to be recognized as a model of neurodevelopmental disorder representing the nexus between neurology and psychiatry [1, 2]. The identification of abnormalities involving the basal ganglia in postmortem [3] and neuroimaging studies [4], the possibility of a post-infectious etiology for some cases of the disorder [5, 6], and the increasing appreciation of the interaction of genetic [7] and environmental factors [8] in disease expression, have all contributed to making TS a model for understanding developmental psychopathology more broadly. The reality for patients is that TS can be a devastating condition, which alone, or in combination with other closely associated forms of psychopathology, causes patients and their families considerable suffering [9, 10].

TS is a childhood-onset neuropsychiatric disorder characterized by chronic motor and vocal tics that are often preceded by premonitory urges [11]. Although tic symptoms in the majority of children with TS improve during adolescence, adults with persistent illness can experience chronic and severe tics [12].

Randomized controlled trials (RCTs) have documented the efficacy of several behavioral and pharmacological treatments for TS [13, 14]. However, approximately one-third of individuals with TS do not benefit from first-line treatments, and several of the most effective medications used to treat tics have significant side effects [15, 16].

Considering that the basal ganglia and the thalamocortical systems play an important role in habit formation and are implicated in the pathophysiology of TS [17], the experimental use of deep brain stimulation (DBS), targeting the thalamus,

A. Mantovani (✉)
Department of Cellular, Molecular and Biomedical Sciences, CUNY School of Medicine, City University of New York, New York, NY, USA

Department of Medicine and Health Sciences "V. Tiberio", Molise University, Campobasso, Italy
e-mail: AMantovani@med.cuny.edu

B. Dell'Osso, G. Di Lorenzo (eds.), *Non Invasive Brain Stimulation in Psychiatry and Clinical Neurosciences*,
https://doi.org/10.1007/978-3-030-43356-7_10

the posteroventrolateral part and the anteromedial part of the globus pallidus internus, the anterior limb of the internal capsule and the nucleus accumbens, has been shown to produce positive results for a proportion of children, adolescents, and adults with severe TS [18–20].

However, to date, the largest RCT failed to prove the efficacy of DBS in TS [21], and the optimal site for electrode placement has yet to be determined [22, 23]. In addition, DBS can be associated with serious adverse effects, including an increased risk of infection [24, 25]. In this context, novel, less-invasive treatments to reduce tic severity are urgently needed, especially for patients with severe TS.

Transcranial magnetic stimulation (TMS) is a noninvasive tool of stimulating targeted cortical regions in TS [26]. Initial repetitive TMS (rTMS) studies targeting motor and premotor cortical sites with either low-frequency (1-Hz) or high-frequency (15-Hz) protocols have had limited or no success in treating individuals with severe TS [27–29]. More recently, several open-label studies have reported that 1-Hz rTMS targeting the supplementary motor area (SMA) can decrease the frequency and intensity of tics [30–35].

Based on the importance of sensory signals and their integration with subsequent motor acts [36–38], the SMA seems to be a promising target for rTMS. As early as the 1980s, Eccles [39] speculated that the SMA was involved in the intentional preparation of movements [40]. More recently, event-related functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) techniques have implicated the SMA in the preparation and organization of voluntary movements [41, 42]. Not only does stimulation of this region produce both movements and urges to move (reminiscent of the premonitory urges of TS) but also the nature of the movements or corresponding urges ranges from simple motor acts to complex movements, paralleling the range of simple to complex tics experienced in TS [43]. Neuroimaging studies examining patterns of brain activation in individuals with TS have consistently identified the SMA as one of the structures that is active simultaneously with tics as well as in the seconds preceding tics [44–48].

Hampson et al. [49] compared the temporal patterns of brain activity during tics in 16 TS patients to those during intentional “tic-like” movements in control subjects. Rather than relying on a subjective judgment of when tics occurred, a novel method was employed that first identified that part of the motor cortex specific to each patient’s tic movement, and then cross-correlated activity in that region with activity in other brain areas during tics. Regions implicated in sensory urges, particularly the SMA and somatosensory cortex, were hypothesized to show differential time courses in patients and controls. A nearly identical sequence of brain activity was observed across groups. However, only the SMA showed a significantly different profile with cross-correlations to motor cortex extending over a significantly broader time window in the patients relative to controls. The SMA was active both earlier and later in the patients, implying that it is involved in both tics and intentional movements. These findings highlight the potential importance of the SMA in tic generation and point toward novel focal brain stimulation intervention strategies for TS.

An RCT with 1-Hz rTMS targeting the SMA failed to find a statistical difference in clinical improvement between the active and the sham (placebo) groups after 3 weeks. However, in the 3-week open-label continuation phase of the study, patients who received a total of 6 weeks of rTMS showed on average 30% decrease in the Yale Global Tic Severity Score (YGTSS) with a sizable proportion of the TS subjects who received active rTMS for 6 weeks judged to be responders (57.1%) [50].

rTMS was administered with the Magstim super-rapid stimulator (Magstim Company Ltd, UK) using a vacuum-cooled 70-mm figure-of-eight coil. Stimulation parameters were 1-Hz, 30-min train (1800 pulses/day) at 110% of resting motor threshold-MT (using the lowest value of right or left hemisphere), once a day, 5 days/week, for 3 (in the double-blind phase) to 6 weeks (in the continuation open-label phase). The coil was positioned over pre-SMA using the International 10–20 EEG System coordinates. Pre-SMA was defined at 15% of the distance between inion and nasion anterior to Cz (vertex) on the sagittal midline [33]. Brainsight TMS navigation system was used to locate and monitor online the stability of coil placement during each rTMS session. The coil was placed with the handle along the sagittal midline, pointing toward the occiput to stimulate bilaterally and simultaneously the pre-SMA.

Sham rTMS was administered using the Magstim sham coil, which contains a mu-metal shield that diverts the majority of the magnetic flux so that a minimal (<3%) magnetic field is delivered to the cortex [51]. To maintain the blind, raters were blinded to treatment condition with a separation between the clinical team and rTMS treating physician(s). Moreover, patients who had received TMS treatments in the past were excluded.

Before and after each session, patients were asked a series of questions in a structured form to rate rTMS side-effects. In addition, subjects were asked to complete the Systematic Assessment for Treatment Emergent Effects (SAFTEE) [52].

Twenty patients entered and 18 completed phase 1 (3-week double-blind phase). Regarding the 20 patients who met criteria for TS, a 33% (3/9) response rate was observed in those randomized to active rTMS and 18% (2/11) with sham rTMS (Fisher's exact test, $p = 0.62$). Analysis of 18 completers showed a response rate of 37.5% (3/8) with active and 20% (2/10) with sham rTMS (Fisher's exact test, $p = 0.61$) at the end of the double-blind phase.

Seventeen patients entered and 16 completed the open-label phase (seven initially randomized to active and nine to sham). Nine patients initially randomized to sham had no significant change in their YGTSS total tic scores after 3 weeks of active rTMS (from 32.9 ± 8.4 to 31.8 ± 8.5; $F = 0.64$, df = 2,16, $p = 0.54$). Seven patients initially randomized to active rTMS, who received an additional 3-week active rTMS, showed further improvements from weeks 3 to 6 on the YGTSS total tic scores (from 31.1 ± 9.5 to 25.3 ± 6.7, $F = 0.58$, df = 2,12, $p = 0.57$). The mean improvement in the total tic severity score from baseline to 6 weeks [mean reduction of YGTSS score = 10.7 points (29.7%)] for the 7 patients who completed the 6 weeks of active treatment was statistically significant ($t = 2.6$, df = 6, $p = 0.04$).

No major side effects were noted during the course of treatment. Specifically, there were no seizures, neurological complications, or complaints about memory or

concentration difficulties. Headache, neck pain, and muscle sprain were the only side effects reported as "severe" in active treatment. Only in one instance was there a "severe" side effect, i.e., a severe headache, judged to be treatment related.

A major limitation of this study is the relatively small sample size and short blinded phase. A larger sample and longer blinded phase will be needed to definitively evaluate whether 6 weeks of low-frequency rTMS targeting the SMA is clinically efficacious in reducing tic severity. This is an important consideration given that optimal antidepressant effects result from the application of rTMS for 4–6 weeks [53].

In fact, recently, three patients with severe, medication-refractory TS, and comorbid obsessive-compulsive disorder (OCD) in two of them, received rTMS at 1-Hz to the SMA for 4-week duration. The first two cases of TS-OCD showed, on average, 57% improvement in the YGTSS scores and 45% improvement in Yale-Brown Obsessive–Compulsive Scale (Y-BOCS) scores; the third case of pure-TS showed marginal improvement of 10% only. The improvement in TS-OCD patients with rTMS treatment was maintained at the end of 3-month follow-up, with an average reduction of about 49% and 36% observed in YGTSS and Y-BOCS scores, respectively [54].

rTMS to the SMA has been successfully tested in treatment-resistant OCD in RCTs [55–57] and as an augmentation to pharmacotherapy [58–60]. A recent meta-analysis showed that low-frequency rTMS of the SMA yielded the greatest reductions in Y-BOCS scores relative to other cortical targets in the short- and long-term follow-ups [61]. Specifically, the clinical effect of 1-Hz rTMS to the SMA correlated with changes in cortical excitability measures, consistent with an inhibitory action of rTMS on dysfunctional premotor and motor circuits in OCD [62]. The SMA target was selected, based on the results of a deficient sensory gating and enhanced precentral somatosensory-evoked potentials in OCD, which might reflect the inability to modulate sensory information due to a tonic high level of cortical excitability of motor and related areas [63].

Recently, optogenetic stimulation revealed that secondary motor area (M2) post-synaptic responses in central striatum were significantly increased in strength and reliability in *Sapap3* knockout mouse model of compulsive behaviors, suggesting that increased M2-striatal drive may contribute to both striatal hyperactivity and compulsive behaviors. Because M2 is thought to be homologous to pre-SMA/SMA in humans, regions considered important for movement preparation and behavioral sequencing, these results are consistent with a model in which increased drive from M2 leads to the excessive selection of sequenced motor patterns and support a potential role for pre-SMA/SMA in the pathology and treatment of compulsive behavior disorders, like OCD and Tourette syndrome [64].

Considering the overlap in the pathophysiology of OCD and TS [65], with OCD symptoms reported in 50–90% of patients with TS [66], with studies suggesting an involvement of the basal ganglia circuit, especially disruption of the indirect pathway resulting in repetitive behaviors and thoughts in comorbid OCD and TS [67], and considering that single and paired-pulse TMS found a deficit in intracortical inhibition in both OCD and TS [68], it is plausible to think that the application of

low-frequency rTMS to the SMA might be particularly helpful in patients with comorbid TS-OCD.

Studies using motor-evoked potential (MEP) and phosphene threshold have shown that 1-Hz rTMS to motor and occipital cortex, respectively, reduces cortical excitability [69, 70]. One-Hertz rTMS to prefrontal cortex reduces blood flow [71, 72]. Studies have demonstrated that suppressive effects of rTMS to one region can be propagated to other cortical regions via functional connections. For example, 1-Hz rTMS to motor cortex reduces MEP induction in the contralateral motor cortex [73] and reduces the Bereitschaftspotential, a slow negative EEG potential arising from the SMA [74].

The mechanism of action of 1-Hz rTMS is thought to be analogous to long-term depression induced by direct electrical stimulation. One-Hertz rTMS may produce neuroplastic effects similar to that produced by direct 1-Hz electrical stimulation of gray matter in animal studies, which often produces a phenomenon known as long-term depression (LTD). LTD in the hippocampus and cerebral cortex has been widely replicated [75–77]. Like 1-Hz rTMS, LTD requires 15–30 minutes of continuous 1-Hz stimulation, has cumulative effects if stimulation is repeated over many days, and propagates trans-synaptically to other functionally connected brain regions [78]. LTD can last for many weeks, indeed as long as the experimental animal can be maintained [79]. If 1-Hz rTMS produces LTD-like effects, rTMS-induced alterations in brain function may produce clinically significant effects lasting beyond the period of stimulation.

Our pioneering open-label study, which targeted the SMA, demonstrated that 1-Hz rTMS produced a significant clinical improvement (67% reduction in tic severity) in patients with comorbid OCD and TS [33]. We demonstrated in two other cases affected with TS and comorbid OCD a 52% clinical improvement that matches or exceeds approved behavioral or pharmacological interventions for TS [80].

The clinical efficacy of rTMS in patients with TS and OCD was reported in a recent meta-analysis. The authors included eight studies, with a sample of 113 subjects, and showed that rTMS significantly improved tic ($g = -0.61$; CI: −0.94 to −0.29) and OCD ($g = -0.48$; CI: −0.83 to −0.14) symptoms in TS patients. Stimulation of the SMA was more effective in tic symptoms than the stimulation of other areas ($g = -0.70$; CI: −1.11 to −0.30 vs. $g = -0.36$; CI: −0.84 to 0.14), and younger age was associated with a better treatment effect (coefficient = 0.03, $p = 0.027$) [81].

Wu et al. [82] suggested using a patient-specific targeting procedure and a novel rTMS paradigm, named continuous theta burst stimulation (cTBS). In their RCT, mean YGTSS scores decreased in both active (27.5 ± 7.4 to 23.2 ± 9.8) and sham (26.8 ± 4.8 to 21.7 ± 7.7) groups. No significant difference in video-based tic severity rating was detected between the two groups. However, the two-day post-treatment fMRI activation during finger tapping decreased significantly with active rTMS and not with sham in the SMA ($p = 0.02$), left M1 ($p = 0.0004$), and right M1 ($p < 0.0001$). Therefore, active fMRI-navigated cTBS administered over 2 days to the SMA induced significant inhibition in the motor network (SMA, bilateral M1),

but larger sample size and protocol modifications (i.e., higher number of rTMS sessions) may be needed to produce clinically significant tic reduction.

Since cTBS provides more potent inhibitory neuromodulatory effects [83], the efficacy of fMRI targeted cTBS should be evaluated over a longer period of time in TS patients before any definite conclusions can be made concerning its clinical efficacy. In addition, based on our laterality findings in TS and OCD patients' right hemisphere cortical excitability measures after active rTMS but not sham [33, 50, 56, 57, 62], and the recent work of Obeso et al. [84], a case can potentially be made to target preferentially the right pre-SMA with cTBS. Specifically, combining cTBS with oxygen 15-labeled water ($H_2{}^{15}O$) PET scans acquired during a stop signal task, Obeso and colleagues found that cTBS-induced changes in the excitability of the right pre-SMA (as compared to sham cTBS) enhanced response inhibition. They also found that cTBS over the right pre-SMA was associated with increased blood flow in the left pre-SMA, the left inferior frontal gyrus, as well as the right premotor and right inferior parietal cortex. If cTBS over the right pre-SMA can enhance response inhibition, then it might also have a beneficial effect on tics. In a recent RCT, including 27 treatment-refractory OCD patients, fMRI-guided rTMS to the pre-SMA improved significantly symptoms, and such improvement correlated with measures of cortical excitability (i.e., % of reduction on self-reported YBOCS correlated with increased MT) [85]. In another study, bilateral stimulation of the pre-SMA induced a clinical improvement in OCD symptoms and increased functional connectivity between the rTMS target and the right inferior frontal gyrus and orbitofrontal cortex (Mantovani et al. unpublished data).

Therefore, based on the preliminary evidence of a clinical and neurophysiological effect of rTMS applied to the SMA in patients with TS and OCD, the application of low-frequency rTMS protocols holds promise in the treatment of refractory cases and might be tried in the future with improved target selection and stimulation procedures before the application of more invasive interventions, such as electroconvulsive therapy [86], DBS [20], and gamma knife capsulotomy [87].

References

1. Leckman JF. Tourette syndrome. Lancet. 2002;360:1577–86.
2. Leckman JF, Vaccarino FM, Kalanithi PS, Rothenberger A. Annotation: Tourette syndrome: a relentless drumbeat driven by misguided brain oscillations. J Child Psychol Psychiatry. 2006;47:537–50.
3. Kalanithi PS, Zheng W, DiFiglia M, DiFiglia M, Grantz H, Saper CB, et al. Altered parvalbumin-positive neuron distribution in basal ganglia of individuals with Tourette syndrome. Proc Natl Acad Sci U S A. 2005;102:13307–12.
4. Albin RL, Mink JW. Recent advances in Tourette syndrome research. Trends Neurosci. 2006;29:175–82.
5. Mell LK, Davis RL, Owens D. Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder. Pediatrics. 2005;116:56–60.
6. Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry. 1998;155:264–71.

7. Abelson JF, Kwan KY, O'Roak BJ, Baek DY, Stillman AA, Morgan TM, et al. Mutations in *SLITRK1* are associated with Tourette syndrome. Science. 2005;310:317–20.
8. Lin H, Katsovich L, Ghebremichael M, Findley DB, Grantz H, Lombroso PJ, et al. Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. J Child Psychol Psychiatry. 2007;48:157–66.
9. Davis KK, Davis JS, Dowler L. In motion, out of place: the public space(s) of Tourette syndrome. Soc Sci Med. 2004;59:103–12.
10. Elstner K, Selai CE, Trimble MR, Robertson MM. Quality of Life (QOL) of patients with Gilles de la Tourette's syndrome. Acta Psychiatr Scand. 2001;103:52–9.
11. Leckman JF, Bloch MH, Sukhodolsky DG. Phenomenology of tics and sensory urges: the self under siege. In: Martino D, Leckman JF, editors. Tourette syndrome. New York: Oxford University Press; 2013. p. 3–25.
12. Bloch MH, Peterson BS, Scahill L, Otka J, Katsovich L, Zhang H, et al. Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. Arch Pediatr Adolesc Med. 2006;160:65–9.
13. McGuire JF, Piacentini J, Brennan EA, Lewin AB, Murphy TK, Small BJ, et al. A meta-analysis of behavior therapy for Tourette syndrome. J Psychiatr Res. 2014;50:106–12.
14. Roessner V, Rothenberger A, Rickards H, Ludolph AG, Rizzo R, Skov L, et al. European clinical guidelines for Tourette syndrome and other tic disorders. Eur Child Adolesc Psychiatry. 2011;20:153–4.
15. Robertson MM, Stern JS. Gilles de la Tourette syndrome: symptomatic treatment based on evidence. Eur Child Adolesc Psychiatry. 2000;9:60–75.
16. Roessner V, Rothenberger A. Pharmacological treatment of tics. In: Martino D, Leckman JF, editors. Tourette syndrome. New York: Oxford University Press; 2013. p. 454–62.
17. Groenewegen HJ, van den Heuvel OA, Cath DC, Voorn P, Veltman DJ. Does an imbalance between the dorsal and ventral striatopallidal systems play a role in Tourette's syndrome? A neuronal circuit approach. Brain Dev. 2003;25(Suppl 1):S3–S14.
18. Baldermann JC, Schüller T, Huys D, Becker I, Timmermann L, Jessen F, et al. Deep brain stimulation for Tourette syndrome: a systematic review and meta-analysis. Brain Stimul. 2016;9:296–304. https://doi.org/10.1016/j.brs.2015.11.005.
19. Coulombe MA, Elkaim LM, Alotaibi NM, Gorman DA, Weil AG, Fallah A, et al. Deep brain stimulation for Gilles de la Tourette syndrome in children and youth: a meta-analysis with individual participant data. J Neurosurg Pediatr. 2018;23:236–46. https://doi.org/10.3171/2018.7.PEDS18300.
20. Martinez-Ramirez D, Jimenez-Shahed J, Leckman JF, Porta M, Servello D, Meng FG, et al. Efficacy and safety of deep brain stimulation in Tourette syndrome: the international Tourette syndrome deep brain stimulation public database and registry. JAMA Neurol. 2018;75:353–9.
21. Welter ML, Houeto JL, Thobois S, Bataille B, Guenot M, Worbe Y, et al. STIC study group. Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial. Lancet Neurol. 2017;16:610–19.
22. Johnson KA, Fletcher PT, Servello D, Bona A, Porta M, Ostrem JL, et al. Image-based analysis and long-term clinical outcomes of deep brain stimulation for Tourette syndrome: a multisite study. J Neurol Neurosurg Psychiatry. 2019;90(10):1078–90. pii: jnnp-2019-320379. https://doi.org/10.1136/jnnp-2019-320379.
23. Kakusa B, Saluja S, Tate WJ, Espil FM, Halpern CH, Williams NR. Robust clinical benefit of multi-target deep brain stimulation for treatment of Gilles de la Tourette syndrome and its comorbidities. Brain Stimul. 2019;12:816–8.
24. Buhmann C, Huckhagel T, Engel K, Gulberti A, Hidding U, Poetter-Nerger M, et al. Adverse events in deep brain stimulation: a retrospective long-term analysis of neurological, psychiatric and other occurrences. PLoS One. 2017;12:e0178984. https://doi.org/10.1371/journal.pone.0178984.
25. Servello D, Sassi M, Gaeta M, Ricci C, Porta M. Tourette syndrome bears a higher rate of inflammatory complications at the implanted hardware in deep brain stimulation. Acta Neurochir (Wien). 2011;153:629–32.

26. Orth M. Transcranial magnetic stimulation in Gilles de la Tourette syndrome. J Psychosom Res. 2009;67:591–8.
27. Chae JH, Nahas Z, Wassermann E, Li X, Sethuraman G, Gilbert D, et al. A pilot safety study of repetitive transcranial magnetic stimulation in Tourette's syndrome. Cogn Behav Neurol. 2004;17:109–17.
28. Munchau A, Bloem BR, Thilo KV, Trimble MR, Rothwell JC, Robertson MM. Repetitive transcranial magnetic stimulation for Tourette syndrome. Neurology. 2002;59:1789–91.
29. Orth M, Kirby R, Richardson MP, Rothwell JC, Trimble MR, Robertson MM, et al. Subthreshold rTMS over pre-motor cortex has no effect on tics in patients with Gilles de la Tourette syndrome. Clin Neurophysiol. 2005;116:764–8.
30. Bloch Y, Arad S, Levkovitz Y. Deep TMS add-on treatment for intractable Tourette syndrome: a feasibility study. World J Biol Psychiatry. 2016;17:557–61. https://doi.org/10.3109/15622975.2014.964767.
31. Kwon HJ, Lim WS, Lim MH, Lee SJ, Hyun JK, Chae JH, et al. 1-Hz low frequency repetitive transcranial magnetic stimulation in children with Tourette's syndrome. Neurosci Lett. 2011;492:1–4.
32. Le K, Liu L, Sun MHL, Xiao N. Transcranial magnetic stimulation at 1 Hertz improves clinical symptoms in children with Tourette syndrome for at least 6 months. J Clin Neurosci. 2013;20:257–62.
33. Mantovani A, Lisanby SH, Pieraccini F, Ulivelli M, Castrogiovanni P, Rossi S. Repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder and Tourette's syndrome. Int J Neuropsychopharmacol. 2006;9:95–100.
34. Mantovani A, Leckman JF, Grantz H, King RA, Sporn AL, Lisanby SH. Repetitive transcranial magnetic stimulation of the supplementary motor area in the treatment of Tourette syndrome: report of two cases. Clin Neurophysiol. 2007;118:2314–5.
35. Salatino A, Momo E, Nobili M, Berti A, Ricci R. Awareness of symptoms amelioration following low-frequency repetitive transcranial magnetic stimulation in a patient with Tourette syndrome and comorbid obsessive-compulsive disorder. Brain Stimul. 2014;7:341–3.
36. Alexander G, Crutcher M, DeLong M. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal", and "limbic" functions. Prog Brain Res. 1990;85:119–46.
37. Graybiel AM. The basal ganglia: learning new tricks and loving it. Curr Opin Neurobiol. 2005;15:638–44.
38. Haber SN. The primate basal ganglia: parallel and integrative networks. J Chem Neuroanat. 2003;26:317–30.
39. Eccles JC. The initiation of voluntary movements by the supplementary motor area. Arch Psychiatr Nervenkr. 1982;231:423–41.
40. Wiesendanger M. Eccles' perspective of the forebrain, its role in skilled movements, and the mind-brain problem. Prog Neurobiol. 2006;78:304–21.
41. Cunnington R, Windischberger C, Moser E. Premovement activity of the pre-supplementary motor area and the readiness for action: studies of time-resolved event-related functional MRI. Hum Mov Sci. 2005;24:644–56.
42. Lerner A, Bagic A, Hanakawa T, Boudreau EA, Pagan F, Mari Z, et al. Involvement of insula and cingulate cortices in control and suppression of natural urges. Cereb Cortex. 2009;19:218–23.
43. Fried I, Katz A, McCarthy G, Sass KJ, Williamson P, Spencer SS, et al. Functional organization of human supplementary motor cortex studied by electrical stimulation. J Neurosci. 1991;11:3656–66.
44. Bohlhalter S, Goldfine A, Matteson S, Garraux G, Hanakawa T, Kansaku K, et al. Neural correlates of tic generation in Tourette syndrome: an event-related functional MRI study. Brain. 2006;129:2029–37.
45. Braun AR, Stoetter B, Randolph C, Hsiao JK, Vladar K, Gernert J, et al. The functional neuroanatomy of Tourette's syndrome: an FDG-PET study. Regional changes in cerebral glucose metabolism differentiating patients and controls. Neuropychopharmacology. 1993;9:277–91.

46. Chase TN, Geoffrey V, Gillespie M, Burrows GH. Structural and functional studies of Gilles de la Tourette syndrome. Rev Neurol. 1986;142:851–5.
47. Eidelberg D, Moeller JR, Antonini A, Kazumata K, Dhawan V, Budman C, et al. The metabolic anatomy of Tourette's syndrome. Neurology. 1997;48:927–34.
48. Stern E, Silbersweig DA, Chee KY, Holmes A, Robertson MM, Trimble M, et al. A functional neuroanatomy of tics in Tourette Syndrome. Arch Gen Psychiatry. 2000;57:741–8.
49. Hampson M, Tokoglu F, King RA, Constable RT, Leckman JF. Brain areas coactivating with motor cortex during chronic motor tics and intentional movements. Biol Psychiatry. 2009;65:594–9. https://doi.org/10.1016/j.biopsych.2008.11.012.
50. Landeros-Weisenberger A, Mantovani A, Motlagh MG, de Alvarenga PG, Katsovich L, Leckman JF, et al. Randomized sham controlled double-blind trial of repetitive transcranial magnetic stimulation for adults with severe Tourette syndrome. Brain Stimul. 2015;8:574–81. https://doi.org/10.1016/j.brs.2014.11.015.
51. Rossi S, Ferro M, Cincotta M, Ulivelli M, Bartalini S, Miniussi C, et al. A real electromagnetic placebo device for sham transcranial magnetic stimulation. Clin Neurophysiol. 2007;118:709–16.
52. Levine J, Schooler NR. SAFETEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacol Bull. 1986;22:343–81.
53. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry. 2007;62:1208–16.
54. Singh S, Kumar S, Kumar N, Verma R. Low-frequency repetitive transcranial magnetic stimulation for treatment of Tourette syndrome: a naturalistic study with 3 months of follow-up. Indian J Psychol Med. 2018;40:482–6.
55. Hawken ER, Dilkov D, Kaludiev E, Simek S, Zhang F, Milev R. Transcranial magnetic stimulation of the supplementary motor area in the treatment of obsessive-compulsive disorder: a multi-site study. Int J Mol Sci. 2016;17:420. https://doi.org/10.3390/ijms17030420.
56. Mantovani A, Simpson HB, Fallon BA, Rossi S, Lisanby SH. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. Int J Neuropsychopharmacol. 2010;13:217–27. https://doi.org/10.1017/S1461145709990435.
57. Mantovani A, Westin G, Hirsch J, Lisanby SH. Functional magnetic resonance imaging guided transcranial magnetic stimulation in obsessive-compulsive disorder. Biol Psychiatry. 2010;67:e39–40. https://doi.org/10.1016/j.biopsych.2009.08.009.
58. Kumar N, Chadda RK. Augmentation effect of repetitive transcranial magnetic stimulation over the supplementary motor cortex in treatment refractory patients with obsessive compulsive disorder. Indian J Psychiatry. 2011;53:340–2. https://doi.org/10.4103/0019-5545.91909.
59. Lee YJ, Koo BH, Seo WS, Kim HG, Kim JY, Cheon EJ. Repetitive transcranial magnetic stimulation of the supplementary motor area in treatment-resistant obsessive-compulsive disorder: an open-label pilot study. J Clin Neurosci. 2017;44:264–8. https://doi.org/10.1016/j.jocn.2017.06.057.
60. Pallanti S, Marras A, Salerno L, Makris N, Hollander E. Better than treated as usual: transcranial magnetic stimulation augmentation in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder, mini-review and pilot open-label trial. J Psychopharmacol. 2016;30:568–78. https://doi.org/10.1177/0269881116628427.
61. Rehn S, Eslick GD, Brakoulias V. A meta-analysis of the effectiveness of different cortical targets used in repetitive transcranial magnetic stimulation (rTMS) for the treatment of obsessive-compulsive disorder (OCD). Psychiatry Q. 2018;89:645–65. https://doi.org/10.1007/s11126-018-9566-7.
62. Mantovani A, Rossi S, Bassi BD, Simpson HB, Fallon BA, Lisanby SH. Modulation of motor cortex excitability in obsessive-compulsive disorder: an exploratory study on the relations of neurophysiology measures with clinical outcome. Psychiatry Res. 2013;210:1026–32. https://doi.org/10.1016/j.psychres.2013.08.054.

63. Rossi S, Bartalini S, Ulivelli M, Mantovani A, Di Muro A, Goracci A. Hypofunctioning of sensory gating mechanisms in patients with obsessive-compulsive disorder. Biol Psychiatry. 2005;57:16–20.
64. Corbit VL, Manning EE, Gittis AH, Ahmari SE. Strengthened inputs from secondary motor cortex to striatum in a mouse model of compulsive behavior. J Neurosci. 2019;39:2965–75. https://doi.org/10.1523/JNEUROSCI.1728-18.2018.
65. Hirschtritt ME, Darrow SM, Illmann C, Osiecki L, Grados M, Sandor P, et al. Genetic and phenotypic overlap of specific obsessive-compulsive and attention-deficit/hyperactive subtypes with Tourette syndrome. Psychol Med. 2018;48:279–93. https://doi.org/10.1017/S0033291717001672.
66. Gaze C, Kepley HO, Walkup JT. Co-occurring psychiatric disorders in children and adolescents with Tourette syndrome. J Child Neurol. 2006;21:657–64.
67. Nambu A, Tokuno H, Takada M. Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neurosci Res. 2002;43:111–7.
68. Bunse T, Wobrock T, Strube W, Padberg F, Palm U, Falkai P, et al. Motor cortical excitability assessed by transcranial magnetic stimulation in psychiatric disorders: a systematic review. Brain Stimul. 2014;7:158–69.
69. Boroojerdi B, Prager A, Muelibacher W, Cohen LG. Reduction of human visual cortex excitability using 1-Hz transcranial magnetic stimulation. Neurology. 2000;11:1529–31.
70. Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology. 1997;48:1398–403.
71. Speer AM, Kimbrell TA, Wassermann EM, Repella J, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry. 2000;48:133–41.
72. Speer AM, Willis MW, Herscovitch P, Daube-Witherspoon M, Shelton JR, Benson BE, et al. Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with H215O positron emission tomography: II. Effects of prefrontal cortex rTMS. Biol Psychiatry. 2003;54:826–32.
73. Wassermann EM, Wedegaertner FR, Ziemann UI, George MS, Chen R. Crossed reduction of human motor cortex excitability by 1-Hz transcranial magnetic stimulation. Neurosci Lett. 1998;250:141–4.
74. Rossi S, Pasqualetti P, Rossini PM, Feige B, Ulivelli M, Glocker FX, et al. Effects of repetitive transcranial magnetic stimulation on movement-related cortical activity in humans. Cereb Cortex. 2000;10:802–8.
75. Artola A, Brocher S, Singer W. Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. Nature. 1990;347:69–72.
76. Kirkwood A, Dudek S, Gold JT, Aizenman CD, Bear MF. Common forms of synaptic plasticity in the hippocampus and neocortex in vitro. Science. 1993;260:1518–21.
77. Stanton PK, Sejnowsky TJ. Associative long-term depression in the hippocampus induced by hebbian covariance. Nature. 1989;339:215–8.
78. Hoffman RE, Cavus I. Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. Am J Psychiatry. 2002;159:1093–102.
79. Bliss TVP, Gardner-Medwin AR. Long-lasting potentiation of the synaptic transimission in the detate area of the unanesthatized rabbit following stimulation of the perforant path. J Physiol. 1973;232:357–75.
80. Scahill L, Leckman JF, Schultz RT, Katsovich L, Peterson BS. A placebo-controlled trial of risperidone in Tourette syndrome. Neurology. 2003;60:1130–5.
81. Hsu CW, Wang LJ, Lin PY. Efficacy of repetitive transcranial magnetic stimulation for Tourette syndrome: a systematic review and meta-analysis. Brain Stimul. 2018;11:1110–8.
82. Wu SW, Maloney T, Gilbert DL, Dixon SG, Horn PS, Huddleston DA, et al. Functional MRI-navigated repetitive transcranial magnetic stimulation over supplementary motor area in chronic tic disorders. Brain Stimul. 2014;7:212–8.

83. Di Lazzaro V, Dileone M, Pilato F, Capone F, Musumeci G, Ranieri F, et al. Modulation of motor cortex neuronal networks by rTMS: comparison of local and remote effects of six different protocols of stimulation. J Neurophysiol. 2011;105:2150–6. https://doi.org/10.1152/jn.00781.2010.
84. Obeso I, Cho SS, Antonelli F, Houle S, Jahanshahi M, Ko JH, et al. Stimulation of the pre-SMA influences cerebral blood flow in frontal areas involved with inhibitory control of action. Brain Stimul. 2013;6:769–76.
85. Mantovani A, personal communication. Transcranial magnetic stimulation in obsessive-compulsive disorder: clinical, neurophysiolOGY and neuroimaging outcomes. In: Italian Society of Psychiatry National Meeting, June 23-26, 2019.
86. Dos Santos-Ribeiro S, de Salles Andrade JB, Quintas JN, Quintas JN, Baptista KB, Moreira-de-Oliveira ME, et al. A systematic review of the utility of electroconvulsive therapy in broadly defined obsessive-compulsive-related disorders. Prim Care Companion CNS Disord. 2018;18:20.
87. Zhang C, Deng Z, Pan Y, Zhang J, Zeljic K, Jin H, et al. Pallidal deep brain stimulation combined with capsulotomy for Tourette's syndrome with psychiatric comorbidity. J Neurosurg. 2019;4:1–9. https://doi.org/10.3171/2018.8.JNS181339.