**Supplemental material for:**

**Safety and recommendations (version 3.0) for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues**

A Consensus Statement from the IFCN Workshop on “Present and Future of TMS: Safety and Ethical Guidelines”, Siena, October 17-20, 2018 \*

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§ The views expressed are the authors’ own and do not necessarily represent the views of the National Institutes of Health or the United States Government.

**Table S1. Studies using TMS in patients with implanted stimulating/recording electrodes**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Authors | Year | Patients or ex vivo setup | Type of electrode | Electrodes location | Electrode connections | Parameters of stimulation for implanted electrodes | TMS | | Results |
| Ex-vivo studies | | | | | | | | | |
| Kumar et al | 1999 | Ex vivo magnetic stimulation over DBS leads and implanted pulse generator (IPG) | Model 3387, Medtronic (Minneapolis, MN, USA) | Conductive gel phantom; 3 lead loops (5 cm diameter) | Leads not connected; leads connected to Medtronic Itrel Model 3625 IPG; only IPG | Usual parameters for stimulation of GPI, stimulation on and off | Figure-8 coil or circular coil,single or pairedmonophasic pulses, 100% intensity (Magstim 200, Whitland, Wales, UK); coil–IPG distance 2–30 cm | | Maximum induced voltage of 0.08 V differentially between two electrode contacts at proximal end of lead (IPG not connected). TMS–IPG distances < 10 cm and < 2 cm altered and damaged IPG operation, respectively. |
| Kühn et al | 2003 | Ex vivo magnetic stimulation over DBS electrode in skull phantom | Kinetra, Medtronic | Skull phantom |  |  | Figure-8 coil with monophasic pulses (Magstim 200) | | Maximum induced voltage of 0.7 V (likely differentially between two electrode contacts). TMS–IPG distances < 10 cm and < 2 cm altered and damaged IPG operation, respectively. |
| Schrader et al | 2005 | Ex vivo magnetic stimulation directly overVNS leads and IPG | Cuff VNS electrodes | Conductive gel phantom | Leads connected to stimulator Model 102 IPG(Cyberonics, Inc., Houston, TX, USA) | Stimulation off | Figure-8, single biphasic pulses, 100% intensity (Magstim 220) | | Maximum induced current of 200 nA differentially between electrode contacts. No effect on IPG operation. |
| Shimojima et al | 2010 | Ex vivo magnetic stimulation over DBS electrode in gel and in phantom | Model 3389 electrode, Medtronic | Conductive gel phantom; no lead loop or 2 lead loops (3 cm diameter) | Soletra IPG, Medtronic |  | Figure-8 and double cone coil,monophasic pulses,5–100% intensity (Magstim 200), single pulses to 0.2 Hz rTMS | | No electrode displacement; no heating; maximum induced peak-to-peak amplitude of 7.7 V with no lead looping and 34 V with double loop at 50% output; charge density of 30 µC/cm2/phaseexceeded for 75% intensity with 2 loops or for more loops |
| Deng et al | 2010 | Ex vivo magnetic stimulation of DBS electrode lead connected to IPG | Libra electrodes (St. Jude Medical, Plano, TX, USA) | 1.2 kΩresistor to IPG case; 0–3 loops in lead (5 cm diameter) | Libra IPG (St. Jude Medical) | Stimulation off or on (0 mA or 4 mA) | Figure-8 coil, single monophasic pulses, up to 100% intensity (Magstim 200); circular coil, single biphasic pulses up to 20% intensity (Magstim Theta) | | At 100% intensity of Magstim 200, maximum induced peak voltage of 17 V and 100 V with 0 and 3lead loops, respectively. In on state IPG conducts for any induced voltage; in off stateIPG conducts for induced voltage > 5 V. |
| Kühn et al | 2011 | Ex vivo magnetic stimulation over DBS electrode lead with IPG | Model 3389, Medtronic | Air, no load, IPG 15 cm away from TMS coil | Activa PC and Activa RC, Medtronic | 4 V (contacts 0–, 3+), 90 μs, 10 Hz | Figure-8 coil, single monophasic pulses, 100% intensity (Magstim 200), every 3 s, 200 pulses | Maximum induced voltage of 2.8 V differentially between two contacts at distal end of leads. No changes to IGP settings or battery state. | |
| Phielipp et al | 2017 | Ex vivo magnetic stimulation over subdural cortical electrode in gel and in phantom | Resume II subdural cortical electrode model 3587A Metronic | Electrodes in conductive gel and phantom, with and without 1 lead loop | Lead not connected or connected to IPG Medtronic-Itrel II 7424 | 0–6 V, 90 μs, 90 Hz | Figure-8 coil, single biphasic pulses, 10–100% intensity (Magstim Super Rapid Plus); rTMS, 80% intensity, 20 Hz, 2,300 pulses | | No electrode displacement; induced heating near electrode likely insignificant; no IPG malfunction; maximum induced voltage of 25 V and 41 Vwith 0 and 1 lead loop, respectively; maximum charge density of 30.4 µC/cm2/phase |
| Spinal Electrodes | | | | | | | | |
| Kofler et al | 1991 | In vivo evaluation in 4 patients | Neuromed 1980JF lead, Medtronic Pisces Quad lead, Neuromed 1994JF lead | Spinal level: T11, T12, C3 | Medtronic Itrel II, model 7424 | Stimulator on and off | Focal TMS | |
| Di Lazzaro et al | 1998 | 2 conscious patients with intractable pain | Model Quad 3487A Medtronic | High cervical epidural space | Not connected to IPG | No stimulation | Focal single and paired pulse TMS | |
| Di Lazzaro et al | 1998 | 3 conscious patients with intractable pain | Model Quad 3487A Medtronic | High cervical epidural space | Not connected to IPG | No stimulation | Focal single pulse TMS | |
| Chen R et al | 1999 | 1 conscious patient | Resume Lead 3587A, Medtronic | C5-C7 epidural space | Not connected to IPG | No stimulation | Single pulse TMS, circular coil | |
| Tokimura et al | 2000 | 5 conscious patients with intractable pain | Model Quad 3487A Medtronic | High cervical epidural space | Not connected to IPG | No stimulation | Focal single pulse TMS | |
| Di Lazzaro et al | 2001 | 4 conscious patients with intractable pain | Model Quad 3487A Medtronic, | High cervical epidural space | Not connected to IPG | No stimulation | Focal monophasic and biphasic single pulse TMS | |
| Di Lazzaro et al | 2001 | 6 conscious patients with intractable low-back pain | Model Quad 3487A Medtronic | Thoracic epidural space | Not connected to IPG | No stimulation | Focal single and paired pulse TMS. Anodal electric stimulation | |
| Di Lazzaro et al | 2002 | 2 conscious patients with intractable dorso-lumbar pain | Model Quad 3487A Medtronic | High cervical epidural space | Not connected to IPG | No stimulation | Focal and non focal monopulse TMS and focal paired pulse TMS; Anodal electric stimulation | |
| Di Lazzaro et al | 2002 | 2 conscious patients with intractable dorso-lumbar pain | Quadripolar Medtronic electrode | High cervical epidural space | Not connected to IPG | No stimulation | rTMS: 5 Hz, Focal single and paired pulse TMS | |
| Di Lazzaro et al | 2003 | 3 conscious patients with intractable dorso-lumbar pain | Quadripolar Medtronic electrode | High cervical epidural space | Not connected to IPG | No stimulation | Single pulse TMS | |
| Di Lazzaro et al | 2005 | 4 conscious patients with intractable dorso-lumbar pain | Quadripolar Medtronic electrode | High cervical epidural space | Not connected to IPG | No stimulation | rTMS: ctbs; focal single pulse TMS | |
| Di Lazzaro et al | 2006 | 6 conscious patients with intractable dorso-lumbar pain | Quadripolar Medtronic electrode | High cervical epidural space | Not connected to IPG | No stimulation | Focal single and paired pulse TMS | |
| Di Lazzaro et al | 2007 | 1 patient with intractable dorso-lumbar pain | Quadripolar Medtronic electrode | High cervical epidural space | Not connected to IPG | No stimulation | rTMS: repetitive paired pulse stim. Focal single pulse TMS | |
| Di Lazzaro et al | 2009 | 4 patients with intractable dorso-lumbar pain | Quadripolar Medtronic electrode | High cervical epidural space | Not connected to IPG | No stimulation | Repetitive focal TMS paired with peripheral stimulation | |
| Lefaucheur et al | 2010 | 2 patients with intractable pain | Quadripolar Pisces Quad Lead Model 3487A Medtronic+ 2 quadripolar Resume II Lead Model 3587A Medtronic | Cervical spine epidural space (Pisces Quad electrode) + motor cortical epidural space (Resume electrodes) | Not connected to IPG | No stimulation | Focal single-pulse TMS | |
| Ni et al | 2011 | 2 patients with intractable pain | Resume Lead Model 3587A Medtronic, | High cervical epidural space | Not connected to IPG | No stimulation | Focal single and paired pulse TMS | |
| Weise et al | 2013 | 1 patient with intractable dorso-lumbar pain | Quadripolar Medtronic electrode | High cervical epidural space | Not connected to IPG | No stimulation | Focal single and paired pulse TMS | |
| Hamada et al | 2014 | 1 patient with intractable dorso-lumbar pain | Quadripolar Medtronic electrode | High cervical epidural space | Not connected to IPG | No stimulation | Repetitive focal TMS paired with peripheral stimulation | |
| Deep Brain Stimulation Electrodes | | | | | | | | |
| Chen et al | 2001 | 7 PD patients | Model  3387, Medtronic | Globus pallidus int. | Connected to IPG | Optimal parameters, half amplitude, off | Focal single and paired pulse TMS | |
| Cunic et al | 2002 | 12 PD patients | Model 3387, Medtronic | Subthalamic nucleus | Connected to IPG | Optimal parameters, half amplitude, off | Focal single and paired pulse TMS | |
| Dauper et al | 2002 | 8 PD patients | Medtronic | Subthalamic nucleus | Connected to IPG | On at 2.8 V, 60 µs, 130 Hz and off | Focal single and paired pulse TMS | |
| Kühn et al | 2002 | 5 dystonia patients | Medtronic | Globus pallidus internus, ventral intermedius (VIM) nucles of thalamus | Connected to IPG Kinetra | Stimulator off | Focal single pulse TMS | |
| Pierantozzi et al. | 2002 | 4 PD patients | Model 3389 for STN Model 3387 for GP1 | Subthalamic nucleus and globus pallidus internus | Connected to an external stimulator | STN 2-3.5 V, 90 µs, 165 Hz; gpi 2-5 V, 210 µs, 185 Hz; Stimulator on and off | Focal single and paired pulse TMS | |
| Kühn et al | 2003 | 9 dystonia patients | Medtronic | Globus pallidus int | Connected to IPG Kinetra; | 130 Hz, 1.2-5.5 V; 210 μs | Focal single and paired pulse TMS | |
| Kühn et al | 2004 | 10 dystonia patients | Medtronic | Globus pallidus int | Connected to IPG Kinetra | Frequency 5 Hz, pulse width 450 μs | Focal single and paired pulse TMS | |
| Molnar et al | 2004 | 6 patients with essential tremor | Model 3387, Medtronic, | Unilateral ventralis intermedius (VIM) nucleus of thalamus | Connected to IPG | Optimal therapeutic setting, half optimal frequency, off | Focal single and paired pulse TMS over the motor cortex and cerebellum | |
| Hanajima et al | 2004 | 14 PD, 1 pain, 2 dystonia patients | Model 3387, Medtronic, 3-7 days after implantation with leads externalized | Subthalamic nucleus, Sensory thalamus, Globus pallidus int | Connected to an external stimulator (model A360D-B, World Precision Instruments,) | Single stimuli just below the threshold for current spread to the corticospinal pathway | Focal single and paired pulse TMS | |
| Wagner et al | 2004 | 1 epileptic patient | Eight depth electrodes | Bilaterally within the cingulum, orbital frontal cortex, amygdala, and hippocampus | Connected to IPG | No stimulation | Focal single pulse TMS | |
| Strafella et al | 2004 | 6 PD patients undergoing DBS surgery | 5 tungsten bipolar microelectrodes | Subthalamic nucleus | Connected to electrophysiological recording system, not connected to IPG | No stimulation | Single pulse TMS, 9 cm circular coil | |
| Molnar et al | 2005 | 7 patients with essential tremor | Model 3387, Medtronic | Ventralis intermedius (VIM) nucleus of thalamus | Connected to Xtrel or Itrel II IPG, Medtronic | Optimal parameters, half optimal amplitude, off | Focal single and paired pulse TMS | |
| Hidding et al | 2006 | 8 PD patients | Model 3389, Medtronic | Subthalamic nucleus | Connected to Kinetra IPG, Medtronic | IPG OFF | Focal single and paired pulse TMS | |
| Molnar et al | 2006 | 5 epileptic patients | Model 3387, Medtronic | Anterior nucleus of thalamus | Connected to IPG | Contacts 1 and 2 -; case +, 4 V, 100 Hz, 90 μs, cycling mode (1 minute on, 5 minutes off) and continuous stimulation | Focal single and paired pulse TMS | |
| Tisch et al | 2007 | 10 patients with primary generalised dystonia | Model 3389 Medtronic | Globus pallidus int. | Connected to IPG Kinetra model 7428, Medtronic | 3.5-3.9 V, 90 μs, 130 Hz, DBS on and off in separate sessions | rTMS, PAS+, and single pulse TMS | |
| Sailer et al | 2007 | 7 PD patients | Model 3387, Medtronic | Subthalamic nucleus | Connected to IPG | Optimal stimulator setting, stimulator off | Focal single pulse TMS paired with median nerve stimulation | |
| Gaynor et al | 2008 | 9 PD patients | Model 3389, Medtronic | Subthalamic nucleus | Not connected to IPG | No stimulation through the electrode | Focal single pulse TMS | |
| Potter-Nerger et al | 2008 | 10 PD patients |  | Subthalamic nucleus | Connected to IPG | 3.1+0.2 V, 64 μs, 148.8+9.2 Hz, stimulation on and off | Focal single pulse TMS | |
| Fraix et al. | 2008 | 15 PD patients | Model 3389, Medtronic | Subthalamic nucleus | Connected to IPG Kinetra, Medtronic | 2.9+0.5 V and 4.4+1.1 V, 90 μs, 130-185 Hz, stimulation on and off | Focal single and paired pulse TMS | |
| Ayache et al. | 2009 | 1 Multiple Sclerosis patient with action tremor | Model 3387, Medtronic | Ventralis intermedius (VIM) nucleus of thalamus | Connected to IPG | 3 V, 90 μs, 130 Hz, stimulation on and off | Double TMS pulses on the cerebellum (double cone coil) and primary motor cortex (focal coil) | |
| Kuriakose et al. | 2010 | 8 PD patients | Model 3387, Medtronic | Subthalamic nucleus | Connected to IPG | Clinical parameters except frequency was at 3 or 30 Hz | Focal single pulse TMS | |
| Ruge et al | 2011 | 10 DYT 1 gene-positive dystonic patients | Model 3389 Medtronic, | Globus pallidus int. | Connected to IPG Soletra Kinetra model 7428, Medtronic | 0.5-2.1 V, 450 μs, 130 Hz, stimulation on and off | Focal single and paired pulse TMS | |
| Wagle Shukla et al | 2013 | 11 PD patients | Model 3387, Medtronic | Subthalamic nucleus | Connected to IPG | Clinical DBS parameters, stimulation on and off | Focal single pulse TMS paired with median nerve stimulation | |
| Kim SJ et al | 2015 | 8 PD patients | Model 3387, Medtronic | Subthalamic nucleus | Connected to IPG | Clinical DBS parameters, stimulation on and off | Repetitive focal TMS paired with peripheral stimulation | |
| Kobayashi et al | 2016 | 9 PD patients |  | Subthalamic nucleus | Connected to IPG | 2-3 V, 60-90 μs, 130 Hz, stimulation on and off | Focal single and paired pulse TMS over motor cortex | |
| Udupa et al. | 2016 | 10 PD patients | Model 3387, Medtronic | Subthalamic nucleus | Connected to IPG | Repetitive STN DBS (1.5-4 V, 60 μs, 3 Hz) paired with focal TMS at 167 ms interstimulus interval | Focal TMS | |
| Wessel et al | 2016 | 9 PD patients | Model 3387, Medtronic | Subthalamic nucleus | Not connected to IPG | No stimulation through the electrode | Single pulse, focal TMS | |
| Ni Z et al | 2018 | 8 dystonia patients | Model 3387, Medtronic | Globus pallidus int. | Cnnected to IPG | Repetitive gpi DBS (2.1-4.5 V, 60-120 μs, 0.1 Hz) paired with focal TMS at 10-25 ms interstimulus intervals, 180 stimuli | Focal TMS | |
| Wagle Shukla et al | 2018 | 10 dystonia patients | 5 patients, model 3387, 5 patients, model 3389, Medtronic | Subthalamic nucleus | Connected to IPG | Clinical DBS parameters, stimulation on and off | Focal single pulse TMS paired with median nerve stimulation | |
| Miron et al | 2018 | 1 patient with obsessive compulsive disorder and depression | Model 3387, Medtronic | Bilateral nucleus accumbens and anterior arm of the internal capsule | Connected to IPG Activa AC, Medtronic | Stimulation off | 1 Hz rTMS to right orbitalfrontal cortex, 100% motor threshold, 300 pulses, > 12 sessions; 10 Hz rtms to DLPFC, 3000 pulses, 30 sessions | |
| Vagus Nerve Stimulation Electrodes | | | | | | | | |
| Di Lazzaro et al | 2004 | 5 patients with medically refractory epilepsy | - | Vagus nerve | Connected to stimulator device Kinetra, Medtronic | 30 seconds on and 5 minutes off, 30 Hz, | Focal single and paired pulse TMS | |
| Bajbouj et al | 2007 | 10 patients with treatment resistant depression | - | Vagus nerve | Connected to IPG Prosthesis System, Cyberonics | Amplitude: 1.1 ± 0.4 mA, pulse width: 300 ± 105.4 ms, frequency: 19.5 ± 1.6 Hz, stimulation on and off | Focal single and paired pulse TMS over motor cortex | |
| Philip et al | 2014 | 20 patients with treatment resistant depression |  | Vagus nerve |  | Stimulation off in most of the patients | rTMS | |
| Cortical Electrode | | | | | | | | |
| Lefaucheur et al | 2010 | 2 patients with intractable pain (CRPS-II and brachial plexus injury) | Medtronic Pisces Quad electrode (model 3487A)+ 2 quadripolar Resume II Lead Model 3587A Medtronic | Cervical spine epidural space (Pisces Quad electrode) + motor cortical epidural space (Resume electrodes) | Not connected to IPG | No stimulation | Focal single-pulse TMS | |
| Phielipp et al | 2017 | 1 patient with pain (postherpetic neuralgia) | Medtronic Resume II subdural cortical electrode (model 3587A) | Subdural electrode over right motor cortex | Connected to pulse generator Medtronic Itrel II 7424 | Stimulation off | rTMSto R motor cortex, 20 Hz, 90% resting motor threshold, 2000 pulses, 10 sessions | |
| Cardiac Pacemaker | | | | | | | | |
| Hizli Sayer et al | 2016 | 1 patient with depression | Cardiac pacemaker, Symphony DR 2550; Ela Medical Inc |  |  | Stimulation on | rTMSto L DLPFC, 10 Hz, 110% motor threshold, 1000 pulses, > 6 sessions | |
| Wei et al | 2018 | 1 patient with migraine | Cardiac pacemaker, Symphony DR 2550, Sorin Biomedica |  |  | Dual chamber rate responsive cardiac, pacemaker, patient remained in atrial paced rhythm, stimulation on | Single pulse TMS to occipital cortex | |

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**Table S2: Randomized controlled multicenter trials investigating safety of rTMS in psychiatric disorders**.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Authors | Disorder  Number of subjects per  condition (n) | rTMS coil, stimulator,  target region  Conditions | rTMS parameters | Adverse events (%)  Active rTMS | | | | | | Adverse events (%)  Comparator# | | SAE (n)  Active rTMS | | | SAE (n)  Comparator# | | Outcome of SAEs | | Significant differences between active and sham groups | | Comment | | | |
| O’Reardon et al. [1] | MDD  Active TMS: n=165  Sham TMS: n=158 | Neuronetics  Model 2100 Therapy System  Left DLPFC  Active TMS: iron core coil  Sham TMS: sham coil | 10 Hz, 120% RMT, 30 sessions/6 weeks,  3000 stimuli/day, 4 sec trains, 26 sec ITI, session duration 37.5 min | |  |  | | --- | --- | | Eye pain | 10 (6.1) | | Toothache | 12 (7.3) | | Application site discomfort | 18 (10.9) | | Application site pain | 59 (35.8) | | Facial pain | 11 (6.7) | | Muscle twitching | 34 (20.6) | | Pain of skin | 14 (8.5) | | | | | | | |  | | --- | | 3 (1.9) | | 1 (0.6) | | 2 (1.3) | | 6 (3.8) | | 5 (3.2) | | 5 (3.2) | | 1 (0.6) | | | n = 9  disease-related exacerbation:   |  |  | | --- | --- | | Suicidality | 1 (0.6%) | | exacerbation of depression | 1 (0.6%) | | suicide gesture | 0 |   Increase of suicidality on HAMD: n = 1 | | | n = 7  (3) 1.9%  (3) 1.9%  (1) <1%  n = 10 | | - | | There was a higher incidence of scalp discomfort and pain with active than sham rTMS.  The incidence of headache did not differ between active and sham TMS conditions. | | In this study, rTMS was well tolerated and safe. Adverse events reported were principally limited to scalp discomfort or pain within the confines of the rTMS session itself and were mostly transient phenomena in the first weeks of the rTMS course.  Despite rTMS being administered here at 120% of motor threshold and 3000 pulses/session, an elevated rate of serious adverse events relative to sham was not detected. | | | |
| Herwig et al. [2] | MDD  Active TMS: n=62  Sham TMS: n=65 | Magstim Rapid, Medtronic Maglite r25 or Medtronic Magpro  Active TMS: 70 mm figure-8 coil  Sham TMS: 5 cm lateral to F3, above the left temporal muscle; coil angled at 45°, touching the skull with the anterior rim, stimulation intensity at 90% RMT | 10 Hz, 110% RMT, 15 sessions/3 weeks, 2000 stimuli/day, 2 sec trains, 8 sec ITI, 100 trains | Headache  Dizziness  Painful local sensations  Nausea | | 3  0  1  1 | | | | 1  1  2  0 | | none | | | none | | NA | | no statistical information | | | This was the only study where rTMS was applied together with a new antidepressant medication, i.e. either mirtazapine (mean dosage: 34 and 32 mg) or venlafaxine (mean dosage: 164 and 161 mg). However, only adverse events “related to rTMS” were reported. | | |
| George et al. [3] | MDD  Active TMS: n=92  Sham TMS: n=98 | Neuronetics Inc.  Target: left DLPFC  Active TMS: solidcore coil  Sham TMS: sham coil with metal insert  blocking magnetic field, scalp electrodes delivering matched somatosensory sensations | 10 Hz, 120% RMT, 15 sessions/3 weeks, 3000 stimuli/day,  4 s trains, 26 s ITI;  sham treatment with identical  parameters  no sufficient improvement after 3 weeks: cross over to open treatment  Improvement:  Continued treatment for up to 3 weeks  Improvers but nonremitters continued treatment for 3 weeks if showing  progressive improvement | Headache  Discomfort at stimulation site  Insomnia  Worsening of depression/ anxiety  Gastrointestinal  Fatigue  Muscle aches  Vertigo  Skin pain  Facial muscle twitching  Other | | 29 (32)  17 (18)  7 (7.6)  6 (7)  6 (7)  5 (5)  4 (4)  2 (2)  1 (1)  0  18 (20) | | | | 23 (23)  10 (10)  10 (10)  8 (8)  3 (3)  4 (4)  4 (4)  2 (2)  1 (1)  1 (1)  15 (15) | | n=1  syncope  (unlikely related to the study) | | | n=1  paranoid ideation  (possibly related to the study) | | no long-term sequelae | | adverse events did not significantly differ by treatment arm | | | The treatment  was relatively well tolerated, with no difference in adverse  events between the active sham and the active TMS  treatment arms. There were no seizures, and retention was  high. | | |
| Levkovitz et al. [4] | MDD  Active dTMS: n=89  Sham dTMS: n=92 | Brainsway  dTMS system  Target: left DLPFC  active dTMS: H1-coil  sham TMS:  sham coil | 20 sessions/4 weeks, 24 sessions in following 12 weeks (min. 48h pause), 18 Hz, 120% RMT, 2 s trains, 20 s ITI, 55 trains/session,  1980 stimuli/session | application site discomfort  application site pain  headache  muscle twitching  back pain  insomnia  anxiety | 3 (3.0)  5 (5.0)  27 (26.7)  2 (2.0)  2 (2.0)  2 (2.0)  NR | | | | | 2 (1.8)  0  21 (18.9)  0  3 (2.7)  4 (3.6)  2 (1.8) | | n=3  elbow fracture (1)  cluster headache (1),  generalized seizure following excessive consumption of alcohol on the night before treatment (1) | | | n=4  suicidality (2)  nausea and vomiting (1)  nephrolithiasis (1) | | seizure with no additional medical intervention | | significant difference between  study groups regarding application site pain (p=0.02)  The incidence of headache did not significantly differ between active and sham TMS conditions. | | | dTMS was well tolerated by the majority of patients and the main side effect was pain during application, usually not  requiring any special care. There was one seizure induced  by dTMS in this study, which may have been related to alcohol  consumption the night before treatment. | | |
| Wobrock et al. [5] | predominant negative symptoms in schizophrenia  Active rTMS:  n=76  Sham rTMS:  n=81 | MagPro X100 (Medtronic A/S), passively cooled MCF-B65  figure-8 coils (Medtronic A/S)  Target: left DLPFC  Sham TMS:  magnetic coil  tilted over one wing (45 degrees) | 15 sessions/ 3 weeks, 10 Hz,  110% RMT , 20  trains with 50 stimuli per train, 30 s ITI, 1000 stimuli/ session | headache  facial muscle twitching  fatigue  psychotic ideation  discomfort at stimulation site  general discomfort | | 12  3  1  1  1  1 | | | | 4  3  1  1  0  0 | | Without withdrawal from study:  n=1 (suicidality)  With withdrawal from study:  n=1 (acute deterioration  in symptoms)  extension phase:  n=2 (hospitalizations  owing to deterioration in symptoms) | | | Without withdrawal from study:  n=1 (event requiring hospitalization )  With withdrawal from study:  n=2  suicidality (1)  unspecified (1)  extension phase:  n=4  hospitalizations (2),  suicidality(1), melperone intoxication (1) | | no information given | | no statistical information | In terms of  side effects, the active rTMS intervention was well tolerated,  and the main challenge for patient acceptance appears to be  the need for treatment 5 days per week. | | |
| Blumberger et al. [6] | Treatment resistant MDD  10 Hz rTMS: n=205  iTBS: n=209 | rTMS: MagPro X100 or R30 stimulator, equipped with a B70 fluid­cooled coil and high­performance cooler (MagVenture)  Target: left DLPFC  Neuronavigation: ANT Neuro, Enschede, Netherlands | rTMS: 120% RMT; 10 Hz; 4 s on and 26 s off; 3000 pulses per session; total duration of 37·5 min  iTBS: 120% RMT, triplet 50 Hz bursts, repeated at 5 Hz; 2 s on and 8 s off; 600 pulses per session; total duration of 3 min 9 s  4 weeks with 20 sessions, no remission – additional 2 weeks with 10 sessions | |  |  | | --- | --- | | Headache | 131 (64) | | Nausea | 22 (11) | | Dizziness | 8 (4) | | Unrelated medical problem | 47 (23) | | Fatigue | 14 (7) | | Insomnia | 14 (7) | | Anxiety or agitation | 8 (4) | | Back or neck pain | 7 (3) | | Unrelated accidents | 2 (1) | | Vomiting | 1 (<1) | | Tinnitus | 1 (<1) | | Migraine aura | 3 (1) | | Abnormal sensations | 2 (1) | | | | |  | |  | | --- | | 136 (65) | | 14 (7) | | 18 (9) | | 46 (22) | | 16 (8) | | 10 (5) | | 9 (4) | | 6 (3) | | 3 (1) | | 1 (<1) | | 3 (1) | | 4 (2) | | 4 (2) | | | 1/205 (<1%): myocardial infarction (not rTMS related) | | | 3/209 (1%): agitation that led to hospital admission, worsening of suicidal ideation, hospital admission due to worsening of depression | | SAE: no significant difference (Fisher’s exact test, p=0·6232) | | Numbers of adverse events: p>0·05 on Fisher’s exact tests for each pair of proportions  intensity of pain associated with treatment was greater in the iTBS group than in the 10 Hz rTMS group (mean score on verbal analogue scale 3·8 [SD 2·0] vs 3·4 [2·0] out of 10; p=0·011); did not translate into increased discontinuation rates | | iTBS showed non­inferior effectiveness and a similar adverse event profile and  HRSD-17 score acceptability compared with the standard, FDA­approved 10 Hz rTMS protocol for treatment­resistant depression. | | | |
| Yesavage et al. [7] | Treatment resistant MDD in US veterans  Active rTMS: n=81  Sham rTMS: n=83 | MagPro R30 (MagVenture) device, Cool-B65-A/P coil  Target: left DLPFC | 10 Hz, 120% RMT, 4000 pulses/session  5 session blocks over a period of 5 to 12 calendar  days, between 20 and  30 sessions of rTMS in total  Remission after initial 20 to 30 sessions - additional 6 taper sessions over 3 weeks | Nasopharyngitis  Depression  Falls  Headache  Abnormal results of hearing tests | | | 8  8  3  15  18 | | | 8  3  7  16  18 | | Suicidal ideation | 3 | | 4 | | No suicides or seizures occurred during the study and  there were no deaths | | AE/SAE did not differ significantly  between treatment groups and were generally consistent  with expected background medical issues in this population | | Abnormal results of hearing  tests believed to be an artifact of frequent, imprecise testing | |

Legend:

MDD=major depressive disorder, # in the majority of studies sham TMS, serious adverse events (SAE), DLPFC = dorsolateral prefrontal cortex, NR = not reported

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**Table S3. Safety table fopr QPS parameters**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | |
| **Target** | **ISI** | **Intensity** | **IBI (sec)** | **Total pulse number** | **Duration** | **Coil** |
|  | | | | | | |
| **M1** | **1.5, 5, 10, 30, 50, 100, 200, 1250** | **90-130% AMT for hand muscle** | **2.5-5** | **1440-2880** | **30min** | **figure of eight** |
| **PM** | **5, 50** | **90% AMT for hand muscle** | **5** | **1440** | **30min** | **figure of eight** |
| **S1** | **5, 50** | **90% AMT for hand muscle** | **5** | **1440** | **30min** | **figure of eight** |
| **DLPFC** | **5, 50** | **90% AMT for hand muscle** | **5** | **1440** | **30min** | **figure of eight** |
| **SMA** | **5, 50** | **90% AMT for TA** | **5** | **1440** | **30min** | **figure of eight** |

**Table S4. QPS studies**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First authorA1:L13** | **Year** | **Subjects** | **Number** | **Target area** | **ISI** | **Intensity** | **Waveform** | **IBI (sec)** | **Total pulse number** | **duration** | **side effects** |
| **Published papers** | | | | | | | | | | | |
| Hamada | 2007 | N | 16 | M1 | 1,5 | 0.9, 1.3 AMT | M | 5 | 1440, 720 | 30 | No |
| Hamada | 2008 | N | 10 | M1 | 1.5, 5, 10, 30, 50, 100, 1250 | 0,9 | M | 5 | 1440 | 30 | No |
| Hamada | 2009 | N | 9 | M1,SMA | 1.5, 5, 10, 30, 50, 100 | 0.9 AMT for hand muscles, 0.9 AMT for TA | M | 5 | 1440 | 30 | No |
| Nakamura | 2011 | N | 12 | M1 | 5, 50 | 0.9 AMT for hand muscles, 0.10 AMT for TA | M | 5 | 1440 | 30 | No |
| Nakatani-Enomoto | 2011 | N | 8 | M1 | 5, 50 | 0.9 AMT for hand muscles, 0.11 AMT for TA | M | 5 | 1440 | 30 | No |
| Nakatani-Enomoto | 2012 | N | 11 | S1, M1, PM | 5, 50 | 0.9 AMT for hand muscles, 0.12 AMT for TA | M | 5 | 1440 | 30 | No |
| Enomoto | 2011 | PD | 10 | M1 | 5, 50 | 0.9 AMT for hand muscles, 0.13 AMT for TA | M | 5 | 1440 | 30 | No |
| Hirose | 2011 | N | 10 | M1 | 5, 50 | 0.9 AMT for hand muscles, 0.14 AMT for TA | M | 5 | 1440, 288 | 30, 6 | No |
| Groiss | 2012 | N | 10 | M1, S1 | 5, 50 | 0.9 AMT for hand muscles, 0.15 AMT for TA | M | 5 | 288 | 6 | No |
| Groiss | 2012 | N | 10 | M1 | 5,50 | 0.9 AMT for hand muscles, 0.16 AMT for TA | M | OPS: 5, QPS: 2.5, 5 | OPS:2880, QPS:2880, 1440 | 30 | No |
| Watanabe | 2014 | N | 6 | M1 | 5, 50 | 0.9 AMT for hand muscles, 0.17 AMT for TA | M | 5 | 1440 | 30 | No |
| Tsutsumi | 2014 | N | 10 | M1 | 5, 50 | 0.9 AMT for hand muscles, 0.18 AMT for TA | M | 5 | 1440 | 30 | No |
| Tanaka | 2015 | N | 24 | M1 | 5 | 0.9 AMT for hand muscles, 0.19 AMT for TA | M | 5 | 1440 | 30 | No |
| Kadowaki | 2015 | N | 13 | M1 | 5, 50 | 0.9 AMT for hand muscles, 0.20 AMT for TA | M | 5 | 1440 | 30 | No |
| Enomoto | 2015 | N | 10 | M1 | 5, 50 | 0.9 AMT for hand muscles, 0.21 AMT for TA | M | 5 | 1440 | 30 | No |
| Watanabe | 2015 | N |  | SMA | 5, 50 | 0.9 AMT for hand muscles, 0.22 AMT for TA | M | 5 | 1440 | 30 | No |
| Nakatani-Enomoto | 2016 | N, ME | 10N, 6ME | M1, S1 | 5, 30, 50, 100, 500 | 0.9 AMT for hand muscles, 0.23 AMT for TA | M | 5 | 1440 | 30 | No |
| Nakamura | 2016 | N | 35 | M1 | 5, 50 | 0.9 AMT for hand muscles, 0.24 AMT for TA | M, Bi | 2.5, 5, 7.5, 10 | 720, 1440 | 15, 30 | No |
| Simeoni | 2016 | N | 20 | M1 | 5, 50 | 0.9 AMT for hand muscles, 0.25 AMT for TA | M | 5 | 1440 | 30 | No |
| Hanajima | 2018 | N | 107 | M1 | 5 | 0.9 AMT for hand muscles, 0.26 AMT for TA | M | 5 | 1440 | 30 | No |

**Table S5. TBS studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Reference | Stimulation site | Pulse number | Intensity | Number of subjects | Remarks |
| 6 | L MPFC | two 1800-pulse trains of cTBS (120 s on, 60 s off, 120 s on; 3600 pulses over a total of 5 min) | 110%RMT | 78 | Cocaine (and alcohol) abuse protocol |
| 7 | M1 | iTBS | 80%AMT | 19 | Healthy |
| 8 | SMA | cTBS | 80% AMT | 15 | Healthy |
| 9 | M1 | cTBS | 80% AMT | 31 (twice each) | Healthy |
| 10 | VLPFC | cTBS + ITBS sep sessions | 80% AMT | 15 (twice each) | Healthy |
| 11 | PFC (F1) | iTBS | 50, 75, 100 RMT | 16 (3x each) | Healthy |
| 12 | M1 | iTBS | 80% AMT | 17 | Healthy |
| 13 | M1 | cTBS | 80% AMT | 20 | Healthy |
| 14 | M1 | cTBS | 80% AMT | 17 | Healthy |
| 15 | M1  M1 then cbllm | cTBS | 80% AMT | 15 | IGE (drug free) |
| 16 | M1 | iTBS | 80% AMT | 14 (twice each) | Healthy sedentary |
| 17 | RMPFC  RLPFC  vertex | cTBS | 80% AMT | 18 (3x each) | Healthy |
| 18 | M1 | iTBS + cTBS (each hemisph) | 80% RMT | 10; 10 (twice each) | Stroke; healthy |
| 19 | M1 | iTBS | 80% AMT | 9; 15; 12 (twice each) | Probable AD; diabetes T2; healthy |
| 20 | M1 | cTBS | 80% AMT | 15 | Healthy |
| 21 | DLPFC (f3) | iTBS | 80% AMT | 17 | Healthy |
| 22 | IFG | cTBS (900) | 100% AMT | 23 | Healthy |
| 23 | M1 | cTBS (2 trains separated 10min) | 80% AMT | 31 | Healthy |
| 5 | VMPFC | cTBS (6 trains; 1min interval (3600 pulses) | 110% RMT | 25; 24 | Cocaine users; alcoholics |
| 24 | Lateral Cbllm | cTBS | 80% AMT | 12 | Healthy25 |
| 26 | M1; parieto-occipital | iTBS | 80% AMT | 14 (twice each) | Stroke |
| 27 | F3 | cTBS; iTBS | 80% RMT | 10 (twice each) | Healthy |
| 28 | Cbllm vermis | cTBS | 100% RMT | 20 (half nemantine) | Healthy |
| 29 | Cbllm (2 sites DAN; DMN)) | iTBS | 80% RMT or 100% AMT | 15 (twice each) | Healthy |
| 30 | M1 | iTBS (unidirectional) | 80% AMT | 19 (3x each; one lower intensity AP) | Healthy |
| 25 | Precuneus | cTBS | 80% distance adjusted RMT | 15 | Healthy |
| 31 | M1; S1; SPL | cTBS | 80% RMT | 16; 34; 17 (once per site) | Healthy |
| 32 | M1 | iTBS | 80% AMT | 10; 8; 10 | PD; LRRK; Healthy |
| 33 | M1 | iTBS | 80% AMT | 16; 15 | Adolescents normal; post concussive |
|  | Angular gyrus | cTBS | 40% output | 16 | Healthy |
| 34 | M1 | iTBS | 80% AMT | 27 (twice) | Healthy |
| 35 | M1 | cTBS | 70% RMT | 34 (twice) | Healthy |
| 36 | STS or vertex | cTBS (900) | 80% AMT | 17 (twice) | Healthy |
| 37 | R&L DLPFC | cTBS (1800) + iTBS (1800) daily for 10 sessions | 30% & 32% output | 1 | Depression |
| 38 | M1 | cTBS; iTBS | 80% AMT | 35 (twice) | Healthy |
| 39 | DLPFC | iTBS | 80% RMT | 27 | Healthy |
| 40 | IPL | cTBS; imTBS | 80% AMT | 16 | Healthy |
| 41 | Operular-insular | Deep cTBS; double cone v flat | 80% RMT for TA; 80% RMT FDI | 17 (twice) | Healthy NB TWO SEIZURES double cone cTBS |
| 42 | VLPFC; R; L; Vertex | cTBS | 80% AMT | 18 (3 times) | Healthy |
| 43 | Cbllm | cTBS | 80% RMT | 41 | Healthy |
| 44 | M1 | cTBS | 80% AMT | 13 | Healthy |
| 45 | iLPFC | cTBS; iTBS; imTBS | 80% RMT | 17, 16, 16 | Healthy |
| 46 | pIPC; S1 | cTBS | 80% AMT | 25 | Healthy |
| 47 | premotor | cTBS | 80% AMT | 12 | Healthy |
| 48 | Premotor; vertex | cTBS | 40% ouptut | 16 | Healthy |
| 49 | L & R BA46 | cTBS (20 Hz; 3600-4800 pulses) + iTBS (20 Hz; 4950 pulses) | 90 - 95% RMT | 57 daily for 5 days | Depression |
| 50 | SMGp | cTBS | 55% output | 12 | Healthy |
| 51 | Occipital | cTBS | 30% ouput | 6 | Healthy |
| 52 | M1 | iTBS + TACS (gamma; beta) | 80% AMT | 14 | Healthy |
| 53 | M1 | iTBS (600) + 10 Hz rTMS (2000) | 80% RMT | 21 | CRPS |
| 54 | aPFC; DLPFC; PM | cTBS | 80% AMT | 27 (three times) | Healthy |
| 55 | DLPFC | cTBS | 80% AMT | 15 | Healthy |
| 56 | F1 | iTBS; iTBS (2 blocks 15min interval) | 75% RMT | 18 (twice) | Healthy |
| 57 | PPC; SMA; M1 | cTBS | 80% AMT | 25 | Healthy |
| 58 | Cbllm (left/right) | cTBS | 55% output | 18 (twice) | Healthy |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

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