TMS GUIDELINES

TRANSCRANIAL MAGNETIC STIMULATION IN PSYCHIATRY

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List of abbreviations

ACC / ACG: anterior cingulate cortex / anterior cingulate gyrus

ALAT: alanine aminotransferase

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AR: adverse reactions

ASAT: aspartate aminotransferase

aTBS: accelerated theta-burst stimulation

BDNF: brain derived neurotrophic factor

CBT: cognitive behavioral therapy

CE: Conformité Européenne

CI: confidence interval

CSTC: cortico-striatal-thalamo-cortical

cTBS: continuous theta-burst stimulation

DLPFC: dorsolateral prefrontal cortex

dmPFC: dorsomedial prefrontal cortex

DPS: Dansk Psykiatrisk Selskab / Danish Psychiatric Society

dTMS: deep TMS

ECT: electroconvulsive therapy

e.g.: exempli gratia

etc.: et cetera

EMA: European Medicines Agency

FDA: U.S. Food and Drug Administration

fMRI: functional magnetic resonance imaging

GABA: gamma-aminobutyric acid

HAM-D17: Hamilton Depression Rating Scale (17-item)

Hz: hertz

iTBS: intermittent theta-burst stimulation

LTD: long-term depression

LTP: long-term potentiation

MDI: Major Depression Inventory

MEP: motor evoked potentials

MRI: magnetic resonance imaging

NMDA: N-Methyl-D-aspartate

OCD: obsessive-compulsive disorder

OFC: orbitofrontal cortex

OR: odds ratio

PET: positron emission tomography

PEth: phosphatidylethanol

PFC: prefrontal cortex

PTSD: post-traumatic stress disorder

RCT: randomized controlled trial

rMT: resting motor threshold

rTMS: repetitive transcranial magnetic stimulation

SSRI: selective serotonin reuptake inhibitor

TBS: theta-burst stimulation

tDCS: transcranial direct-current stimulation

TMS: transcranial magnetic stimulation

TRD: treatment-resistant depression

TSH: thyroid stimulating hormone

mTMS: maintenance TMS

Y-BOCS: Yale-Brown Obsessive Compulsive Scale

YMRS: Young Mania Rating Scale

Summary and purpose

This report, prepared by a task force from the ECT and Neurostimulation Committee of the Danish Psychiatric Society, provides guidelines for the use of transcranial magnetic stimulation (TMS).

It explains the historical and theoretical background of TMS, mechanisms of action, effectiveness, safety, indications and contraindications, etc. The report includes practical instructions for TMS administration, staff training and development, and the organizational structure of TMS units. In this document, specific MagVenture® devices are referenced, as all TMS stimulators used in public healthcare in Denmark in 2023 were manufactured by this company (Cabral Barata et al., 2024).

The psychiatric disorders for which there is sufficient evidence for the use of TMS are moderate to severe unipolar depression and obsessive-compulsive disorder. There are many ongoing studies on the use of TMS in other mental illnesses, such as bipolar disorder, post-traumatic stress disorder and schizophrenia. Still, there is insufficient data to recommend TMS as standard treatment in these patient populations.

TMS is considered a well-tolerated treatment with few short-term side effects, such as headache and fatigue. A typical treatment series consists of 20-30 treatments, administered once daily from Monday to Friday over 4 to 6 weeks. Treatments last from 3 to 25 minutes and do not involve general anesthesia.

The field of TMS is rapidly evolving, which means that some of the data and recommendations in this guide will eventually become outdated before new guidelines can be developed. The reader is therefore advised to use the most up-to-date evidence-based treatment. The recommendations in this document are in the nature of professional advice and are not legally binding. In some cases, a treatment method with a lower strength of evidence may be preferable because it is better suited to the patient's situation. Ultimately, clinical judgment in each specific case determines the appropriate medical approach.

The authors, January 15, 2025

Quick guide to recommendations for TMS in psychiatric disorders

Unipolar depression

rTMS is recommended for moderate to severe TRD (treatment-resistant depression) without psychotic symptoms.

Obsessive-compulsive disorder (OCD)

Deep TMS is recommended as an add-on in patients with moderate to severe OCD resistant to both SSRI and cognitive behavioral therapy.

Bipolar depression

The ECT and Neurostimulation Committee does not recommend the use of rTMS as standard treatment for bipolar disorder. However, rTMS can be considered for moderate to severe bipolar depression after other treatment options with higher levels of evidence have shown insufficient efficacy or are intolerable, including psychotropic drugs and electroconvulsive therapy.

Schizophrenia

The Committee does not recommend the use of rTMS as standard treatment for schizophrenia. rTMS can be considered for auditory hallucinations or negative symptoms of at least moderate severity where monotherapy with 2 different antipsychotics and clozapine in sufficient dose and duration plus good compliance has not proven effective.

Historical background

The first attempts to treat mental illnesses with electricity date back to the early 19th century. Electrical stimulation was particularly explored in the late 18th and early 19th centuries, primarily by Alessandro Volta (1745-1827), Luigi Galvani (1737-1798) and Giovanni Aldini (1762-1834). Volta and Galvani's work was crucial to the development of modern understanding of electricity and electrophysiology, originally described as "animal electricity" or galvanism. It was Galvani's experiments with muscle contractions in frog legs in the 1790s in particular that elegantly supported the idea of internal electrical activity in organisms and laid the foundation for future research and treatment. Throughout the early years of the 1800s, Aldini used a voltaic pile, an early battery consisting of alternating disks of zinc and copper in an electrolyte solution, to stimulate the muscles of human cadavers as an extension of the hypothesis on galvanic response of muscles.

Aldini tried to make use of electrical stimulation to treat patients. He adapted a voltaic pile, so that patients had to place one hand at the bottom of the pile, while a wire from the top of the pile was connected to the patient's skull via the parietal lobe. The treatment was cumbersome and uncomfortable for the subjects. Aldini tested the stimulation on himself before using it on other subjects, and his memoirs indicate he found the experience unpleasant. After personally verifying the safety of the device, Aldini reported that this treatment tool was used on a patient with melancholia in 1801 (Bolwig and Fink, 2009), and he further described a successful treatment of parkinsonism. Nowadays, a variant of this technique has been further explored in the form of transcranial direct current stimulation (tDCS) for the treatment of psychiatric disorders.

In 1938, ECT was introduced as a treatment for psychiatric disorders by Ugo Cerletti and Lucio Bini in Rome. However, the difference between ECT and the other forms of stimulation techniques was that the goal of this treatment was the stimulation of brain activity to induce a generalized seizure. Further improvements to the ECT technique, such as the use of general anesthesia, muscle relaxation, and modified waveforms of the electrical stimulus, improved the safety and tolerability of ECT over time. Despite these improvements, ECT has practical limitations, including the need for general anesthesia and postoperative monitoring, and cognitive side effects like transient retrograde and anterograde amnesia.

Michael Faraday (1791-1867), James Clerk Maxwell (1831-1879) and Hans Christian Ørsted (1777-1851) explored the important connection between electricity and magnetism. Building on electromagnetic induction, Anthony Barker and colleagues from the Royal Hallamshire Hospital in Sheffield developed the first TMS device for research, which they described in The Lancet in 1985 (Barker et al., 1985). Barker was optimistic about the future of the technique and its potential in the stimulation of corticospinal pathways for clinical investigation in various neurological conditions. For example, nerve conduction velocity could be studied by stimulating the motor cortex and then measuring when the corresponding muscle contracted. In his original publication, Barker noted that "magnetic stimulation of the cortex is particularly effective (compared to electrical stimulation) because of the ability of the field to pass through high-resistance structures", i.e. the scalp and skull bones. Subsequently, the coil itself, which delivers the fluctuating electric field, was further developed. The original coil was circular; later, figure-of-eight coils were developed, and the latest addition is the so-called Hesed coil (Roth et al., 2002), which can stimulate deep in the brain. For several years, TMS was used as a tool to examine patients with neurological disorders.

Concurrent with Barker's work, the biological revolution in psychiatry in the 1970s and 1980s sought to uncover the neural substrates of mental illness. This was aided by the development of computed tomography and functional magnetic resonance imaging (fMRI), which allowed researchers to study in vivo structural and functional relationships where previously only the structure of cadaveric brains could be studied. Around 1990, TMS began to be used therapeutically and not just as a research technique. Initially, it was applied in Parkinson's disease, but in the mid-90s Mark George and others attempted to use the technique to treat depression, and gradually the number of studies stimulating the left dorsolateral prefrontal cortex (DLPCF) grew (George et al., 1997). There are several reasons why this particular structure was chosen. A 1984 study by Robinson and colleagues, examining a relatively small group of stroke patients, showed that the involvement of this area frequently resulted in post-stroke depression (Robinson et al., 1984). This finding has since been disputed, but other studies have reinforced the interest in such structure (Kimbrell et al., 1999; Pascual-Leone, 1994). The DLPFC is important for executive functions, particularly task switching, attention regulation, planning, and working memory: functions that are often compromised in depression. In addition, the role of the DLPFC in the processing of emotions, especially the integration of emotion and cognition, has been explored. Here, the close coupling to the anterior

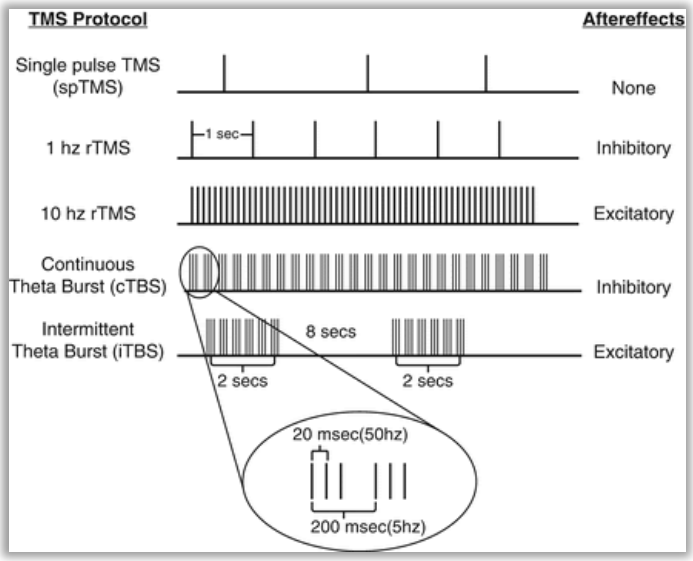
cingulate gyrus (ACG) is probably important and is thought to assign valence to emotions (that is, how pleasant or unpleasant an emotion is). Reduced activity in the DLPFC has been found in several PET (Positron Emission Tomography) studies in patients with depression (Mayberg et al., 1999).

These considerations suggested that stimulation of this structure could be a specific treatment for depression, probably involving long-term potentiation in cortical neurons and inhibition of ACG. This led to the preference for stimulation of the left DLPFC when using TMS in depressed patients.

In 2008, TMS was approved by the U.S. Food and Drug Administration following a double-blind randomized controlled trial (RCT) involving 301 patients with treatment-resistant depression (TRD) (O'Reardon, 2007). However, the study has since been criticized due to methodological challenges related with TMS studies in general, namely that they are difficult to blind, because patients can feel whether they are being stimulated or not (e.g. the stimulation causes the chewing muscles to contract because the magnetic field also induces current in these muscles). Furthermore, TMS was criticized for being a very cumbersome treatment because it required 4-6 weeks of treatment daily for up to an hour. However, the technique has been further developed since these trials. Stimulation-related variables, including stimulus intensity, frequency, time between stimulations, treatment duration, number of trains and total number of stimuli have been modified to improve treatment response.

The latest addition is theta-burst stimulation (TBS), where very high-frequency stimulation is delivered in pulse trains with short pauses (see Figure 1 - Overview of TMS protocols). This means that the stimulation of the brain is more effective, and treatment time can be shortened to a few minutes. Several randomized studies of TBS for treatment-resistant depression (TRD) have found the technique to be effective (Blumberger, 2018; Kishi et al., 2024b). Recently, a research group developed the so-called SAINT or Stanford Neuromodulation Treatment protocol, which uses multiple intermittent TBS treatments throughout the day to shorten treatment duration from several weeks to just 5 days (Cole et al., 2020, 2022). The results, published in the American Journal of Psychiatry, showed that this treatment was superior to sham stimulation in patients with TRD. Such data needs replication, but if it can be verified, it will be a significant step forward in the time-efficiency of TMS treatment.

Figure 1 - Overview of TMS protocols



Now, nearly 40 years after the development of the first TMS prototype, TMS is recognized as an effective treatment tool for a variety of conditions, with FDA approval for the treatment of depression (2008), cortical mapping (2009), treatment of migraine with aura (2013), treatment of obsessive-compulsive disorder (2017), smoking cessation (2020), and treatment of major depressive disorder with comorbid anxiety (2021), which considers a variety of devices and stimulation parameters (Cohen et al., 2022). TMS is best studied for the treatment of depression; in a meta-analysis, the odds ratio for treatment response was 3.17 for rTMS compared to sham (Mutz et al. 2019). Although this odds ratio is smaller than the reported odds ratio for response to bilateral ECT in the same study (odds ratio = 8.91), the future of rTMS is promising, with the potential for further advancements in technique and even greater efficacy.

Theoretical background and mechanisms of action

Theoretical background

Theoretical background

TMS is a Non-invasive Brain Stimulation (NIBS) technique, which, as mentioned, is based on Ørsted and Faraday's principles of electromagnetic induction (George and Taylor, 2014; Rotenberg et al., 2014). Ørsted's law states that a steady electric current through a wire creates a magnetic field around it. Faraday's law of induction is a quantitative relationship expressing that a changing magnetic field induces a voltage in a circuit, and that the magnitude of the electromotive force is proportional to the rate of change of the magnetic flux (Di Lazzaro and Falato, 2020; Faraday, 1839; Lanocha, 2018). In TMS, a transient electric current is generated in a capacitor, which is transferred to a coil made up of turns of copper wire (Di Lazzaro and Falato, 2020). The current sent to the coil can be rapidly switched on and off, generating a fluctuating magnetic field (Davey and Epstein 2000; Rotenberg et al., 2014). The magnetic field, which propagates perpendicular to the coil, passes through the scalp and skull without resistance. If the electric current induced by the magnetic field in the cortex is strong enough, the electric potential in the neuronal membrane changes and an action potential is generated (Di Lazzaro and Falato, 2020; Eldaief et al., 2013; George and Taylor, 2014). However, action potential generation is not universal for TMS: it is seen with high frequency stimulation (>10 Hz) but not with low frequency rTMS (1-5 Hz) (Moretti and Roger, 2022). Influencing the action potential is only one of several mechanisms of action of rTMS.

The geometry of the induced electric field depends on various factors, including the shape of the magnetic pulse, the orientation, and the type of coil (Lefaucheur, 2019). Therefore, coil selection depends on the stimulation target (Deng et al., 2014). See Variability and features of TMS devices for more details on the different types of coils.

Typically, the coil is placed perpendicularly to the central cerebral sulcus to induce a current in the posterior-anterior direction (Di Lazzaro and Falato, 2020). TMS (in contrast to deep TMS) typically affects only the superficial cortical layers of the brain. This limitation arises because, according to the principle of electromagnetic induction, the strength of the induced electric field declines exponentially with distance from the coil (Deng et al., 2013).

Single-pulse TMS

The single-pulse TMS paradigm involves stimulation with isolated pulses in specific cortical areas. In addition to being diagnostically useful, this stimulation paradigm is used to determine the cortical activation threshold (Rotenberg et al., 2014). The effects of single pulses can be recorded using electroencephalography (TMS-evoked potentials), electromyography (motor evoked potentials, MEP) or observed with the naked eye (resting motor threshold, rMT). See Treatment intensity and stimulation target for the use of single-pulse TMS in clinical practice.

Paired-pulse stimulation

Paired-pulse TMS involves two consecutive pulses delivered through the same coil, with either a short interstimulus interval of a few milliseconds or a longer interval of tens to hundreds of milliseconds (Klomjai et al., 2015). Both pulses are applied over the same point in the dominant hemisphere above the motor cortex to explore inhibitory or excitatory intracortical networks, depending on the intensity and interstimulus interval used (Di Lazzaro and Falato, 2020, Rotenberg et al., 2014). Paired-pulse TMS can also explore inter-hemispheric inhibition if applied at the same location in the motor cortex of opposite hemispheres (Ferbert et al., 1992).

Repetitive TMS (rTMS)

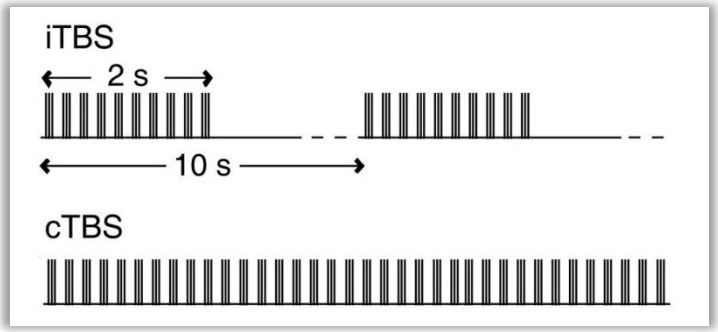
While single-pulse and paired-pulse TMS are primarily used for studying brain function, repetitive TMS (rTMS) can induce changes in brain activity that persist beyond the stimulation period (Klomjai et al., 2015). This ability to modulate cortical activity beyond the stimulation period has made rTMS a treatment method for neurological and psychiatric disorders. There are several rTMS protocols available for clinical use.

Theta-burst stimulation (TBS)

Theta-burst stimulation (TBS) is a newer form of rTMS protocol that consists of 3 bursts of 50 Hz stimulation with a 200-millisecond interval between bursts (i.e., 3 bursts of 50 Hz given at 5 Hz). The TBS pattern is based on the brain's natural theta rhythm occurring in the hippocampus (Klomjai et al., 2015): the term "theta burst" itself means high frequency bursts (50-200 Hz) with a theta rhythm

(3-8 Hz) (Huang et al., 2005). Different patterns of TBS produce different effects on the excitability of the motor cortex (Huang et al., 2005): when TBS is given in an intermittent form (intermittent TBS, iTBS), it induces long-term potentiation; whereas a continuous form (continuous TBS, cTBS) is associated with long-term inhibition (Kirkovski et al., 2023). See Figure 2 for illustrations of iTBS and cTBS stimulation and "Indications in psychiatry" and Practical guidance on TMS treatment for Depression and OCD" for clinical applications of rTMS/TBS.

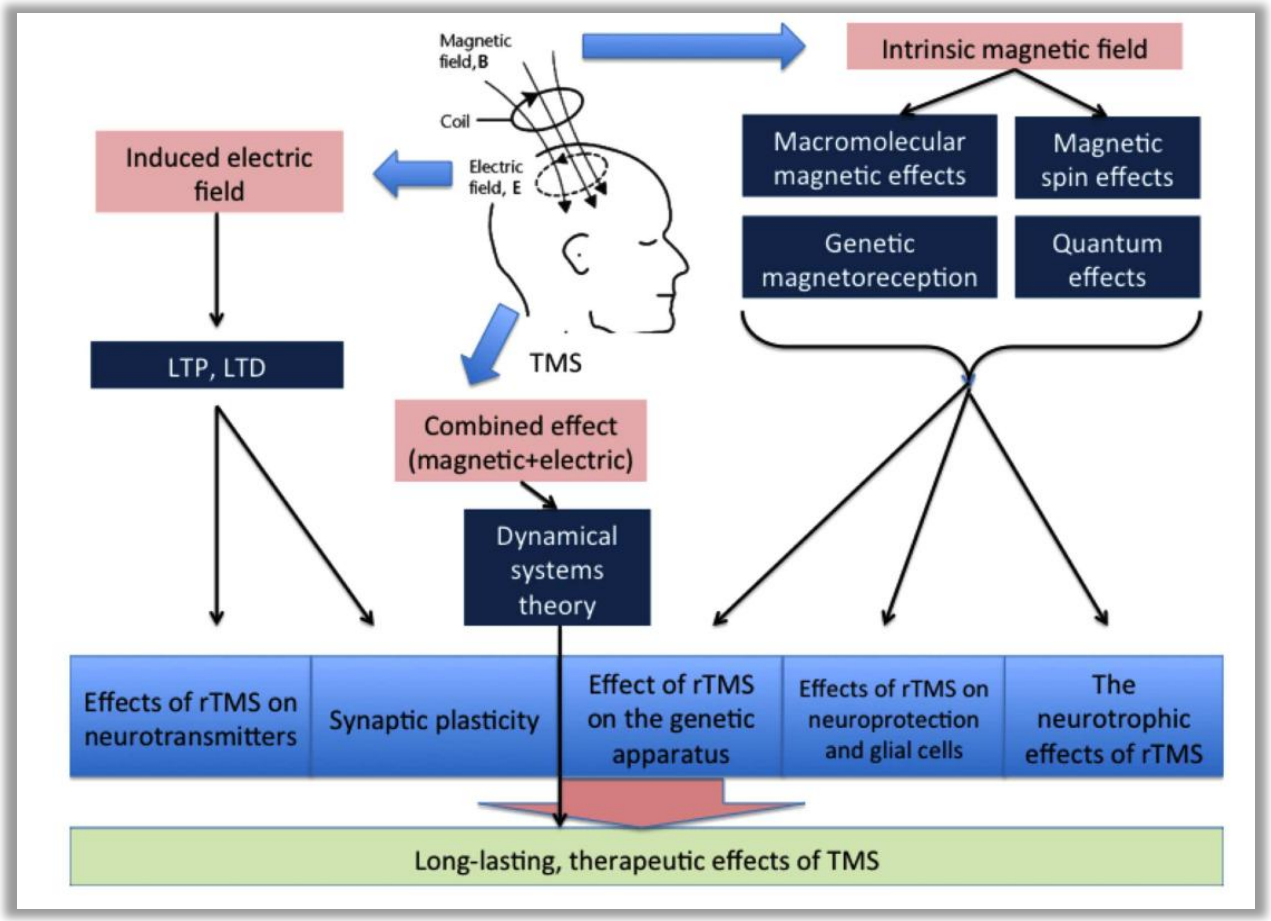
***Figure 2** - Illustrations of iTBS and cTBS stimulation*



Mechanisms of action

Despite the widespread use of TMS and its positive effects in the treatment of different neurological and psychiatric disorders, the exact underlying mechanisms have yet to be elucidated (Chervyakov et al., 2015). Overall, TMS acts at genetic, molecular, cellular and systemic levels, with modulation of internal calcium signalling appearing to be the main mechanism (Moretti and Roger, 2022). See Figure 3 for a schematic illustrating the biological effects of TMS treatment.

Figure 3 *- Schematic of the effects of TMS-related magnetic and electric fields [adapted from Chervyakov et al., 2015, under Creative Commons Attribution 4.0 (http://creativecommons.org/licenses/by/4.0/); LTP: long-term potentiation; LTD: long-term depression]*



Genetic effects

Numerous studies have shown that TMS pulses influence gene expression and the secondary production of several enzymes. These effects likely underlie the long-lasting therapeutic effects of TMS (Simis et al., 2013).

Here are some examples of the genetic effects of TMS:

- Increased cortical (Ji et al., 1998; Hausmann et al., 2000) and limbic mRNA expression of c-fos (Aydin-Abidin et al., 2008)
- Increased cortical expression of zif268 with iTBS and 10 Hz stimulation, but not 1 Hz (Aydin-Abidin et al., 2008)
- Downregulation of astrocyte-related genes associated with inflammation, cytoskeleton, neuroplasticity and signaling (Clarke et al, 2021)

The above examples are primarily from in vitro experiments, which is why further studies are needed to investigate how rTMS can affect neuron-glia interactions and bridge the gap between in vitro and in vivo experiments (Moretti and Roger, 2022).

Neurotransmission

Acute exposure to TMS promotes the activity of several neurotransmitters involved in the pathophysiology of various neuropsychiatric disorders (e.g., dopamine, glutamate, GABA, and serotonin). However, evidence suggests that it is the dopaminergic system that undergoes the most significant change, especially when the target of stimulation is the frontal cortex (Ben Sachar et al., 1997; Keck et al., 2000; Medina and Kanno Túnez, 2013).

As there are numerous connections between cortical dopaminergic pathways and other brain regions, TMS stimulation promotes an increase in dopamine activity in areas such as the nucleus accumbens and dorsal striatum (Strafella et al., 2003). Experimental studies conducted on rodents (Godlevskii and Kobolev, 2005), primates (Ohnishi et al., 2004), healthy subjects (Pogarell et al., 2007; Cho and Strafella, 2009), and patients with Parkinson's disease (Bornke et al, 2004) suggest that at least part of the beneficial effects of TMS observed in a variety of neuropsychiatric disorders may be mediated by dopaminergic activation at the mesolimbic and mesostriatal pathways (Keck et al., 2002; Medina and Túnez, 2013).

In addition, rTMS affects the expression levels of various neuroreceptors and other neuromodulators. After exposure to rTMS, a reduction in the number of β-adrenoreceptors in the

frontal and cingulate cortex and an increase in the number of NMDA receptors in the ventromedial thalamus, amygdala and parietal cortex are observed (Lisanby and Belmaker, 2000).

Synaptic plasticity

It is widely demonstrated in the literature that the effects of rTMS continue after the stimulation itself is over (George & Taylor, 2014). Most authors hypothesize that the long-term therapeutic effects of rTMS (days, weeks or even months) are due to processes of long-term potentiation (LTP) and long-term depression (LTD) (Chervyakov et al., 2015; Hoogendam et al., 2010). LTP increases synaptic strength in the long term and is typically evoked by high-frequency or theta-burst stimulation, while LPD weakens synaptic strength in the long term and is evoked by low-frequency stimulation (Bi and Poo, 1998; Duffau, 2006).

The molecular mechanisms involved in the changes induced by TMS, and more precisely in the induction of LTP, rely on NMDA and AMPA receptors, which allow calcium to enter the postsynaptic neuron (Medina and Túnez, 2013) and the subsequent activation of second messenger systems. The induction of LTP is also associated with increased expression of genes encoding BDNF (Brain Derived Neurotrophic Factor), which plays a crucial role in long-term plasticity (Bramham et al., 1996; Morimoto et al., 1998). Thus, the effect of TMS on the expression and production of BDNF (as well as other factors) leads to the conclusion that TMS exerts its therapeutic effects by consolidating neuroplasticity (Medina and Túnez, 2013). However, the effects of TMS may also have a broader impact on brain plasticity and not be limited to the synaptic level.

Studies performed on patients with depression have shown structural changes induced by rTMS: larger axonal diameter, increased myelination and fiber density in the white matter of the left middle frontal gyrus with high-frequency protocols (Peng et al., 2012); and bilateral gray matter growth in temporal lobes and thalamus with low-frequency TMS (May et al., 2007).

Inflammation and prevention of neuronal death

The above-mentioned structural changes observed in patients with depression (May et al., 2007; Peng et al., 2012) appear to be the end product of TMS effects on neurogenesis, synaptogenesis, angiogenesis, gliogenesis, increased cell size and cerebral blood flow (Chervyakov et al., 2015).

Several studies on transient ischemic attack and long-term ischemia models have shown that rTMS has a neuronal anti-apoptotic effect while modulating blood flow and cerebral metabolism (Chervyakov et al., 2015).

Moreover, TMS has a beneficial effect on mitochondrial metabolism by improving energy production and oxidative balance, thus modulating not only cellular apoptosis mechanisms and the transcription factors involved in their regulation, but also the phenomena associated with the production of proinflammatory cytokines (Medina and Túnez, 2013).

Mechanisms of action in depression

Several studies have investigated the effect of rTMS on depression by comparing brain activity before and after applying neuromodulation protocols. The results point to an association between depression and hypoexcitability in the left prefrontal cortex and/or hyperexcitability in the right prefrontal cortex (Fitzgerald and Daskalakis, 2022).

Imaging studies seemed to reinforce this finding in depression by describing a potential dysregulation of cortical activity in the dorsolateral prefrontal cortex with decreased activity on the left side and increased activity on the right side (Abou-Saleh, 1999; Baxter et al., 1989). Furthermore, treatment with TMS in depression has shown evidence of reducing these dysregulations in cortical activity (Fitzgerald and Daskalakis, 2022; Kimbrell et al., 1999; Pascual-Leone, 1994).

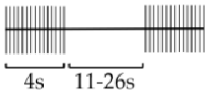
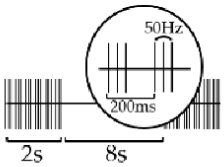
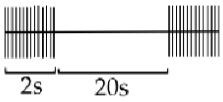
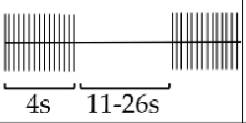
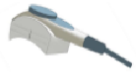
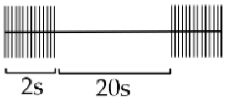
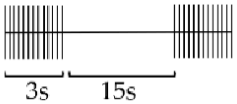
However, evidence suggests that the response to treatment with different rTMS protocols is not only linked to a simple redistribution of left-right cortical activity, but also to changes in cortical-subcortical connectivity (Peng et al., 2012). Standard magnetic resonance imaging (MRI) (Peng et al., 2012) and active-task functional MRI (Fitzgerald et al., 2007) studies of TMS in depression treatment have shown that rTMS induces both local and distal brain connectivity changes.

Indications in psychiatry

Both the U.S. Food and Drug Administration (FDA) and Conformité Européenne (CE) mark (CE mark under EU Directive 93/42/EEC) have approved rTMS for use in several psychiatric disorders, including TRD, depression with comorbid anxiety and obsessive-compulsive disorder. In addition, the FDA has approved rTMS for smoking cessation; and TMS devices have been CE marked for the treatment of psychoactive substance use disorders. Table 1 provides an overview of rTMS protocols/TMS devices with FDA-clearance for the treatment of psychiatric disorders.

In addition, international evidence-based recommendations from clinical experts have been published to support the clinical use of rTMS based on the most up-to-date clinical evidence (Lefaucheur et al., 2020; McClintock et al., 2018; Trapp et al., 2025).

Table 1 *- FDA-cleared protocols for the treatment of psychiatric disorders [from Cotovio et al., 2023; Creative Commons Attribution (CC BY) license – https://creativecommons.org/licenses/by/4.0/]*

Disorder	Frequency	Ses. Pulses (Duration)	Schedule (No Ses.)	Target Region	Examples of TMS Manufacturers (Coils)
Major Depressive Episode	10Hz rTMS 	3000 (18′ 48″ to 37′ 30″)	1/d (20–30d)	L-DLPFC	NeuroStar 
				L-DLPFC	Magstim (e.g., HORIZON® Coils) 
				BL-DLPFC (L-DLPFC)	Brainsway (H1 coil) 
				L-DLPFC	Magventure (e.g., B65 coil) 
	Intermittent Theta Burst 	600 (3′ 9″)	1/d (20–30 d)	L-DLPFC	NeuroStar  Magstim  Magventure 
		18000 (9′ 27″)	Accelerated: 10/d (5 d)	L-DLPFC	Magventure (B65 coil) 
With Comorbid Anxiety	20Hz rTMS 	1980 (20′ 12″)	1st: 1/d (20 d) 2nd: 2/w (12 w)	BL-DLPFC (L-DLPFC)	Brainsway (H1 coil) 
	10Hz rTMS 	3000 (18′ 48″)	1st: 1/d (30 d) 2nd: ~2/w (3 w)	L-DLPFC	NeuroStar 
Obsessive Compulsive Disorder	20Hz rTMS 	2000 (18′)	1/day (29 d)	ACC/mPFC	Brainsway (H7 coil) 
				ACC/mPFC	Magventure (DB-80 coil) 
Smoking Cessation	10Hz rTMS 	1800 (17′ 48″)	1st: 1/d (15d) 2nd: 1/w (3 w)	BL-lPFC BL-Insula	Brainsway (H4 coil) 

['-minutes; ''-seconds; ACC-anterior cingulate cortex; BL-bilateral; d-days; DLPFC-dorsolateral prefrontal cortex; Hz-Hertz; L-left; lPFC-lateral prefrontal cortex; mPFC-medial prefrontal cortex; No-number; s-seconds; Ses. - sessions; w-weeks]

Unipolar depression

rTMS is FDA-cleared and CE-approved for the treatment of treatment-resistant depression (TRD). The FDA and European Medicines Agency (EMA) define TRD as failure to respond to two or more antidepressant regimens despite adequate dose and duration and good compliance (U.S. Food and Drug Administration, 2018a; European Medicines Agency, 2018).

The Danish Health Technology Council ("Behandlingsrådet") was established by Danish Regions in 2021 to evaluate the use of healthcare resources in cost-effective technologies and interventions. In a 2024 report on TMS in the treatment of depression, this Council concluded that rTMS has a clinically meaningful effect and is cost-effective when used as an adjunct to standard treatment in patients with moderate to severe TRD. Based on these findings, the Council issued a positive recommendation for the use of rTMS in this patient group (Behandlingsrådet, 2024).

rTMS is recommended for the treatment of TRD in several clinical guidelines (Hebel et al, 2022; Lam et al, 2024; McClintock et al, 2018; Trapp et al, 2025). The Lefaucheur et al. (2020) evidence-based guidelines recommend rTMS for depression at Level A ("definitely effective").

40-60% patients with (non-treatment resistant) unipolar depression achieve remission with rTMS treatment (Lefaucheur et al., 2020). An exploratory post-hoc analysis of O'Reardon et al.'s (2007) RCT found an effect size of 0.83 (CI 0.20-1.48) for active vs. sham rTMS regarding change in depressive symptoms in patients with one failed antidepressant (n=164), whereas the effect size was 0.42 (CI 0.30-1.15) for active vs. sham in the group with 2-4 failed treatment attempts with antidepressants (n=137) (Lisanby et al., 2009). These results suggest that rTMS is more effective in patients with less existing treatment resistance to antidepressants. A systematic review of rTMS in patients with treatment-naïve depression (5 RCTs, n=674; 5 observational studies; n=665) concluded that there is high-quality evidence supporting the clinical efficacy of rTMS in patients with ≤1 failed antidepressant treatments (Voigt et al., 2019).

The THETA-DEP and THREE-D studies showed 15-32% remission and 33-49% response in patients with TRD (Blumberger et al., 2018; Bulteau et al., 2022). A multicenter RCT (n=82) demonstrated that rTMS was more effective than antidepressant switching in reducing depressive symptoms

according to the Hamilton Depression Scale (17-item) (HAM-D17) in the treatment of patients with moderate TRD (response 37.5% vs. 14.6%, OR 3.5; remission 27.1% vs. 4.9%, OR 7.2) (Dalhuisen et al., 2024). There are several RCTs and meta-analyses supporting the efficacy of different forms of TMS treatment for TRD (Blumberger et al., 2018; Bulteau et al., 2022; Brunoni et al., 2017; Cao et al., 2018; Cole et al., 2022; Gaynes et al., 2014; Kishi et al., 2024b; Mutz et al., 2018; O'Reardon et al., 2007; Sehatzadeh et al., 2019; Voigt et al., 2021). However, these meta-analyses also conclude that there are uncertain blinding procedures and methodological heterogeneity. See Table 2 for a more detailed description of systematic reviews and meta-analyses of TMS for unipolar depression.

Table 2 *- Description and quality assessment of meta-analyses on RCT of TMS treatment of unipolar depression/major depression [AMSTAR: A MeaSurement Tool to Assess systematic Reviews - Shea et al., 2017; AMSTAR 2 rating of confidence in results: critically low, low, moderate or high]*

The study	Included studies (n)		Active treatment (n)	Sham (n)	Odds ratio		RR / WMD	Confidence interval (95%)	AMSTAR 2 rating
Brunoni et al, 2017 [see study for results on other protocols, e.g. bilateral or deep TMS]	Response	81	4 233		HF	3.07	-	2.24 - 4.21	Moderate
					LF	2.37		1.52 - 3.68	
					TBS	2.54		1.07 - 6.05	
	Remission				HF	2.73	-	1.78 - 4.20	
					LF	2.70		1.51 - 4.82	
					TBS	3.37		0.52 - 22.05	

Gaynes et al. 2014	Response	15	369	284	-	RR 3.38	2.24 - 5.10	Low
	Remission	7	195	164	-	RR 5.07	2.50 - 10.30	
Kishi et al, 2024b [TBS for depression; see study for results on other protocols]	Response	23	960		-	iTBS (occipital lobe)	RR 10.67	1.15 - 98.60	Low
						iTBS	RR 2.00	1.28 - 3.13	
						cTBS+ iTBS	RR 1.90	1.11 - 3.24	
	Remission					iTBS (occipital lobe)	RR 2.67	0.08 - 86.59	
						iTBS	RR 2.16	1.01 - 4.62	
						cTBS+ iTBS	RR 1.59	0.61 - 4.12	

Mutz et al, 2018 [see study for results on other protocols]	Response	56	1598	1460	HF	3.75	-	2.44 - 5.75	Moderate
					LF	7.44		2.06 - 26.83	
					iTBS	4.7		1.14 - 19.38	
	Remission				HF	2.52	-	1.62 - 3.89	
					LF	14.10		2.79 - 71.42	
					iTBS	6.22		0.28 - 136.90	
Sehatzadeh et al, 2019 [results for unilateral TMS; see study for information on bilateral TMS]	23		860	680	-		WMD 3.36	1.85 - 4.88	Moderate
Voigt et al., 2021 [TBS for depression]	Response	6	153	122	-		RR 2.4	1.27 - 4.55	Moderate
	Remission	1	39	17	-		*no statistically significant difference*	-	

[HF: high-frequency TMS; L-DLPFC: left dorsolateral prefrontal cortex; LF: low-frequency TMS; RR: relative risk; TBS: theta-burst stimulation; R-DLPFC: right dorsolateral prefrontal cortex; WMD: weighted mean difference]

The Danish Psychiatric Society ECT and Neurostimulation Committee recommends that TMS be considered for *moderate to severe treatment-resistant depression (TRD) without psychotic symptoms in adult patients*. As previously mentioned, both the FDA and EMA define TRD as failure to respond to two or more antidepressant regimens despite adequate dose and duration and good compliance (U.S. Food and Drug Administration, 2018a; European Medicines Agency, 2018). The use of rTMS under this recommendation appears to be cost-effective (Fitzgibbon et al., 2020; Zemplényi et al., 2022; Behandlingsrådet, 2024).

In rare cases, it may be appropriate to use rTMS as monotherapy in patients with moderate to severe unipolar depression without psychotic symptoms who do not tolerate antidepressant treatment at therapeutic doses due to unusual sensitivity regarding side effects. This point is a consensus assessment among the guideline authors.

In contrast, rTMS is not suitable for treating patients with major depression with psychotic symptoms, severe agitation, delirium, or acute suicide risk (Trapp et al., 2025) – Electroconvulsive Therapy (ECT) is, in these situations, an effective and fast-acting treatment (Ren et al., 2014). ECT is also more effective than rTMS in severe depression without psychotic symptoms (Mutz et al., 2019). Saelens et al. (2024) has also found ECT to be more effective than rTMS in TRD [OR for response, ECT=12.86 (CI 4.07-40.63); rTMS=4.01 (CI 2.36-6.81)].

The duration of rTMS treatment effect remains controversial. A systematic review and meta-analysis by Senova et al (2019) on depressed patients with both TRD and non-TRD showed that the antidepressant effect can be durable, with approximately 50% of patients experiencing no relapse within the first year. Specifically, 66.5% was relapse-free after 3 months; 52.9% after 6; and 46.3% after 12 months. The study also showed that maintenance rTMS (mTMS) appears to reduce the risk of recurrence, but there is no clear guideline on which patients would benefit from mTMS or how such maintenance course should look like (Senova et al., 2019; Wilson et al. 2022). Read the section Tapering and Maintenance TMS for further details.

Obsessive-compulsive disorder

The cortico-striatal-thalamo-cortical (CSTC) circuit appears to have an essential role the pathophysiology of obsessive-compulsive disorder (OCD) (Brem et al., 2012; Stein et al., 2019), which is why most rTMS protocols for OCD treatment target such circuit. Several targets within this network, like the anterior cingulate cortex (ACC), are thought to be located deep in the brain. Such targets require the use of special TMS coils, like H-coils, which allow deeper stimulation up to about 4 cm below the skull (vs.≈ 1 cm for figure-of-8 coils) – this is called deep TMS (dTMS) (Tendler et al., 2016). See General design and components under Device selection for more information on TMS coils.

rTMS combined with exposure therapy was approved by the FDA for the treatment of OCD in 2018 (U.S. Food and Drug Administration, 2018b). In the study underlying the approval (Carmi et al., 2019), 99 patients with treatment-resistant OCD at 11 centers around the world were randomized to either dTMS in the ACC and dorsomedial prefrontal cortex (dmPFC) or sham, given from Monday to Friday for six weeks. Prior to each TMS session (or sham session), participants underwent exposure exercises to activate the brain regions associated with OCD (Carmi et al., 2019; Tendler et al., 2019). Results showed that 38.1% of patients receiving the TMS treatment achieved response (≥ 30% symptom reduction on the Y-BOCS) vs. 11.1% in the control group. 54.8% of TMS patients experienced ≥20% symptom reduction vs. 26.7% in the control group. Across randomized controlled trials, rTMS has shown a moderate effect size (Hedges' g = 0.65) on OCD symptom severity and a 3 times higher likelihood of response (relative risk = 3.15) compared to sham (Steuber and McGuire, 2023).

Suhas et al. (2023) examined the treatment strategies for adult patients with SSRI-resistant OCD in a meta-analysis. This study included 55 RCTs, 19 treatment options, and 2011 patients. The authors concluded that dTMS, ondansetron, cognitive behavioral therapy (CBT), and aripiprazole could be considered first-line add-ons in SSRI-resistant OCD (i.e., inadequate response to ≥1 SSRIs). The results were limited by studies with low numbers of subjects and large confidence intervals, and should therefore be interpreted with caution.

A recent cost-effectiveness analysis compared dTMS to other established treatment options for treatment-resistant OCD (Gregory et al. 2022). The study concluded that dTMS may provide a treatment alternative as an add-on to antidepressant treatment in SSRI-resistant patients, in cases where CBT is not available. The cost-effectiveness analysis also concluded that dTMS outperformed antipsychotics as an add-on to antidepressant treatment.

dTMS appears to be effective in the treatment of OCD in cases where CBT and several antidepressants have not proven effective (Roth et al, 2020). This may be attributed to the distinct mechanism dTMS, which, unlike psychotropic drugs and CBT, directly modulates the CSTC circuit (Carmi et al., 2019).

The level of evidence for the efficacy of TMS for OCD is lower than for unipolar depression, and Lefaucheur's evidence-based guidelines recommend rTMS for OCD at Level C (possibly effective) (Lefaucheur, 2020). Although several meta-analyses have concluded that rTMS is more effective than sham in OCD treatment, the evidence of efficacy is limited by small studies, methodological heterogeneity and publication bias (Fitzsimmons et al., 2022; Liang et al., 2021; Steuber and McGuire, 2023; Vinod et al., 2024). These meta-analyses mention the need for more and larger RCTs with a higher degree of generalizability and more effective blinding to verify the effect of specific protocols. See Table 3 for a more detailed description of the studies on TMS for OCD.

Although MagVenture advises against the use of dTMS for OCD in patients younger than 22 years and older than 68 years (MagVenture, 2021), dTMS appears to be safe in children and adolescents (Allen et al., 2017), as well as in older patients (Cappon et al., 2021; Roth et al., 2024).

The ECT and Neurostimulation Committee recommends that deep TMS be considered as an add-on treatment in patients with moderate to severe SSRI-resistant OCD (i.e., inadequate response to ≥ 1 SSRIs), when combination with structured CBT has not proven effective.

Table 3 – Description and quality assessment of meta-analyses on RCT of TMS treatment for OCD [AMSTAR: A MeaSurement Tool to Assess systematic Reviews - Shea et al., 2017; AMSTAR 2 rating of confidence in results: critical low, low, moderate or high]

The study	Included studies (n)	Active treatment (n)	Sham (n)	Stimulation type	Hedges' g RR WMD		Confidence interval (95%)	AMSTAR 2 rating
Fitzsimmons et al, 2022 [only effective protocols are described; see study for other protocols]	15	368	294	All	g	0.502	0.296 - 0.708	High
	2	29	20	LF right DLPFC	g	1.03	0.36 - 1.70	
	6	95	88	LF bilat preSMA	g	0.56	0.17 - 0.95	
	3	20	21	HF bilat DLFPC	g	0.90	0.34 - 1.47	
Liang et al., 2021 [only effective protocols are described; see study for other protocols]	22	365	333	All	-		-	Low
	4	57	48	LF DLPFC (left and right pooled together)	WMD	6.34	2.12 - 10.42	
	6	95	88	LF bilat preSMA	WMD	4.18	0.83 - 7.62	
	9	124	120	HF DLFPC (left and right pooled together)	WMD	3.75	1.04 - 6.81	

Steuber and McGuire, 2023	25	860	All	g	0.65	0.46 - 0.84	Low
				RR (for response)	3.15	2.13 - 4.68	
Vinod et al, 2024 [only effective protocols are described; see study for other protocols]	33	589 / 498	All	-		-	Moderate
	4	151	LF right DLPFC	g	0.82	0.31 - 1.32	
	10	345	LF/cTBS bilat preSMA	g	0.55	0.21 - 0.89	
	2	64	LF dmPFC/ACC	g	0.83	0.04 - 1.61	
	4	93	HF bilat DLFPC	g	0.93	0.30 - 1.56	
	2	135	**HF dmPFC/ACC** (FDA approved)	g	0.83	0.17 - 1.49	

[ACC: anterior cingulate cortex; bilat: bilateral; DLPFC: dorsolateral prefrontal cortex; dmPFC: dorsomedial prefrontal cortex; HF: high-frequency TMS; LF: low-frequency TMS; RR: relative risk; SMA: pre-supplementary motor area; TBS: theta-burst stimulation; WMD: weighted mean difference]

Bipolar depression

Current data on the use of rTMS in patients with bipolar depression is still limited.

10 Hz rTMS over the left DLPFC and 1 Hz over the right DLPFC, but not iTBS, appear to be significantly superior to sham in bipolar depression (Hsu et al., 2024). A major limitation of the available studies on the use of transcranial magnetic stimulation (TMS) in bipolar disorder is the small number of studies and the limited sample sizes (Hsu et al., 2024; Konstantinou et al., 2022). Additional significant limitations include heterogeneity in study designs, variability in patient and control group selection, differences in rTMS parameters, and inconsistency in outcome measures (Hsu et al., 2024; Konstantinou et al., 2022). More and larger sham-controlled studies are needed to confirm the efficacy of rTMS in bipolar depression (Hsu et al., 2024; Kishi et al., 2024a; Konstantinou, 2022) and to support its recommendation as a routine treatment option (Nguyen et al., 2021). Larger clinical trials are also needed to determine whether rTMS has an effect on manic and mixed episodes, as well as its role in mood stabilization and suicide risk reduction (Konstantinou, 2022).

The International College of Neuropsychopharmacology (Collegium Internationale Neuro-Psychopharmacologicum, CINP) guidelines for bipolar depression identify rTMS as a potential therapeutic strategy for treatment-resistant bipolar depression, assigning it a Level 2 recommendation (Fountoulakis et al., 2020). However, the same guidelines note that the evidence regarding the efficacy of TMS in bipolar depression remains insufficient.

The Committee does not recommend rTMS as standard treatment for bipolar disorder. Nevertheless, rTMS may be considered for moderate to severe bipolar depression where higher level evidence-based treatment options – including psychotropic medications (including quetiapine, lurasidone, lamotrigine, cariprazine, olanzapine-fluoxetine) (Yildiz et al, 2023) and electroconvulsive therapy (Dierckx et al., 2012; Keramatian et al., 2023) – have proven ineffective or have caused intolerable side effects. To reduce the risk of manic shifts in rTMS treatment of bipolar patients, it is recommended that patients remain on mood stabilizing medication during TMS treatment (Xia et al., 2008). Furthermore, patients should be closely monitored for the development of manic symptoms - clinical monitoring can be supplemented with the use of a symptom scale such as the Modified Bech-Rafaelsen Mania Scale (MAS-M) or Young's Mania Rating Scale (YMRS).

Schizophrenia

There is mixed evidence for the use of rTMS to treat positive symptoms in schizophrenia (Marzouk et al., 2020). Most studies have focused primarily on auditory hallucinations and have included small, highly heterogeneous populations (Lefaucher et al., 2020). Low frequency rTMS over the left temporoparietal cortex appears to have some effect against auditory hallucinations (Hoffman et al., 1999; Lefaucher et al., 2020).

rTMS has also been investigated as a treatment option for negative symptoms in schizophrenia. Studies indicate that structural and functional changes in the prefrontal cortex (PFC), as well as its altered connectivity with striatal regions, may be associated with negative symptoms in schizophrenia (Bègue I, et al., 2020; Howes, 2024; Shukla et al., 2019), making the PFC a potential target for rTMS. A recent network meta-analysis with 48 RCTs and 2211 patients concluded that high-frequency rTMS protocols over the left DLPFC appear to improve negative symptoms in schizophrenia (Tseng et al., 2022). Another meta-analysis of 57 RCTs and 2633 patients showed statistically significant efficacy of TMS in negative symptoms (Cohen's d = 0.41; CI: 0.26 - 0.56; $p < 0.001$), corresponding to a number needed to treat of 5 (Lorentzen et al., 2022). rTMS > 1 Hz targeting the left DLPFC was the most effective protocol, but the optimal TMS parameters could not be determined. However, authors of both meta-analyses highlighted that included studies featured small sample sizes and methodological heterogeneity in technical procedures. They recommended using these findings as a foundation for larger, rigorous RCTs with extended follow-up periods to explore rTMS' impact on negative symptoms and establish standardized treatment protocols.

Expert guidelines from Lefaucher et al. (2020) recommend rTMS for auditory hallucinations (low frequency rTMS over the left temporoparietal cortex) and for negative symptoms (high frequency rTMS over the left DLPFC): both protocols are assigned a Level C evidence rating (i.e., possibly effective).

The Committee does not recommend the use of rTMS as standard treatment in schizophrenia. However, rTMS can be considered as an add-on treatment for auditory hallucinations or negative symptoms of at least moderate severity, where monotherapy with 2 different antipsychotics and clozapine in sufficient dose and duration plus good compliance has not proven effective.

Post-traumatic stress disorder (PTSD)

rTMS has demonstrated efficacy for PTSD in several small randomized controlled trials (Boggio et al., 2010; Cohen et al., 2004) and in a systematic review suggesting that high-frequency rTMS over the right DLPFC may be effective (Cirillo et al., 2019). However, a recent Cochrane meta-analysis of 13 RCTs concluded with moderate to high certainty that active rTMS is unlikely to differ from sham stimulation in reducing PTSD severity immediately after treatment (Brown et al., 2024). The analysis also highlighted substantial heterogeneity among studies and emphasized the need for further research to assess remission rates, treatment response, and PTSD severity at various follow-up intervals.

The use of TMS for PTSD is not currently approved by either the FDA or CE (Cotovio et al, 2023). The comprehensive evidence-based rTMS guidelines from Lefaucheur et al (2020) recommend rTMS for PTSD at Level C – "possibly effective".

The Committee does not recommend the use of rTMS as standard treatment for PTSD.

Smoking cessation

Current data on the use of rTMS for smoking cessation is still limited.

Bilateral high-frequency dTMS targeting the lateral PFC and insula has been shown in a study by Dinur-Klein et al. (2014) to reduce tobacco consumption, achieving a 44% abstinence rate at the end of treatment. These findings contributed to FDA clearance of this protocol for smoking cessation; however, CE certification is still pending (Cotovio et al., 2023). Guidelines from Lefaucheur et al. (2020) recommend high-frequency rTMS over the left DLPFC for tobacco cessation with a Level C evidence rating (“possible effective”).

The Committee does not recommend the use of rTMS as standard treatment for smoking cessation.

Psychoactive Substance Use Disorders

High-frequency rTMS over the left DLPFC has received CE approval for use in Psychoactive Substance Use Disorders based on based on studies demonstrating reductions in cocaine use: a retrospective observational study of 284 outpatients (Madeo et al., 2020) and a RCT with 32 patients (Terraneo et al., 2016).

Lefaucheur et al (2020) recommend rTMS for substance abuse with Level C ("possibly effective").

The Committee does not recommend the use of rTMS as standard treatment in substance abuse.

Other conditions

TMS has been studied for the treatment of a number of neurological disorders, but has not been approved by the FDA (Cotovio et al., 2023). The clinical guidelines from Lefaucheur et al. (2020) recommend rTMS for:

- Alzheimer's disease at Level C evidence level (i.e., possibly effective).
- Motor symptoms in Parkinson's disease at Level B (probably effective)
- Depression in Parkinson's disease at Level B

The level of evidence for the use of rTMS in other mental health disorders, such as ADHD and autism, is poor (or negative), and lack approval from regulatory authorities and formal recommendations in expert guidelines (Lefaucher et al., 2020).

Tolerability and safety

rTMS is generally considered a safe treatment; however, it can be associated with side effects (Lefaucheur et al., 2020; McClintock et al., 2018; Trapp et al., 2025).

Wassermann published the first TMS safety guidelines in 1996. In 2009, Rossi et al. published the second set of safety guidelines, developed during a multidisciplinary consensus meeting held in Siena, Italy, on behalf of the International Federation of Clinical Neurophysiology. More than a decade later, an updated third safety guideline was published in 2021 (Rossi et al., 2021).

The recommendations in this document regarding contraindications, risk factors, and points of attention are largely based on the latest and most updated international safety guidelines published in 2021 (Rossi et al., 2021). The use of rTMS in accordance with these safety guidelines is considered generally safe. Any contraindications and risk factors for rTMS should be screened before treatment with rTMS using a safety checklist (an example of a safety checklist is shown in Appendix 1). Assessment of contraindications/risk factors and referral for TMS treatment is a medical task.

In the presence of contraindications or risk factors (see below), consultation with a TMS medical specialist is recommended to assess the potential benefits and risks of rTMS treatment. Extreme caution should be exercised when considering rTMS for patients with risk factors, such as a history of seizures. The most appropriate and safest protocol should be carefully selected, and the risk-benefit ratio should be thoroughly discussed in high-risk situations.

Tolerability

rTMS has been approved or cleared for "safety and efficacy" in various therapeutic indications by regulatory bodies such as the FDA (Lefaucher et al., 2020). iTBS has specifically been reported in expert guidelines as "safe" (Rossi, 2021). A meta-analysis of neuromodulation in TRD has found no significant difference in acceptability between rTMS and sham controls (Li et al., 2021). Treatment adherence to iTBS in RCTs has been reported to be 90% or higher (Blumberger et al., 2018; Bulteau et al., 2022).

The most common side effects of TMS are mild and self-limited (Rossi et al., 2021). The most frequent adverse effects are transient discomfort or pain in the head or scalp at or near the site of the TMS stimulation; this discomfort can spread to adjacent areas of the face, including around the ipsilateral eye, ear, nose, and jaw (McClintock et al., 2018). The THETA-DEP study reported asthenia (6-13%) and headache (3-17%) as the most common adverse events of moderate to severe intensity (Bulteau et al., 2022). Teeth chattering may occur due to contractions of the jaw muscles. If this presents a problem, for example because of poor dental status, the use of a bite guard is recommended.

The risk of seizures triggered by rTMS is very low and, if they occur, they do so during treatment (Rossi et al., 2021). In a survey of 300.000 TMS sessions conducted between 2012-2016 found a seizure rate of 1:60.000 treatments (Lerner et al., 2019).

Although rTMS side effects are generally mild and well tolerated by patients, it is recommended to monitor their occurrence and implement mitigating measures when needed (e.g. use of earplugs, pain killers, reduction of stimulus percentage relative to rMT) (McClintock et al., 2018; Rossi et al., 2021).

Contraindications

- **Implanted electronic/medical devices in the head or within a certain distance from the TMS coil** that can be affected by the induced magnetic field (e.g. cochlear implants or pacemakers). The Rossi et al. (2021) guidelines recommends **a minimum of 10 cm**. TMS device manufacturers recommend **a minimum** distance **of 30 cm** between the implanted device and the coil (Rossi and Lefaucheur, 2014; Trapp et al., 2025). However, such risks do not appear to apply to a new generation of cochlear implants developed by MED-EL. Mandalà et al. subjected two MED-EL titanium-housed cochlear implants (Mi1000 Concerto and Mi1200 Synchrony) to single-pulse TMS, low frequency (1 Hz) and high frequency (10 Hz) rTMS (Mandalà et al., 2021). Interestingly, the cochlear implant and all its electronic components remained fully functional even when the frequency, intensity, and number of pulses exceeded safety guidelines for TMS in humans (Rossi et al., 2009). The authors concluded that the use of rTMS in patients with these specific cochlear

implants posed no risk of electronic damage, demagnetization, or displacement when delivered through a focal figure-of-eight coil, and if specific tools were used to protect the implants from the electromagnetic field:

  - A small copper plate placed over the cochlear implant to shield it from the electromagnetic field generated by the TMS coil.
  - Due to the rapid heating of the copper plate during repeated TMS, a simple heat sink was used. The heat sink is necessary to avoid replacing the copper plate or interruptions in treatment. In the study, a lightweight acrylonitrile butadiene styrene (ABS) shell was used to enclose the copper layer.

- **Conductive ferromagnetic or other magnetically sensitive metals implanted in the head or within 10 cm (according to Rossi et al., 2021) / 30 cm (according to manufacturers) of the treatment coil** (e.g., aneurysm clips, stents, fragments from projectiles, metal shrapnel, cerebral shunts, vagus nerve stimulators):
  - Plastic electrodes with low conductivity are less likely to heat up. And radial slits that prevent induced currents can also reduce heating in electrodes and skull plates.
  - Titanium skull plates tend to have low heating, as this metal has low conductivity and the plates are either small in size or have radial slits. Similarly, titanium rods for spinal implants show no significant temperature change when exposed to magnetic stimulation.

- **Ongoing substance misuse, including alcohol and benzodiazepines**, due to increased risk of seizures when taking illegal drugs (Brust, 2008) or at withdrawal when abusing alcohol or benzodiazepines (Tendler et al., 2018). Use of stable doses of prescribed benzodiazepines is not a contraindication for TMS treatment. Patients unable to reliably abstain from alcohol during daily TMS treatments should not be referred for rTMS therapy.

- **Moderate to severe electrolyte disturbances** (P-sodium <129mmol/L or >150mmol/L) (P-potassium <3.0mmol/L or >6.0mmol/L), due to increased risk of seizures (Stultz et al., 2020).

Blood samples should be no older than three months, or more recent if clinically indicated by the patient's medical condition (e.g., in patients with known electrolyte disturbances).

Risk factors

Some disorders may increase the risk of seizures during TMS treatment. In this sense, patients with the following conditions should not be referred for TMS without prior consultation with the responsible TMS consultant and documentation of the risk assessment:

- Epilepsy or history of seizures.
- Other somatic brain disorders, e.g.: cerebral infarction, cerebral hemorrhage, brain tumor, intracranial hypertension, previous severe head trauma, previous neurosurgical intervention.
- Other risk factors:
    - Insomnia is mentioned as a risk factor in TMS treatment in Rossi et al. (2021), as sleep deprivation has long been recognized as a trigger for seizures (Kotagal and Yardi, 2008). However, moderate sleep deprivation (i.e. 2-3 hours less than average) does not appear to increase the likelihood of seizures at the group level (Stirling et al., 2023). It is total sleep deprivation that has been associated with an increased risk of seizures, particularly in patients diagnosed with epilepsy (Kotagal and Yardi, 2008).
    - Immunosuppressive therapy (e.g. cyclosporine, tacrolimus or others that may cause posterior reversible leukoencephalopathy syndrome), dialysis, systemic infections and fever may also be associated increased risk of seizures with TMS treatment.
- Psychopharmacological treatment that can affect the seizure threshold (e.g. clozapine, tricyclic antidepressants, bupropion). However, the risk is low (Rossi et al., 2021).

It is recommended to conduct thorough screening and identification of the above risk factors, followed by the implementation of appropriate safety measures. These may include close clinical monitoring during TMS sessions, staff training in seizure management, the use of low-frequency stimulation protocols, and optimization of antiepileptic medication as needed (McClintock et al., 2018; Rossi et al., 2021).

Special considerations

- Significant medication changes during TMS should be avoided (e.g. significant dose modifications, discontinuation or initiation of new medications), as this can lead to variations in the patient's motor threshold and the required treatment intensity. This is particularly important for drugs that can increase (e.g., benzodiazepines or antiepileptics) or decrease the seizure threshold (e.g., antipsychotics, especially clozapine, and certain antidepressants, especially bupropion and tricyclic antidepressants). Please see "Ongoing pharmacological treatment" for more details.

- Consumption of alcohol or illegal drugs also affects the patient's motor threshold and may increase the risk of seizures. Alcohol consumption is discouraged throughout the entire course of TMS, especially during daily treatments. In patients with known alcohol dependence or harmful alcohol use, or if there is doubt about the patient's abstinence, ordering blood phosphatidylethanol (B-PEth) may be indicated (Helander and Hansson, 2023).

- Special attention to patients known to have tinnitus and/or hearing loss. In rare cases, TMS can worsen tinnitus and hearing loss. The patient should always be offered earplugs during with TMS treatment. If worsening of tinnitus or hearing loss occurs during treatment, the TMS unit should be informed immediately.

- Pregnancy: TMS appears to be effective and safe for the treatment of depression in pregnant women; however, larger studies are needed to fully establish its safety and efficacy in this population (Cole et al., 2019; Lee et al., 2021). Therefore, the DPS ECT and Neurostimulation Committee is unable to make a specific recommendation regarding the use of rTMS in pregnancy at this time.

Pre-treatment assessments and considerations

It is recommended to prepare an informational booklet for patients and their relatives, which can be distributed prior to the start of treatment – ideally together with the invitation to the first session. Additionally, it should be assessed whether the patient has the capacity to attend daily sessions throughout the rTMS treatment series, and arrangements should be made as needed to support their attendance.

Clinical experience suggests that interruptions in treatment, such as vacations, can trigger relapses just as therapeutic effects emerge. Therefore, treatment schedules should be carefully planned to avoid prolonged breaks. It is also recommended to arrange appropriate follow-up for patients after completing rTMS treatment, particularly for those receiving extensive psychopharmacological therapy.

Screening blood tests such as creatinine, potassium, sodium, hemoglobin, aspartate aminotransferase (AST), albumin, thyroid stimulating hormone (TSH), folate, vitamin B12, vitamin D, hemoglobin A1c, lipid panel and electrocardiogram are recommended, as TRD patients have a higher prevalence of somatic – often undiagnosed – disorders that may be a precipitating or maintaining factor for depression (Berk at al., 2023). Communication with the referring physician is recommended if any untreated somatic illness is identified that could contribute to the depressive episode (such as hypothyroidism or anemia). In patients with obsessive-compulsive disorder (OCD), screening for somatic disorders is also important, particularly for cardiometabolic disorders, given their increased prevalence in this population (Holmberg et al., 2024).

Suspicion of alcohol and drug abuse may warrant supplementation of AST with alanine aminotransferase (ALT) and/or gamma-glutamyltransferase (GGT), as well as relevant drug-related urine or blood tests, etc. PEth measurement can be used to rule out active alcohol consumption in patients with a history of alcohol abuse (Helander and Hansson, 2023). Special attention should be given to patients with suspected alcohol and/or drug abuse: staff should be trained in seizure management, and inhibitory protocols (e.g. 1 Hz stimulation over the DLPFC) can be considered as a first-line treatment option.

It is important to check that the diagnostic indication for rTMS treatment is fulfilled, that there are no contraindications and if there are risk factor or special considerations for the use of rTMS; this can be done, for example, through the use of a safety checklist – see Appendix 1 for an example. The diagnosis should always be confirmed, either by reviewing existing medical records from the referring physician or by inviting the patient for an interview at the TMS unit.

The degree of treatment resistance should be measured using the Maudsley scale (Fekadu et al., 2009, 2018) – see Appendix 2.

Standardized symptom scales are a valuable tool to improve the assessment of psychopathological symptoms in terms of validity and reliability (Möller, 2009), and the combination of interview-based and self-report instruments has been considered the optimal approach to achieve the most accurate prediction of clinical outcome (Uher et al., 2012). Therefore, depression severity should be assessed with an interview-based depression scale [e.g., Hamilton Depression Scale (17-item)] together with a depression self-assessment scale [e.g., Major Depression Inventory (MDI) or self-reported Hamilton Depression Scale (6-item)] at least at baseline, at the end of daily treatments, and at the end of tapering/maintenance treatment. Weekly symptom scale assessments may be beneficial in clinical practice, as <20% improvement after 2 weeks has a negative predictive value of 82.6% for non-response, which may help expedite therapeutic decisions (Feffer et al., 2018b). Similar assessment of OCD severity and treatment efficacy can be made by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), for example.

Side effects should be recorded at each treatment (Rossi et al., 2021) and preferably quantitatively using scales specific to TMS such as, for example, TMSens_Q (Giustiniani et al., 2022).

Adverse reactions potentially related to rTMS treatment, such as headaches or tinnitus, should be documented in the medical record (Rossi et al., 2021). Where possible, use standardized templates in the electronic patient record with pre-filled fields for relevant information, such as treatment number, patient experience, interview-based depression scale scores, self-assessment scale scores, and any adverse reactions.

Ongoing pharmacological treatment

Clarification of roles regarding responsibility for the patient's pharmacological treatment during rTMS treatment is important. As rTMS treatment typically lasts for 6 weeks with 30 daily treatments on weekdays, and, if effective, for a further 12 weeks, there may be a need for plasma monitoring of drugs (e.g., tricyclic antidepressants and lithium), as well as ongoing assessment of interactions, side effects, and adherence.

Whether pharmacological treatment can increase the risk of seizures in TMS treatment is unclear. The literature indicates that medications known to lower the seizure threshold, such as tricyclic antidepressants (Detyniecki, 2022; Tallarico et al., 2023) or clozapine (Williams and Park, 2015), may increase the risk of rTMS-induced seizures. However, the evidence supporting this association is limited, and the overall risk appears to be low (Rossi et al., 2021).

Generally, no adjustments should be made to psychopharmacological treatment during TMS treatment to avoid changes in the seizure threshold and allow independent assessment of the clinical efficacy of TMS. However, significant medical side effects can be an exception to this rule. Necessary changes in medication should be done in collaboration with the TMS team, who then will assess whether an extra measurement of the resting motor threshold (rMT) should be performed.

Practical guidance on TMS treatment for depression and OCD

The following general description of the practical administration of TMS treatment does not account for local conditions at individual TMS units. It is expected that each unit develops its own workflow, making any necessary adaptations to suit local needs.

Treatment intensity and stimulation target

Before starting a TMS treatment course, it is necessary to individually determine a set of parameters that include:

1. **Determination of treatment intensity**
2. **Localization of the stimulation target**
3. **TMS protocol selection (next subchapter)**

1. Determination of treatment intensity

There are different methods for determining treatment intensity in TMS therapy. In these TMS Guidelines, the Committee recommends visual determination of stimulation/treatment intensity using the resting motor threshold (rMT) at the very first TMS session. rMT is an internationally recognized measure of individual brain sensitivity and can be identified visually according to the Rossini-Rothwell algorithm: the weakest impulse that, after unilateral stimulation of the motor cortex, is able to activate a specific muscle group on the opposite side in 5 out of 10 stimulations (Pridmore et al, 1998). This procedure is recommended in clinical TMS guidelines (McClintock et al., 2018) and is often used in rTMS research (Turi et al., 2021).

Example of a standardized procedure for the examination of contralateral thumb rMT (Groppa et al., 2012; Fitzgerald and Daskalakis, 2022; Schutter DJ and van Honk J, 2006):

1. Preparation: the patient is asked to sit in a comfortable chair and to relax the contralateral arm by placing it on the homolateral leg.

2. A cotton cap customized for TMS treatment is placed on the patient's head. This standardizes and improves the accuracy of treatment intensity calculations and stimulation target localization.

- If scalp-based methods are used for localization of the stimulation target, the relevant measurements should be taken before estimation of rMT for pragmatic reasons (see next subchapter Localization of the stimulation target for more details)

3. Determination of rMT:

   - Place the figure-of-8 coil in the scalp midline, halfway between the vertex and the ear. The handle of the coil should point towards the back of the patient and form a 45˚ angle to the sagittal plane.

   - Place the free hand gently – but firmly – on the other side of the patient's head. Be careful not to press too hard with the hand or the coil. Make sure the patient is as relaxed as possible, especially in the arms and hands.

   - Start rMT estimation at 30% of the treatment intensity with an interstimulus interval of maximum 0.2 Hz (i.e., administering pulses no more frequently than every 5 seconds). Move the coil around slowly and apply 1 or 2 pulses at each site. It is important to begin at a low intensity to help the patient relax, minimize discomfort, and allow them to become familiar with the procedure. This process may be quicker for patients who have previously undergone rTMS treatment.

   - The purpose of the above steps is to find the area where single pulse stimulation with the TMS coil activates the contralateral hand muscles (mostly *abductor pollicis brevis* or the first *dorsal interossei*; e.g. contralateral thumb) at a given stimulus intensity of 5 out of 10 stimulations.

   - If no movement/twitch is observed in the contralateral hand at this stimulus intensity, the rMT for that person is higher than the current TMS output setting. Therefore, increase the output by 5% at each attempt, while testing the response at several scalp locations before the next increase.

- When a hand and/or wrist movement is observed, the stimulus intensity is close to rMT. Test the response in several areas and mark the location on the scalp that appears to produce the greatest motor response.

4. Evaluation: stimulate at the identified location, gradually decreasing the intensity by 1% to 2% at a time, until at least 5 out of 10 pulses still produce visually identifiable twitches. The presence of a second observer may be considered to increase reliability.

5. Optimization: After the first qualified guess with the visual method, continue the rMT estimation by systematically searching for an alternative scalp location that exceeds the 50% response criterion of the first MT estimation (i.e. at least 6 out of 10 MEPs or muscle movements).

    - This is done by testing the response to 2 or 3 pulses over an imaginary grid of points surrounding the location that has been marked at the end of step 3:

        i. Moving the coil in 0.5-1 cm intervals lateral and medial to the original marked point to determine the optimal stimulation site in the lateral/medial plane.

        ii. Once the above is done, move the coil back and forth in the ventral/dorsal plane to explore the possibility of further optimization

        iii. If the optimal position has been moved in ii., repeat steps i. and ii. until no locations can be found where stronger muscle twitches can be induced (at >50% of impulses) with the same treatment intensity. Mark the optimized location.

What to do if it's hard to find an initial rMT? (Fitzgerald and Daskalakis, 2022)

If no response is observed when reaching between 60% and 70% of the treatment intensity, the TMS practitioner can request the patient to perform a tonic contraction in the relevant hand, which will reduce the intensity required to produce a motor response and will help localize the site. For a tonic contraction, ask the patient to press the index finger against the thumb (abduction movement of the finger) while applying a small amount of tension. If you find the hotspot that produces a motor response, then make sure to ask the patient to relax in order to find the actual threshold.

rMT estimation in the leg (i.e., rMT of the contralateral hallux) is performed by stimulating the medial primary motor cortex with double-cone coil. The technique can be found in an informative video in Dunlop et al (2015).

The Committee recommends that the estimation of the rMT for contralateral thumb be started at 30-35% of machine output and 50-55% for the rMT in the leg (applicable to MagVenture® TMS devices). General rules of treatment intensity relative to rMT:

- 120% of the rMT of the contralateral thumb in TMS treatment of depression over the dorsolateral prefrontal cortex (DLPFC)
- 120% of the rMT in the leg in TMS treatment of depression over the dorsomedial prefrontal cortex (dmPFC)
- 100% of the rMT in the leg in TMS treatment of OCD over the dmPFC.

Correct determination of the rMT is essential to ensure safe and effective TMS treatment (Bourla et al., 2023; McClintock et al 2018). It is worth noting that the rMT can vary over time due to a wide range of factors, including changes in the patient's physiological state and use of concomitant medications (Rossi et al., 2021). Therefore, routine reassessment of the rMT may be necessary to maintain optimal rTMS treatment parameters throughout the treatment course (Bourla et al., 2023; Cotovio et al., 2021). Because rTMS can vary daily in the same patient, some authors have recommended daily to weekly reassessments of the rMT during the course of TMS (Cotovio et al.,

2021). As daily rMT reassessments can be difficult to implement in clinical practice, **the Committee recommends** that the rMT is reassessed at least every 14 days – ideally every week.

2. Localization of the stimulation target

After measuring the rMT and calculating the treatment intensity, it is important to ensure that the electromagnetic pulses reach the relevant brain areas in order to optimize TMS effectiveness. There are several methods available to identify the specific brain regions to be stimulated. These methods typically fall into two main groups: neuroimaging-based methods and scalp-based methods. **The Committee recommends** scalp-based methods**.**

Neuroimaging-based methods are considered expensive and time-consuming, but they are very precise when it comes to targeting specific brain regions. This type of method uses (Modak and Fitzgerald, 2021; Roalf, et al., 2024):

1. Cerebral MRI to guide TMS use more precisely
2. Electroencephalography (EEG) to identify abnormal brainwave activity so clinicians can target areas of the brain with atypical electrical patterns
3. Individual brain connectivity maps (often derived from functional MRI) to guide TMS to regions showing abnormal functional connectivity
4. Resting state functional MRI (fMRI) to identify brain regions that are functionally connected at rest.

Standard scalp-based methods use simple rules based on anatomical landmarks on the scalp, and are the most widely used methods in clinical settings because of their practicality and cost-effectivity. At the time of writing, it is still uncertain whether neuroimaging methods are associated with higher antidepressant efficacy than scalp-based methods (Wang et al., 2023).

Below are the most used scalp-based methods, according to stimulation sites often selected for TMS treatment of psychiatric disorders such as unipolar depression and OCD:

- Left dorsolateral prefrontal cortex (L-DLPFC)

- Right dorsolateral prefrontal cortex (R-DLPFC)
- Dorsomedial prefrontal cortex (dmPFC)
- Right lateral orbitofrontal cortex (R-OFC)

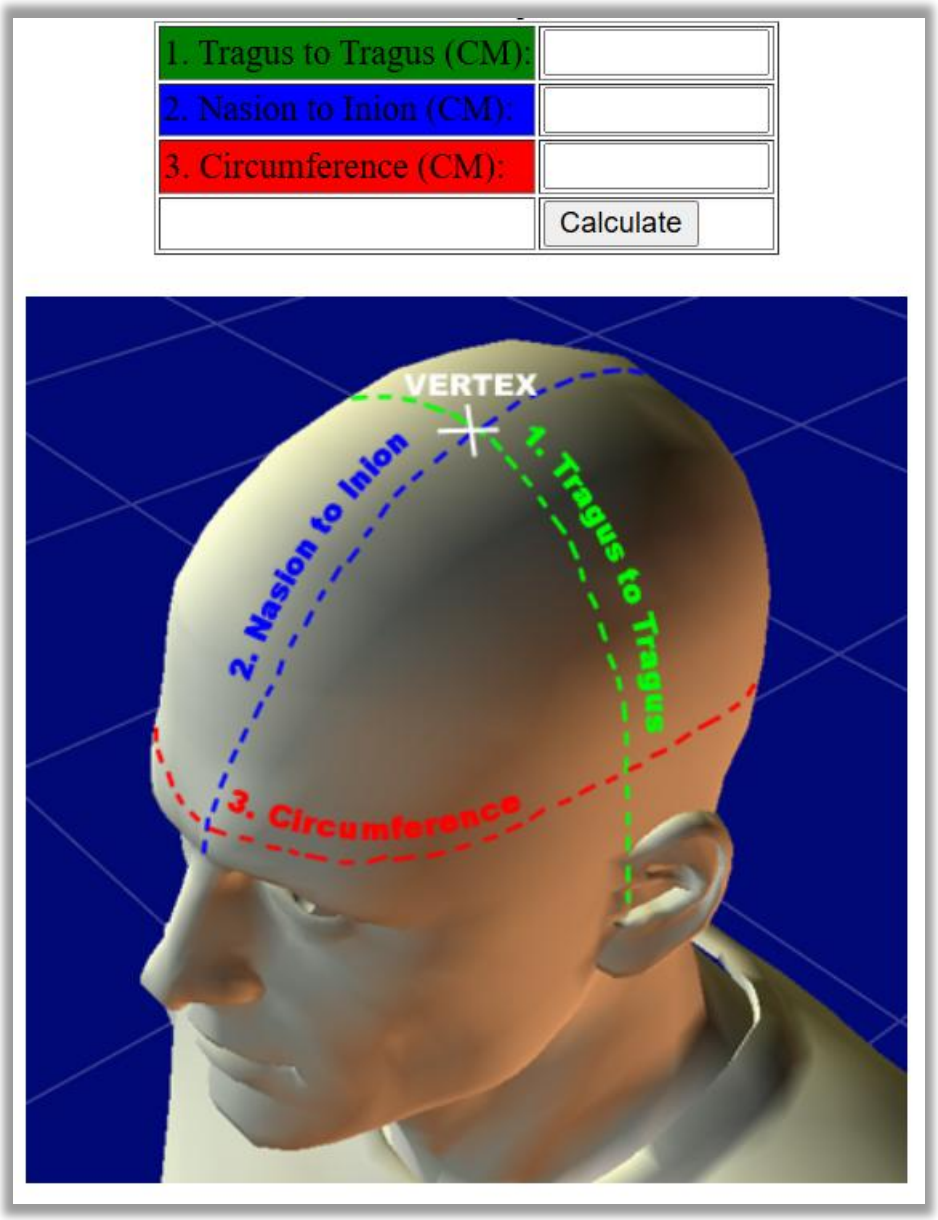
Left dorsolateral prefrontal cortex (L-DLPFC): This is a common region for TMS treatments, especially in depression. There are two general strategies that can be used: "5-6 cm rules" and the "Beam F3 method". Both methods are recommended as they are fast, well-studied and equally effective scalp-based methods in depression treatment with rTMS (Trapp et al., 2023).

- 5-6 cm rules include a 5 cm (Johnson et al., 2013), a 5.5 cm (McClintock et al., 2018) and a 6 cm rule (Fitzgerald et al., 2020): these are the most popular and simplest methods to target the left DLPFC. The TMS coil is placed over the motor cortex and once the motor hotspot area is identified (i.e. when TMS elicits a motor movement in the contralateral hand), the coil is moved 5, 5.5 or 6 cm forward along the parasagittal plane – this point is thought to correspond to the left DLPFC.

- The Beam F3 method (Beam et al., 2009) uses the international 10-20 EEG system to identify the F3 location on the scalp. This method is widely used in clinical practice for the treatment of depression, is considered to be more accurate than the 5.5 cm rule (Trapp et al., 2020) and is performed as follows:
    1. Identify the nasion (depression between forehead and nose) and inion (bony protrusion at the back of the skull);
    2. Measure the distance from nasion to inion (measurement taken along the scalp midline).
        - The midpoint between these two references is marked as Cz, and serves as the reference point (see next point).
    3. Measure the distance from tragus to tragus:
        - The intersection of the line from this measurement with the line of the nasion-inion measurement is the Cz point.
    4. Measure the head circumference at the widest point.

5. Calculate the location of F3:
    - The Beam F3 method usually moves 20% of the nasion-inion distance towards the left pre-auricular area and slightly forward, where the F3 position on the scalp is usually located.
    - The committee recommends the use of the free online software https://clinicalresearcher.org/F3/ for the F3 location – under (F3) Distance from vertex (Y), both standard and adjusted (Mir-Moghtadaei A, 2015) values are accepted.
6. Mark the F3 position: Once the F3 position has been found, mark it on the cap. See Figure 4 for an illustration of the measurements.

Figure 4 *- Illustration of scalp measurements using the Beam F3 method (source: https://*clinicalresearcher.org/F3/)

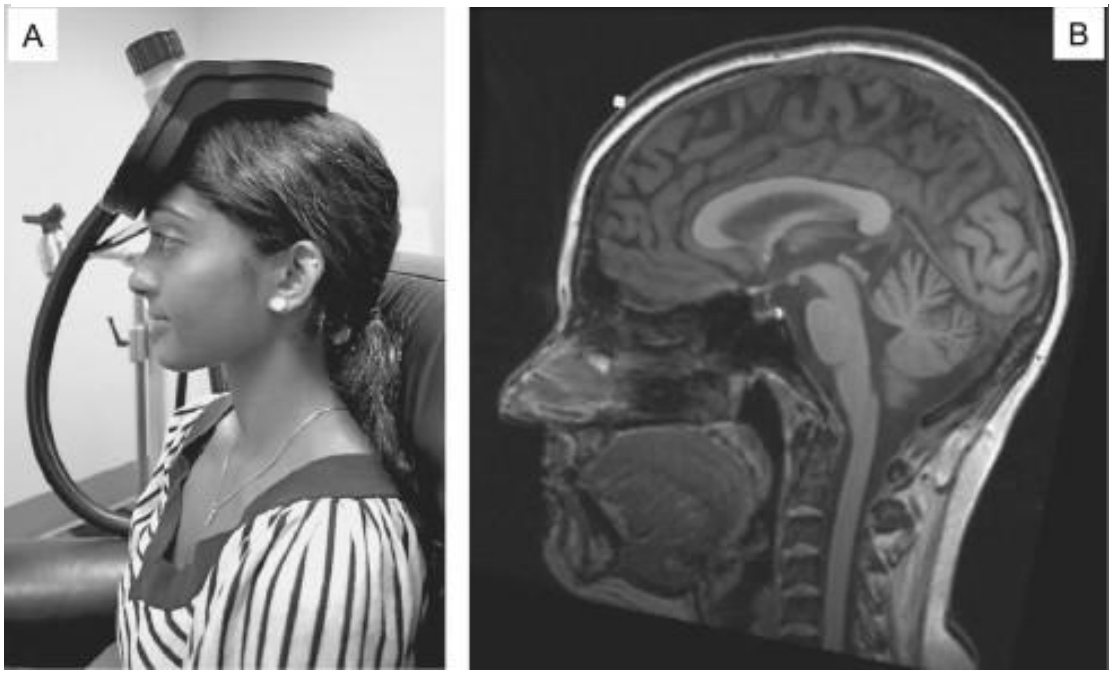


Right dorsolateral prefrontal cortex (R-DLPFC): area usually stimulated with the low frequency (1 Hz) rTMS protocol. In this case, either the 6 cm rule (Fitzgerald et al., 2020) or the Beam F4 method (which is performed similarly to the Beam F3 method but in the contralateral hemisphere) is used.

Dorsomedial prefrontal cortex (dmPFC): a key region in treating OCD and depression. The stimulation site corresponding to the dmPFC can be localized by the following strategy proposed by Mir-Moghtadaei et al (2016):

1. Mark Cz on the cap: the point halfway between nasion and inion (50% of the distance).
2. Mark the stimulation site on the cap by calculating 25.8% of the total "nasion to inion" distance, starting from nasion.
    - Example for a patient with a distance from nasion to inion of 35 cm: 35 x 0.258 = 9.03 cm. The treatment site is therefore located 9 cm from the nasion along the centerline. See Figure 5.

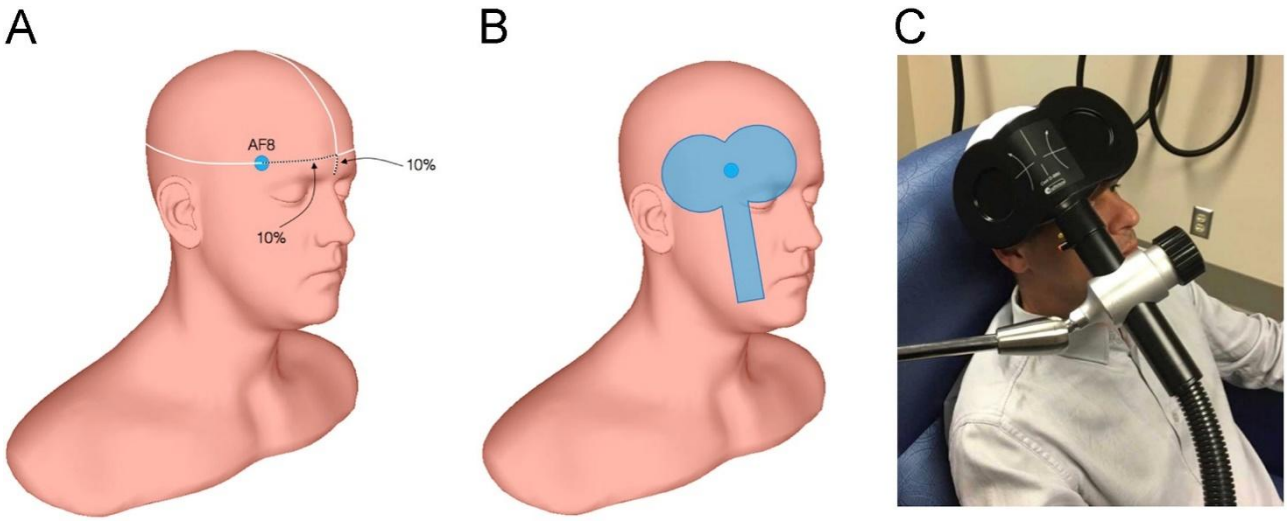
Figure 5 - Coil placement procedure for dmPFC. Translated from Downar et al, 2014 (under CC BY-NC-ND 4.0, https://creativecommons.org/licenses/by-nc-nd/4.0/)



(A) TMS coil placement for dmPFC stimulation with orientation of current flow to achieve preferential stimulation of the left hemisphere. In this series, 3000 pulses of 10 Hz stimulation at 120% resting motor threshold were applied to the left and then right hemisphere at each session. (B) T1 anatomical magnetic resonance scan with a small white square indicating the location of the coil vertex in a representative subject. To achieve dorsomedial prefrontal cortex coverage, the coil was placed at a scalp location corresponding to ~25% of the nasion-inion distance

Right lateral orbitofrontal cortex (R-OFC): A brain region that has recently begun to emerge as a target of interest in depression and which may be considered for stimulation in patients who have not responded to traditional protocols (Feffer et al., 2018a, Prentice et al., 2023; Tadayonnejad et al., 2023). The coil placement procedure for R-OFC can be seen in Figure 6.

Figure 6 - Coil placement procedure for right OFC – rTMS. Translated from Feffer, 2018 (under CC BY-NC-ND 4.0, https://creativecommons.org/licenses/by-nc-nd/4.0/)



***(A)** The AF8 stimulation site was located by first measuring 10% of the nasion-to-inion distance along the sagittal midline (corresponding to the 10-20 EEG site FPz), followed by measuring 10% of the head circumference to the right. This location corresponds to the AF8 site in the 10-20 EEG system. **(B)** Coil orientation for OFC-rTMS was shown with handles under the coil and current flowing upward to optimize the field orientation for stimulation of the horizontal shelf of the OFC. (C) Illustrative example of coil positioning for right OFC-rTMS.*

After measuring the rMT, calculating the treatment intensity and locating the stimulation target, a magnetic coil is placed over the area of the brain to be stimulated. The patient should wear a cotton cap with the area of the primary motor cortex and the treatment target marked. The cap makes it easier to locate the primary motor area in reassessments of the rMT, as well as the correct position of the magnetic coil in each treatment.

Standard TMS protocols for unipolar depression

The Committee recommends 3 TMS protocols for the treatment of unipolar depression:

- **iTBS over the left DLPFC (L-DLPFC)**
- **10 Hz rTMS over the left DLPFC (L-DLPFC)**
- **1 Hz above the right DLPFC (R-DLPFC)**

The above protocols are supported by substantial evidence from RCTs, systematic reviews and meta-analyses (Brunoni et al, 2017; Blumberger et al, 2018; Bulteau et al, 2022; Cao et al, 2018; Li et al, 2021, Voigt et al, 2021) and recommended in clinical guidelines (Lam et al, 2024; Lefaucheur et al, 2020; Trapp et al, 2025). Please refer to chapter "Indications in Psychiatry" for the underlying evidence. All of the protocols listed, except for the 1 Hz protocol, are FDA-cleared (Cotovio et al., 2023). In 2023, only the abovementioned protocols were used with TMS devices in public practice in Denmark (Cabral Barata et al., 2024).

The Committee recommends that either iTBS or 10 Hz rTMS over the L-DLPFC be considered as first choice – 1 Hz over the R-DLPFC may be the most adequate protocol for selected patients (e.g. comorbid epilepsy) or when the other two protocols are not tolerable.

iTBS (50 Hz) over the L-DLPFC

- **Example of a coil:** Cool B-70 (applicable for MagVenture® equipment)
- **TMS Timing**: 2 seconds on, 8 seconds off
- **Stimulation intensity**: typically, 120% of rMT
- **Session duration**: 3 minutes and 9 seconds
- **Number of pulses**: 600 pulses per treatment session.
- **Schedule**: 5 sessions per week (Monday to Friday) for 4 to 6 weeks (20-30 sessions in total)

Notes: iTBS is as effective as 10 Hz rTMS and requires much less time per session, which is more cost-effective and improves patient compliance (Blumberger, et al., 2018). In 2023, 70% of Danish TMS units used this protocol (Cabral Barata et al, 2024).

High frequency (10 Hz) rTMS over the L-DLPFC

- **Example of a coil:** Cool B-70
- **TMS Timing**: 4 seconds on, 11 seconds off
- **Stimulation intensity**: typically, 120% of rMT
- **Session duration**: 18 minutes and 48 seconds
- **Number of pulses**: 3.000 pulses per treatment session.
- **Schedule**: 5 sessions per week for 4 to 6 weeks (20-30 sessions in total).

Notes: Most used protocol in Denmark in 2023 (Cabral Barata et al, 2024).

Low frequency (1 Hz) over the R-DLPFC

- **Example of a coil:** Cool B-70
- **TMS Timing**: continuous rTMS for 25 minutes
- **Stimulation intensity**: typically, 120% of the rMT
- **Session duration**: 25 minutes
- **Number of pulses**: 1.500 pulses per treatment session.
- **Schedule**: 5 sessions per week for 4 to 6 weeks (20-30 sessions in total).

Notes: 1 Hz over the R-DLPFC is a suitable alternative to 10 Hz or iTBS over the L-DLPFC, as it has a higher safety and tolerability profile (e.g., lower risk of TMS-induced seizures) (Cao et al., 2018; Fitzgerald et al, 2020; Miron et al., 2020). To date, low-frequency rTMS has been shown to be superior to placebo, and the literature suggests similar efficacy to high-frequency protocols (Berlow et. al., 2020). 1 Hz over the R-DLPFC was used in 50% of TMS devices in Denmark in 2023 (Cabral Barata et al, 2024).

Accelerated TMS in unipolar depression

Another interesting protocol is the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) or Stanford Neuromodulation Therapy (Cole et al., 2020, 2022), a form of neuronavigated accelerated TBS for unipolar depression that reduces treatment time from 4-6 weeks to 5 days. This protocol consists of 10 daily sessions, each separated by a 50-minute break, administered over 5 days at 90% of rMT. SAINT has shown promising results with a significant reduction of symptoms in patients with TRD in two small studies: an open-label with 22 patients (Cole et al., 2020) and an RCT with 29 participants (Cole et al., 2022). SAINT was approved by the FDA in 2022 but is not currently in use in Danish public practice (Cabral Barata et al, 2024). Possible explanations could be the relatively recent approval and the cost and expertise associated with neuronavigational devices.

Access to fast-acting accelerated TMS protocols in selected patients, for whom longer standard protocols are not an option (e.g. long travel distance between home and hospital), expands the available toolbox of effective TMS treatments and addresses one of the major practical hurdles in patient experience: treatment duration and frequent clinic visits (Cortright et al., 2024). In this way, the SAINT protocol may be particularly relevant in hospitalized patients with moderate to severe TRD without psychotic symptoms who refuse ECT treatment.

SAINT includes fMRI-guided personalized targeting, and it is still unclear whether this aspect of the protocol is necessary to achieve the reported clinical effect sizes (Cole, 2022). This unresolved question has major practical and financial implications, as training and costs associated with neuronavigation can be challenging in public psychiatric departments. Furthermore, the SAINT protocol requires collaboration with the company commercializing the specific algorithm for analyzing the personalized connectivity-based treatment target.

There are also several unanswered questions regarding SAINT: are ten treatments per day required or can it be shortened to eight to meet an eight-hour workday for a TMS administrator? How long does the clinical effect last? There is a lack of data on comparing such an expensive TMS approach with the more affordable standard TMS protocols (van Rooji et al., 2023). Further studies are needed to provide additional, independent evidence regarding the published SAINT clinical trials. These studies should evaluate the reproducibility of the MRI targeting algorithm, its feasibility in clinical

practice, and the duration of the clinical response (Trapp et al., 2025). Studies comparing the SAINT protocol with other FDA-approved rTMS protocols or with modified accelerated protocols (e.g. without fMRI targeting) are needed to clarify the relative weight of specific TMS treatment parameters on overall safety and antidepressant efficacy (Trapp et al., 2025). An example of these needs is the ongoing COMPACT study (Copenhagen Magnetic Personalized Accelerated Brain Circuit Trial), where a modified SAINT protocol is being tested in a randomized controlled trial (Region Hovedstadens Psykiatri, 2024).

The Committee does not recommend SAINT protocol as a standard treatment for depression. However, SAINT may be considered in hospitalized patients with moderate to severe unipolar depression without psychotic symptoms, where standard TMS protocols and ECT are not a therapeutic option.

Alternative TMS protocols for unipolar depression

Other protocols besides the above (iTBS, 10Hz and 1Hz), like continuous TMS or bilateral stimulation over the left and right DLPFC, have also been shown to be clinically effective, but have lower levels of evidence and have yet to receive regulatory approval (Cotovio et al., 2023; Lefaucher et al., 2020).

For patients with unipolar depression who do not respond to standard rTMS over the DLPFC (iTBS, low-frequency, or high-frequency protocols), two alternative protocols may offer benefit. Evidence supporting these approaches is derived mainly from small, open-label clinical trials reporting positive outcomes.

High frequency (10 Hz) over the dorsomedial prefrontal cortex (dmPFC)

- **Example of a coil:** Cool D-B80 (applicable for MagVenture® equipment)
- **TMS Timing**: 5 seconds on, 10 seconds off
- **Stimulation intensity**: 120% of the rMT in the leg (i.e., rMT of the contralateral hallux). rMT in the leg is found by visual inspection of the resting motor threshold of the contralateral hallux extension (activation of the *extensor hallucis longus*) by stimulation of the right and left primary motor cortex, determined by visual inspection according to previously published methods (Schutter and Van Honk, 2006).
- **Session duration**: 30 minutes
- **Number of pulses**: 3.000 pulses per treatment session, per hemisphere (6.000 in total).
- **Schedule**: 5 sessions per week for 4 weeks (20 sessions in total).

Notes: The above protocol has shown potential in several small clinical trials (Bakker et al, 2015; Downar et al, 2014; Dunlop et al, 2015; Schulze et al, 2016, 2018), but well powered RCTs are needed to further develop and establish this promising TMS approach (Kreutzer et al, 2019).

Low frequency (1 Hz) over the right orbitofrontal cortex (R-OFC), as used in Prentice et al. (2023)

- **Example of a coil:** Cool D-B80
- **TMS Timing**: continuous rTMS for 20 minutes
- **Stimulation intensity**: 120% of rMT
- **Session duration**: 20 minutes
- **Number of pulses**: 1.200 pulses
- **Schedule**: 5 sessions per week for 4-6 weeks.

Notes: 1 Hz over the R-OFC is an alternative protocol for the treatment of depression and may be considered in case of lack of response to a full course of rTMS with a traditional protocol in the DLPFC. Positive results in various open-label trials show the clinical potential of 1 Hz over the R-OFC (Feffer et al., 2018a; Prentice et al., 2023). However, controlled studies are needed to systematically investigate the efficacy and safety of this treatment option.

TMS protocols for OCD

The Committee recommends using the FDA-approved protocol for OCD: high frequency (20 Hz) stimulation of the anterior cingulate cortex/dorsomedial prefrontal cortex (ACC/dmPFC). The protocol should be combined with exposure exercises to activate the brain areas affected in OCD.

Other protocols have been shown to be more effective than sham treatment in meta-analyses of rTMS for OCD. However, these conclusions are limited by small sample sizes (n ≤ 60), methodological heterogeneity, and the risk of publication bias. Larger randomized controlled trials are needed in this area. For more details, see the subchapter "Obsessive-compulsive disorder" in "Indications in psychiatry".

High frequency (20 Hz) over ACC/dmPFC

- **Example of a coil:** Cool D-B80 (applicable for MagVenture® equipment)
- **TMS Timing**: 2 seconds on, 20 seconds off
- **Stimulation intensity**: typically, 100% of rMT in the leg. It is found by visual inspection of the resting motor threshold of the contralateral hallux extension (activation of the *extensor hallucis longus*) by stimulation of the right and left primary motor cortex, determined by visual inspection according to previously published methods (Schutter and Van Honk, 2006).
- **Session duration**: 18 minutes
- **Number of pulses**: 2.000 pulses per treatment session
- **Schedule**: 1 session per day (Monday to Friday) for 29 days (approximately 6 weeks).

Description of the exposure method to be combined with the above protocol (Carmi et al., 2019):

An exposure of 3-5 minutes is performed prior to each TMS session to activate the relevant neural networks. A problem and goal list developed during the initial interview serves as a foundation for identifying themes to be addressed during exposure. Based on this list, a decision is made during the initial interview on the specific theme for which an exposure plan is drawn up. The exposure plan includes specific exercises arranged according to severity on a scale from 0 (no anxiety/anxiety)

to 10 (most severe anxiety). The exercises are subsequently documented in the patient's journal on a weekly basis.

TMS staff conduct exposure exercises as described above, targeting a difficulty level between 4 and 7. The TMS psychologist reassesses and adjusts the expected anxiety level weekly as the patient progresses. Once the desired level of anxiety or arousal is reached before TMS, instruct the patient to focus on the specific obsession during treatment. To sustain arousal, remind the patient about the exposure exercise 3–5 minutes into the session (e.g., “Remember to think about the doorknob you just touched.”).

TMS series

It is important to mention that both depression and OCD have well-established/FDA-approved TMS protocols, but the effectiveness of treatment often depends on individual characteristics. In clinical practice, protocols should be adapted to the patient's needs by adjusting the stimulation intensity, frequency and number of sessions. In clinical practice, TMS protocols should be individualized by adjusting stimulation parameters such as intensity, frequency, and the total number of sessions. To improve tolerability, clinicians may employ a "ramping" (or "ramp-up") strategy, beginning stimulation below the target intensity and gradually increasing it in subsequent sessions, rather than starting at the full intended level. For example, treatment could commence at 80% of the resting motor threshold (rMT), with the intensity increased by 10% in each session until the target (e.g., 120% rMT) is reached. This stepwise approach has the potential to reduce adverse effects (Fitzgerald & Daskalakis, 2022; Trapp et al., 2025).

While it seems desirable to achieve the predefined treatment intensities (typically 120% of the rMT in standard TMS protocols for depression), the effects of rTMS in depression are clearly visible already at 80% of the rMT in iTBS over the left DLPFC (L-DLPFC) and at 110% in 10 Hz stimulation of the same area (Bulteau et al., 2022). In the treatment of depression, it may be preferable for a patient to complete a course of therapy at 80% (iTBS) or 110% (10 Hz rTMS) of the rMT, rather than discontinue treatment due to intolerance of higher stimulation intensities. This approach is supported by clinical data, which do not indicate a linear relationship between stimulation dose and efficacy (Fitzgerald and Daskalakis, 2022).

At the first treatment session:

- Measure the patient's head circumference.
- Assign each patient an individual treatment cap labeled with their name, which should be used at every session. Align the cap with the midline of the patient's head (front view) and fit it securely. Measure and record the distance from inion to nasion and tragus to tragus.
- For TMS stimulation over the DLPFC (most common in depression treatment), measure and mark the motor hotspot corresponding to the contralateral thumb (i.e., the point where the lowest TMS single-pulse elicits a motor movement in the contralateral thumb). For TMS

targeted at the dmPFC (common in OCD treatment), identify and mark the motor hotspot corresponding to the contralateral hallux.

- Determine and calculate the resting motor threshold (rMT) and the treatment intensity. See Treatment Intensity and Stimulation Target for a more detailed description.

Before each session:

- Complete the safety questionnaire to assess whether there have been any changes in usual medication or alcohol/other drugs have been consumed, as well as to rule out other factors that may interfere with treatment.
- Recalculate the rMT every two weeks. Perform additional rMT reassessments as needed, for example, in the event of medication changes.
- Administer an interviewer-based scale (e.g. HAM-D17 for depression; Y-BOCS for OCD) and a self-report symptom scale (e.g. MDI for depression) every week.

At each treatment session:

- Ask the patient to seat in a comfortable chair, while you correctly adjust the cap on the patient's head, ensuring that the distance between the nasion and the cap matches the distance previously noted on the cap.
- Offer earplugs to the patient to minimize the side effects from the device's clicking sound.
- Switch the TMS equipment on. Select the treatment protocol and intensity on the machine.
- Recline the treatment chair, ensuring a comfortable and relaxed position for the patient.
- Choose the coil according to the treatment protocol and check the coil's integrity.
- Place the coil on the stimulation site marked on the cap and press it lightly against the patient's head. Place the coil tangentially and in direct contact with the patient's head. From the moment the coil is placed, it is important to ensure that it no longer moves during treatment. Keep the head stable by using the vacuum cushion supporting the neck.
- Patients are allowed to drive after TMS treatment unless they experience severe fatigue as a side effect.

Special considerations for rTMS courses in depression treatment

According to the available evidence, a standard course of rTMS for the treatment of depression should consist of at least 30 sessions (Hutton et al., 2023, Razafsha, et al., 2023). The sessions are administered daily, 5 days a week (typically Monday through Friday) for 6 weeks. Efficacy should be evaluated between the 25th and 30th treatment.

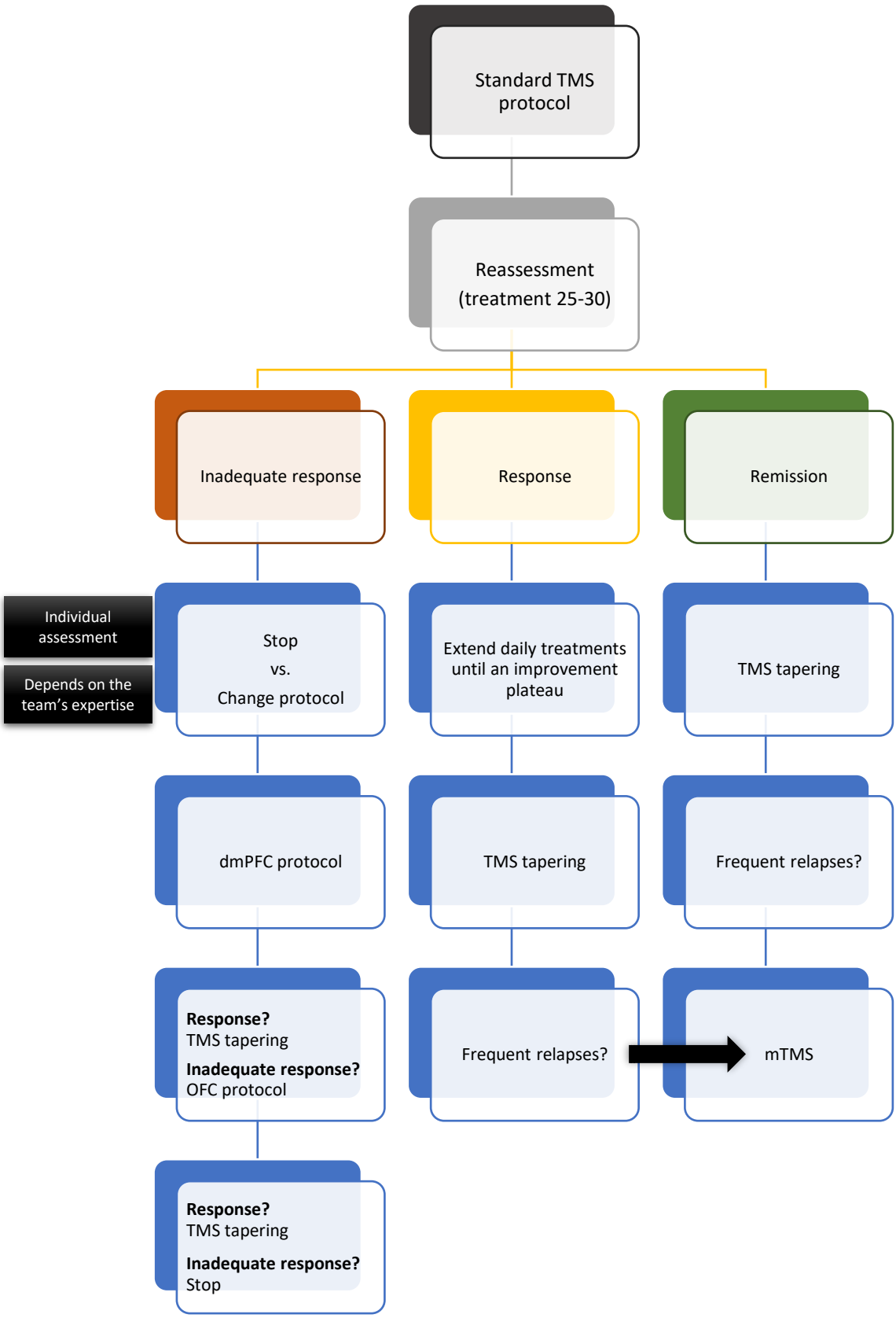
In cases of patients who show some response without remission (>20% reduction in interviewer-based or self-rating symptom scale and clinical impression of clinical improvement), extension of the TMS course should be considered until a plateau of symptom improvement is reached, as studies show a strong correlation between the number of sessions and the extent of symptom improvement (Hutton et al., 2023). In some cases, a rTMS series (i.e., daily TMS treatments) can reach a total number of 72 daily sessions (Razafsha, et al., 2023).

In patients who achieve full remission of symptoms (HAM-D17 < 7 and clinical impression) during the standard treatment of 6 weeks, it is recommended to proceed to a defined tapering period (d'Andrea et al., 2023).

In the specific case of patients who do not show sufficient response (≤20% reduction in either objective and/or subjective symptom scale contextualized in the clinical impression) after 30 treatment sessions, switching to alternative TMS protocols can be considered in order of priority: 10Hz over dmPFC (Bakker et al, 2015; Downar et al, 2014; Dunlop et al, 2015; Schulze et al, 2016, 2018) or 1Hz over R-OFC (Prentice et al, 2023). Evidence for these protocols is limited to small positive open-label trials in patients with no response to standard protocols. Thus, the use of 10 Hz over the dmPFC and 1Hz over the R-OFC is reserved for patients with unipolar depression refractory to first-line protocols (iTBS or 10 Hz rTMS over the L-DLPFC; 1 Hz over the R-DLPFC), and TMS clinics with experience and knowledge about these alternative treatments.

See Figure 7 for a flowchart of rTMS treatment for unipolar depression.

Figure 7 - Flowchart *of rTMS treatment in unipolar depression (standard TMS protocols: iTBS or 10 Hz rTMS over the L-DLPFC as first choice; 1 Hz over the R-DLPFC as an alternative for selected patients)*



Tapering and Maintenance TMS

Unipolar Depression

Although formal guidelines are lacking, maintenance TMS (mTMS) may prolong positive clinical effects and help prevent relapse in patients with TRD who have responded to daily TMS (d'Andrea et al., 2023). mTMS is typically initiated after a successful rTMS course and involves ongoing treatment sessions that gradually decrease in frequency over time, similar to maintenance ECT (d'Andrea et al., 2023).

The frequency of mTMS sessions can vary, ranging from individual sessions scheduled regularly over a total period of 2 or 3 months following a TMS course (e.g., weekly, every other week, every other month, or monthly), to short periods of daily mTMS treatment, known as cluster mTMS. mTMS may be administered over 1, 2, 3, 9, or 12 months, or even several years (Brem et al., 2020).

Despite the highly heterogeneous design of the available studies, patients generally show moderate to significant benefits of mTMS (compared to no treatment). These patients can achieve remission lasting from 3 months to up to 5 years. (Brem et al., 2020; Rachid, 2018).

Thus, in patients with high relapse rates, a tapering period of rTMS (e.g. twice a week for 2 weeks, once a week for 4 weeks, once every other week for 4 weeks) can be followed by a mTMS protocol of, for example, 1 session every two or three weeks for several months or years (Benadhira et al., 2017; Brem et al., 2020).

However, it should be noted that there is currently no consensus on maintenance TMS protocols for unipolar depression. Further studies are urgently needed to evaluate the long-term effectiveness of maintenance protocols (D'Andrea et al., 2023) and to determine the optimal pharmacological strategies for relapse prevention (Trapp et al., 2025).

Obsessive-compulsive Disorder

Further research is needed to establish specific protocols for tapering or maintaining TMS treatment after a successful course of therapy for OCD.

Most published studies focus on the acute effects and target optimization of TMS in OCD, rather than on the maintenance of treatment effects over time (Steuber and McGuire, 2023). Evidence suggests that treatment effects last at least four weeks (Perera et al., 2021), with follow-up periods in RCTs ranging from 1 to 12 weeks (Perera et al., 2021; Steuber and McGuire, 2023). Consequently, there is a lack of longer-term RCTs and other longitudinal studies to assess the durability of TMS effects in OCD following an acute treatment course (Harmelech et al., 2022).

Device selection

Devices and brands

There are several commercial and non-commercial transcranial magnetic stimulation (TMS) devices available on the market. However, as interest in using TMS in research and therapy increases, many more devices are expected to enter the market in the coming years (Gutiérrez-Muto et al., 2023).

All existing commercial TMS devices comply with internationally recognized standards to ensure their safety and quality for medical use. These standards regulate various aspects of device design, manufacturing, testing and performance. Compliance with international standards is essential to obtain approval from the relevant authorities. In the European Union, devices comply with the legal framework for CE marking, while the FDA ensures the certification procedures in the United States (Cotovio et al., 2023). However, it should be mentioned that FDA approval and CE marking are not equivalent regulatory processes: essentially, the CE marking process focuses primarily on safety, but also on the manufacturer's heightened obligation regarding device claims, i.e. ensuring that the device does what it claims to do. The FDA sets additional requirements to evaluate effectiveness (Mishra, 2017). CE marking tends not to address specific TMS protocols but conditions where TMS can be safely used, whereas the FDA approves the use of specific protocols in treating specific conditions (Cotovio, 2023). In this way, the presence of a CE mark on a particular device does not necessarily mean the device is effective in treating a specific disorder (Mishra, 2017).

Currently, several TMS devices have been FDA cleared and/or CE marked for various therapeutic applications, particularly for the treatment of depression and, to a lesser extent, OCD and smoking cessation. The number of approved devices and therapeutic applications is expected to increase as more devices are developed and approved for broader applications (Gutiérrez-Muto et al., 2023). Currently, at least 8 TMS devices have received FDA approval for specific indications (Cohen et al., 2022). Practically all devices that are FDA-approved in the United States of America are also CE marked, but the indication range in Europe is broader. An up-to-date, open-access online database summarizing the key features and applications of both commercial and non-commercial TMS devices is available at http://www.tmsbase.info (Gutiérrez-Muto et al., 2023). Table 4 lists some relevant CE marked TMS devices with corresponding FDA approvals.

Table 4 - Relevant CE marked TMS devices with corresponding FDA approvals

Equipment	FDA approval	Manufacturer	Notes
NeuroStar Advanced Therapy System	MDD	Neuronetics	First TMS device approved by the FDA for TRD
BrainsWay Deep TMS System	MDD	BrainsWay	Uses H-coil technology for deep rTMS
	OCD		
	Smoking cessation		
MagVenture TMS Therapy System	MDD	MagVenture	Allows both standard rTMS and aTBS.
	OCD		
	PSUD		
Magstim Horizon	MDD	Magstim	Offers tailored TMS protocols for clinical and research use
Nexstim NBT System	MDD	Nexstim	Incorporates neuronavigation system
CloudTMS System	MDD	Neurosoft	-
Apollo TMS System	MDD	Mag & More GmbH	Standard rTMS protocols
Remed	MDD	Yiruide Medical Equipment	Standard rTMS protocols

[aTBS: accelerated Theta Burst Stimulation; MDD: Major Depressive Disorder; OCD: obsessive-compulsive disorder; PSUD: Psychoactive substance use disorder, TRD: treatment-resistant depression]

General design and components

The available TMS devices are relatively homogeneous in terms of generic design and components. Each device consists of a main unit and a stimulation coil, all designed to operate under high voltage and high current. More details on the design and components of TMS devices can be found in Gutiérrez et al. (2020), Gutiérrez-Muto et al. (2023) and Rotenberg et al. (2014).

1. **The main unit** consists of the following components:

    1.1. High voltage power supply/charging system that generates the current used to create the magnetic field. Typically, voltages are in the order of 2.000 V and capable of delivering currents of over 5.000 A.

    1.2. One or more high-voltage capacitors that act as energy storage capacitors, allowing multiple energy pulses to be generated, stored and discharged in quick succession. Multiple capacitors are required for repetitive TMS protocols.

    1.3. Energy recovery circuitry that allows the main unit to recharge after discharge.

    1.4. A current switch, usually a thyristor, capable of switching large currents over a short period of time. In this case, the thyristor acts as a bridge between the capacitor and the coil, transferring 500 joules in less than 100 milliseconds.

    1.5. A pulse waveform circuit used to generate either monophasic or biphasic pulses. This waveform depends on the designed power electronic architecture based on insulated gate bipolar transistors (IGBTs), thyristors or diode thyristors.

    1.6. A cooling system with special liquid used to cool the TMS coils.

2. **The stimulation coil** consists of one or more insulated coils of copper wire (often encased in a molded plastic cover).

2.1. When current flows through these coils, different patterns of magnetic fields are generated, which in turn generate a current in the opposite direction in any nearby conductor.

2.2. Coils exist in a variety of shapes and sizes. The specific geometry of each coil determines the shape, strength and overall focalization of the resulting induced electric field and thus of the brain stimulation.

Variability and features of TMS devices

Although commercial TMS devices share a common generic design, they vary in many key features, including technology, coil design, stimulation depth, frequency protocols, measurement accuracy, and user interfaces (Gutiérrez-Muto et al., 2023; Cook, 2018; Rotenberg et al. 2014). Here are the main primary differences between the devices:

1. **Electronics**: some devices include thyristors and diodes, while other devices include new power components such as insulated gate bipolar transistors (IGBTs) or metal–insulator–semiconductor field-effect transistors (MOSFETs) due to advances in semiconductor technology.

2. **Waveform**: some devices use monophasic pulses that only generate unidirectional voltage, while others use biphasic pulses that generate full positive/negative voltage swings.

3. **Coil design**: TMS systems offer a wide range of coils [more details on coil design can be found in Ibrahin Gutiérrez et al. (2022)]. See Table 1 for images and Figure 8 for schematic drawings.

    3.1. Circular coil: the oldest and simplest TMS coil design. This type of coil provides a more diffuse stimulation that covers a wider area and is useful for protocols that require single pulses and peripheral stimulation.

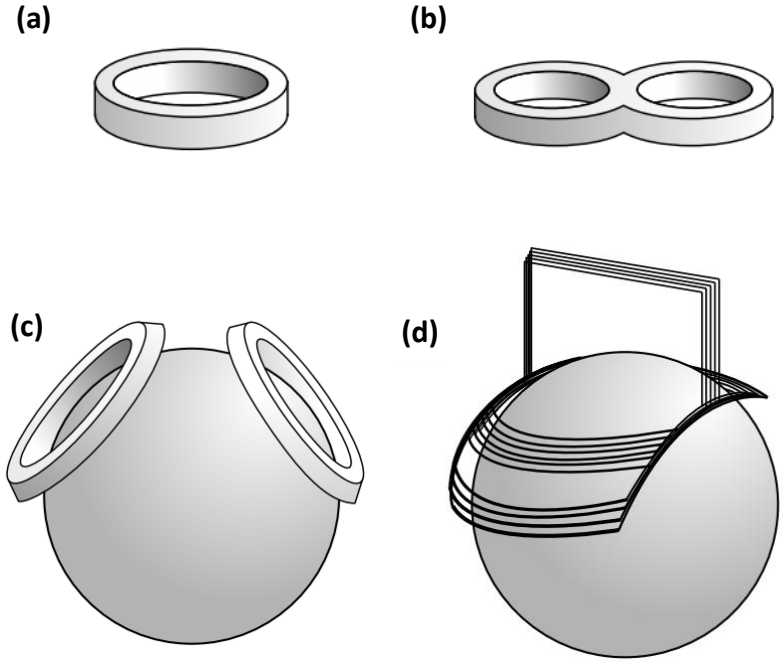
    3.2. Figure-of-8 coil: the most common coil design. This type of coil is often preferred for clinical and academic applications of TMS, including repetitive TMS. Provides a more focal stimulation that targets specific brain regions with precision. It can achieve a spatial resolution of approximately 5 mm^3 of brain volume (e.g. Magstim, NeuroStar).

3.3. Cone-shaped/double coils: used for targeted deep TMS, for example in dmPFC stimulation in the treatment of TRD and OCD (e.g. MagVenture).

3.4. H-coil: aims to stimulate deeper brain structures, up to approximately 4 cm below the cortical surface – vs. up to 1 cm with figure-of-8 coils (Tendler et al., 2016). This increased stimulation depth is achieved because of the multi-plane windings within the H-coil helmet. The magnetic fields from these windings enhance the depth penetration of the electromagnetic field without the need for increased electrical intensity. Although deep stimulation can also be achieved with a large circular coil or a dual coil, their electromagnetic fields decay faster and, to reach significantly deep targets, much higher intensities must be applied to the surface (Pell et al., 2011; Roth et al., 2014), intensities that can be uncomfortable and potentially unsafe for the patient. Finally, H-coils stimulate larger areas, i.e. approximately 17 cm^3 of brain tissue with H1 coil compared to approximately 5 cm^3 with conventional figure-of-8 coils when both are used at 120% of motor threshold. H-coil are used to treat TRD and OCD (e.g. BrainsWay, MagVenture).

3.5. Sham coils: these offer scalp and sound stimulation without effective stimulation of the cortex, with almost the same appearance as treatment coils (Smith et al., 2018; Gordon et al., 2018).

Figure 8 - Schematic drawings of different types of TMS coils (adapted from Gutierrez et al, 2013 under CC BY 4.0, https://creativecommons.org/licenses/by/4.0/)



(a) circular coil, (b) figure-of-8 coil, (c) conical/double coil, (d) Hesed/H coil

4. **Stimulation intensity and depth**: Some devices, like NeuroStar, offer surface stimulation, while devices like BrainsWay's H-Coil technology penetrate deeper into the brain. The intensity of the magnetic field also varies from device to device, typically from 0.5 to 3 Tesla, which affects the depth and effectiveness of stimulation.

5. **Targeting capabilities**: Some devices integrate neuronavigation systems to improve coil position precision and targeting accuracy (e.g. Magstim Horizon or Axilum Robotics TMS-Robot). In contrast, most devices require manual targeting of the treatment site using standard coordinates and visual mapping.

6. **User interface and software**: some TMS devices are preloaded with FDA-approved protocols for depression (e.g. NeuroStar), while other devices allow users to change parameters such as frequency, intensity and exercise duration for research and specialized treatments (e.g. MagVenture and Magstim).

7. **Regulatory approval and indications**: Some devices are FDA approved for depression (e.g. NeuroStar, BrainsWay, MagVenture), while others are primarily used for research or other conditions such as OCD or smoking cessation (e.g., BrainsWay). Please see "Devices and brands".

8. **Treatment duration and protocols**: Some devices are approved to run traditional rTMS, which requires 37-40 minutes per session, typically over 4-6 weeks (e.g., NeuroStar). Other devices are approved to run accelerated protocols like Intermittent Theta Burst Stimulation (iTBS) protocols, lasting 3 minutes per session (e.g., MagVenture and Magstim).

9. **Cost and availability**: Equipment from MagVenture and NeuroStar are more affordable for clinics, while systems like BrainsWay, which offer deep TMS, are generally more expensive due to the advanced technology. Long-term costs include not only the initial purchase but also maintenance, calibration and coil replacement. Both the TMS device and the stimulation coils have a limited lifespan. The average lifespan of TMS devices varies depending on the manufacturer and the number of pulses the system generates. Similarly, stimulation coils have their own lifespan depending on the number of discharges.

Conclusion

Available commercial TMS devices share a basic design and core components. However, they differ significantly in aspects such as coil design, stimulation depth, frequency protocols, measurement accuracy, cost, regulatory approval, and user interfaces. Ultimately, clinicians select devices based on treatment goals, the specific conditions being treated, patient needs, and cost considerations.

TMS internationally

Interest in TMS treatment has grown rapidly over the past decades, with an increasing number of countries implementing it as a standard treatment. There are TMS societies with more than 1.000 members from 45 different countries (Clinical TMS Society, 2024). TMS research is also widespread and can be found on different continents, including America (Cole, 2022), Europe (Bourla et al., 2020; Sierra et al., 2024) and Asia (Deng et al., 2020; Noda et al., 2023).

Ekman et al (2023) have recently published a register-based study on TMS practice in Sweden, showing increasing use of this form of neuromodulation in the country: the number of Swedish TMS devices increased from 6 in 2017 to 17 in 2020. iTBS over L-DLPFC was identified as the most popular protocol in Sweden, with which 695 patients were treated from January 2018 to June 2021, an average of 199 patients per year. 18% (n=99) of depressed patients (n=542) treated with iTBS had bipolar depression.

TMS in Denmark

The use of rTMS in psychiatry in Denmark began in 1999, when the Psychiatric Hospital in Aarhus introduced it in clinical research and as an add-on treatment to antidepressants for selected patients with unipolar depression.

A nationwide survey of public TMS practices in psychiatry in Denmark was recently published (Cabral Barata et al., 2024). The study found that 37% of adult psychiatry departments had rTMS devices and that TMS was available in 3 out of 5 Danish regions. In 2023, 383 patients were treated with TMS for psychiatric disorders in Denmark, with unipolar depression being the only indication for treatment – off-label treatments were not examined. The authors also concluded that rTMS practice included evidence-based protocols and was consistent with recommendations from international expert guidelines.

Organization of TMS Clinics within Psychiatry Departments

The international guidelines from the International Federation of Clinical Neurophysiology (IFCN) recommend that each TMS unit include a physician specialized in the relevant medical field. This is considered essential to ensure proper assessment of treatment indications, selection of the most appropriate TMS protocol, and supervision of TMS practitioners, thereby maintaining a high standard of care (Fried et al., 2021).

The Committee recommends that TMS units have a permanent team comprising:

- One TMS specialist in psychiatry
- At least two TMS therapists, preferably nurses
- Including a junior doctor in the TMS team may also be beneficial for educational and organizational purposes

A permanent team of dedicated staff is essential for achieving and maintaining high levels of professionalism, expertise, organizational continuity, and ongoing professional development. Supporting both local initiatives and collaborative or international TMS research can further help maintain high professional standards and ensure state-of-the-art treatment. TMS units should develop evidence-based local guidelines and detailed descriptions of working procedures tailored to their specific conditions and needs. Regular team meetings (e.g., monthly) are recommended to discuss clinical, scientific, and organizational matters.

rTMS is still relatively unknown to the general public and underutilized by psychiatrists (Goldbloom and Gratzer, 2020). Lack of education or understanding of TMS among healthcare professionals is a known barrier to treatment (Cortright et al., 2024). Holding regular clinical sessions on TMS and incorporating TMS education into medical student training on psychiatric wards can help address these challenges. Establishing a professional network among medical and nursing staff from different units is also recommended, as it provides a platform for sharing experiences and fosters clinical and scientific development.

Training and continuing education in TMS

Minimum training requirements and continuing education for TMS staff

Various TMS expert guidelines emphasize the importance of training and competency for all members of a TMS unit, including physicians, nurses, and other relevant professionals (Fried et al., 2021; McClintock et al., 2018; Trapp et al., 2025). The International Federation of Clinical Neurophysiology (IFCN) recommends that TMS training includes three main components: theoretical training, an observation period and hands-on experience with TMS equipment.

The Committee proposes the following training program for TMS staff:

- Theoretical training module
    - Review of relevant literature on TMS and local procedures
    - At least one hour of theoretical training in TMS from a senior TMS physician
    - Participation in a TMS certification course, either from a psychiatric or neuromodulation organization

- Observation period and hands-on experience
    - Covers both introduction to the TMS device, introduction to logistics, record keeping, patient registration, procedure codes, other practical tasks, etc.
    - Observation of at least 2 TMS treatments, followed by the completion of a minimum of:
        - 5 scalp measurements
        - 10 rMT measurements
        - 5 iTBS treatments
        - 5 low frequency (1 Hz) treatments
    - A qualified colleague (either a TMS physician or experienced TMS nurse) will supervise, guide, and support the trainee. Approval is granted only when the trainee demonstrates satisfactory performance in all procedures.

- Ongoing training/updating
    - Psychiatrist specialized in TMS
        - Attend a new certification course every 5 years
        - Attend a minimum of 1 TMS conference every 2 years
        - Annual hands-on training in TMS
    - Nurses and other relevant healthcare professionals
        - Annual TMS update organized by the lead TMS psychiatrist, consisting of a half-day of theoretical instruction and a half-day of practical training

Information about TMS for patients and caregivers

All patients and their families must be adequately informed about TMS by the referring physician before treatment is initiated. Information should be provided both orally and in writing. The department's TMS information booklet/pamphlet can be provided to the patient. Both the patient and their relatives should be offered a follow-up conversation to address any questions.

A booklet or pamphlet about TMS should include:

1) Brief explanation about TMS, its mechanisms of action and indications
2) The effectiveness of TMS
3) TMS side effects
4) Practical procedures and precautions
5) Relapse prevention considerations

An educational piece should address the most frequently asked questions about TMS (e.g. "How does TMS work?"; "Can TMS damage the memory and the brain?", etc.). It is recommended to note in the medical record that the patient has received oral and written information.

The **ECT and Neurostimulation Committee** has prepared the following written information for patients. It is intended as inspiration for designing similar leaflets or booklets locally, but it can of course also be used in its current form.

What is TMS?

Transcranial Magnetic Stimulation, or TMS, is a safe and effective treatment, in use since 1985, indicated for certain mental disorders.

You are awake and can sit and relax during TMS treatment. Using an electromagnetic coil, a pulsed magnetic field is applied to the brain, inducing weak current in the brain tissue. Research conducted over the past twenty years has shown that such repeated stimulation of the brain induces antidepressant effects, while also offering therapeutic benefits in other conditions, such as obsessive-compulsive disorder..

Unlike ECT treatment, TMS does not induce seizures and does not require general anesthesia.

TMS treatment stimulates certain brain areas that are thought to be negatively affected when you for example have depression or OCD (obsessive-compulsive disorder).

What disorders can TMS be used for?

TMS has been most extensively studied for depression, particularly in cases where medication has been ineffective. There is also some evidence that TMS may be beneficial for other psychiatric disorders, including obsessive-compulsive disorder (OCD).

How does TMS work?

As mentioned, you are awake during the treatment, sitting in a specially designed chair. During treatment, a magnetic coil is placed on the scalp over the area of the brain to be stimulated.

You will wear a cotton cap during the treatment, which helps to ensure that the magnetic coil is correctly positioned during each treatment. You will also be offered earplugs to protect you from the noise (a clicking sound) emitted by the device. A single TMS treatment lasts no more than 25 minutes. Some types of treatment are shorter in duration (like iTBS). Depending on the treatment strategy chosen, the number of treatments can vary from a few days to 6 weeks.

Treatment effect

Approximately two out of three patients benefit from TMS treatment. Some will notice an effect after relatively few treatments, but others will only notice an effect later. Some patients may benefit from ongoing maintenance treatments to help prevent a return of symptoms.

Planning the treatment

Once it has been decided that a course of TMS treatment is relevant, you will receive a written invitation.

In the invitation, you will find practical information about the time and place of the treatment. You are welcome to bring a relative for the first treatment.

Before you go home after your first treatment, we will have agreed with you when your next treatments will take place.

You can take your usual medication throughout treatment. However, let your TMS practitioner know if you start a new medication or if the dose of your current medication is changed.

You may drive during the TMS program, unless you experience severe fatigue.

Avoid drinking alcohol during TMS treatment, as it can increase the risk of seizures and reduce the effectiveness of the therapy.

Who do you meet in the TMS unit?

You will be treated by healthcare professionals. The department has certified TMS therapists, and a psychiatrist specialized in TMS treatment.

Before you start treatment, you will receive thorough information about what will happen and have the opportunity to ask questions.

Possible side effects of TMS

Most people experience few, if any, side effects from the treatment. Some patients have no side effects at all.

However, you may experience some pain and muscle pulling where the magnetic coil is placed. This is most pronounced during the first few treatments, after which most people get used to it.

If you experience discomfort during treatment, the treatment intensity can be reduced and then increased more gradually, as the threshold for discomfort often increases.

Some patients experience transient tension headaches, which can be treated with a mild analgesic, such as acetaminophen. Some experience worsening of fatigue during treatment. In extremely rare cases, seizures may occur in patients who are susceptible, particularly if they suffer from epilepsy.

Years of TMS research show that the treatment has no long-term side effects and does not damage brain tissue. Unlike ECT, TMS does not affect memory.

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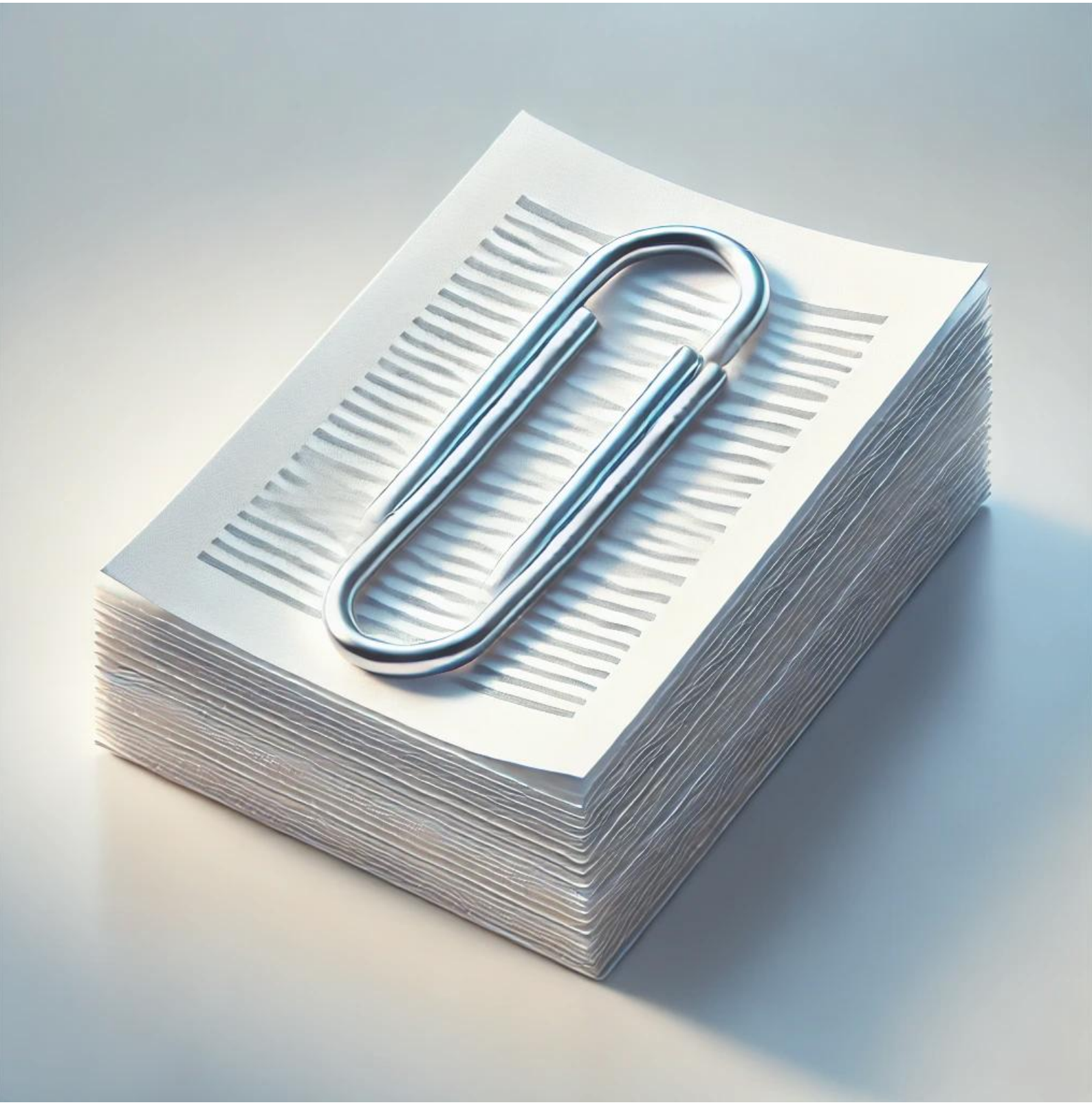
Appendix



Appendix 1 - *Example of TMS safety checklist*

	TMS safety checklist	YES	NO
1	**Ferromagnetic material or implanted electronic/medical devices in the head, neck or thorax**		
	Metal clips, stents, plates or screws in the head or chest cavity		
	Metal splinters or shrapnel in the head or chest cavity		
	Ferromagnetic heart valves		
	Implants/metal splinters in the eyes		
	Cochlear implant		
	Deep Brain Stimulation (DBS) or Vagus Nerve Stimulator (VNS)		
	Pacemaker		
	Other types of ferromagnetic material or implants Equipment:		
2	**Current misuse of alcohol, benzodiazepines or other drugs**		
3	**Moderate to severe electrolyte imbalance** (blood tests must be no more than 3 months old) Serum sodium <129 or >150 mmol/L | Serum potassium <3.0 or >6.0 mmol/L		
4	**The patient makes a reliable commitment to abstain from alcohol during TMS treatment**		
5	**Pregnancy**		
6	**Somatic brain disorders**		
	Epilepsy or history of seizures		
	Previous cerebral infarction/hemorrhage		
	Brain tumor/intracranial hypertension		
	Previous severe head trauma		
	Previous neurosurgical intervention		
	Other:		
7	**Psychotic symptoms, acute suicide risk, severe agitation or delirium**		

- ***"YES" answer to questions 1-3 or "NO" answer to question 4:*** TMS treatment may be **contraindicated**
- ***"YES" answer to questions 5-7:*** requires consultation with the TMS supervising physician prior to initiating treatment

Appendix 2 – Maudsley Staging Method [(adapted from Fekadu et al., 2018 under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)]

Parameters/dimensions	Categories	Item
Duration	Acute (≤ 12 months)	1
	Subacute (13-24 months)	2
	Chronic (> 24 months)	3
Baseline severity	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychotic symptoms	4
	Severe with psychotic symptoms	5
Failed treatments		
Antidepressants	1-2	1
	3-4	2
	5-6	3
	7-10	4
	>10	5
Add-ons	Not used	0
	Used	1
ECT	Not used	0
	Used	1
Total score (range: 3-15)		___/15
Score categories	Mild	3-6
	Moderate	7-10
	Severe	11-15