Superior
Health Council

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

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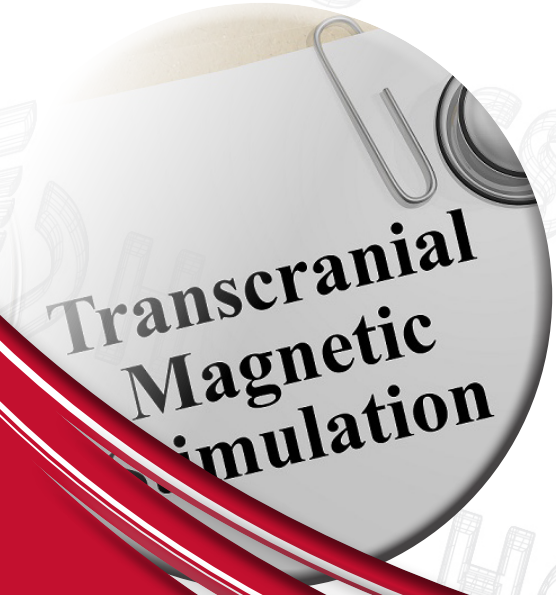

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Superior Health Council

ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 8778

Transcranial Magnetic Stimulation (TMS)

In this scientific advisory report on public health policy, the Superior Health Council of Belgium provides recommendations on efficacy and safety of Transcranial Magnetic Stimulation.

This report aims at providing researchers and doctors with specific recommendations on efficacy and safety of Transcranial Magnetic Stimulation.

This version was validated by the Board on
February 2018[1]

SUMMARY

In this advisory report, the Superior Health Council (SHC) provides an answer to the questions submitted by the Minister of Public Health regarding Transcranial Magnetic Stimulation (TMS) and, more specifically, on the efficacy and safety of this technique, as well as on the conditions for using it (setting and user training).
TMS involves delivering a magnetic pulse to the cerebral cortex through the skull using a coil. According to the law of Lenz-Faraday, the rapid change in magnetic flux induces an electric field which modifies neuronal activity in the area being treated. In clinical applications repetitive TMS (rTMS), a type of TMS that occurs in a rhythmic and repetitive form, is mostly used to treat neuropsychiatric illnesses. This makes it possible to diagnose and provide treatment for neurological and psychiatric disorders. TMS also contributes to neuroscientific research by providing a better insight into the role of specific regions in motor or cognitive performance in human beings.
After a careful examination of the scientific research on this fairly new technique, the SHC takes the view that there is sufficient scientific evidence in support of its effectiveness as a means to treat (drug-resistant) major depression and neuropathic pain. Next, we can conclude that rTMS is probably effective in the treatment of motor symptoms and depression related to Parkinson's disease (PD) as well as in the treatment of motor disorders after a cerebrovascular accident (CVA). The literature also shows a possible effect in the treatment of tinnitus, epilepsy, post-traumatic stress disorder (PTSD), negative symptoms and auditory hallucinations in schizophrenic patients but further research is necessary to confirm these data.

As regards the safety of (r)TMS, the SHC takes the view that this technique is fairly safe. The most common adverse effects are epileptic seizures, but this risk is low (< 1% of all TMS interventions), certainly when adhering to the current safety guidelines.

[1] The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

The only contraindication is the presence of a metal object in the body of the patient receiving treatment. TMS should therefore not be used in patients with an implant, unless this is medically justified. Similarly, children and pregnant women should not undergo TMS without a thorough medical assessment of the benefits/disadvantages ratio.

In view of an integrated care the use of (r)TMS for diagnostic or therapeutic purposes should be conducted in a medical setting and should be in collaboration with a psychiatrist for psychiatric disorders, a neurologist for neurological disorders or a specialist in physical medicine for locomotor disorders who all succeeded in an additional training regarding (r)TMS.

A medical setting (hospital or appropriately equipped outpatient clinic) is needed for all clinical applications of (r)TMS (i.e. diagnostic or therapeutic procedures of neuromodulation). Out-patient (r)TMS treatments can be delivered outside the hospital. However, it is strongly advisable that in these settings and in other medical environments, appropriate life-support equipment and emergency medical facilities are available.

Given that (r)TMS is a medical act, only certified healthcare professionals - as far as this falls within the scope of their field of expertise - should apply (r)TMS, both in a clinical setting as well as for (medical) research purposes.

Theoretically spoken, clinical psychologists and physiotherapists could also be allowed to practice (r)TMS as far as this act falls within their respective field of application. But there does not exist any official document stating the place that (r)TMS could occupy in their respective field of application nor is precisely described what is understood by an appropriate scientific clinically psychological or physiotherapeutical reference framework.

As this implementation framework does not exist until present the SHC proposes to reserve the clinical applications of (r)TMS only for medical specialists (i.e. psychiatrist, neurologist and specialist in physical medicine) who succeeded in an additional training regarding (r)TMS. Clinical psychologists and physiotherapists (under certain conditions) could then be allowed to practice (r)TMS once the respective implementation frameworks are filled in.

The SHC wants to stress its concerns about the absence up till now of any concrete and practical regulation or even guideline related to the place of (r)TMS practice in the application area of the clinical psychology and physiotherapy, if any.
Therefore, it is strongly advisable to consult the existing professional and scientific societies of psychiatrists, neurologists, clinical psychologists and physiotherapists in giving (r)TMS a place in today's health care and scientific research practice.
Furthermore, scientific publications in the domain must be followed in order to update the medical indications of (r)TMS use.

Since the exercising of a medical experiment is always linked with the Law of May 10th, 2015 regarding the exercising of a health care profession, the SHC proposes that the same health care professionals as for clinical applications should apply (r)TMS for research purposes involving patients.

A submission of research projects to the ethics committee (EC) recognized by law is legally required. The EC has not only the obligation to thoroughly perform a risk assessment regarding the experiments proposed by researchers but also to verify that all researcher have obtained the necessary certifications. The EC should evaluate the procedure adopted by the research institute to guarantee that appropriate medical interventions will be available in the event of an emergency.

In a conservative interpretation of the Belgian law concerning the exercising of a healthcare profession only physicians, could use (r)TMS in an experimental setting involving other subjects than patients. But since the current Belgian legislation is not clear whether other professionals can carry out (r)TMS in research involving other subjects than patients, the SHC proposes a distinction should be made between two classes of protocols.
Indeed, it is true that scientific and practical evidence shows that some forms of TMS (i.e. single pulse TMS, paired-pulse TMS, rTMS at low frequency or rTMS at higher frequencies for very short durations, with stimulation parameters that fall within the internationally recognized safety guidelines) can be considered safe when administered to healthy individuals[2]. The SHC proposes that other professionals than physicians - as far as this falls within the scope of their field of expertise - should be able to apply those protocols in settings involving other subjects than patients, as currently implemented worldwide.
Other protocols cannot be considered as being safe (although the risk might be still very low). This is the case for rTMS protocols, using stimulation parameters that fall outside the internationally recognized safety guidelines or when stimulation is applied to participants suffering from conditions potentially related to brain dysfunction. In this case, a medical setting and medical supervision is necessary.

There is currently no official training for TMS users in Belgium, nor does the literature offer any training requirements. Still, the SHC strongly advises that all users (including physicians) be trained at the existing university centres, and that such training be formally organized.

[2] The stimulation parameters that are considered to be safe as described in the guidelines apply to single session studies. In case of studies implying multiple sessions within the same participants it has to be taken into account that the accumulated frequency and duration parameters do not exceed those defined by the single sessions.

Keywords and MeSH *descriptor terms*[3]

MeSH terms*	Keywords	Sleutelwoorden	Mots clés	Schlüsselwörter
Transcranial Magnetic Stimulation	Transcranial Magnetic Stimulation	Transcraniële Magnetische Stimulatie	Stimulation Magnétique Transcrânienne	Transkranielle Magnetstimulation
	repetitive Transcranial Magnetic Stimulation	repetitieve Transcraniële Magnetische Stimulatie	Répétitives stimulation magnétique transcrânienne	wiederholende Transkranielle Magnetstimulation
	Stroke	Beroerte	Accident vasculaire cérébral	Schlaganfall
Stroke	Parkinson's disease	De ziekte van Parkinson	Maladie de Parkinson	Parkinson-Krankheit
Parkinson's disease	Anxiety Disorders	Angststoornissen	Troubles anxieux	Angststörungen
	Depression	Depressie	Dépression	Niedergeschlagenheit
Anxiety Disorders	Tinnitus	Tinnitus	Acouphènes	Tinnitus
Depression	Epilepsy	Epilepsie	Epilepsie	Epilepsie
Tinnitus	Schizophrenia	Schizofrenie	Schizophrénie	Epilepsie
Epilepsy	Safety	Veiligheid	Sécurité	Sicherheit
Schizophrenia	Contra-indications	Tegen-indicatie	Contre-indication	Gegenanzeigen
Safety				
	cerebral functions	Hersenfuncties	Fonctions cérébrales	Gehirnfunktionen

MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed http://www.ncbi.nlm.nih.gov/mesh.

[3] The Council wishes to clarify that the MeSH terms and keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".

CONTENTS

ABBREVIATIONS AND SYMBOLS

APA	American Psychiatric Association
CANMAT	Canadian Network for Mood and Anxiety Treatments
CNS	Central Nervous System
cTBS	Continuous Theta Burst Stimulation
CVA	Cerebrovascular Accident
DLPFC	Dorsolateral Prefrontal Cortex
EC	Ethical Committee
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EFNS	European Federation of Neurological Societies
FDA	Food and Drug Administration
GAD	Generalised Anxiety Disorder
HF	High Frequency
H&Y	Hoehn and Yahr rating scale
HDRS	Hamilton Depression Rating Scale
Hz	Hertz
iTBS	Intermittent Theta Burst Stimulation
LF	Low Frequency
M1	Primary motor cortex
MCES	Motor Cortical Electrical Stimulation
MEG	Magnetoencephalography
MEP	Motor Evoked Potentials
MT	Motor Threshold
OCD	Obsessive-Compulsive Disorder
PTSD	Post-traumatic stress disorder
PD	Parkinson disease
PET	Positron Emission Tomography
PFC	Prefrontal cortex
RCT	Randomized Controlled Trial
RMT	Resting Motor Threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
SMA	Supplementary motor area
SPECT	Single photon emission computed tomography
SSRI	Selective Serotonin Reuptake Inhibitor
TBS	Theta Burst Stimulation
TIA	Transient Ischemic Attacks
TMS	Transcranial Magnetic Stimulation
TPC	Temporoparietal Cortex
UPDRS	Unified Parkinson's Disease Rating Scale
WFSBP	World Federation of Societies of Biological Psychiatry

I INTRODUCTION AND ISSUE

The Minister of Public Health has requested the SHC to issue an advisory report on Transcranial Magnetic Stimulation (TMS). TMS is a medical non-invasive technique which involves placing a coil against the patient's head to generate a variable magnetic field which in turn induces an electric current through a specific area of the brain. This method can be used for the diagnosis and treatment of neurological and psychiatric disorders, as well as for neuroscientific research purposes.

More precisely, the SHC was asked to provide an answer to the following questions on TMS:

- How safe is this technique as regards any short and long-term medical risks, especially for pregnant women?
- What are the current scientific facts/what scientific evidence is there regarding the efficacy of the therapeutic applications?
- What are the necessary qualifications and areas of expertise for using TMS?
- What are the requirements in terms of setting, supervision, and quality that must be met to use TMS, both in a medical setting as well as for research purposes?

In order to provide an answer to these questions, an *ad hoc* working group was set up which included experts in bioelectromagnetics, psychiatry, neurology, neurosciences, physiotherapy, non-ionising radiation, ethics, and law.

II CONCLUSION AND RECOMMENDATIONS

1. Efficacy for therapeutic purposes

In conclusion, after analysing the data from the scientific literature, the SHC takes the view that the clinical use of repetitive transcranial magnetic stimulation (rTMS) is an effective technique that can be used for some therapeutic indications when other treatments have failed. These indications are evidence-rated from A (established as effective) over B (probable effect) and C (possible effect) to D (no recommendation can be made). The following provides an overview of these levels of evidence.

Level of evidence A

Depression:
rTMS is a definite effective technique in the treatment of unipolar major depression, also in the event that antidepressants have failed. Further research on this subject is necessary to optimize the stimulation parameters (number of sessions, number of stimulations per session ...).

Neuropathic pain:
Definite analgesic effect of HF rTMS of M1 contralateral to pain side.

Level of evidence B

Cerebrovascular Accident (CVA):
rTMS has a positive effect on motor recovery in patients who have suffered a stroke, especially a subcortical stroke / chronic motor stroke.

Parkinson's disease:
Probable antidepressant effect of HF rTMS of the left DLPFC.

Level of evidence C

Parkinson's disease:
Possible antiparkinsonian effect of HF rTMS of bilateral (multiple) M1 regions.

Motor stroke: Possible effect of LF rTMS of the contralesional motor cortex in (post-)acute and chronic motor stroke.

Tinnitus:
Possible effect of repeated sessions of LF rTMS of the left (or contralateral to tinnitus) TPC.

Epilepsy:
Possible antiepileptic effect of focal LF rTMS of the epileptic focus.

Post-traumatic stress disorder (**PTSD):**
rTMS is possibly effective for PTSD (which is not the case for other anxiety disorders) but more studies are needed.

Schizophrenia (Persistent auditory hallucinations):
Possible therapeutic effect with low-frequency stimulation of the left temporoparietal cortex.

Schizophrenia (negative symptoms):
The latest data show that rTMS is likely to have an effect on negative symptoms (blunted affect, abulia, anhedonia ...).

Level of evidence D

There are not enough data yet to conclude that rTMS is effective for Obsessive-Compulsive Disorder, generalized anxiety disorder, panic disorder and panic attack. Nor for fibromyalgia, migraine, visceral pain, Alzheimer's disease, dystonia, multiple sclerosis, amyotrophic lateral sclerosis, Tourette's syndrome and essential tremor.

2. Safety

In terms of safety, the only absolute contraindication to TMS/rTMS is the presence of metallic hardware in close contact to the discharge coil. If the TMS coil is not near the Internal Pulse Generator (IPG), (r)TMS can be applied. However, given the fact that the required distance is unclear, patients with implanted stimulators should only receive TMS if there are evidence-based medically compelling reasons to do so.

The most severe acute adverse effects are (r)TMS-induced seizures, though there is no doubt that this risk is very low.
For patients with an additional risk of seizure, it is required to involve a physician with expertise in the recognition and acute treatment of seizures.
The benefit/risk ratio of applying rTMS should be carefully considered prior to administering it to patients on epileptogenic medication.

The most common side effect of (r)TMS is pain. Patients and subjects should be warned that TMS may be unpleasant and may induce pain. Headaches may occasionally persist but no TMS-associated migraine attacks have been described.

Given the fact that there isn't a significant amount of data available on its potential for adverse effects, (r)TMS should not be performed in children without compelling clinical reasons for doing so, such as the treatment of refractory epilepsy or certain psychiatric conditions.

It seems unlikely that foetuses could be directly affected by (r)TMS, but actually, there exists no scientific consensus on this issue. Therefore, a conservative view of the use of (r)TMS in pregnancy is to consider weighing the benefits against the risks for each single case.

Particular care should be taken to prevent (r)TMS-devices with an excessive induction field from being available on the Belgian market. Indeed, the CE marking process doesn't set any limits in terms of patient exposure. Furthermore, the practitioner should weigh the benefits of the treatment against the risk associated with the induced currents. Also, due to the interaction of the induced voltages with the nervous system (working principal of (r)TMS), it is recommended to keep the induced electric field in the head and the body below 0.4 V/m around 1 kHz. Hence it should be recommended to the practitioners to avoid exceeding such a level in the tissues which are not supposed to be excited. The device documentation should provide information to the operator about this issue. As regards operator exposure:

- the exposure levels in Directive 2013/35/EU can be exceeded by some devices under certain conditions;
- the current legislation doesn't ensure that operator exposure does not exceed the action levels of Directive 2013/35/EU;
- the action levels mentioned in Directive 2013/35/EU do not address the operators for long-term effects;
- the level of exposure should be assessed for each type of device.

3. Necessary qualifications

In accordance with the current Belgian legislation, (r)TMS may only be carried out by physicians in clinical applications (both for diagnostic and therapeutic purposes) and experiments involving patients insofar as this falls within the scope of their respective field of expertise. Besides, the overall ethical principle stating that one can only carry out those medical acts falling within the scope of one's field of expertise has certainly always to be taken into account.

In view of an integrated care the use of (r)TMS for diagnostic or therapeutic purposes should be conducted in a medical setting and should be in collaboration with a psychiatrist for psychiatric disorders, a neurologist for neurological disorders or a specialist in physical medicine for locomotor disorders who all succeeded in an additional training regarding (r)TMS.

Theoretically spoken, clinical psychologists and physiotherapists are allowed to practice (r)TMS as far as this act falls within their respective field of application. Indeed, the basic legal reference framework does exist, but there does not exist any official document stating the place that (r)TMS could occupy in their respective field of application nor is precisely described what is understood by an appropriate scientific clinically psychological or physiotherapeutical reference framework.
As this implementation framework does not exist until present the SHC proposes to reserve the clinical applications of (r)TMS only for medical specialists (i.e. psychiatrist, neurologist and specialist in physical medicine) who succeeded in an additional training regarding (r)TMS. Clinical psychologists and physiotherapists (under certain conditions) could then be allowed once the respective implementation frameworks are filled in.

Experimental protocols must be submitted to an ethics committee (EC) recognized by law which has the obligation to thoroughly perform a risk assessment. Experiments involving subjects other than patients may be conducted in a non-medical setting with experienced medical specialists who are aware of the potential adverse effects (although the risk is very low) and are trained to detect them and provide the necessary initial support.

Since the exercising of a medical experiment is always linked with the Law of May 10th, 2015 regarding the exercising of a health care profession, the SHC proposes that the same health care professionals as for clinical applications should apply (r)TMS for research purposes involving patients.

For experiments involving other subjects than patients (e.g. movement and cognitive neuroscience research in non-patients), things are strictly legally spoken less clear. Interpreting the current Belgian law in a very conservative way implies that (r)TMS experimental research involving other subjects than patients could only be carried out by physicians, as far as this falls within the field of application of their respective expertise. Interpreting the same Belgian law the other way than the very conservative way corresponds to the topical internationally recognized daily practice in TMS research involving other subjects than patients.

Indeed, for research involving other subjects than patients, a distinction has to be made between two classes of protocols. Scientific and practical evidence shows that some forms of TMS (i.e. single pulse TMS, paired-pulse TMS, rTMS at low frequency or (r)TMS at higher frequencies for very short durations, with stimulation parameters that fall within the internationally recognized safety guidelines) can be considered safe when administered to healthy individuals[4]. Hence, the SHC proposes that other professionals than physicians should be able to apply these protocols in non-medical settings, as currently done worldwide.

Other protocols cannot be considered as being safe (although the overall risk is still low). This is the case for rTMS protocols, using stimulation parameters that fall outside the internationally recognized safety guidelines or when stimulation is applied to participants suffering from conditions potentially related to brain dysfunction. In this case, a medical setting and medical supervision is necessary.

In addition, the SHC unmistakably recommends setting up an official training program on the use of TMS. This training program should cover among others the following topics: basic mechanisms of (r)TMS, elementary knowledge of neuroanatomy, neurophysiology, interactions with pharmacological products, physiological changes induced, and potential risks of (r)TMS procedures. It should also include the ability to deal with potential acute complications of TMS and certify these skills.

[4] The stimulation parameters that are considered to be safe as described in the guidelines apply to single session studies. In case of studies implying multiple sessions within the same participants it has to be taken into account that the accumulated frequency and duration parameters do not exceed those defined by the single sessions.

4. Precautional remark

Regarding the necessary qualifications for applying (r)TMS: this is only true from a strictly legal point of view in relation to the autonomy of the clinical psychologist for example.
However, the SHC wants to stress its concerns about the topical absence of any concrete and practical regulation or even guideline related to the place of (r)TMS practice in the application area of the clinical psychology and physiotherapy.
Therefore, it is strongly advisable to consult the existing professional and scientific societies of psychiatrists, neurologists, clinical psychologists and physiotherapists in giving (r)TMS a place in today's health care and scientific research practice.
Furthermore, scientific publications in the domain must be followed in order to update the medical indications of rTMS use.

The overall ethical principle stating that a health care professional or scientific researcher is only allowed to carry out those acts falling within the scope of his expertise has always to be taken into account as a golden standard in everyday (r)TMS practice.
Therefore, the SHC emphasizes the utmost importance of an adequate training for every user of (r)TMS, whether or not it concerns a physician.

The SHC further judges that the working out of for example a curriculum for (r)TMS users does not belong to its primary area of competence but refers for this item among others to the existing and future bodies and scientific associations representing clinical psychologists, psychiatrists, neurologists and physiotherapists in order to establish practical guidelines to guarantee a maximum of safety for all patients and research subjects.

III METHODOLOGY

After analysing the request, the Board identified the necessary fields of expertise. An *ad hoc* working group was then set up which included experts in bioelectromagnetics, psychiatry, neuroradiology, neurology, physiotherapy, psychology, electrical engineering, civil engineering, ethics and law. The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts.

In this review the recent scientific literature is taken under scrutiny in order to determine whether (r)TMS may be indicated as a treatment module. This critical investigation aims at issuing recommendations on the efficacy and at justifying indications for (r)TMS. In order to do so, we based our analysis among others on the findings by our French colleagues (Lefaucheur et al., 2011). In late 2014, Lefaucheur et al. published evidence-based guidelines regarding the therapeutic use of rTMS. Here, a group of European experts was commissioned (by the first author) to establish guidelines on the therapeutic use of repetitive transcranial magnetic stimulation from evidence published up until March 2014, regarding pain, movement disorders, stroke, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, consciousness disorders, tinnitus, depression, anxiety disorders, obsessive-compulsive disorder, schizophrenia, and craving/addiction. This overview was completed with an updated literature search from 2014 to 2017. Safety issues were based on the paper of Rossi et al. (2009) which was the result of a A Consensus Statement from the International Workshop on "Present and Future of TMS: Safety and Ethical Guidelines", Siena, March 7-9, 2008 and the paper of Wasserman, 1998 which was the result of a June 1996 workshop organized to review the available data on safety of rTMS and to develop guidelines for its safe use. This article summarizes the workshop's deliberation.

In addition to issues of risk and safety, it also addresses the principles and applications of rTMS, nomenclature, and potential therapeutic effects of rTMS.

For each proposed indication, the literature from 2005 - 2017 on was searched using predefined keywords (Transcranial magnetic stimulation, repetitive transcranial magnetic stimulation, safety, contra-indications, cerebral functions).
After analyzing the articles and evaluating the concerned studies they were classified according to criteria set by the "European Federation of Neurological Societies" (EFNS) (Brainin et al., 2004) as is showed in table 1.

Table 1: Classification of the rules for therapeutic procedures (Brainin et al., 2004)

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population, or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:
(a) randomization concealment
(b) primary outcome(s) is/are clearly defined
(c) exclusion/inclusion criteria are clearly defined
(d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
(e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial (RCT) in a representative population that lacks one of the criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Rating of recommendations
Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies
Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence
Level C (possibly effective, ineffective, or harmful) rating requires at least two convincing class III studies
Level D rating implies that the information collected so far does not allow for any recommendations to be made.

Once the advisory report was endorsed by the working group, it was ultimately validated by the Board.

IV ELABORATION AND ARGUMENTATION

1 Transcranial Magnetic Stimulation: definition

Transcranial Magnetic Stimulation (TMS) is a medical technique developed in the mid-'80s for the diagnosis and treatment of neurological and psychiatric disorders, as well as for neuroscientific research purposes.

This technique involves painless and non-invasive electrical stimulation, during which a variable magnetic field is created by passing an electric current near the head via a coil. This magnetic field will induce an electrical activity in the cortex, and thus alter the neuronal activity. Low-frequency currents (< 1Hz) reduce this activity and have an inhibitory effect, whilst high-frequency currents (> 5Hz) increase it, although this effect may vary, in particular depending on the intensity of stimulation and the number of pulses delivered. Such a classification is based on the different physiological effects and degrees of risk associated with low- and high-frequency stimulation.

TMS can be applied one stimulus a time (single-pulse TMS), in pairs of stimuli separated by a variable interval (paired-pulse TMS), or in trains (*repetitive* TMS or *r*TMS). rTMS most often used in a clinical setting, will in turn emit several pulses during a certain period of time to significantly alter the activity of a specific brain region.
Patterned rTMS refers to repetitive application of short rTMS bursts at a high inner frequency interleaved by short pauses of no stimulation. Most used to date are the different theta burst (TBS) protocols in which short bursts of 50 Hz rTMS are repeated at a rate in the theta range (5 Hz) as continuous (cTBS), or intermittent (iTBS) trains (Rossi et al., 2009).

In the context of neuroscientific research (which is an example of a non-medical research), the use of TMS makes it possible to improve our understanding of the role of specific brain regions in human beings by subjecting them to a magnetic field and by observing the effect on motor or cognitive performance. Moreover, the neuronavigation systems that are currently used to guide these devices make it possible to pinpoint the site of stimulation.

2 Efficacy of rTMS in various therapeutic applications

2.1 Introduction

Repetitive Transcranial Magnetic Stimulation might be therapeutically used in various psychiatric and neurological pathologies as there are: major depression, anxiety disorders, schizophrenia, Parkinson's disease, stroke, neuropathic pain, epilepsy, tinnitus.

2.2 rTMS in the treatment of psychiatric disorders

2.2.1 Introduction

A review of the current scientific literature on this subject reveals that several authors suggest that rTMS could be an effective treatment strategy for major depression and other psychiatric disorders. Given this potential efficacy and the relative ease of use of this technique, the question arises whether it should be given a place as one of the modern tools for the treatment of psychiatric patients. It should be noted that several countries, including the United States and Canada, have already approved its use for some psychiatric indications (mainly major depression) (Rossi et al., 2009; Milev et al., 2016). Also in Europe, the number of rTMS centres is on the rise, though here; this treatment is not always recognized nor refunded yet (with the exception of Finland, Germany and the Netherlands) (De Graaf et al., 2017).

2.2.2 Major Depression

Major depression is a common mental disorder with an annual prevalence among the general population that varies between 5 and 15% (Nemeroff, 2007). Unfortunately, not all depressed patients respond to the available pharmacotherapies. It follows that refractory depression is not uncommon (Fava, 2003). It is estimated that therapy resistance occurs in 50% of depressed patients who are receiving proper treatment with first-line antidepressant medication (Akil et al. in press). Over ten per cent of these patients remain resistant to various psychopharmacological interventions, even when treatment guidelines are consistently followed (Fagiolini & Kupfer, 2003).
Nevertheless, it is very important to provide proper care in the event of a major depressive episode, as this psychiatric disorder tends to relapse (up to 85%) or to become chronic (on average 20% of the cases). Here, therapeutic alternatives may be necessary, optimising medication dosages, changing antidepressant medication, combining different types of antidepressant medication, with or without additional psychotherapeutic care, such as cognitive behavioural therapy or interpersonal therapy, or using electroconvulsive therapy (ECT). Although the possible position of rTMS has not been clearly defined yet, it is generally assumed that rTMS has a higher chance of success when it is administered in the acute phase (an on-going depressive episode which has lasted for less than one year) to relatively young people (<65 years) known to have a limited level of resistance to treatment (one or two failed pharmacological trials, with or without psychotherapy) or only in case of partial response to treatment (George and Post, 2011).
In the past decades, two clear directions for the treatment of depression with rTMS emerged: high-frequency stimulation (inducing neuronal excitation) of the left dorsolateral prefrontal cortex (DLPFC) (mainly hypoactive in case of depression) or low-frequency stimulation (inducing neuronal inhibition) of the right DLPFC (presumably hyperactive in case of depression) (De Raedt et al., 2015).

Methodology
A comprehensive PubMed literature search for publications on this subject (keywords: repetitive transcranial magnetic stimulation AND depression AND efficacy) yielded 224 references. Upon entering three additional criteria: "(randomized) clinical trial", "review", and "meta-analysis", the number of selected studies dropped to 79. Only studies that met the criteria (i) prospective, (ii) controlled (as opposed to a comparator and/or placebo (sham)), (iii) a minimum of 10 patients per group, and (iv) published after 2005 were retained. With the methodological quality of the studies published before 2005 being more heterogeneous in terms of stimulation parameters and patient selection, the decision was made to focus only on those published after 2005. Finally 40 controlled studies were retained by applying this filter: 21 studies assessed the efficacy of high-frequency rTMS of the left DLPFC, 5 studies examined low-frequency rTMS of the right DLPFC, 5 other trials looked at the effect of right vs. left DLPFC stimulation, and 9 studies compared bilateral rTMS (table 2).

Table 2: rTMS studies for the indication of major depression

Articles	Number of patients	with antidepressant medication	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class evidence
High-frequency rTMS of the left dorsolateral prefrontal cortex (DLPFC)							
1. Rossini et al., 2005 a	54	-	Raised coil	15Hz, 80-100% RMT	600 pulses, 10 sessions	positive	II
2. Rossini et al., 2005 b	99	+	Raised coil	15Hz, 100% RMT	900 pulses, 10 sessions	positive	II
3. Rumi et al., 2005	46	+	Sham coil	5Hz, 120% RMT	1250 pulses, 20 sessions	positive	I
4. Su et al., 2005	30	-	Raised coil	20/5Hz, 100% RMT	1600 pulses, 10 sessions	positive	II
5. Avery et al., 2006	68	-	Raised coil	10Hz, 110% RMT	1600 pulses, 15 sessions	positive	I
6. Anderson et al., 2007	29	+	Sham coil	10Hz, 110% RMT	1000 pulses, 20 to 30 sessions	positive	II
7. Bortolomasi et al., 2007	19	+	Raised coil	20Hz, 90% RMT	800 pulses, 5 sessions	positive	III
8. Herwig et al., 2007	127	+	Raised coil	10Hz, 110% RMT	2000 pulses, 10 sessions	negative	II
9. Loo et al., 2007	38	-	inactive coil	10Hz, 110% RMT	1500 pulses, 20 sessions	positive	I
10. O' Reardon et al., 2007	301	-	Sham coil	10Hz, 120% RMT	3000 pulses, 10 to 30 sessions	positive	I
11. Bretlau et al., 2008	49	+	inactive coil	8Hz, 90% RMT	1289 pulses, 10 sessions	positive	II
12. Jorge et al., 2008	30	-	Sham coil	10Hz, 110% RMT	1200 pulses, 10 sessions	positive	II
13. Mogg et al., 2008	59	+	Sham coil	10Hz, 110% RMT	1000 pulses, 10 sessions	negative	I
14. Carretero et al., 2009	28	+	Raised coil	20Hz, 110% RMT	1200 pulses, 20 sessions	negative	II
15. George et al., 2010	199	-	Sham coil	10Hz, 120% RMT	3000 pulses, 10 to 30 sessions	positive	I
16. Paillere-Martinot et al., 2010	48	-	Sham coil	10Hz, 90% RMT	1600 pulses, 10 sessions	positive	II
17. Triggs et al., 2010	48	-	Sham coil	5Hz, 100% RMT	2000 pulses, 10 sessions	negative	II
18. Lisanby et al., 2010	301	-	Sham coil	10Hz, 120% RMT	3000 pulses, 20 sessions	positive	I
19. Ray et al., 2011	45	-	Raised coil	10Hz, 90% RMT	1200 pulses, 10 sessions	positive	III

20. Baeken et al., 2013	20	-	Raised coil	20Hz, 110% RMT	1560 pulses, 20 sessions	positive	II
21. Duprat et al., 2016	50	Left DLPFC	Sham stim crossover	Accelerated iTBS RMT 100%	20 sessions in 4 days (5sessions a day)	No differences	I

Recommendation: clearly demonstrable antidepressant effect of high-frequency rTMS of the left DLPFC (level A rating)

Low-frequency rTMS of the right DLPFC

1. Januel et al., 2006	27	-	Sham coil	1Hz, 90% RMT	120 pulses, 16 sessions	positive	I
2. Fitzgerald et al., 2008 a	60	+	Raised coil	1Hz (6 Hz priming), 110% RMT	900 pulses, 20 sessions	positive	II
3. Bares et al., 2009	60	+	Raised coil	1Hz, 100% RMT	600 pulses, 20 sessions	No difference	III
4. Aguirre et al., 2011	60	+	Raised coil	1Hz, 110% RMT	1200 pulses, 20 sessions	No difference	III
5. Brunelin et al., 2014	170 (active: 115; control: 55)	Right DLPFC, F8c	Sham coil	1Hz, 120%RMT	360 pulses, 10-30 sessions	Positive Add-on treatment No difference between rTMS, venlafaxine and rTMS + Venlafaxine	I

Recommendation: clearly demonstrable antidepressant effect of low-frequency rTMS of the right DLPFC (level B rating)

Studies comparing high-frequency rTMS of the left DLPFC with low-frequency rTMS of the right DLPFC							
1. Chistyakov et al., 2005	59	-	Raised coil	10/3Hz, 100/110% RMT	450 pulses, 10 sessions	No difference	III
2. Fitzgerald et al., 2006	50	-	Raised coil	10/1Hz, 110% RMT	750 pulses (10 Hz) / 420 pulses (1 Hz), 10 - 30 sessions	positive	III
3. Fitzgerald et al., 2009	27	-	Blinded researcher	10/1Hz 100%/110% RMT	1500 pulses (10 Hz) / 720 pulses (1 Hz), 15 sessions	positive	III
4. Rossini et al., 2010	74	-	Blinded researcher	15/1Hz 100% RMT	600 pulses 10 sessions	positive	III
5. Del'Osso et al., 2015	33	Right or left	None	10/1Hz 110% RMT stim/ 10/1Hz 110% RMT 13/10Hz, 80% RMT	420 pulses/ 900 pulses/ 750 pulses 20 sessions	significant reduction of primary outcome measures (HAM-D, MADRS and CGI-S total scores: t=8.1, P<0.001; t=8.6, P<0.001; t=4.6, P<0.001 respectively) No difference Heterogeneity of population and low power of high frequency stimulation	III
Recommendation: possibly no difference regarding the antidepressant effect of high-frequency rTMS of the left DLPFC vs. low-frequency rTMS of the right DLPFC (level C rating)							

Studies combining high-frequency rTMS of the left DLPFC and low-frequency rTMS of the right DLPFC (bilateral stimulation)							
1. Garcia-Toro et al., 2006	30	+	Raised coil	10Hz then 1 Hz, 110% RMT	1200 pulses (10Hz) / 180 pulses (1Hz), 10 sessions	positive	II
2. McDonald et al., 2006	62	-	Raised coil	1 and 10Hz randomised 110% RMT	1000 pulses (10Hz) / 600 pulses (1Hz), 10 sessions	negative	III
3. Palanti et al., 2010	60	+	Sham coil	1Hz then 10Hz, 110% RMT	420 pulses (1Hz) / 1000 pulses (10Hz), 15 - 30 sessions	negative	II
4. Fitzgerald et al., 2011	219	+	None	1Hz then 10Hz, 100-120% RMT	1450 pulses (10Hz) or 465 (1Hz) + 750 (10Hz) pulses, 15 - 30 sessions	positive	I
5. Blumberger et al., 2012b	74	+	Raised coil	1Hz then 10Hz, 100-120% RMT	1500 (10Hz) + 900 (sham) pulses or 900 (1Hz) + 1500 (10Hz) pulses, 15 - 30 sessions	positive	II
6. Fitzgerald et al., 2012	66	+	Raised coil	1Hz then 10Hz, 120% RMT	1500 (10Hz) + 900 (sham) pulses or 900 (1Hz) + 1500 (10Hz) pulses, 15 - 30 sessions	negative	II
7. Fitzgerald et al., 2013	179		None	1Hz then 10Hz, 120% RMT	1500 (10Hz) + 900 (sham) pulses or 900 (1Hz) + 1500 (10Hz) pulses, 15 - 30 sessions No difference	No difference	I
8. Li et al., 2014	60 (15 per groups)	Left DLPFC and Right DLPFC (MRI localization; junction between 9 and 46)	Titled coil	cTBS, 80%RMT iTBS 80%RMT cTBS + iTBS 80%RMT Sham	1800 pulses, 10 sessions 1800 pulses, 10 sessions 3600 pulses, 10 sessions 1800 pulses, 10 sessions	4 groups (cTBS, iTBS, bilat, Sham) Positive for iTBS left and bilateral	II
9. Prasser et al., 2014	56	Left DLPFC and Right DLPFC (6cm)	Sham	1HZ right + 10Hz left 110%RMT CTBS right + iTBS left 80%RMT	2000 pulses, 15 sessions 2400 pulses, 15 sessions	No difference Trend to long term effect for TBS (W11)	III
Recommendation: possibly no antidepressant effect of bilateral rTMS in the following combination: low-frequency (right) and high frequency (left) rTMS (level C rating)							

DLPFC: dorsolateral prefrontal cortex; RMT: resting motor threshold; Hz: Hertz

rTMS in the treatment of major depression

The selected studies show a considerable degree of heterogeneity. Whilst some studies specifically compared different frequencies of rTMS at different stimulation sites and/or with a placebo (sham) treatment, other studies looked at the influence of various stimulation parameters (intensity, lateralization or priming). Finally, a number of studies investigated the combination of rTMS and antidepressant medication.

When taking into account all placebo-controlled studies in which the DLPFC was stimulated, we found 26 studies with positive results, 7 negative studies (including 12 Class I studies, 17 Class II studies, and 11 class III studies) and 7 studies showing no difference. Moreover, the meta-analysis of Schutter et al. (2009) showed that a positive publication bias does not affect the reporting of rTMS results, presumably because scientists want to publish every finding (including negative ones).The two class I studies of the highest methodological quality yielded positive results, showing the efficacy of high-frequency rTMS supplied to the left DLPFC in the treatment of unipolar depression that does not respond to at least one antidepressant medication (O'Reardon et al., 2007; George et al., 2010). These results were a strong argument that led the Food and Drug Administration (FDA) in the United States to approve the use of rTMS in 2009 for the treatment of major depressive episodes unresponsive to at least one antidepressant medication. In addition, there are various meta-analyses that conclude that rTMS has a significant antidepressant effect, thus supporting the use of rTMS for this indication (cf. the meta-analyses of Berlim et al., 2013 a and b). The therapeutic efficacy or rTMS has clearly improved in more recent studies, which may simply be due to the fact that the stimulation parameters are applied in a more effective manner. At present, most clinical studies use multiple high-frequency rTMS sessions applied to the left DLPFC (Brunoni et al., 2016).

rTMS versus antidepressant medication

One comparative study has been reported on (Bares et al., 2009), a comparison between low-frequency rTMS of the right DLPFC versus venlafaxine (150-375 mg). No clinical difference was found between the two groups. However, there was no control group, which is typical of a class III study.

Moreover, antidepressant medication was not discontinued in many of the studies mentioned above in which rTMS was found to have effects. Regarding the additive effect - when medication was introduced during rTMS treatment ("add-on therapy") or was maintained (enhancing effect) - 6 studies can be selected (Two Class I and four Class II studies) (Bretlau et al., 2008, Garcia-Toro et al., 2006, Herwig et al., 2007, Rossini, Magri, Lucca et al., 2005, Rumi et al., 2005; Brunelin et al., 2014). Based on these studies we can conclude that the combined use of antidepressant medication and rTMS treatment has a positive efficacy (**level A evidence**). For the analyses regarding the enhancing effect, six studies were selected (one Class I, 3 Class II and two Class III) (Anderson et al., 2007, Bortolomasi et al., 2007, Carretero et al., 2009, Fitzgerald et al., 2008, Mogg et al., 2008, Pallanti et al., 2010). They confirm the enhancing effect of antidepressant medication combined with rTMS treatment (**level A evidence**).

rTMS versus electroconvulsive therapy (ECT)

The greatest problem one encounters when comparing rTMS and ECT in the treatment of major depression is the lack of controlled studies. In addition, the available studies (single-blind open studies) show a low level of evidence in terms of effects (Rosa et al., 2006, Eranti et al., 2007, Hansen et al., 2011). Several meta-analyses show that rTMS is less effective than ECT, especially in the case of depression with psychotic features (Slotema et al., 2010; Ren et al., 2014). Hence, based on the actual state of scientific knowledge **no formal recommendation** in favour of the use of rTMS compared to ECT can be formulated at the moment.

rTMS in the treatment of bipolar depression

Regarding bipolar depression, three class III studies (Nahas et al. 2003; Hu et al., 2016, Fitzgerald et al., 2016) showed heterogonous outcome emphasizing that we do not currently have sufficient data to draw conclusions and establish recommendations as regards rTMS for bipolar disorder, especially since medication treatment was continued during this study (including anti-epileptic drugs and mood stabilisers). Though there are other studies with bipolar patients, unfortunately they always involved larger cohorts which also included non-bipolar depressed patients, which makes it impossible to make any comparisons. In sum, there are currently **insufficient data** to formulate any recommendation regarding rTMS treatment in bipolar depression. On the other hand no evidence was found suggesting that rTMS is associated with an elevated risk for such a switch compared to sham treatment

Conclusions concerning rTMS as an indication for major depression

Based on a thorough review and on data from the literature, it can be concluded that high-frequency rTMS of the left prefrontal cortex and low-frequency rTMS of the right prefrontal cortex have an established antidepressant effect, mainly in the acute phase of a unipolar depression episode (<1 year) (**level A evidence**). This also applies to the treatment of mild unipolar depression in patients who failed to respond to at least one class of antidepressant medication. In summary, a similar efficacy was found for both types of stimulation (low-frequency right and high-frequency left), in similar groups of patients (Table 2). These recommendations for the use of rTMS in the treatment of mood disorders are consistent with those of the American Psychiatric Association (APA), the Canadian Network for Mood and Anxiety Treatments (CANMAT), and the World Federation of Societies of Biological Psychiatry (WFSBP) (Kennedy et al. 2009; Milev et al, 2016). rTMS can be represented as a useful technique in the treatment of major depression in the event of antidepressant medication being discontinued, except for cases of depression with psychotic features, for which the use of ECT is advisable. Notwithstanding the fact that the methodology has been significantly improved since 2000, especially regarding the optimisation of the stimulation parameters, there is still some variation in the number of proposed sessions (10 to 30) and the number of stimuli per session (120 to 3000) in actual clinical practice, which requires further investigation in the context of rTMS parameter optimisation.

2.2.3 Anxiety disorders

Anxiety disorders are among the most persistent psychiatric disorders. Prevalence estimates range from 1.2% to 15% in general and from 1% to 28% in the medical environment. The prevalence of clinically significant anxiety symptoms ranges from 15% to 52% in the population and 15% to 56% in medical environments (Lenze and Wetherell, 2011). Anxiety disorders, such as post-traumatic stress disorder (PTSD), panic disorder (PD), and obsessive-compulsive disorder (OCD) are currently treated with antidepressant medication, either with or without additional psychotherapy (cognitive behavioural therapy). The traditional treatments have insufficient effect on the symptoms of many patients. As a result, rTMS has a potential to treat (residual) anxiety symptoms.

2.2.3.1 Post-traumatic stress disorder (PTSD)

Only a few studies have been conducted on the therapeutic efficacy of rTMS in PTSD. The PubMed literature search (keywords: repetitive transcranial magnetic stimulation and post-traumatic stress disorder), yielded only four controlled studies with at least 10 patients (Table 3). The right and/or left dorsolateral prefrontal cortex (DLPFC) was always the site of stimulation, to which low- or high-frequency rTMS was applied. Although the results are fairly straightforward, they are based on relatively small groups and show methodological differences regarding stimulation site, stimulation parameters, and concomitant treatment with psychopharmaceuticals.

Three of these four studies are class II, a forth is a class III study. This allows us to give a level C (possibly effective) recommendation for the treatment of PTSD with rTMS.

Table 3: rTMS studies for the indication post-traumatic stress disorder (PTSD)

Articles	**Number of patients**	**Site of stimulation**	**Control condition**	**Stimulation frequency and intensity**	**Number of pulses/session and number of sessions**	**Results**	**Class evidence**
Cohen et al., 2004	24	right DLPFC	Raised coil	1/10Hz, 80% RMT	100 pulses (1Hz) or 400 pulses (10Hz), 10 sessions	positive	III
Boggio et al., 2010	30	Right or left DLPFC	Raised coil	20Hz, 80% RMT	1600 pulses/session 10 sessions	positive	II
Watts et al., 2012	20	right DLPFC	Sham coil	1Hz, 90% RMT	400 pulses/session 10 sessions	positive	II
George et al., 2014	41	left DLPFC	Sham coil	10Hz, 1200% RMT	6000 pulses/session, 3 sessions	positive	II
Recommendation: rTMS is probably possibly effective for post-traumatic stress disorder (PTSD) (level C)							

DLPFC: dorsolateral prefrontal cortex; RMT: resting motor threshold, Hz: Hertz

2.2.3.2 Obsessive-compulsive disorder

Only a few therapeutic studies have been conducted for this indication. Six controlled studies that involved least 10 patients were selected from the literature search performed in PubMed from 2005-2017 (keywords: repetitive transcranial magnetic stimulation and obsessive-compulsive disorder) (table 4).

Table 4: rTMS studies for the indication obsessive-compulsive disorder

Articles	Number of patients	Site of stimulation	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class evidence
high-frequency rTMS							
Sachdev et al., 2007	18	left DLPFC	Raised coil	10Hz, RMT	10 pulses, 20 sessions	negative	III
Sarkhel et al., 2010	42	right DLPFC	Raised coil	10Hz, 110% RMT	8000 pulses, 10 sessions	negative	II
Mansur et al., 2011	27	right DLPFC	Raised coil	10Hz, 110% RMT	60 000 pulses, 30 sessions	No difference	III
Gomes et al., 2012	22	right DLPFC	Raised coil	1Hz, 110% RMT	12 000 pulses, 10 sessions	positive	III
No recommendation							
low-frequency rTMS							
Prasko et al., 2006	33	left DLPFC	Raised coil	1Hz, 110% RMT	1800 pulses, 10 sessions	No difference	II
Ruffini et al., 2009	23	Left orbitofrontal cortex	Raised coil	1Hz, 80% RMT	600 pulses, 15 sessions	No difference	III
Kang et al., 2009	20	Right DLPFC, SMA	Raised coil	1Hz, 110% RMT	1200 pulses, 10 sessions	No difference	
low-frequency rTMS and high-frequency rTMS							
Elbeh et al., 2016	45	left DLPFC, Right DLPFC,	Tilted coil	1Hz, 10Hz, 100% RMT	2000 pulses, 10 sessions	positive	II
Recommendation: no recommendation of high- or low-frequency rTMS of the DLPFC in treating obsessive-compulsive disorders (level D).							

DLPFC: dorsolateral prefrontal cortex; RMT: resting motor threshold, Hz: Hertz

The results of these studies are inconclusive, with two negative, one positive and four trials with no difference. Given the small number of studies and patients included (especially of Class III), it is only possible to provide **a level D recommendation regarding the potential inappropriateness** of low-frequency rTMS applied to the prefrontal cortex in the treatment of OCD. No recommendation can be made for other protocols.

2.2.3.3 Panic disorder and generalised anxiety disorder

The therapeutic application of rTMS in other anxiety disorders mainly concerns panic disorder (PD) and panic attacks (five studies published to date, not retained according to our selection criteria). Only one study has been conducted on panic disorder and one on generalised anxiety disorder (GAD). The results of these studies are inconclusive. The inclusion criteria, stimulation parameters and evaluation methods are very heterogeneous. The level of evidence is still insufficient, with only two controlled studies displaying heterogeneous results (Class III).
This evidence is **not strong enough to suggest a recommendation for the therapeutic use of rTMS in the treatment of panic disorder and generalised anxiety disorder.**

2.2.3.4 Conclusions concerning the indication for rTMS as a treatment for anxiety disorder

For the indication posttraumatic stress disorder, the results are fairly straightforward, despite the limited number of studies that are available. With two Class II studies (Boggio et al., 2010, Watts et al., 2012) and a third Class III (Cohen et al., 2004), the **treatment of PTSD with rTMS is possible to be effective.** We can therefore issue a **level C** recommendation.
On the other hand, the current data from the literature are **not conclusive to advise the use of rTMS in the treatment of obsessive-compulsive disorder (level D)**. Regarding the other anxiety disorders the level of evidence is still insufficient and therefore no recommendation can be given.

2.2.4 Schizophrenia

Schizophrenia is a complex and debilitating condition that usually starts in late adolescence/early adulthood and is marked by hallucinations and delusions (commonly known as positive symptoms), social withdrawal, alogia, affective flattening (negative symptoms), and cognitive impairments. Schizophrenia affects about 1% of the population worldwide and is a long-lasting burden for the individuals and families concerned. In addition, the costs for society are considerable, amongst other things as a result of shorter life-expectancy (Gogtay et al., 2011). Schizophrenic patients who receive proper medication treatment with antipsychotics may still experience hallucinations, which is not only liable to be a source of stress, but also increases the risk of relapse.

2.2.4.1 Auditory hallucinations

Patients suffering from schizophrenia often experience paracusia or auditory hallucinations, sometimes also other sensory experiences such as visual hallucinations (Fitzgerald et al., 2005). During auditory hallucinations, brain areas involved in the perception of speech (primary auditory cortex and language association areas in the left hemisphere) show hyperactivity, mainly in the temporoparietal cortex (TPC). It follows that inhibiting neuronal TPC excitability through low-frequency rTMS was the most commonly applied form of treatment in patients with resistant auditory hallucinations (Hoffman et al., 1999).
A review of the literature in PubMed from 2005 on (keywords: repetitive transcranial magnetic stimulation and auditory hallucinations and schizophrenia) yielded 69 publications. With regard to the acute treatment of auditory hallucinations, 13 controlled studies were selected. They are mentioned in Table 5. All of these studies are based on low-frequency stimulation (1 Hz) of the left TPC, and involve more than 300 patients.

Table 5: rTMS studies for the indication auditory hallucinations

Articles	Number of patients	Site of stimulation	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class evidence
Chibaro et al., 2005	16	Left temporoparietal cortex	Raised coil	1Hz, 90% RMT	960 pulses, 4 sessions	positive	II
Fitzgerald et al., 2005	33	Left temporoparietal cortex	Raised coil	1Hz, 90% RMT	960 pulses, 10 sessions	negative	I
Hoffman et al., 2005	50	Left temporoparietal cortex	Raised coil	1Hz, 90% RMT	480-960 pulses, 9 sessions	positive	I
Lee et al., 2005	39	Left and right temporoparietal cortex	Raised coil	1Hz, 90% RMT	1200 pulses, 10 sessions	negative	II
Poulet et al., 2005	10	Left temporoparietal cortex	Sham coil	1Hz, 90% RMT	1000 pulses, 10 sessions	positive	II
Brunelin et al., 2006	14	Left temporoparietal cortex	Sham coil	1Hz, 90% RMT	1000 pulses, 5 sessions	positive	II
Saba et al., 2006	18	Left temporoparietal cortex	Sham coil	1Hz, 80% RMT	300 pulses, 10 sessions	negative	II
Vercammen et al., 2009	38	Bilateral or left temporoparietal cortex	Sham coil	1Hz, 90% RMT	1200 pulses, 6 sessions	positive	I
Loo et al., 2010	18	Bilateral temporoparietal cortex	Vertex stimulation, raised coil	1Hz, 90% RMT	240-480 pulses, 3 sessions	negative	III
De Jesus et al., 2011	17	Left temporoparietal cortex	Raised coil	1Hz, 90% RMT	1200 pulses, 20 sessions	positive	II
Slotema et al., 2011	62	Left temporoparietal cortex or site of stimulation defined by fMRI.	Raised coil	1Hz, 90% RMT	1200 pulses, 15 sessions	negative	II
Blumberger et al., 2012a	51	Left TPC	Raised coil	1Hz, 115% RMT vs. 6Hz-primed 1Hz, 90% RMT	1200 pulses, 20 sessions	negative	III
Klirova et al., 2013	15	Left TPC	Raised coil	0.9Hz, 100% RMT	1080 pulses, 10 sessions	positive	III

Recommendation: Possible effect of low-frequency rTMS of the left temporoparietal cortex on auditory hallucinations (level C)

DLPFC: dorsolateral prefrontal cortex; RMT: resting motor threshold, Hz: Hertz

Based on the results of the studies summarized in Table 5 we can advise **(evidence Level C) a possible efficacy of low-frequency rTMS of the left temporoparietal cortex in the treatment of auditory hallucinations.** It is important that only a stimulation frequency of 1 Hz has been validated for this indication. For other stimulation parameters (other stimulation sites or frequencies), no recommendation can be made because of a lack of data. A minimum of 10 daily sessions is advisable. The stimulation intensity should generally be 90% of the RMT. In this respect, it is important that the therapeutic effect on auditory hallucinations is significant. However, the impact of low-frequency rTMS on other aspects of schizophrenia has not been demonstrated.

2.2.4.2 Negative symptoms

Schizophrenia is often described in terms of positive and negative (or deficit) symptoms. Positive symptoms are those that most individuals do not normally experience but are present in people with schizophrenia like there are disordered thoughts and speech, delusions, tactile, auditory, visual, olfactory and gustatory hallucinations. Positive symptoms generally respond well to medication (Sims et al., 2002). Negative symptoms are deficits of normal emotional responses or of other thought processes, and respond less well to medication (Carson et al., 2000). They commonly include flat expressions or little emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation.

Due to the potential “hypofrontality” in schizophrenia patients, it seems logical to restore frontal cortex activity by using high-frequency rTMS (Novak et al., 2006). Implementing such a strategy in schizophrenia aims at restoring cognitive decline and treating negative symptoms.

A search in PubMed (keywords: repetitive transcranial magnetic stimulation and negative symptoms and schizophrenia) yielded 8 controlled studies, which are mentioned in table 6. All of these studies focused on the acute treatment of negative symptoms in patients with schizophrenic disorders. A significant effect of active stimulation as opposed to "sham" stimulation on these negative symptoms was observed in 7 out of 12 studies. No study was conducted on the long-term effects of rTMS or the importance of the maintenance treatment. However, if we consider HF rTMS (10Hz) of the left DLPFC, which is the most frequent stimulation setting, seven studies (of Class II-III) provided positive results and one class I and one Class III study was negative. Therefore, one could propose a Level C of recommendation for a possible efficacy of HF rTMS of the left DLPFC.

Table 6. rTMS studies for the indication negative symptoms of schizophrenia

Articles	Number of patients	Site of stimulation	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class evidence
1. Novak et al., 2006	16	left DLPFC	Not mentioned	20Hz, 90% RMT	2000 pulses, 10 sessions	negative	II
2. Jin et al., 2006	35	Bilateral DLPFC	Disconnected coil	(8–13Hz), 3, or 20Hz, 80% RMT	120-800 pulses, 10 sessions	positive	III
3. Goyal et al., 2007	10	left DLPFC	Raised coil	10Hz, 110% RMT	980 pulses, 10 sessions	positive	II
4. Mogg et al., 2007	17	left DLPFC	Sham coil	10Hz, 110% RMT	2000 pulses, 10 sessions	negative	II
5. Prikryl et al., 2007	22	left DLPFC	Raised coil	10Hz, 110% RMT	1500 pulses, 15 sessions	positive	II
6. Schneider et al., 2008	51	left DLPFC	Raised coil	10 or 1Hz, 110% RMT	2000 pulses, 20 sessions	positive	II
7. Fitzgerald et al., 2008 b	20	Bilateral DLPFC	Raised coil	10Hz, 110% RMT	1000 pulses, 15 sessions	negative	II
8. Cordes et al., 2010	35	left DLPFC	Raised coil	10Hz, 110% RMT	1000 pulses, 10 sessions	positive	II
9. Barr et al., 2012	25	Bilateral DLPFC	Raised coil	20Hz, 90% RMT	750 pulses per hemisphere, 20 sessions	negative	III
10. Prikryl et al., 2013	40	left DLPFC	Raised coil	10Hz, 110% RMT	2000 pulses, 15 sessions	positive	II
11. Dlabac-de Lange et al., 2015	32	Bilateral DLPFC	Raised coil	10Hz, 90% RMT	2000 pulses, 15 sessions	positive	III
12. Wobrock et al., 2015	175	left DLPFC	Raised coil	10Hz, 110% RMT	1000 pulses, 15 sessions	negative	I
Recommendation: possible effect of HF rTMS of the left DLPFC on negative symptoms of schizophrenia (Level C)							

DLPFC: dorsolateral prefrontal cortex; RMT: resting motor threshold, Hz: Hertz

2.2.4.3 Conclusions concerning the indication for rTMS as a treatment for schizophrenia

Level C evidence can be posited for using low-frequency rTMS (1Hz) of the left TPC to treat schizophrenic patients who still have **persistent auditory hallucinations** despite their receiving proper medication treatment. It follows that low-frequency rTMS can be proposed as a complementary therapy to the usual pharmacotherapy for persistent hallucinations. Yet it is possible for a relapse to occur after a successful rTMS treatment, on average within 8 weeks after stimulation. Still, no recommendation can be made on the basis of the current state of knowledge regarding maintenance treatment to prevent relapse.
As regards the negative symptoms that are typical of schizophrenia, the current studies yield contradictory results, which means that more research is necessary to draw any conclusions. We can **recommend a level C** with regard to the indication of rTMS to treat **negative symptoms** in schizophrenia.

2.2.5 Summary and conclusions on rTMS in the treatment of psychiatric disorders

This summary is an evidence-based synthesis of existing and potential therapeutic applications of rTMS for well-defined psychiatric disorders (Table 7). For some indications (major depression, negative symptoms in schizophrenia), there is sufficient evidence in support of a therapeutic indication of rTMS that is useful for clinical practice with the understanding that only **level A evidence** is exclusively reserved for treating major **depression. Negative symptoms in schizophrenia remains at level C** (Table 7). Or to put in other words, rTMS for the treatment of major depression has enough evidence to conclude clear indication for rTMS treatment of this disorder. All level C suggest that there is some potential of rTMS in treating these indications, but one should be more conservative on the beneficial outcome.
Further controlled studies for other potential indications are necessary to extend the rTMS application in psychiatric clinical practice. Although probably effective for post-traumatic stress disorder, the efficacy of this technique still needs to be proven for other anxiety disorders.

Table 7: Summary of the recommendations regarding the efficacy of rTMS in the most important clinical psychiatric indications

Major Depression	Clearly demonstrable antidepressant effect of high-frequency rTMS of the left dorsolateral prefrontal cortex or low-frequency rTMS of the right dorsolateral prefrontal cortex (**level A)**.
	Possibly no difference between left and right stimulation and no indication for bilateral dorsolateral prefrontal stimulation (**level C**).
Anxiety disorders	rTMS of the dorsolateral prefrontal cortex is possibly effective for post-traumatic stress disorder (**level C**).
	Most probably no effect of low-frequency rTMS of the dorsolateral prefrontal cortex for obsessive-compulsive disorder (**level D**).
Schizophrenia	Possible effect of low-frequency rTMS of the left temporoparietal cortex for auditory hallucinations in schizophrenia (**level C)**
	Level C recommendation for rTMS to treat negative symptoms of schizophrenia

2.3 rTMS in the treatment of neurological disorders

2.3.1 Stroke

Introduction

Stroke (cerebrovascular accident or CVA) is characterized by the loss of brain functions as a result of a disturbance in the oxygen supply due to an interference in cerebral blood flow.
Much of the spontaneous recovery from stroke after the acute phase involves plastic changes in the brain. The task for rehabilitation after stroke is to find ways to facilitate plasticity so that the changes occur more rapidly and more completely. CVA deficits can be divided in 3 broad clinical classifications: motor deficit, aphasia and hemineglect.
When given in form of pulse trains rTMS can be used to modulate cortical activity by either up-regulating or down-regulating cortical excitability depending on rTMS parameters used. Single- or repetitive-pulse stimulation of the brain causes the spinal cord and peripheral muscles to produce neuroelectrical signals known as motor evoked potentials (MEPs).

Clinical application used for post-stroke motor rehabilitation

rTMS can be used to modulate cortical activity by either up-regulating or down-regulating cortical excitability depending on rTMS parameters used. Normally the motor cortices in the left and right hemispheres of the human brain are strongly interconnected, with each side naturally inhibiting the activity of the other side achieving a natural balance. If one side is lesioned as in stroke, however, its activation is decreased and its inhibition to the other side is reduced, leading to increased activation in the non-lesioned side. Additionally, the non-lesioned side still provides inhibitory signals to the lesioned side, even more than in the prior healthy balance situation. This mismatch leads to a condition where the lesioned hemisphere cannot easily deliver action potentials to the lower motor neuron and the corresponding muscles. As result, the ability to participate in motor training which is necessary for recovery of function is severely challenged.

Thus, two potential roles have been described for rTMS in stroke recovery:

(1) excite the lesioned side (using for example 10 Hz rTMS);
(2) inhibit, i.e., down-regulate the non-lesioned side (using for example low frequent 1 Hz rTMS).

Excitatory stimulation of the lesioned side (high frequent)

Since much of good recovery depends on plasticity in the lesioned hemisphere, one therapeutic approach is to try to increase brain plasticity in the lesioned region with brain stimulation. In one study (class II), either rTMS or sham stimulation was given over the ipsilesional motor cortex daily for 10 days to two randomly assigned groups of 26 patients with acute ischemic stroke (Khedr et al., 2005). Disability scales measured before rTMS, at the end of the last rTMS session, and 10 days later showed that real rTMS improved patients' scores on various functional scales more than sham. In a cross-over, single blind, sham controlled study (class III), 15 patients with chronic (at least more than 6 months after stroke occurred) hemiparetic stroke practiced a complex, sequential finger motor task using their paretic fingers either after 10Hz or sham rTMS over the ipsilesional primary motor cortex (M1) (Kim et al., 2006). The basic hypothesis of this study was that focal 10Hz rTMS to the motor cortex of the affected hemisphere in conjunction with motor practice intervention paradigm would enhance the corticomotor excitability, which would improve the motor performance in chronic stroke patients. As anticipated, high-frequency rTMS produced a larger increase in corticospinal excitability than the sham stimulation. Moreover, this corticomotor excitability change was associated with enhanced motor skill acquisition. These findings are consistent with previous studies, which reported an enhancement of the symptoms in stroke patients (Hummel et al., 2005; Uy et al.,2003).

Both the changes in the behavior and corticomotor excitability before and after the intervention were examined by measuring the movement accuracy, the movement time, and the MEP amplitude rTMS resulted in a significantly larger increase in the MEP amplitude than the sham rTMS, and the plastic change was positively associated with an enhanced motor performance accuracy (Kim et al., 2006).
Another study by Emara et al. (2010) (Class II) with 40 patients (20 sham exposed included) suffering from chronic stroke symptoms, applying a 5Hz ipsilesional motor cortex stimulation showed a statiscal significant improvement of manual moto abilities and functional status lasting at least 12 weeks.

Inhibitory stimulation of the non-lesioned side
rTMS can be used to deliver a low frequency, for example, 1Hz rTMS to down-regulate the non-lesioned hemisphere with the goal of improving response to motor training by reducing interhemispheric inhibition and potentially facilitating activity in the lesioned hemisphere. This approach to brain stimulation targets the contralesional side of the CVA. The contralesional M1 inhibits the ipsilesional M1 via transcallosal inhibition. One study of 20 patients using sham control tested whether a decreased excitability of the contralesional M1 induced by 1 Hz rTMS could cause improved motor performance of the affected hand in stroke patients by decreasing the transcallosal inhibition (Takeuchi et al., 2005). This study reported for the first time that a noninvasive cortical stimulation using rTMS over contralesional M1 can reduce the transcallosal inhibition and improve the motor function of the affected hand of stroke patients.
When compared with sham stimulation, rTMS reduced the amplitude of motor-evoked potentials in contralesional M1 and the transcallosal inhibition duration, and rTMS immediately induced an improvement in pinch acceleration of the affected hand, although a plateau in motor performance had been reached by the previous motor training. This improvement in motor function after rTMS was significantly correlated with a reduced transcallosal inhibition duration. Other studies showed similar results (Mansur et al., 2005).
The available literature that includes data of approximately 300 patients establishes the capability of low-frequency 1 Hz rTMS delivery to the contralesional motor cortex to improve upper limb motor recovery in patients with stroke (cfr. table 8).

Table 8: Published studies evaluating effects of contralesional (non-lesioned) 1Hz rTMS on motor function in post-acute patients suffering from stroke

Study	Patients (N)	rTMS protocol	Outcome measures	Results	Class evidence
Fregni et al., 2006	10 rTMS, 5 sham	1Hz (100%) 5 daily sessions 1200 pulses/train	Daily pre- and post-rTMS and on day 14: 4 motor function tests. Motor threshold (MT) on day 5.	3 motor function tests improved until day 14, 4th until d5. MT decreased in affected, increased in unaffected hemisphere. Sham no effect.	III
Takeuchi et al., 2005	10 rTMS, 10 sham	1Hz (90%), 1 25min session 1500 pulses	Immediately and 30min post-rTMS administration: pinch force, acceleration, motor evoked potential (MEP) amplitude and TCI	Acceleration and MEP amplitude improved, TCI decreased in rTMS immediately post-rTMS, changes not seen at 30min. Sham no effect.	III
Mansur et al., 2005	10 patients Each received rTMS to motor cortex, rTMS to pre-motor cortex, sham to motor cortex	1Hz(100%) The 3 different sessions 1h apart. 600 pulses each	Baseline and after each rTMS. 4 motor function tests	3 of 4 tests improved after rTMS delivered to motor cortex, 1 had positive trend. Sham no effect.	III
Kirton et al., 2008	10 (pediatric) 5 rTMS, 5 sham	1Hz (100%) 1200 pulses once a day 8 days	Baseline, d5, d10, d17: upper extremity function, grip strength, peg board, finger tapping, in-hand manipulation	Grip strength improved D10 and D17 UEF improvement better with rTMS than sham D10, not D17	II
Khedr et al., 2009	36 (12 each in rTMS 1Hz, 3Hz and Sham) 7-20 days post stroke	5 daily sessions 1Hz(100%) 900 pulses; 3Hz(130%) 900 pulses	Hand Grip, Finger tapping and Peg board NIHSS and Barthel Index Baseline, 2 days 5 days 1 mo, 2 mo, 3 mo.	After 3 months, both TMS groups superior to Sham. 1Hz group superior to 3Hz group	II
Theilig S, et al., 2011	24 Active 12 Sham 12 Both groups received also EMG-triggered functional neuromuscular stimulation	1Hz, 100% MT, 900 pulses to motor cortex. 10 daily sessions during 2 weeks.	Motor function and spasticity measured at baseline and after 2 weeks of therapy. Wolf Motor Function Test and Tardieu scale for both hands. TMS elicited MEP size from first dorsal interosseus muscle.	Wolf Motor Function test and Tardieu scale improved in both rTMS and sham groups. No significant difference between active rTMS and sham	III.
Liepert J, et al., 2007	12 Active and sham rTMS, single session crossover	1Hz 90% MT, 1200 pulses to motor cortex	Grip strength Nine hole peg test before and after each rTMS session	Nine hole peg test results improved by active but not sham rTMS. No effect on grip strength.	III
Takeuchi N, et al., 2008 (a)	20 10 active rTMS 10 sham	1Hz, 90%MT 1500 pulses	Pinch force and acceleration, pre and immediately post-rTMs, after 7 days.	Pinch force and acceleration improved after rTMS. Effect lasted for 1 week. Sham no effect.	III

Pomeroy et al., 2007	27	1Hz, 120% MT, 200 pulses, 8 sessions		No effect on clinical motor parameters	II
Emara et al., 2010	40	1Hz, 110-120%, MT, 150 pulses, 10 sessions		Augmentation of manual dexterity	I
Theilig et al., (2011)	24	1Hz, 100% RMT		Similar improvement of motor performance with active and sham rTMS followed by functional electrical stimulation	III
Avenanti et al., (2012)	30	1Hz, 90% RMT		Improvement in manual dexterity (9HPT, JTT, grip force); rebalance of interhemispheric excitability; clinical and neurophysiological	III
Etoh et al., (2013)	18	1Hz, 90% RMT		Improvement in motor performance (ARAT); no change in spasticity	III

Meta-analysis and final conclusion

A meta-analysis of effects of rTMS on motor function in patients with stroke has been published a few years ago (Hsu et al., 2012). The goal of the analysis was to evaluate the effects of rTMS on upper limb motor recovery by systematically reviewing available data. In addition, as a secondary goal the analysis aimed at evaluating whether low frequency rTMS targeting the healthy hemisphere or high frequency rTMS targeting the lesioned hemisphere would have greater effects on motor function. The authors searched for randomized controlled trials starting from January 1990 in PubMed, Medline, Cochrane, and CINAHL using the following key words: stroke, cerebrovascular accident, and repetitive transcranial magnetic stimulation. The mean effect size and a 95% CI were estimated for the motor outcome using fixed and random effect models. The analysis included 18 randomized controlled trials in a total of 392 patients.

A positive significant effect size of 0.55 was found for motor outcome (95% CI, 0.37–0.72). Further subgroup analyses demonstrated more prominent effects for subcortical stroke (mean effect size, 0.73; 95% CI, 0.44–1.02) or studies applying low-frequency (1Hz) rTMS (mean effect size, 0.69; 95% CI, 0.42–0.95).

This meta-analysis concluded that rTMS has a positive effect on motor recovery in patients with stroke, especially for those with subcortical stroke. Low-frequency rTMS over the unaffected hemisphere may be more beneficial than high-frequency rTMS over the affected hemisphere as the effect size of low-frequency rTMS was larger.

Some studies have reported that bilateral neuromodulation can more effectively facilitate neural plasticity and induce motor recovery after stroke (Takeuchi et al., 2012). The clinical efficacy of inhibitory (1Hz) rTMS targeting the healthy hemisphere maybe superior to that of high-frequency (10Hz) rTMS of the lesioned hemisphere, although there is evidence for both approaches and choice of implementation of which specific intervention should be considered in the context of the clinical situation of the patient.

Based on the literature review rTMS use in stroke rehabilitation using parameters consistent with the safety guidelines is safe both in general and as complementary therapy (Takeuchi et al., 2012). These recommendations are conform the guidelines for rTMS in stroke (Lefaucheur et al., 2014), and with recent meta-analyses (e.g. Dionísio et al., in press).

In summary, excitability-increasing HF rTMS of ipsilesional M1 in post-acute and chronic motor stroke (level C) or excitability-decreasing LF rTMS of contra-lesional M1 in chronic motor stroke (level B) is likely to improve motor abilities in stroke patients.

However, the therapeutic value of either modality of stimulation remains to be determined with respect to the phase of stroke recovery (acute or sub-acute vs. chronic) and that statistical group effects may not reflect actual clinical benefit in daily practice.

2.3.2 rTMS in Parkinson's disease

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder with a world-wide prevalence of approximately 10 million people. Projecting on current demographic changes, estimated prevalence of PD is expected to double by 2050 (Bach et al., 2011). It is estimated that Parkinson's disease affects approximately 30.000 or 1/400 people in Belgium.

As such, PD remains an important public health problem due to the chronic and progressive nature of the disease for which there is no cure at present (Fox et al., 2011, Seppi et al., 2011).

In PD large numbers of dopaminergic neurons located within basal ganglia circuitry degenerate. Evidence suggests that symptoms in PD are related to a larger pathological process. Clinical Parkinsonism can be responsive to pharmacological therapies other than dopaminergic agents such as serotonergic and cholinergic drugs. As such, the neuropathology of PD also involves non-dopaminergic systems or cortical structures of the nervous system not directly involved in motor control. This results in clinical motor symptomatology including the hallmark triad: bradykinesia, tremor, rigidity, as well as non-motor symptoms (NMS). NMS may antedate motor symptoms and affect the majority -if not all- of PD patients in time. Moreover, with PD progression, NMS can be more disabling than the motor symptoms (Chaudhuri et al., 2006). NMS in PD include cognitive changes, emotional dysregulation, anxiety, apathy, depression, and sensory symptoms such as pain.
Among these non-motor features of PD, depression is common with widely varying prevalence rates. In Belgium, the PARKIDEP study group analyzed 1 086 patients with idiopathic Parkinson's disease. Based on the Mini-International Neuropsychiatric Interview (MINI), 15.6% of the patients presented with a current major depressive episode. In this study population, 30% of all patients had a history of mood disorders and 46% received either an anxiolytic, antidepressant or an atypical neuroleptic medication either alone or in combination (Vanderheyden et al., 2010).

Of importance is that it is not uncommon for PD patients with depression to be resistant to pharmacological treatment. Depression in PD may be only partially a reactive process and there is evidence that in addition it may be related to the neurodegenerative process of PD itself (Lieberman et al., 2006). Thus, PD with depression remains a major public health concern.

Moreover, virtually all persons with Parkinson's will develop motor complications under dopaminergic substitution therapy over time. These motor complications comprise wearing off, on-off phenomenon, freezing of gait and dyskinesia. Since no cure for the disease exists clinically managing Parkinson's disease remains a challenge.

Prior clinical trials of rTMS in PD

Among studies that have applied rTMS in PD patients with clinical outcomes, the factors under which rTMS is applied vary widely across 3 rTMS factors: site of stimulation, frequencies tested, and overall treatment durations. While treatment durations vary between studies, both single session and multisession studies have suggested benefit across a range of cortical sites with most multisession studies following a model of daily sessions over 7-14 days. Study designs, patient populations, duration of follow-up, and outcome measures are highly variable.

For clinical outcome measures, all but one study (Mally et al., 2004) used the unified Parkinson's Disease Rating Scale (UPDRS) as clinical outcome measures. For particular symptoms, additional rating scales for depression (Dragasevic et al., 2002; Okabe et al., 2003; Fregni et al., 2004; Epstein et al., 2007) or dyskinesias (Brusa et al., 2006) were employed. Many early studies were not placebo- or sham-controlled. Three meta-analyses reveal an overall beneficial effect of rTMS, including a sub analysis restricted to sham-controlled studies (Fregni et al., 2005; Elahi et al., 2009; Chung et al., 2016).

Different brain sites of stimulations can be targeted as there are: prefrontal cortex, primary motor cortex and supplementary motor areas. The efficacy of rTMS regarding these stimulation sites will be analyzed in next section.

Prefrontal cortex stimulation in PD

The DLPFC is a key cortical target for the prefrontal cortical-subcortical loop, a circuit that is involved in mood regulation, attention and working memory. A majority of studies applying rTMS as treatment for depression have employed high-frequencies to left DLPFC with focal figure-8 coils. All DLPFC rTMS studies have been multisession studies and several have focused on depressed PD patients. Some early DLPFC studies also used circular coils centered over prefrontal regions (Dragasevic et al., 2002) using nonfocal coils with very low frequencies (0.2 Hz) which, in normal control subjects, do not produce long-lasting excitability change.

In PD, Fregni et al., (2004) using a 15Hz rTMS over the DLPFC with and without placebo medication (SSRI fluoxetine, antidepressant) in a 10-day sham-rTMS intervention study showed efficacy of rTMS on depression rating scales which were equivalent to fluoxetine plus sham rTMS persisting over 10 weeks. Imaging studies using fluoxetine and rTMS suggest a normalization or hypoacitivty of the DLPFC in depressed PD patients (Fregni et al., 2006; Cardoso et al., 2008). Taken as a whole, 2 convincing Class II studies (one of which was divided into several satellite Class III studies by the same group) justify a Level B recommendation (''probable efficacy'') for the use of HF rTMS of the left DLPFC in the treatment of depressive symptoms associated with PD.

Motor cortex stimulation in PD

The primary motor cortex (M1) is a common site for cortical neuromodulation to facilitate deficient thalamo-cortical drive. M1 is often used as the cortical target for the motor cortical-subcortical loop. In the pathophysiology of PD the standard basal ganglia circuit model implicates impaired basal ganglia-thalamo-cortical drive as a cause for motor PD symptoms.
The first encouraging report of rTMS in PD patients used subthreshold (low intensity) 5 Hz rTMS over M1 and found improvement in reaction time and pegboard task performance (Pascual-Leone et al., 1994).
A meta-analysis (Fregni, Simon, Wu, Pascual-Leone, 2005) and a systematic review of the literature (Wu et al., 2008) demonstrate the potential for clinically significant motor benefits from rTMS in PD. A separate meta-analysis (Elahi et al., 2009) reached a similar conclusion that high frequency rTMS is effective in improving motor signs in PD whereas low frequency rTMS is not. These results support the hypothesis that HF rTMS of the primary motor cortex (M1) can yield clinically meaningful improvements in the motor symptoms of patients with PD.

The mean magnitude of benefit in these studies was nearly 6 points on the UPDRS Part III, representing an improvement of more than 20%, with even greater improvements seen in the subset of studies that utilized multiple rTMS sessions. However, most of these studies involved relatively few patients and varied greatly in terms of rTMS dosing regimens, outcome measures, inclusion/exclusion criteria, use of sham-TMS, and rigorousness in monitoring safety and tolerability.

Additional open-label rTMS treatments (daily sessions for 3 days) at monthly intervals appeared to sustain the benefits from previous rTMS treatments (Wu et al., 2008).

Combined motor and premotor
Due to the use of several cortical targets at the same time, results of such paradigms are difficult to interpret and are for that reason not further treated in this text.

Supplementary motor area
To date, most studies have targeted the primary motor cortex (M1) or prefrontal cortex. In contrast, the supplementary motor area (SMA) was used less, even though some evidence indicates the involvement of the SMA in PD. Hamada et al. (2008, 2009) demonstrated the efficacy of 5Hz rTMS at high intensity i.e. 110% of the active motor threshold, once a week during eight weeks over the SMA in PD. A randomized, double-blind, sham-controlled, multicenter study with a parallel design, examined the efficacy of a different frequency stimulation over the SMA (Shirota et al., 2013). The effects were monitored up to 20 weeks. Subjects were assigned to 1 of 3 arms of the study: low-frequency (1Hz) rTMS, high frequency (10Hz) rTMS, and realistic sham stimulation. The primary end point was the score change of the Unified Parkinson's Disease Rating Scale part III (motor) from the baseline. Several nonmotor symptom scales such as the Hamilton Rating Scale for Depression, apathy score, and nonmotor symptoms questionnaire were defined as secondary end points. The conclusion was that 1Hz rTMS over the SMA was effective for motor but not nonmotor symptoms in PD providing class I evidence. As this study has still to be independently replicated, no recommendation regarding stimulation of the SMA can be issued until present.

Treatment of PD complications
Dyskinesia is a motor complication of long term pharmacological dopaminergic treatment. Over activation in the motor cortex (M1) is reported in advanced patients (Haslinger et al., 2001, Sabatini et al., 2000). For PD dyskinisa rTMS of ≤ 1Hz over the M1 has been proposed. Low-frequency rTMS (≤ 1Hz) has been reported to result in a decrease of cortical excitability (Chen et al., 1997) and improvement in dyskinesia (Koch et al., 2005). In a placebo controlled, single blinded cross-over study on 10 PD patients with prominent dyskinesias using low frequency (1Hz) over the M1, a small but significant reduction in dyskinesia was found following real rTMS but not placebo (Filipovic et al., 2009).

Non-motor symptoms in PD
No significant effects on any non-motor symptoms were reported by stimulating the SMA (Shirotata et al., 2013).

Conclusion
rTMS could become an important adjuvant therapy in PD. While rTMS may not replace pharmacologic therapy or deep brain stimulation surgery it has the potential to provide a safe and non-invasive additional treatment to PD motor symptoms. This especially in the moderate-to-advanced patients, with complications, in those whose symptoms are insufficiently controlled by available medications, or those with concomitant depression who remain resistant to first-line antidepressants. Recommendations made for the use of rTMS in PD are summarized in Table 9. Probable (level B) here in clinical terms indicates that PD patients with comorbid depression are likely to benefit from rTMS treatment, but the outcome on motor symptoms is less univocal to be successful (level C).
Prospective studies are needed to determine the potential clinical benefits of rTMS specifically in PD and depression. Today there is not enough published scientific evidence in favour of the therapeutic use of rTMS in the stimulation of an isolated primary target.

Table 9: Recommendation regarding the use of rTMS in the treatment of Parkinson's disease

Probable antidepressant effect of high-frequency rTMS of the left dorsolateral prefrontal cortex in Parkinson's disease **(level B)**
Possible antiparkinsonian effect (motor symptoms) of high-frequency rTMS of the primary motor cortex stimulation (M1) **(level C)**

2.3.3 The use of rTMS in the treatment of severe neuropathic pain

Severe neuropathic pain is a debilitating chronic pain caused by damage to the peripheral or central nervous system. It affects some 8% of the general population and occurs in various pathologies after a destructive lesion or dysfunction of the peripheral or central sensory pathways (amputation, nerve or plexus avulsion, stroke, etc.) (Zimmermann et al., 2001). This type of pain can be difficult to treat because traditional painkillers usually have little effect. The treatment is based primarily on the use of other types of medication, such as some antidepressant medication or anti-epileptic drugs with potentially serious side effects (Schwartzman et al., 2001, Finnerup et al., 2007). It follows that the constancy and intensity of neuropathic pain and the side effects of the medication affect the quality of life of the patients. Many of them find it difficult to perform their daily activities, with significant psychosocial consequences (depression, loss of employment, social withdrawal,...) (Jensen et al., 2007).

The cause of severe neuropathic pain is poorly understood but is probably related to the compensatory plasticity mechanisms that disturb the balance between excitatory and inhibitory activity in the different nerve structures.

In some patients, the pain does not respond to pharmacotherapy of any kind. In these cases, the only potential long-term therapeutic alternative is motor cortical electrical stimulation (MCES), which involves the surgical implantation of epidural electrodes. MCES has significant analgesic efficacy in over 50% of patients (Garcia-Larrea et al., 2007).

Several studies also suggest that repetitive transcranial magnetic stimulation of the primary motor cortex has a transient analgesic effect similar to MCES and that a positive response to rTMS is predictive of a good response to MCES (Lefaucheur et al., 2006). A meta-analysis of five prospective studies (class III) involving a total of 149 patients shows that rTMS of the primary motor cortex provides a significant percentage reduction in pain (using a visual analogue scale) compared to a placebo (sham stimulation) from 15 to 20% (average: 16.7 %) (Leung et al., 2009). The following effects on pain have been observed for different anatomical locations: the trigeminal nerve (28.8% reduction), supraspinal stroke (16.7%), spinal cord (14.7%), nerve root (10%), and peripheral nerve (1.5%). In addition, stimulation protocols using multiple sessions and low stimulation frequencies (1-10 Hz) seem to give better results than single sessions or sessions using higher stimulation frequencies (>10 Hz) (Leung et al., 2009). A former meta-analysis accordingly suggested that rTMS may have a possible analgesic effect on pain of central origin with low-frequency stimulation spread over several sessions seeming to give the best results. However, the five studies included in this meta-analysis involve small patient samples (12 to 60 patients) and use different methodologies. These methodological differences also underline the importance of class I prospective studies involving large patient populations in order to confirm the role of rTMS in this potentially promising clinical indication. Indeed, based on the recent review including larger patient samples Lefaucheur et al. (2014), concluded **a Level A recommendation** for neuropathic pain (target: M1 contralateral to pain side). Nevertheless, maintenance studies are needed to evaluate its effects on the long-term (Galhardoni et al., 2015). In other words patients with chronic pain most likely may benefit from rTMS treatment (level A).

2.3.4 The use of rTMS in the treatment of tinnitus

Tinnitus is a unilateral or bilateral auditory sensation (ringing, buzzing, hissing, whistling, pure tones) that is unrelated to any auditory stimulation external to the body. Tinnitus affects many people for short periods of time or more chronically.
Two forms can be distinguished: objective and subjective tinnitus (Jastreboff 1990, Møller 2007, KNO-vereniging 2016). In case of objective tinnitus the person hears a real sound that is produced within his or her own body, e.g. by the cardiovascular system. In the latter case - subjective tinnitus - there is a sound perception but no measureable sound. Subjective tinnitus is the most common form.
Five to 15% of the general population suffers from permanent tinnitus in a way that it disrupts daily activities like work and social life. In 1-3% of the general population (100.000 to 300.000 people in Belgium) tinnitus causes sleep or psychiatric disorders (Henry et al., 2005). However, precise prevalence data are lacking. A recent review of world wide data listed figures ranging from 5 to 40 % (McCormack et al 2016). Prevalence data are commonly obtained using questionnaires to assess self-reported tinnitus. The wide range is partly explained by differences in the questions used and reflects differences in tinnitus definitions. Even in reports based on the most common type of question ('tinnitus lasting for more than five minutes at a time') prevalence figures range from 10 to 30 %.
Most cases of permanent tinnitus are associated with hearing loss induced by auditory trauma (concert, nightclub, firecracker, loud noise, etc.) or develop as a corollary of the ageing process (Eggermont et al., 2004). However, tinnitus can also be associated with emotions, depression and burn-out (Langguth et al., 2013, Van de Heyning et al., 2015).
A Cochrane report concluded that there is little support for the use of rTMS in tinnitus patients (Meng et al 2011). Improvements on patients' quality of life and tinnitus loudness were observed, but are not very robust given the small size and methodological weaknesses of the studies.
Further, different studies (class III or IV) show that rTMS of the auditory cortex significantly reduces tinnitus severity in around 50% of patients (Theodoroff et al., 2013). It remains unclear why rTMS has a beneficial effect in only 50% of patients. Most studies involve small samples of patients (4 to 114 patients) and use different means to examine the effect of treatment (duration, scales, etc.) as well as different control conditions. These methodological differences probably account for the different results obtained on the effect of rTMS on tinnitus. The authors also underline the importance of well-conducted prospective studies that involve large patient populations in order to determine more accurately what the significance of rTMS could be in this apparently promising clinical indication.
Two types of stimulation protocols are usually proposed in the literature, a session of high-frequency rTMS (10 Hz, motor threshold, 30-200 stimuli), which induces a transient reduction or disappearance of the tinnitus (a few minutes to several days) in about 50% of patients (cfr. Table 1 from Theodoroff & Folmer Otology & Neurotology, 2013) or several sessions of low-frequency rTMS (1 Hz, 1200-2000 stimuli/ session, 1 session/day, 5-10 sessions), which induces a prolonged effect in the reduction of tinnitus severity (3-6 months) in 50 to 80% of patients (cfr. Table 2 from Theodoroff & Folmer Otology & Neurotology, 2013). Based on these data, several sessions of low-frequency rTMS unilaterally applied to temporal or temporoparietal cortical areas appear to lead to better clinical outcomes and are therefore to be preferred (Theodoroff et al., 2013). As the studies mentioned in Table 1 and Table 2 are classified as Class III and Class IV studies (Plewnia et al., 2007) we cannot recommend the general use of rTMS in the treatment of tinnitus. Therefore, the working group agrees in that prospect with a **level C recommendation**. This indicates that according to the current stage of rTMS treatment it remains unsure that all patients will benefit. This is in line with data mentioned in an earlier recommendation of the SHC on prevention, diagnosis and therapy of tinnitus (Superior Health Council, 2017, Report nr. 9332).

TABLE 1. *Early studies of repetitive transcranial magnetic stimulation for tinnitus used high stimulation rates but fewer pulses delivered during a single session*

Authors	No. of subjects	Control condition included	Frequency of stimulation	Stimulation intensity	No. of pulses	Tinnitus assessment method	Results
Plewnia et al. 2003 (48)	14	Yes: coil tilted away from the cranium	10 Hz	120% rMT	30	Patients rated relative change in tinnitus: 0 – none, 1 – slight, 2 – marked, 3 – strong, 4 – complete suppression	8 patients (58%) experienced tinnitus suppression (varied from slight to complete suppression)
De Ridder et al. 2005 (49)	114	Yes: after subjects had active TMS sessions, coil placement was changed	1, 3, 5, 10, and 20 Hz	90% rMT	200	Patients rated % of decrease in tinnitus. 0%–19%: no effect, 20%–79%: partial effect, 80%–100%: good effect	28 patients (25%) reported good effect; 32 patients (28%) reported partial suppression; and 54 patients (47%) reported no effect
Folmer et al. 2006 (50)	15	Yes: audio recording of active TMS played while inactive coil was in contact with scalp	10 Hz	100% rMT	150	Patients rated tinnitus loudness on a 1-to-10 scale	6 patients (40%) experienced tinnitus suppression (mean amount of reduction: 55%)
Fregni et al. 2006 (51)	7	Yes: cross-over study design	10 Hz	120% rMT	30	Used the same scale as Plewnia et al. (48)	3 patients (42%) experienced tinnitus suppression from ''marked'' to ''strong''

rMT indicates Resting motor threshold (this is the minimum amount of TMS power delivered to motor cortex that results in electromyographic activity in contralateral skeletal muscles).

TABLE 2. *Later studies of repetitive transcranial magnetic stimulation for tinnitus used lower stimulation rates, delivered greater numbers of pulses per session, and repeated the procedure during multiple sessions.*

Authors	No. of subjects	Control condition included	Frequency of stimulation	No. of pulses per session	No. of sessions	Tinnitus assessment method	Results
Kleinjung et al. 2005 (52)	14	Yes: crossover study design	1 Hz	2,000	5	Tinnitus Questionnaire (TQ—(58)	11 patients (79%) experienced reductions in TQ scores; range: 0.7–8.8 TQ points
Langguth et al. 2006 (53)	28	No	1 Hz	2,000	10	Tinnitus Questionnaire (TQ)	23 patients (82%) experienced reductions in TQ scores; average: 5–10 TQ points
Plewnia et al. 2007 (54)	6	Yes: crossover study design	1 Hz	1,800	10	Tinnitus questionnaire (TQ)	3 patients (50%) experienced reductions in TQ scores
Rossi et al. 2007 (55)	16	Yes: coil tilted away from the cranium; crossover study design	1 Hz	1,200	5	Patients rated tinnitus-related discomfort on a 0-to-100 scale	8 patients (50%) experienced tinnitus improvement (33% average improvement)
Smith et al. 2007 (56)	4	Yes: cross-over study design	1 Hz	1,800	5	Tinnitus Severity Index (59)	3 patients (75%) experienced reductions in TSI scores, from 10% to 19%
Khedr et al. 2008 (57)	66	Yes: coil placed over occipital cortex	1, 10, and 25 Hz	1,500	10	Tinnitus Handicap Inventory (THI—(60)	38 patients (58%) experienced reductions in THI scores, from 21%–100%

In general, two methods have been proposed to identify the optimal cortical target for this type of stimulation without one method having been shown to be superior to another yet. On the one hand a series of approaches suggest that rTMS should be guided by neuronavigation by integrating data from functional neuroimaging (positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG)) that either identify the primary or secondary auditory cortex or the auditory area of the brain with neural hyperactivity (Kleinjung et al., 2008, Langguth et al., 2008). The other approach is to guide rTMS on the basis of the anatomical landmarks for positioning electro-encephalography electrodes (10-20 EEG international system) (Londero et al., 2006).
Further research is needed to confirm earlier results of this possibly effective technique in the treatment of tinnitus. Because of the high variability of studies design and reported outcomes replication studies with a large number of patients and long-term follow-up is needed before further conclusions can be drawn (Soleimani et al., 2016).

2.3.5 The use of rTMS in the treatment of refractory epilepsy

Epilepsy is a chronic disorder characterized by recurrent seizures, which are defined as clinical events resulting from excessive and transient activity of a group of neurons. There are various causes of epilepsy. Its prevalence in the general population is 0.8% and its incidence is about 50 per 100.000 population per year. The treatment of epilepsy is primarily based on anti-epileptic drugs (Duncan et al., 2007). However, a surgical option may be considered when the following criteria are met:

- persistent seizures despite well-conducted pharmacotherapy that impede the patient's lifestyle, cognitive function or psychomotor development in the case of children;
- the cause of the epilepsy is believed to be symptomatic, i.e. due to a structural brain lesion.

These criteria are met in around 15% of patients.

During the past decade, some studies have investigated the effect of low-frequency repetitive transcranial magnetic stimulation on epileptic activity and the frequency of seizures. The theoretical basis on which these studies are grounded is related to the putative inhibitory effect of this type of stimulation on neuronal activity, which is therefore believed to reduce or stop excessive neuronal activity in the epileptic focus. A (class III) prospective, randomized, double-blind study using placebo stimulation ("sham stimulation") involving 21 patients with refractory focal epilepsy associated with malformations of cortical development shows that rTMS (1 Hz, 70% of the maximum stimulation intensity, 20-minute stimulation/session, 1 session/day for 5 days) significantly reduces the number of seizures compared with placebo stimulation and that this anti-epileptic effect lasts for at least two months (Fregni et al., 2006). In addition, rTMS induced a significant decrease in the number of interictal epileptic discharges immediately after and one month after rTMS. Cognitive assessments have also suggested that cognitive function improves following this treatment. Another (class III) prospective, randomized, single-blind study involving 64 patients with refractory focal epilepsy compares the effect of low-frequency rTMS (0.5Hz, 500 stimuli/session, 3 sessions at 10-minute intervals/day, 2 weeks of treatment) depending on the intensity of stimulation (90% versus 20% of the motor threshold (Sun et al., 2012). This study shows that high-intensity rTMS (90% of the motor threshold) resulted in a significant drop in the frequency of seizures and interictal epileptic activity for up to 10 weeks after the rTMS treatment was initiated and that low-intensity rTMS (20% of the motor threshold) had no effect.
Other (class III) studies using protocols from the different methodologies have shown no effect of rTMS on the frequency of epileptic seizures (Jo et al., 2007, Cantello et al., 2007).
This suggests that other class I studies involving larger numbers of patients are needed to determine more accurately what the significance of rTMS could be in the treatment plan for refractory focal epilepsy. Therefore, based on the actual state of scientific knowledge the working group cannot yet recommend in a general way the clinical use of rTMS in the treatment of refractory epilepsy. Though, this therapeutic approach may be an attractive alternative to epilepsy surgery in some patients (**level C recommendation**) determined case by case by the treating medical specialist. The evidence for efficacy of rTMS for seizure reduction is still scarce despite that rTMS seems effective at reducing epileptiform discharges (Chen et al., 2016). Again, level C indicates that it is unsure that the majority of patients will benefit from rTMS treatment.
Interestingly, studies involving epileptic patients show that the side effects of this kind of treatment are generally mild and occur in less than 20% of cases (mainly headaches in about 10% of the patients). In a literature review on safety and tolerability of rTMS in patients with epilepsy, Bae et al state that rTMS rarely induces epileptic seizures (4 out of 280 patients or 1.4%) and does not cause status epilepticus (Bae et al., 2007).

3 TMS in movement and cognitive neuroscience research

TMS is now a well-established investigative tool in the cognitive neurosciences to study perception, attention, action control, learning, language, and awareness, among many other psychological processes or functions. TMS's popularity is due to the unique space it occupies in the neuroscience methods. Unlike many other techniques, it can provide excellent spatial and temporal resolution, allowing researchers to determine *which* brain regions support specific human behaviours, and *when* they do so. However, it is not just the spatial and temporal selectivity that make TMS a useful experimental approach; it is also its ability to transiently influence brain functions (Walsh & Conway, 2000). Therefore, TMS also allows causal inferences (i.e. it has functional resolution; Walsh & Conway, 2000), unlike popular neuroimaging methods such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI).

In this section, we will briefly review the two main research applications of TMS, namely (1) TMS to probe the current state of neural systems and (2) TMS to determine causal relationships between brain and behaviour.

3.1 TMS to probe the current state of neural (motor) systems

Flexible and goal-directed human behaviour depends on an interplay between multiple basic cognitive processes. A difficult challenge in humans is to isolate and characterize these.
In the action-control domain, major progress has been made thanks to TMS. When a brief single pulse is applied to the primary motor cortex, TMS can cause minor contralateral muscular responses (MEPs). These responses can be quantified using surface electromyography and provide a measure of corticospinal excitability (Hallet, 2007). MEPs are useful to examine influences on the (pre-)motor cortex because they can be measured before a stimulus appears and provide an opportunity to examine how actions unfold with millisecond precision (Bestmann & Duque, 2016).

Single-pulse protocols can be extended by providing a conditioning pulse first, and examine how it modulates the effects of the second TMS pulse over motor cortex. Such paired-pulse TMS protocols can reveal cortical interactions and the relative contribution of excitatory and inhibitory neural circuitries (some other popular neuroscience methods cannot do). For example, TMS has shown how efficient and controlled human behaviour involves preparation of a select number of action options, combined with an inhibitory impulse control mechanism to prevent their premature execution (Duque et al., 2017).

Single- and paired pulse TMS over motor cortex within the safety limits determined by the Safety of TMS Consensus Group (Rossi et al., 2009) is considered to be safe (Di Iorio and Rossini, 2017, p.68). Therefore, these protocols are currently being used in psychology, movement science and neuroscience labs across the world without the involvement of physicians or health-care professionals to provide unique insights in action control, and human behaviour more generally.

3.2 TMS to determine causal relationships between brain and behaviour

TMS can also be used to temporarily alter the function of neurons in the underlying small cortical brain territory. This can reveal whether and when the cognitive process carried out by that region is crucial for performance. A distinction can be made between single, twin-coil, and repetitive protocols.

In single-coil protocols, the coil is placed over a cortical region close to the scalp. Researchers then examine how the delivery of a pulse at a certain point in time influences behaviour or underlying neural processing (when combined with e.g. EEG). This can reveal *when* a brain region or pathway is causally involved in various aspects of human behaviour. For example, TMS revealed how a region in the parietal cortex mediates spatial orienting during two distinct time periods after the onset of a behaviourally relevant event, suggesting two critical neural pathways for visual attention (Chambers et al., 2004).

In case of twin-coil protocols, a “conditioning” pulse over one area is delivered to investigate whether and how it modulates the effects of a subsequent TMS pulse to another area. Such twin-coil designs can reveal cortico-cortical and cortico-spinal interactions (i.e. functional networks of brain regions).The protocols are relevant to study interactions between brain regions (Fujiyama et al., 2016).

As noted above, rTMS can be further subdivided in conventional (a train of pulses at a certain frequency) and patterned (high bursts of pulses with short intervals without stimulation) protocols.

Unlike single- and twin-coil protocols, rTMS is usually delivered before behavioural or neural measures are obtained. Therefore, these protocols lack temporal precision but may be more robust (Derosière et al., 2017).

3.3 Safety of TMS protocols falling within the international safety guidelines

It is generally agreed that at low stimulation intensity, delivering one (single-pulse), two or more (rTMS) pulses alters the signal-to-noise ratio in the underlying brain region (Walsh & Conway, 2000). At higher intensities, TMS may also have transient inhibitory or facilitatory effects on neural functioning (depending on the frequency and protocol). In the case of single-pulse designs, the neural effects are very short-lived (typically milliseconds to a second). In the case of rTMS, effects can last longer (typically seconds to minutes) (Harris et al., 2008).

As noted in the recent review by Di Iorio and Rossini (Di Iorio and Rossini, 2017), *"In almost three decades of TMS experiments and for hundreds of thousands examined subjects, only few cases of TMS-induced seizures have been reported, and the vast majority of seizures were induced during rTMS (Rossi et al. 2009). The risk to induce a seizure with single-pulse TMS is very low: it has been estimated that less than 5% of the known TMS-related seizures occurred during single-pulse TMS studies and always in subjects having epileptogenic brain lesions or under proactive medication (Groppa et al. 2012)."* This led them to conclude: *"Single- or paired-pulse TMS or conventional LF or HF rTMS (…) with parameters of stimulation within the 2009 safety limits" should be considered to be safe.*

In case of single-pulse, paired-pulse, and low frequency rTMS, this is not surprising. For example, in a study designed to uncover the mechanisms of TMS, it was found that adding visual noise to a stimulus presented on a computer screen had similar or even larger effects on human behaviour than the delivery of a TMS pulse (Harris et al., 2008). Similarly, actively executing a motor action in response to an external stimulus will have a much larger effect on cortical and electromyographic (EMG) activity than a single TMS pulse, and actively withholding an action typically produces a larger decrease in EMG activity than the delivery of a conditioning pulse in paired-pulse designs. In other words, the effects of single- and paired-pulse TMS are generally subtle (compared with normal patterns of neural activity or patterns of activity induced by other means).

Theoretically, the risk is higher for sustained high-frequency rTMS, patterned TMS, TMS using non-standard coils (e.g. H-coils to stimulate deeper brain areas), or other protocols that fall outside the safety limits (although it should be noted that even for such protocols, the number of adverse effects is still very low;). Nevertheless, it is important to distinguish between the different protocols when determining safety guidelines and terms of use.

3.4 Conclusions

TMS is a scientific device that allows researchers with various backgrounds to study human brain-behaviour relationships. It is generally considered to be safe, and has many advantages over other research methods. Unlike neuroimaging methods, it allows causal inferences. In theory, such inferences are also possible via lesion studies (i.e. the study of patients with specific brain lesions); however, the study of the abnormal brain is complicated by neural reorganisation and compensatory strategies. Therefore, in the last two decades, TMS work has provided unique and important insights in the normal functioning of the human brain.

4 Safety of TMS for patients and medical staff

Very few information is available about the effects of induced currents in the tissues not supposed to be excited. Rossi (Rossi et al., 2009) states that it is unclear whether the high intensity, pulsed stimulation of TMS has the same long-term effects of continuous, low-intensity, occupational exposure but that it is worth noting that chronic exposure to electro-magnetic fields appears safe at levels even greater than those possible with TMS. This statement is most probably true for the devices investigated by the author. Nevertheless, nothing prevents to find (r)TMS devices with higher excitation fields on the market.

It has to be pointed out that, at the European level, the CE marking process for medical devices under the scope of the 93/42/EEC directive (MDD) doesn't require any safety assessment concerning the induction of currents and voltages in the body. No harmonised standard provide any assessment criteria for such phenomena. They do exist for microwave radiations but not for the lowest part of the radiofrequency spectrum which is used with TMS. The consequence is that a manufacturer of (r)TMS devices willing to work with a very high level induction field will encounter no legal barrier before placing his product on the European market. Hence particular attention should be considered by the Belgium Government in order to avoid on the Belgian market TMS devices with an excessive induction field.

On the other side, the practitioner should assess the compromise between the benefits of the treatment and the risk encountered with the induced currents. Due to the interaction of the induced voltages with the nervous system (working principle of TMS), the International Commission of non-Ionizing Radiation Protection or ICNIRP (2010) recommends to keep the induced electric field in the head and the body below 0.4 V/m around 1 kHz for the general public. Hence it should be recommended to the practitioners to avoid exceeding such a level in the tissues which are not supposed to be excited. The device documentation should provide information to the operator about this issue.

4.1 Exposure of patients

4.1.1 Contraindications and side-effects

Present recommendations concerning contraindications and safety issues are mostly based on the published guidelines by Rossi et al. (2009) and Lefaucheur et al. (2014).

As TMS is a neurostimulation and neuromodulation technique which can modulate cortical excitability, the use of TMS has therefore some safety and ethical concerns to take into account.

The only absolute contraindication to TMS/rTMS is the presence of metallic hardware in close contact to the discharging coil (such as cochlear implants, or an internal pulse generator (IPG) in case of deep brain stimulation for example or medication pumps). Under these circumstances there is a risk of inducing malfunctioning of such implanted devices. Nevertheless, based on *ex vivo* and *in vivo* studies, it appears that TMS can be safely applied to patients who have implanted stimulators of the central and peripheral nervous system when the TMS coil is not in close proximity to the internal pulse generator. However, it is not clear what constitutes a safe distance between the TMS coil and the implanted stimulator, and how coil shape and coil angulation influence this relation. Therefore, TMS should only be done in patients with implanted stimulators if there are medically-scientifically compelling reasons justifying it.

All the known side effects linked with the use of TMS are summarized in Table 1 taken from Rossi et al. (2009). TMS and rTMS can be considered as safe if published safety guidelines are closely followed. First guidelines were issued by Wassermann during an International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation in 1998. They were slightly adapted based on the current state of knowledge by Rossi et al. (2009).

Table 1

Potential side effects of TMS. Consensus has been reached for this table.

Side effect	Single-pulse TMS	Paired-pulse TMS	Low frequency rTMS	High frequency rTMS	Theta burst
Seizure induction	Rare	Not reported	Rare (usually protective effect)	Possible (1.4% crude risk estimate in epileptic patients; less than 1% in normals)	Possible (one seizure in a normal subject during cTBS) (see para 3.3.3)
Transient acute hypomania induction	No	No	Rare	Possible following left prefrontal stimulation	Not reported
Syncope	Possible as epiphenomenon (i.e., not related to direct brain effect)				Possible
Transient headache, local pain, neck pain, toothache, paresthesia	Possible	Likely possible, but not reported/addressed	Frequent (see para. 3.3)	Frequent (see para. 3.3)	Possible
Transient hearing changes	Possible	Likely possible, but not reported	Possible	Possible	Not reported
Transient cognitive/neuropsychologial changes	Not reported	No reported	Overall negligible (see Section 4.6)	Overall negligible (see Section 4.6)	Transient impairment of working memory
Burns from scalp electrodes	No	No	Not reported	Occasionally reported	Not reported, but likely possible
Induced currents in electrical circuits	Theoretically possible, but described malfunction only if TMS is delivered in close proximity with the electric device (pace-makers, brain stimulators, pumps, intracardiac lines, cochlear implants)				
Structural brain changes	Not reported	Nor reported	Inconsistent	Inconsistent	Not reported
Histotoxicity	No	No	Inconsistent	Inconsistent	Not reported
Other biological transient effects	Not reported	Not reported	Not reported	Transient hormone (TSH), and blood lactate levels changes	Not reported

Induction of seizures is the most severe acute adverse effect regarding (r)TMS. Several cases of accidental seizures (typically seizure duration < 1 minute) induced by rTMS have been reported to date, most of them in the early days prior to the definition of safety limits (Rossi et al., 2009). Considering the large number of subjects and patients who have undergone (r)TMS studies since the safety guidelines published in 1998 (Wassermann et al.) and the small number of seizures, we can assert that the risk of (r)TMS to induce seizures is very low. Most of the seizures reported in the literature occurred in patients taking epileptogenic medications or may represent non-epileptic events. It is important to note that no episode of status epilepticus following (r)TMS has been reported.
A review on the safety of rTMS in epilepsy (Bae et al., 2007) indicates a 1.4% crude per-subject risk to develop a seizure (4 out of 280 patients) and no cases of status epilepticus.
For patients with an additional risk of seizure (history of seizure, epileptogenic medication, brain disorders that modify cortical excitability, sleep deprivation, alcoholism), rigorous monitoring is still critical. In such instances, the involvement of a physician with expertise in the recognition and acute treatment of seizures is recommended.

Rossi et al. (2009) states that single-pulse TMS is in general well tolerated; patients describe the feeling during these sessions as painless. As some pain sensation is in fact the most reported side effect, (r)TMS can be painful. Bae et al. (2007) and Maizey et al. (2013) reported the absence of side effects in about 85% of cases. For the remaining 15% the main side effect was transient headache. In a review by Loo et al. (2008) about nearly 30% of patients experienced headache and nearly 40% complained about pain or discomfort. The intensity of pain experienced varies from subject to subject, depending on individual susceptibility, scalp location, coil design, intensity and frequency of stimulation.

Patients and subjects should be warned that (r)TMS may not be pleasant and may cause pain. In the majority of subjects/patients experiencing local pain during (r)TMS, the effect rapidly vanishes. Headache may occasionally persist, however, after TMS application; in this case, a common analgesic administered orally may be helpful. No migraine attacks have been described following (r)TMS, neither in people without a headache history nor in migraine patients who underwent rTMS applications as treatment (Brighina et al., 2004). It is further reported by Anderson et al. (2009) that the local painfulness usually declines over the first days of daily treatment. The cutaneous sensation could be caused by stimulation of the scalp muscles which is described as uncomfortable by some and as painful by others. It is not known until present what exactly causes the painfulness.

Drugs

Rossi et al. (2009) reports that intake of or withdrawal from certain central nervous system (CNS) active drugs lowers seizure threshold. The actual risk for seizure induction may depend on factors such as drug dose, speed of dose increase (or decrease), and combination with other CNS active drugs. The majority of reported rTMS-induced seizures have occurred in subjects/patients on drugs with seizure threshold lowering potential. Therefore, careful consideration of the benefit/risk ratio of (r)TMS should be performed before (r)TMS in participants who take epileptogenic drugs.

Pediatrics

Considering the absence of an appreciable volume of data on the potential for adverse effects with (r)TMS, children should not be used as subjects for rTMS without compelling clinical reasons, such as the treatment of refractory epilepsy or particular psychiatric conditions.

Pregnancy

Magnetic fields attenuate rapidly with distance, so it seems unlikely that the foetus might be directly affected by (r)TMS. Currently, there are anecdotal reports of pregnant women who underwent successful rTMS treatment for depression, and no side effects to the child were reported (Klirova et al., 2008). According to the actual state of the scientific research, there exists no consensus whether rTMS might have a detrimental effect on the foetus (for example epigenetic effects).Therefore, a conservative view of the use of (r)TMS in pregnancy might consider to balancing the risk/benefit ratio for each single case by the healthcare professional.

4.2 Exposure of operators

Rossi (Rossi et al., 2009) states that safety issues are rarely addressed for operators who are exposed to magnetic field several hours every day for years by performing TMS.

Only one study has been performed using the MagPro machine (Medtronic), MC-B70 butterfly coil, 5 Hz frequency, and stimulus intensity of 60–80% stimulator output (Karlström et al., 2006). In these conditions, worker's exposure limits for the magnetic field pulses (2013/35/EU directive) are transgressed at distances of about 0.7 m from the surface of the coil. This single observation makes further research necessary to confirm it and to determine the limiting distance to the coil according to the type of TMS machine, the type of coil, the frequency/intensity of stimulation and the total exposure time. Furthermore, directive 2013/35/EU states explicitly that the levels given as action values do not protect the operator against long term effects. Hence, the following consideration should be taken into account:

- the exposure levels of directive 2013/35/EU can be exceeded by some devices in case the worker is located very close to the device (less than 1 m),
- the present legislation doesn't ensure that the exposure level of the operators does not exceed the action values of 2013/35/EU directive,
- the levels given as action values in 2013/35/EU directive do not protect the operators against long term effects, if any,
- the exposure level should be assessed for each type of device.

5 Terms of use in clinical practice and research

The increasing use of (r)TMS makes it necessary to consider places where it can be carried out safely, taking into consideration both clinical needs and research.
The overall ethical principle – which is also mentioned in article 31/1 of the Law of May 10th, 2015 - stating that a health care professional or scientific researcher is only allowed to carry out those acts falling within the scope of his expertise has always to be taken into account as a golden standard in everyday (r)TMS practice.

5.1 Clinical applications

Based on literature review and expert opinion, the SHC agrees with the fact that a medical setting (hospital or appropriately equipped outpatient clinic) is needed for all clinical applications of (r)TMS (i.e. diagnostic or therapeutic procedures of neuromodulation). Out-patient (r)TMS treatments can be delivered outside the hospital. However, it is strongly advisable that in these settings and in other medical environments, appropriate life-support equipment and emergency medical facilities are available.

Based on the strict Belgian legislation, all medical applications of (r)TMS are to be considered as medical acts and therefore should be done by a physician, responsible for handling all adverse events and complications. Within the legal framework of the Law of May 10th, 2015 regarding the exercising of the health care professionals, competent health care staff, such as nurses, etc., can assist the physician.
Article 23 of the Law of May 10th, 2015 foresees the possibility to delegate particular tasks to other professionals, but this can only be done on the base of a Royal Decree. And up till now such a delegation regarding (r)TMS has not been allowed by any Royal Decree. Thus legally there are no arguments in favour of letting practice (r)TMS by other professionals than physicians, even in the framework of a medical research activity.

Theoretically, clinical psychologists could be legally competent within the scope of the Law of May 10th, 2015 to perform these applications of (r)TMS which fall into their field of application.

Indeed, from September 1st, 2016 on, clinical psychologists fall within the scope of the Law of May 10th, 2015 according to the Law of July 10th, 2016 amending the Law of April 4th, 2014 regulating the mental health professions and amending the Royal Decree nr. 78 of November 10th, 1967 concerning the exercising of health care professions coordinated May 10th, 2015.
As a matter of fact according to the Law of May 10th, 2015 (article 43) also physiotherapists may apply non-invasive physical stimuli like electromagnetic radiation in order to treat musculoskeletal, neurophysiological and psychomotor functional problems among others.
As a physiotherapist is not allowed to do this autonomously, it has always to take place in the framework of a referral by a physician, provided that (r)TMS falls within the field of application of physiotherapy.
Thus, theoretically and legally spoken, clinical psychologists and physiotherapists are allowed to practice (r)TMS as far as this act falls within their respective field of application. Indeed, the basic legal reference framework does exist, but there does not exist any official document stating the place that (r)TMS could occupy in it; nowhere is determined or described what is meant by an appropriate scientific clinically psychological or physiotherapeutical reference framework.
As this implementation framework does not exist until present the SHC proposes to reserve the clinical applications of (r)TMS only for medical specialists with a particular field of application related to scientifically indicated pathologies (i.e. psychiatrist, neurologist and specialist in physical medicine) who succeeded in an additional training regarding (r)TMS. Clinical psychologists and physiotherapists (under certain conditions) could be allowed once the respective implementation frameworks are filled in.
Therefore, the SHC wants to stress its concerns about the topical absence of any concrete and practical regulation or even guideline related to the place of (r)TMS practice in the application area of the clinical psychology and physiotherapy.
It is strongly advisable to consult the existing professional and scientific societies of psychiatrists, neurologists, clinical psychologists and physiotherapists in giving (r)TMS a place in today's health care and scientific research practice.
Furthermore, scientific publications in the domain must be followed in order to update the medical indications of rTMS use.

5.2 Research

The Belgian Act of May 7th, 2004 concerning experiments to the human person has to be applied when the purpose of the human-based (r)TMS research is the development of knowledge concerning health care (Article 2, 11°).

If (r)TMS is carried out with this goal, the obligation to submit the experiment to an ethics committee (EC) recognized by law (Article 2, 4°) is legally required. This committee is tasked with verifying whether the participants are well protected and not subjected to any risk, as well as whether all precautions have been taken and whether an insurance has been underwritten (Article 11 § 4). If this is not the case, those conducting the study are liable to prosecution (Article 33). The ethics committee has the obligation to thoroughly perform a risk assessment regarding the experiments proposed by researchers. A licensed physician who is intimately familiar with the study protocol, the risks of (r)TMS, the treatment of any of its possible complications and side effects, and the condition of any patients undergoing (r)TMS, should be involved in the design and conduct of study protocols.
In article 2, 17° of the Act of May 7th, 2004 regarding experiments to the human person a healthcare researcher is defined as: physician or other person exercising a profession like stipulated in the Law of May 10th, 2015 regarding the exercising of a profession in the health care and who is qualified to carry out an experiment. The researcher is responsible for the performing of the experiments on a certain location.

5.2.1. Experiments involving patients

A person carrying out (r)TMS in the framework of an experiment is legally authorized to do it only when he is authorized to do it within the Law of May 10th, 2015. As already mentioned, in the most strict interpretation of this law, only physicians are allowed to carry out (r)TMS since it is a medical act.
Since the exercising of a medical experiment is always linked with the Law of May 10th, 2015 regarding the exercising of a health care profession, the SHC proposes that the same health care professionals as for clinical applications should apply (r)TMS for experiments involving patients.
Be trained and/or already having experience in the field does not allow to perform (r)TMS experiments when the researcher does not comply with the conditions foreseen in the Law of May 10th, 2015.

Experiments involving patients should be conducted in a medical environment adapted to the conditions of the patients involved.

5.2.2. Experiments involving other subjects than patients

Considering the fact that there is on the international level more than sufficiently convincing scientific and practical evidence in daily worldwide (r)TMS practices to claim that some (r)TMS protocols can be used safely by professional users other than physicians (Harris et al., 2008) and considering the fact that there are internationally recognized safety guidelines (Rossi et al., 2009) (developed by world-leading experts, various stake holders, and public bodies) which, if adhered to, makes the (r)TMS protocol safe (Di Iorio et al., 2017), the SHC proposes that for experiments involving other subjects than patients a distinction should be made between two types of TMS.

First, single-pulse and paired-pulse TMS and rTMS at frequencies lower than or equal to 1 Hz or (r)TMS at higher frequencies for very short durations, with stimulation parameters that fall within the internationally recognized safety guidelines (i.e. conventional LF and HF rTMS with parameters of stimulation within the 2009 safety limits (Rossi et al., 2009)) on healthy volunteers - i.e. non patients – could be carried out by trained professionals other than physicians (e.g. biologists, engineers, technicians, movement scientists) in a non-medical setting under the responsibility of the principal investigator of the study[5]. It is not mandatory that the latter is a physician, but this person should be an expert in TMS with knowledge about principles, physiology and potential side effects.

Second, other (r)TMS protocols outside the 2009 safety limits require a medical setting and medical supervision. Appropriate emergency medical attention for possible (r)TMS complications should always be planned for.

Thus, regarding the safe use of (r)TMS by other professionals than physicians (insofar as this falls within the scope of their respective field of expertise), the specific combination of at least the following experimental parameters has to be evaluated referring to the internationally recognized safety guidelines (Rossi et al., 2009): frequency TMS, pulse train duration, and intensity of stimulation (expressed in % of the rest motor threshold).

Experiments involving other subjects than patients may be conducted in a non-medical environment with experienced medical specialists aware of the possible undesirable side effects and trained to detect these effects and to provide initial necessary medical support.

[5] The stimulation parameters that are considered to be safe as described in the guidelines apply to single session studies. In case of studies implying multiple sessions within the same participants it has to be taken into account that the accumulated frequency and duration parameters do not exceed those defined by the single sessions.

Depending on the type of TMS, the EC might request for each participant a medical screening that has confirmed the absence of medical conditions bearing a higher risk of undesirable side effects. The EC will also evaluate the procedure adopted by the research institute to guarantee the availability of appropriate medical intervention in case of emergency.

Both research and clinical practice must be carried out on an informed consent base. A person's decision to participate must be voluntary while all relevant information including potential risks has been provided. Besides, the likelihood of a research or clinical benefit must similarly outweigh the potential adverse effects or risks.

5.3 Training

To date, there does not exist any officially recognized training regarding to (r)TMS use, nor any criterion to be met. In anticipation of such a training, the SHC vigorously recommends that all users of (r)TMS, including physicians, should go for a training in the academic centers already involved in TMS practice in Belgium. Topics should include, but are not limited to: basic mechanisms of (r)TMS, elementary knowledge of neuroanatomy, neurophysiology, interactions with pharmacological products, physiological changes induced, and potential risks of (r)TMS procedures. The principal investigator of a study or the physician in charge of the diagnostic or therapeutic (r)TMS procedure is responsible for guaranteeing the proper training of (r)TMS operators working with him/her. Such a training should also include the ability and certification to deal with potential acute complications of (r)TMS.
The SHC highly recommends installing an officially recognized (r)TMS training course regarding the topics cited here above.

The overall ethical principle stating that a health care professional or scientific researcher is only allowed to carry out those acts falling within the scope of his expertise has always to be taken into account as a golden standard in everyday (r)TMS practice.
Therefore, the SHC emphasizes the utmost importance of an adequate training for every user of (r)TMS, whether he is a physician or not.

The SHC further judges that the working out of for example a curriculum for (r)TMS users does not belong to its primary area of competence but refers for this item among others to the existing and future bodies and scientific associations representing clinical psychologists, psychiatrists, neurologists and physiotherapists in order to establish practical guidelines to guarantee a maximum of safety for all patients and research subjects

V REFERENCES

Aguirre I, Carretero B, Ibarra O, Kuhalainen J, Martínez J, Ferrer A, et al. Age predicts low-frequency transcranial magnetic stimulation efficacy in major depression. J Affect Disord 2011;130:466-9.

Akil H, Gordon J, Hen R, Javitch J, Mayberg H, McEwen B, Meaney MJ, Nestler EJ. Treatment resistant depression: A multi-scale, systems biology approach. Neurosci Biobehav Rev. 2017 Aug 30. pii: S0149-7634(17)30368-8. doi: 10.1016/j.neubiorev.2017.08.019.

Anderson IM, Delvai NA, Ashim B, Ashim S, Lewin C, Singh V, et al. Adjunctive fast repetitive transcranial magnetic stimulation in depression. Br J Psychiatry 2007;190:533-4.

Anderson BS, Kavanagh K, Borckardt JJ, Nahas ZH, Kose S, Lisanby SH et al. Decreasing procedural pain over time of left prefrontal rTMS for depression: initial results from the open-lbel phase of a multi-site trial (OPT-TMS). Brain Stimul. 2009;2:88-92.

Avenanti A, Coccia M, Ladavas E, Provinciali L, Ceravolo MG. Low-frequency rtms promotes use-dependent motor plasticity in chronic stroke: a randomized trial. Neurology 2012;78:256–64.

Avery DH, Holtzheimer PE, 3rd, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry 2006;59(2):187-94.

Bach JP, Ziegler U, Deuschl G, Dodel R, Doblhammer-Reiter G. Projected numbers of people with movement disorders in the years 2030 and 2050. Mov Disord 2011;26(12):2286-90.

Bae EH, Schrader LM, Machii K, Alonso-Alonso M, Riviello JJ, Jr., Pascual-Leone A, et al. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. Epilepsy Behav 2007;10(4):521-8.

Baeken C, De Raedt R. Neurobiological mechanisms of repetitive transcranial magnetic stimulation on the underlying neurocircuitry in unipolar depression. Dialogues Clin Neurosci 2011;13(1):139-45.

Baeken C, Vanderhasselt MA, Remue J, Herremans S, Vanderbruggen N, Zeeuws D, et al. Intensive HF-rTMS treatment in refractory medication-resistant unipolar depressed patients. J Affect Disord 2013;151:625-31.

Bares M, Kopecek M, Novak T, Stopkova P, Sos P, Kozeny J, et al. Low frequency (1-Hz), right prefrontal repetitive transcranial magnetic stimulation (rTMS) compared with venlafaxine ER in the treatment of resistant depression: a double-blind, single-centre, randomized study. J Affect Disord 2009;118(1-3):94-100.

Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med 2013:1-15.

Berlim MT, Van den Eynde F, Jeff Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. Neuropsychopharmacology 2013;38(4):543-51.

Bestmann, S., & Duque, J. (2016). Transcranial Magnetic Stimulation. The Neuroscientist, 22(4), 392–405. https://doi.org/10.1177/1073858415592594

Blumberger DM, Christensen BK, Zipursky RB, Moller B, Chen R, Fitzgerald PB, et al. MRI-targeted repetitive transcranial magnetic stimulation of Heschl's gyrus for refractory auditory hallucinations. Brain Stimul 2012a;5:577-85.

Blumberger DM, Mulsant BH, Fitzgerald PB, Rajji TK, Ravindran AV, Young LT, et al. A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. World J Biol Psychiatry 2012b;13:423-35.

Boggio PS, Rocha M, Oliveira MO, Fecteau S, Cohen RB, Campanha C, et al. Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. J Clin Psychiatry 2010;71(8):992-9.

Bortolomasi M, Minelli A, Fuggetta G, Perini M, Comencini S, Fiaschi A, et al. Long-lasting effects of high frequency repetitive transcranial magnetic stimulation in major depressed patients. Psychiatry Res 2007;150(2):181-6.

Boylan LS, Pullman SL, Lisanby SH, Spicknall KE, Sackeim HA. Repetitive transcranial magnetic stimulation to SMA worsens complex movements in Parkinson's disease. Clin Neurophysiol 2001;112(2):259-64.

Bradley JK, Nyekiova M, Price DL, Lopez LD, Crawley T. Occupational exposure to static and time-varying gradient magnetic fields in MR units. J Magn Reson Imag. 2007;26:1204-9

Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces--revised recommendations 2004. Eur J Neurol 2004;11(9):577-81.

Bretlau LG, Lunde M, Lindberg L, Unden M, Dissing S, Bech P. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. Pharmacopsychiatry 2008;41(2):41-7.

Brighina F, Piazza A, Vitello G, Palermo A, Daniele O, et al. rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. J Neurol Sci. 2004; 227:67-71.

Brunelin J, Poulet E, Bediou B, Kallel L, Dalery J, D'Amato T, et al. Low frequency repetitive transcranial magnetic stimulation improves source monitoring deficit in hallucinating patients with schizophrenia. Schizophr Res 2006;81(1):41-5.

Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, Carvalho AF. Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. JAMA Psychiatry. 2017 Feb 1;74(2):143-152.

Brusa L, Versace V, Koch G, Iani C, Stanzione P, Bernardi G, et al. Low frequency rTMS of the SMA transiently ameliorates peak-dose LID in Parkinson's disease. Clin Neurophysiol 2006;117(9):1917-21.

Cantello R, Rossi S, Varrasi C, Ulivelli M, Civardi C, Bartalini S, et al. Slow repetitive TMS for drug-resistant epilepsy: clinical and EEG findings of a placebo-controlled trial. Epilepsia 2007;48(2):366-74.

Cardoso EF, Fregni F, Martins Maia F, Boggio PS, Luis Myczkowski M, Coracini K, et al. rTMS treatment for depression in Parkinson's disease increases BOLD responses in the left prefrontal cortex. Int J Neuropsychopharmacol 2008;11(2):173-83.

Carretero B, Martin MJ, Juan A, Pradana ML, Martin B, Carral M, et al. Low-frequency transcranial magnetic stimulation in patients with fibromyalgia and major depression. Pain Med 2009;10(4):748-53.

Carson VB (2000). Mental health nursing: the nurse-patient journey, W.B. Saunders p. 638.

Chambers, C. D., Payne, J. M., Stokes, M. G., & Mattingley, J. B. (2004). Fast and slow parietal pathways mediate spatial attention. Nature Neuroscience, 7(3), 217–218.

Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006;5(3):235-45.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48(5):1398-403.

Chen R, Spencer DC, Weston J, Nolan SJ. Transcranial magnetic stimulation for the treatment of epilepsy. Cochrane Database Syst Rev. 2016 Aug 11;(8):CD011025.

Chibbaro G, Daniele M, Alagona G, Di Pasquale C, Cannavo M, Rapisarda V, et al. Repetitive transcranial magnetic stimulation in schizophrenic patients reporting auditory hallucinations. Neurosci Lett 2005;383(1-2):54-7.

Chistyakov AV, Kaplan B, Rubichek O, Kreinin I, Koren D, Feinsod M, et al. Antidepressant effects of different schedules of repetitive transcranial magnetic stimulation vs. clomipramine in patients with major depression: relationship to changes in cortical excitability. Int J Neuropsychopharmacol 2005;8(2):223-33.

Chung CL, Mak MK. Effect of Repetitive Transcranial Magnetic Stimulation on Physical Function and Motor Signs in Parkinson's Disease: A Systematic Review and Meta-Analysis. Brain Stimul. 2016 Jul-Aug;9(4):475-87.

Cohen H, Kaplan Z, Kotler M, Kouperman I, Moisa R, Grisaru N. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. Am J Psychiatry 2004;161(3):515-24.

Cordes J, Thunker J, Agelink MW, Arends M, Mobascher A, Wobrock T, et al. Effects of 10 Hz repetitive transcranial magnetic stimulation (rTMS) on clinical global impression in chronic schizophrenia. Psychiatry Res 2010;177(1-2):32-6.

Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, Official Journal of the European Union L 169 of 12 July 1993.

Dell'Osso B, Oldani L, Camuri G, Dobrea C, Cremaschi L, Benatti B, Arici C, Grancini B, Altamura AC. Augmentative repetitive Transcranial Magnetic Stimulation (rTMS) in the acute treatment of poor responder depressed patients: a comparison study between high and low frequency stimulation. Eur Psychiatry. 2015 Feb;30(2):271-6.

Derosiere G, Vassiliadis P, Demaret S, Zénon A, Duque J.
Learning stage-dependent effect of M1 disruption on value-based motor decisions.
Neuroimage. 2017 Nov 15;162:173-185.

De Graaf TA, Baeken C, Sienaert P, Aleman A, and Sack AT. Brain stimulation: the most direct form of neurostimulation. Tijdschrift voor Psychiatrie 2017, 59 (10): 588-593.

de Jesus DR, Gil A, Barbosa L, Lobato MI, Magalhaes PV, Favalli GP, et al. A pilot double-blind sham-controlled trial of repetitive transcranial magnetic stimulation for patients with refractory schizophrenia treated with clozapine. Psychiatry Res 2011;188(2):203-7.

De Raedt R, Vanderhasselt MA, Baeken C. Neurostimulation as an intervention for treatment resistant depression: From research on mechanisms towards targeted neurocognitive strategies. Clin Psychol Rev. 2015 Nov;41:61-9.

De Ridder D, De Mulder G, Verstraeten E, Seidman M, Elisevich K, Sunaert S, et al. Auditory cortex stimulation for tinnitus. Acta Neurochir Suppl 2007;97(Pt 2):451-62.

Di Iorio, R., & Rossini, P. M. (2017). Safety Considerations of the Use of TMS. In S. M. Krieg (Ed.), Navigated Transcranial Magnetic Stimulation in Neurosurgery (pp. 67–83). Cham: Springer International Publishing.

Dionísio A, Duarte IC, Patrício M, Castelo-Branco M. The Use of Repetitive Transcranial Magnetic Stimulation for Stroke Rehabilitation: A Systematic Review. J Stroke Cerebrovasc Dis. 2017 Oct 27. pii: S1052-3057(17)30479-2.

Directive 2004/40/ec of the European parliament and of the council of 29 April 2004 on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (electromagnetic fields) (18th individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC), Official Journal of the European Union L 184 of 24 May 2004

Directive 2013/35/eu of the European parliament and of the council of 26 June 2013 on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents electromagnetic fields) (20th individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) and repealing Directive 2004/40/EC, Official Journal of the European Union L 179 of 29 June 2013.

Dlabac-de Lange JJ, Bais L, van Es FD, Visser BG, Reinink E, Bakker B, van den Heuvel ER, Aleman A, Knegtering H. Efficacy of bilateral repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: results of a multicenter double-blind randomized controlled trial. Psychol Med. 2015 Apr;45(6):1263-75.

Dragasevic N, Potrebic A, Damjanovic A, Stefanova E, Kostic VS. Therapeutic efficacy of bilateral prefrontal slow repetitive transcranial magnetic stimulation in depressed patients with Parkinson's disease: an open study. Mov Disord 2002;17(3):528-32.

Duncan JS. Epilepsy surgery. Clin Med 2007;7(2):137-42.

Duprat R, Desmyter S, Rudi de R, van Heeringen K, Van den Abbeele D, Tandt H, Bakic J, Pourtois G, Dedoncker J, Vervaet M, Van Autreve S, Lemmens GM, Baeken C. Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: A fast road to remission? J Affect Disord. 2016 Aug;200:6-14.

Duque, J., Greenhouse, I., Labruna, L., & Ivry, R. B. (2017). Physiological Markers of Motor Inhibition during Human Behavior. Trends in Neurosciences. https://doi.org/10.1016/j.tins.2017.02.006

Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132(3):237-51.

Eggermont JJ, Roberts LE. The neuroscience of tinnitus. Trends Neurosci 2004;27(11):676-82.

Elahi B, Chen R. Effect of transcranial magnetic stimulation of Parkinson motor function: systematic review of controlled clinical trials. Mov Disord 2009;24:357-363.

Elbeh KAM, Elserogy YMB, Khalifa HE, Ahmed MA, Hafez MH, Khedr EM. Repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorders: Double blind randomized clinical trial. Psychiatry Res. 2016 Apr 30;238:264-269.

Emara TH, Moustafa RR, Elnahas NM et al. Repetitive transcranial magnetic stimulation at 1 Hz and 5 Hz produces sustained improvement in motor function and disability after ischaemic stroke. Eur J Neurol 2010;17:1203-9.

Epstein C, Evatt M, Funk A et al. An open study of repetitive transcranial magnetic stimulation in treatment-resistant depression with Parkinson's disease. Clin Neurophysiol 2007;118(10):2189-94.

Eranti S, Mogg A, Pluck G, Landau S, Purvis R, Brown RG, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. Am J Psychiatry 2007;164(1):73-81.

Etoh S, Noma T, Ikeda K, Jonoshita Y, Ogata A, Matsumoto S, et al. Effects of repetitive trascranial magnetic stimulation on repetitive facilitation exercises of the hemiplegic hand in chronic stroke patients. J Rehabil Med 2013;45:843–7.

Fagiolini A, Kupfer DJ. Is treatment-resistant depression a unique subtype of depression? Biol Psychiatry 2003;53(8):640-8.

Fava M. The role of the serotonergic and noradrenergic neurotransmitter systems in the treatment of psychological and physical symptoms of depression. J Clin Psychiatry 2003;64 Suppl 13:26-9.

Filipovic SR, Rothwell JC, van de Warrenburg BP, Bhatia K. Repetitive transcranial magnetic stimulation for levodopa-induced dyskinesis in Parkinson's disease. Mov Disord 2009;24:246-53.

Finnerup NB, Otto M, Jensen TS, Sindrup SH. An evidence-based algorithm for the treatment of neuropathic pain. MedGenMed 2007;9(2):36.

Finnerup NB, Sindrup SH, Jensen TS. Chronic neuropathic pain: mechanisms, drug targets and measurement. Fundam Clin Pharmacol 2007;21(2):129-36.

Fitzgerald PB, Benitez J, Daskalakis JZ, Brown TL, Marston NA, de Castella A, et al. A double-blind sham-controlled trial of repetitive transcranial magnetic stimulation in the treatment of refractory auditory hallucinations. J Clin Psychopharmacol 2005;25(4):358-62.

Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatry 2006;163(1):88-94.

Fitzgerald PB, Hoy K, McQueen S, Herring S, Segrave R, Been G, et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. J Clin Psychopharmacol 2008;28(1):52-8.

Fitzgerald PB, Herring S, Hoy K, McQueen S, Segrave R, Kulkarni J, et al. A study of the effectiveness of bilateral transcranial magnetic stimulation in the treatment of the negative symptoms of schizophrenia. Brain Stimul 2008;1(1):27-32.

Fitzgerald PB, Hoy K, Daskalakis ZJ, Kulkarni J. A randomized trial of the anti-depressant effects of low- and high-frequency transcranial magnetic stimulation in treatment-resistant depression. Depress Anxiety 2009;26(3):229-34.

Fitzgerald PB, Hoy K, Gunewardene R, Slack C, Ibrahim S, Bailey M, et al. A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression. Psychol Med 2011;41:1187-96.

Fitzgerald PB, Hoy KE, Herring SE, McQueen S, Peachey AV, Segrave RA, et al. A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression. J Affect Disord 2012;139:193-8.

Fitzgerald PB, Hoy KE, Singh A, Gunewardene R, Slack C, Ibrahim S, et al. Equivalent beneficial effects of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in a large randomized trial in treatment-resistant major depression. Int J Neuropsychopharmacol 2013b;16:1975-84.

Fox SH, Katzenschlager R, Lim SY et al. The Movement Disorders Society Evidence-Based Revieuw Update: Treatments for the motor symptoms of Parkinson's disease, Mov Disord 2001; 26 Suppl:S2-41

Fregni F, Otachi PT, Do Valle A, Boggio PS, Thut G, Rigonatti SP, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. Ann Neurol 2006;60(4):447-55.

Fregni F, Santos CM, Myczkowski ML et al., Repetitive transcranial magnetic stimulation is as effective as flouxetine in the treatment of depression in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2004; 75(8):1171-4.

Fregni F, Simon DK, Wu A, Pascual-Leone A. Non-invasive brain stimulation for Parkinson's disease : a systematic review and meta-analysis of the literature. J Neurol Neurosurg Psychiatry 2005;76:1614-1623.

Fujiyama H, Van Soom J, Rens G, Cuypers K, Heise KF, Levin O, Swinnen SP. Performing two different actions simultaneously: The critical role of interhemispheric interactions during the preparation of bimanual movement. Cortex. 2016 Apr;77:141-154.

Galhardoni R, Correia GS, Araujo H, Yeng LT, Fernandes DT, Kaziyama HH, Marcolin MA, Bouhassira D, Teixeira MJ, de Andrade DC. Repetitive transcranial magnetic stimulation in chronic pain: a review of the literature. Arch Phys Med Rehabil. 2015 Apr; 964 (Suppl):S156-72.

Gandhi OP. Electromagnetic fields: human safety issues. Annu Rev Biomed Eng. 2002;4:211-34.

Garcia-Toro M, Salva J, Daumal J, Andres J, Romera M, Lafau O, et al. High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjuvant treatment in medication-resistant depression. Psychiatry Res 2006;146(1):53-7.

Garcia-Larrea L, Peyron R. Motor cortex stimulation for neuropathic pain: From phenomenology to mechanisms. Neuroimage 2007;37 Suppl 1:S71-9.

George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 2010;67(5):507-16.

George MS, Post RM. Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression. Am J Psychiatry 2011;168(4):356-64.

Gogtay N, Vyas NS, Testa R, Wood SJ, Pantelis C. Age of onset of schizophrenia: perspectives from structural neuroimaging studies. Schizophr Bull 2011;37(3):504-13.

Gomes PV, Brasil-Neto JP, Allam N, Rodrigues de Souza E. A randomized, double blind trial of repetitive transcranial magnetic stimulation in obsessive compulsive disorder with three-month follow-up. J Neuropsychiatry Clin Neurosci 2012;24:437–43.

Goodman JH. Brain stimulation as a therapy for epilepsy. Adv Exp Med Biol 2004;548:239-47.

Goyal N, Nizamie SH, Desarkar P. Efficacy of adjuvant high frequency repetitive transcranial magnetic stimulation on negative and positive symptoms of schizophrenia: preliminary results of a double-blind sham-controlled study. J Neuropsychiatry Clin Neurosci 2007;19(4):464-7.

Gragwasevic N, Potrebic A, Damjanovic A et al. Therapeutic efficacy of bilateral prefrontal slow repetitive transcranial magnetic stimulation in depressed patients with Parkinson's disease: an open study. Mov Disord 2002;17(3):528-32.

Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, et al. A practical guide to diagnostic
transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol. 2012;123:858–82

Hallett, M. Transcranial magnetic stimulation and the human brain. Nature 2000; 406(6792), 147–150.

Hamada M., Ugawa Y, Tsuji S et al. High-frequency rTMS over the supplementary motor area for treatment of Parkinson's disease. Mov Disord 2008;23:1524-1531.

Hamada M, Ugawa Y, Tsuji S. High-frequency rTMS over the supplementary motor area improves bradykinesia in Parkinson's disease: subanalysis of double-blind sham-controlled study. J Neurol Sci 2009;287(1-2):143-6.

Hansen PE, Ravnkilde B, Videbech P, Clemmensen K, Sturlason R, Reiner M, et al. Low-frequency repetitive transcranial magnetic stimulation inferior to electroconvulsive therapy in treating depression. J ECT 2011;27(1):26-32.

Harris, J. A., Clifford, C. W. G., & Miniussi, C. The functional effect of transcranial magnetic stimulation: Signal suppression or neural noise generation? Journal of Cognitive Neuroscience 2008;, 20(4), 734–740.

Haslinger B, Erhard P, Kampfe N, Boecker H, Rummeny E, Schwaiger M, et al. Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. Brain 2001;124(Pt 3):558-70.

Henry JA, Dennis KC, Schechter MA. General review of tinnitus: prevalence, mechanisms, effects, and management. J Speech Lang Hear Res 2005;48(5):1204-35.

Herwig U, Fallgatter AJ, Hoppner J, Eschweiler GW, Kron M, Hajak G, et al. Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. Br J Psychiatry 2007;191:441-8.

Hoffman RE, Boutros NN, Berman RM, Roessler E, Belger A, Krystal JH, et al. Transcranial magnetic stimulation of left temporoparietal cortex in three patients reporting hallucinated "voices". Biol Psychiatry 1999;46(1):130-2.

Hummel F, Cohen LG. Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. Neurorehabil Neural Repair 2005;19(1):14-9.

Hoffman RE, Gueorguieva R, Hawkins KA, Varanko M, Boutros NN, Wu YT, et al. Temporoparietal transcranial magnetic stimulation for auditory hallucinations: safety, efficacy and moderators in a fifty patient sample. Biol Psychiatry 2005;58(2):97-104.

Hsu WY, Cheng CH, Liao KK, Lee IH, Lin YY. Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: a meta-analysis. Stroke 2012; 43: 1849-57.

Hu SH, Lai JB, Xu DR, Qi HL, Peterson BS, Bao AM, Hu CC, Huang ML, Chen JK, Wei N, Hu JB, Li SL, Zhou WH, Xu WJ, Xu Y. Efficacy of repetitive transcranial magnetic stimulation with quetiapine in treating bipolar II depression: a randomized, double-blinded, control study. Sci Rep. 2016 Jul 27;6:30537.

ICNIRP – International Commission of non-Ionizing Radiation Protection. Guidelines for limiting exposure to time-varying electric and magnetic fields (1 Hz to 100 kHz). Health Physics 2010;99(6):818-836.

Januel D, Dumortier G, Verdon CM, Stamatiadis L, Saba G, Cabaret W, et al. A double-blind sham controlled study of right prefrontal repetitive transcranial magnetic stimulation (rTMS): therapeutic and cognitive effect in medication free unipolar depression during 4 weeks. Prog Neuropsychopharmacol Biol Psychiatry 2006;30(1):126-30.

Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci Res 1990;8(4):221-54.

Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology 2007;68(15):1178-82.

Jin Y, Potkin SG, Kemp AS, Huerta ST, Alva G, Thai TM, et al. Therapeutic effects of individualized alpha frequency transcranial magnetic stimulation (alphaTMS) on the negative symptoms of schizophrenia. Schizophr Bull 2006;32(3):556-61.

Joo EY, Han SJ, Chung SH, Cho JW, Seo DW, Hong SB. Antiepileptic effects of low-frequency repetitive transcranial magnetic stimulation by different stimulation durations and locations. Clin Neurophysiol 2007;118(3):702-8.

Jorge RE, Moser DJ, Acion L, Robinson RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. Arch Gen Psychiatry 2008;65(3):268-76.

Karlström EF, Lundström R, Stensson O, Mild KH. Therapeutic staff exposure to magnetic field pulses during TMS/rTMS treatments. Bioelectromagnetics 2006;27:156-8.

Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. J Affect Disord 2009;117 Suppl 1:S44-53.

Khedr EM, Ahmed MA, Fathy N, Rothwell JC. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. Neurology 2005;65(3):466-8.

Kim Y, You S, Ko M et al. Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. Stroke 2006 Jun;37(6):1471-76.

Kleinjung T, Vielsmeier V, Landgrebe M, Hajak G, Langguth B. Transcranial magnetic stimulation: a new diagnostic and therapeutic tool for tinnitus patients. Int Tinnitus J 2008;14(2):112-8.

Klirova M., Novak T, Kopecek M, Mohr P, Strunzova V. Repetitive transcranial magnetic stimulation (rTMS) in major depressive episode during pregnancy. Neuro Endocrinol Lett. 2008;29:69-70.

Klirova M, Horacek J, Novak T, Cermak J, Spaniel F, Skrdlantova L, et al. Individualized rTMS neuronavigated according to regional brain metabolism ((18)FGD PET) has better treatment effects on auditory hallucinations than standard positioning of rTMS: a double-blind, sham-controlled study. Eur Arch Psychiatry Clin Neurosci 2013;263:475-84.

KNO-vereniging, 2016 - Richtlijn Tinnitus. Utrecht: Nederlandse Vereniging voor Keel–Neus–Oorheelkunde en Heelkunde van het Hoofd–Halsgebied; 2016.

Koch G, Brusa L, Caltagirone C, Peppe A, Oliveri M, Stanzione P, et al. rTMS of supplementary motor area modulates therapy-induced dyskinesias in Parkinson disease. Neurology 2005;65(4):623-5.

Langguth B, de Ridder D, Dornhoffer JL, Eichhammer P, Folmer RL, Frank E, et al. Controversy: Does repetitive transcranial magnetic stimulation/ transcranial direct current stimulation show efficacy in treating tinnitus patients? Brain Stimul 2008;1(3):192-205.

Langguth B, Kreuzer PM, Kleinjung T, De Ridder D. Tinnitus: causes and clinical management. Lancet Neurol 2013;12(9):920-30, doi:10.1016/S1474-4422(13)70160-1.

Lee SH, Kim W, Chung YC, Jung KH, Bahk WM, Jun TY, et al. A double blind study showing that two weeks of daily repetitive TMS over the left or right temporoparietal cortex reduces symptoms in patients with schizophrenia who are having treatment-refractory auditory hallucinations. Neurosci Lett 2005;376(3):177-81.

Lee SH, Kim W, Chung YC, Jung KH, Bahk WM, Jun TY, et al. A double blind study showing that two weeks of daily repetitive TMS over the left or right temporoparietal cortex reduces symptoms in patients with schizophrenia who are having treatment-refractory auditory hallucinations. Neurosci Lett 2005;376(3):177-81.

Lefaucheur JP. The use of repetitive transcranial magnetic stimulation (rTMS) in chronic neuropathic pain. Neurophysiol Clin 2006;36(3):117-24.

Lefaucheur JP. New insights into the therapeutic potential of non-invasive transcranial cortical stimulation in chronic neuropathic pain. Pain 2006;122(1-2):11-3.

Lefaucheur JP, Andre-Obadia N, Poulet E, Devanne H, Haffen E, Londero A, et al. [French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): safety and therapeutic indications]. Neurophysiol Clin 2011;41(5-6):221-95.

Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 2014;125(11):2150-206.

Lenze EJ, Wetherell JL. A lifespan view of anxiety disorders. Dialogues Clin Neurosci 2011;13(4):381-99.

Leung A, Donohue M, Xu R, Lee R, Lefaucheur JP, Khedr EM, et al. rTMS for suppressing neuropathic pain: a meta-analysis. J Pain 2009;10(12):1205-16.

Li CT, Chen MH, Juan CH, Huang HH, Chen LF, Hsieh JC, Tu PC, Bai YM, Tsai SJ, Lee YC, Su TP. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain. 2014 Jul;137

Lieberman A. Depression in Parkinson's disease -- a review. Acta Neurol Scand 2006;113(1):1-8.

Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology 2009;34(2):522-34.

Londero A, Langguth B, De Ridder D, Bonfils P, Lefaucheur JP. Repetitive transcranial magnetic stimulation (rTMS): a new therapeutic approach in subjective tinnitus? Neurophysiol Clin 2006;36(3):145-55.

Loo CK, Mitchell PB, McFarquhar TF, Malhi GS, Sachdev PS. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. Psychol Med 2007;37(3):341-9.

Loo CK, McFarquhar TF, Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. Int J Neuropsychopharmacol. 2008;11:131-47.

Loo CK, Sainsbury K, Mitchell P, Hadzi-Pavlovic D, Sachdev PS. A sham-controlled trial of left and right temporal rTMS for the treatment of auditory hallucinations. Psychol Med 2010;40(4):541-6.

Maizey, L., Allen, C. P. G., Dervinis, M., Verbruggen, F., Varnava, A., Kozlov, M., … Chambers, C. D. (2013). Comparative incidence rates of mild adverse effects to transcranial magnetic stimulation. Clin Neurophysiol. 2013; 124(3), 536–44.

Mally J, Farkas R, Tothfalusi L, Stone TW. Long-term follow-up study with repetitive transcranial magnetic stimulation (rTMS) in Parkinson's disease. Brain Res Bull 2004;64(3):259-63.

Mansur CG, Fregni F, Boggio PS et al. A sham stimulation controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005;64:1802-4.

Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005;64:1802-4.

Mantovani A, Simpson HB, Fallon BA, Rossi S, Lisanby SH. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. Int J Neuropsychopharmacol 2010;13(2):217-27.

Martens L. Different basic dosimetric quantities for the characterization of exposure to low-frequency electric and magnetic fields and the implication for practical exposure conditions and guidelines. Health Phys. 2007;92:515-20.

McCormack A, Edmondson-Jones M, Somerset S, Hall D. A systematic review of the reporting of tinnitus prevalence and severity. Hear Res 2016;337:70-9, doi:10.1016/j.heares.2016.05.009.

McDonald WM, Easley K, Byrd EH, Holtzheimer P, Tuohy S, Woodard JL, et al. Combination rapid transcranial magnetic stimulation in treatment refractory depression. Neuropsychiatr Dis Treat 2006;2(1):85-94.

Meng Z, Liu S, Zheng Y, Phillips JS. Repetitive transcranial magnetic stimulation for tinnitus. Cochrane Database Syst Rev 2011;2011(10):CD007946, doi:10.1002/14651858.CD007946.pub2.

Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, Modirrousta M, Patry S, Vila-Rodriguez F, Lam RW, MacQueen GM, Parikh SV, Ravindran AV; CANMAT Depression Work Group.
Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments.Can J Psychiatry. 2016 Sep;61(9):561-75.

Mogg A, Purvis R, Eranti S, Contell F, Taylor JP, Nicholson T, et al. Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: a randomized controlled pilot study. Schizophr Res 2007;93(1-3):221-8.

Mogg A, Pluck G, Eranti SV, Landau S, Purvis R, Brown RG, et al. A randomized controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. Psychol Med 2008;38(3):323-33.

Møller AR. Tinnitus and pain. In: Langguth B et al., editors. Progr Brain Res. Volume 166: Elsevier; 2007. p. 47-53.

Nahas Z, Kozel FA, Li X, Anderson B, George MS. Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. Bipolar Disord 2003;5(1):40-7.

Nemeroff CB. Prevalence and management of treatment-resistant depression. J Clin Psychiatry 2007;68 Suppl 8:17-25.

Novak T, Horacek J, Mohr P, Kopecek M, Skrdlantova L, Klirova M, et al. The double-blind sham-controlled study of high-frequency rTMS (20 Hz) for negative symptoms in schizophrenia: negative results. Neuro Endocrinol Lett 2006;27(1-2):209-13.

O'Connell NE, Wand BM, Marston L et al. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev 2014;4;CD008208.

Okabe S, Ugawa Y, Kanazawa I. 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson's disease. Mov Disord 2003;18(4):382-8.

O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007;62(11):1208-16.

Paillere Martinot ML, Galinowski A, Ringuenet D, Gallarda T, Lefaucheur JP, Bellivier F, et al. Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: a [(18)F]-fluorodeoxyglucose PET and MRI study. Int J Neuropsychopharmacol 2010;13(1):45-59.

Pallanti S, Bernardi S, Di Rollo A, Antonini S, Quercioli L. Unilateral low frequency versus sequential bilateral repetitive transcranial magnetic stimulation: is simpler better for treatment of resistant depression? Neuroscience 2010;167(2):323-8.

Pascual-Leone A, Vallo-Sole J, Brasil-Neto JP et al. in Parkinson's disease. II. Effects of subthreshold repetitive transcranial motor cortex stimulation. Neurology1994;44:892-8.

Paus T, Barrett J. Transcranial magnetic stimulation (TMS) of the human frontal cortex: implications for repetitive TMS treatment of depression. J Psychiatry Neurosci 2004;29(4):268-79.

Plewnia C, Reimold M, Najib A et al. Moderate therapeutic efficacy of positron-emission tomography-navigated repetitive transcranial magnetic stimulation for chronic tinnitus: a randomized controlled pilot study. J Neurol Psychiatry 2007;78:152-6.

Poulet E, Brunelin J, Bediou B, Bation R, Forgeard L, Dalery J, et al. Slow transcranial magnetic stimulation can rapidly reduce resistant auditory hallucinations in schizophrenia. Biol Psychiatry 2005;57(2):188-91.

Prasko J, Paskova B, Zalesky R, Novak T, Kopecek M, Bares M, et al. The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive compulsive disorder. A randomized, double blind, sham controlled study. Neuro Endocrinol Lett 2006;27(3):327-32.

Prasser J, Schecklmann M, Poeppl TB, Frank E, Kreuzer PM, Hajak G, Rupprecht R, Landgrebe M, Langguth B. Bilateral prefrontal rTMS and theta burst TMS as an add-on treatment for depression: a randomized placebo controlled trial. World J Biol Psychiatry. 2015 Jan;16(1):57-65.

Prikryl R, Kasparek T, Skotakova S, Ustohal L, Kucerova H, Ceskova E. Treatment of negative symptoms of schizophrenia using repetitive transcranial magnetic stimulation in a double-blind, randomized controlled study. Schizophr Res 2007;95(1-3):151-7.

Ray S, Nizamie SH, Akhtar S, Praharaj SK, Mishra BR, Zia-ul-Haq M. Efficacy of adjunctive high frequency repetitive transcranial magnetic stimulation of left prefrontal cortex in depression: a randomized sham controlled study. J Affect Disord 2011;128(1-2):153-9.

Ren J, Li H, Palaniyappan L, Liu H, Wang J, Li C, Rossini PM. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2014 Jun 3;51:181-9.

Richter GT, Mennemeier M, Bartel T, Chelette KC, Kimbrell T, Triggs W, et al. Repetitive transcranial magnetic stimulation for tinnitus: a case study. Laryngoscope 2006;116(10):1867-72.

Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA. Ringing ears: the neuroscience of tinnitus. J Neurosci 2010;30(45):14972-9.

Rosa MA, Gattaz WF, Pascual-Leone A, Fregni F, Rosa MO, Rumi DO, et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. Int J Neuropsychopharmacol 2006;9(6):667-76.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120(12):2008-39.

Rossini D, Lucca A, Magri L, Malaguti A, Smeraldi E, Colombo C, et al. A symptom-specific analysis of the effect of high-frequency left or low-frequency right transcranial magnetic stimulation over the dorsolateral prefrontal cortex in major depression. Neuropsychobiology 2010;62(2):91-7.

Rossini D, Lucca A, Zanardi R, Magri L, Smeraldi E. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. Psychiatry Res 2005;137(1-2):1-10.

Rossini D, Magri L, Lucca A, Giordani S, Smeraldi E, Zanardi R. Does rTMS hasten the response to escitalopram, sertraline, or venlafaxine in patients with major depressive disorder? A double-blind, randomized, sham-controlled trial. J Clin Psychiatry 2005;66(12):1569-75.

Ruffini C, Locatelli M, Lucca A, Benedetti F, Insacco C, Smeraldi E. Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation. Prim Care Companion J Clin Psychiatry 2009;11(5):226-30.

Rumi DO, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, et al. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. Biol Psychiatry 2005;57(2):162-6.

Saba G, Verdon CM, Kalalou K, Rocamora JF, Dumortier G, Benadhira R, et al. Transcranial magnetic stimulation in the treatment of schizophrenic symptoms: a double blind sham controlled study. J Psychiatr Res 2006;40(2):147-52.

Sabatini U, Boulanouar K, Fabre N, Martin F, Carel C, Colonnese C, et al. Cortical motor reorganization in akinetic patients with Parkinson's disease: a functional MRI study. Brain 2000;123 (Pt 2):394-403.

Sachdev PS, Loo CK, Mitchell PB, McFarquhar TF, Malhi GS. Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. Psychol Med 2007;37(11):1645-9.

Sarkhel S, Sinha VK, Praharaj SK. Adjunctive high-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) was not effective in obsessive-compulsive disorder but improved secondary depression. J Anxiety Disord 2010;24(5):535-9.

Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med 2009;39(1):65-75.

Schwartzman RJ, Grothusen J, Kiefer TR, Rohr P. Neuropathic central pain: epidemiology, etiology, and treatment options. Arch Neurol 2001;58(10):1547-50.

Schneider AL, Schneider TL, Stark H. Repetitive transcranial magnetic stimulation (rTMS) as an augmentation treatment for the negative symptoms of schizophrenia: a 4-week randomized placebo controlled study. Brain Stimul 2008;1(2):106-11.

Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. Mov Disord 2011;26 Suppl 3:S42-80.

Shirota Y, Ohtsu H, Hamada M, Enomoto H, Ugawa Y. Research Committee on rTMS treatment of Parkinson’s disease. Supplementary motor area stimulation for Parkinson’s disease: a randomized controlled study. Neurology 2013;80:1400-5.

Sims A (2002), Symptoms in the mind: an introduction to descriptive psychopathology. Philadelphia: W. B. Saunders Ltd, 3rd Edition, 430 p.

Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 2010;71(7):873-84.

Slotema CW, Blom JD, de Weijer AD, Diederen KM, Goekoop R, Looijestijn J, et al. Can low-frequency repetitive transcranial magnetic stimulation really relieve medication-resistant auditory verbal hallucinations? Negative results from a large randomized controlled trial. Biol Psychiatry 2011;69(5):450-6.

Soleimani R, Jalali MM, Hasandokht T. Therapeutic impact of repetitive transcranial magnetic stimulation (rTMS) on tinnitus: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol. 2016 Jul;273(7):1663-75.

Strafella AP, Ko JH, Grant J, Fraraccio M, Monchi O. Corticostriatal functional interactions in Parkinson's disease: a rTMS/[11C]raclopride PET study. Eur J Neurosci 2005;22(11):2946-52.

Su TP, Huang CC, Wei IH. Add-on rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. J Clin Psychiatry 2005;66(7):930-7.

Sun W, Mao W, Meng X, Wang D, Qiao L, Tao W, et al. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: a controlled clinical study. Epilepsia 2012;53(10):1782-9.

Superior Health Council. Prevention, diagnosis and therapy of tinnitus. Health effects of recreational sound in children and young adults, Brussels: Superior Health Council, 2017, Report nr. 9332.

Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke 2005;36(12):2681-6.

Takeuchi N, Tada T, Toshima M, Chuma T, Matsuo Y, Ikoma K. Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranical magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. J Rehabil Med 2008;40(4):298-303.

Takeuchi N, Toshima M, Chuma T, Matsuo Y, Ikoma K. Repetitive transcranial magnetic stimulation of the unaffected hemisphere in a patient who was forced to use the affected hand. Am J Phys Med Rehabil 2008;87(1):74-7.

Takeuchi N, Izumi S. Noninvasive brain stimulation for motor recovery after stroke: mechanisms and future views. Stroke Res Treat 2012;2012:584727.

Theilig S, Podubecka J, Bosl K, Wiederer R, Nowak DA. Functional neuromuscular stimulation to improve severe hand dysfunction after stroke: does inhibitory rTMS enhance therapeutic efficiency? Exp Neurol 2011;230(1):149-55.

Theodoroff SM, Folmer RL. Repetitive transcranial magnetic stimulation as a treatment for chronic tinnitus: a critical review. Otol Neurotol 2013;34(2):199-208.

Triggs WJ, Ricciuti N, Ward HE, Cheng J, Bowers D, Goodman WK, et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. Psychiatry Res 2010;178(3):467-74.

Uy J, Ridding MC, Hillier S, Thompson PD, Miles TS. Does induction of plastic change in motor cortex improve leg function after stroke? Neurology 2003;61(7):982-4.

Vanderheyden JE, Gonce M, Bourgeois P, Cras P, De Nayer AR, Flamez A, et al. Epidemiology of major depression in Belgian parkinsonian patients. Acta Neurol Belg 2010;110(2):148-56.

Van de Heyning P, Gilles A, Rabau S, Van Rompaey V. Subjective tinnitus assessment and treatment in clinical practice: the necessity of personalized medicine. Curr Opin Otolaryngol Head Neck Surg 2015;23(5):369-75.

Vercammen A, Knegtering H, Bruggeman R, Westenbroek HM, Jenner JA, Slooff CJ, et al. Effects of bilateral repetitive transcranial magnetic stimulation on treatment resistant auditory-verbal hallucinations in schizophrenia: a randomized controlled trial. Schizophr Res 2009;114(1-3):172-9.

Walsh, V., & Cowey, A. Transcranial magnetic stimulation and cognitive neuroscience. Nature Reviews Neuroscience 2000; 1(1), 73–79.

Wassermann, EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalography and clinical Neurophysiology 1998, 108(1), 1–16.

Watts BV, Landon B, Groft A, Young-Xu Y. A sham controlled study of repetitive transcranial magnetic stimulation for posttraumatic stress disorder. Brain Stimul 2012;5(1):38-43.

Wet van 10 mei 2015 betreffende de uitoefening van de gezondheidszorgberoepen, gecoördineerd door het koninklijk besluit van 10 mei 2015, Belgisch Staatsblad, 18 juni 2015

Wet inzake experimenten op de menselijke persoon. Belgisch Staatsblad, 18 mei 2004 Ed. 2, pp. 39516-39534.

Wobrock T, Guse B, Cordes J, Wölwer W, Winterer G, Gaebel W, Langguth B, Landgrebe M, Eichhammer P, Frank E, Hajak G, Ohmann C, Verde PE, Rietschel M, Ahmed R, Honer WG, Malchow B, Schneider-Axmann T, Falkai P, Hasan A. Left prefrontal high-frequency repetitive transcranial magnetic stimulation for the treatment of schizophrenia with predominant negative symptoms: a sham-controlled, randomized multicenter trial. Biol Psychiatry. 2015 Jun 1;77(11):979-88.

Wu AD, Fregni F, Simon DK, Deblieck C, Pascual-Leone A. Noninvasive brain stimulation for Parkinson's disease and dystonia. Neurotherapeutics 2008;5(2):345-61.

Zimmermann M. Pathobiology of neuropathic pain. Eur J Pharmacol 2001;429(1-3):23-37.

VI COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group ***in a private capacity***. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Dirk ADANG**; the scientific secretaries were Sylvie GERARD and Eric JADOUL.

ADANG Dirk	Bioelectromagnetics	UCL
BAEKEN Chris	Psychiatry	UGent
DE TIEGE Xavier	Neurology	ULB
DUCHATEAU Jacques	Neuroscience	ULB
DUQUE Julie	Physiotherapy	UCL
FIAS Wim	Psychology	UGent
KORNREICH Charles	Psychiatry	ULB
ORBAN DE XIVRY Jean-Jacques	Civil engineering	UCL
STOCKBROECKX Benoit	Electrical engineering	ANPI
SWINNEN Stephan	Physiotherapy	KUL

The following experts were heard but did not take part in endorsing the advisory report:

BALERIAUX Danielle	Neuroradiology	ULB
GOFFIN Tom	Law	KUL
GOLDMAN Serge	Ethics	ULB
NYS Herman	Law	KUL
OLIVIER Etienne	Neurology	UCL
PICKUT Barbara	Neurology	UA
RUBENS Robert	Ethics	UZGent

About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 30 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.hgr-css.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

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