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NEUROPHYSIOLOGICAL AND NEUROPSYCHIATRIC ASPECTS OF TRANSCRANIAL MAGNETIC STIMULATION

Giancarlo Giupponi, Roger Pycha, Bernardo Dell'Osso, Maurizio Pompili, Michaela Walpoth,
Armand Hausmann, Jan Di Pauli, Andreas Erfurth, and Andreas Conca

Abstract

Objective: The authors review the literature in the field of transcranial magnetic stimulation (TMS).

Method: For this purpose a PubMed search was performed. Additional information was gained by cross-referencing from papers found in the data base.

Results: Data from controlled studies as well as supplementary information from relevant review articles pertinent to the topic were used. History and the basics of TMS and repetitive transcranial magnetic stimulation (rTMS) are presented. The ability of rTMS to non-invasively modulate higher cognitive functions such as learning and memory has developed a new and exciting field. TMS, in fact, allows one to transiently disrupt ongoing cortical processing, thus helping to enlighten the causal role of a specific brain area in a certain observable behaviour. Finally, rTMS-clinical effectiveness in mood disorders, anxiety disorders, schizophrenic spectrum disorders and Parkinson's disease as well as in pain syndrome is discussed.

Conclusions: rTMS in concert with functional neuroimaging methods allows to analyze neuronal networks. Long term potentiation (LTP) and long term depression (LTD) are phenomena seen in preclinical studies after rTMS, and reflect plastic neuromodulation. Changes in brain plasticity are thought to be mechanisms that underlie the pathophysiology of psychiatric diseases like major depression.

Key Words: repetitive transcranial magnetic stimulation (rTMS), neuromodulation, long term potentiation (LTP), long term depression (LTD), mood disorders, schizophrenia, obsessive compulsive disorder, Parkinson' s disease, pain-syndromes, higher cognitive functions

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Giupponi Giancarlo[1], Pycha Roger[3], Dell'Osso Bernardo[4], Pompili Maurizio[5], Walpoth Michaela[2], Hausmann Armand[2], Di Pauli Jan[6], Erfurth Andreas[7] and Conca Andreas[1,2]*

[1] Department of Psychiatry, Bolzano, Italy; [2] Department of Psychiatry, University of Innsbruck, Austria; [3] Department of Psychiatry, Brunico, Italy; [4] Department of Psychiatry, University of Milan; Fondazione IRCCS Policlinico, Milano, Italy; [5] Department of Psychiatry, Sant'Andrea Hospital, "Sapienza" University of Rome, Italy; McLean Hospital – Harvard Medical School, Boston, MA – USA; [6] Department of Psychiatry of Rankweil, Department of Psychiatry I, Austria; [7] Department of Psychiatry, University of Vienna

Corresponding Author
Prof. Dr. Andreas Conca, Department of Psychiatry of Bolzano,
BöhlerStr. 4 39100, Italy
Tel: +39-0471-909800 - Fax : +39-0471-305829
andreas.conca@asbz.it

I. INTRODUCTION

1. Development of TMS

Transcranial magnetic stimulation (TMS) has been used for years in the clinical and neurological setting to assess the speed of neuronal transmission. Since the beginning of the last decade, it has been investigated in the treatment of neurological and psychiatric diseases (George et al. 2003). There are two traditionally major fields of application of TMS in scientific research: 1) to assess the relationship between stimulus intensity and strength of the aimed effect as a measure of the excitability of cortical areas; 2) to modulate the cortical excitability and, as a consequence, the cortical function.

TMS allows non-invasive stimulation of the cerebral cortex by applying a magnetic field generated with a coil. The magnetic field goes through the skull and transforms into an electric field directly at the level of the cerebral cortex.

Both single-pulse and short-interstimulus double-pulse stimulators have been developed, as well as stimulators for repetitive transcranial magnetic stimulation (rTMS), serial transcranial magnetic stimulation, high or low frequency transcranial magnetic stimulation. Unlike single-pulse stimulators,

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whose stimulation index has a maximum of 0.25 to 0.33 Hz, modern repetitive stimulators may obtain up to 60 Hz. RTMS has shed light on new therapeutic approaches in several psychiatric and neurological diseases, and has enabled the modulation of neuronal structures in relationship to the frequency of the stimulation applied.

2. Neurophisiological effects of TMS

The stimulators currently used produce a magnetic field from 1.5 to 2.2 Tesla. The maximal focality that can be reached through an octagonal-section coil is 0.5 cm^2 (Brasil-Neto et al. 1992). Stimulation can penetrate to a depth of 1.5 – 2 cm under the skull surface (De Groot et al. 2001, Rudiak & Marg 1994). The form and orientation of the coil in relation to the neuronal surface determine the spot and the action of stimulation (Amassian et al. 1992). The magnetic field itself diminishes with an inverse proportionality to the distance from the stimulating coil. The penetration depth is proportional to the diameter of the coil used. TMS activation takes place transynaptically, especially at the level of tangentially aligned interneurons. The configuration and propagation of the induced magnetic field and electric field can be calculated; nevertheless, it is difficult to foresee the currents induced. The stimulation effectiveness is also related to the distance between the coil and the cortex, and this value is higher in elderly patients due to the frontal cortical atrophy that manifests earlier, probably for the aforementioned reason (George et al. 2003, McConnell et al. 2001). A newly developed and more realistic stimulator, than that currently used, takes all these aspects and factors into consideration (Wagner et al. 2004).

3. Diagnostic application of TMS

3.1. Pyramidal trajectory

In order to assess the motor function, single-pulse TMS is applied on the primary motor cortex [M1]. For this purpose, the motor evoked potentials (MEPs) of each target contralateral muscle are assessed by means of superficial electrodes. The stimulation intensity is typically given as a percentage of the threshold intensity, which creates a MEP of precise amplitude (Wassermann et al. 1992).

3.2. Mapping

Single-pulse TMS is applied in the field of cerebral mapping (Grafman & Wassermann 1999). During stimulation of several, subsequent regions of the brain in short time intervals with a focal coil it is possible to infer simultaneously the motor evoked potentials with respect to the scalp position and to compare their amplitude values. As a result, brain cartography can be obtained (Brasil-Neto et al. 1992, Wassermann et al. 1992, Cohen et al. 1991, Mortifee et al. 1994). In this way it is also possible to analyze the faculty of vision, motion and language production.

3.3. Inhibitory and excitatory intercortical mechanisms

The technique of double-pulse magnetic stimulation (paired pulse TMS) has recently proved to be a useful method for the assessment of neurophysiological activity of intracortical neurons. The principle of ppTMS consists of the application of an invasive threshold stimulus (inferior to the motor threshold), also called conditioning, and test upper threshold stimulus (superior to the motor threshold), with particular consideration of the interstimulus interval (ISI). A modulation of MEP amplitude is carried out independently from the ISI.

It is also possible to assess the ipsilateral and contralateral silent period, the long latency intercortical and intracortical inhibition. Both physiological and pathologic cerebral processes, as well as pharmacological effects, are objects of analysis (Pascual-Leone et al. 1992, Valls-Solé et al. 1992, Day et al. 1989, Pascual-Leone et al. 1993).

4. Therapeutic application of rTMS

The possibility of carrying out stimulation on circumscribed cortical areas through rTMS independently from frequency led to the fact that this technique has come to play a very particular role in neuropsychiatry (Post et al. 1999).

Although the mechanism of action is only partly known, neurophysiological effects caused by rTMS indicate some plastic alterations of the neuronal membrane (Siebner & Rothwell 2003). The concept of "neuronal plasticity" describes the capacity of constant alteration of the structural and functional brain properties. This includes the modification of membrane proteins (molecular plasticity), morphological alterations, such as the regeneration processes (structural plasticity), and the modification of synaptic transfer (functional plasticity). Long term alterations can be caused by long term potentiation (LTP), or long term depression (LTD). It is well known that electric high frequency stimulation provokes a long-lasting strengthening of the postsynaptic response to stimulus (LTP) (20). LTP has been object of research in some studies as the requirement of special forms of learning (Gustafsson & Wigstrom 1988, Iriki et al. 1991, Silkis et al. 1994). Low frequency electric stimulation provokes LTD, which has an inverse effect compared to LTP. LTP and LTD have also been demonstrated in preclinical studies with rTMS (Wu et al. 2000). Clinical studies with rTMS indirectly point at a similar mode of action in humans. Neurophysiological phenomena such as EEG alterations, as well as alterations in the visual output – in relationship with the theoretical theories of plastic-neuronal modulation – have been observed independently from the rTMS frequency (Wu et al. 2000, Catafau et al. 2001, Chen et al. 1997, Knecht et al. 2003, Muelbacher et al. 2000). Recently, it has been possible to provide some indirect evidence to support the theory of cortical plastic alterations provoked by rTMS in humans.

Low frequency stimulation of left premotor cortex modifies the MEP amplitude at the level of the ipsilateral motor cortex, as well as the excitability threshold, which were assessed even one week after the day of the experiment. Moreover, in this way it was possible to demonstrate the neuronal function-control system between areas 4 and M1 (Baeumer et al. 2003). The onset of psychiatric diseases is due to the dysfunction of different areas that are linked to each other. For this purpose, crucial importance is given to some new concepts, such as the brain's ability to modify at the plastic level both as a consequence of stressful factors, and of pathologies like Major Depression and, on the other hand, as a consequence of treatments (Spedding et al. 2003). Therefore, the idea of integrating rTMS in modulation therapy of these dysfunctions seems to be rational. The clinical applications of rTMS are based on intervening directly on specific cortical areas in order to increase or diminish their activity. Therefore, rTMS has been introduced in the treatment of syndromes that are likely to be characterized by cortical excitability, such as auditory hallucinations (Hoffmann et al. 2003). Several studies have identified a dysfunction at the level of the dorsolateral prefrontal cortex in patients with Major Depression. Nevertheless, not only the effects described in cortical areas that can be directly stimulated with TMS, but also of alterations induced by rTMS were observed in subcortical areas, which play an essential role in the causes of depression (Hausmann et al. 2000, Hausmann et al. 2002, Keck et al. 2002).

II. BASIC RESEARCH OF THE SUPERIOR CEREBRAL FUNCTIONS

1. General

Currently, there is intense activity in the field of research on superior cerebral functions by means of TMS/rTMS. Such perspective was also supported by a general article published in Science "Faster thinking thanks to rTMS" (Helmuth 2001). After a strong impulse of the last years on the application of TMS in depression, research has also concentrated on the application of TMS in the modulation of further cognitive processes (George et al. 1999). Through the induction of excitatory and inhibitory effects on the neuronal membrane it is possible to provoke transitory functional lesions that are defined in their spatio-temporal coordinates in different cerebral areas (Pascual-Leone et al. 2000). In this way, for instance, it is possible to interrupt language production or the linguistic flux through high frequency stimulation of the motor linguistic area on the dominant hemisphere (Epstein et al. 1999). A suppression of the field of vision after rTMS on the parietal cortex was also detected (Grafman et al. 1994). Cognitive functions seem thus to depend on an interaction between different centres that might be topographically distant from each other, as well as their neuronal connections. Research with Positron emission tomography (PET) and functional Magnetic Resonance Imaging (fMRI) confirms a perspective of this kind (Hallett 2000). However, these techniques are affected by a methodological limitation; they have a higher spatial resolution than rTMS, but a reduced temporal resolution, and cannot for example establish relations between the activation of one area and its respective function (Cracco et al. 1999). rTMS can modulate cognitive functions in several circumscribable areas, so that topography and function can be correlated in a minimal time interval. This spatio-temporal relationship is defined as "causal chronometry" (Pascual-Leone et al. 2000, Nikulin et al. 1993).

2. Modulation of cognitive functions

2.1. Plasticity of the visual cortex

The aforementioned capacity of TMS to induce a stimulus in a circumscribed area has been used to assess the reorganization or plasticity of human motor cortex as a consequence of several diseases. TMS presents therefore an investigating function in order to detect neuronal nets, and not for therapeutic intervention alone. Pascual-Leone and Torres (Pascual-Leone & Torres 1993) were able in this way to determine that blind patients who read Braille activate an expanded cortical area for the finger they use while reading when compared to the non-Braille-reading control group. Stimulation of the occipital visual cortex worsens tactile perception in blind subjects, whereas correspondent topograhic stimulation for sighted patients did not display such suppression. The authors came to the conclusion that the visual cortex in blind patients can be taken into consideration as a secondary aspect compared with other somatosensitive tasks, thus giving evidence that tactile perception is more sensitive in blind subjects than in normals (Cohen et al. 1997). Cohen et al. (1999) have shown in 5 subjects suffering from acquired blindess as compared with subjects with congenital blindness or blindness acquired in early years, that modal crossed plastic elaboration (visual cortex is activated in the Braille-reading-patient through tactile stimuli) is limited to the case of those subjects who have lost their faculty of vision before age 14. Nonetheless, research using TMS in healthy subjects has shown that visual perception is altered in the central representation of visual stimuli after rTMS application to the occipital cortex (area 17). It has been possible to make this activation in the occipital cortex visible also by means of a visual activation paradigm through PET (Kosslyn et al. 1999). Therefore, this research has acquired a pivotal role, since it witnesses a long-term alteration. Further research that proves the "causal chronometry" of the visual cortex (striate and parastriate areas) during the tactile discriminatory faculty was published by Zangaladze et al. (1999). The authors combined TMS and PET with the derivation of evoked potentials. In the course of a tactile- oriented task it has been possible to assess an activation of the occipital cortex through PET. The potentials correlated to an event have shown the involvement of cortex in relationship to time in the area under the scalp.

2.2. Plasticity of the motor cortex

In a first study, Olivieri et al. (1999) were able to show laterality with dominance of right hemisphere in the stimuli perceptions as a consequence of the administration of a very weak electric stimulus that was applied in the first, third and fifth finger of either hand or both hands at the same time. Single-pulse TMS on the right parietal cortex after 20 or 40 ms from the moment of stimulation of the fingers reduced patients ability to perceive this stimulus, especially after stimulation of both sides. Stimulation of the left side of the parietal cortex had as a consequence an analogue effect but to a lesser extent. Subsequently, the same group (Olivieri et al. 1999) examined patients with lesions in the right hemisphere using the same stimulation parameters. In the case of electric stimulation on both sides, patients often were not able to perceive the stimulus coming from the left side. TMS at the level of the frontal cortex, but not at the parietal cortex, has reduced the number of non-perceived digital electric stimuli significantly. These results have sustained the hypothesis that spatial perception might be explained through interhemispheric competition. Competition might thus be asymmetrical (Kinsbourne 1993). This phenomenon has been described in animal models as unilateral spatial neglect, a syndrome consisting of an attentional and spatial deficit opposed to the brain lesion. In this way, rTMS could play an interesting role in the treatment of patients suffering from spatial attention or neglect syndrome through long-term alterations of cortical excitability. As a consequence of unilateral amputation of one upper extremity, patients showed a reduced motor threshold compared to healthy subjects, and an extended cortical excitability area of the motor cortex representing proximal muscles (Cohen et al. 1991, Fuhr et al.1992, Levy et al. 1991). Kew et al. (Kew et al. 1994) have shown a reorganisation of cortical blood flow (rCBF) that is assessed by means of PET in patients who had undergone amputation of the upper extremity. Even the transient functional deafference of peripheral nerves has an effect on a fast plastic reorganisation. In this way, a nervous ischemic stroke was carried out at the level of the forearm, with an associated cortical stimulation. Results have demonstrated that a transient functional deafference in the peripheral nerves leads as a consequence to a rapid plastic alteration of the respective cortical areas (Ziemann et al. 1998).

2.3. Learning / Memory

TMS allows both the research and the modulation of learning processes. Pascual-Leone et al. have assessed cortical excitability through TMS by carrying out a test on motor reaction. When subjects become accustomed to a test, they develop an implicit consciousness of the test's recursive models. This leads to a progressive enlargement of the cortical representations in the motor areas involved in the task (Pasqual-Leone et al. 1994) and gives further evidence of the fast functional plasticity of cortical areas. The same group has shown that, by carrying out TMS on the left temporal cortex and dorsolateral prefrontal

Table 1. *Parkinson's Disease treatment*

Author	n	Stimulation Spot	Intensity	Frequency (Hz)	Total stimulus	Effectiveness
Pascual-Leone	6	M1	90%MS	5		yes
Siebner	12	M1	90%MS	5	2250	yes
Malley	49	Cz	variable	1	420	yes
Shimamato	8	prefrontal	700 Volt	0,2	480	yes
Glabra	11	M1	90%MS	5	?	no
Tergau	7	Cz	90%MS	1-20	1000	no
Siebner	10	M1	90%MS	5	2250	yes
de Groot	9	M1	90%MS	5	2250	yes
Boylan	10	SMA	100%MS	10	2000	no
Okabe	85	CZ, 0z	110%MS	0,2	800	no
Ikeguchi	12	frontal, occipital	700 Volt	0,2	600	no
Khedr	36	M1	>100%	5	20000	yes

SANS = Scale for Assessment of Negative Symptoms; PSYRATS = Psychotic Symptom Rating Scale; BPRS = Brief Psychiatric Rating Scale; BDI = Beck Depression Inventory; STAI = State Trait Anxiety Inventory (Y form)[121]; PANSS = Positive and Negative Syndrome Scale; Hallucination Change Scale [123]; MS % = Motor threshold in percentage; M1 = Primary motor cortex; Cz, Oz = International system 10-20 EEG; SMA = supplementary motor area; MS = motor threshold temporal bilateral cortex (DLPFC), newly learnt words from a list were retrieved from memory faster. This shows a positive effect of rTMS as far as brain functions are concerned (Mottaghy et al. 1999). Another study has described the role of left DLPFC in identifying analogies. This kind of recognition is essential when the subject has to filter specific details from different types of information. After stimulation with high frequency rTMS (5 Hz) recognition times were significantly reduced (Boroojerdi et al. 2001).

TMS can also reduce brain performance, according to the area stimulated and application parameters (Grafman et al. 1994). High frequency stimulation on either right or left DLPFC, but not on the frontal medial area made working memory worse in healthy subjects. Despite a similar effect on the brain, in the images obtained through PET, stimulation of left DLPFC showed only a significant reduction of blood flow in the area directly below to the stimulation point, whereas stimulation of right DLPFC also caused a biparietal reduction of blood flow (Mottaghy et al. 2000, Rami et al. 2003).

III. Clinical application

1. Treatment of Parkinson's Disease

The first attempts to treat Parkinson's Disease with rTMS date back to an experiment carried out by Pascual-Leone et al. (Pasqual-Leone et al. 1994) who managed to demonstrate that high frequency rTMS (5 Hz) on primary motor cortex (M1) improved reaction times significantly. In experiments on animals it was possible to prove that high frequency rTMS frontal brain areas had modulatory effects in the mesostrial and mesolimbic dopaminergic system. Moreover, some alterations in the excitability of the cortical inhibitory system took place (Keck et al. 2002).

During a controlled study, Siebner et al. (1999) have shown how 12 patients suffering from Parkinson' s disease who were not given any medicines showed a significant improvement in their level of bradykinesia through rTMS at the level of M1, even beyond the stimulation end. Despite the fact that up to that point some clinical improvements had been reported on motricity after treatment with TMS, data on efficacy were controversial. Even the same group (Siebner et al. 2000) could not replicate the prior results when the number of cases was extended to 11 patients who underwent the procedure under threshold stimulation (5 Hz). A survey that had been carried out by Khedr et al. has reported an improvement of motor functions compared to placebo (Khedr et al. 1993). Columbia University research team hypothesized an improvement of clinical symptomatology as a consequence of stimulation of the supplementary motor area (SMA). However, a partial worsening of whatever SMA does was assessed (Boylan et al. 2001).

Due to the heterogeneity of samples studied of the course of the disease, concomitant pharmacological treatments, different stimulation points and intensity levels, as well as the discordant results, a routine clinical application of rTMS in the treatment of Parkinson's disease is not advisable to date.

2. Treatment of Mood Disorders

2.1. Treatment of Major Depression

Most clinical studies with rTMS in psychiatric disorders have actually been focused on the efficacy of the technique in Major Depression (Hausmann et al. 2002), which is also the psychiatric field where rTMS has received more indications and approvals worldwide. However, in the meta-analysis carried out, authors came to the conclusion that in spite of statistical meaningfulness, clinical results were not totally convincing and current rTMS application in the treatment of mood disorders is still to be considered at an experimental stage (Burt et al. 2004). Anyway, it is important to emphasize that, by the end of 2008, the FDA gave first instruction on how to use high frequency TMS in the treatment of pharmacoresistant major depression. Further multicentric studies in this field are however essential for a better definition of stimulation parameters (session duration, number of sessions, necessity of a preservation therapy). Most published current literature on rTMS refers to experiences with small patient groups. In the case of studies with an adequate number of patients, O'Reardon et al. have shown an antidepressive effectiveness value of 0.4, slightly higher than the placebo value (O'Reardon et al. 2007).

It should be considered that a metanalysis of 52 studies on pharmacological treatment of major depression with antidepressives (which have a doubtless clinical effectiveness) was not able to show any effectiveness as for placebo in 50% of cases (Parker 2003). Actually, using rTMS as "augmentation" to pharmacological treatment truly represents one of the major foci in clinical research with this procedure (Rumi et al. 2007). Herwig et al., in a survey on the effectiveness of TMS in "augmentation", have reported negative results (Herwig et al. 2007), whereas two recent studies have on the contrary reported positive results (Bretlau et al. 2008, Avery et al. 2008). It is essential to consider again a series of parameters with further research in order to optimize the clinical effectiveness of rTMS. For instance, a longer lasting treatment of at least four weeks seems to be crucial in order to obtain a clinical response (Fitzgerald et al. 2003, Holtzheimer et al. 2004, Martin et al. 2002). Moreover, as pointed out in recent studies, the so called "priming", that is stimulation prior to therapeutic stimulation for a neuronal excitatory effect, could be able to significantly improve the antidepressive effectiveness of TMS (Fitzgerald et al. 2008).

Anyhow, technique can be applied with a high safety level; also no secondary cognitive effects have been reported, even with aggressive stimulation parameters (Hausmann et al. 2004). The clinical aspect referring to short and long term tolerability is surely one of the most interesting, and is the main focus of TMS. The technique does not require anaesthesia, it is painless (there may be an irritating feeling due to high frequency stimulation) and generally without significant side effects. The most common side effect may be headache that is generally very light and lasts only a short time after stimulation. As far as the likeliness of occurrence of other events is concerned it is important to point out again the possibility that TMS can cause convulsions. This event seems to disappear completely if the treatment is carried out within safe parameters and follows some general guidelines. The latter are published on patients, as well as on non-patients that are not likely to have specific risk factors.

As far as the comparison between the effectiveness of rTMS as a possible substitute to electroconvulsant therapy (ECT), it seems that ECT (is characterized by a completely different mechanism of action than TMS) can be more efficient than TMS on Major Depression. In a meta analysis, Burt et al. (Burt et al. 2002) compared the effectiveness of rTMS with that of ECT and found an average reduction of 28.94 ± 23.19 % in the Hamilton Depression Rating Scale (HDRS) in studies with rTMS, compared with a reduction of 72 % in studies with bilateral ECT. Similarly, also the survey by McLoughlin et al. dating back to 2007 confirms this difference in the therapeutic effectiveness between ECT and rTMS, and also points at an economic advantage for EST (McLoughlin et al. 2007). Nonetheless, it is worthwhile to highlight that the two techniques have substantially different mechanisms of action and tolerability profile being ECT certainly more invasive than rTMS and clinical comparisons between the two interventions in terms of efficacy may be of limited value. Other issues of clinical interest in relation to the use of rTMS in major depression include the efficacy of the technique in bipolar depression where limited studies exist (Nahas et al. 2003, Dell'Osso et al. 2009), the ability of augmentative rTMS to boost and accelerate response to antidepressant medications (Rossini et al. 2005, Bretlau et al. 2008) and the discontinuation effects of rTMS as well as the long-term efficacy of maintenance sessions of rTMS (Dell'Osso et al. 2009).

2.2. Treatment of mania

TMS has also been investigated in the treatment of mania, though at a far lesser extent than for Major Depression. Grisaru et al. (Grisaru et al. 1998b) have compared in a double-blind study, a group of patients suffering from manic episodes (n=9) that had been treated with high frequency stimulation (20 Hz) for more than 10 days, and a second group (n=7) which was stimulated at the level of the right DLPC. Antimanic pharmacological therapy was maintained during the survey period. There was a significant improvement in patients who had been stimulated on the right side, as opposed to the group stimulated on the left. Similar results have been assessed in a recent study (Xia et al. 2008). However Kaptsan et al. (Kaptsan et al. 2003) have shown that TMS at the level of the right DLPC was not more effective than simulated stimulation (placebo). In comparison with baseline, patients have shown more psychotic symptoms and active stimulation on the left DLPFC, which may have falsified positive results through a worsening of manic symptomatology. Currently, there is not enough evidence to hypothesize a reliable role of rTMS in the treatment of manic states (Mukherjee et al. 1994).

3. Treatment of Anxiety Disorders

The possibilities of resorting to rTMS as therapy for the obsessive compulsive disorder was the subject of research on the part of the National Institute for Mental Health (NIMH) in Bethesda (Greenberg et al. 1997). Lateral right, high frequency stimulation for a time interval longer than 20 minutes with series of 2 seconds per minute has proven to improve obsessive-compulsive symptoms for hours (n=12) even after one single session. Alfonso et al. (2001) used different stimulation parameters, such as a low frequency stimulation, and they found no significant difference in the reduction of obsessive compulsive symptoms, apart from a slight reduction of obsessive thoughts. Two further controlled studies, carried out with again different stimulation parameters, such as low and high frequency on the left DLPC, have given negative results (Prasko et al. 2006, Sachdev et al. 2007). Neither in the treatment of bulimia nervosa rTMS showed convincing results (Walpoht et al. 2008). McCann et al. (1998) have reported cases of two subjects suffering from a post-traumatic stress disease (PTSD), who have shown a symptomatological improvement after low frequency TMS (1 Hz) on the frontal right cerebral cortex. Grisaru et al. (1998a) have stimulated similarly 10 patients suffering from PTSD on the motor cortex and have noticed an improvement in the phobia symptomatology. Cohen et al. (2004) have described in their study 24 patients treated with right lateral cortex stimulation by

Table 2. *Manic disorders therapy*

Author	n	Kind of survey	Spot	Frequency (Hz)	%MS	Sessions	Stimula	Significance
Grisaru	16	Double blind parallel	RDLPC vs. LDLPC	20 Hz	80	10	8000	yes
Kaptsan	19	Double blind placebo	RDLPC vs sham	20Hz	80	10	8000	no

10 Hz, 1 Hz, or placebo stimulation in 80%. Patients who were treated at 10 Hz showed a generalised improvement. Schönfeldt–Lecuona et al. (Schonfeldt-Lecuona et al. 2003) treated some patients affected by a functional paralysis with high frequency rTMS. Application on workdays with 4000 stimuli a day went on for more than 12 weeks. Motor functions, as well as the muscular mass were able to reorganise, and hypersensitivity diminished.

In conclusion, at least for the present, therapeutic application of TMS in the treatment of anxiety disorders still has to be verified and is at present to be considered experimental.

4. Treatment of Schizophrenia

Some studies have shown that symptoms of Schizophrenia, such as hallucinations, can be modified, even though for a short period of time, by applying low frequency rTMS as treatment (D'Alfonso et al. 2002, Hoffmann et al. 2000). Nevertheless, as for the hypothesis of using it in the clinical field, there are still some doubts. In a double-blind crossover study, a significant improvement was noticed in the negative symptomatology in patients suffering from schizophrenia. During this study, 15 patients underwent stimulation of left DLPC, (20 Hz, 100% MS, 40 x 2 sec for over 20 minutes) (Nahas et al. 2000). Rollnik et al. (2000) carried out stimulation on 12 psychotic patients suffering from hallucinations [20 Hz, 80 % MS], once again at the level of left DPFC for over 14 days, within a crossover study. The Brief Psychiatric Rating Scale (BPRS), which mainly assesses productive symptoms, has shown a significant improvement of psychotic symptoms, whereas affective and negative symptoms were unchanged. Hoffman et al. (2003) have shown in a recent study a considerable improvement of acoustic hallucinations within the context of low frequency stimulation and at an intensity of 90% of motor threshold on the left temporal lobe. There was a significant reduction of hallucination frequency in the actively treated group compared with the placebo group. In 52% of the treated patients, this effect remained at the least for 15 weeks. A recent meta-analysis proves the effectiveness of rTMS in suppressing auditory hallucinations (Aleman et al. 2007). Due to the variability of technical parameters of rTMS itself, this technique is proving to be an interesting option, though still experimental, in the treatment of schizophrenic syndrome in its different manifestations, as well as in research on neural circuits that are responsible for the syndrome (Stanford et al. 2008).

5. Potential therapeutic possibilities in the treatment of pain

Symptomatic pain therapy has up to now been carried out through either spinal cord stimulation (SCS) or electric stimulation of the motor cortex (Carroll et al. 2000, Tsubokawa et al. 1993). In 2000, Pridmore and Oberoi (2000) first described the basic hypothesis that contributed to a potential analgesic effect caused by TMS. Secondly they assumed that nociceptive stimulation may cause some plastic alterations in the central nervous system, and that TMS may act at the neuroplastic level. In this way, plastic alterations may be compensated by nociceptive stimulation. In the meantime, several other clinical studies have been published. Lefaucheur et al. (Lefaucheur et al. 1999) were among the first researchers to carry out a study

Table 3a. *Therapy of schizophrenia*

Authors	n	Kind of survey	Spot	Frequency (Hz)	%MS	Sessions	Stimula
Nahas	15	crossover sham	LDLPC	20	100	1	1600
Rollnik	12	Double blind crossover	LDLPC	20	80	10	8000
Hoffman	12	Double blind crossover	Temporal parietal left	1	80	4	?
d'Alfonso	9	open	temporal left	1	80	10	12000
Hoffman	24	Double blind randomized	Temporal parietal left	1	90	9	7920

Table 3b. *Therapy of schizophrenia*

Authors	Results
Nahas	Significance after 1 day nel SANS
Rollnik	Significative improvement of BPRS after 14 days. No significancy in case of depressive symptoms (BDI) and phobia symptoms (STAI)
Hoffman	Significative improvement of the symptomatic on a scale from 0 to 10 points on the third and fourth day
d'Alfonso	Significative improvement after one week on a standardized hallucination scale
Hoffman	Significative reduction of hallucinations on the *Hallucination Change Scale* in the verum group in comparison with the placebo group 75 % of patients with active stimulation were receptive

with TMS, in which 4 out of 8 patients under treatment showed a considerable improvement of their chronic pain symptoms. Rollnik et al. (2002) have reported an improvement of symptomatology in a cross-over study with 12 patients suffering from chronic pain symptoms, but no statistically significant difference was assessed between the two groups of patients (active stimulation versus placebo). The research team led by Kanda (Schonfeldt-Lecuona et al. 2003) demonstrated that TMS on sensory-motor cortex may lead to reworking central pain; TMS on the secondary sensory-motor cortex would suppress central pain reworking.

This fact represents a first step towards understanding these mechanisms and the therapeutic possibilities of pain treatment with TMS. In spite of an increasing number of partly controlled studies and already assessed data, stimulation parameters to be used, as well as the stimulation spot still seem to be far from being perfectly clarified and specified (Schonfeldt-Lecuona et al. 2003).

6. rTMS in the treatment of tinnitus

Low frequency rTMS was also suggested to alleviate tinnitus perception, as it inhibits cortical activity associated with tinnitus. Some positive results are available in several studies (Lefaucheur 2008). It must be noted that it was possible to combine rTMS with neuroimaging methodologies in this field, in order to select both the stimulation spot, and the adequate stimulation individually, thus opening the way to a further potential application field of TMS, that is in therapeutic adaptation of the individual patient (Kleinjung et al. 2007).

Summary

The application of TMS / rTMS is a safe method and has moderate and, above all, well known side effects. Stimulation techniques represent a reliable survey and diagnostic tool; moreover, it has a high potential in the therapeutic field, most of which is still experimental, but surely able to extend current treatment possibilities that are now available for the clinician, as has been the case with mood disorders.

Research on complex cognitive functions through TMS, combined with such diagnostic procedures as PET, SPECT or fMRI, may open new doors to neuropsychiatry. In fact, TMS and rTMS enable to understand the functioning of neuronal networks and to have an idea of brain organisation. After a traumatic episode, improvement of the cognitive performances by means of non-invasive magnetic stimulation may develop into a promising discipline in many ways and application fields. Thanks to the possibility to modulate higher cognitive functions from the outside and without any invasive operation, TMS represents a unique research tool that is still able to give essential information on brain organising structure.

The challenge of the next years will be to understand how to adopt dynamic configuration of rTMS physioelectricity in an optimal way. In fact, in addition to the repeated survey parameters to be inquired such as the coil design, frequency, duration of the single stimulus and of the whole number of sessions, intensity, interval between two stimulation sessions, and so on, also stimulation frequencies called theta, beta and alpha burst are being developed and researched on. The latter are based on a model consisting of neuronal groups associated to specific functions and their activities are very similar to the activities of neurons themselves (Plewina et al. 2007).

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References

Aleman A, Sommer IE & Kahn RS (2007). Efficacy of slow repetitive transcranial magnetic stimulation in the treatment of resistant auditory hallucinations in schizophrenia: a meta-analysis. *Journal Clinical Psychiatry* 68, 416-21.

Alfonso P, Pujol J, Cardoner N, Benlloch L, Deus J & Menchon JM (2001). Right prefrontal repetitive transcranial magnetic stimulation in obcessive-compulsive disorder: a double-blind, placebo-controlled study. *American Journal Psychiatry* 158, 7, 1143-1145.

Amassian VE, Eberle L, Maccabee PJ & Cracco R.Q. (1992). Modeling magnetic coil excitation of human cerebral cortex with a peripheral nerve immersed in a brain-shaped volume conductor: The significance of fiber bending in excitation. *Electroencephalography and Clinical Neurophysiology* 85, 9-16.

Avery DH, Isenberg KE, Sampson SM, Janicak PG, Lisanby SH, Maixner DF, Loo C, Thase ME, Demitrack MA & George MS (2008). Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *Journal Clinical Psychiatry* 69, 441-51.

Baeumer T Lange R, Liepert J, Weiller C, Siebner HR, Rothwell JC & Muenchau A (2003). Repeated premotor rTMS leads to cumulative plastic changes of motor cortex excitability in humans. *Neuroimage* 20, 550-560.

Boroojerdi B, Philipps M, Kopylev L, Wharton CM, Cohen LG & Grafman J (2001). Enhancing analogic reasoning with rTMS over the left prefrontal cortex. *Neurology* 56, 526-528.

Boylan LS, Pullman SL, Lisanby SH, Spicknall KE & Sackeim HA (2001). Repetitive transcranial magnetic stimulation to SMA worsen complex movements in Parkinson´s disease. *Clinical Neurophysiology* 112, 259-264.

Brasil-Neto JP, McShane LM, Fuhr P, Hallett M & Cohen LG (1992). Topographic mapping of the human motor cortex with magnetic stimulation: factors affecting accuracy and reducibility. *Electroencephalography and Clinical Neurophysiology* 85, 9-16.

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

Burt T, Lisanby SA & Sackeim HA (2002). Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int Journal Neuropsychopharmacology* 5, 73-103.

Carroll D, Joint C, Maartens N, Shlugman D, Stein J & Aziz T (2000). Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. *Pain* 84, 431-437.

Catafau AM, Rerez V, Gironell A, Martin JC, Kulisevsky J & Estorch M (2001). SPECT mapping of cerebral activity changes induced by repetitive transcranial magnetic stimulation in depressed patients. A pilot study. *Psychiatry Research* 106, 151-160.

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M & Cohen LG (1997). Depression of motor cortex excitability by low frequency transcranial magnetic stimulation. *Neurology* 48, 5, 1398-1403.

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

Cohen LG, Bandinelli S, Findley TW & Hallett M (1991). Motor recorganization after upper limb amputation in man. A study with local magnetic stimulation. *Brain* 114, 615-27.

Cohen LG, Bandinelli S, Topka HR, Fuhr P, Roth BJ & Hallett M (1991). Topographic maps of human motor cortex in normal and pathological conditions: mirror movements, aputations and spinal cord injuries. In Levy WJ, Cracco RQ, Barker AT, Rothwell J (eds) *Magnetic motor stimulation: Basic principles and clinical experience*. Elsevier, New York, 36-50.

Cohen LG, Celnik P, Pascual-Leone A, Corwell B, Falz L & Dambrosia J (1997). Functional relevance of cross-modal plasticity in blind humans. *Nature* 389, 6647, 180-183.

Cohen LG, Roth BJ, Nilsson J, Dang N, Panizza M, Bandinelli S, Friauf W & Hallett M (1990). Effects of coil design on delivery of focal magnetic stimulation: Technical considerations. *Electroencephalography and Clinical Neurophysiology* 75, 350-357.

Cohen LG, Weeks RA, Sadato N, Celnik P, Ishii K & Hallett M (1999). Period of susceptibility for cross-modal plasticity in the blind. *Annals of Neurology* 45, 451-460.

Cracco RQ, Cracco JB, Maccabee PJ & Amassian VE (1999). Cerebral function revealed by transcranial magnetic stimulation. *Journal Neuroscience Methods* 86, 209-219.

D'Álfonso AA, Aleman A, Kessels RP, Schouten EA, Postma A, van der Linden JA, Cahn W, Greene Y, de Haan EH & Kahn RS (2002). Transcranial magnetic stimulation of left auditory cortex in patients with schizophrenia: effects on hallucinations and neurocognition. *Journal Neuropsychiatry Clinical Neuroscience* 14, 1, 77-9.

Day BL, Rothwell JC & Thompson PD (1989). Delay in the execution of voluntary mouvement by electrical or magnetic brain stimulation in intact man. *Brain* 112, 649-663.

Dell'Osso B, Mundo E, D'Urso N, Pozzoli S, Buoli M, Ciabatti M, Rosanova M, Massimini M, Bellina V, Mariotti M, Altamura AC (2009). Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression. *Bipolar Disorder* 11, 1, 76-81.

Dell'Osso B, Altamura AC (2009). Augmentative transcranial magnetic stimulation (TMS) combined with brain navigation in drug-resistant rapid cycling bipolar depression: A case report of acute and maintenance efficacy. *World Journal Biological Psychiatry*, in press.

De Groot M, Hermann W, Steffen J, Wagner A & Grahmann F (2001). Contralateral and ipsilateral repetitive transcranial magnetic stimulation in Parkinson patients. *Der Nervenarzt* 72, 932-938.

De Ridder D, van der Loo E, van der Kelen K, Menovsky T, van de Heyning P & Moller A (2007). Theta, alpha and beta burst transcranial magnetic stimulation: brain modulation in tinnitus. *International Journal of Medical Sciences* 4, 237-41.

Epstein CM, Meador KJ, Loring DW, Wright RJ, Weissman JD & Sheppard S (1999). Localization and characterization of speech arrest during transcranial magnetic stimulation. *Clinical Neurophysiology* 110, 6, 1073-1079.

Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A & Kulkarni J (2003). Transcranial Magnetic Stimulation in the Treatment of Depression: A double-blind, placebo-controlled trial. *Archives General Psychiatry* 60, 10, 1002-1008.

Fitzgerald PB, Hoy K, McQueen S, Herring S, Segrave R, Been G, Kulkarni J & Daskalakis ZJ (2008). Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *Journal Clinical Psychopharmacology* 28, 52-58.

Fuhr P, Cohen LG, Dang N, Findley T, Haghighi S & Oro J (1992). Physiological analysis of motor representation following lower limb amputation. *Electroencephalography and Clinical Neurophysiology* 85, 1, 53-60.

George MS, Lisanby SA & Sackeim HA (1999). Transcranial magnetic stimulation: applications in neuropsychiatry. *Archives General Psychiatry* 56, 300-311.

George MS, Nahas Z, Kozol FA, Li X, Yamanaka K, Mishory A & Bohning DE (2003). Mechanisms and the current state of transcranial magneticstimulation. *CNS Spectrum* 8, 7, 496-514.

Grafman J & Wassermann EM (1999). Transcranial magnetic stimulation can measure and modulate learning and memory. *Neuropsychologia* 37,159-167.

Grafman J, Alway D, Nichelli P & Hallett M (1994). Induction of visual extinction by rapid-rate transcranial magnetic stimulation of parietal lobe. *Neurology* 44, 494-498.

Grafman J, Pascual-Leone A, Alway D, Nichelli P, Gomez-Tortosa E & Hallett M (1994). Induction of a recall deficit by rapid rate transcranial magnetic stimulation. *Neuroreport* 5, 1157-1160.

Greenberg BD, George MS, Martin JD, Benjamin J, Schlaepfer TE, Altemus M, Wasserman EM, Post RM & Murphy DL (1997). Effect of prefrontal transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. *American Journal Psychiatry* 154, 867-869.

Grisaru N, Amir M, Cohen H & Kaplan Z (1998a). Effect of transcranial magnetic stimulation in posttraumatic stress disorder. a preliminary study. *Biological Psychiatry* 44, 52-55.

Grisaru N, Chudakov B, Yaroslavsky Y & Belmaker RH (1998b). Transcranial Magnetic Stimulation in mania. A controlled study. *American Journal Psychiatry* 155, 11, 1608-1610.

Gustafsson B & Wigstrom H (1988). Physiological mechanisms underlying long-term potentiation. *Trends Neuroscience* 11, 4,156-162.

Hallett M (2000). Transcranial magnetic Stimulation and the human brain. *Nature* 406, 147-150.

Hausmann A, Kemmler G, Walpoth M, Mechtcheriakov S, Kramer-Reinstadler K, Lechner T, Walch T, Deisenhammer EA, Kofler M, Rupp CI, Hinterhuber H & Conca A (2004). No benefit derived from repetitive transcranial magnetic stimulation (rTMS) in depression: a prospective, monocenter, randomized, double-blind, sham controlled "add-on"-trial. *Journal of Neurology, Neurosurgery and Psychiatry* 75, 2, 320-322.

Hausmann A, Pascual-Leone A, Kemmler G, Rupp CI, Lechner T, Kramer-Reinstadler K, Walpoth M, Mechtcheriakov S, Conca A & Weiss EM (2004). No deterioration of cognitive performance in an aggressive antidepressant uni- and bilateral "add-on" rTMS trial. *Journal Clinical Psychiatry* 65, 6, 772-782.

Hausmann A, Walpoth M, Kramer-Reinstadler K, Hoertnagl C, Hinterhuber H & Conca A (2002). Wirkmechanismus und Wirksamkeit der Repetitiven transkraniellen Magnetstimulation (rTMS) in der Therapie der Depression. *Neuropsychiatrie* 16, 3-4.

Hausmann A, Weis C, Marksteiner J, Hinterhuber H & Humpel C (2000). Chronic repetitive transcranial magnetic stimulation (rTMS) enhances c-fos in a definite pattern in the parietal cortex. *Brain Research. Molecular Brain Research* 76, 2, 355-362.

Helmuth L (2001). Boosting brain activity from outside. *Science* 292, 5520,1284-1286.

Herwig U, Fallgatter AJ, Höppner J, Eschweiler GW, Kron M, Hajak G, Padberg F, Naderi-Heiden A, Abler B, Eichhammer P, Grossheinrich N, Hay B, Kammer T, Langguth B, Laske C, Plewnia C, Richter MM, Schulz M, Unterecker S, Zinke A, Spitzer M & Schönfeldt-Lecuona C (2007). Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. *British Journal Psychiatry* 191, 441-8.

Hoffman RE, Boutros NN, Hu S, Berman R, Krystal JH & Charney DS (2000). Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. *Lancet* 355, 1073-1075.

Hoffman RE, Hawkins KA, Gueorguieva R, Boutros NN, Rachid F & Carroll K (2003). Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. *Archives General Psychiatry* 60, 1, 49-56.

Holtzheimer PE, Russo J, Claypoole KH, Roy-Byrne P & Avery DH (2004). Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. *Depression and Anxiety* 19, 1, 24-30.

Iriki A, Pavlides C, Keller A & Asanuma H (1991). Long-term potentation of thalamic input to the motor cortex induced by coactivation of thalamocortical and corticocortical afferents. *Journal Neurophysiology* 65, 6, 1435-1441.

Kaptsan A, Yaroslavsky Y, Applebaum J, Belmaker RH & Grisaru N (2003). Right prefrontal TMS versus sham treatment of mania: a contolled study. *Bipolar Disorders* 5, 36-39.

Keck ME, Welt T, Muller MB, Erhardt A, Ohl F, Toschi N, Holsboer F & Sillaber I (2002). Repetitive transcranial mangetic stimulation increases the release of dopamine in the mesolimbic and mesostrialral system. *Neuropharmacology* 43,101.

Kew JJ, Ridding MC, Rothwell JC, Passingham RE, Leigh PN & Sooriakumaran S (1994). Reorganization of cortical blood flow and transcranial magnetic stimulation maps in human subjects after upper limb amputation. *Journal Neurophysiology* 72, 5, 2517-2524.

Khedr EM, Farweez HM & Islam H (2003). Therapeutic effect of repetitive transcranial magnetic stimulation on motor function in Parkinson´s disease patients. *European Journal of Neurology* 10, 567-572.

Kinsbourne M (1993). Mechansims of neglect. Implications for rehabilitation. *Neuropsychological rehabilitation* 4, 151-153.

Kleinjung T, Steffens T, Londero A & Langguth B (2007). Transcranial magnetic stimulation (TMS) for treatment of chronic tinnitus: clinical effects. *Progress in Brain Research* 166, 359-67.

Knecht S, Ellger T, Breitenstein C, Ringelstein EB & Henningsen H (2003). Changing cortical excitability with low-frequency transcranial magnetic stimulation can induce sustained disruption of tactile perception. *Biological Psychiatry* 53, 175-179.

Kosslyn SM, Pascual-Leone A, Felician O, Camposano S, Keenan JP & Thompson WL (1999). The role of area 17 in visual imagery: convergent evidence from PET and rTMS. *Science* 284, 5416, 167-170.

Lefaucheur J, Drouot X, Pollin B & Nguyen J (1999). Chronic pain treated by rTMS of motor cortex. *Electroencephalography and Clinical Neurophysiology* 110, 166-172.

Lefaucheur JP (2008). Use of repetitive transcranial magnetic stimulation in pain relief. *Expert Review of Neurotherapeutics* 8, 799-808.

Levy WJ, Amassian VE, Schmid UD & Jungreis C (1991). Mapping of motorcortex gyral sites non-invasively by transcranial magnetic stimulation in normal subjects and patients. In Levy WJ, Cracco RQ, Barker AT, Rothwell J(eds) *Magnetic motor stimulation. Basic principles and clinical experience*. Elsevier, New York.

Maccabee PJ, Amassia VE, Eberle LP & Cracco RQ (1993). Magnetic coil stimulation of straight and bent amphibian and mammalian peripheral nerve in vitro: locus of excitation. *Journal of Physiology* 460, 201-219.

Martin JL, Barbanoj MJ, Schlaepfer TE, Clos S, Perez V & Kulisevsky J (2002). Transcranial magnetic stimulation for treating depression. Cochrane Database of Systematic Reviews (2), CD003493.

McCann UD, Kimbrell TA, Morgan CM, Anderson T, Geraci M & Benson BE (1998). Repetitive Transcranial magnetic stimulation for posttraumatic stress disorder. *Archives General Psychiatry* 55, 276-279.

McConnell KA, Nahas Z, Shastri A, Lorberbaum JP, Kozel FA, Bohning DE & George MS (2001). The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. *Biological Psychiatry* 49, 454-459.

McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, Landau S, Brown R, Rabe-Heskith S, Howard R, Philpot M, Rothwell J, Romeo R & Knapp M (2007). The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis. *Health technology assessment* 11, 1-54

Mortifee P, Stewart H, Schulzer M & Eisen A (1994). Reliability of transcranial magnetic stimulation for mapping the human motor cortex. *Electroencephalography and Clinical Neurophysiology* 93, 2, 131-137.

Mottaghy FM, Hungs M, Brugmann M, Sparing R, Boroojerdi

B & Foltys H (1999). Facilitation of picture naming after repetitive transcranial magnetic stimulation. *Neurology* 53, 8, 1806-1812.

Mottaghy FM, Krause BJ, Kemma LJ, Topper R, Tellmann L & Beu M (2000). Modulation of the neuronal circuity subserving working memory in healthy human subjects by repetitive transcranial magnetic stimulation. *Neuroscience Letters* 280, 3, 167-170.

Muellbacher W, Ziemann U, Borojeerdi B & Hallett M (2000). Effects of repetitive transcranial magnetic stimulation on motor excitability and basic motor behavior. *Clinical Neurophysiology* 111, 1002-1007.

Mukherjee S, Sacheim HA & Schnur DB (1994). Electroconvulsive therapy of acute manic episodes: a review of 50 year's experience. *American Journal Psychiatry* 151, 2, 169-76.

Nahas Z, McConnell K, Collins S, Molloy M, Christie S & Horner M (10.Mai 2000). Non-invasive direct brain stimulation suggests that the lateral prefrontal cortex modulates the negative symptoms of schizophrenia. Chicago: 3rd Annual Meeting of the International Society of Transcranial Magnetic Stimulation (ISTS).

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

Nikulin VV, Kicic D, Kahkonen S & Ilmoniemi RJ (1993). Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. *European Journal Neuroscience* 18, 5, 1206-12.

Olivieri M, Rossini PM, Pasqualetti P, Traversa R, Cicinelli P & Palmieri MG (1999). Interhemispheric asymmetries in the perception of unimanual and bimanual cutaneous stimuli. A study using transcranial magnetic stimulation. *Brain* 122, 1721-1729.

Olivieri M, Rossini PM, Traversa R, Cicinelli P, Filippi MM & Pasqualetti P (1999). Left frontal transcranial magnetic stimulation reduces contralesional extinction in patients with unilateral right brain damage. *Brain* 122, 1731-1739.

O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, Demitrack MA, George MS & Sackeim HA (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biological Psychiatry* 62, 1208-16.

Parker GB (2003). Depressions Black and Blue: changing the Zeitgeist. *The Medical Journal of Australia* 179, 7, 335-336.

Pascual-Leone A, Wassermann EM, Grafman J & Hallett M (1996). The role of the dorsolateral prefrontal cortex in implicit procedural learning. *Experimental Brain Research* 107, 3, 479-485.

Pascual-Leone A, & Torres F (1993). Plasticity of the sensomotor cortex representation of the reading finger in braille readers. *Brain* 116, 39-52.

Pascual-Leone A, Gates JR & Dhuna A (1991). Induction of speech arrest and counting errors with rapid-rate magnetic stimulation. *Neurology* 41, 697-702.

Pascual-Leone A, Grafman J & Hallett M (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science* 263, 1287-1289.

Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J & Sato S (1993). Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroencephalography and Clinical Neurophysiology* 89,120-130.

Pascual-Leone A, Valls-Sole J, Brasil-Neto JP, Cammarota A, Grafman J & Hallett M(1994). Akinesia in Parkinson´s Desease II. Effects of subthreshold repetitive transcranial motor cortex stimulation. *Neurology* 44, 5, 892-8.

Pascual-Leone A, Valls-Solé J, Wassermann EM, Brasil-Neto JP, Cohen LG & Hallett M (1992). Effect of focal transcranial magnetic stimulation on simple reaction time to acoustic, visual and somatosensory stimuli. *Brain* 115, 1045-1059.

Pascual-Leone A, Walsh V & Rothwell J (2000). Transcranial magnetic stimulation in cognitive neuroscience-virtual lesion, chronometry, and functional connectivity. *Current Opinion in Neurobiology* 10, 232-237.

Plewnia C, Reimold M, Najib A, Brehm B, Reischl G, Plontke SK & Gerloff C (2007). Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation. *Human Brain Mapping* 28, 238-46.

Post RM, Kimbrell TA, McCann UD, Dunn RT, Osuch EA, Speer AM & Weiss SRB (1999). rTMS as a neuropsychiatric tool: present status and future potential. *Journal ECT* 15, 39-59.

Prasko J, Pasková B, Záleský R, Novák T, Kopecek M, Bares M & Horácek J (2006). The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive compulsive disorder. A randomized, double blind, sham controlled study. *Neuro Endocrinology Letters* 27, 327-32.

Pridmore S & Oberoi G (2000). Transcranial magnetic applications and potential use in chronic pain. Studies in waiting. *Journal of the Neurological Sciences* 182, 1-4.

Rahmann H & Rahmann M (1988). Das Gedächtnis. In Bergmann JF (ed) *Neurobiologische Grundlagen*. Verlag, München.

Rami L, Gironell A, Kulisevsky J, Garcia-Sanchez C, Berthier M & Estevez-Gonzalez A (2003). Effects of repetitive transcranial magnetic stimulation on memory subtypes: a controlled study. *Neuropsychologia* 41, 14, 1877-83.

Rollnik JD, Huber TJ, Mogk H, Siggelkow S, Kropp S, Dengle R (2000). High frequency repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex in schizophrenic patients. *Neuroreport* 11, 18, 4013-4015.

Rollnik JD, Wustefeld S, Dauper J, Karst M, Fink M & Kossev A (2002). Repetitive transcranial magnetic stimulation for the treatment of chronic pain – a pilot study. *European Neurology* 48, 1, 6-10.

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

Rudiak D & Marg E (1994). Finding the depth of magnetic brain stimulation: a re-evaluation. Electroenceph. *Clinical Neurophysiology* 93, 358-371.

Rumi D, Conca A, Herwig U, Gattaz W & Marcolin MA (2007). Repetitive Transcranial Magnetic Stimulation in Augmentation of Antidepressant Drugs. In Marcolin MA, Padberg F (eds) Transcranial Brain Stimulation for Treatment of Psychiatric Disorders. *Advances in Biological Psychiatry* 23, 84-96.

Sachdev PS, Loo CK, Mitchell PB, McFarquhar TF & Malhi GS (2007). Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. *Psychological Medicine* 37, 1645-1649.

Schonfeldt-Lecuona C, Connemann BJ, Spitzer M & Herwig U (2003). Transcranial magnetic stimulation in the reversal of motor conversion disorder. *Psychotherapy and Psychosomatics* 72, 5, 286-8.

Siebner HR & Rothwell J (2003). Transcranial magnetic stimulation: new insights into representational cortical plasticity. *Experimental Brain Research* 148,1-16.

Siebner HR, Mentschel C, Auer C & Conrad B (1999). Repetitive transcranial magnetic stimulation has a beneficial effect on bradykinesia in parkinson's disease. *Neuro Report* 10, 589-594.

Siebner HR, Mentschel C, Auer C, Lehner C & Conrad B (2000).

Repetitive transcranial magnetic stimulation causes a short-term increase in the duration of the cortical silent period in patients with Parkinson´s disease. *Neuroscience Letters* 284, 147-150.

Sil'kis IG, Rapoport SSH, Veber NV & Gushchin AM (1994). Neurobiology of the integrative activity of the brain: some properties of long-term posttetanic heterosynaptic depression in the motor cortex of the cat. *Neuroscience and Behavioral Physiology* 24, 6, 500-506.

Spedding M, Neau I & Harsing L (2003). Brain plasticity and pathology in psychiatric disease: sites of action for potential therapy. *Current Opinion in Pharmacology* 3,1, 33-40.

Stanford AD, Sharif Z, Corcoran C, Urban N, Malaspina D & Lisanby SH (2008). rTMS strategies for the study and treatment of schizophrenia: a review. *International Journal of Neuropsychopharmacoly* 11, 563-76.

Tsubokawa T, Katyama Y, Yamamoto T, Hirayamam T & Koyama S (1993). Chronic motor cortex stimulation in patients with thalamic pain. *Journal Neurosurgery* 78, 393-401.

Valls-Solé J, Pascual-Leone A, Wassermann EM & Hallett M (1992). Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalography and Clinical Neurophysiology, 85, 355-364.

Wagner T, Zahn M, Grodzinsky AJ & Pascual-Leone A (2004). Three-dimensional head model stimulation of transcranial magnetic stimulation. *IEEE Transactions on Bio-Medical Engineering* 51, 9,1586-98.

Walpoth M, Hoertnagl C, Mangweth-Matzek B, Kemmler G, Hinterhölzl J, Conca A & Hausmann A (2008). Repetitive transcranial magnetic stimulation in bulimia nervosa: preliminary results of a single-centre, randomised, double-blind, sham-controlled trial in female outpatients. *Psychotherapy and Psychosomatics* 77, 57-60.

Wassermann EM, McShane LM, Hallett M & Cohen LG (1992). Noninvasive mapping of muscle representations in human motor cortex. *Electroencephalography and Clinical Neurophysiology* 85, 1-8.

Wu T, Sommer M, Tergau F & Paulus W (2000). Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. *Neuroscience Letters* 287, 37-40.

Xia G, Gajwani P, Muzina DJ, Kemp DE, Gao K, Ganocy SJ & Calabrese JR (2008). Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. *International Journal of Neuropharmacology* 11, 119-30.

Zangaladze A, Epstein CM, Grafton ST & Sathian K (1999). Involvement of visual cortex in tactile discrimination of orientation. *Nature* 401, 587-590.

Ziemann U, Hallett M & Cohen LG (1998). Mechanisms of deafferention-induced plasticity in human motor cortex. *Neuroscience* 18, 17, 7000-7007.