



Guidelines

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)



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Abbreviations: AHRS, auditory hallucination rating scale; ALS, amyotrophic lateral sclerosis; AMT, active motor threshold; ARAT, action research arm test; BDI, Beck depression inventory; BDNF, brain-derived neurotrophic factor; BOLD, blood-oxygen-level-dependent; BPRS, brief psychiatric rating scale; CANMAT, Canadian Network for Mood and Anxiety Treatments; CAPS, clinician-administered PTSD scale; Cc, circular coil; CGI, clinical global impression scale; CRPS, complex regional pain syndrome; cTBS, continuous theta burst stimulation; DBS, deep brain stimulation; DCc, double-cone coil; DLPFC, dorsolateral prefrontal cortex; DPD, depersonalization disorder; dPMC, dorsal premotor cortex; ECT, electroconvulsive therapy; EEG, electroencephalography; EMCS, Epidural motor cortex stimulation; FDA, Food and Drug Administration; F8c, figure-of-eight coil; FCD, focal cortical dysplasia; FDG, 18F-fluorodeoxyglucose; (f)MRI, (functional) magnetic resonance imaging; GABA, gamma-aminobutyric acid; H-coil, Heschl coil; HDRS, Hamilton depression rating scale; HF, high-frequency; IFG, inferior frontal gyrus; ISI, interstimuli interval; iTBS, intermittent theta burst stimulation; JTT, Jebsen-Taylor hand function test; LF, low-frequency; LTD, long-term depression; LTP, long-term potentiation; M1, primary motor cortex; MADRS, Montgomery-Asberg depression rating scale; MEP, motor evoked potential; MSO, maximum stimulator output; NICE, National Institute for Health and Clinical Excellence; 9HPT, 9-hole pegboard test; OCD, obsessive-compulsive disorder; PaD, panic disorder; PANSS, positive and negative symptoms scale; PAS, paired associative stimulation; PD, Parkinson's disease; PET, positron emission tomography; PT, physical therapy; PTSD, posttraumatic stress disorder; QPS, quadripulse magnetic stimulation; rCBF, regional cerebral blood flow; RMT, resting motor threshold; (r)TMS, (repetitive) transcranial magnetic stimulation; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SANS, scale for the assessment of negative symptoms; SAPS, scale for the assessment of positive symptoms; SMA, supplementary motor area; SPECT, single photon emission computed tomography; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; TPC, temporoparietal cortex; UPDRS, unified Parkinson's disease rating scale; VS, vegetative state; Y-BOCS, Yale-Brown obsessive compulsive scale.

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HIGHLIGHTS

- Numerous studies have shown that repetitive transcranial magnetic stimulation (rTMS) produced significant clinical effects in patients with various neurological and psychiatric disorders.
- This review presents guidelines on the therapeutic use of rTMS issued by a group of European experts.
- Level A or B evidence supports an efficacy of rTMS protocols in depression, pain, motor stroke and schizophrenia.

ABSTRACT

A group of European experts was commissioned to establish guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) 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, craving/addiction, and conversion. Despite unavoidable inhomogeneities, there is a sufficient body of evidence to accept with level A (definite efficacy) the analgesic effect of high-frequency (HF) rTMS of the primary motor cortex (M1) contralateral to the pain and the antidepressant effect of HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC). A Level B recommendation (probable efficacy) is proposed for the antidepressant effect of low-frequency (LF) rTMS of the right DLPFC, HF-rTMS of the left DLPFC for the negative symptoms of schizophrenia, and LF-rTMS of contralesional M1 in chronic motor stroke. The effects of rTMS in a number of indications reach level C (possible efficacy), including LF-rTMS of the left temporoparietal cortex in tinnitus and auditory hallucinations. It remains to determine how to optimize rTMS protocols and techniques to give them relevance in routine clinical practice. In addition, professionals carrying out rTMS protocols should undergo rigorous training to ensure the quality of the technical realization, guarantee the proper care of patients, and maximize the chances of success. Under these conditions, the therapeutic use of rTMS should be able to develop in the coming years.

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1. Principles and mechanisms of action of transcranial magnetic stimulation

1.1. Principles

In 1831, Michael Faraday stated his law establishing that a time-varying current creates a magnetic field which, in turn, can induce an electric field and hence a secondary current within a nearby conducting medium. One hundred and fifty years later, [Barker et al. \(1985\)](#) proposed the first magnetic stimulator designed to stimulate the human brain transcranially, providing the prerequisite for subsequent clinical use of transcranial magnetic stimulation (TMS) ([Barker, 1999](#)). A number of TMS techniques are nowadays used for routine diagnostic application ([Chen et al., 2008](#)). The interested reader is referred to the guidelines of the International Federation of Clinical Neurophysiology ([Rossini et al., 1994](#)).

The equipment consists of a high current pulse generator able to produce a discharge current of several thousand amperes that flows through a stimulating coil, generating a brief magnetic pulse with field strengths up to several Teslas. If the coil is placed on the head of a subject, the magnetic field thus created undergoes little attenuation by extracerebral tissues (scalp,

cranial bone, meninges, and cerebrospinal fluid layer) and is able to induce an electrical field sufficient to depolarize superficial axons and to activate neural networks in the cortex. The extent of action of the current density generated into the brain depends on many physical and biological parameters, such as the type and orientation of coil, the distance between the coil and the brain, the magnetic pulse waveform, the intensity, frequency and pattern of stimulation, and the respective orientation into the brain of the current lines and the excitable neural elements. Large “circular” coils (Cc) have a wide action radius (for instance, when placed over the vertex they induce bilateral effects), which limits their use if focal stimulation is sought. Focusing is better with a “figure-of-eight” coil (F8c), reducing the stimulation zone to a few square centimeters ([Thielscher and Kammer, 2004](#)) and making it sensitive to coil handle orientation. The “double cone” angulated coil (DCc) consists of 2 large circular coils forming an obtuse angle. At the expense of stronger focus, this type of coil is useful for reaching deep targets such as the representation of the lower limbs in the primary motor cortex (M1) located within the inter-hemispheric fissure. A better compromise between depth and focus may be obtained with new types of coils that allow a lesser rate of decrease of field magnitude as a function of distance (such as the “Hesed-coil” (H-coil), “C-core coil”, or

“circular crown-coil”, among others) (Roth et al., 2007; Deng et al., 2008; Salvador et al., 2009).

Monophasic magnetic pulses are commonly used for single-pulse experiments. Conversely, for reasons of lower energy requirements, repetitive transcranial magnetic stimulation (rTMS), which will be dealt with in this paper, usually requires a biphasic stimulus waveform (Sommer et al., 2006). However, rTMS using monophasic pulses activates a relatively uniform population of neurons and could therefore be more effective in producing sustained after-effects than biphasic pulses which generate a more complex pattern of neural activation (Sommer et al., 2002b; Arai et al., 2005). For example, MEP size reduction following 1 Hz-rTMS delivered over M1 (Taylor and Loo, 2007) and MEP enhancement following 10 Hz-rTMS (Arai et al., 2007) are more marked and prolonged when monophasic pulses are used. In addition, the effects of monophasic and biphasic magnetic pulses can only be compared if the second and decisive phase of the biphasic pulse is taken as the equivalent of the initial monophasic pulse (Di Lazzaro et al., 2001; Sommer et al., 2013). Studies may be confusing when the initial phase of the biphasic pulse is retained for comparison, also given that the direction of the current can be reversed depending on the manufacturer (Kammer et al., 2001).

Most of current data on TMS effects have been derived from stimulation of M1 in healthy subjects due to the ease of obtaining motor evoked potentials (MEPs). Indeed, a suprathreshold TMS pulse delivered over the precentral region easily evokes a muscle response in normal subjects, the size of this MEP reflecting the excitability of motor corticospinal output. When the handle of an F8c is oriented parallel to the interhemispheric midline (postero-anterior direction), motor cortex TMS activates the pyramidal tract only indirectly, through the recruitment of cortical interneurons (Sakai et al., 1997). At spinal level, this is demonstrated by the recording of a succession of descending volleys (“indirect waves”, I-waves), showing the activation of various interneuronal circuits (Di Lazzaro et al., 1998, 2004a). When the handle of an F8c is oriented perpendicular to the interhemispheric midline (latero-medial direction), TMS to the M1 area can also directly activate the pyramidal tract, evoking direct waves (D-waves) at spinal level (Di Lazzaro et al., 2003). Thus, when using an F8c, the net effect of TMS will depend on the position and orientation of the coil over a gyrus or a sulcus and the direction of the current induced in the brain. An important principle is that axons rather than cell bodies are preferentially activated by pulsed neurostimulation, with respect to their spatial orientation and diameter (reviewed in Lefaucheur, 2008). Therefore, TMS generates local activation but the stimulation is at the origin of biological effects that are not only local but also occur at a distance from the stimulation site via the activated networks.

In practice, when using an F8c to stimulate M1, the lowest intensity threshold to elicit MEPs is achieved when the stimulus creates a postero-anterior current that is orthogonal to the central sulcus (Di Lazzaro et al., 2008b), i.e., with the handle of the F8c oriented 45° posteriorly and laterally. Using the reverse orientation (antero-posterior) makes the latency time increase by several milliseconds and generates late indirect waves (I3-waves). The simplest explanation why the optimal postero-anterior activation of M1 elicits MEPs would be that the Brodman area 4p in the anterior wall of the central sulcus is activated preferentially to area 4a at the crown of the precentral gyrus (Geyer et al., 1996; Fox et al., 2004). However, at least for selected parameters of stimulation, there is a preferential activation of pyramidal fibers in the most superficial cortical layers (Esser et al., 2005), as also shown by modeling studies (Miranda et al., 2003; Wagner et al., 2004). Therefore, the postero-anterior stimulation of the top of the anterior bank of the central sulcus seems to be a good site to activate the motor cortex by TMS, justifying image-guided navigation to

improve accuracy and repeatability of M1 stimulation (Ahdab et al., 2010; Mylius et al., 2013). Nevertheless, the multiplicity of geometrical configurations of induced currents and cortical foldings seemingly complicates the modeling of axonal activation schemas by TMS/rTMS (Ahdab et al., 2014). Conversely, there is evidence that an opposite current flow (antero-posterior) is better suited for inducing motor cortex plasticity (Sommer et al., 2013).

1.2. A summary of possible mechanisms of action

As mentioned above, the physiological effects of rTMS have been assessed mainly on MEP size changes in response to M1 stimulation performed in healthy and relatively young subjects. Extrapolation to non-motor cortical regions, especially under pathological conditions, should therefore be extremely cautious. Pascual-Leone et al. (1992) were among the first to study the effects of rTMS on motor cortex excitability, by showing that a series of 20 consecutive TMS pulses delivered at a frequency greater than 2 Hz gave rise to significant MEP amplitude enhancement. From the results obtained in different studies based on MEP measurement in healthy subjects, some form of consensus appeared to consider low-frequency (LF) stimulation (≤ 1 Hz) as “inhibitory” and high-frequency (HF) stimulation (≥ 5 Hz) as “excitatory”, with some nuances as a function of the intensity of stimulation and the number of delivered shocks (Siebner and Rothwell, 2003). Following these “classic” protocols, various new TMS paradigms have been developed, aimed at modifying cortical excitability (reviewed in Lefaucheur (2009a)). One of the most popular is the “theta burst stimulation” delivered as a continuous (cTBS) or intermittent (iTBS) train, the former protocol being “inhibitory” and the latter being “excitatory”, according to the changes produced in MEP size when cTBS/iTBS is applied to the M1 of healthy subjects (Huang et al., 2005). Such a dichotomy (“inhibitory” LF rTMS/cTBS vs. “excitatory” HF rTMS/iTBS) is appealing, as it is closely reminiscent of the effects of long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission obtained in the hippocampus or cerebellum of animal models (Bliss and Lomo, 1973; Malenka, 1991). However, this dichotomy is not entirely satisfying, and it has been shown that both HF and LF rTMS may have mixed excitatory and inhibitory effects (Houdayer et al., 2008). Even when the effect on the motor cortex appears specific, doubling the duration of stimulation, for example, can reverse the outcome from inhibition to excitation and vice versa (Gamboa et al., 2010). The underlying mechanisms of “excitatory” versus “inhibitory” aspects of rTMS paradigms should also be taken as relative, because MEP increase after “excitatory” HF rTMS might be in fact the result of a decrease of gamma-aminobutyric acid (GABA)-mediated intracortical inhibition (hence inhibition of inhibition), rather than a direct enhancement of motor cortex excitability (Wu et al., 2000; Di Lazzaro et al., 2001; Ziemann, 2004). Conversely, LF rTMS can enhance the net inhibitory corticospinal control, probably via GABA-B transmission, since this protocol lengthens corticospinal silent period duration, as observed in healthy subjects (Cincotta et al., 2003; Daskalakis et al., 2006; Eichhammer et al., 2007) and in patients with movement disorders (Murase et al., 2005; Borich et al., 2009; Filipović et al., 2010a). In fact, it should be considered that the effects of the various TMS protocols suppressing or enhancing cortical excitability are not homogeneous and may result from targeting and modulating various cortical circuits (Di Lazzaro et al., 2010, 2011). For example, LF rTMS can selectively suppress the excitability of circuits producing late I-waves (Di Lazzaro et al., 2008a), while cTBS reduces the excitability of circuits generating instead the early I-wave (I1) component (Di Lazzaro et al., 2005). On the other hand, it has been recently demonstrated (Hamada et al., 2013) that the concept of “excitatory” effect of iTBS vs. “inhibitory” effect of cTBS on MEP

size was highly variable between individuals, depending on differences in the interneuronal cortical networks that are preferentially recruited by the TMS pulse. This study also showed that, at a given site of stimulation, different populations of cortical interneurons are more easily activated at different times in the TMS train. This may explain why an rTMS train delivered at 5 Hz over M1 can either increase or decrease cortical excitability according to a continuous or intermittent pattern (Rothkegel et al., 2010). Thus, a comparison between studies using different protocols, even those considered equally “excitatory” or “inhibitory”, should be made with caution, in particular regarding TBS. A more recent protocol, called quadripulse magnetic stimulation (QPS) and consisting of repeated trains of 4 monophasic TMS pulses, is supposed to produce less variable effects on cortical excitability in normal subjects. When delivered over M1, QPS facilitates MEP for interstimulus intervals (ISIs) of 1.5–10 ms and suppresses MEP for ISIs of 30–100 ms (Hamada et al., 2008a). In fact, QPS modulates intracortical excitatory circuits of M1 in a manner consistent with metaplasticity (see next paragraph), whether QPS priming was delivered over M1 or the supplementary motor area (SMA) (Hamada et al., 2008a, 2009a). QPS priming over M1 or the dorsal premotor cortex (dPMC) can also modulate excitability of the primary somatosensory cortex (S1) (Nakatani-Enomoto et al., 2012). Therefore, QPS can be an effective approach to produce sustained clinical effects, but this protocol pattern has not yet been used for therapeutic purpose to date.

The level of cortical excitability in each subject at baseline, before the stimulation, is an important source of inter- and intra-individual variability of rTMS effects (Siebner and Rothwell, 2003). This could explain why rTMS effects on intracortical inhibition depend more on baseline individual values than on stimulation frequency (Daskalakis et al., 2006). For example, when cortical excitability is lowered by a previous session of transcranial direct current stimulation (tDCS), the “classically inhibitory” LF rTMS may have surprising facilitatory actions (Siebner et al., 2004), while the mirror effect (i.e., reversal of the facilitatory effect of HF rTMS) can be obtained if cortical excitability is previously tuned to a high pre-stimulus level (Lang et al., 2004). For instance, “facilitatory” HF rTMS of M1 increased intracortical inhibition in patients with chronic pain who showed defective intracortical inhibition at baseline (Lefaucheur et al., 2006a). Generally speaking, previous neuronal activity modulates the capacity for subsequent plastic changes and this major influence refers to processes of homeostatic plasticity and metaplasticity (Bienenstock et al., 1982; Abraham and Tate, 1997; Turrigiano and Nelson, 2004). Therefore, the impact of disease-related plasticity and ongoing pharmacological treatments should also be taken into account when viewing the large variability of biological or clinical effects produced by apparently identical rTMS protocols. Moreover, age, gender and genetic aspects can modify the biological and clinical effect of rTMS. In particular, still rather poorly understood genetic differences contribute to individual liability to “LTP- and LTD-like” synaptic events produced by rTMS and form a further potential source of variation in therapeutic responses (Hoogendam et al., 2010). Thus, it can be difficult to know whether the failure of a protocol of rTMS to produce a clinical effect in a given study is related to an intrinsic therapeutic inefficacy of the protocol or to the inclusion of non-responders to this protocol arising from the usually large variability of rTMS effects.

From therapeutic and rehabilitative perspectives, the main interest of rTMS resides in the persistence of clinical changes well beyond the time of stimulation. The duration of such after-effects increases with the number of stimuli delivered, and may persist minutes to hours or even days after the end of an rTMS session (Chen et al., 1997; Maeda et al., 2000; Touge et al., 2001; Gangitano et al., 2002). Again, such after-effects are reminiscent

of the data obtained from animal models, in which long-lasting enhancement of synaptic efficacy (LTP) is reported following repetitive trains of HF electrical stimulation (Bliss and Lomo, 1973). Notwithstanding these striking similarities between rTMS effects and experimental data on long-term synaptic plasticity, Ziemann and other authors (Ziemann, 2004; Cooke and Bliss, 2006; Ziemann et al., 2008) have underscored that the plausibility of such a hypothesis was only based on indirect arguments and common output effects. One must be also aware of possible placebo effects in the case of prolonged therapeutic response, with clinical remission persisting up to several months beyond the time of stimulation in patients with chronic disorders. Overall, possible long-lasting after-effects should be considered in rTMS studies with a crossover design, as these usually have a short wash-out period (1 week to 1 month), resulting in a high probability of carry-over effects.

Finally, rTMS can interact with spontaneous oscillatory rhythms existing in the cortical circuits activated by the stimulation (Houzé et al., 2013). This may induce an activity-dependent modulation according to phase-locking synchrony between cortical oscillations and the pattern of the stimulation (Bear and Kirkwood, 1993; Morris et al., 2003). It is known that the pathophysiology of various brain disorders, such as Parkinson's disease (PD) (Brown, 2006), relies on the existence of pathological rhythms in neural networks between cortical and deep brain structures. Modulating these rhythms may be a valuable therapeutic approach, optimally designed in closed-loop stimulation techniques (Beuter et al., 2014). It is tempting to consider that the frequency- and pattern-dependent therapeutic effects of rTMS could come, at least in part, from an interaction with some altered oscillations involving cortical networks (Fuggetta and Noh, 2013).

All these aspects may contribute to the fact that an rTMS protocol is effective or not, depending on subtle differences in the parameters of stimulation. For example, in 2007, one large, multicenter, randomized, placebo-controlled trial of rTMS in depression, performed in the USA and Australia, showed positive results in favor of the antidepressant efficacy of rTMS and led to Food and Drug Administration (FDA) approval of rTMS for this disease in the USA (O'Reardon et al., 2007b). At the same time, a German and Austrian multicenter trial, also based on 10 Hz rTMS applied to the left dorsolateral prefrontal cortex (DLPFC), reported a lack of efficacy compared to placebo (Herwig et al., 2007). In fact, several methodological differences might have contributed to this discrepancy, including the intensity of stimulation (120% vs. 110% of RMT), the position of the coil (5 cm anterior to M1 vs. F3), the duration of stimulus train (4 s vs. 2 s) and intertrain interval (26 s vs. 8 s), the number of stimuli per session (3000 vs. 2000), the total duration of the daily sessions (37.5 min vs. 16.6 min) and protocol (4–6 vs. 3 weeks of stimulation), and most important, the pharmacological treatment (drug-free vs. add-on antidepressant medication). Thus, one must be very careful when considering the positive or negative outcome of rTMS studies and should go into the details of the methods for any comparative analysis. This also means that the technique must be rigorous and justifies a very specific training for rTMS operators.

1.3. Distant actions

Depending on the intrinsic properties and geometrical orientation of fibers within the cortical region stimulated, the magnetic stimulus not only activates local interneuronal circuits, but also those fibers projecting ortho- or antidromically to distant structures (Fox et al., 1997; Siebner et al., 2008; Di Lazzaro et al., 2011; Lefaucheur, 2012). One example of these distant effects is inter-hemispheric interaction between homologous networks in both M1 cortices, whereby a stimulus delivered over one motor

cortex can exert, some milliseconds later, either inhibitory (Ferbert et al., 1992) or facilitatory (Hanajima et al., 2001) effects over the contralateral motor area. This inter-hemispheric M1 interaction may also produce secondary effects on the responsiveness of S1 through cortico-cortical connections (Mochizuki et al., 2004).

The distant actions of rTMS were initially demonstrated in studies exploring the functional connectivity between M1 and the dPMC, showing that rTMS over the dPMC modulated M1 excitability to a higher extent than direct M1 stimulation itself (Gerschlag et al., 2001; Munchau et al., 2002a; Rizzo et al., 2004). Studies coupling rTMS and functional imaging have lent support to these neurophysiological data (Bestmann et al., 2005; Siebner et al., 2008). Thus, even at a stimulation intensity below the resting motor threshold (RMT), HF rTMS of the dPMC entails a significant change of blood-oxygen-level-dependent (BOLD) signal within large and distant areas of the cortex, including the contralateral DLPFC, SMA, S1, motor cingulate and inferior temporal cortices, as well as in sub-cortical structures such as the caudate nucleus and cerebellum (Bestmann et al., 2005). Using single photon emission computed tomography (SPECT), LF rTMS of M1 was also found to produce large and distant, significant changes in regional cerebral blood flow (rCBF) in the contralateral M1, cerebellar hemisphere, parietal lobules, premotor areas, and SMA (Okabe et al., 2003a).

A number of studies have also evidenced the influence of cortical stimulation over the basal ganglia. In particular, HF stimulation of the DLPFC or M1 can increase dopamine release within basal ganglia (Keck et al., 2000, 2002; Strafella et al., 2001, 2003; Ohnishi et al., 2004; Kim et al., 2008). The stimulation of M1 might even modulate non-motor neurotransmission systems in deep brain structures, for example by enhancing endogenous opioid secretion (de Andrade et al., 2011), perhaps within the periaqueductal grey matter and the anterior cingulate (Maarrawi et al., 2007), similar to what was observed following DLPFC stimulation of experimental pain in humans (Taylor et al., 2012, 2013).

Besides distant activations due to the recruitment of various neural pathways at the site of stimulation, the extent of action of TMS also depends on the spreading of the current generated into the brain, which goes deeper in parallel with increasing stimulation intensity. Therefore, in rTMS practice, the “dose” of stimulation is usually standardized according to a percent of RMT, determined in each individual. However, RMT measurement is subject to many sources of variability, in particular according to the method used (Rossini et al., 1994; Awiszus, 2003; Hanajima et al., 2007; Silbert et al., 2013) and primarily assesses the excitability of the motor cortex. Correlation may be lacking between RMT and excitability threshold in other cortical areas, such as the visual cortex (Antal et al., 2004). Therefore, interindividual intensity calibration for rTMS outside the motor cortex continues to be a challenge.

1.4. Placebo rTMS: methodological criteria and neurobiological effects

Since the 1990s, medical or pharmaceutical studies have seldom been accepted in the absence of a randomized, parallel or crossover design, and comparison of any supposedly active treatment with a placebo or an active comparator. This is especially so when the outcome assessment is based on subjective parameters (Hrobjartsson and Gotzsche, 2001), as is typically the case in studies on antidepressant or analgesic effects. Placebo effects can even induce comparable changes to actual neuromodulatory treatments in the brain activity of PD patients implanted with deep brain stimulation (DBS) (Benedetti et al., 2004). Hence, assessment of the therapeutic action of rTMS does not escape the rule, and a definition is required of the optimal conditions for the use of sham rTMS in comparative studies. The ideal placebo rTMS should fulfill a number of criteria (Loo et al., 2000): (i) the position of the active

and placebo coils over the scalp should be the same; (ii) the subjective somatic scalp sensation (due to activation of superficial nerves/muscles) and the acoustic artifacts during stimulation should also be the same for active and sham coils, but (iii) no physiological effect on the targeted cortical region should occur for the placebo stimulation. Early work tended to consider as “placebo” the effect of an active coil positioned over an area distant from that stimulated during the active condition. This solution is not optimal, as the patient can detect the difference in stimulation site, and the “placebo” placement may induce uncontrolled physiological effects. Alternatively, the coil may be kept over the same scalp position, but oriented with an angle of 45° or 90° relative to the scalp, instead of tangentially. This strategy allows the magnitude of the field actually delivered to be decreased but does not abolish it (Lisanby et al., 2001) and does not mimic the sensation on the scalp; it is therefore not ideal either. “Sham coils” have been marketed since the 2000’s, based on different technical solutions for blocking most of the magnetic field delivered by a coil, e.g., using Mu-metal (a nickel-iron alloy) for magnetic shielding. The auditory artifact produced by a sham coil is strictly comparable to that of a “real” coil, but a sham coil induces almost no scalp sensation, therefore even naïve subjects can detect whether they are receiving placebo or real TMS. In order to reproduce such a sensation, systems associating a cutaneous electrical stimulator to the placebo coil have been developed and commercialized (O’Reardon et al., 2007b; Rossi et al., 2007b; Mennekeier et al., 2009). Although this type of stimulation theoretically meets completely the criteria for a “perfect” placebo, the cutaneous sensation remains different from that produced by a “real” coil in about half of the cases, in particular for stimulation intensities higher than 80% of RMT (Rossi et al., 2007b; Arana et al., 2008). In the quest for a “perfect” placebo condition, the inherent multimodal nature of rTMS has to be considered. TMS always combines cortical stimulation with auditory and somatosensory stimulation, which have physiological effects on their own or in combination with the cortical stimulation. Somatosensory peripheral stimulation of the scalp for example has been shown to have analgesic effects (Zunhammer et al., 2011). Therefore, the experimental design, the outcome criteria and the purpose of the study should be taken into account for choosing the best possible placebo condition. In general it is highly recommended that a “sham coil” be used, preferentially associated with concomitant electrical skin stimulation, i.e., so-called “realistic sham stimulation” (Okabe et al., 2003b; Tamura et al., 2004), while mere changes in coil orientation and placement cannot be reasonably considered as a valid placebo. Interestingly, new placebo coils have become available that allow completely blind research design: (i) the device can be pre-programmed so that the operator performing the stimulation does not know whether the condition is active or sham; (ii) the patient (or subject of investigation) cannot distinguish between sensations induced by the realistic sham and the active coil; (iii) the investigators in charge of the assessment and ratings are not aware of the applied condition. Nevertheless, efficient blinding should be controlled for by systematically questioning the patients about their guess as to group allocation.

The neurobiological effects underlying placebo, extensively studied in relation with pharmacological therapies, are multiple and imperfectly elucidated. They comprise psychological trait factors (anxiety, suggestibility), as well as the conscious expectancy of response to treatment, and an unconscious conditioning by previous treatments (Colloca and Benedetti, 2006). Placebo effects are associated with the release of several neurotransmitters, of which the most studied have been endogenous opioids (Petrovic et al., 2002) and dopamine (Strafella et al., 2003; Benedetti et al., 2005). In particular, the placebo analgesic response appears to result from a balance between endogenous opioid and cholecysto-

kinin secretion (Benedetti et al., 2005). One study on the analgesic effects of motor cortex rTMS has shown that the pain-relieving action of a placebo rTMS session was significantly enhanced when it followed a “real” session with significant analgesic effects, as compared with following a “real” but unsuccessful session (André-Obadia et al., 2011). Such differential placebo effects have also been demonstrated with analgesic drugs, such as morphine, and are probably related to an unconscious conditioning phenomenon that may contribute to the important inter-individual variability of results. The placebo effect therefore reflects a complex mixture of neurobiological effects, involving the activation of a vast neuronal network where the prefrontal regions appear to play a fundamental role (Benedetti, 2010; Krummenacher et al., 2010). Functional imaging studies suggest that the regions activated during placebo experiments closely mimic those triggered by the active therapy to which the placebo is compared. Thus, in positron emission tomography (PET) studies, placebo analgesic effects appeared to be associated with enhanced endogenous endorphin release and hyperactivity of brain regions involved in opioid analgesia, such as the perigenual cingulate (Petrovic et al., 2002), while placebo motor improvement appeared to be associated with enhanced endogenous dopamine release (Strafella et al., 2006). In view of the complexity of the neurobiological and cognitive interactions (notwithstanding the possible effect linked to the patient's awareness of the existence of a placebo condition), it would be of interest for information to be gathered in the future from “head-to-head” study designs. In such designs, a novel procedure, like rTMS, is contrasted against a “reference” treatment, thus allowing a straightforward appraisal of increased efficacy relative to existing therapies, without the uncertainties linked to placebo effects. However, such a study design with active control conditions raises other problems, such as the difficulty of efficient blinding or the choice of outcome criteria if the active treatments have differential effects on different aspects of the disease.

2. Clinical applications of rTMS: methodology followed to derive the present guidelines

For each possible indication, bibliographic research was carried out independently by several experts, using keywords that will be specified at the beginning of each section. Each expert then proceeded to a critical reading of all selected publications in order to classify them according to the following criteria, used in a previous French version of the guidelines (Lefaucheur et al., 2011a) and derived from those proposed by the European Federation of Neurological Societies (Brainin et al., 2004). First, the studies were classified (I–IV) according to decreasing value of evidence. A Class I study is an adequately data-supported, prospective, randomized, placebo-controlled clinical trial with masked outcome assessment in a representative population ($n \geq 25$ patients receiving active treatment). It should include (a) randomization concealment; (b) clearly defined primary outcomes; (c) clearly defined exclusion/inclusion criteria; (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias, and (e) relevant baseline characteristics substantially equivalent among treatment groups or appropriate statistical adjustment for differences. A Class II study is a randomized, placebo-controlled trial performed with a smaller sample size ($n < 25$) or that lacks at least one of the above-listed criteria a–e. Class III studies include all other controlled trials. Class IV studies are uncontrolled studies, case series, and case reports.

With the aim of establishing recommendations for good practice, the experts then compared their respective classifications until they reached a consensus and applied these to the levels of evidence (A–C, as follows) for each of the putative therapeutic indi-

cations of a given rTMS protocol. Level A (“definitely effective or ineffective”) requires at least 2 convincing Class I studies or one convincing Class I study and at least 2 consistent, convincing Class II studies. Level B (“probably effective or ineffective”) requires at least 2 convincing Class II studies or one convincing Class II study and at least 2 consistent, convincing Class III studies. Level C (“possibly effective or ineffective”) requires one convincing Class II study or at least 2 convincing Class III studies. No recommendation will be made in the absence of at least 2 convincing Class III studies providing similar results on the same type of clinical features with similar stimulation method. For this grading, when several studies with the same indication and methodology came from a single research group, they were only considered once (according to their best class).

For each indication, clinical results reported in placebo-controlled studies, including at least 10 patients receiving active stimulation, are summarized in a table, when at least 2 comparable studies (same cortical target and same stimulation frequency, except for epilepsy) were published by independent groups before the end of the bibliographic search (March 2014). These tables give the number of patients who actually received rTMS therapy, excluding dropouts. In trials with parallel arms, the respective number of patients in the active and control groups are indicated. The absence of indication means a crossover design with both active and control conditions applied to all patients. In the “Results” column, the main results are usually summarized as a function of the significance of the effect of active rTMS versus control condition. Following this analysis, we propose an overview of the level of evidence that can be currently recommended for a given therapeutic indication of rTMS, according to specified parameters of stimulation.

3. Pain

The present literature review and recommendations exclusively concern ongoing chronic pain and therefore exclude publications on the use of rTMS to relieve provoked acute or experimental pain, which has been reviewed elsewhere (Mylius et al., 2012b). Chronic pain can be neuropathic (originating from a lesion or disease of somatosensory systems, either peripheral or central), non-neuropathic (due to an excess of nociception secondary to inflammation or tissue lesion, or psychogenic), or without proven cause. Actually, rTMS has been proposed in the treatment of chronic neuropathic or non-neuropathic pain, although the underlying pathophysiological mechanisms are different. For the sake of clarity, we shall report separately the literature analysis and recommendations in these 2 nosological settings.

3.1. Motor cortex target in neuropathic pain

Neuropathic pain is a major public health problem because of its prevalence (affecting up to 6–7% of the general population (Torrance et al., 2006; Bouhassira et al., 2008) and because of the limited efficacy of current therapies: only 30–40% of patients declare they receive satisfactory (>50%) relief from their chronic pain through pharmacological treatment (Attal et al., 2006). Epidural stimulation of the motor cortex (EMCS) was proposed by Tsubokawa and his colleagues in the early 1990s (Tsubokawa et al., 1991) to treat drug-resistant neuropathic pain. Although this procedure can give long-lasting pain relief to roughly half of the implanted patients (Crucchi et al., 2007), its mechanisms of action remain largely unknown and it has so far been impossible to derive unambiguous clinical criteria to identify, preoperatively, the candidates likely to benefit from implantation (Nutti et al., 2005). Therefore, rTMS of the motor cortex was first proposed (i) to repro-

duce the analgesic properties of EMCS, (ii) to select candidates for subsequent implanted stimulation, and (iii) to better understand the mechanisms underlying the analgesic effects of EMCS (Lefaucheur, 2006).

A PubMed search (keywords: rTMS/TBS AND neuropathic/neurogenic pain) identified 68 papers, including 19 original placebo-controlled studies with at least 10 patients with chronic neuropathic pain who received active LF or HF rTMS of M1 using an F8c (Table 1). The analyzed results cover 688 patients. Stimulation was always applied to the motor (precentral) cortex of the hemisphere contralateral to pain (usually the area corresponding homotopically to the painful zone). A responder is usually defined as a patient showing pain relief of more than 30–40% on a visual analogue scale.

Because the implantation procedure for cortical stimulation in the treatment of chronic neuropathic pain targeted M1, all the initial rTMS protocols also targeted M1. However, stimulation parameters differ between these neurostimulation techniques. For example, rTMS is usually performed at 5–20 Hz, whereas EMCS frequency is 40 Hz or more. Several rTMS studies aimed to define the optimal parameters of stimulation, comparing the respective efficacy of rTMS delivered at LF (0.5 or 1 Hz) or HF (5–20 Hz). Six Class II–III studies (Lefaucheur et al., 2001a, 2006, 2008; André-Obadia et al., 2006; Irlbacher et al., 2006; Saitoh et al., 2007), for a total of 138 patients (Table 1), consistently reported the absence of any significant analgesic effect of LF rTMS of M1 delivered contralateral to the pain side. Thus, this approach is probably ineffective (Level B recommendation). In contrast, Tamura et al. (2004) showed that 1 Hz rTMS of M1 could reduce acute pain induced by intradermal capsaicin injection in healthy subjects. Pain reduction correlated with rCBF decrease in the medial prefrontal cortex and rCBF increase in the anterior cingulate cortex in a SPECT study. However, the results of rTMS in experimental pain differ widely from those observed in chronic pain (Mylius et al., 2012b) and therefore cannot be transposed to the treatment of pain patients.

In a total of 511 patients with chronic neuropathic pain, HF rTMS delivered over M1 was found to produce significant pain-relieving effects (Table 1). Three studies, covering 50 patients, failed to observe significant analgesic effects from active HF rTMS compared to sham stimulation. These studies had methodological drawbacks, including study design and randomization (Irlbacher et al., 2006) or small sample size (André-Obadia et al., 2006; Kang et al., 2009). Negative results were also reported in a controlled study using non-focal coils (Cc and DCc) rather than a focal F8c to perform rTMS (Rollnik et al., 2002).

Regarding the effect of single rTMS sessions, a distinction should be made between earlier studies in which pain scores were assessed immediately after the stimulation and more recent studies in which pain relief was found to be significant within the first days following the rTMS protocol (Lefaucheur et al., 2011b, 2012a; André-Obadia et al., 2008, 2011; Jetté et al., 2013), since the most robust analgesic effects were found to occur 2–4 days after an rTMS session delivered to M1 (Lefaucheur et al., 2001b). Moreover, considering a therapeutic application of rTMS against chronic pain, recommendations should be based principally on studies that analyzed the persisting analgesic effect of repeated rTMS sessions (assessed during the days or weeks following the rTMS protocol), rather than that of single rTMS sessions. Six studies met this criterion (Khedr et al., 2005b; Irlbacher et al., 2006; Defrin et al., 2007; Kang et al., 2009; Ahmed et al., 2011; Hosomi et al., 2013). Two of them investigated refractory lower limb pain due to spinal cord injury (Defrin et al., 2007; Kang et al., 2009), although this is probably not the best clinical condition in which to observe pain relief by means of M1 rTMS (Lefaucheur et al., 2004b). In the first study, rTMS showed some efficacy, but detailed statistics on the long-

term effect were not provided (Defrin et al., 2007). In the second study, active rTMS seemed to perform better than sham rTMS, but statistics failed to reach significance, probably due to too small sample size (Kang et al., 2009). One (negative) study suffered from strong methodological limitations (Irlbacher et al., 2006). Two studies clearly showed long-lasting pain relief following a 5-day protocol of 20 Hz rTMS of M1 in patients with post-stroke pain (Khedr et al., 2005b), trigeminal neuropathic pain (Khedr et al., 2005b), and phantom limb pain due to amputation (Ahmed et al., 2011). Finally, the largest study to date, by Hosomi et al. (2013), was based on a 10-day protocol of 5 Hz rTMS of M1 in a multicenter series of 64 patients with chronic neuropathic pain of various origins. They found modest but significant pain reduction following active vs. sham rTMS, but they used a rather low frequency of stimulation (5 Hz) and a limited number of pulses (500) per session.

Considering all these observations, we can make a Level A recommendation for the truly significant analgesic effect of HF rTMS of M1 applied contralaterally to the pain side in patients with neuropathic pain. The main question is whether this effect could be of interest in the therapeutic management of patients with neuropathic pain in daily clinical practice. Hosomi et al. (2013) have stated that repeated daily rTMS therapy could be useful in responders, but they did not address the issue of designing a maintenance protocol for long-term efficacy. This is a crucial point. Another issue is to determine the best stimulation parameters, especially regarding how M1 is targeted. It has been nicely demonstrated by André-Obadia et al. (2008) that M1 should be stimulated with an F8c directed parallel to the interhemispheric midline (posteroanterior or anteroposterior orientation). This is based on the fact that the analgesic effects are likely produced by the stimulation of superficial fibers, tangential to the surface of the precentral gyrus (Lefaucheur et al., 2010; Nguyen et al., 2011). However, an optimal placement of the target within the precentral gyrus remains challenging (Lefaucheur et al., 2006b). Only a few studies have used image-guided navigation to perform rTMS of M1 in pain patients (Hirayama et al., 2006; Lefaucheur et al., 2012a). In particular, data provided by diffusion tensor fiber tracking could be of interest with regard to integrating a navigated approach, since it has been shown that the analgesic efficacy of rTMS is correlated with the integrity of the thalamocortical tract (Goto et al., 2008; Ohn et al., 2012).

The conclusions of our analysis of the literature data on rTMS of M1 contralateral to the pain side in patients with neuropathic pain are in accordance with those proposed by various reviews and meta-analyses published on this topic (Cruccu et al., 2007; Leo and Latif, 2007; Lefaucheur et al., 2008a; Leung et al., 2009; O'Connell et al., 2010, 2011), namely: (i) absence of efficacy of LF rTMS (pain decrease of 4% on average and >30% in only 5% of patients); (ii) significant efficacy of HF rTMS (pain relief >30% in 46–62% of patients and >50% pain relief in 29%); (iii) modest but significant analgesic effect in the long term with repeated HF rTMS sessions. The efficacy of a single HF rTMS session tends to persist for a few days and may be enhanced and prolonged with session repetition, while optimal stimulation parameters (targeting method, stimulation frequency, number of pulses per session, and number and planning of sessions) have not been determined as yet. Other “increasing-excitability” TMS protocols, such as iTBS, do not seem to be of use in producing analgesic effects, unless as a priming protocol before HF rTMS application (Lefaucheur et al., 2012a).

Whether different types of neuropathic pain respond differently to rTMS is unclear, since positive results have been reported for various neuropathic pain syndromes of both central and peripheral origins (Lefaucheur et al., 2004b; Khedr et al., 2005b; Ahmed et al., 2011; Hosomi et al., 2013). One important point for future therapeutic application is that tolerance and safety can be rated as

In this latter context, it has been shown that HF rTMS of M1 could predict the outcome of EMCS (Lefaucheur et al., 2004a; André-Obadia et al., 2006, 2014; Hosomi et al., 2008). However, rTMS tests can be used only to confirm the indication of EMCS therapy but not to exclude patients from implantation. This would require sham-controlled sessions (Lefaucheur et al., 2011b; André-Obadia et al., 2014) and a rigorously established timing of placebo sessions (André-Obadia et al., 2011). In any case, it is good clinical practice to perform such preoperative rTMS tests before considering EMCS therapy.

3.2. Non-motor cortical targets in neuropathic pain

The available evidence on the analgesic efficacy of rTMS applied to cortical targets other than M1 is quite scarce to date. A single study on 20 patients using neuronavigated HF rTMS ([Hirayama et al., 2006](#)), whose results were later reproduced in another publication from the same group ([Saitoh et al., 2006](#)), described the lack of analgesic efficacy of rTMS applied over the dPMC, SMA, or S1, whereas stimulation of M1 provided pain relief.

The possible value of DLPFC stimulation is under investigation, motivated by the proven efficacy of this target in depression, and the well-known relation between depression and chronic pain. Two pilot studies on, respectively, 4 and 9 patients with neuropathic pain, have suggested a pain-relieving effect of rTMS applied either at LF over the right DLPFC or at HF over the left DLPFC, these analgesic effects being independent of the changes in mood induced by the stimulation (Borckardt et al., 2009; Sampson et al., 2011).

3.3. Non-neuropathic pain

The analgesic effects of rTMS have been assessed in connection with various pain syndromes of non-neuropathic origin, such as fibromyalgia, migraine, complex regional pain syndrome (CRPS) of type I, and visceral and postoperative pain. A PubMed search (keywords: rTMS/TBS AND (complex regional pain syndrome OR fibromyalgia OR migraine OR visceral pain) identified 45 papers, including 11 original placebo-controlled studies with at least 10 patients who received active stimulation for fibromyalgia, CRPS or visceral pain.

CRPS Type I. Two sham-controlled studies evaluated the efficacy of HF rTMS of M1 in patients with non-neuropathic CRPS Type I. They showed a significant reduction of pain intensity, starting

almost immediately during the stimulation, but outlasting stimulation very shortly on average (Pleger et al., 2004; Picarelli et al., 2010). Actually, there was high variation between the patients regarding the duration of treatment response, one patient experiencing total pain relief for up to 3 months following rTMS (Picarelli et al., 2010). Together, these 2 Class II–III studies involve a total of 32 patients and report a possible analgesic effect from HF rTMS of M1 on CRPS Type I (Level C recommendation) (Table 2). There are currently no studies specifically assessing rTMS efficacy in CRPS Type II.

Fibromyalgia. The literature search identified 7 rTMS studies on the treatment of pain associated with fibromyalgia (total of 135 patients). These included 6 controlled studies with 2 papers on the same series of patients (Mhalla et al., 2011; Baudic et al., 2013) and one case series (Sampson et al., 2006). A prospective, randomized, controlled, double-blind study (Class II) carried out with 30 fibromyalgia patients (15 active rTMS vs. 15 sham rTMS) showed a significant reduction of global pain on a numerical scale, and improvement of quality of life for up to 1 month following 10 daily sessions of HF rTMS of the left M1 (Passard et al., 2007). A second study from the same team carried out with 30 fibromyalgia patients (16 active rTMS vs. 14 sham rTMS) confirmed these results and suggested maintenance sessions to achieve a possible prolonged effect of several months (Mhalla et al., 2011). However, no table can be presented for HF rTMS of M1 in fibromyalgia, because all of the controlled studies were performed by the same group (Passard et al., 2007; Mhalla et al., 2011; Baudic et al., 2013). The potential efficacy of HF rTMS delivered to the left M1 has not been reported to date by another team in a series of patients with fibromyalgia.

HF rTMS also showed analgesic efficacy (mean 29% difference in pain relief between active and sham conditions) when applied to the left DLPFC in 10 patients with fibromyalgia and depression, as compared with 10 other receiving sham stimulation ([Short et al., 2011](#)). Another controlled study on a small sample size (5 active rTMS vs. 5 sham rTMS but performed at LF) confirmed the efficacy of HF rTMS of the left DLPFC, while LF rTMS of the right DLPFC appeared to be more efficacious ([Lee et al., 2012b](#)). Two further studies assessed the value of LF rTMS of the right DLPFC in patients with fibromyalgia and depression. The first open study (Class IV) showed rTMS efficacy in a case series of only 4 patients ([Sampson et al., 2006](#)), whereas the second study (Class III) ([Carretero et al., 2009](#)) did not find any analgesic effect in the 14 treated patients, compared to the 12 patients receiving sham rTMS. Thus, no conclusion can be drawn as yet on the possible value of the DLPFC target in fibromyalgia. Again, no table can be presented because the literature does not provide 2 independent studies of at least 10 patients receiving either HF rTMS of the left DLPFC or LF rTMS of the right DLPFC. Therefore no recommendations can be made for this target in this indication.

Migraine. Compared to fibromyalgia, there are much less data on the therapeutic potential of rTMS in migraine. First, most rTMS studies performed with migraineurs assessed the effects of rTMS

Table 2
rTMS studies in complex regional pain syndrome type I (target: primary motor cortex).

[illegible]

on various neurophysiological markers, such as visual evoked potentials or various occipital or motor cortex excitability parameters (Bohotin et al., 2002; Brighina et al., 2002, 2005, 2010; Fierro et al., 2003; Fumal et al., 2006; Conte et al., 2010), but not the clinical impact of rTMS on migraine. Second, we must differentiate studies using “conventional” rTMS protocols from those based on single or double TMS shocks delivered during the aura of a migraine attack (Lipton et al., 2010). Despite rather debatable results, this particular approach has been the subject of a recent publication of a guidance from the National Institute for Health and Clinical Excellence (NICE) in the UK supporting the use of TMS for the prevention and treatment of migraine (<http://www.nice.org.uk/guidance/IPG477>, issued: January 2014). This recommendation was issued a few weeks after FDA approval of a specific single-pulse TMS device for this clinical application.

The efficacy of HF rTMS of the left DLPFC in the treatment of headache was first reported in 2 patients (Class IV study) who were treated for chronic depression (O'Reardon et al., 2007a). Two randomized, double-blinded, sham-controlled studies of repeated sessions of HF rTMS of the left DLPFC in patients with chronic migraine have been reported (Brighina et al., 2004; Conforto et al., 2014). The first one showed a significant decrease in the frequency and intensity of migraine attacks, as well as a reduction in oral medication, up to 1 month following 12 sessions of HF rTMS of the left DLPFC (Brighina et al., 2004). Although this study was prospective, randomized and double-blinded, only 6 patients were treated by active rTMS (vs. 5 by sham rTMS) (Class III). Conversely, in the second study, a Class III study of 18 patients with chronic migraine, a series of 23 sessions of active HF rTMS delivered over the left DLPFC during 8 weeks was found to be less efficacious than sham rTMS in decreasing the number of headache days (Conforto et al., 2014).

Another group assessed the value of HF rTMS of the motor cortex using an F8c with antero-posterior orientation, as for neuropathic pain. They first report an open study of 51 patients, showing the value of 10 Hz rTMS delivered at 70% of RMT over the hand motor hotspot of the left hemisphere to reduce the frequency of migraine attacks up to 1 month after a series of 3 rTMS sessions (Misra et al., 2012). Clinical improvement was associated with an increase in beta-endorphin plasma level (Misra et al., 2013a). More recently, these authors report a randomized, sham-controlled study of 100 patients, equally distributed in the active and sham groups, using the same rTMS protocol as described above (Misra et al., 2013b). Headache frequency, pain score and functional disability improved significantly after active rTMS compared to sham.

Finally, one controlled rTMS study was performed in 27 migraineurs and showed negative results for LF rTMS (1 Hz) applied to the vertex with a Cc (Teepker et al., 2010). In conclusion, in the absence of replicated, large controlled studies, no recommendations can be made to date for the application of any rTMS protocol in migraineurs.

Visceral pain. Literature data is still very scarce concerning the treatment of chronic visceral pain with rTMS. One pilot study reported the results of LF rTMS (1 Hz) delivered to the right secondary somatosensory cortex (S2) in 5 patients with visceral pain secondary to chronic pancreatitis (Fregni et al., 2005a). The same team replicated and extended these preliminary results in a series of 17 patients with chronic visceral pancreatic pain, but with only 9 patients receiving active treatment (Fregni et al., 2011). One caveat regarding this approach is the depth of S2, which makes it relatively difficult to target specifically. Another team reported immediate and short-term analgesic effects of HF rTMS of the left DLPFC with significant reduction of morphine consumption in 2 series of patients suffering from postoperative visceral pain sec-

ondary to gastric bypass surgery (Borckardt et al., 2006, 2008). The results of these 2 different approaches in 2 different clinical conditions of visceral pain await replication by other teams in larger placebo-controlled studies. Therefore, no recommendations can yet be made.

Conclusions. Although rTMS might represent a useful treatment for non-neuropathic pain, no conclusion can be firmly drawn given the small number of convincing studies published to date by independent teams, except for CRPS Type I, for which a Level C recommendation (possible analgesic effect) can be made. The guidelines for future research in this domain should be: (i) to compare the respective value of various cortical targets (prefrontal, precentral, or parietal regions), depending on the side (right or left hemisphere) and frequency (low or high) of stimulation; (ii) to appraise the respective effect of rTMS protocols on the various clinical aspects of these pain syndromes, especially regarding sensory-discriminant, affective-emotional, and cognitive components of fibromyalgia. Several studies already considered a “symptomatic” rather than “syndromic” approach (Lee et al., 2012b; Baudic et al., 2013). A personalized approach should reduce the very high variability in rTMS analgesic response between individuals. This objective needs to further study the rTMS response with respect to pain symptoms, pain mechanisms, cortical targets, and stimulation parameters.

4. Movement disorders

The bibliography on the use of rTMS in movement disorders is particularly extensive, with more than one hundred references, mainly concerning PD (Edwards et al., 2008). A number of these studies have, however, been discarded for this review due to various methodological limitations. First, the potential application of rTMS has not been considered in this work unless it was supported by at least 2 studies published by 2 independent research groups. Thus, despite the amount of published work, the data in the literature is still too limited to date to support any recommendation regarding therapeutic use of rTMS in cerebellar ataxia, myoclonia or Huntington's disease. In contrast, there are much more convincing data regarding PD, dystonia (in particular writer's cramp), essential tremor and Tourette's syndrome, which will be detailed here. Regarding PD, the effects of motor/premotor stimulation on motor symptoms will be presented separately from those reported for DLPFC stimulation in the treatment of depressive symptoms.

4.1. Stimulation of motor or premotor cortex in Parkinson's disease

Published studies on reducing motor impairment in PD by means of rTMS are numerous, and comprise a wide multiplicity of targets and stimulation protocols (reviewed in Wu et al., 2008; Elahi et al., 2009; Lefaucheur, 2009b). This, together with the variability of patient profile (various pharmacological treatment, disease duration, severity and type of motor symptoms) makes the emergence of a consensus on any set of stimulation procedures extremely difficult. While M1 was the most frequently studied target, clinical efficacy has been more modest using this target compared to the SMA target, the value of which was emphasized in recently published, large multicenter trials (Hamada et al., 2008b, 2009b; Shirota et al., 2013).

A PubMed search (keywords: rTMS/TBS AND Parkinson's disease) identified 159 papers, including 15 original controlled studies with at least 10 PD patients who received active LF or HF rTMS of motor cortical regions using an F8c and in which clinical motor effects of rTMS were assessed (Table 3). The analyzed results cover 454 patients.

One meta-analysis tended to show that HF rTMS produced better results than LF rTMS, regardless of which motor or premotor regions were stimulated (Elahi et al., 2009). In fact, literature regarding LF rTMS of M1 in PD is rather scarce. Following a single session of LF rTMS of M1, a few studies reported significant improvement in timed motor tasks (Sommer et al., 2002a; Grüner et al., 2010) or rigidity (Lefaucheur et al., 2004c), effects rarely described following HF rTMS in PD. However, a lack of clinical efficacy has been reported in controlled trials using repeated sessions of LF rTMS of M1 (Arias et al., 2010a; Filipović et al., 2010b), although significant changes in cortical excitability were found (Filipović et al., 2010a), as well as significant reduction in levodopa-induced dyskinesia (Wagle-Shukla et al., 2007; Filipović et al., 2009) with this type of protocol. Therefore, both positive and negative results are inconclusive and no recommendation can be made for LF rTMS of M1 in PD.

Regarding HF rTMS of M1, the first description of clinical changes was published by Pascual-Leone et al. (1994), who noted a decrease in both movement times and choice-reaction times during subthreshold 5 Hz rTMS of M1 in 6 PD patients. Although this result was not confirmed in a replicate study performed in 11 PD patients (Ghabra et al., 1999), at least 25 subsequent studies have assessed the effects of HF rTMS of M1 in PD patients. The majority of these studies supported the “therapeutic” value of HF rTMS of M1 in PD, showing global improvement of UPDRS part III motor scores, especially of movement speed or gait velocity, following the focal stimulation of hand representation (Siebner et al., 1999a, 2000a; de Groot et al., 2001; Börnke et al., 2004; Lefaucheur et al., 2004c; Kim et al., 2008) or the bilateral stimulation of a larger M1 area (Khedr et al., 2003, 2006, 2007; González-García et al., 2011). Such improvement could be related to an increase in dopamine release, although these results also suggest the possibility of placebo effects (Strafella et al., 2005, 2006; Khedr et al., 2007; Kim et al., 2008). In one controlled study, 20–22 PD patients were equally randomized for active or sham HF (5 Hz) rTMS of the leg area of M1 contralateral to the more affected leg; stimulation was 6 min followed by 30 min of treadmill training (Mak, 2013; Yang et al., 2013b). A “therapeutic” course of 12 combined rTMS sessions and treadmill training over 4 weeks resulted in increased walking speed and various neurophysiological changes, including silent period prolongation following active versus sham stimulation. Finally, a few studies have reported negative results of HF rTMS of M1 in PD (Rothkegel et al., 2009; Sedláčková et al., 2009; Benninger et al., 2011, 2012).

In summary, there are 2 positive Class III studies from independent groups, but one negative Class III study. Therefore no recommendation can be made for unilateral, “conventional” HF (5–10 Hz) rTMS of M1 of hand representation using an F8c. Such a protocol can also produce neurophysiological changes, like silent period prolongation (Siebner et al., 2000a) or modulation of intracortical facilitation (Lefaucheur et al., 2004c). However, improvement of motor performance is much more significant on statistical grounds rather than clinically relevant, especially following single sessions.

Performing repeated sessions of HF rTMS of the bilateral M1 representation of both hands and legs using an F8c is likely to increase the clinical impact of the stimulation, especially for gait and walking speed (Khedr et al., 2003, 2006). A recent study confirmed that bilateral M1 stimulation, even restricted to the lower limb representation area can be effective in producing significant motor improvement involving both finger tapping and walking (Maruo et al., 2013). Therefore, if we consider that the stimulation of a large M1 region can improve motor performance in PD patients, one may wonder if widespread, non-focal stimulation, using a Cc or H-coil could not be more effective than focal stimulation using an F8c in this context (Dragasevic et al., 2002; Málly

et al., 2004). A large Japanese multicenter trial, based on repeated rTMS sessions for 2 months using a Cc to perform “frontal cortex” stimulation at LF provided conflicting results (Shimamoto et al., 2001; Ikeguchi et al., 2003; Okabe et al., 2003b). A more recent study, based on non-focal LF (1 Hz) rTMS using a Cc centered over the vertex and performed in only 9 PD patients receiving active stimulation compared to 9 patients receiving suboptimal sham stimulation, was found to be negative (Arias et al., 2010a). Following a safety study (Benninger et al., 2009), Benninger et al. (2012) also showed that HF rTMS delivered at 50 Hz to the M1 representation of the hand on both hemispheres using a Cc was ineffective in improving motor performance in PD patients, but could prolong the cortical silent period. In contrast, a recent open-label study reported a significant motor improvement (average reduction of 11 points on UPDRS-III score) in 27 PD patients who underwent 12 sessions of HF (10 Hz) rTMS bilaterally delivered with an H-coil over M1 and DLPFC during 4 weeks (Spagnolo et al., 2014). These studies based on ‘non-focal’ stimulation are not really comparable with studies performed with an F8c. However, if we consider the trials based on bilateral stimulation of M1 (over the representation of the hands and/or legs), the balance between several positive Class II–III studies from 3 independent groups and a negative Class II study lead us to suggest a possible antiparkinsonian effect of this protocol approach (Level C recommendation).

In 2 controlled studies, rTMS was applied to multiple cortical targets over motor and also prefrontal regions within the same session (Lomarev et al., 2006; Benninger et al., 2011). The first study, based on HF (25 Hz) rTMS applied for 8 days in 18 PD patients, showed improvement in walking speed and reduction of bradykinesia for the right hand without significant change in the global UPDRS part III score (Lomarev et al., 2006). The second study, based on iTBS applied for 8 days in 26 PD patients, reported a lack of efficacy for motor performance (timed testing of gait and bradykinesia, UPDRS motor scores) and cortical excitability parameters (Benninger et al., 2011). These results are isolated and do not allow recommendations to be made. It should be noted that iTBS of M1, applied with an F8c, has been assessed in 2 other studies, one being negative (Rothkegel et al., 2009) and the other positive (Degardin et al., 2012) regarding clinical motor changes induced by the stimulation.

As to premotor stimulations, we must distinguish between a medial target, i.e., the SMA, and a more lateral target, i.e., the dPMC. Boylan et al. (2001) were the first to publish the effects of HF rTMS delivered to a premotor region (SMA) in PD patients. They noted a worsening of writing abilities and reaction times after stimulation, and underscored the unpleasant character of this stimulation protocol, which was not tolerated by 2 of the 10 subjects participating to the study. Notwithstanding this negative result, Hamada et al. (2008b, 2009b) launched a large, multicenter study in Japan on the motor and cognitive effects of HF rTMS of the SMA in PD. In this study, patients received 5 Hz rTMS sessions at high intensity (110% of active motor threshold, AMT) once a week, during 8 weeks. The first report (Hamada et al., 2008b) showed an improvement of the global UPDRS score, while the second (Hamada et al., 2009b), which selectively focused on the motor effects, highlighted that improvement essentially concerned bradykinesia. A recent multicenter Japanese trial did not confirm the efficacy of a prolonged protocol of weekly HF rTMS of SMA on motor symptoms in PD: improvement was only transient and similar to control condition (Shirota et al., 2013). Nevertheless, this study also showed that LF (1 Hz) rTMS delivered to the same target with the same protocol schedule produced significant sustained effects (improvement of 6.8 points on UPDRS-III motor score at the last visit, 20 weeks after rTMS onset, without any change in nonmotor symptoms). This Class I study providing evidence for

the efficacy of LF rTMS of the SMA on PD motor symptoms remains to be replicated by an independent team. The influence of disease severity should also be investigated further. Finally, it should be noted that LF rTMS of the SMA was also shown to improve levodopa-induced dyskinesia (Koch et al., 2005; Brusa et al., 2006) (see following Section).

HF rTMS of the dPMC is a way to modulate M1 excitability and premotor–motor interactions, which are altered in PD patients under levodopa (Buhmann et al., 2004; Mir et al., 2005). However, neither Sedláčková et al., 2009 using 10 Hz rTMS, nor Bäumer et al., 2009 using 1 Hz rTMS showed any clinical motor improvement following rTMS of the dPMC. These results are insufficient to draw any conclusions regarding dPMC target value in PD. This is the same for LF (1 Hz) rTMS of the cerebellum, which was recently found to have some impact on the motor performance of PD patients (Minks et al., 2011).

In brief, data published to date suggest possible antiparkinsonian effects of rTMS on motor symptoms, especially when applied at HF on large M1 regions of the both hemispheres. However, as reviewed by Benninger (2013), the evidence is in favor of modest effects, at most, but which on clinical grounds are irrelevant for routine treatment. Therefore, the development of a therapeutic application of rTMS in PD will require substantial improvement of the technique and protocol used.

4.2. Effects on levodopa-induced dyskinesias in Parkinson's disease

Improving limb motor performance was the goal of the majority of rTMS studies in PD. A few studies addressed other aspects of PD, such as speech production and vocal function (Dias et al., 2006; Hartelius et al., 2010; Murdoch et al., 2012; Eliasova et al., 2013), bladder function (Brusa et al., 2009), sleep (van Dijk et al., 2009; Arias et al., 2010b), or cognitive function (Srovnalova et al., 2011, 2012). No recommendations for the use of rTMS can be made for any of these disease aspects, in view of the paucity of the reported results. On the other hand, the amount of data is more significant for the impact of rTMS on depressive symptoms (see next Section) and levodopa-induced dyskinesia.

Koch et al. (2005) were the first to report the effects of rTMS on levodopa-induced dyskinesia in a controlled Class III study, based on a single session of subthreshold bilateral LF (1 Hz) rTMS of the SMA performed in 8 PD patients. HF (5 Hz) rTMS, on the other hand, was ineffective. Later, in another controlled Class III study (Brusa et al., 2006), the same group replicated their previous findings, with a reduction of dyskinesia of up to 15 min following 1 Hz rTMS of the SMA in 10 PD patients, but they did not find any enhancement of the effect after 5 repeated daily sessions.

In an open study with 6 patients, Wagle-Shukla et al. (2007) showed significant reduction in dyskinesia following 10 daily sessions of 1 Hz rTMS of M1 contralateral to the more affected side. Subsequently, in a Class II controlled study, Filipović et al. (2009) also found significant dyskinesia reduction following 4 daily sessions of 1 Hz rTMS of M1 contralateral to the more affected side. In these studies, rTMS effects were observed within 1–3 days following the intervention. However, the effect seems to have been of limited duration since it was no longer present when re-checked 2-weeks later (Wagle-Shukla et al., 2007). Similarly, a beneficial effect from 4 days of 1 Hz rTMS of M1 was recently reported in a patient with biphasic dyskinesia (Filipović et al., 2013). Extending the application of the method to other complications of long-term dopaminergic treatment, Kodama et al. (2011) showed a beneficial effect from several weeks of treatment with a once weekly application of 1 Hz rTMS of M1 coupled with physical therapy (PT) in a patient with painful off-period dystonia. Interestingly, no effect was seen when the SMA was targeted.

One group also reported a trend towards improvement of L-dopa-induced dyskinesias after a 5-day protocol of HF rTMS of the left DLPFC (Rektorova et al., 2008). Finally, reduction of peak-dose dyskinesia for up to 4 weeks was described following repeated sessions of excitability-decreasing cTBS delivered bilaterally to the lateral cerebellum in a first Class III study (Koch et al., 2009). Similar results were recently obtained by another group in another Class III study (Kishore et al., 2014), confirming that cerebellar cTBS seems to have an antidyskinetic effect in PD patients with L-dopa-induced dyskinesias. The rationale for cerebellar stimulation arises from the possibility of modulating in this way intracortical inhibition of M1 (Koch et al., 2008a) and paired associative cortical plasticity (Popa et al., 2013b). However, it should be mentioned that cerebellar TMS is particularly prone to activate peripheral afferents at the cervical level (Werhahn et al., 1996; Gerschlagner et al., 2002) and induces strong contractions in the neck muscles, making placebo control extremely difficult to perform. These caveats should be kept in mind in interpreting any results provided by cerebellar rTMS.

On the whole, all of these reports are encouraging, but there are no replicated results to date, from large controlled studies using the same target and the same parameters of stimulation. Therefore, no recommendations can be made for the control of dyskinesia and the search for the most effective protocol (LF rTMS of SMA or M1, or even HF rTMS of the left DLPFC or cerebellar cTBS) is still in progress (Koch, 2010).

4.3. HF stimulation of the prefrontal cortex in PD-related depression

A PubMed search (keywords: rTMS/TBS AND prefrontal AND depression AND Parkinson's disease) identified 14 studies on the effects of HF rTMS of the DLPFC on depressive symptoms in PD patients. Six of these studies were classified as Class IV since they were uncontrolled studies (lack of placebo or other valid control). Among the others, only 5 studies were placebo-controlled, including at least 10 patients receiving active stimulation (Table 4).

Most studies used validated scales for the evaluation of depressive symptoms (Beck depression inventory – BDI, Hamilton depression rating scale – HDRS, or Montgomery–Åsberg rating scale – MADRS), cognitive state (Mini-Mental State, or Stroop test), and motor function (Unified Parkinson's disease rating scale – UPDRS). Two studies were of Class II (Fregni et al., 2004; Pal et al., 2010) and 4 studies (Boggio et al., 2005; Dias et al., 2006; Fregni et al., 2006b; Cardoso et al., 2008) were variations derived from an original work conducted by the same group (Fregni et al., 2004). These studies aimed at comparing the effect of either real or sham HF (15 Hz) rTMS of the left DLPFC, associated with fluoxetine. The studies were conducted on 22–42 PD patients with depression, randomly distributed into the 2 groups. Taken as a whole, the studies showed a beneficial effect of rTMS, comparable to that of fluoxetine. In addition, studies from Fregni et al. (2004) and Boggio et al. (2005) also revealed a significant improvement in a number of cognitive tests under rTMS, compared to fluoxetine alone. The 2 types of treatment differed in changes induced in rCBF or BOLD activity (Fregni et al., 2006b; Cardoso et al., 2008). Pal et al. (2010) studied 22 patients with minor depression, divided into 2 groups, who underwent either sham or active rTMS at 5 Hz (600 daily stimuli during 10 consecutive days). Stimulation produced beneficial effects on depression up to 30 days after the end of the stimulation sessions. An open study of 14 PD patients also showed highly significant improvement in depression, anxiety, movement scores, and some neuropsychological measures up to 6 weeks after a 10-day protocol of HF rTMS of the left DLPFC (Epstein et al., 2007). Finally, the absence of any significant motor effect, but an improvement in depressive symptoms, was reported in at least 2 studies. One used 10 Hz rTMS of the DLPFC contralat-

Table 4
rTMS studies in depression with Parkinson's disease (target: left prefrontal cortex).

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
Fregni et al. (2004)	42 (active: 21; control: 21)	Left DLPFC, F8c	Sham coil	15 Hz, 110% RMT	3000 pulses, 10 sessions	Compared to fluoxetine: similar antidepressant effects, but less side-effects and greater motor and cognitive improvement	II
Boggio et al. (2005)	25 (active: 13; control: 12)	Left DLPFC, F8c	Tilted coil	15 Hz, 110% RMT	3000 pulses, 10 sessions	Compared to fluoxetine: similar improvement of executive functions	III
Fregni et al. (2006b)	26 (active: 13; control: 13)	Left DLPFC, F8c	Tilted coil	15 Hz, 110% RMT	3000 pulses, 10 sessions	Compared to fluoxetine: similar antidepressant effects, with increased blood flow in DLPFC and anterior cingulate gyrus	III
Cardoso et al. (2008)	21	Left DLPFC, F8c	Tilted coil	5 Hz, 120% RMT	3750 pulses, 12 sessions	Compared to fluoxetine: similar antidepressant effects, with BOLD activity reduced in the right DLPFC and increased in the left DLPFC and anterior cingulate gyrus	III
Pal et al. (2010)	22 (active: 12; control: 10)	Left DLPFC, F8c	Sham coil	5 Hz, 90% RMT	600 pulses, 10 sessions	Improvement on depression rating scales (BDI by 44% and MADRS by 26%), accuracy of Stroop test (by 16%), and motor scores (UPDRS-III by 32%), 30 days after treatment ended	II
Recommendation: probable antidepressant effect of HF rTMS of the left DLPFC in Parkinson's disease (Level B)							

eral to the affected side, but had only 8 PD patients receiving active rTMS (Del Olmo et al., 2007) and the other used iTBS of both DLPFC and M1 (Benninger et al., 2011).

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. Whether iTBS on the same target should be used as an alternative strategy remains to be determined.

4.4. LF stimulation of motor or premotor cortex in dystonia

All published studies on rTMS treatment of dystonia are based on LF stimulation of M1 or dPMC, aimed at reducing the excitability of motor cortical regions. A PubMed search (keywords: rTMS/TBS AND dystonia) retrieved 44 papers, including several original controlled studies, but we could not find at least 2 comparable studies from independent groups with more than 10 patients who received active stimulation on the same target with similar parameters of stimulation.

The clinical results concerning stimulation of M1 are scarce. In an open study of 16 patients with writer's cramp, Siebner et al. (1999b) found a significant reduction of mean writing pressure after a single session of subthreshold 1 Hz rTMS of M1 that was clinically relevant in 6 patients. In contrast, Murase et al. (2005), in a placebo-controlled study, did not find any clinical effect following one session of 0.2 Hz rTMS of M1.

In almost all other studies published so far, the rTMS target was the dPMC contralateral to the affected side. Neurophysiological and clinical effects were described in several open reports, as well as in 5 controlled studies collected for this review, 4 on focal hand dystonia (Siebner et al., 2003; Murase et al., 2005; Borich et al., 2009; Kimberley et al., 2013) and one on blepharospasm (Kranz et al., 2010). The first sham-controlled study was published by Siebner et al. (2003), who assessed the effect on timed motor tasks and rCBF of LF (1 Hz) rTMS delivered over a dPMC target defined as located 3 cm anterior to the motor hotspot. They found significant rCBF changes in cortical, subcortical and cerebellar regions following active LF rTMS of the dPMC contralateral to the more affected limb. However, this study suffered from various limitations: (i) its design was not to evaluate the potential therapeutic value of rTMS on dystonia and indeed no significant impact on motor performance was observed; (ii) only 7 patients were evaluated, compared to 7 healthy volunteers who showed roughly the same neuroimaging changes following rTMS.

Regarding patients with writer's cramp, other "sham-controlled" studies demonstrated significant improvement in writing abilities, such as precision, velocity, or exerted pen pressure following LF rTMS of the dPMC (Murase et al., 2005; Borich et al., 2009; Kimberley et al., 2013). However, the evidence-based value of these studies should be tempered due to the heterogeneity of the stimulation parameters (frequency and duration), the actual relevance of the observed effects in terms of daily life activities, and the small number of patients studied. In fact, there were only 9 and 6 dystonic patients evaluated in the first 2 studies, respectively, compared to 7 and 9 healthy controls. In the third one (Kimberley et al., 2013), 12 patients with focal hand dystonia received active LF rTMS over the dPMC, but sham stimulation was only performed in 5 additional patients. One study was based on a single rTMS session (Murase et al., 2005), whereas patients underwent 5 daily sessions in the other studies (Borich et al., 2009; Kimberley et al., 2013). In any case, clinical impact on dystonia was small and very short-lasting. Finally, clinical improvement following repeated sessions of LF (1 Hz) rTMS of the dPMC was also reported in a small open case series of patients

with segmental primary dystonia (Allam et al., 2007) or generalized secondary dystonia (Lefaucheur et al., 2004d).

Although some physiological data also support the promising strategy of acting on dystonia by inhibiting the premotor–motor interactions with an “excitability-decreasing” rTMS protocol (Huang et al., 2010), none of the aforementioned data provide a sufficient level of evidence to establish recommendations on the use of LF rTMS of the dPMC in dystonia patients, even for focal dystonia of the upper limb.

More recently, S1 was proposed as another cortical target for a therapeutic rTMS trial in dystonia. The potential of this target was based on the demonstration of functional S1 abnormalities in patients with writer's cramp, and also on modulation by LF (1 Hz) rTMS of the sensorimotor integration parameter called short-latency afferent inhibition (Bäumer et al., 2007). In addition, one open study showed that HF (5 Hz) rTMS of S1 could improve sensory discrimination in association with greater task-related activation in functional magnetic resonance imaging (fMRI) of the basal ganglia when applied in normal subjects but not in patients with focal hand dystonia (Schneider et al., 2010). The rationale of one controlled Class III study (Havrankova et al., 2010), i.e., to counteract the disturbed functioning of S1 with one session of LF (1 Hz) rTMS of S1, was found to produce significant improvement in writing abilities in 15 patients with writer's cramp. In addition, fMRI showed significant bilateral activation in the posterior parietal cortex, SMA, and S1 following rTMS. However, the results of this single study are insufficient for any recommendations to be made regarding S1 stimulation in dystonia.

Two recent studies should also be mentioned, although they cannot be included in any type of recommendation. The first one is a randomized, sham-controlled study, in which 12 patients with blepharospasm were found to be clinically improved up to 1 h after a single session of LF (0.2 Hz) rTMS of the anterior cingulate cortex, using a Cc or an H-coil (Kranz et al., 2010). However, this study suffered from methodological limitations, namely the unreliability of precisely targeting deep structures such as the cingulate cortex with standard coils and the inadequacy of the control procedure (disconnected Cc). The second study reported normalization of eyeblink classical conditioning using cTBS of the right cerebellar hemisphere in 8 patients with cervical dystonia (Hoffland et al., 2013).

4.5. Cerebellar stimulation in essential tremor

A PubMed search (keywords: rTMS/TBS AND essential tremor) identified 6 papers, including only one original controlled study with at least 10 patients (Gironell et al., 2002). The cerebellum plays a key role in the temporal synchronization of muscle activities during voluntary movement. In patients with essential tremor, a significant hyperactivity of both deep cerebellar nuclei and cerebellar cortex was demonstrated by Colebatch et al. (1990). The first published attempt to “normalize” cerebellar excitability using rTMS was reported by Gironell et al. (2002). This double blind, placebo-controlled Class III study assessed the influence of a single session of a very short train of 1 Hz rTMS (300 pulses) of the cerebellum, applied on the midline, 2 cm below inion, in patients with essential tremor of the upper limbs. As compared to placebo, rTMS induced a significant decrease of the tremor on the clinical rating scale (subjective assessment of tremor) and a reduction of the frequency tremor peak in spectral analysis immediately after the stimulation, though this did not last. This first study was partly confirmed by a second one (Class IV) which evaluated the effect – at several frequencies – of LF stimulation of the lateral cerebellum on the timing accuracy of rhythmic finger movements (thumb-index contact) (Avanzino et al., 2009). However, this study assessed the immediate effects of a short train of 1 Hz rTMS (600

pulses) in only one controlled experiment performed with 7 patients using an undescribed sham condition. One recent open trial (Class IV) showed the efficacy of one-week rTMS of the cerebellum on essential tremor in 11 patients, with significant effects persisting for 3 weeks after the last session (Popa et al., 2013a). However, to date, there is insufficient controlled data to make any recommendation regarding the use of LF rTMS of the cerebellum in essential tremor. Finally, the most recent study investigated the effect of a single session of cTBS delivered to the left M1 or dPMC (Chuang et al., 2014). A slight reduction of tremor amplitude was observed following active but not sham stimulation in patients with essential tremor. The concomitant inhibition of cortical parameters was significantly reduced compared to what was produced by cTBS in healthy controls.

4.6. Stimulation of the supplementary motor area in Tourette's syndrome

A PubMed search (keywords: rTMS/TBS AND Tourette's syndrome) identified 11 papers, including only one original controlled study with at least 10 patients (Munchau et al., 2002b). Since motor and premotor cortices are hyperexcitable in Tourette's syndrome (Ziemann et al., 1997), the first attempts to treat Tourette's syndrome using inhibitory LF rTMS targeted these regions. However, this approach proved to be unsuccessful when M1 or dPMC was targeted (Munchau et al., 2002b; Chae et al., 2004; Orth et al., 2005).

The possible beneficial effects of modulating the excitability of the SMA in Tourette's syndrome (associated or not associated with obsessive-compulsive disorders) was explored some years later by Mantovani et al. (2006) using LF rTMS. The underlying idea was again that, due to synaptic connectivity between the SMA, premotor cortex, and basal ganglia, the inhibition of the SMA by rTMS could act on the disinhibited sensorimotor neural networks at the origin of Tourette's tics. Although the study should be regarded as Class IV because of the lack of a control condition and the small sample size, the results obtained by Mantovani et al. (2006) are encouraging. They show a significant improvement in the Yale–Brown obsessive compulsive scale (Y–BOCS) immediately following several sessions of LF stimulation (1 Hz), as well as a long-lasting benefit in the Y–BOCS and clinical global impression scale (CGI), an effect that persisted up to 3 months. Preliminary indications suggest that rTMS efficacy can be improved if higher intensity is used (Mantovani et al., 2007). These results were recently confirmed in open studies of 10 and 25 children (aged under 16 years) with Tourette's syndrome (Kwon et al., 2011; Le et al., 2013), in whom 20 daily sessions of LF (1 Hz) rTMS of the SMA at 110% of RMT led to a significant improvement on both the CGI and Yale global tic severity scales lasting up to at least the 6-month follow-up. Thus, controlled studies are now needed to validate the potential therapeutic benefit of LF rTMS of the SMA for the treatment of tics, and no formal recommendation can be made as yet on this issue.

5. Stroke

The use of rTMS for therapeutic purposes or as part of a neurorehabilitation strategy for stroke recovery is relatively recent and the first clinical trials were begun in 2001 (see historical background in Hummel et al., 2008). Application of cortical stimulation in stroke is aimed at either correcting maladaptive brain plasticity induced by the cerebrovascular accident or enhancing adaptive brain plasticity during rehabilitation. This goal may be achieved by locally modifying cortical excitability or by changing connectivity in neuronal networks. The potential therapeutic value and underlying mechanisms of action of cortical stimulation depend

on the lesion size and site and the time between stroke onset and treatment application. Therefore, recommendations may depend on whether rTMS is applied during the acute, post-acute (subacute), or chronic period of stroke recovery. The acute stage is commonly defined as the first one-to-three weeks after stroke, corresponding to an acute hospital setting, although this varies greatly from country to country. The post-acute (subacute) stage is defined as the period of time immediately after discharge from the acute care unit until the chronic phase, which is commonly taken to start 6 months after stroke onset. The chronic stage is characterized by a marked slowing in the rate of naturally occurring functional recovery.

In the acute phase, there is a loss of function within the stroke-lesioned region and connected areas, altering modulatory control, especially via transcallosal projections onto homologous regions of the contralesional hemisphere (Murase et al., 2004; Floel et al., 2008). Traversa et al. (1998) first showed data suggesting that poststroke hyperexcitability of the contralesional hemisphere may in turn further decrease the excitability of the ipsilesional hemisphere, again via transcallosal projections, representing a poor prognostic factor for clinical outcome. However, there is an emerging body of literature suggesting that, in some patients at least, increased activity within the contralesional hemisphere may be adaptive and promote functional recovery (Johansen-Berg et al., 2002; Gerloff et al., 2006; Lotze et al., 2006).

While there is evidence that the neural process of interhemispheric balance and rivalry can affect both M1 and S1 (Schambra et al., 2003; Mohajerani et al., 2011), this cannot be generalized to the entire cortex. It has, for example, been shown that the degree of inhibitory interaction between the hemispheres was highly skewed in the parietal regions involved in visuospatial control (Koch et al., 2011).

In the literature, 3 types of poststroke disorders appear to benefit most greatly from cortical stimulation techniques: motor deficit, aphasia and hemineglect. The therapeutic trials in these 3 conditions commonly aimed to directly increase the excitability of the ipsilesional hemisphere or to decrease the excitability of the contralesional hemisphere, which results in a reduction of its inhibitory influence onto the lesioned hemisphere. The studies reviewed here include either “conventional” (HF or LF) rTMS protocols or TBS protocols, considering that LF rTMS and cTBS are excitability-decreasing protocols and HF rTMS and iTBS are excitability-increasing protocols. However, it is important to note that this might be a simplistic interpretation of the effects of these protocols (see Section 1.2).

5.1. Motor stroke

A PubMed search (keywords: rTMS/TBS AND motor stroke) identified 174 papers, including 19 original placebo-controlled studies with at least 10 patients who received either active LF rTMS over the contralesional hemisphere or HF rTMS over the ipsilesional hemisphere (Table 5). The analyzed results cover 501 patients. A stimulation frequency of 1 Hz was used in all LF rTMS studies, while frequencies ranged from 3 to 20 Hz in HF rTMS studies. Studies using cTBS or iTBS are sparse and to date the data emerging from them are conflicting. They are therefore not presented in Table 5. Recent comprehensive reviews and meta-analyses are available (Adeyemo et al., 2012; Ayache et al., 2012; Hsu et al., 2012; Edwardson et al., 2013; Hao et al., 2013; Le et al., 2014).

One of the first therapeutic rTMS trials to show a beneficial effect on motor performance in patients in the chronic stage of recovery after stroke used a single session of LF rTMS applied to the contralesional M1 (Mansur et al., 2005). Since then, several controlled studies have confirmed the value of this approach in the chronic, but also in the acute or post-acute phase of stroke

recovery. The number and methodological quality of these studies were sufficient to reach a Level B of probable efficacy of contralesional motor cortex LF rTMS in the chronic phase of stroke recovery. In addition, one group also demonstrated the efficacy of this protocol in a series of studies using vertex stimulation as control condition (Dafotakis et al., 2008; Nowak et al., 2008; Grefkes et al., 2010). Finally, one Japanese group has published a number of open-label studies, sometimes based on large series of patients (up to 204) with chronic stroke who seemed to benefit from repeated sessions of contralesional LF rTMS (Kakuda et al., 2010b, 2011a, 2012; Takekawa et al., 2013; Kondo et al., 2014). In these studies, rTMS was combined with intensive occupational therapy. A major, largely unresolved question from the literature is to what extent rTMS is synergistic with motor training or PT. The hypothesis that rTMS may be synergistic with motor training was supported by some studies (Avenanti et al., 2012; Conforto et al., 2012), but not by others, especially not by one recent study based on a 3-week protocol (Sieniów et al., 2012).

Fewer studies were based on HF rTMS delivered to the ipsilesional motor cortex. Soon after stroke, beneficial results were mainly reported by Khedr et al. (2005a, 2009a, 2010b). Similar results were reported by 2 other teams, one Korean (Chang et al., 2010, 2012) and the other Japanese, but this latter only in a group of 9 patients (Sasaki et al., 2013). Ipsilesional HF rTMS can be given a Level C recommendation (“possibly useful”) for patients in the acute or post-acute stage of stroke recovery. A similar recommendation can be made for chronic stroke patients, although only 2 controlled studies of more than 10 patients receiving active rTMS can be found in the literature. The first one was based on a 10-day protocol (Emara et al., 2009, 2010) (Class II), but the second one reports the results of a single session only (Kim et al., 2006) (Class III). One additional sham-controlled study showed negative clinical results, despite significant changes in motor cortex excitability in 9 patients treated by 10 sessions of ipsilesional HF rTMS combined with constraint-induced therapy (Malcolm et al., 2007).

Two comparative studies showed that contralesional LF rTMS produced a greater improvement in motor function than ipsilesional HF rTMS (Khedr et al., 2009a; Takeuchi et al., 2009). However, the reverse was reported in a third study (Sasaki et al., 2013) and both approaches appeared to perform equally in a fourth study performed in patients with chronic stroke (Emara et al., 2009, 2010). Finally, one recent open-label pilot study combined the sessions of 40-min bihemispheric motor cortex rTMS (1 Hz contralesional plus 10 Hz ipsilesional, 2000 stimuli for each hemisphere) and 240-min intensive occupational therapy (120-min one-to-one training and 120-min self-training) in hemiparetic poststroke patients at the chronic phase (Yamada et al., 2013). Motor function of the affected upper limb improved significantly, on the basis of changes in Fugl–Meyer Assessment and Wolf Motor Function Test, together with spasticity decrease according to the Modified Ashworth Scale. Nevertheless, the question of whether contralesional LF rTMS, ipsilesional HF rTMS, or both should be used still requires further investigation. In addition, we must keep in mind that the real therapeutic impact of rTMS on the daily living of patients with stroke also remains to be determined, particularly in the long term (Rossini and Johnston, 2005; Kalra and Rossini, 2010).

Some additional results are worth to be reported. First, several studies suggest that the beneficial effect of rTMS is more marked in subcortical rather than cortical stroke (Ameli et al., 2009; Emara et al., 2009). Second, there are few data on pediatric applications. One sham-controlled study showed positive results of contralesional LF rTMS in a small series of 5 children with chronic motor stroke, more than 2 years after stroke (Kirton et al., 2008). Contralesional LF rTMS combined with constraint-induced therapy was recently confirmed to be safe, feasible, and efficacious in a series of children with congenital hemiparesis aged between 8 and

Table 5
rTMS studies in motor stroke (target: primary motor cortex).

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
<i>LF rTMS of the contralesional motor cortex: acute or post-acute stroke</i>							
Liepert et al. (2007)	12	M1 contralesional, F8c	Sham coil	1 Hz, 90% RMT	1200 pulses, 1 session	Increase of manual dexterity (not of the force)	III
Pomeroy et al. (2007)	24 (active: 10; control: 14)	M1 contralesional, F8c	Sham coil	1 Hz, 120% RMT	200 pulses, 8 sessions (combined with motor practice in half of the patients)	No clinical changes but increased cortical excitability	III
Khedr et al. (2009a)	24 (active: 12; control: 12)	M1 contralesional, F8c	Tilted coil	1 Hz, 100% RMT	900 pulses, 5 sessions	More improvement of manual motor abilities than after ipsilesional HF rTMS at 3 months	III
Conforto et al. (2012)	29 (active: 15; control: 14)	M1 contralesional, F8c	Tilted coil	1 Hz, 90% RMT	1500 pulses, 10 sessions, followed by PT	Improvement in manual dexterity (JTT) and grip strength	III
Sasaki et al. (2013)	20 (active: 11; control: 9)	M1 contralesional, F8c	Tilted coil	1 Hz, 90% RMT	1800 pulses, 5 sessions	Improvement in grip strength and finger tapping frequency (but less beneficial than ipsilesional HF rTMS performed in 9 patients)	III
Seniów et al. (2012)	40 (active: 20; control: 20)	M1 contralesional, F8c	Sham coil	1 Hz, 90% RMT	1800 pulses, 15 sessions, followed by motor training	No differences between active and sham rTMS to improve hand motor function or the level of neurological deficit	III
Recommendation: possible effect of LF rTMS of the contralesional motor cortex in (post-)acute motor stroke (Level C)							
<i>LF rTMS of the contralesional motor cortex: chronic stroke (>6 months after stroke)</i>							
Mansur et al. (2005)	10	M1 contralesional, F8c	Tilted coil	1 Hz, 100% RMT	600 pulses, 1 session	Improvement of manual motor abilities, including shorter reaction and execution times	III
Takeuchi et al. (2005)	20 (active: 10; control: 10)	M1 contralesional, F8c	Tilted coil	1 Hz, 90% RMT	1500 pulses, 1 session	Improvement of manual motor abilities (movement acceleration, but not force), lasting less than 30 min	III
Fregni et al. (2006a)	15 (active: 10; control: 5)	M1 contralesional, F8c	Sham coil	1 Hz, 100% RMT	1200 pulses, 5 sessions	Improvement of manual motor abilities, lasting for 2 weeks	III
Takeuchi et al. (2008)	20 (active: 10; control: 10)	M1 contralesional, F8c	Tilted coil	1 Hz, 90% RMT	1500 pulses, 1 session	Improvement of manual motor abilities, PT efficacy, and cortical excitability, lasting for one week	III
Emara et al. (2009, 2010)	20 (active: 20; control: 20)	M1 contralesional, F8c	Tilted coil	1 Hz, 110–120% RMT	150 pulses, 10 sessions	Improvement of manual motor abilities and functional status, lasting at least 12 weeks (idem ipsilesional HF rTMS); less improvement for cortical vs. subcortical stroke	II
Theilig et al. (2011)	24 (active: 12; control: 12)	M1 contralesional, F8c	Sham coil	1 Hz, 100% RMT	900 pulses, 1 session, followed by 20 min of functional electrical stimulation	Similar improvement of motor performance with active and sham rTMS followed by functional electrical stimulation	III
Avenanti et al. (2012)	30 (active: 16; control: 14)	M1 contralesional, F8c	Tilted Cc	1 Hz, 90% RMT	1500 pulses, 10 sessions, preceded or followed by PT	Improvement in manual dexterity (9HPT, JTT, grip force); rebalance of interhemispheric excitability; clinical and neurophysiological improvements more robust and stable when rTMS was followed by PT	III
Etoh et al. (2013)	18	M1 contralesional, F8c	1 Hz rTMS 5cm posterior to M1	1 Hz, 90% RMT	240 pulses, 10 sessions, followed by repetitive motor exercises	Improvement in motor performance (ARAT); no change in spasticity	III
Recommendation: probable effect of LF rTMS of the contralesional motor cortex in chronic motor stroke (Level B)							
<i>HF rTMS of the ipsilesional motor cortex: acute or post-acute stroke</i>							
Khedr et al. (2005a)	52 (active: 26; control: 26)	M1 ipsilesional, F8c	Tilted coil	3 Hz, 120% RMT	300 pulses, 10 sessions	Improvement on various functional scales	II
Khedr et al. (2009a)	24 (active: 12; control: 12)	M1 ipsilesional, F8c	Tilted coil	3 Hz, 130% RMT	900 pulses, 5 sessions	Less improvement of manual motor abilities than after contralesional LF rTMS at 3 months	III
Chang et al. (2010)	28 (active: 18; control: 10)	M1 ipsilesional, F8c	Tilted coil	10 Hz, 90% RMT	1000 pulses, 10 sessions	Improvement of manual motor abilities for subcortical strokes, till 3 months after rTMS	III
Khedr et al. (2010b)	48 (active 3 Hz: 16; active 10 Hz: 16; control: 16)	M1 ipsilesional, F8c	Tilted coil	3 Hz, 130% RMT or 10 Hz, 100% RMT	750 pulses, 5 sessions	Improvement on various functional and motor scales (idem for 3 and 10 Hz). Improvement remained significant at 1 year	III
Recommendation: possible effect of HF rTMS of the ipsilesional motor cortex in (post-)acute motor stroke (Level C)							
<i>HF rTMS of the ipsilesional motor cortex: chronic stroke (>6 months after stroke)</i>							
Kim et al. (2006)	15	M1 ipsilesional, F8c	Tilted coil	10 Hz, 80% RMT	160 pulses, 1 session (combined with motor practice)	Improvement of cortical excitability, movement accuracy and execution time of a motor task during and immediately after stimulation	III
Emara et al. (2009, 2010)	40 (active: 20; control: 20)	M1 ipsilesional, F8c	Tilted coil	5 Hz, 80–90% RMT	750 pulses, 10 sessions	Improvement of manual motor abilities and functional status, lasting at least 12 weeks (idem contralesional LF rTMS)	II
Recommendation: possible effect of HF rTMS of the ipsilesional motor cortex in chronic motor stroke (Level C)							

17 years (Gillick et al., 2014). Third, at least 2 studies showed an improvement of walking ability or velocity after LF (1 Hz) rTMS of the leg motor area of the contralesional hemisphere (Wang et al., 2012) or HF (10 Hz) rTMS of both leg areas using a DCc (Kakuda et al., 2013). Finally, poststroke dysphagia was found to be improved from 2 weeks to 2 months after a series of repeated daily sessions of HF rTMS of the pharyngeal or oesophageal M1 representation (Khedr et al., 2009b; Khedr and Abo-Elfetoh, 2010; Park et al., 2013a).

To conclude this section, studies based on the use of cTBS/iTBS protocols should be discussed. First, it was reported in a pilot study of 6 patients with chronic stroke that one session of iTBS of ipsilesional M1 (but not cTBS of contralesional M1) could transiently improve motor performance and corticospinal output in paretic hands (Talelli et al., 2007). A second controlled study of 10 patients confirmed that one session of iTBS (600 pulses) applied to ipsilesional M1 could improve grip-lift kinetics, but without any change in motor performance (action research arm test, ARAT), whereas patients even deteriorated after cTBS of contralesional M1 (Ackerley et al., 2010). A third study reported improvement of upper extremity Fugl–Meyer assessment but not of ARAT score following iTBS of ipsilesional M1 in a small series of patients in the post-acute phase of stroke (Hsu et al., 2013). In contrast to these studies, one study showed beneficial effects of a single session of contralesional cTBS on manual dexterity of patients with chronic stroke (Meehan et al., 2011). It is difficult to draw any conclusion from this heterogeneity of findings. A controlled study of 41 chronic stroke patients demonstrated that neither iTBS of ipsilesional M1 nor cTBS of contralesional M1 followed by PT daily for 10 consecutive working days produced any differences in motor performance between the active and sham conditions (Talelli et al., 2012). A more recent study of chronic hemiplegic stroke patients did not support the value of iTBS of the ipsilesional M1 given alone, but showed a significant effect from a combined protocol consisting of LF (1 Hz) rTMS of the contralesional M1 followed by ipsilesional iTBS (Sung et al., 2013). Finally, one sham-controlled, double-blinded, parallel-group study of 48 patients with motor stroke at 2–6 months poststroke investigated a combination of 10 sessions of 1 Hz rTMS over the contralesional M1 followed by 10 sessions of iTBS over the ipsilesional M1, or the reverse (Wang et al., 2014). The first combination produced a better improvement of hand function than the second one, on various motor scores and muscle strength. This effect persisted for at least 3 months. Thus, the value of excitability-increasing iTBS delivered to ipsilesional M1 might be enhanced by a prior excitability-decreasing protocol delivered to the contralesional hemisphere. However, no substantial and replicated results have been yet published to justify any recommendation regarding the use of cTBS of the contralesional motor cortex or iTBS of the ipsilesional motor cortex in motor stroke rehabilitation.

5.2. Aphasia

A PubMed search (keywords: rTMS/TBS AND aphasia) identified 75 papers, including Class IV studies (single cases or case series) and a few Class III placebo-controlled studies. In most of these studies, LF rTMS was applied to the contralesional right homologue of Broca's area, which is the apical portion of Brodmann area 45 in the inferior frontal gyrus (IFG). As for motor stroke, the rationale for these studies was to down-regulate increased cortical activity in the contralesional hemisphere, thereby reducing the deleterious interhemispheric inhibition exerted by the contralesional hemisphere onto the lesioned cortical regions. Functional imaging studies have shown that increased activation of the right homologue of Broca's area is associated with unsuccessful recovery of

language performance, whereas reactivation of language network areas in the lesioned hemisphere was associated with the quality of language recovery (Crosson et al., 2007; Saur and Hartwigsen, 2012). The rationale and results of rTMS in aphasia were recently reviewed (Naeser et al., 2010; Mylius et al., 2012c; Murdoch and Barwood, 2013; Wong and Tsang, 2013).

In most single cases or case series, the stimulation target was the pars triangularis of the right IFG, which was determined by using fMRI localization of language areas or by producing language disruption with TMS (Martin et al., 2004, 2009; Naeser et al., 2005a,b, 2011; Hamilton et al., 2010b; Kakuda et al., 2010a). All these studies, although uncontrolled and based on few cases, reported significant positive effects of LF rTMS applied to the homologue of Broca's area in the contralesional hemisphere. In some patients, particularly those with extensive lesions, LF rTMS was applied to the most active area showing compensatory hyperactivation to language disruption on PET or fMRI examination, located in either the right or the left frontal/temporal cortex (Winhuisen et al., 2005; Kakuda et al., 2010a; Abo et al., 2012).

In addition, several of the most recent studies investigated the value of combining rTMS and speech and language therapy (Cotelli et al., 2011b; Kakuda et al., 2011b; Weiduschat et al., 2011; Waldowski et al., 2012; Heiss et al., 2013; Seniów et al., 2013; Thiel et al., 2013; Khedr et al., 2014). Adding speech and language therapy to rTMS may have a synergistic action, but increases the risk of a ceiling effect and can mask the actual therapeutic impact of rTMS.

The first controlled study included 10 patients with different types of poststroke aphasia (fluent, nonfluent, and global) in the post-acute (subacute) phase (up to 16 weeks), with parallel-group design and vertex stimulation as the control condition (Weiduschat et al., 2011). Unfortunately, all included patients with nonfluent Broca's aphasia received sham treatment. Almost all patients who received real LF rTMS to the right hemisphere had fluent Wernicke's aphasia. Nevertheless, following real rTMS, significant improvement in several language functions were noted, while there were no changes following sham treatment. The same group published 2 other studies including more patients (24–29), but with the same design (20-min daily sessions of 1 Hz rTMS of the right IFG at an intensity of 90% of RMT followed by 45-min speech and language therapy for 10 days, with vertex stimulation as control condition) and in a similarly heterogeneous group of patients (about 50% of fluent Wernicke's aphasia, 17% of nonfluent Broca's aphasia, 17% of global aphasia, and 17% of amnesic aphasia) (Heiss et al., 2013; Thiel et al., 2013). The reported results confirmed a global efficacy of the protocol combining LF rTMS of the right IFG followed by speech and language therapy, but these studies were underpowered to determine a specific effect according to aphasia type. In one of these studies (Heiss et al., 2013), 2 left-handed patients were included and also improved, but to a lesser extent.

A second group reported 2 controlled studies of LF rTMS of the right IFG in a heterogeneous group of aphasic patients, but with a lack of efficacy of the procedure (Waldowski et al., 2012; Seniów et al., 2013). The first study (Waldowski et al., 2012) included 26 right-handed aphasic patients in the post-acute phase (up to 12 weeks) of a first-ever left hemisphere ischemic stroke. The protocol was very close to that of the previous group, with 30-min daily sessions of 1 Hz rTMS of the right IFG at an intensity of 90% of RMT followed by 45-min speech and language therapy for 15 days over 3 weeks. However, compared to the previous group, the control condition was performed by using a sham coil (rather than active vertex stimulation) and the clinical profile of the patients was different, with 23% fluent Wernicke's aphasia, 23% nonfluent Broca's aphasia, and 54% global aphasia. In this study, aphasic patients receiving active and sham rTMS improved

similarly in their naming abilities. The same group confirmed this negative result in a series of 40 patients (Seniów et al., 2013).

Considering the contrary results reported by these 2 groups in heterogeneous groups of patients, it is impossible to draw any conclusion regarding the efficacy of LF rTMS of the right IFG in patients with non-selected type of aphasia in the post-acute phase.

It appears more appropriate to consider the value of rTMS in more specific forms of aphasia. There are several controlled studies of LF rTMS of the right IFG specifically applied in patients with non-fluent Broca's aphasia. First, one group showed positive effects of LF rTMS of the right pars triangularis in one study reported in 2 separate papers (Barwood et al., 2011a,b). This study included 12 patients with chronic nonfluent Broca's aphasia, 6 patients receiving active rTMS and 6 patients receiving sham rTMS. These effects persisted for at least 2 months after the period of stimulation. LF rTMS-induced improvement in behavioural language performance was detailed by the authors in a subsequent study of 7 nonfluent aphasic patients (Barwood et al., 2012). In a series of 10 patients with mild to moderate poststroke nonfluent aphasia, LF rTMS of the right IFG was found to facilitate discourse production but not to improve grammatical accuracy (Medina et al., 2012). However, this study was sham-controlled for only 5 patients. Finally, only one controlled (Class III) study included more than 10 patients receiving active stimulation (Tsai et al., 2014). A significant efficacy of 1 Hz rTMS of the right IFG (10 sessions over 2 weeks) was reported in this study of 56 patients with nonfluent aphasia who were randomly allocated to active ($n = 33$) or sham ($n = 23$) stimulation. Post-rTMS improvement concerned aphasia score, object-naming accuracy, and naming reaction time and was persistent at 3 months. Patients who had lower RMT benefited the most from rTMS.

In conclusion, although various case reports and controlled studies on small samples show promising results, no recommendation can be made for the use of LF rTMS of the right IFG (contralateral hemisphere) in patients with nonfluent Broca's aphasia, considering that only one convincing Class III controlled study has been published to date.

In contrast to motor stroke (cf. Table 5), data are very scarce regarding HF rTMS of the ipsilesional hemisphere to rehabilitate aphasia. HF rTMS of the damaged left IFG was assessed in only one patient (Dammekens et al., 2014), whereas 10 sessions of fMRI-navigated iTBS of the stroke-lesioned Broca's area were performed in 8 patients with chronic poststroke aphasia (Szaflarski et al., 2011). These studies showed positive effects on several language functions, including verbal fluency, associated with normalization of neural activities on electroencephalography (EEG) and fMRI parameters in both IFGs. Finally, in a pilot study of 3 chronic stroke patients with nonfluent aphasia, HF rTMS was applied daily over the left DLPFC (BA8/9) for 4 weeks, leading to a significant improvement in object naming (Cotelli et al., 2011b). However, these preliminary results are insufficient to make any recommendation regarding the use of excitability-increasing protocols (HF rTMS or iTBS) involving a cortical target located in the ipsilesional hemisphere to promote recovery of patients with nonfluent Broca's aphasia.

Still regarding nonfluent aphasia, one recent study proposed an original design (Khedr et al., 2014). Thirty patients with nonfluent aphasia in the post-acute phase of stroke recovery received 1 Hz rTMS at 110% of RMT over the right IFG and 20 Hz rTMS at 80% of RMT over the homologous left IFG for 10 consecutive days followed by speech and language therapy. A significantly greater improvement in language score and in the aphasic depression questionnaire was observed after active rTMS compared with sham rTMS and was persistent at 2 months. Similarly, Vuksanović et al. (2014) reported the improvement of several language functions in a right-handed patient with chronic poststroke nonfluent aphasia following the application of 15 daily sessions of bilateral TBS of

the IFG, combining cTBS on the right and iTBS on the left hemisphere. However, as for motor stroke, the potentially cumulative or synergic effect of bihemispheric stimulation deserves further investigation in language rehabilitation.

Finally, regarding fluent Wernicke's aphasia, the target is rather located in the superior temporal gyrus (Hamilton et al., 2010a). So far, only one uncontrolled study reported the effects of LF rTMS applied to the homologue of Wernicke's area in the right hemisphere in 2 patients with fluent aphasia (Kakuda et al., 2010c). Therefore, no recommendation can be made for this type of aphasia.

5.3. Hemispatial neglect

A PubMed search (keywords: rTMS/TBS AND neglect) identified 35 papers, including 3 original placebo-controlled studies with at least 10 neglect patients who received active cTBS trains on the contralesional left posterior parietal cortex (Table 6). The analyzed results cover 47 patients. The studies using rTMS, including cTBS, in poststroke neglect were recently reviewed (Mylius et al., 2012a; Müri et al., 2013; Yang et al., 2013a).

Hemispatial neglect is defined as the inability to respond or move toward novel stimuli presented in the space contralateral to brain damage. Neglect occurs in 30% of patients following stroke in the territory of the right middle cerebral artery. Most often, a lesion of the right posterior parietal and superior temporal gyri is at the origin of neglect (Ellison et al., 2004). Although a satisfactory improvement takes place spontaneously in most cases, a third of patients manifest a chronic form of neglect even one year after their neurological incident (Karnath et al., 2011).

Following the pioneering publications by Oliveri et al. (1999, 2000), most published work studying rTMS as a putative therapeutic intervention in neglect so far has focused on excitability-decreasing paradigms (LF rTMS or cTBS) applied to the left hemisphere. The effects of excitability-increasing paradigms (HF rTMS or iTBS) over the lesioned cortical regions have not yet been really evaluated. Other rTMS studies have been performed which used brief HF rTMS trains in a "virtual lesion" approach to disrupt activity within the contralesional cortex. The first study using brief HF rTMS trains in neglect was a controlled study of 7 patients (Class III), where a reduction in errors on the bisection line test during a "virtual lesion" of the posterior parietal cortex was demonstrated (Oliveri et al., 2001). Using a twin-coil approach to measure excitability within the intact left hemisphere of neglect patients, it was shown that a single session of 1 Hz rTMS to the contralesional hemisphere could ameliorate visual neglect and reduce contralesional brain hyperactivity in a visual test of chimeric objects (Koch et al., 2008b).

Four studies have assessed the effects of a 10-day course of LF rTMS of the contralesional left parietal cortex (Brighina et al., 2003; Shindo et al., 2006; Song et al., 2009; Lim et al., 2010). They report various features of clinical improvement, but none of them was placebo-controlled. In 2 of these studies, the authors used a group of untreated patients as controls (Song et al., 2009; Lim et al., 2010). Long-term effects were not followed up, except in one study (Shindo et al., 2006). In fact, the only sham-controlled study compared the therapeutic effect of LF rTMS of the contralesional left parietal cortex to that of HF rTMS of the ipsilesional right parietal cortex in a 10-day course performed in 27 patients with visuospatial neglect in the acute stroke period (Kim et al., 2013). This study showed a better improvement in the right HF rTMS group compared to the left LF rTMS and sham groups. Therefore, no conclusion can be drawn regarding a recommendation for the use of "conventional" paradigms of rTMS (LF, HF) in the treatment of visuospatial neglect in stroke patients.

Table 6
rTMS (cTBS) studies in hemispatial neglect (target: left posterior parietal cortex).

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
Nyffeler et al. (2009)	11 (12–1080 days after stroke)	P3, Cc	Sham coil	cTBS, 100% RMT	2–4 cTBS trains, 1 session	Improvement in a visuospatial task for 8 h after two TBS trains and for 32 h after 4 TBS trains	III
Cazzoli et al. (2012)	24 (mean 27 days after stroke)	P3, Cc	Sham coil	cTBS, 100% RMT	4 cTBS trains, 2 sessions	Improvement (37%) on various tasks and scales for at least 3 weeks after the stimulation	III
Koch et al. (2012)	20 (24–102 days after stroke) (active: 10; control: 10)	P3, F8c	Sham coil	cTBS, 80% AMT	2 cTBS trains, 10 sessions	Improvement (23%) in the Behavioral Attention Test at 1 month after the stimulation	III

Recommendation: possible effect of cTBS of the contralesional left posterior parietal cortex in hemispatial neglect (Level C)

Regarding TBS, 3 studies have assessed the effect of an excitability-decreasing paradigm (cTBS) applied to the contralesional hemisphere (Nyffeler et al., 2009; Cazzoli et al., 2012; Koch et al., 2012). Several series of cTBS trains were repeated on the same day in subjects and patients enrolled in either physiological or clinical studies (Nyffeler et al., 2006, 2009; Goldsworthy et al., 2012). In a first Class III study (Nyffeler et al., 2009), a significant improvement in a visual attention task was observed for more than 24 h after 4 cTBS trains were applied within 75 min to the left posterior parietal cortex in 11 patients with poststroke neglect. The same group applied 8 trains of cTBS over 2 consecutive days in 24 sub-acute stroke patients with right-hemispheric infarcts in a randomized, double-blind, sham-controlled Class III study (Cazzoli et al., 2012): cTBS but not sham stimulation induced a significant amelioration in the activities of daily living and a better performance in the neuropsychological tests, lasting for at least 3 weeks after cTBS. Finally, in another randomized, double-blind, sham-controlled Class III study, another group performed ten sessions over 2 weeks of 2 cTBS trains delivered daily to the left posterior parietal cortex in 20 patients with subacute right hemispheric stroke (Koch et al., 2012). This study showed that cTBS but not sham stimulation decreased the severity of spatial neglect as assessed by the standardized Behavioral Inattention Test and had after-effects lasting for 2 weeks after treatment.

Given the consistent results of several convincing Class III studies from at least 2 independent teams, we can make a Level C recommendation (“possible efficacy”) for the application of cTBS paradigm to the contralesional left hemispheric posterior parietal cortex in the treatment of poststroke neglect in the post-acute phase.

5.4. Summary

Excitability-increasing HF rTMS of ipsilesional M1 or excitability-decreasing LF rTMS of contralesional M1 is likely to improve motor abilities in stroke patients (Levels B or C recommendation). It must be emphasized that 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. In addition, it should be noted that applying excitability-increasing stimulation at the site of injury in the acute phase of stroke raises safety issues, including the risk of seizures. This safety concern has also been raised with regard to chronic stroke patients (Lomarev et al., 2007). However, the risk might be the same for contralesional stimulation, as it leads to an indirect (via interhemispheric interactions) increase of excitability in the lesioned hemisphere. In fact, there is no reported evidence to support safety concerns (including seizure induction) for either contralesional or ipsilesional stimulation in stroke patients.

On the other hand, the use of LF rTMS to reduce the hyperactivity of the contralesional hemisphere must be approached with caution, because, as aforementioned, this hyperactivity may be adaptive and promote stroke recovery (Johansen-Berg et al., 2002; Lotze et al., 2006; Gerloff et al., 2006). Prolonged effects of rTMS in stroke rehabilitation in the long term also remain to be evaluated at clinical and daily living levels. Thus, despite some conceptual relevance and possible or probable efficacy of rTMS in motor stroke, we are still far from being able to propose strategies for the use of rTMS in daily practice.

A possible efficacy also exists (Level C recommendation) for the use of repeated trains of cTBS delivered to the posterior parietal cortex of the contralesional left hemisphere in hemispatial neglect. Confirmation of promising results are expected very soon regarding the use of LF rTMS of the pars triangularis of the IFG of the contralesional right hemisphere in nonfluent Broca's aphasia.

In the future, large-scale, adequately sham-controlled randomised trials using parallel design with long follow-up time (up to 1 or 2 years), giving emphasis to the clinical relevance of rTMS effect, and also controlled for the natural recovery of vascular brain damage, are needed. The combination of rTMS therapy with conventional rehabilitation techniques, such as PT for motor stroke or language and speech therapy for aphasia, is particularly appealing. Furthermore, possible benefits from individual tailoring of the rTMS targets utilizing neuronavigation and functional brain imaging should also be investigated in stroke patients.

6. Amyotrophic lateral sclerosis

The rationale for using rTMS as a therapeutic tool in amyotrophic lateral sclerosis (ALS) is based on the hypothesis that these protocols are capable of reducing motor cortex excitability and, thus, it would be theoretically possible to antagonize excitotoxicity of an enhanced glutamate transmission in the motor corticospinal system. Moreover, it has been demonstrated that rTMS may modulate plasma levels of brain-derived neurotrophic factor (BDNF), a potent survival factor for motor neurons, in humans (Angelucci et al., 2004; Yukimasa et al., 2006; Zanardini et al., 2006). A neuroprotective effect of rTMS is also suggested by an experimental study that demonstrated in a model of transient brain ischemia in gerbils that HF rTMS delivered 2–5 days before common carotid artery occlusion has a protective effect against delayed neuronal death of hippocampal neurons (Fujiki et al., 2003).

A PubMed search (keywords: rTMS/TBS AND amyotrophic lateral sclerosis) identified 9 papers, including 3 original controlled studies with at least 10 patients, 2 from one group using cTBS (Di Lazzaro et al., 2006, 2009) and 1 from one group using 5 Hz rTMS (Zanette et al., 2008).

The effects of rTMS on ALS have been investigated in several small studies and further analyzed in systematic Cochrane reviews (Guo et al., 2011; Fang et al., 2013). A total of 50 ALS patients were enrolled in the 3 randomised trials (Di Lazzaro et al., 2006, 2009; Zanette et al., 2008). The studies by Di Lazzaro et al. (2006) and Zanette et al. (2008) reported some improvement in the real rTMS group compared to the sham rTMS group, but no significant effects were observed by Di Lazzaro et al. (2009). In addition, whereas the studies of Di Lazzaro et al. (2006, 2009) used an excitability-decreasing cTBS protocol, Zanette et al. (2008) used excitability-increasing HF rTMS. Therefore no recommendation can be made for the use of rTMS in ALS, according to the conclusions of the Cochrane reviews (Guo et al., 2011; Fang et al., 2013). Further studies may be helpful to explore the potential benefit of rTMS in ALS but this needs to be balanced with the demands of trial participation for ALS patients. Finally, it should be emphasized that HF rTMS might even have some detrimental effect in ALS as suggested by a small study in which the effects of HF rTMS were compared with those of LF rTMS (Di Lazzaro et al., 2004b).

7. Multiple sclerosis

A PubMed search (keywords: rTMS/TBS AND multiple sclerosis) identified 15 papers, but only 3 papers addressed therapeutic issues. In these 3 studies, performed by the same group, the effects of a 2-week protocol of 5 Hz rTMS delivered over the motor cortex were found to be beneficial for: (i) hand dexterity in a series of 8 multiple sclerosis patients with cerebellar symptoms (Koch et al., 2008c); (ii) lower limb spasticity in a series of 19 patients with relapsing-remitting multiple sclerosis (Centonze et al., 2007a); (iii) bladder dysfunction and lower urinary tract symptoms by ameliorating the voiding phase (Centonze et al., 2007b). Improvement of spasticity, in particular, was long-lasting (at least 7 days

after the end of treatment) (Centonze et al., 2007a). However, obviously no recommendation can be made in this context, due to the absence of replicated controlled studies.

8. Epilepsy

About 20% of patients with primary generalized epilepsy and up to 60% of patients with focal epilepsy do not respond adequately to antiepileptic drugs and develop drug-resistant epilepsy (Pati and Alexopoulos, 2010). Some of these patients may benefit from surgical treatment based on the resection of the epileptogenic zone. For the rest of the patients, it is important to develop alternative treatments, including neurostimulation techniques. Since rTMS modulates cortical excitability, which plays a major role in the occurrence of seizures, the therapeutic potential of this technique rapidly prompted its application in the field of epilepsy. A PubMed search (keywords: rTMS/TBS AND epilepsy) identified 102 papers, but only 5 original placebo-controlled studies with at least 10 epileptic patients who received active stimulation (Table 7). The analyzed results cover 165 patients.

The first clinical results regarding the efficacy of rTMS in patients with epilepsy were published in 1999 (Tergau et al., 1999). This pivotal study was followed by single case reports and small scale series describing the effects of TMS on various seizure types (simple and complex partial seizures, secondary generalized tonic-clonic seizures, myoclonias and absences) due to a wide spectrum of etiologies (reviewed in Nitsche and Paulus, 2009; Sallet et al., 2009; Kimiskidis, 2010; Hsu et al., 2011; Kimiskidis et al., 2014). Overall, results were encouraging but need to be interpreted cautiously given the uncontrolled design of these studies. In the context of randomized, controlled trials (Table 7), the antiepileptic effects of active rTMS varied widely from no beneficial effects (Theodore et al., 2002) to significant clinical and electrographic improvement (Fregni et al., 2006c; Sun et al., 2012). Therefore, more than 10 years after the onset of rTMS studies in epilepsy, the published data still do not allow us to state with certainty the efficacy of this emerging treatment modality. Several factors could account for the heterogeneity of published results and the difficulty of drawing definitive conclusions, as emphasized in recent reviews (Nitsche and Paulus, 2009; Sallet et al., 2009; Kimiskidis, 2010; Hsu et al., 2011). These methodological limitations and a review of key factors influencing the observed results are discussed below.

The first methodological limitation relates to the sample size of relevant studies. To date, only 5 rTMS studies have included more than 20 epileptic patients (Theodore et al., 2002; Fregni et al., 2006c; Cantello et al., 2007; Joo et al., 2007; Sun et al., 2012) and therefore, a low statistical power is the first limitation to the interpretation of results. In addition, the lack of a control condition in most studies leads to a low level of evidence (for example, Joo et al., 2007). Five studies compared sham and active stimulations (Theodore et al., 2002; Tergau et al., 2003; Fregni et al., 2006c; Cantello et al., 2007; Sun et al., 2012) (Table 7), and only 2 of them (Fregni et al., 2006c; Sun et al., 2012) showed a significant effect on seizure frequency in the treated group. In 2 other studies (Theodore et al., 2002; Tergau et al., 2003), there was only a trend towards a reduction of seizure frequency, while Cantello et al. (2007) did not observe clinical changes, despite an improvement of EEG abnormalities. Finally, the targeting method frankly differed between studies, from non-focal stimulation using a Cc positioned at the vertex (Tergau et al., 2003) to focal stimulation using an F8c placed over the cortical epileptic focus (Sun et al., 2012).

Given the heterogeneity and limitations of the reported studies, recommendations for the use of rTMS in epilepsy do not exceed

Table 7
rTMS studies in epilepsy (various cortical targets).

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
Focal LF rTMS of epileptic focus							
Theodore et al. (2002)	24 (3 frontal, 1 parietal, 10 mesio-temporal, 10 latero-temporal) (active: 12; control: 12)	Epileptic foci, F8c	Tilted coil	1 Hz, 120% RMT	900 pulses, 14 sessions	No significant reduction of seizure frequency	III
Fregni et al. (2006c)	21 (17 partial, 4 diffuse/multifocal) (active: 12; control: 9)	Epileptic foci (n = 17) or Cz (n = 4), F8c	Sham coil	1 Hz, 70% MSO	1200 pulses, 5 sessions	Up to 72% reduction of seizure frequency, 2 weeks after rTMS; reduction of interictal EEG abnormalities	III
Sun et al. (2012)	60 (21 frontal, 3 mesio-temporal, 26 centro-parietal, 3 latero-temporal, 7 occipital) (active: 31; control: 29)	Epileptic foci, F8c	Active coil at very low stimulus intensity (20% RMT)	0.5 Hz, 90% RMT	1500 pulses, 14 sessions	Significantly greater seizure reduction rate in active vs. control group (80% vs. 2%); reduction of interictal EEG abnormalities	II
Recommendation: possible antiepileptic effect of focal LF rTMS of the epileptic focus (Level C)							
Non-focal LF rTMS at the vertex							
Tergau et al. (2003)	17 (11 extra-temporal, 2 mesio-temporal, 2 multifocal, 2 generalized)	Vertex, Cc	Sham coil	0.33–1 Hz, 100% RMT	1000 pulses, 5 sessions	30–40% reduction of seizure frequency, 2 weeks after rTMS (only for 0.33 Hz)	III
Cantello et al. (2007)	43 (41 partial, 2 generalized)	Vertex, Cc	Active coil placed over a non-connected coil	0.3 Hz, 100% RMT (n = 34), 65% MSO (n = 9)	1000 pulses, 5 sessions	No significant reduction of seizure frequency; reduction of EEG abnormalities; no change in cortical excitability	II
No recommendation for the antiepileptic effect of non-focal LF rTMS at the vertex							

Level C recommendation (“possible efficacy”), at least for focal LF rTMS of epileptic focus. However, we have to mention that in a large open study (Joo et al., 2007), rTMS efficacy did not depend on the targeting (focal or non-focal) but on the total number of delivered pulses. Finally, whatever the significance of clinical improvement in terms of seizure frequency, at least 6 studies (Menkes and Gruenthal, 2000; Fregni et al., 2006c; Cantello et al., 2007; Joo et al., 2007; Brodbeck et al., 2010; Sun et al., 2012) showed that interictal EEG abnormalities could be significantly reduced by rTMS. Moreover, rTMS may improve the psychological burden related to severe epilepsy, as suggested by Sun et al. (2011).

8.1. Influencing factors: anatomical and etiological classification of epilepsies

The clinical and therapeutic classification of epileptic syndromes (responsiveness to antiepileptic treatment, prognosis) may influence the results obtained by using rTMS. However, in most studies, the type of epileptic syndrome was not considered as such, and the data were interpreted across groups of patients including heterogeneous epileptic syndromes and etiologies, limiting the value of analysis.

Although it has not been observed in all studies (e.g., Cantello et al., 2007), a recent meta-analysis (Hsu et al., 2011) overall supports the notion that the location of the epileptic focus in the neocortex is significantly associated with favorable response to rTMS. For example, the positive studies of Fregni et al. (2006c) and Sun et al. (2012) included a majority of patients with epileptogenic zones in hemispheric convexity. In contrast, negative results were reported in the studies of Cantello et al. (2007) and Theodore et al. (2002) that included a significant number of patients with mesial temporal lobe epilepsy. In fact, Sun et al. (2012) showed that active LF rTMS was only effective in patients with neocortical epileptic foci, but not in mesial temporal lobe epilepsy. From an anatomical point of view, it is conceivable that this association may simply reflect a better accessibility to TMS of neocortical epileptic foci compared to deeply localized epileptic foci (Theodore et al., 2002).

From an etiological point of view, structural epilepsies associated with focal cortical dysplasia (FCD) and a single EEG focus may be a particularly suitable target group for rTMS (Menkes and Gruenthal, 2000; Daniele et al., 2003; Brasil-Neto et al., 2004; Rossi et al., 2004; Misawa et al., 2005; Fregni et al., 2006c), for a number of reasons: (a) the epileptic focus can be more precisely localized due to the anatomically identifiable lesion; (b) the stimulation target is on the cerebral convexity and therefore readily accessible to TMS; and (c) epileptogenesis in these patients may be associated with the phenomenon of LTP or reflect an imbalance between excitatory and inhibitory mechanisms and theoretically may be restored to normality by the application of TMS. Because rTMS studies of series of FCD patients are rare, there is a likely publication bias regarding this clinical condition (only positive case reports are published). However, the randomized, double-blind, sham-controlled study of Fregni et al. (2006c) concluded that rTMS targeted to the area of the FCD significantly decreased seizure frequency for at least 2 months and, in addition, reduced the number of epileptiform discharges and improved some aspects of cognitive function. Although these positive results were not confirmed in all studies (Cantello et al., 2007), the meta-analysis of Hsu et al. (2011) revealed that the presence of FCD was a significant predictor of a favorable response to rTMS. Nevertheless, the level of evidence for epilepsy with FCD still warrants a Level C recommendation because most of the reported results have an open-label design, are based on small population size, and use a variety of targeting methods.

For other etiologies, no definite conclusions can be drawn from the literature. Although a wide spectrum of etiological substrates were included in the relevant studies (e.g., hippocampal sclerosis, arachnoid cysts, cerebromalacia, tuberous sclerosis, cerebral hemiatrophy, multifocal post-traumatic sequelae), the analysis of the results did not consider each etiological factor separately. Finally, in some types of epilepsy, the effects of rTMS are contradictory. For instance, rTMS was efficacious in one case of Rasmussen's syndrome and inefficacious in another one (Graff-Guerrero et al., 2004; Rotenberg et al., 2008).

The severity of drug-resistant epilepsy with antiepileptic polytherapy is another potential confounder that likely interferes with the subtle molecular and synaptic changes underlying the response to rTMS (Cantello et al., 2007). Unfortunately, the positioning of rTMS as a second-line "palliative" technique, i.e., an alternative to surgery for inoperable partial epilepsy, made inevitable the recruitment of such refractory cases for rTMS trials.

8.2. Influence of stimulation parameters

The stimulation frequency used to provide a reduction in seizure frequency ranged from 0.3 Hz to 1 Hz (Tergau et al., 1999, 2003; Daniele et al., 2003; Fregni et al., 2005b, 2006c; Kinoshita et al., 2005; Santiago-Rodriguez et al., 2008; Sun et al., 2011). It is not recommended that frequencies above 1 Hz be used, due to the higher risk of inducing seizures (Wassermann, 1998; Rossi et al., 2009). It should be noted that brief bursts of rTMS delivered at higher frequencies (20–100 Hz) have been reported to be effective in controlling seizures and aborting electrographic discharges (Rotenberg et al., 2009b) but this warrants further study. The intensity of stimulation should be at least 90% of RMT, but some effects were obtained at an intensity of 50% of the maximum stimulator output (MSO) (Graff-Guerrero et al., 2004), which probably corresponds to a higher stimulation intensity. The "optimal" number of pulses is likely to be at least of 1000 per session or per day, which can be problematic in terms of length of sessions if the frequency of stimulation is very low (<0.5 Hz). At least 5 consecutive days of stimulation seem desirable. In the particular case of epilepsy partialis continua, the efficacy of a single rTMS session has been highlighted by some observations and repeated sessions were not usually required to maintain the effect (Menkes and Gruenthal, 2000; Graff-Guerrero et al., 2004; Misawa et al., 2005; Rotenberg et al., 2009b). Regarding the possibility of a dose-effect, Joo et al. (2007) randomized 35 patients with drug-resistant epilepsies to receive 1500 or 3000 pulses daily, at a frequency of 0.5 Hz and intensity of 100% RMT for 5 consecutive days. The authors observed that patients receiving more pulses per day tended to have greater seizure reduction (–23% for 3000 daily pulses vs. –3% for 1500 daily pulses). Increasing the daily dose of rTMS may possibly enhance its efficacy.

The issue of targeting the epileptic focus is a factor of critical importance. As previously discussed, patients with deep-seated epileptogenic focus may be not a suitable population for rTMS therapy, compared to patients with neocortical focus directly accessible to TMS-induced electric field. Usual TMS techniques permit only superficial stimulation of the brain, approximately 2 cm from the scalp, because the intensity of the induced electric field declines rapidly as a function of the distance between the stimulating coil and the targeted structure. In line with this view, the recent analysis by Bae et al. (2011) of pooled data on 87 subjects from 3 controlled trials, indicated that TMS targeting the epileptic focus resulted in significantly higher responder rates (subjects with $\geq 50\%$ reduction in seizure frequency) compared to sham stimulation or nontargeted rTMS (where the coil was not positioned directly over the seizure focus). Finally, one should note that case

reports have also been published with beneficial antiepileptic effects obtained after cerebellar rTMS at HF (Brighina et al., 2006).

Regarding the type of coil, the most convincing results were obtained with an F8c (Daniele et al., 2003; Fregni et al., 2005b, 2006c; Santiago-Rodriguez et al., 2008; Rotenberg et al., 2009a,b; Sun et al., 2012), although the positive results of these studies may well be attributed to accurate targeting of the epileptic focus, as discussed above. The negative results of the study by Cantello et al. (2007), who used a Cc at the vertex, or the weak effect obtained with a Cc in the studies of Tergau et al. (2003) and Kinoshita et al. (2005) are in line with this, while the positive results of Tergau et al. (1999) and Joo et al. (2007), who used a Cc, somewhat counterbalance this hypothesis. In addition, a Cc was significantly more effective compared to an F8c in aborting epileptiform discharges (interictal discharges and subclinical electrographic seizures) in patients with frontal lobe epilepsy (Kimiskidis et al., 2013), indicating that a greater critical mass of brain tissue must be stimulated in order to obtain this effect. These partly contradictory results do not allow any clear conclusions to be drawn regarding the optimal type of stimulating coil in this clinical condition.

Finally, there is no compelling argument to date for optimizing cortical targeting by using an MRI-guided neuronavigation system rather than anatomical landmarks from the International 10–20 system of EEG electrode positioning, as there are no comparative studies published on the subject.

8.3. Safety

Various studies that focused exclusively on the use of rTMS in patients with epilepsy showed that rTMS is safe in this context. Bae et al. (2007) reported the absence of side effects in 83% of cases. For the remaining 17%, the main side effect was transient headache that responded to simple analgesics (no migraine characteristics). The other most common side effect was a nonspecific feeling of discomfort (or weakness). The most feared side effect is the occurrence of seizures during and/or subsequent to a session of rTMS. This is a rare event, associated with a crude risk of 1.4% (4 occurrences in 280 reported patients) as reported in the study of Bae et al. (2007). The same team (Rotenberg et al., 2009a) described 5 cases of seizures during rTMS sessions in young patients (mean age = 15.4 years) whose usual seizure frequency was high (1–10 seizures per day). The seizures that occurred during rTMS were of the same type as the spontaneous seizures in these patients, and were neither more intense nor followed by greater post-ictal confusion. Three of these 5 patients actually benefited from a reduction in seizure frequency in the days following the rTMS sessions.

8.4. Perspectives

Currently available data do not allow us to draw definite conclusions in favor or against the use of rTMS as a treatment for epilepsy, although a recent meta-analysis (Hsu et al., 2011) on eleven studies found that LF rTMS had a favorable effect on seizure reduction, including the location of epileptic focus and the underlying etiology as significant moderators. Due to the heterogeneity of studied populations and stimulation parameters, the best level of evidence that can be attained is that of "possible efficacy" (Level C recommendation), at least for focal LF rTMS delivered to a neocortical epileptic focus. This favors maintaining rTMS in the research domain for this indication. Interestingly, the magnitude of the placebo effect of rTMS in epilepsy is relatively low (Bae et al., 2011) and large-scale, controlled studies are clearly warranted to establish the effectiveness of this promising treatment modality. Stronger treatment effects were reported for FCD and

neocortical epilepsy, related to a more superficial localization of epileptic foci on hemispheric convexity (frontocentral foci), i.e., a localization that can be easily reached by rTMS (Hsu et al., 2011). In this type of epilepsy, a therapeutic effect is expected if LF rTMS is applied to the foci defined on EEG, with an F8c, at a dose of at least 1000 pulses per day for at least 5 consecutive days. However, the extremely encouraging results obtained in one study (Fregni et al., 2006c) still await replication in independent multicenter studies. Finally, recent case reports also suggest that the therapeutic perspectives of LF rTMS in patients with refractory status epilepticus in the intensive care unit merit further investigation (Thordstein and Constantinescu, 2012; Liu et al., 2013).

9. Disorders of consciousness

An emerging, clinical application of rTMS focuses on chronic disorders of consciousness, a term currently used in the literature to indicate either a vegetative state (VS) or a minimally conscious state. A PubMed search (keywords: rTMS/TBS AND vegetative state OR disorders of consciousness) identified 9 papers, but no sham-controlled studies were found. Two case reports suggested the possibility that HF rTMS might produce some arousal in permanent VS patients, associated with an improvement of auditory pathways conduction (Louise-Bender Pape et al., 2009) or EEG reactivity (Piccione et al., 2011). In a patient with post-traumatic VS, a non-significant trend toward neurobehavioral gains has been reported after the application of a patterned rTMS protocol over the right DLPFC (Louise-Bender Pape et al., 2009). Recently, in a minimally conscious patient, Piccione et al. (2011) reported some arousal, with a transient increase in meaningful behaviors and EEG changes in the 6 h after a single session of 20 Hz rTMS of M1. This has raised interest in the neuroscientific community, but has also had disproportionate resonance in the mass media, creating strong expectations among the patients' families. A recent open-label study investigated EEG reactivity and clinical response to a protocol of HF rTMS of the motor cortex in 6 severely brain-injured patients with disorders of consciousness (VS and minimally conscious state) (Manganotti et al., 2013). This study reported rather negative results, with long-lasting EEG and behavioral changes observed in only one patient in minimally conscious state. Similarly, a randomised, double blind, sham-controlled trial conducted in 11 VS patients (9 post-anoxic, 2 post-traumatic) with a crossover design failed to identify clinical changes following 5 sessions of 20 Hz rTMS (1000 pulses/session) of the left M1 at 60% of MSO (Cincotta et al., unpublished data). Hence, there is no evidence for a therapeutic effect of rTMS in VS, at least with conventional coils and current safety parameters, and it is clear that no recommendation can be made so far for this indication.

10. Alzheimer's disease

A PubMed search (keywords: rTMS/TBS AND Alzheimer's disease) identified 48 papers. While several rTMS studies addressed the question of cortical excitability changes in patients with Alzheimer's disease, only few data are available on the possible clinical impact of rTMS protocols in these patients. First, the effect of HF rTMS delivered to the right or left DLPFC on language abilities, especially naming accuracy, and sentence comprehension has been assessed, showing positive results (Cotelli et al., 2006, 2008, 2011a). Another group confirmed that 5 daily sessions of HF (20 Hz) rTMS applied over the left then the right DLPFC could improve cognitive function in patients with mild to moderate Alzheimer's disease for up to 3 months after the stimulation period (Ahmed et al., 2012). The same protocol performed at LF (1 Hz) was ineffective. Finally, a third group investigated the relevance

of a 6-week protocol combining daily sessions of HF rTMS delivered over various cortical sites and cognitive training also reported significant improvement on various clinical scales (Bentwich et al., 2011; Rabey et al., 2013). All these results favor the design of further HF rTMS trials in Alzheimer's disease, especially in combination with cognitive therapy, but they are not sufficient, to date, to warrant any recommendation, because of the absence of replicated placebo-controlled studies (with similar stimulation protocols and methods of assessment) reported from independent groups.

11. Tinnitus

The use of rTMS in the treatment of tinnitus stems from the development of models of central generation and maintenance of disabling subjective tinnitus (Langguth et al., 2003; Plewnia et al., 2003). Tinnitus usually follows acute or chronic cochlear injury or disease (acoustic trauma, drug toxicity, presbycusis) and its neural correlates reflect central changes induced by auditory deafferentation (neural plasticity with hypersynchrony or hyperactivity of cortical and subcortical auditory and non-auditory areas) (Eggermont, 2007; De Ridder et al., 2011a). The deafferentation hypothesis of tinnitus is supported by several experimental animal studies (Norena and Eggermont, 2005; Eggermont, 2005) and functional human brain imaging (Lanting et al., 2008). This central nervous system dysfunction is the target of neuromodulation by using rTMS or chronic cortical stimulation with surgically implanted electrodes.

A PubMed search (keywords: rTMS/TBS AND tinnitus) identified 111 papers, including 20 original placebo-controlled studies with at least 10 tinnitus patients who received active treatment (Table 8). The analyzed results cover 263 patients for single-session trials and 601 patients for repeated-session trials. Controlled trials with an active comparator (e.g. Kleinjung et al., 2008) are not listed. A responder is usually defined as a patient showing tinnitus relief of more than 30–40% on a visual analogue scale or a reduction in the Tinnitus Questionnaire score of more than 5–10 points.

In tinnitus, rTMS trials aimed at modulating auditory cortex activity and mainly at reducing putative focal cortical hyperactivity by applying an “inhibitory” LF paradigm (e.g., more than 1000 pulses per session, delivered at 1 Hz, with daily sessions repeated over a period of one to several weeks). The temporoparietal cortex (TPC) is usually targeted, based on either anatomical or functional neuroimaging definition. Some studies also evaluated the efficacy of single sessions, HF stimulation, or stimulation applied outside auditory cortical areas (reviewed in Londero et al., 2006; Kleinjung et al., 2007a; Meeus et al., 2009b; Plewnia, 2011).

From the analysis of literature data, it appears that single LF rTMS sessions, when delivered to the auditory cortex contralateral to the tinnitus side, justify a Level C recommendation (“possible efficacy”), since no study exceeds Class III. Despite a larger number of positive studies, including Class II (Anders et al., 2010), repeated rTMS sessions also only receive a Level C recommendation (“possible efficacy”), since the most recent Class I studies (Hoekstra et al., 2013; Langguth et al., 2014) show non-significant changes between active and placebo conditions. The poor quality of tinnitus studies is mainly due to small sample sizes and their exploratory character, without clearly defined primary outcome criteria. In addition, long-lasting after-effects in some tinnitus patients (e.g., Kleinjung et al., 2005; Khedr et al., 2008, 2009c; Marcondes et al., 2010), lead to a high risk of carry-over effects interfering with the results in crossover studies with relatively short wash-out periods.

Table 8
rTMS studies in tinnitus (target: temporal or temporoparietal cortex).

Articles	Number of patients	Target, coil type (placement)	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
<i>Single sessions</i>							
Plewnia et al. (2003)	14 (active: 14; control: 14)	Various scalp positions, F8c (10–20 EEG system)	Stimulation of non-auditory cortical areas and tilted coil	10 Hz, 120% RMT	30 pulses, 1 session	Significant tinnitus reduction (58% responders) after left temporoparietal stimulation	III
De Ridder et al. (2005)	114	Auditory cortex contralateral to tinnitus, F8c (anatomical landmarks)	Tilted coil	1.5/10/20 Hz, 90% RMT	200 pulses, 1 session	Significant tinnitus reduction (53% responders to active stimulation vs. 33% responders to sham stimulation); better results at 20 Hz for “old” tinnitus	III
Folmer et al. (2006)	15	Right or left TPC, F8c (10–20 EEG system)	“Noisy” sham coil	10 Hz, 100% RMT	150 pulses, 1 session	Significant tinnitus reduction (40% responders to active stimulation (2/3 contralateral to tinnitus; 1/3 ipsilateral) vs. 13% responders to sham stimulation)	III
De Ridder et al. (2007a)	46	Auditory cortex contralateral to tinnitus, F8c (anatomical landmarks)	Tilted coil	5/10/20 Hz ‘tonic’ or ‘burst’, 90% RMT	200 pulses, 1 session	Only 14 patients who had no response to sham rTMS were analysed: ‘burst’ stimulation more effective than ‘tonic’ stimulation on narrow band/white noise tinnitus; no difference for pure tone tinnitus	III
Meeus et al. (2009a)	64	Auditory cortex contralateral to tinnitus, F8c (anatomical landmarks)	Tilted coil	1.5/10/20 Hz ‘tonic’ or ‘burst’, 50% MSO	200 pulses, 1 session	Only 50 patients who had no response to sham rTMS were analysed: ‘burst’ stimulation more effective than ‘tonic’ stimulation on bilateral narrow band tinnitus; no difference for pure tone tinnitus; better effects in patients with lower MT; no difference for pure tone tinnitus	III
Lorenz et al. (2010), Müller et al. (2013)	10	Auditory cortex contralateral to tinnitus, F8c (10–20 EEG system)	Tilted coil	1/10 Hz, c/iTBS	1000 pulses (1/10 Hz)/600 pulses (c/iTBS), 1 session	Significant tinnitus reduction for 1 Hz rTMS and cTBS; effect correlated to the variation of alpha power, gamma power and ‘auditory steady-state responses’ measured on magnetoencephalography	III
Recommendation: possible effect of a single session of “burst” or LF rTMS of the auditory cortex (contralateral to the affected ear) in tinnitus (Level C)							
<i>Repeated sessions</i>							
Kleinjung et al. (2005)	14	Auditory cortex activation area in PET, F8c (FDG-PET-guided navigation)	Sham coil	1 Hz, 110% RMT	2000 pulses, 5 sessions	Significant tinnitus reduction (prolonged effect up to 6 months)	III
Rossi et al. (2007a)	16	Left TPC, F8c (navigation and 10–20 EEG system)	Tilted coil combined with electrical skin stimulation	1 Hz, 120% RMT	1200 pulses, 5 sessions	Significant tinnitus reduction (no prolonged effect)	III
Khedr et al. (2008, 2009c)	66 (active: 16,17,17; control: 16)	Left TPC, F8c (10–20 EEG system)	Stimulation of non-auditory cortical areas	1/10/25 Hz, 100% RMT	1500 pulses, 10 sessions	Significant tinnitus reduction for all active conditions (prolonged effect up to 12 months); less efficacious for tinnitus with longer duration	III
Anders et al. (2010)	42 (active: 22; control: 20)	Auditory cortex, F8c (10–20 EEG system)	Tilted coil	1 Hz, 110% RMT	1500 pulses, 10 sessions	Significant tinnitus reduction (not initially, but at 3–6 months after the stimulation)	II
Marcondes et al. (2010)	19 (active: 10; control: 9)	Left superior temporal cortex, F8c (10–20 EEG system)	Sham coil	1 Hz, 110% RMT	1020 pulses, 5 sessions	Significant tinnitus reduction (prolonged effect up to 6 months); effect correlated to a reduced activity of inferior temporal cortices in SPECT	III
Mennemeier et al. (2011)	21	Auditory cortex activation area in PET, F8c (FDG-PET-guided navigation)	Sham coil combined with electrical skin stimulation	1 Hz, 110% RMT	1800 pulses, 5 sessions	Significant tinnitus reduction (43% responders, 33% improvement); no correlation with activity changes in PET	II
Piccirillo et al. (2011)	14	Left TPC, F8c (navigation and 10–20 EEG system)	Sham coil	1 Hz, 110% RMT	1500 pulses, 10 sessions	Non-significant tinnitus reduction	III
Chung et al. (2012)	22 (active: 12; control: 10)	Left auditory cortex, F8c (navigation)	Sham coil	cTBS, 80% RMT	900 pulses, 10 sessions	Significant tinnitus reduction; more efficacious on emotional component of tinnitus	III
Plewnia et al. (2012)	48 (active: 16,16; control: 16)	Bilateral temporal cortex or TPC, F8c	Active stimulation	cTBS, 80% RMT	900 pulses, 20 sessions	Non-significant tinnitus reduction	III

(continued on next page)

Table 8 (continued)

Articles	Number of patients	Target, coil type (placement)	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
Hoekstra et al. (2013)	50 (active: 25; control: 25)	Bilateral primary auditory cortex, F8c (navigation)	behind the mastoid Sham coil	1 Hz, 110% RMT	4000 pulses (2000 left, 2000 right), 5 sessions	Non-significant tinnitus reduction	I
Lee et al. (2013)	15	Left temporal cortex, F8c (10–20 EEG system)	Tilted coil	1 Hz, 100% RMT	1200 pulses, 10 sessions	Significant tinnitus reduction, negatively correlated to the duration of tinnitus	III
Piccirillo et al. (2013)	14	Left temporoparietal junction, F8c	Sham coil	1 Hz, 110% RMT	1500 pulses, 20 sessions	Non-significant tinnitus reduction	III
Bilici et al. (2014)	75 (active 30, 15; control 30)	Left TPC, Cc	Sham coil	1/10 Hz, 110% RMT	900 pulses (1 Hz) or 600 pulses (10 Hz), 10 sessions	Significant tinnitus reduction for all active conditions, less pronounced in combination with paroxetine	III
Langguth et al. (2014)	185 (active: 47,48,46; control: 44)	PET-guided temporal cortex, left temporal cortex, combined left temporal + prefrontal cortices, F8c (navigation and 10–20 EEG system)	Sham coil	1 Hz (temporal cortex), 20 Hz (prefrontal cortex), 110% RMT	2000 or 4000 pulses, 10 sessions	Significant tinnitus reduction for all 3 active conditions, but no statistical significant difference in comparison to sham; better effects on a descriptive level for combined frontal and temporal rTMS	I

Recommendation: possible effect of repeated sessions of LF rTMS of the TPC (on the left hemisphere or contralateral to the affected ear) in tinnitus (Level C)

Thus, many uncertainties remain about the current relevance of the use of rTMS as a treatment for tinnitus, especially in the long term. Tinnitus reduction after rTMS is, indeed, generally described as partial (complete disappearance of tinnitus is rare) and temporary (ranging from days to years) with large interindividual variations (Londero et al., 2006; Burger et al., 2011). In several studies, this effect is dose-dependent (Plewnia et al., 2007a; Rossi et al., 2007a). Some studies suggest that tinnitus of short duration (less than 2 years) (Kleinjung et al., 2007b; Khedr et al., 2008) and normal hearing (Marcondes et al., 2010) could be predictors for beneficial treatment outcome, but this was not confirmed in the analysis of larger samples (Frank et al., 2010).

11.1. Target and stimulation frequency

To date, most studies used LF rTMS delivered unilaterally to temporal or temporoparietal cortical areas with the goal of “inhibiting” a supposedly lateralized hyperactive auditory cortex. The efficacy of LF rTMS could not be enhanced by a priming strategy using HF (6 Hz) rTMS (Langguth et al., 2008). On the other hand, one group showed a greater and more prolonged efficacy from HF (10/25 Hz) rTMS used alone, compared to LF rTMS (Khedr et al., 2008, 2009c). A very recent study also reported a beneficial effect of HF (10 Hz) rTMS applied to the left auditory cortex, although cTBS applied bilaterally on auditory cortices was even more efficacious (Forogh et al., 2014). In another study, cTBS of the auditory cortex also reduced tinnitus, especially its emotional component (Chung et al., 2012).

An increasing amount of data also suggest that the efficacy of rTMS therapy in tinnitus can be enhanced by stimulating frontal or prefrontal cortical areas in addition to the TPC (Kleinjung et al., 2008; Kreuzer et al., 2011; De Ridder et al., 2013; Lehner et al., 2013a,b; Langguth et al., 2014). Although tinnitus was found to increase after DLPFC stimulation in some patients treated for depression (Marcondes et al., 2006), several studies have investigated the DLPFC as a target for rTMS in tinnitus patients, both in isolation and in a multi-site stimulation approach (Kleinjung et al., 2008; Kreuzer et al., 2011; De Ridder et al., 2013; Lehner et al., 2013a,b; Park et al., 2013b; Langguth et al., 2014). The most recent studies report the value of a multi-site rTMS protocol that combines HF rTMS of the left DLPFC and LF rTMS of both the right and left TPC (Lehner et al., 2013a,b), which provides even better tinnitus relief than unilateral LF rTMS of the TPC (Lehner et al., 2013a). Conversely, LF rTMS applied bilaterally only on auditory cortices was found to be inefficacious in another recent study (Hoekstra et al., 2013).

These results are in line with imaging findings of increased functional connectivity between frontal and temporal cortical areas in tinnitus patients (Schlee et al., 2008). Studies using functional neuroimaging also reported a correlation between the therapeutic effect of rTMS on tinnitus and the level of activation of both primary and secondary auditory cortices in response to sound stimulation, as well as of non-auditory areas involved in high-level associative processes, such as the anterior cingulate cortex (Plewnia et al., 2007b). This region is putatively targeted by a DCC placed over the frontal areas (Hayward et al., 2007) and this approach has been recently assessed in tinnitus patients (Vanneste et al., 2011; Vanneste and De Ridder, 2013).

11.2. Methodological considerations

Many methodological and practical problems remain to be solved before rTMS therapy for tinnitus can really develop in clinical practice. These problems especially concern the method of targeting the temporal or temporoparietal cortical areas to stimulate. There is no certainty as to whether it is preferable to target rTMS

on the area of maximum cortical hyperactivity (as defined on fMRI, PET, or magnetoencephalography) or on an anatomical target centred on the primary (Heschl's gyrus) or secondary auditory cortex (Langguth et al., 2010). Due to lack of comparative studies, it is currently not known whether rTMS requires image-guided navigation system or can be based on landmarks provided, e.g., by the International 10–20 system of EEG electrode positioning (Langguth et al., 2010). It should be stressed that few ENT departments have dedicated neuronavigation systems to optimizing cortical targeting. The quantitative and qualitative importance of “human resources” necessary for this technique is also certainly an important limitation to its wider use for an audiological indication outside the scope of clinical research. Moreover, it is not clear whether rTMS over temporal areas exerts its effects by modulating the primary or the secondary auditory cortex (Lorenz et al., 2010). In fact, the influence exerted by the stimulation pattern may depend on the acoustic characteristics of the tinnitus, there being a need to differentiate between tonal-type tinnitus (related to tonotopic involvement of the lateral lemniscal tract) and white-noise or narrow-band tinnitus (related to non-tonotopic involvement of extralemniscal tracts) (De Ridder et al., 2007b). Finally, when TMS is applied to the TPC according to external landmarks, functional changes in both temporal and parietal areas may be relevant for mediating the effect.

The side of the stimulation is also debatable. Should we stimulate the cortex contralateral to the tinnitus if tinnitus is unilateral? Which side needs to be stimulated if tinnitus is bilateral (De Ridder, 2010)? Is there any evidence for a left-sided lateralization of hemispheric dominance of central auditory processing that justifies the application of rTMS always to the left hemisphere, regardless of tinnitus side (Geven et al., 2014)? One group showed that rTMS therapy consisting of 10 daily sessions delivered at 1 Hz or 25 Hz contralateral to the side of tinnitus provided greater beneficial effect than either ipsilateral or left-sided stimulation (Khedr et al., 2010a). However, in a more recent study of 40 patients with unilateral tinnitus, daily treatment with 1 Hz rTMS of the TPC delivered either contralaterally or ipsilaterally to the symptomatic ear had similarly significant beneficial effects (Kim et al., 2014).

Finally, even if rTMS is a safe technique (Wassermann, 1998; Rossi et al., 2009), some precautions need to be met, mainly due to the theoretical risk of triggering a seizure (though extremely improbable with LF rTMS) or especially of inducing auditory changes because of the noisiness of rTMS at high intensities. Actually, rTMS has recently been reported to transiently decrease the amplitude of the otoacoustic emissions, reflecting active cochlear effects (Tringali et al., 2012). Despite the absence of recognized auditory toxicity (Schönfeldt-Lecuona et al., 2012), some patients with tinnitus may complain of a worsening of hyperacusis and painful hypersensitivity to noises after rTMS therapy (Lefaucheur et al., 2012b).

11.3. Conclusions

LF (1 Hz) rTMS unilaterally applied to temporal or temporoparietal cortical areas can interact with an abnormal hyperactivity of auditory cortices that may constitute the neural correlate of tinnitus perception. Literature data showed that this type of rTMS protocol has a possible therapeutic efficacy (Level C recommendation) in this clinical condition. The efficacy of active rTMS is superior to placebo in the treatment of subjective tinnitus, but the effects are usually partial and transient at clinical level. In addition, the best method of targeting is not yet fully validated. Therefore, the application of LF rTMS of the auditory cortex still remains subject to numerous uncertainties about its feasibility and usefulness in the context of clinical routine (Frank et al., 2010). On the other hand, it is premature to propose any recom-

mendation for the other rTMS approaches (HF rTMS or cTBS of the auditory cortex or HF rTMS of the left DLPFC combined with LF rTMS of both the right and left TPC).

Finally, in patients with the most refractory forms of tinnitus, resistant to conventional drugs, sound therapy and psychotherapy, rTMS has been proposed as a preoperative test before considering surgical implantation of electrodes for chronic cortical electrical stimulation (De Ridder et al., 2011b). Although this may be substantiated by an analogous approach in neuropathic pain (André-Obadia et al., 2006; Lefaucheur et al., 2011b), data regarding rTMS as a preoperative test in functional neurosurgery of tinnitus are still too disparate and not replicated, which prevents any recommendation in this context.

12. rTMS and psychiatry: general considerations

For 20 years, many studies have suggested that rTMS could be efficacious in the treatment of major depression and other psychiatric indications. This literature has gradually expanded and the methodological quality of work has improved along with the changes in stimulation protocols. Given its potential efficacy and its ease-of-use, the place of this technique in the therapeutic armamentarium at our disposal is an important issue, especially since several countries outside Europe (USA, Canada, Brazil, Australia, or Israel) have already approved its use in several psychiatric indications, mainly depression (see Rossi, 2013).

In Europe, the number of centres using rTMS to treat psychiatric disorders is increasing and new institutions regularly consider implementing this technique in routine, although the legal framework remains to be clarified. To our knowledge, rTMS is recognized for the treatment of major depression (especially the acute phase of treatment-resistant depression) at least by the Finnish Medical Association (since 2010), the Serbian Ministry of Health (since 2011), and the German Institute of Medical Documentation and Information (since 2014) with a Level A recommendation in the guidelines for good clinical practice. In the other European countries, rTMS is carried out in the frame of research activities or can be used privately for therapeutic purposes, but without any reimbursement by standard medical insurances.

At the same time there are still several open questions with respect to the clinical use of rTMS. For instance, should rTMS be considered as a first-line treatment or should it be used in case of resistance to standard pharmacological approaches only? Should rTMS be used as monotherapy or as an add-on therapy, combined with other treatments for potentiating therapeutic effects? What place should this treatment have in the standard classification of medical procedures? And above all, which rTMS paradigm is superior in each indication and what can be done to optimize rTMS protocols, to move from statistically significant results to clinically relevant effects?

In this paper, we successively present the data on the treatment of depression, anxiety disorders, obsessive-compulsive disorder, positive and negative symptoms of schizophrenia, addiction/craving, and conversion, and put forward recommendations on efficacy but also on the stimulation parameters to be preferentially used in these indications.

13. Depression

According to studies conducted in the general population, depression is a common mental condition with an annual prevalence ranging between 5% and 15%. Unfortunately, not all patients respond to the available pharmacological treatment algorithms (Fava, 2003; Nemeroff, 2007). The French Agency for Sanitary Safety of Health Products (AFSSAPS) indicated that about one-third

of patients do not respond to an initial antidepressant treatment after 4–8 weeks of treatment (“On the good use of antidepressants in the treatment of depressive disorders and anxiety disorders in adults”, AFSSAPS, October 2006). Taking proper care of the first depressive episode is important since depression is a condition that tends to reoccur (50–85% of cases) or to become chronic (20% of depressive episodes). Finally, 10% or even more of patients suffering from major depression are chronically resistant to several psychopharmacological interventions, even when adhering to treatment guidelines (Berlim and Turecki, 2007).

In these cases, therapeutic actions are to increase medication dosages, to change or combine antidepressants with or without adding psychotherapeutic approaches such as cognitive behavioral or interpersonal therapy, or to use electroconvulsive therapy (ECT). Although there is good evidence for beneficial antidepressant effects of rTMS, the appropriate place of this technique in the therapeutic decision tree is not clearly defined to date (Padberg and George, 2009). Nevertheless, rTMS is an accepted, evidence-based treatment option by the American Psychiatric Association (APA), the Canadian Network for Mood and Anxiety Treatments (CANMAT), and the World Federation of Societies of Biological Psychiatry (WFSBP). In general, it is assumed that rTMS has higher success rates when applied at the acute state (a current depressive episode of less than one year), in relatively young individuals (less than 65 years old), with a limited level of treatment resistance (one or two unsuccessful medical interventions, with or without the combination of focused psychotherapy), or with only partial treatment response (George and Post, 2011).

Historically, the effect of TMS on mood was accidentally discovered from physiological studies (Bickford et al., 1987; Pascual-Leone et al., 1996a). The selection of cortical targets in the treatment of mood disorders is based on pathophysiological changes considered to underlie these disorders. Functional brain imaging in depressed patients has shown a decrease in rCBF as well as glucose and oxygen consumption in the left frontal regions (Kennedy et al., 1997) reflecting a hypometabolic state, with concomitant hypermetabolism in the right prefrontal regions (Bench et al., 1995). A number of electroencephalographic studies also revealed interhemispheric asymmetry of frontal activation in favor of the left hemisphere and the rate of asymmetry correlated with clinical scores of depression (Schaffer et al., 1983; Koek et al., 1999; Diego et al., 2001; Knott et al., 2001). The DLPFC is easily accessible to TMS application and is synaptically connected to the limbic system involved in mood regulation (striatum, thalamus, and anterior cingulate cortex) (Petrides and Pandya, 1999; Barbas, 2000; Paus et al., 2001). The initial hypothesis was that rTMS of the DLPFC would modulate brain networks, which are implicated in the pathophysiology of depression (Kimbrell et al., 1999; Nobler et al., 2000). Further research in animals and in patients suffering from depression revealed that frontal rTMS can also affect various neurotransmitter systems, neurotrophic factors, rCBF, and cortical excitability.

Based on the concept of frontal asymmetry of cortical activities in depression, 2 main lines of research have been developed for the treatment of depression with rTMS: LF stimulation (inducing neural inhibition) on the right DLPFC (presumably hyperactive in depression), HF stimulation (putatively inducing neural excitation) on the left DLPFC (presumably hypoactive in depression), or a combination of the two (Klein et al., 1999b; George et al., 2000; Speer et al., 2000).

A PubMed search (keywords: rTMS/TBS AND depression) retrieved 786 papers, including 61 original placebo-controlled studies with at least 10 patients who received active stimulation (Table 9). Among these studies, 38 examined the efficacy of HF rTMS of the left DLPFC; 5 used LF rTMS of the right DLPFC; 8

assessed bilateral rTMS; and 10 compared right and left DLPFC stimulation. The analyzed results cover 3682 patients, which is clearly the largest experience concerning the clinical effect of rTMS for any potential therapeutic indication. Among the 61 selected studies, 20 focused on samples of more than 30 actively treated patients. The North American multicenter studies (O'Reardon et al., 2007b; George et al., 2010) are remarkable for the large number of patients included (301 and 199), the control of drug treatment, and the design with parallel arms of active condition versus sham condition. A responder is usually defined as a patient showing a reduction of HDRS score of more than 50%.

There is a substantial heterogeneity of goals and stimulation parameters among the studies. While some of them specifically compared rTMS at different frequencies on different targets or with a placebo treatment, others tested the influence of various stimulation parameters (intensity, frequency, lateralization, or priming). Finally, a number of studies assessed the potentiating effect of rTMS as an add-on technique to pharmacotherapy. Despite such diversity, 2 types of rTMS protocols tend to emerge from analysis: one based on HF stimulation of the left DLPFC and the other on LF stimulation of the right DLPFC. When looking at the evolution over time of the methodological quality of published studies, it appears that the work reported before 2000 had a greater heterogeneity, both in the choice of stimulation parameters and in the targeted populations. The therapeutic efficacy is clearly better in more recent studies. To date, most clinical studies currently use multiple sessions of HF rTMS applied to the left DLPFC.

The interested reader is referred to the many reviews and meta-analyses published in this domain, addressing the different mechanistic, methodological, technical and clinical aspects of this therapy (e.g., in the last 5 years: Schutter, 2009, 2010; Croarkin et al., 2010; Höppner et al., 2010; Schönfeldt-Lecuona et al., 2010a; Slotema et al., 2010; Broadbent et al., 2011; Fitzgerald and Daskalakis, 2011, 2012; Dell'osso et al., 2011; Paes et al., 2011; Lee et al., 2012a; Minichino et al., 2012; Pallanti et al., 2012; Sampaio et al., 2012; Berlin et al., 2013a,c,d,e,f, 2014; Chen et al., 2013; George et al., 2013; Hovington et al., 2013; Xie et al., 2013; Ren et al., 2014).

13.1. General results and influence of the side of stimulation

When taking into account all controlled studies against placebo that applied left DLPFC stimulation, a recent meta-analysis identified 29 studies, totaling 1371 patients (Berlin et al., 2014). The average rate of responders was 29% and 10% of patients receiving active and sham left HF rTMS, respectively. We found 26 positive studies and 14 negative studies, including 7 Class I studies. The two Class I studies of highest methodological quality were positive, supporting the efficacy of HF rTMS delivered to the left DLPFC in the treatment of unipolar depression, which did not respond to at least one antidepressant, with a calculated effect size of 0.87 (O'Reardon et al., 2007b; George et al., 2010). These results were a strong argument for the FDA in the USA to validate “an indication of rTMS in the treatment of major depressive episodes resistant to at least one antidepressant medication” in October 2008. In addition, various meta-analyses have confirmed a significant antidepressant effect of rTMS ranging from mild to medium intensity (Ellis, 2010; Hovington et al., 2013). Thus, the efficacy of HF rTMS of the left DLPFC in depression is definite, with a Level A recommendation.

In the analysis of the effect size and rTMS efficacy, the nature of the placebo control may be influential, whether a sham coil or a tilted active coil was used. A recent meta-analysis (Berlin et al., 2013a) including 9 randomized controlled trials since 2003 showed that the respective sham conditions were sufficient to keep the blinding on an acceptable level. Moreover, in another

Table 9
rTMS studies in depression (target: dorsolateral prefrontal cortex).

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
<i>HF rTMS of the left DLPFC</i> Pascual-Leone et al. (1996b)	17	Left DLPFC, F8c	Tilted coil or active coil on irrelevant cortical sites	10 Hz, 90% RMT	2000 pulses, 5 sessions	Positive (24% responders, 48% improvement)	III
George et al. (1997)	12	Left DLPFC, F8c	Tilted coil	20 Hz, 80% RMT	800 pulses, 10 sessions	Positive (8% responders, 16% improvement)	III
Loo et al. (1999)	18	Left DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	1500 pulses, 10 sessions	Negative (0% responders, 23% improvement)	III
Padberg et al. (1999)	18 (active: 12; control: 6)	Left DLPFC, F8c	Tilted coil	10 Hz or 0.3 Hz, 90% RMT	250 pulses, 5 sessions	Negative (6% improvement after 10 Hz, 19% after 0.3 Hz)	III
Berman et al. (2000)	20 (active: 10; control: 10)	Left DLPFC, F8c	Tilted coil	20 Hz, 80% RMT	800 pulses, 10 sessions	Positive (10% responders, 35% improvement)	III
Eschweiler et al. (2000)	12	Left DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	1500 pulses, 10 sessions	Negative (0% responders, 23% improvement)	III
George et al. (2000)	30 (active: 20; control: 10)	Left DLPFC, F8c	Tilted coil	20/5 Hz, 100% RMT	1600 pulses, 10 sessions	Positive (20 Hz: 30% responders, 28% improvement; 5 Hz: 60% responders, 48% improvement)	III
Garcia-Toro et al. (2001a)	35 (active: 17; control: 18)	Left DLPFC, F8c	Tilted coil	20 Hz, 90% RMT	1200 pulses, 10 sessions	Positive (29% responders, 30% improvement); 29% of non-responders to sham rTMS will then respond to active rTMS	III
Garcia-Toro et al. (2001b)	22 (active: 11; control: 11)	Left DLPFC, F8c	Tilted coil and sertraline	20 Hz, 90% RMT	1200 pulses, 10 sessions	Negative compared to sertraline (36% responders, 38% improvement); no additive efficacy to sertraline	III
Manes et al. (2001)	20 (active: 10; control: 10)	Left DLPFC, F8c	Vertex stimulation	20 Hz, 80% RMT	800 pulses, 5 sessions	Negative (30% responders, 37% improvement)	III
Boutros et al. (2002)	21 (active: 12; control: 9)	Left DLPFC, F8c	Sham coil	20 Hz, 90% RMT	800 pulses, 10 sessions	Negative (25% responders, 29% improvement)	III
Padberg et al. (2002)	31 (active: 20; control: 10)	Left DLPFC, F8c	Tilted coil	10 Hz, 90-100% RMT	1500 pulses, 10 sessions	Positive (20-30% responders, 15-30% improvement)	III
Nahas et al. (2003)	23 (active: 11; control: 12)	Left DLPFC, F8c	Tilted coil	5 Hz, 110% RMT	1600 pulses, 10 sessions	Negative (36% responders, 25% improvement)	III
Fregni et al. (2004)	42 (active: 21; control: 21)	Left DLPFC, F8c	Sham coil and fluoxetine	15 Hz, 110% RMT	3000 pulses, 10 sessions	Negative compared to fluoxetine (43% responders, 38% improvement); improvement for more than 2 months after rTMS as with fluoxetine, but with less adverse events for rTMS	III
Hausmann et al. (2004a)	25 (active: 12; control: 13)	Left DLPFC, F8c	Sham coil	20 Hz, 100% RMT	2000 pulses, 10 sessions	Negative (46% improvement)	III
Jorge et al. (2004)	20 (active: 10; control: 10)	Left DLPFC, F8c	Tilted coil	10 Hz, 100% RMT	1000 pulses, 10 sessions	Positive (30% responders, 38% improvement)	III
Koerselman et al. (2004)	52 (active: 26; control: 26)	Left DLPFC, C	Tilted coil	20 Hz, 80% RMT	800 pulses, 10 sessions	Negative (19% improvement)	II
Mosimann et al. (2004)	24 (active: 15; control: 9)	Left DLPFC, F8c	Tilted coil	20 Hz, 100% RMT	1600 pulses, 10 sessions	Negative (6% responders, 20% improvement)	III
Rossini et al. (2005a)	54 (active: 37; control: 17)	Left DLPFC, F8c	Tilted coil	15 Hz, 80-100% RMT	600 pulses, 10 sessions	Positive (80% RMT: 28% responders; 100% RMT: 61% responders)	II
Rossini et al. (2005b)	99 (active: 50; control: 49)	Left DLPFC, F8c + escitalopram, sertraline, or venlafaxine	Tilted coil	15 Hz, 100% RMT	900 pulses, 10 sessions	Positive (51% responders at 2 weeks; 80% responders at 5 weeks)	II
Rumi et al. (2005)	46 (active: 22; control: 24)	Left DLPFC, F8c + amitriptyline	Sham coil	5 Hz, 120% RMT	1250 pulses, 20 sessions	Positive (95% responders, 57% improvement); rTMS increases and speeds up the efficacy of amitriptyline	II
Su et al. (2005)	30 (active: 20; control: 10)	Left DLPFC, F8c	Tilted coil	20/5 Hz, 100% RMT	1600 pulses, 10 sessions	Positive (20 Hz: 60% responders, 58% improvement; 5 Hz: 60% responders, 54% improvement)	III
Avery et al. (2006), Herbsman et al. (2009)	68 (active: 35; control: 33)	Left DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	1600 pulses, 15 sessions	Positive (20/3% responders between active and sham rTMS). Better response with more anterior and lateral stimulation sites	I
Anderson et al. (2007)	29 (active: 13; control: 16)	Left DLPFC, F8c	Sham coil	10 Hz, 110% RMT	1000 pulses, 20-30 sessions	Positive (43% responders, 55% improvement)	III
Bortolomasi et al. (2007)	19 (active: 12; control: 7)	Left DLPFC, F8c	Tilted coil	20 Hz, 90% RMT	800 pulses, 5 sessions	Positive (significant reduction of HDRS and Beck scores at 1-4 weeks)	III

(continued on next page)

Table 9 (continued)

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
Herwig et al. (2007)	127 (active: 62; control: 65)	Left DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	2000 pulses, 10 sessions	Negative (31% responders)	I
Loo et al. (2007)	38 (active: 19; control: 19)	Left DLPFC, F8c	Inactive coil	10 Hz, 110% RMT	1500 pulses, 20 twice-daily sessions	Positive (on MADRS score at 2 weeks and up to 6 weeks)	III
O'Reardon et al. (2007b)	301 (active: 155; control: 146)	Left DLPFC, F8c	Sham coil	10 Hz, 120% RMT	3000 pulses, 10–30 sessions	Positive (23% responders)	I
Bretlau et al. (2008)	45 (active: 22; control: 23)	Left DLPFC, F8c	Inactive coil	8 Hz, 90% RMT	1289 pulses, 10 sessions	Positive (33% responders)	III
Jorge et al. (2008)	92 (active: 48; control: 44)	Left DLPFC, F8c	Sham coil	10 Hz, 110% RMT	1200 pulses, 10–15 sessions	Positive (33–39% responders (33–42% improvement) vs. 7% (14–18% improvement) with sham rTMS)	I
Mogg et al. (2008)	59 (active: 29; control: 30)	Left DLPFC, F8c	Sham coil	10 Hz, 110% RMT	1000 pulses, 10 sessions	Negative (32% responders)	II
Lisanby et al. (2009)	301 (active: 155; control: 146)	Left DLPFC,	Sham coil	10 Hz, 120% RMT	3000 pulses, 20 sessions	Positive (MADRS total score decreases, especially in patients with one failed adequate medication trial)	I
George et al. (2010)	190 (active: 92; control: 98)	Left DLPFC, F8c	Sham coil	10 Hz, 120% RMT	3000 pulses, 10–30 sessions	Positive (on remission)	I
Paillère Martinot et al. (2010)	48 (active: 34; control: 14)	Left DLPFC, F8c	Sham coil	10 Hz, 90% RMT	1600 pulses, 10 sessions	Positive (for rTMS applied to the region of reduced frontal metabolism, only if lateralized to the left hemisphere)	II
Triggs et al. (2010)	48 (left: 16; right: 18; control: 14)	Left or right DLPFC, F8c	Sham coil combined with electrical skin stimulation	5 Hz, 100% RMT	2000 pulses, 10 sessions	Active rTMS was more efficacious than sham rTMS only on the left side, but, overall, right rTMS (sham or rTMS) was more efficacious than left rTMS	III
Ray et al. (2011)	40 (active: 20; control: 20)	Left DLPFC, F8c	Tilted coil	10 Hz, 90% RMT	1200 pulses, 10 sessions	Positive (BPRS scores decreased in psychotic and non-psychotic depression)	III
Baeken et al. (2013, 2014)	20	Left DLPFC, F8c	Tilted coil	20 Hz, 110% RMT	1560 pulses, 20 sessions	Positive (35/0% responders between active and sham rTMS). Efficacy negatively correlated to the connectivity between subgenual and prefrontal cortices	II
Recommendation: definite antidepressant effect of HF rTMS of the left DLPFC (Level A)							
<i>LF rTMS of the right DLPFC</i>							
Klein et al. (1999b)	70 (active: 36; control: 34)	Right DLPFC, F8c	Tilted coil	1 Hz, 110% RMT	120 pulses, 10 sessions	Positive (49% responders, 47% improvement)	II
Januel et al. (2006)	27 (active: 11; control: 16)	Right DLPFC, F8c	Sham coil	1 Hz, 90% RMT	120 pulses, 16 sessions	Positive (64% responders, 54% improvement)	III
Fitzgerald et al. (2008b)	60	Right DLPFC, F8c	Tilted coil	1 Hz (6 Hz priming), 110% RMT	900 pulses, 20 sessions	Positive (30% responders for 6 Hz primed rTMS; 11% responders for non-primed rTMS)	II
Bares et al. (2009)	60 (active: 29; control: 31)	Right DLPFC, F8c	Tilted coil	1 Hz, 100% RMT	600 pulses, 20 sessions	No difference of efficacy between rTMS (33% responders) and venlafaxine (39% responders)	II
Aguirre et al. (2011)	34 (active: 19; control: 15)	Right DLPFC, F8c	Tilted coil	1 Hz, 110% RMT	1200 pulses, 20 sessions	No difference of efficacy between active and sham rTMS, except for patients younger than 45 years old	III
Recommendation: probable antidepressant effect of LF rTMS of the right DLPFC (Level B)							
<i>Studies comparing HF rTMS of the left DLPFC and LF rTMS of the right DLPFC</i>							
Fitzgerald et al. (2003)	60 (left: 20; right: 20; control: 20)	Left or right DLPFC, F8c	Tilted coil	10/1 Hz, 100% RMT	1000 pulses (10 Hz)/300 pulses (1 Hz), 10 sessions	No difference between 10 Hz and 1 Hz Efficacy enhanced by the repetition of the sessions.	II
Höppner et al. (2003)	30 (left: 10; right: 10; control: 10)	Left or right DLPFC, F8c	Tilted coil	20/1 Hz, 90%/110% RMT	800 pulses (20 Hz)/120 pulses (1 Hz), 10 sessions	No difference between 20 Hz and 1 Hz	III
Chistyakov et al. (2005)	59 (active: 43; control: 16)	Left or right DLPFC, F8c	Tilted coil	10/3 Hz, 100%/110% RMT	450 pulses, 10 sessions	No difference between 10 Hz and 3 Hz. Efficacy correlated to various excitability parameters (silent period, MT)	III
Isenberg et al. (2005)	28 (active: 14; control: 14)	Left or right DLPFC, F8c	None	20/1 Hz	450 pulses, 20 sessions	No difference between 20 Hz and 1 Hz. Positive (32/32% responders)	III
Fitzgerald et al. (2007)	26 (active: 15; control: 11)	Left or right DLPFC, F8c	None	10/1 Hz, 100%/110% RMT	750 pulses (10 Hz)/420 pulses (1 Hz), 15 sessions	No difference between 10 Hz and 1 Hz	III

meta-analysis conducted by Brunoni et al. (2009), the placebo effect was investigated in studies using either escitalopram or rTMS to treat depression. The placebo effect was important in both cases, but higher in studies evaluating pharmacological treatment compared to rTMS studies. The placebo effect was lower in drug-resistant patients or when rTMS was used as an “add-on” therapy.

Placebo-controlled studies are less numerous for LF rTMS of the right DLPFC than for HF rTMS of the left DLPFC (three to 5 times less). A recent meta-analysis identified 8 studies, totaling 263 patients (Berlim et al., 2013c). The average rate of responders was 38% and 15% of patients receiving active and sham right LF rTMS, respectively. According to smaller sample sizes, the antidepressant effect of LF rTMS of the right DLPFC can be defined only as probable (Level B recommendation) and not as definite, in contrast to HF rTMS of the left DLPFC. However, several comparative studies, in which both protocols were performed in the same series of patients, demonstrated that LF rTMS of the right DLPFC and HF rTMS of the left DLPFC have in fact similar efficacy (Fitzgerald et al., 2003, 2007, 2009a; Höppner et al., 2003; Chistyakov et al., 2005; Isenberg et al., 2005; Stern et al., 2007; Rossini et al., 2010) (Table 9). A recent meta-analysis (Chen et al., 2013), which identified 8 randomized controlled trials that directly compared HF rTMS and LF rTMS applied on the left and right DLPFC, respectively, totaling 249 patients, confirmed that both rTMS approaches were equally effective. This statement can be proposed with a Level B recommendation (probably no difference between the 2 methods). One study further showed that there was a significant but modest likelihood of response to left HF rTMS in patients who fail right LF rTMS (Fitzgerald et al., 2009c). In the follow-up open phase of a large sham-controlled trial (McDonald et al., 2011), the reverse was also demonstrated: patients who do not respond to left HF rTMS may benefit from right LF rTMS. Therefore, in terms of individual management of depressive patients in routine practice, it would appear advisable that if a patient does not initially respond to left HF rTMS, (s)he should receive right LF rTMS, and vice versa. In the future, the challenge will be to identify responders to the right or left stimulation, and to provide the right strategy for personalized medicine. One study addressed this question by showing the correlation between the lateralization of frontal hypometabolism on 18F-fluorodeoxyglucose PET (FDG-PET) and the specific efficacy of left-sided stimulation (Paillère Martinot et al., 2010, 2011) (see Section 13.4).

Following the pioneering work of Loo et al. (2003), various studies have assessed whether additional efficacy could be obtained by the combination of LF (1 Hz) stimulation on the right DLPFC and HF (10 Hz) stimulation on the left DLPFC during the same sessions in the same patients. A recent meta-analysis identified 7 randomized controlled trials combining HF rTMS and LF rTMS applied on the left and right DLPFC, respectively, totaling 279 patients (Berlim et al., 2013f). In fact, 7 studies compared the efficacy of bilateral rTMS to a sham condition (Table 9). A significant efficacy of the active condition was observed in 3 of the studies (Fitzgerald et al., 2006; Garcia-Toro et al., 2006; Blumberger et al., 2012b), but not in the others (Hausmann et al., 2004b; McDonald et al., 2006; Pallanti et al., 2010; Fitzgerald et al., 2012). Bilateral rTMS was also directly compared to unilateral rTMS in 7 studies (Table 9). Only one study showed a superior efficacy of bilateral rTMS (compared to left HF rTMS) (Blumberger et al., 2012b), while bilateral rTMS was as effective as left HF or right LF rTMS in other studies (Conca et al., 2002; Hausmann et al., 2004b; Fitzgerald et al., 2011, 2013b). However, 2 studies also reported a lower efficacy of bilateral rTMS compared to right LF or left HF rTMS (Pallanti et al., 2010; Fitzgerald et al., 2012). Therefore, no recommendation can be proposed regarding the value of bilateral rTMS, because of highly contradictory results, and there is no reason to perform such a protocol for treating a depressive patient to date.

13.2. Influence of the number of pulses and sessions

Most of the controlled studies selected in our analysis are satisfactory in terms of study design and methodology, but remain generally heterogeneous in terms of stimulation parameters.

For example, only one Class I study reported a lack of antidepressant efficacy of HF rTMS of the left DLPFC (Herwig et al., 2007), but this negative result may be explained by suboptimal parameters of stimulation, as discussed in Section 1.2. Actually, in the reported trials, there is some variability regarding these parameters, e.g., in the number of stimuli per session (120–3000) or the number of sessions proposed (10–30). This is of importance, since it has been demonstrated that the therapeutic benefit was higher for a higher number of sessions and rTMS pulses per session, at least for HF rTMS of the left DLPFC (Gershon et al., 2003). These authors showed that the rate of responders very significantly increased when the number of sessions was greater than 10, the total number of pulses delivered per session greater than 1000, and the stimulation intensity greater than 100% RMT. Recently, a meta-analysis demonstrated a similar influence of the parameters of stimulation for LF rTMS of the right DLPFC, showing higher levels of response when more than 1200 pulses were delivered per session (Berlim et al., 2013c).

The gain provided by methodological improvement on the efficacy of HF rTMS of the left DLPFC was calculated in the meta-analysis published by Gross et al. (2007), comparing the rate of efficacy of 5 recent studies with the results observed in a previous meta-analysis performed by Couturier (2005). This gain corresponded to an effect size of 0.75 for HF rTMS of the left DLPFC in the most recent studies. Note also that a meta-analysis specifically dedicated to LF rTMS of the right DLPFC found that this type of stimulation, with an effect size of 0.63, was significantly effective (Schutter, 2010).

13.3. Influence of the frequency of stimulation

The frequency of stimulation in depression is intrinsically linked to the side stimulated (HF on the left vs. LF on the right). The left stimulation is usually performed at 10 Hz. At least 13 controlled studies used a frequency of stimulation of 20 Hz and achieved a level of antidepressant efficacy comparable to that of 10 Hz rTMS. In the absence of direct comparative studies, possible differences in efficacy between these 2 frequencies remain unknown.

In a few studies, HF stimulation was performed at 5 or 15 Hz. A frequency of 5 Hz was applied in 5 controlled studies (George et al., 2000; Nahas et al., 2003; Rumi et al., 2005; Su et al., 2005; Triggs et al., 2010) (Table 9). Two of these studies compared stimuli at 20 Hz and 5 Hz and found no significant differences in antidepressant efficacy (George et al., 2000; Su et al., 2005). One study, addressing combined treatment (rTMS and amitriptyline), showed a remarkable efficacy of rTMS performed at 5 Hz (Rumi et al., 2005). However, the last 2 studies did not confirm such efficacy relative to the control condition (Nahas et al., 2003; Triggs et al., 2010).

A frequency of 15 Hz has been applied in 2 controlled studies of Class II by Rossini et al., one investigating a combined treatment (rTMS together with venlafaxine, escitalopram, or sertraline) (2005b) and the other including a comparison of 2 intensities of stimulation (2005a). Both studies found a significant antidepressant effect of rTMS performed at 15 Hz.

After all these observations, it is difficult to judge whether there is an optimal frequency of stimulation between 5 Hz and 20 Hz. But it does seem reasonable to perform HF rTMS of the left DLPFC at a frequency of 10 Hz or 20 Hz, according to the usual experience of investigators.

13.4. Influence of the targeting method

Almost all controlled rTMS studies in depression targeted the right or left DLPFC according to a “standard procedure” using external landmarks and blind determination of the “hand motor hotspot” (that is to say the scalp site where TMS produced hand MEPs of maximum amplitude). This “standard procedure” defined the DLPFC target as a point located 5 cm in front of the “hand motor hotspot” in a parasagittal plane pointing anteriorwards. Such a method implies significant biases related to the experience of the investigators in determining the “motor hotspot” and, more importantly, to the interindividual variability of cortical anatomy. Several studies have demonstrated that the “standard procedure” of targeting the DLPFC (the “5 cm rule”) was anatomically incorrect: the resulting targeted area reached using this rule was in the majority of the cases the premotor cortex and the frontal eye field rather than prefrontal cortex (Brodmann’s areas 46 and 9). The correct average distance between the “motor hotspot” and the DLPFC is closer to 7 cm (Herwig et al., 2001; Ahdab et al., 2010). Another proposed method for targeting the left DLPFC was based on the F3 location using the International 10–20 system of EEG electrode positioning (Herwig et al., 2003).

Although the use of a neuronavigation system dedicated to rTMS practice is a way of placing the coil accurately over the desired brain area (Schönfeldt-Lecuona et al., 2005), only one study to date used MRI-guided neuronavigation to specifically target the stimulation over the DLPFC at the border of Brodmann’s areas 46 and 9 and compared this method to the “standard procedure” (Fitzgerald et al., 2009b). This study showed a significant increase in efficacy by using navigated rTMS. The relevance of neuronavigated rTMS was recently supported by Fox et al. (2012), who observed that antidepressant efficacy of rTMS depends on how well the DLPFC target region connected with the subgenual cingulate gyrus. Finally, Paillère Martinot et al. (2010, 2011) demonstrated the value of combining neuronavigation and functional imaging to improve the efficacy of rTMS in depression and also to better understand its mechanism of action. In this study, rTMS applied with the standard procedure for targeting DLPFC rTMS did not show superior efficacy in the active condition compared to sham treatment. However, targeting rTMS to the hypometabolic maximum as determined by FDG-PET was significantly more effective, but only if this region was lateralized on the left hemisphere. Apart from its interesting methodological aspects, this study supports the hypothesis that the antidepressant effect of HF rTMS may be based on the modulation of an underlying hypoactive left prefrontal region. Thus, brain imaging techniques, such as PET (Speer et al., 2009; Paillère Martinot et al., 2010, 2011; Kito et al., 2012), SPECT (Langguth et al., 2007; Richieri et al., 2011), or resting state fMRI (Baeken et al., 2014; Salomons et al., 2014) could be used as predictors for rTMS outcome in depressed patients, or at least to better understand the underlying mechanisms of action. Neurophysiological techniques, such as cortical excitability studies (Bajbouj et al., 2005; Chistyakov et al., 2005) and EEG (Arns et al., 2012; Micoulaud-Franchi et al., 2012; Noda et al., 2013) may be used for the same purpose.

Although brain image-guided targeting is valuable in various rTMS applications (Lefaucheur et al., 2007; Lefaucheur, 2010; Ruohonen and Karhu, 2010), further work is still necessary before issuing a recommendation on the use of any neuronavigation system for rTMS therapy in depression (Schönfeldt-Lecuona et al., 2010b). In this context, it will be important to address the issue of the exact location of the navigated DLPFC target for depression therapy, given the wide extent of DLPFC representation on cortex anatomy (Mylius et al., 2013).

13.5. Efficacy of rTMS in the treatment of unipolar or bipolar depression

An important point concerns the distinction between unipolar and bipolar depression, as both entities differ regarding pathophysiological mechanisms and therapeutic management. In most studies investigating rTMS for the treatment of depression, the 2 populations are mixed, without differentiating the specific effect obtained for each of them. Among the trials addressing specifically the question of unipolar depression, we found 10 positive Class I–II studies. Among these studies, 8 used HF stimulation of the left DLPFC and two used LF stimulation of the right DLPFC. Based on these studies, we can confirm the efficacy of rTMS in the treatment of unipolar depression with a Level A recommendation (“definite efficacy”) for both HF rTMS of the left DLPFC and LF rTMS of the right DLPFC. This applies also for the treatment of moderate-intensity unipolar depressive episodes that do not respond to at least one class of antidepressant drugs.

Regarding bipolar depression, one Class III study was negative (Nahas et al., 2003). It is difficult to draw conclusions about the relevance of this study, which allowed the continuation of drug intake (including anticonvulsants and mood stabilizers). Ten other studies enrolled bipolar patients, but the heterogeneity of the population was a clearly specified drawback. An important issue of antidepressant interventions in bipolar patients is the risk of triggering mania. To date, there is no evidence suggesting that rTMS is associated with an elevated risk for such an event compared to sham treatment (Xia et al., 2008).

Further work is necessary, because the development of rTMS in this indication is interesting due to the difficulty of using antidepressants in these patients. A number of studies, including case reports, seem to advocate the use of rTMS. A naturalistic open-label study showed that improvement during rTMS treatment of patients with bipolar depression was comparable to that of patients with unipolar depression (Frank et al., 2011). Similarly, a recent meta-analysis did not find any significant difference in the efficacy of HF rTMS between the studies that included only patients with primary unipolar depression and those with mixed samples of unipolar and bipolar depression (Berlim et al., 2014). However, we do not currently have sufficient data to draw conclusions and establish recommendations as regards rTMS for bipolar disorder.

13.6. Efficacy of rTMS in the treatment of depression in special populations

In specific populations with depression, such as vascular or stroke patients, patients with chronic fatigue syndrome or fibromyalgia, data are insufficient to make any recommendation. However, we note that we proposed above a Level B recommendation (“probable efficacy”) for the antidepressant effect of HF rTMS delivered to the left DLPFC in PD patients (see Section 4.3).

13.7. rTMS compared to antidepressants

Only 2 comparative studies directly addressing this question have been identified (Fregni et al., 2004; Bares et al., 2009): one comparing LF rTMS of the right DLPFC versus venlafaxine (150–375 mg) and the other HF rTMS of the left DLPFC versus fluoxetine in patients with PD. Both studies showed no difference between the 2 groups in terms of efficacy, but they were underpowered ($n = 42$ and 60) to prove equal efficacy and did not include any control group.

Another question is to determine the additive and potentiating antidepressant effect of rTMS in patients receiving antidepressant drugs. Among all publications on rTMS in depression, most of them

involved patients concomitantly receiving rTMS and pharmacological treatments, as highlighted in a previous review (Rachid and Bertschy, 2006). In fact, antidepressant medication is not interrupted in the majority of published studies assessing rTMS effects, and there is no controlled data regarding the administered drugs, including dosages and time of administration. We have analyzed the few studies that have controlled these parameters by studying the additive effect of drugs and rTMS when medication was introduced together with rTMS (combined treatment or “add-on therapy”) or was kept stable throughout the course of rTMS (augmenting effect of rTMS).

Regarding combined treatment, there are 5 studies (one Class I, two Class II, and two Class III) (Garcia-Toro et al., 2001b; Rossini et al., 2005b; Rumi et al., 2005; Bretlau et al., 2008; Herwig et al., 2007). Although the largest Class I study (Herwig et al., 2007) failed to demonstrate a superiority of active rTMS over placebo rTMS in addition to simultaneously initiated antidepressant medication (usual doses of mirtazapine or venlafaxine) and one Class III study (Garcia-Toro et al., 2001b) showed no additive efficacy of rTMS to sertraline, the other studies allow us to conclude a probable additive efficacy of rTMS to antidepressant drugs (Level B recommendation). This is also supported by a recent meta-analysis, which identified 6 randomized controlled trials, totaling 392 patients (Berlim et al., 2013e). The average rate of responders was 43% and 27% of patients receiving antidepressants in combination with active and sham left HF rTMS, respectively.

Regarding an augmentation of antidepressant medication by rTMS, we selected 5 studies (one Class II and four Class III) (Anderson et al., 2007; Bortolomasi et al., 2007; Mogg et al., 2008; Carretero et al., 2009; Pallanti et al., 2010) in which rTMS was added to a stable antidepressant regime. Again, two studies were negative, but the 3 others (Class III studies) (Anderson et al., 2007; Bortolomasi et al., 2007; Pallanti et al., 2010) offer a convincing basis from which to conclude a possible potentiating effect of rTMS on antidepressant drugs (Level C recommendation).

13.8. rTMS compared to electroconvulsive therapy

In addressing this issue, an important methodological problem is the lack of placebo-controlled studies comparing the 2 techniques. Furthermore, ECT applications require anesthetic procedures while rTMS does not, making direct comparisons impossible. Available studies have a low level of evidence, being open-labeled or randomized, but single-blinded (Grunhaus et al., 2000, 2003; Pridmore et al., 2000; Janicak et al., 2002; Schulze-Rauschenbach et al., 2005; Rosa et al., 2006; Eranti et al., 2007; Hansen et al., 2011; Keshtkar et al., 2011). A recent meta-analysis identified 9 randomized controlled trials that directly compared rTMS and ECT with a total of 425 patients (Ren et al., 2014). It appears that rTMS has a lower efficacy than ECT, as shown in these meta-analyses (Slotema et al., 2010; Berlin et al., 2013d), especially in the case of depression with psychotic features (Grunhaus et al., 2000; Ren et al., 2014). In patients with non-psychotic depression, rTMS could be as effective as ECT, but data are insufficient to conclude the long-term efficacy (Ren et al., 2014). In addition, the absence of significant differences between ECT and rTMS in some studies may be explained by the small sample size and therefore a considerable beta error, as well as by a lower efficacy of ECT in these studies compared to what is usually reported. Therefore, we can conclude that rTMS is probably ineffective in depression with psychotic features (but no formal recommendation can be proposed yet), a condition that is the main clinical indication for ECT. However, we cannot draw conclusions about the overall respective efficacy of ECT and rTMS depending on the level of resistance (Padberg and George, 2009). The results of a recent meta-analysis comparing rTMS versus ECT indicate that

the efficacy of rTMS is tied to its stimulus parameters (Xie et al., 2013).

13.9. Conclusions

The literature concerning rTMS and depression is very rich, but also heterogeneous in its objectives, in the populations included, and in stimulation settings. The methodology has improved significantly since 2000, with an optimization of stimulation parameters (higher number of sessions and higher number of stimuli per session). A large amount of evidence supports the conclusion that HF rTMS of the left DLPFC and LF rTMS of the right DLPFC exerts an antidepressant effect, at least in the acute phase of an episode of unipolar depression. However, further studies are needed to investigate the efficacy of rTMS in bipolar depression. Another patient characteristic, which is not always well-specified in rTMS studies, is the question of drug-resistance. The majority of studies comprise depressed patients resistant to one or more psychopharmacological interventions. This is not only true for the oldest studies, but also for the most recent ones. In fact, the level of resistance, especially in terms of number of drug treatment failures at the time of the current episode, is highly variable between the studies and this may impact the response to rTMS therapy. A further crucial issue is the combination of pharmacological therapy with the application of rTMS. Some studies showed that the antidepressant effect of rTMS delivered to the DLPFC was probably an additive to the efficacy of antidepressant drugs and possibly potentiating, although not all studies demonstrate an add-on advantage from rTMS combined with antidepressants. These aspects need to be taken into account in the choice and development of therapeutic strategies and in determining the respective place of rTMS and drugs in the management of patients with depression.

Actually, while rTMS appears to be undoubtedly efficacious for depression, the clinical relevance of its efficacy in daily practice is more questionable, as underlined by a recent meta-analysis (Lepping et al., 2014). The NICE guidelines in the UK said that there were “no major safety concerns about this procedure”, but that there were “uncertainties about how to achieve the best results” (<http://www.nice.org.uk/guidance/CG90>, issued: October 2009; updated: April 2012 and IPG242, issued: November 2007; updated: January 2011). These guidelines suggest that “TMS may be a therapeutic option as part of specialist team management” in case of “difficulty of treating patients with severe depression that has failed to respond to other therapies”, but recommend that use of rTMS should be “restricted to research studies until optimal methods are determined”. Therefore, several methodological points should be defined as soon as possible to standardize and optimize the use of rTMS in the treatment of depression in routine clinical practice (Fitzgerald and Daskalakis, 2012). We have already discussed the choice of the side of stimulation, with respect to the assumed existence of differential responders to right LF rTMS versus left HF rTMS, as well as the method for targeting the DLPFC: (i) using a navigation system, (ii) positioning the coil 7 cm anterior to the motor hotspot, or (iii) according to the F3 location in the International 10–20 system of EEG electrode positioning. Since rTMS efficacy surely depends on the “dose” of stimulation (number of delivered pulses during a sequence of treatment), new rTMS protocols are being tested by intensifying the number of delivered pulses over shorter periods of time (Holtzheimer et al., 2010; Hadley et al., 2011). Other protocols propose to combine different rTMS paradigms according to priming strategies or to use stimulating coils other than the focal F8c, e.g., the H-coil, which delivers more widespread current into the depth of the brain. However, to improve rTMS therapy for depression in the future, the key aim will probably be to better define the protocol of maintenance.

There are currently no robust data or consensus regarding how to treat depression with rTMS beyond the acute phase followed by maintenance sessions in the long term. New protocols have been proposed in open-label trials to delay the occurrence of relapse following a successful course of rTMS treatment (Fitzgerald et al., 2013a), but such protocols remain to be validated in large, controlled studies.

To date, taking into account all these issues, rTMS of the DLPFC can be proposed as a relevant technique to treat drug-resistant major depression, except for depression with psychotic features for which the use of ECT is recommended as the first-line adjunctive treatment. Our recommendations on the use of rTMS in the treatment of mood disorders are consistent with those of CANMAT (Kennedy et al., 2009).

14. Anxiety disorders

Anxiety disorders such as posttraumatic stress disorder (PTSD) and panic disorder (PaD) are currently treated by antidepressant drugs or psychotherapy, including cognitive behavioral therapies that have proven their efficacy. However, in some patients, these treatments are insufficient to control symptoms. Thus, rTMS could, on theoretical grounds, be a potential second-line technique to treat residual anxiety symptoms.

14.1. Post-traumatic stress disorder

Currently, only a few studies have evaluated the therapeutic efficacy of rTMS in PTSD. A PubMed search (keywords: rTMS/TBS AND post-traumatic stress disorder) identified 15 papers, including 3 original placebo-controlled studies with at least 10 patients who received active rTMS of the DLPFC (Table 10). The analyzed results cover 74 patients.

In 3 of these studies, the right and left DLPFC targets were stimulated by LF and HF rTMS, respectively. Although the results are fairly homogeneous, they are based on small sample sizes and there are significant methodological differences regarding the side of the cortical target, the parameters of stimulation, the existence of concomitant drug treatment, and the notion of resistance of the treated disorder. This methodological variability precludes making a recommendation higher than Level C (“possible efficacy”) for the use of HF rTMS delivered to the right DLPFC in the treatment of PTSD. In addition, we have to mention a recent sham-controlled study using an H-coil to stimulate at HF (20 Hz) a larger prefrontal cortical area in 26 PTSD patients (Isserles et al., 2013). A series of 12 rTMS sessions led to a significant reduction in total clinician-administered PTSD scale (CAPS) score and subscores. The use of the H-coil to stimulate large cortical regions when there is no specific focal target is a promising technological advance for therapeutic application of rTMS in various indications.

14.2. Panic and generalized anxiety disorders

The therapeutic application of rTMS in anxiety disorders also concerns PaD and panic attacks. A PubMed search (keywords: rTMS/TBS AND panic disorder) identified 12 papers (6 studies published to date) in this domain. Only one study was performed on generalized anxiety disorder. The results of these studies are contradictory. The inclusion criteria, stimulation parameters and evaluation methods are very heterogeneous. Despite a small sample size, [Mantovani et al. \(2013a\)](#) published interesting preliminary results from their first randomized, sham-controlled rTMS trial (Class III study) performed in a series of 25 patients with PaD. These authors showed a significant, dose-dependent, improvement of panic (but not of depression) using LF (1 Hz) rTMS of the right DLPFC. The same authors also published one open-label study on depersonalization disorder (DPD): LF rTMS of the temporoparietal junction reduced DPD symptoms by 68% in 6/12 patients ([Mantovani et al., 2011](#)). Overall, the level of evidence remains insufficient to propose any recommendation in PaD, with 2 controlled studies (Class III) reporting negative and positive results, respectively, about the efficacy of rTMS in this indication.

14.3. Conclusions

To date, studies of rTMS in anxiety disorders have been heterogeneous in terms of methods and results (Pigot et al., 2008; Pallanti and Bernardi, 2009; Zwanzger et al., 2009; Slotema et al., 2010). The studies have important limitations; these particularly comprise the small number of patients included, the lack of a clear definition of inclusion and exclusion criteria, the non-control of concomitant medication, the absence of standardization of stimulation parameters and evaluation measurements, and the lack of data on follow-up after treatment. Thus, current data are not sufficient to allow a proper recommendation to be made regarding the value of rTMS in the treatment of anxiety disorders except for a possible effect (Level C) of HF rTMS delivered to the right DLPFC in PTSD.

15. Obsessive compulsive disorder

Several therapeutic studies have been conducted in this indication. Published studies to date employed very heterogeneous methodologies, reflecting the various hypotheses on the underlying pathophysiological mechanisms. A PubMed search (keywords: rTMS/TBS AND obsessive-compulsive disorder) identified 48 papers, including 9 original placebo-controlled studies with at least 10 patients who received active rTMS of the DLPFC ([Table 11](#)). The analyzed results cover 215 patients.

The results of these studies (mainly Class III) are conflicting, since 4 are positive and 5 are negative about the efficacy of rTMS in OCD. This may be partly explained by the heterogeneity of both

Table 10
rTMS studies in post-traumatic stress disorder (target: dorsolateral prefrontal cortex).

[illegible]

Table 11
rTMS studies in obsessive-compulsive disorder (target: dorsolateral prefrontal cortex).

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
HF rTMS of the DLPFC							
Greenberg et al. (1997)	12	Right or left DLPFC, F8c	Stimulation vertex	20 Hz, 80% RMT	800 pulses, 1 session	Mood improvement and reduction of movement urge after right stimulation	III
Sachdev et al. (2007)	18 (active: 10; control: 8)	Left DLPFC, F8c	Tilted coil	10 Hz, RMT	10 pulses, 20 sessions	No effect on Y-BOCS, even after repeated sessions	III
Sarkhel et al. (2010)	42 (active: 21; control: 21)	Right DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	8000 pulses, 10 sessions	No effect on Y-BOCS	II
Mansur et al. (2011)	27 (active: 13; control: 14)	Right DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	60,000 pulses, 30 sessions	Significant change on Y-BOCS for both active and control conditions	III
Gomes et al. (2012)	22 (active: 12; control: 10)	Right DLPFC, SMA, F8c	Tilted coil	1 Hz, 100% RMT	12,000 pulses, 10 sessions	Significant reduction on Y-BOCS (35% for active vs. 6% for control condition)	III
LF rTMS of the DLPFC							
Alonso et al. (2001)	18 (active: 10; control: 8)	Right DLPFC, C	Tilted coil	1 Hz, 110% RMT	1200 pulses, 18 sessions	No effect on Y-BOCS and HDS	III
Prasko et al. (2006)	33 (active: 20; control: 14)	Left DLPFC, F8c	Tilted coil	1 Hz, 110% RMT	1800 pulses, 10 sessions	No significant effect compared to placebo condition	III
Kang et al. (2009)	20 (active: 10; control: 10)	Right DLPFC, SMA		1 Hz, 110% RMT	1200 pulses, 10 sessions	No significant effect	III
Ruffini et al. (2009)	23 (active: 16; control: 7)	Left orbitofrontal cortex, F8c	Tilted coil	1 Hz, 80% RMT	600 pulses, 15 sessions	Improvement on Y-BOCS up to 10 weeks after the end of the stimulation	III
No recommendation for the effect of HF or LF rTMS of the right or left DLPFC in obsessive-compulsive disorder							

inclusion criteria and stimulation parameters. Given these drawbacks, and also the small number of patients included, it is not possible to propose any recommendation for the use of HF or LF rTMS of the right or left DLPFC in the treatment of OCD. We are in agreement with the NICE recommendation (<http://www.nice.org.uk/guidance/CG26>, issued: March 2005) and the meta-analysis of Slotema et al. (2010) who proposed not retaining OCD as an indication to be treated with rTMS applied to the DLPFC.

For future studies, it appears that targeting the SMA with LF stimulation may be interesting. This was supported by preliminary results showing that targeting the SMA with fMRI-guided-navigation improves rTMS efficacy in this clinical condition (Mantovani et al., 2010b). Only one controlled study (Class II) performed in 21 patients showed the potential value of this approach, which deserves confirmation (Mantovani et al., 2010a). Clinical effects of LF rTMS of SMA on OCD were correlated with inhibitory modulation of motor cortex excitability (Mantovani et al., 2013b).

Recently, Berlim et al. (2013b) published a meta-analysis of 10 controlled rTMS trials in OCD patients (282 patients). They concluded that LF rTMS and protocols targeting the orbitofrontal cortex or the SMA seem to be the most efficacious. Nevertheless, future placebo-controlled rTMS studies in OCD patients should include larger sample sizes and be more homogeneous in terms of demographic and clinical variables, stimulation parameters, and cortical target. As a conclusion, we cannot offer any recommendation for any rTMS protocol in the treatment of OCD patients to date.

16. Schizophrenia

16.1. Auditory hallucinations

During auditory hallucinations, brain areas involved in the perception of speech (primary auditory cortex and associative areas of language in the left hemisphere) show pathological hyperactivity, as determined by neuroimaging studies (Silbersweig et al., 1995; Shergill et al., 2000). Decreasing the excitability of the TPC by LF rTMS became therefore an interesting line of research for the treatment of drug-resistant auditory hallucinations (Hoffman et al., 1999).

A PubMed search (keywords: rTMS/TBS AND auditory hallucinations) identified 84 papers, including 14 original placebo-controlled studies with at least 10 patients who received active LF rTMS (1 Hz) of the left TPC (Table 12). The analyzed results cover 393 patients. A responder is usually defined as a patient showing a reduction of symptoms of more than 30–50% relative to baseline severity.

The studies summarized in Table 12 provided highly controversial results, with 7 positive studies (two Class II and 5 Class III) involving a total of 118 patients treated by active rTMS and 7 negative studies (two Class II, including the largest series to date (Slotema et al., 2011) and 5 Class III) covering altogether 146 patients treated by active rTMS. Therefore, no conclusion could be firmly drawn from these data. However, several meta-analyses clearly concluded an efficacy of LF rTMS of the left TPC, with a significant effect size ranging from 0.4 to 1 depending on the publication (Aleman et al., 2007; Tranulis et al., 2008; Freitas et al., 2009; Slotema et al., 2010; Demeulemeester et al., 2012). As pointed out in the most recent meta-analysis (Slotema et al., 2012a), the size of effect on auditory hallucinations is decreasing with the inclusion of studies with larger sample sizes, though these remain significant. The impact on other dimensions of the disease, especially psychosis, is even smaller, though significant, with an effect size of 0.2 (Slotema et al., 2013). Considering all these elements, it seems legitimate to propose a Level C recommendation

Table 13
rTMS studies in negative symptoms of schizophrenia (target: prefrontal cortex).

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Results	Class of the study
Klein et al. (1999a)	31 (active: 16; control: 15)	Right DLPFC, Cc	Tilted coil	1 Hz, 90% RMT	120 pulses, 10 sessions	Negative (on PANSS and HDRS)	III
Rollnik et al. (2000)	12	Left DLPFC, F8c	Tilted coil	20 Hz, 100% RMT	800 pulses, 10 sessions	Positive (on BPRS)	III
Hajak et al. (2004)	20 (active: 10; control: 10)	Left DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	1000 pulses, 10 sessions	Positive (on PANSS)	III
Holl et al. (2004)	22 (active: 11; control: 11)	Left DLPFC, F8c	Tilted coil	10 Hz, 100% RMT	1000 pulses, 10 sessions	Negative (on PANSS)	III
Jin et al. (2006)	37 (active: 29; control: 8)	Bilateral DLPFC, F8c	Non-connected coil	Three frequencies (randomized): alpha TMS (8–13 Hz), 3, or 20 Hz, 80% RMT	120–800 pulses depending on frequency, 10 sessions	Positive (significant reduction negative subscore of PANSS for the 11 patients receiving alpha TMS)	III
Prikryl et al. (2007)	22 (active: 11; control: 11)	Left DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	1500 pulses, 15 sessions	Positive	III
Schneider et al. (2008)	51 (active: 34; control: 17)	Left DLPFC, F8c	Tilted coil	10 or 1 Hz, 110% RMT	2000 pulses, 20 sessions	Positive (on SANS for 10 Hz rTMS only)	II
Fitzgerald et al. (2008a)	20 (active: 12; control: 8)	Bilateral DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	1000 pulses, 15 sessions	Negative (on SANS and PANSS)	III
Cordes et al. (2010)	35 (active: 20; control: 15)	Left DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	1000 pulses, 10 sessions	Positive (on negative subscore of PANSS)	II
Barr et al. (2012)	25 (active: 13; control: 12)	Bilateral DLPFC, fMRI	Tilted coil	20 Hz, 90% RMT	750 pulses per hemisphere, 20 sessions	Negative (on negative subscore of PANSS and SANS)	III
Prikryl et al. (2013)	40 (active: 23; control: 17)	Left DLPFC, F8c	Tilted coil	10 Hz, 110% RMT	2000 pulses, 15 sessions	Positive (on SANS and all domains of negative symptoms)	II

Recommendation: probable effect of HF rTMS of the left DLPFC on negative symptoms of schizophrenia (Level B)

in favor of a possible efficacy of LF rTMS of the left TPC on auditory hallucinations. For other protocols of stimulation (other targets or stimulation frequencies), data are too scarce to draw any conclusion (Slotema et al., 2013).

Thus, the proposed target in this indication is the left TPC (or even superior temporal gyrus), which can be located either by a rough estimation based on scalp measurements (the middle of the T3–P3 line according to the International 10–20 system of EEG electrode positioning), or by means of a neuronavigation system integrating morphological or functional imaging data, as first demonstrated by Schönfeldt-Lecuona et al. (2004). However, the respective values of these 2 methods of targeting have not been compared to date.

Stimulation intensity is generally set at 90% of RMT. Stimulation intensity higher than 100% of RMT was used in 2 studies, which reported controversial results (Loo et al., 2010; Blumberger et al., 2012a). It remains to determine whether rTMS effects on hallucinations can be optimized by modifying this parameter.

The use of an “inhibitory” frequency of stimulation of 1 Hz is based on an assumed hyperactivity of the TPC and on evidence-based data. However, other stimulation protocols have been proposed. First, 2 studies investigated the value of a priming strategy using 6 Hz rTMS preceding 1 Hz rTMS (Blumberger et al., 2012a; Slotema et al., 2012b). These 2 studies did not show any additional value of this priming strategy, all active conditions being essentially ineffective in reducing the severity of auditory hallucinations. In contrast, an open-label study showed positive results of HF rTMS (20 Hz) of the TPC (Montagne-Larmurier et al., 2009). In addition, several studies comparing rTMS given at 1 Hz and 20 Hz or cTBS did not show any frequency-related differences in terms of efficacy (Homan et al., 2012; Kindler et al., 2013a,b; de Weijer et al., 2014). Therefore, other patterns of stimulation of the left TPC need to be investigated further for this indication.

Regarding clinical practice, LF rTMS of the left TPC can be proposed as an adjunctive therapy to the usual pharmacotherapy in persistent hallucinatory phenomena. This treatment applies particularly to right-handed patients who are stabilized for drug treatment and who continue to have hallucinations. No studies have been conducted in other populations. It would be of interest to explore the effect of rTMS in the initial phase of auditory hallucinations. The influence of the patient's age has also not been specifically addressed. However, it is important to note that some cases reported in the literature deal with late-onset schizophrenia (50 years), while rTMS treatment has also been proposed at younger ages and in childhood (Jardri et al., 2007, 2009). The use of rTMS in these specific populations is interesting, but should be discussed systematically according to the risk-benefit ratio, with respect to the safety guidelines of rTMS.

Finally, it should be noted that the effect of LF rTMS may be shorter than 1 month, despite the fact that a minimum of 10 sessions in 1–2 weeks is usually carried out (Slotema et al., 2012a). When relapse occurs after successful rTMS treatment, a new series of rTMS sessions may be indicated. However, no recommendation can be made on the possible procedures of maintenance to prevent relapse, because to date, published data are very scarce on this subject.

16.2. Negative symptoms

Because of the leading hypothesis about prefrontal dysfunction in schizophrenia, it has been proposed that clinical symptoms may be improved by restoring or at least increasing frontal cortical activity with HF rTMS delivered to the DLPFC. This stimulation might be beneficial on negative symptoms of schizophrenic

patients through an increased dopamine release in the ventral striatum (Paus, 1999).

A PubMed search (keywords: rTMS/TBS AND schizophrenia AND negative symptom) identified 48 papers, including 11 original placebo-controlled studies with at least 10 patients who received active rTMS of the DLPFC (Table 13). The analyzed results cover 315 patients.

All these studies focused on the acute treatment of negative symptoms in patients with schizophrenic disorders. A significant effect on these negative symptoms from active stimulation compared to sham stimulation was observed in 7 out of 11 studies. This is promising as until now treatment options are poor in this clinical condition. Meta-analyses have found a moderate effect size, ranging from significant or non-significant (Dlabac-de Lange et al., 2010; Slotema et al., 2010; Shi et al., 2014) due mainly to the small number of patients included in the studies. Thus, the efficacy of rTMS in the treatment of negative symptoms of schizophrenia is not definite. However, if we consider HF rTMS (10 Hz) of the left DLPFC, which is the most frequent stimulation setting, 6 studies (of Class II–III) presented in Table 13 provided positive results and only one Class III study was negative. Therefore, according to our criteria, one could propose a Level B recommendation for the probable efficacy of HF rTMS of the left DLPFC. Nevertheless, there is a wide heterogeneity in the profile of the patients included, with statistically significant effect, but at best a minor clinical effect. In addition, the studies did not usually specify whether depressive symptoms were controlled, although this could greatly interact with the negative symptoms of schizophrenia. Therefore, rTMS efficacy may be related to an impact on the depressive component of these symptoms, since HF rTMS of the left DLPFC is able to produce antidepressant effects in various conditions. Finally, the duration of the effect was rarely described and no study assessed the long-term effects of rTMS or maintenance treatment.

Regarding the other types of rTMS protocols, i.e., bilateral HF rTMS of the right and left DLPFC and LF rTMS of the right DLPFC, we cannot make any recommendation, pending further controlled studies. In particular, bilateral HF rTMS of DLPFC regions first showed promising results (Jin et al., 2006), but 2 subsequent placebo-controlled studies were negative (Fitzgerald et al., 2008a; Barr et al., 2012).

17. Substance abuse, addiction and craving

Abuse and addiction to substances, such as alcohol, nicotine, cocaine, or other drugs, are major health issues. These disorders are difficult to treat and the relapse rate is high, even following detoxification, pharmacological and psychological interventions (Fant et al., 2009; Heinz et al., 2009). The rationale to use rTMS as a treatment for substance addiction and craving is that the DLPFC, which plays a major role in top-down inhibitory control mechanisms and reward mechanisms, is dysfunctional in these disorders (Goldstein and Volkow, 2002; Wilson et al., 2004).

A PubMed search (keywords: rTMS/TBS AND addiction OR craving) identified 60 papers, including 10 original placebo-controlled studies with at least 10 patients who received active HF rTMS of the left DLPFC (Table 14). The analyzed results cover 265 patients. We also identified about 10 case reports, and a quite similar number of review articles on this topic (e.g., Jansen et al., 2013; Bellamoli et al., 2014, for the most recent ones).

Five studies (of Class II–III) presented in Table 14 provided positive results from the use of HF rTMS (10–20 Hz) of the left DLPFC on cigarette craving and especially on cigarette consumption and nicotine dependence. However, these studies showed a significant heterogeneity in terms of methods (e.g., regarding control condition and the number of sessions) and patients' profile, with one study being performed in schizophrenic

patients (Prikryl et al., 2014). Therefore, according to our criteria, only a Level C recommendation can be proposed for the possible efficacy of HF rTMS of the left DLPFC in reducing cigarette consumption.

Regarding alcohol and food craving, data from placebo-controlled studies published to date are insufficient to consider any therapeutic recommendation. Regarding cocaine craving, there is also one controlled study of 6 patients that showed transient benefit following HF (10 Hz) rTMS of the right but not left DLPFC (Camprodón et al., 2007). Conversely, LF (1 Hz) rTMS of the left DLPFC increased craving for methamphetamine in 10 dependent users (Li et al., 2013b). Finally, one Class III study targeted the left superior frontal gyrus rather the DLPFC (Rose et al., 2011). This study showed a transient reduction of craving for smoking after a single session of the left frontal rTMS performed at 10 Hz but not at 1 Hz.

18. Conversion

Regarding functional neurological symptoms such as motor conversion disorder, a PubMed search (keywords: rTMS/TBS AND conversion) identified 23 papers, but no blinded or placebo-controlled study. There were mostly case reports following the pioneering work of Schönfeldt-Lecuona et al. (2003), Schönfeldt-Lecuona et al. (2006), and less than 10 studies have been published to date (reviewed in Pollak et al., 2014). Stimulation sites were essentially the motor cortex and the vertex, targeted using a Cc or an F8c, and stimulation patterns were either LF rTMS, consisting of single pulses repeated at 0.25 Hz (Chastan and Parain, 2010; Garcin et al., 2013) or HF (15 Hz) rTMS (Schönfeldt-Lecuona et al., 2003, 2006). The largest series, using LF rTMS, reported impressive results, with a clinical improvement of 89% of 70 patients with “hysterical paresis” (Chastan and Parain, 2010) and 75% of 24 patients with psychogenic movement disorders (dystonia, myoclonus, tremor, Parkinsonism or stereotypies) (Garcin et al., 2013). Because the therapeutic management of functional neurological symptoms is challenging in practice, these results are encouraging. However, controlled data are needed before considering the use of rTMS in this domain. It remains to demonstrate that rTMS can have a real impact on the neural mechanisms of this disorder and therapeutic benefit in the long term, beyond inducing a non-specific placebo effect and immediate changes related to the movement produced in a paretic limb.

19. Summary of recommendations

This work presents for the first time an extensive evidence-based synthesis of established and potential therapeutic applications of rTMS in the neurological, ENT, and psychiatric domains. According to this synthesis, there is a sufficient level of evidence to recommend specific rTMS protocols in clinical practice for several indications, as summarized in Table 15.

It should be emphasized that a Level A recommendation has only been achieved so far for the beneficial effect of HF rTMS on neuropathic pain (target: M1 contralateral to pain side) and major depression (target: left DLPFC). However, the heuristic levels of evidence are not the same in these indications, since the efficacy of rTMS has been validated by placebo-controlled studies in more than 3000 patients with depression, but only 700 patients with neuropathic pain.

A level B recommendation (probable efficacy) is conferred for the effect of: (i) LF rTMS of the contralesional motor cortex on chronic motor stroke; (ii) LF rTMS of the right DLPFC on major depression; (iii) HF rTMS of the left DLPFC on depression in PD patients and on negative symptoms of schizophrenia. Finally, there

Table 15

Summary of recommendations on rTMS efficacy according to clinical indication.

Neuropathic pain	Definite analgesic effect of HF rTMS of M1 contralateral to pain side (Level A) LF rTMS of M1 contralateral to pain side is probably ineffective (Level B) No recommendation for cortical targets other than M1 contralateral to pain side
CRPS type I	Possible analgesic effect of HF rTMS of M1 contralateral to pain side (Level C)
Fibromyalgia	No recommendation for HF rTMS of the left M1 or DLPFC or for LF rTMS of the right DLPFC
Migraine	No recommendation for HF rTMS of the left M1 or DLPFC
Visceral pain	No recommendation for LF rTMS of the right S2 or for HF rTMS of the left DLPFC
Parkinson's disease	Possible antiparkinsonian effect of HF rTMS of bilateral (multiple) M1 regions (Level C) No recommendation for LF or HF rTMS of unilateral M1 representation of the hand No recommendation for rTMS of M1 and DLPFC using a non-focal coil or iTBS No recommendation for LF or HF rTMS of SMA or dPMC No recommendation for LF or HF rTMS of SMA, M1, or DLPFC or for cTBS of the cerebellum in levodopa-induced dyskinesia of PD patients Probable antidepressant effect of HF rTMS of the left DLPFC in PD patients (Level B)
Dystonia	No recommendation for LF rTMS of dPMC, M1, or S1
Essential tremor	No recommendation for LF rTMS of the cerebellum
Tourette's syndrome	No recommendation for LF rTMS of SMA, dPMC, or M1
Motor stroke	Possible effect of LF rTMS of the contralesional motor cortex in (post-)acute motor stroke (Level C) and probable effect in chronic motor stroke (Level B) Possible effect of HF rTMS of the ipsilesional motor cortex in (post-)acute and chronic motor stroke (Level C) No recommendation for cTBS of the contralesional motor cortex or iTBS of the ipsilesional motor cortex
Broca's aphasia	No recommendation for LF rTMS of the (contralesional) right IFG No recommendation for HF rTMS or iTBS of the (ipsilesional) left IFG or DLPFC
Wernicke's aphasia	No recommendation for LF rTMS of the right superior temporal gyrus
Hemispatial neglect	Possible effect of cTBS of the (contralesional) left posterior parietal cortex (Level C) No recommendation for LF rTMS of the (contralesional) left posterior parietal cortex No recommendation for HF rTMS of the (ipsilesional) right posterior parietal cortex No recommendation for cTBS or HF rTMS of M1
Amyotrophic lateral sclerosis	No recommendation for HF rTMS of M1
Multiple sclerosis	Possible antiepileptic effect of focal LF rTMS of the epileptic focus (Level C)
Epilepsy	No recommendation for non-focal LF rTMS at the vertex No recommendation for HF rTMS of DLPFC or M1
Disorders of consciousness	No recommendation for HF rTMS of DLPFC
Alzheimer's disease	Possible effect of single sessions of "burst" or LF rTMS of the auditory cortex contralateral to tinnitus (Level C) Possible effect of repeated sessions of LF rTMS of the left (or contralateral to tinnitus) TPC (Level C)
Tinnitus	No recommendation for HF rTMS or cTBS of the auditory cortex No recommendation for HF rTMS of the left DLPFC combined with LF rTMS of both the right and left TPC
Depression	Definite antidepressant effect of HF rTMS of the left DLPFC (Level A) Probable antidepressant effect of LF rTMS of the right DLPFC (Level B) and probably no differential antidepressant effect between right LF rTMS and left HF rTMS (Level B) No recommendation for bilateral rTMS combining HF rTMS of the left DLPFC and LF rTMS of the right DLPFC Definite antidepressant effect of rTMS of DLPFC in unipolar depression (Level A), but no recommendation for bipolar depression Antidepressant effect of rTMS of DLPFC is probably additive to the efficacy of antidepressant drugs (Level B) and possibly potentiating (Level C) No recommendation for the overall respective antidepressant efficacy of rTMS of DLPFC compared to ECT
Anxiety disorders	Possible effect of HF rTMS of the right DLPFC in PTSD (Level C) No recommendation for LF rTMS of the right DLPFC in panic disorders
Obsessive compulsive disorder	No recommendation for HF or LF rTMS of the right or left DLPFC
Auditory hallucinations	No recommendation for LF rTMS of SMA Possible effect of LF rTMS of the left TPC (Level C) No recommendation for HF rTMS or cTBS of the left TPC
Negative symptom of schizophrenia	Probable effect of HF rTMS of the left DLPFC (Level B)
Addiction and craving	No recommendation for bilateral HF rTMS of DLPFC and LF rTMS of the right DLPFC Possible effect of HF rTMS of the left DLPFC on cigarette craving and consumption (Level C) No recommendation for HF rTMS of the right or left DLPFC for food or alcohol craving
Conversion	No recommendation for LF or HF rTMS of M1 or delivered at the vertex, using a focal or a non-focal coil
"No recommendation" means the absence of sufficient evidence to date, but not the evidence for an absence of effect	

is a probable additive effect of rTMS of DLPFC with antidepressant medication.

A level C recommendation (possible efficacy) is agreed for the effect of: (i) LF rTMS of the left TPC on tinnitus and auditory hallucinations (a rather low level, despite many publications); (ii) HF rTMS (5–25 Hz) of bilateral (multiple) M1 areas on motor symptoms of PD; (iii) LF rTMS of the contralesional motor cortex and HF rTMS of the ipsilesional motor cortex on (post-)acute stroke. There is a possible potentiating effect of rTMS of DLPFC with antidepressant medication. Finally, a Level C recommendation is also given for emerging indications, such as CRPS type I (HF rTMS of

M1 contralateral to pain side), hemispatial neglect (cTBS of the (contralesional) left posterior parietal cortex), epilepsy (LF rTMS of the epileptic focus), PTSD (HF rTMS of the right DLPFC), and cigarette consumption (HF rTMS of the left DLPFC). In the near future, a recommendation can be expected for Broca's nonfluent aphasia (LF rTMS of the (contralesional) right IFG).

Further controlled studies in these and all other potential indications are obviously needed to extend and confirm the present recommendations. In addition, in clinical conditions where no recommendation has been proposed, the absence of evidence should not be taken as evidence for the absence of effect. This is especially

true for treatments with very variable individual responses, such as rTMS.

In future studies, special emphasis should be given to providing: (i) randomized study designs in which parallel groups are favored because in crossover designs, timing of placebo treatment may induce critical conditioned responses and long-lasting after-effects may produce substantial carry-over effects; (ii) adequate sample size, as the majority of current rTMS therapeutic studies suffer from insufficient power; (iii) accurate anatomical and functional targeting to properly investigate the potential of individual tailoring in improving response rate, in comparison to standard protocols without neuronavigation; (iv) further investigation of the possibilities of novel cortical targets, taking into account hemispheric lateralization, (v) large enough doses of TMS pulses, combined with new accelerated treatment protocols and priming strategies; (vi) realistic placebo control and double-blinding; (vii) clearly defined and clinically valid endpoint measures; (viii) detailed knowledge of the multiple disease- and patient-related factors influencing treatment outcome; and (ix) application of additional statistical methods, including cluster analysis to allow detailed investigation of the reasons for pronounced differences in individual treatment responses.

The clinical indications of therapeutic rTMS should be developed further in the coming years, in parallel with the optimization of the parameters of stimulation, taking into account safety aspects. Future technical developments will focus mainly on producing new forms of coils and magnetic field geometry, and on advances in neuronavigation, especially coupled with functional imaging (e.g., fiber tracking) and high-resolution EEG, for individual tailoring of rTMS therapy. These methodological improvements may help to reduce the large interindividual variation in efficacy that currently renders the average clinical responses rather modest, although the effects may be very pronounced and even long-lasting in individual patients. However, currently it seems that the major limitation of rTMS therapy will remain the need to determine the optimal time window for its application in a therapeutic decision tree and to go beyond the relatively short duration of the clinical effects produced in most patients. The repetition of the sessions of stimulation, including a schedule of maintenance sessions can compensate, at least in part, this inconvenience. But this opens the door to other techniques of noninvasive cortical stimulation, such as transcranial direct current stimulation (tDCS), or invasive techniques based on the surgical implantation of epidural electrodes, to treat non-remitting, chronic, drug-resistant diseases. The application of rTMS in this context would be to provide preoperative predictive factors for selecting candidates for surgery and to validate the cortical target of where to implant electrodes. Also, as a treatment option by itself, rTMS could be more specifically dedicated to the treatment of disorders of limited duration or to treating patients with contraindications for surgery.

The use of rTMS should also be considered and systematically studied as an adjunctive therapy in combination with medication, PT, or psychotherapy, with the aim of improving or accelerating the efficacy of these treatments. This strategy is already proposed in some psychiatric disorders, such as depression (combined treatment by antidepressant drugs and rTMS) or stroke rehabilitation (combined treatment by PT and rTMS), and it would likely be useful for maintaining therapeutic effects also in other clinical conditions, e.g., pain, movement disorders, or tinnitus. Such a combination of approaches appears to be particularly suitable to promote processes of cortical plasticity and to significantly amplify and stabilize the therapeutic effects of rTMS. Within this kind of multidisciplinary framework, rTMS applications will probably develop in the near future to improve the treatment and rehabili-

tation of patients in various neurological, ENT, and psychiatric disorders.

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