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Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018)

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Abstract

A group of European experts reappraised the guidelines on the therapeutic efficacy of repetitive transcranial magnetic stimulation (rTMS) previously published in 2014 [Lefaucheur et al., Clin Neurophysiol 2014;125:2150-206]. These updated recommendations take into account all rTMS publications, including data prior to 2014, as well as currently reviewed literature until the end of 2018. Level A evidence (definite efficacy) was reached for: high-frequency (HF) rTMS of the primary motor cortex (M1) contralateral to the painful side for neuropathic pain; HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC) using a figure-of-8 or a H1-coil for depression; low-frequency (LF) rTMS of contralesional M1 for hand motor recovery in the post-acute stage of stroke. Level B evidence (probable efficacy) was reached for: HF-rTMS of the left M1 or DLPFC for improving quality of life or pain, respectively, in fibromyalgia; HF-rTMS of bilateral M1 regions or the left DLPFC for improving motor impairment or depression, respectively, in Parkinson's disease; HF-rTMS of ipsilesional M1 for promoting motor recovery at the post-acute stage of stroke; intermittent theta burst stimulation targeted to the leg motor cortex for lower limb spasticity in multiple sclerosis; HF-rTMS of the right DLPFC in posttraumatic stress disorder; LF-rTMS of the right inferior frontal gyrus in chronic post-stroke non-fluent aphasia; LF-rTMS of the right DLPFC in depression; and bihemispheric stimulation of the DLPFC combining right-sided LF-rTMS (or continuous theta burst stimulation) and left-sided HF-rTMS (or intermittent theta burst stimulation) in depression. Level A/B evidence is not reached concerning efficacy of rTMS in any other condition. The current recommendations are based on the differences reached in therapeutic efficacy of real vs. sham rTMS protocols, replicated in a sufficient number of independent studies. This does not mean that the benefit produced by rTMS inevitably reaches a level of clinical relevance.

Keywords: Cortex; indication; neurology; neuromodulation; noninvasive brain stimulation; psychiatry; treatment.

Highlights

- rTMS can produce significant clinical improvement in various neurological and psychiatric disorders.
- Updated guidelines on the therapeutic use of rTMS are presented, including 2014-2018 publications.
- Higher evidence of efficacy is present in the areas of depression, pain, and postacute motor stroke.

1. Introduction

In November 2014, a consensus paper was issued in *Clinical Neurophysiology* (Lefaucheur et al., 2014), reporting guidelines established by a group of European experts on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS), based on evidence published until March 2014. In the light of the many articles published in this domain during the last four years, it appeared necessary to update these recommendations.

The same methodology was used as for the initial article, with bibliographic research and critical reading by at least two experts for each clinical indication. First, studies were classified into four classes. A Class I study was defined as a randomized, sham-controlled clinical trial including 25 or more patients receiving real stimulation therapy, with clearly reported primary outcome, exclusion/inclusion criteria, randomization/blinding procedure, and statistical analyses, and taking into account study bias, due to the heterogeneity of baseline characteristics among treatment groups, possible carry-over effects (for crossover studies), or dropouts for example. A Class II study was a randomized, placebo-controlled trial of between 10 and 25 patients receiving real stimulation therapy with the same high levels of methodological quality as a Class I study or a study with a larger sample but not filling all the aforementioned criteria of high methodological quality. Class III studies were all other controlled trials with lower methodological quality, but only studies with at least 10 patients receiving real stimulation therapy were taken into account in making these recommendations. Class IV studies were uncontrolled studies or case series.

A level of evidence of rTMS efficacy or inefficacy was determined for each indication, taking care that the results were obtained with the same method of stimulation applied in patients with the same clinical profile. A Level A ("definitely effective or ineffective") required at least two Class I studies or one Class I study and at least two Class II studies. Level B ("probably effective or ineffective") required at least two Class II studies or the combination of one Class I or II study and at least two Class III studies. Level C ("possibly effective or ineffective") required at least two Class III studies or any combination of two studies of different Classes I, II or III. The evaluation was based on the overall result of the difference between all studies showing beneficial results and those showing non-significant or detrimental results. No recommendation was made if there were less than two studies of different Classes I, II or III replicating concordant beneficial results in series of 10 or more patients receiving real stimulation therapy. For this grading, when a given research group published several studies with the same methodology for the same clinical indication, only one study from this group was considered (the one of the best class). Trials performed in healthy subjects or using single-session protocols were not considered in this work to focus on the potential therapeutic impact of repeated rTMS sessions in the short or long term.

This article presents tables summarizing the data reported for each indication in which at least two comparable studies (with the same methodology) of Class I to III were published by independent groups from March 2014 to the end of December 2018. This period of literature search is subsequent

to that our previous work. For information, table data corresponding to papers published before March 2014 and reviewed in our previous article (Lefaucheur et al., 2014) are available as e-only supplementary material to the present article (e-table 1). The recommendations proposed in this article refer not only to the 2014-2018 period but also take into account all previous data analyzed in the 2014 article. Thus, for all the sections, the current guidelines are based on the whole literature database since the beginning of rTMS publications.

2. Pain

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND pain) identified 165 papers in the 2014-2018 period, including 17 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions.

2.1. Motor cortex stimulation in neuropathic pain

In our previous work (Lefaucheur et al., 2014), a Level A of definite analgesic effect was stated for the use of HF rTMS of the primary motor cortex (M1) applied contralaterally to the pain side in patients with neuropathic pain. During the 2014-2018 period, four sham-controlled Class II studies with limited sample size were published, all confirming the beneficial effect of this procedure (Table 1).

In one study, a total of 40 patients with postherpetic neuralgia were randomly assigned to receive 10 sessions of real (n=20) or sham (n=20) rTMS of M1 over two weeks (Ma et al., 2015). The pattern of stimulation was relatively unusual, consisting of 300 trains of 5 seconds with an intertrain interval of 3 seconds for a total of 1500 pulses delivered at 80% of the resting motor threshold (RMT) in a session of 40 minutes. The real rTMS group had greater pain reduction than the sham group with an average pain reduction of 45-50% persisting at 3 months after the last rTMS session. Half of the patients who received real rTMS were considered responders (> 50% pain intensity score reduction). Analgesic effects were associated with an improvement in quality of life scores.

Another sham-controlled parallel-arm study assessed the efficacy of 10 daily sessions of 20Hz-rTMS of M1 performed over two weeks in 30 patients (15 real, 15 sham) suffering from neuropathic pain in the context of malignancy (Khedr et al., 2015). The pattern of stimulation was more usual, consisting of 10 trains of 10 seconds with an intertrain interval of 30 seconds for a total of 2000 pulses delivered in a session of 6-7 minutes. The figure-of-8 coil was placed over the M1 representation of the hand on the hemisphere contralateral to the painful side, with coil orientation parallel to the interhemispheric midsagittal line, as recommended (André-Obadia et al., 2008; Lefaucheur, 2016). The group of patients treated with real rTMS had greater improvement in pain intensity scores than the sham group, with an average pain reduction of 35-40% two weeks after the last session, but the beneficial effect disapppeared by one month. More than 80% of the patients were

considered responders (> 30% pain intensity score reduction). A short-lasting difference between real and sham stimulation was also observed in terms of depression and neuropathic symptom score improvement. The short duration of the rTMS sessions in this study (6-7 minutes) could explain the rather modest analgesic effects, regardless of the number of pulses per session, as suggested in another study (Hodaj et al., 2015).

In a third study, the targeting was based on cortical maps provided by motor evoked potential (MEP) recording to TMS performed with a navigation system integrating magnetic resonance imaging (MRI) of the brain (Nurmikko et al., 2016). The trial enrolled 27 patients with unilateral neuropathic pain of various causes and locations who completed the study with the comparisons of three target sites: (i) the motor hotspot (i.e. the cortical site of the “affected hemisphere” where MEPs of maximal amplitude were obtained in the pain region); (ii) a cortical site where MEPs were found in TMS maps of the “affected” hemisphere but not at an equivalent location in the contralateral “unaffected” hemisphere; (iii) the occipital fissure serving as "active" control condition. The pattern of 10Hz-rTMS consisted of 20 trains of 10 seconds with an intertrain interval of 50 seconds for a total of 2000 pulses delivered in a session of 20 minutes. Five daily sessions were performed in a crossover design. Real rTMS produced greater pain reduction, regardless of the type of motor cortical target compared to the control procedure, which was a real stimulation delivered over the occipital fissure. The analgesic effect was very small (less than 15% on average) but maintained at least two weeks, and 30% of the patients were considered responders (> 30% pain intensity score reduction).

Finally, a fourth sham-controlled Class II study with parallel arm design compared the efficacy of 3 daily sessions of 10Hz rTMS of M1 to anodal transcranial direct-current stimulation (tDCS) of the same site in a series of 32 patients with lower limb neuropathic pain due to lumbosacral radiculopathy (21 real, 11 sham) (Attal et al., 2016). In this study, the motor cortical area corresponding to the hand on the painful site was stimulated, although patients had lower limb pain. The pattern of stimulation consisted of 30 trains of 10 seconds with an intertrain interval of 20 seconds for a total of 3000 pulses delivered in a session of 15 minutes. Real rTMS was superior to real tDCS and sham condition by decreasing the intensity of pain by 60% at the end of the stimulation protocol, with a significant pain relief lasting up to 5 days. Unfortunately, the protocol of stimulation was quite short (3-session protocol) and longer lasting effects were not assessed. Also, the mean percentage of pain relief was smaller than in previous studies, but all patients had lower limb neuropathic pain, which is a condition that may be less favorable than face or upper limb neuropathic pain for the efficacy of motor cortex rTMS (Lefaucheur et al., 2004). Nevertheless, this study showed that the rate of responders was greater after real rTMS (> 30% pain intensity score reduction in 43% of patients and > 50% pain intensity score reduction in 30% of patients) than after real tDCS or sham procedure.

In summary, in the light of these recent studies, our recommendation on the level of evidence regarding the analgesic efficacy of HF-rTMS of M1 contralateral to neuropathic pain side did not change (Level A). Some lessons could possibly be drawn from these four studies, suggesting that the

analgesic effect is favored by longer session duration and serial treatment (i.e. greater number of sessions).

- Insert Table 1 -

However, it is still unclear whether targeting the somatotopic area of the motor cortex corresponding to the painful region or only the hand area in all cases is of critical importance to produce analgesic effects. While there is a consensus to stimulate the motor cortex contralateral to the side of pain (or the left cortex in case of bilateral or diffuse pain), the exact location of the optimal target to be stimulated within M1 is not yet defined. Overall, two strategies are possible: either to stimulate the motor cortical representation of the painful region or to stimulate the hand motor area whatever pain location. Then, in each case, two additional possibilities are offered: either to target the motor hotspot (defined as the cortical site where MEPs of maximal amplitude are obtained in a muscle of a given body region) or to target the motor cortical representation of the same body region using a navigation system integrating individual morphological or functional MRI data.

Two studies partially addressed these questions by evaluating the analgesic effects of a single rTMS session performed under neuronavigation guidance. The first study (Andre-Obadia et al., 2018a) compared the value of HF-rTMS delivered to the hand or face motor hotspot in 32 patients suffering of upper limb (n=20) or facial (n=12) pain. This study showed that real rTMS was more efficacious on pain when delivered over the hand motor area than the face area whether pain was located at the hand or the face. Thus, the hand motor hotspot, which is easy to determine, could be the target of choice for neuropathic pain treatment, regardless of the location of pain. In this case, the use of a navigation system could simply consist of registering the target location to facilitate the repositioning of the coil at the same place with the same orientation through the different sessions of an rTMS therapy procedure (Lefaucheur, 2010). However, a second study (Ayache et al., 2016) showed that anatomical targeting using MRI-guided navigation may provide a better target than the motor hotspot. This study included 66 patients with neuropathic pain of various causes and locations and compared the value of a navigated procedure targeting the anatomical representation of the painful zone to a non-navigated procedure targeting the hand motor hotspot. Indeed, for a given muscle territory (e.g., hand muscles), the anatomical cortical representation (e.g., "hand knob") may differ from the functional localization (e.g., "hand motor hotspot") (Ahdab et al., 2016). Navigation improved HF-rTMS efficacy compared to hand motor hotspot targeting, at least in patients with focal upper or lower limb pain.

Although the level of evidence is high in favor of the analgesic efficacy of HF-rTMS of M1, this does not necessarily mean that the procedure is clinically relevant and deserves to be applied in routine practice. Mainly, one of the major limitations of published sham-controlled studies is the fact that they are based on low number of sessions (5 to 10) and duration of follow-up (less than 3 weeks). To address this issue, it is interesting to look at the results provided by open-label naturalistic studies that usually report results obtained over a prolonged period of time in real life setting.

For example, in an open-label study of 18 patients with central poststroke pain (Kobayashi et al., 2015), sessions of HF-rTMS delivered over the motor cortex of the affected hemisphere were

repeated once a week for 12 weeks (3 months). The rTMS sessions produced an average pain relief of 61%. Regarding individual results, pain relief was higher than 40% in 11 of the 18 patients (61%). A sustainable pain relief was observed in the 6 patients who continued the intervention for one year. Notably, the clinical benefit was better in patients without severe dysesthesia.

Another group published two papers on their experience of using HF-rTMS delivered to M1 (motor hand spot) over the long term to treat patients with central neuropathic pain of various origins and locations (Pommier et al., 2016; Quesada et al., 2018). In each rTMS session (26-min duration with 1600 stimulations), a figure-of-8 coil was positioned over the defined cortical target by a robotized arm under navigation guidance. The first phase of the protocol consisted of a series of four sessions performed within two months. Then, in 'responders' (defined as a percentage of pain relief > 10%), the sessions were continued and repeated with intervals adapted to the duration of the analgesic effect for each individual. In their first paper (Pommier et al., 2016), these authors report a cumulative effect across sessions in 31 'responders' (among 40 patients initially enrolled), leading to a mean pain relief of 41% for a duration of more than two weeks. In their second paper (Quesada et al., 2018), results are presented for 71 patients and confirmed the cumulative effect of rTMS sessions in the long term. After the first four sessions, the percentage of pain relief was 28% and the duration of pain relief was 11 days. After 12 months of treatment (15 sessions on average), the percentage of pain relief increased to 48% and the duration of pain relief to 20 days. No adverse events occurred, including no seizure. There was also a decrease in medication consumption, although not significant.

A kind of cumulative impact of the repetition of rTMS sessions on pain relief was also observed in a naturalistic study based on a 6-month navigated rTMS protocol and follow-up and performed in patients with various types of facial pain or headache disorders, including cluster headache (Hodaj et al., 2015). Facial pain could be a favorable condition for the response to navigated 10Hz-rTMS of M1, as also shown by Lawson McLean et al. (2018). In this open-label study, 48 patients with various chronic neuropathic pain conditions (31 patients with facial pain) received 9 HF-rTMS sessions. The overall rate of responders was 58%, but significantly better in patients with facial pain (71%) than limb pain (less than 44%). A shorter pain history (less than five years) was the other predictor of good outcome. At 6-week follow-up after 9 rTMS sessions, 42% of patients still reported a significant level of pain relief.

The analgesic effects of rTMS in patients with chronic neuropathic pain were obtained using a HF, whatever the frequency (5, 10, or 20Hz) (Jin et al., 2015), but not at LF (Lefaucheur et al., 2001; André-Obadia et al., 2006; Saitoh et al., 2007). Regarding patterned rTMS paradigms, such as theta burst stimulation (intermittent (iTBS) or continuous (cTBS) protocols), reported data only concerned experimental or acute provoked pain (Antal and Paulus, 2010; Torta et al., 2013; Moisset et al., 2015; Annak et al., 2019) and TBS used as a priming protocol for HF-rTMS (Lefaucheur et al., 2012a; Gaertner et al., 2018), except one study showing a mild relief of orofacial pain after iTBS of M1 (Kohútová et al., 2017).

Finally, a few words should be added regarding the mechanisms of analgesic action of rTMS delivered to M1. Some recent results highlighted a significant release of endogenous opioids within a bihemispheric brain network involved in the perception and modulation of pain, which was produced by a single session of 10Hz-rTMS of M1 in a positron emission tomography (PET) study based on 10 healthy subjects (Lamusuo et al., 2017). This was consistent with previous observations made in chronic pain patients treated by invasive epidural motor cortex stimulation (Maarrawi et al., 2007, 2013). However, the mechanisms of action of M1 stimulation in pain are surely more complex and multiple, involving various pain modulatory systems concerned in emotion, attention, and/or sensory discrimination processing, related to various neural pathways connecting different brain regions, thalamic nuclei, and/or the spine, and also with various neurotransmitter systems beyond endogenous opioids, such as glutamate, GABA, and/or dopamine for example (Lefaucheur, 2016, Moisset and Lefaucheur, 2019; Moisset et al., 2016; Nguyen et al., 2011). All of these factors can contribute to the development of long-term synaptic plasticity that provides significant pain relief beyond the time of stimulation.

2.2. Other cortical targets in neuropathic pain

A few studies addressed motor cortex rTMS therapy of neuropathic pain with a significantly different targeting approach from the usual procedure, in which a figure-of-8 coil is focally positioned over an anatomically- or functionally-defined motor target. These studies investigated the analgesic effect of repeated daily sessions of HF-rTMS using either various types of figure-of-8 coils applied over the vertex in patients with lower limb pain due to spinal cord injury (Yılmaz et al., 2014; Hodaj et al., 2018) or a H-coil (Onesti et al., 2013; Shimizu et al., 2017). In these two latter studies, a H10 coil provided a large, bilateral stimulation of the motor cortex strip, diffusing deep in the medial longitudinal fissure. The study of Onesti et al. (2013) included 23 patients, all suffering from lower limb pain due to diabetic polyneuropathy. This was a crossover study based on a 5-day 20Hz-rTMS protocol (1500 pulses per session). Real rTMS produced greater pain reduction than sham stimulation, lasting for three weeks. However, these results were not reproduced to date. A second study (Shimizu et al., 2017) enrolled 18 patients with neuropathic pain affecting the lower limb, but of various peripheral or central origins. This study had a cross-over design, with a short wash-out period of 17 days between series of 5Hz-rTMS sessions delivered for 5 days (500 pulses per session) using an active or sham H-coil, or an active figure-of-8 coil, which had no proper sham-controlled condition. A reduction in pain intensity was observed immediately and 1 hour after rTMS using active H-coil but not figure-of-8 coil, compared to sham H-coil condition. This result had no clinical relevance, since no significant analgesic effect was observed in the 16-day period follow-up period after rTMS sessions, whatever the condition.

In the small sham-controlled study of Yilmaz et al. (2014) performed in 16 patients with chronic pain secondary to spinal cord injury (SCI), 10 sessions rTMS delivered over the vertex at

suprathreshold intensity did not show superior analgesic efficacy when applied in real condition (9 patients) versus sham condition (7 patients). This result is consistent with two previous negative rTMS studies on SCI pain (Defrin et al., 2007; Kang et al., 2009a), but also based on very small series of patients: 6 patients who received real stimulation (plus 5 patients in a sham rTMS group) in Defrin et al. (2007) and 11 patients in the sham-controlled crossover study of Kang et al. (2009a). In addition, there were significant differences in the stimulation protocol between these studies, such as targeting the vertex at 110-115% of RMT (Defrin et al., 2007, Yilmaz et al., 2014) or unilateral hand M1 representation at 80% of RMT (Kang et al., 2009a). Thus, these studies may suggest that rTMS is not effective in SCI pain in contrast to other neuropathic pain conditions, but this conclusion deserves confirmation in further larger replication studies.

One group also applied navigated HF-rTMS over the parieto-opercular cortex overlying the right secondary somatosensory area (S2) in patients with chronic neuropathic pain located in the orofacial region (Lindholm et al., 2015, 2016). The stimulation of this target produced significantly better analgesia than the stimulation of the primary sensorimotor cortex or sham rTMS. However, these studies were based on the short term effects of single rTMS sessions (up to 1 month after a single rTMS session given 1 month apart for the three stimulation conditions). The value of the right S2 target in patients with pain is consistent with a previous study in healthy subjects that showed some changes in the thresholds for the detection of thermal pain produced by such a protocol (Valmunen et al., 2009). Nevertheless, the long-term results provided by repeated HF-rTMS sessions over S2 are awaited.

Because of the implication of the insula, especially its posterior part, in the experience of pain (Mazzola et al., 2009; Isnard et al., 2011), insular cortex stimulation with a double-cone coil was proposed as a method for producing pain modulation (Ciampi de Andrade et al., 2012). In two experimental studies, a double-cone coil was used to deliver a cTBS train over the insular cortex (Lenoir et al., 2018) or a brief TMS train over the anterior part of the middle cingulate cortex (D'Agata et al., 2015), both protocols resulting in a reduction of the perception of acute cutaneous pain elicited by laser or electrical stimulation. However, insular cortex stimulation with a double-cone coil recently failed to be effective in chronic central neuropathic pain, as well as cingulate cortex stimulation using a H6-coil (Galhardoni et al., 2019).

One study assessed the value of 10 daily sessions of HF-rTMS delivered to the premotor cortex/dorsolateral prefrontal cortex (PMC/DLPFC) in patients with central poststroke pain (de Oliveira et al., 2014). This study was negative and was terminated after the evaluation of 21 patients because of a significant lack of efficacy in the real rTMS arm. In another study, HF-rTMS of the left PMC/DLPFC was applied in 12 patients with chronic neuropathic pain related to cervical or thoracic spinal cord injury (10 sessions of 1250 pulses/session over 2 weeks) (Nardone et al., 2017). Daily pain scores significantly decreased during rTMS sessions in the 6 patients who received real rTMS, but not in the 6 patients who received sham rTMS. However, pain relief did not last beyond the period of stimulation. Finally, it should be noted that no studies in the context of neuropathic pain treatment

used an appropriate DLPFC targeting method, which requires the application of a relevant neuronavigation approach (Mylius et al., 2013; Pommier et al., 2017).

From all these results, no convincing alternative to focal stimulation using a figure-of-8 coil over M1 contralateral to pain side is currently relevant in rTMS therapy of neuropathic pain.

2.3. Fibromyalgia and other dysfunctional chronic pain syndromes

In our previous work, no recommendation was made for the use of rTMS to treat fibromyalgia, because two different targets had been evaluated (left M1 and left DLPFC) and most studies came from the same group of researchers for a given target, without results reproduced by independent teams in this indication.

Regarding the left M1 target, one additional study was published during the 2014-2018 period. This Class II study with a parallel-arm design (Boyer et al., 2014) enrolled 38 patients with fibromyalgia (19 real, 19 sham) who received HF-rTMS delivered to the left M1 in 14 sessions over 10 weeks. At week 11, the improvement in quality of life, especially in the mental, emotional, and social dimensions, was greater in the real arm than in the sham arm. Conversely, no significant difference was observed between real and sham rTMS concerning changes in pain intensity scores. The fact that rTMS of M1 may be beneficial for pain patients on their daily functioning and quality of life without any pain relief was also reported in neuropathic pain (Hodaj et al., 2018). Various Class II studies of another group (Passard et al., 2007; Mhalla et al., 2011) previously reported a significant improvement of quality of life in patients with fibromyalgia treated by HF-rTMS of M1, comparing real versus sham conditions. Thus, considering these concordant Class II studies, a recommendation can be made for a probable efficacy of HF-rTMS of the left M1 (Level B) in improving quality of life of patients with fibromyalgia (without any conclusion for the proper analgesic effect).

The beneficial impact of HF-rTMS of M1 was also reported by one group in a chronic myofascial pain syndrome close to fibromyalgia. In a first study, these authors randomized 24 women with this clinical condition to receive 10 sessions of 10Hz-rTMS of the left M1 (12 real and 12 sham) (Dall'Agnol et al., 2014). Pain decreased more after real stimulation than sham, with daily pain score reduction by 30% and analgesic use reduction by 45%. In addition, the analgesic effect was associated with an increase in corticospinal excitability, descending inhibitory controls (conditioned pain modulation assessment), and brain-derived neurotrophic factor levels. In a second study performed in 46 patients (23 real and 23 sham), the same group confirmed the beneficial effect of 10Hz-rTMS of the left M1 and did not find any additional effect of performing transcutaneous repetitive magnetic stimulation of muscles (Medeiros et al., 2016).

Regarding the value of HF-rTMS delivered to the left DLPFC in fibromyalgia, a recent Class II study showed evidence for an impact on fatigue (Fitzgibbon et al., 2018). This parallel-arm study enrolled 26 patients with fibromyalgia (14 real, 12 sham) and a greater improvement in physical and general fatigue scores was observed after a total of 20 rTMS sessions over four weeks at one month

follow-up in the real versus sham condition. Regarding the analgesic effects, the difference between real and sham rTMS was observed in terms of responders (> 30% pain relief). A previous Class II study had also shown analgesic efficacy of HF-rTMS of the left DLPFC (29% difference in pain relief between real and sham conditions on average), but did not report the resulting changes in fatigue or sleep quality (Short et al., 2011). Thus, considering two concordant Class II studies, a Level B recommendation can be made for a probable analgesic efficacy of HF-rTMS of the left DLPFC in patients with fibromyalgia. In addition, in both studies, rTMS was well tolerated, with few minor side effects (e.g., discomfort, neck pain, or dizziness during stimulation), not significantly different between real and sham conditions.

Thus, from our literature data analysis, it appears that in fibromyalgia, HF-rTMS of the left DLPFC is rather efficacious on pain, while HF-rTMS of the left M1 is rather efficacious on the quality of life. An opposite conclusion was rather expected, as illustrated for example by the meta-analysis of Hou et al. (2016), in which the pooled mean effect size of rTMS studies in fibromyalgia revealed significant favourable effects, but with subtle evidence for a better analgesic efficacy of M1 stimulation and a better antidepressant efficacy of DLPFC stimulation.

Finally, three studies should be mentioned, addressing the treatment of various pain syndromes that may share with fibromyalgia at least some common mechanisms of central sensitization. Firstly, in 20 patients (12 real, 8 sham) with burning mouth syndrome, 10Hz-rTMS of the left DLPFC was found to induce analgesic effects (Umezaki et al., 2016). At 2 months after the beginning of treatment, the pain intensity decreased by 67%, and 75% of the patients reported >50% pain decrease, without any change in mood or the affective aspect of pain. Secondly, 21 patients with irritable bowel syndrome were enrolled in a crossover study and received 5 daily sessions of rTMS of the left M1 (Melchior et al., 2014). Real and sham stimulations did not differ in the resulting changes in ongoing pain, pain threshold to rectal distension by a barostat balloon, and rectal compliance. However, pain tolerance assessed by the maximum tolerated volume of rectal distension was improved by real, but not by sham rTMS and this effect was greater in the subgroup of patients with the most marked rectal hypersensitivity. Finally, one class II crossover study addressed the value of 10 daily sessions of real or sham stimulation over the whole motor cortex using an H10-coil in 13 patients (7 real and 6 sham) with bladder pain syndrome (Cervigni et al., 2018). Compared to sham, real stimulation improved pain and urinary symptoms and quality of life of the patients. The efficacy of LF-rTMS delivered over the DLPFC of both hemispheres using a figure-of-8 coil was also found to relieve most symptoms of bladder pain syndrome in one illustrative clinical case (Nizard et al., 2018). However, all these results cannot lead to any recommendation to date.

2.4. Other pain conditions

In the complex regional pain syndrome (CRPS) of type I, a Level C recommendation in favor of a possible analgesic effect of HF-rTMS of M1 was stated in our previous guidelines (Lefaucheur et

al., 2014). An additional study was recently published on a particular type of CRPS, i.e. shoulder pain occurring in post-stroke hemiplegic patients (Choi and Chang, 2018). In this study, the motor cortex of the stroke-affected hemisphere was stimulated over 10 sessions in 24 patients at chronic stroke stage. A significant pain relief (of 25-30%) was observed in the real but not the sham group up to 4 weeks beyond the time of stimulation. In contrast, rTMS did not change motor function and motricity index in the affected upper limb. These new results did not change our previous recommendation, which remains at Level C.

Phantom limb pain is a particular neuropathic pain condition. One rTMS study was reported in this domain targeting M1 contralateral to the amputated limb (Malavera et al., 2016). In this large sham-controlled study of 54 patients (27 real and 27 sham), HF-rTMS was delivered 20 minutes per session, during 10 days. Real rTMS induced a greater reduction in pain intensity than sham stimulation, up to two weeks after the last session with a mean between-group difference of 30%. This effect was lost at one month follow-up. The percentage of responders (>30% pain intensity reduction) was 70% in the real group and 41% in the sham group.

One study assessed the value of a 5-day HF-rTMS protocol, delivered at 20Hz over the right M1 (2,000 pulses per session) in 53 patients with low back pain (41 real and 12 sham), plus 26 patients who received physical therapy as a control group (Ambriz-Tututi et al., 2016). The analgesic effect was found significantly better in the real rTMS group than both sham stimulation and physical therapy groups. The beneficial effect of real rTMS lasted up to 9 months using maintenance sessions, first every two weeks, then every two months.

The main two rTMS targets in the pain domain, i.e. M1 and DLPFC, were also investigated in migraine and headache disorders.

Since a first open-label study performed in 51 migraineurs (Misra et al., 2012), one group repeatedly report sham-controlled data in favor of the beneficial effect in migraine of series of 3 HF-rTMS sessions delivered to the left M1 with a protocol similar to that is classically used in neuropathic pain (Misra et al., 2013; Kalita et al., 2016). In addition, the clinical improvement is associated with an increase in beta-endorphin plasma level (Misra et al., 2017). However, to our knowledge, no other group has reported the efficacy of repeated rTMS sessions delivered to the left M1 in migraine. Regarding the DLPFC target, no new data have been published since the two conflicting studies already discussed in our previous work (Brighina et al., 2004; Conforto et al., 2014).

One group assessed the value of 4 sessions of 10Hz-rTMS delivered to the left M1 (Leung et al., 2016) or the left DLPFC (Leung et al., 2018) in chronic headache secondary to mild traumatic brain injury. In a first series of 24 patients, these authors showed a greater reduction in persistent headache intensity one week after real vs. sham M1 stimulation with a higher rate of responders (>50% pain intensity reduction) and a trend towards a lasting efficacy for four weeks (Leung et al., 2016). In a second series of 29 patients (Leung et al., 2018), a greater reduction in persistent headache intensity was found one and four weeks after real vs. sham DLPFC stimulation (23-25% versus 1-2%

of pain relief) together with a higher rate of responders (>50% pain decrease) and a transient benefit on depression scores.

In another series of 12 patients (Choi et al., 2018), the intensity of chronic diffuse pain secondary to mild traumatic brain injury was significantly reduced during and up to 4 weeks after 10 sessions of 10Hz-rTMS applied to M1 of the affected hemisphere (1000 pulses/session) in the 6 patients who received real rTMS compared to the 6 patients who received sham rTMS.

Obviously, data are too sparse in chronic pain syndromes other than neuropathic pain or fibromyalgia to make any recommendation on the value of HF-rTMS delivered to the left M1 or the left DLPFC.

Finally, in postoperative acute pain, only one sham-controlled study has been published in the 2014-2018 period. In this large-sample study (Borckardt et al., 2014), 108 patients who underwent gastric bypass surgery were randomly assigned to receive 2 sessions of real or sham 5Hz-rTMS delivered over the left DLPFC, one session immediately following surgery and the other 4 h later. Both affective and sensory dimensions of pain were reduced in the patients who received 2 real rTMS sessions, but not patient-controlled opioid intake.

3. Movement disorders

3.1. Parkinson's disease: motor symptoms

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND Parkinson's disease) identified 93 papers, including only 5 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions.

As stated in our previous work (Lefaucheur et al., 2014) and in recent meta-analyses (Chou et al., 2015; Zanjani et al., 2015; Yang et al., 2018), reported data suggest an efficacy of HF-rTMS on parkinsonian motor symptoms, especially if delivered bilaterally over motor cortical regions. Additional data were provided by three recent sham-controlled studies (Table 2). First, a randomized crossover Class II study (Kim et al. 2015) included 17 parkinsonian patients and targeted the leg area of M1 with a double-cone coil (lateralized to the dominant hemisphere). Compared to a figure-of-8 coil, a double-cone coil induces a much less focal and more deeply penetrating electric field (Deng et al., 2014). After 5 daily sessions of 10Hz-rTMS, the number of steps required to complete the standing start 180° turn test and the freezing of gait questionnaire (primary outcome measure) significantly improved in the real as compared to the sham condition, with a benefit lasting for at least one week after the last rTMS session. In addition, the global motor performance assessed by the unified Parkinson's disease rating scale (UPDRS) part III score (secondary outcome measure) improved by 26%. The same group later published a pilot study including 8 patients with various atypical parkinsonism (vascular parkinsonism, progressive supranuclear palsy, or multiple system atrophy) and

using exactly the same study design (Chang et al., 2016). In this study, HF-rTMS was delivered over the leg representation of M1 for 5 consecutive days and also improved freezing-of-gait.

Therefore, using a large double-cone coil, but not a focal figure-of-8 coil (Rektorova et al., 2007), beneficial effects of repeated sessions of HF-rTMS applied to M1 leg area may help to improve freezing-of-gait of various origins. Further research is needed to reach a sufficient level of evidence to make specific recommendation.

Finally, the same group assessed the additional value of combining anodal tDCS over the left DLPFC (right supraorbital cathode) with HF-rTMS of M1 (16 patients receiving dual active rTMS and tDCS versus 16 patients receiving real rTMS and sham tDCS) (Chang et al., 2017). The dual stimulation yielded a significantly better outcome in executive functions, but not regarding improvement of freezing, motor and ambulatory functions compared to rTMS of M1 alone.

Two other studies showed that rTMS of bilateral M1 regions, targeted over the motor hotspots of hand representation, was an effective treatment of parkinsonian motor symptoms (Brys et al., 2016; Makkos et al., 2016). In the sham-controlled, parallel-group study of Makkos et al. (2016), the primary endpoint was the change in mood, while motor performance was a secondary endpoint. The patients improved on both aspects after 10 sessions of real rTMS over two weeks (23 patients in the real rTMS arm). The study of Brys et al. (2016) enrolled a large sample of 50 patients with Parkinson's disease also with comorbid major depression (according to DSM-IV criteria), but only 14 patients were analyzed in the real M1 rTMS group (Class II study). In this multicenter, double-blind, sham-controlled, parallel-group study, a "realistic" sham procedure was applied (Rossi et al., 2007), combining the use of a sham coil and electric stimulation of the scalp at the level of the coil with electrodes connected to a constant current stimulator. For each M1 target (defined as the hand motor hotspot), the rTMS protocol consisted of 50 trains of 4 seconds with an intertrain interval of 11 seconds for a total of 1000 pulses delivered in a session of 12.5 minutes. Parkinsonian patients in the "on-drug" state received 10 daily sessions over two weeks, the left and right M1 being sequentially stimulated during each session. At one month after the last rTMS session, the motor symptoms, especially bradykinesia and rigidity, as assessed by the UPDRS-III score, significantly improved after real versus sham stimulation (reduction by 15% (4.9 points) compared to baseline). This effect was considered as a minimal clinical change and was not observed when the left DLPFC was stimulated in addition to the both M1 regions. Previous Class II studies of HF-rTMS delivered to bilateral M1 regions (upper and/or lower limb representation) had shown a significant improvement on UPDRS-III score of 19% (González-Garcıá et al., 2011; Maruo et al., 2013) or ranging between 15 and 49% depending on stimulation frequency (5-20Hz) (Khedr et al., 2003, 2006). Conversely, other studies performed in PD patients did not show any beneficial motor effect of a series of 8 sessions over two weeks using iTBS of M1 and DLPFC regions (Benninger et al., 2011) or 50-Hz rTMS of both motor cortices (Benninger et al., 2012). Overall, the balance is now leaning towards a probable efficacy of HF-rTMS delivered to a large motor cortical region in patients with Parkinson's disease and the level

of evidence increased to Level B. However, as reviewed by Benninger and Hallett (2015), these effects are rather modest and probably not relevant for routine clinical application.

- Insert Table 2 -

One study reassessed the value of LF-rTMS of M1 (Flamez et al. 2016). In this study, 1Hz-rTMS was sequentially applied over the left and right M1 in the same session during a levodopa challenge test in 9 late-stage PD patients, but failed to change motor or executive functions. In a sham-controlled crossover part of the study including 6 patients, a 5-day "accelerated" rTMS protocol with two sessions performed each day, also did not produce significant clinical change.

In a large cohort of 132 PD patients (Li et al., 2015), one study compared the therapeutic value of LF- vs. HF-rTMS delivered to M1 to that of the administration of istradefylline, an analog of caffeine, which is a selective antagonist of the adenosine A2A receptor, able to reduce the duration of wearing-off periods. After 12 weeks of treatment, motor improvement assessed by the UPDRS-III score was similar in all patient groups, receiving either istradefylline with sham rTMS or placebo drug with LF- or HF-rTMS.

Regarding premotor cortex stimulation, most rTMS studies performed in Parkinson's disease targeted the medial part of this region, i.e. the supplementary motor area (SMA) using a figure-of-8 coil over the interhemispheric midline to stimulate both hemispheres simultaneously. A large, multicenter trial showed that a prolonged protocol of weekly sessions of LF- (but not HF-) rTMS of SMA could significantly improve global motor performance assessed on UPDRS-III score (6.8 point reduction) (Shirota et al., 2013). Conversely, a recent Class III study on 17 patients (9 real, 8 sham) (Sayin et al. 2014) did not find any beneficial effect of LF rTMS of bilateral SMA applied for 10 days on global motor performance. Therefore, the value of the SMA target, especially stimulated at LF, to impact on motor symptoms remained to be further investigated in PD patients.

One crossover study (Yokoe et al., 2018) compared four conditions of bihemispheric HF-rTMS (10Hz, 100% of RMT, 3 daily sessions of 1000 pulses in total per session for the both hemispheres using a figure-of-8 coil) in a series of 19 PD patients. These conditions were a real stimulation over the M1 hand area, the SMA (defined as 3cm anterior to the motor hotspot), or the DLPFC (defined as 5.5cm anterior to the motor hotspot), or a sham stimulation (using a "realistic" procedure with superficial electrical stimulation). The 3-day treatments for each condition were spaced at least 4 days apart. The main finding of this study was that the UPDRS-III score improved after bilateral HF-rTMS of the M1 and SMA, but not of the DLPFC compared with the sham condition. The changes tended to be better with the stimulation of M1, especially regarding akinesia and lower limb functions. In contrast, no significant changes were observed in either the depression or apathy scores.

In this regard, in the aforementioned multicenter sham-controlled study (Brys et al. 2016), one group of 12 parkinsonian patients received a treatment consisting of 10 daily sessions of 10Hz-rTMS over the left DLPFC (defined as located only 5cm in front of the hand motor hotspot). No motor improvement was observed in this group, as well as in the group treated by both M1 and DLPFC stimulation, as previously discussed.

In summary, only the M1 target, at least if stimulated bilaterally using HF-rTMS, can be recommended for the treatment of motor parkinsonian symptoms for the moment. Beyond stimulating larger cortical areas, the development of accelerated (intensified) protocols with a greater number of sessions (including even more sessions per day) could be a way to optimize the efficacy of rTMS that should be tested in future studies (Rektorová and Anderková, 2017). Alternatively, noninvasive TMS of M1 could be combined with invasive deep brain stimulation to promote associative plasticity in the brain circuits of motor control, as demonstrated in PD patients by Udupa et al. (2016).

3.2. Parkinson's disease: levodopa-induced dyskinesia

As reported in Lefaucheur et al. (2014), the first report of rTMS effects on levodopa-induced dyskinesias (LIDs) was published by Koch et al. (2005). In this pilot study of 8 PD patients, LIDs were reduced following a single session of 1Hz-rTMS delivered bilaterally over the SMAs. The same group replicated this result in 10 PD patients (Brusa et al., 2006), without finding any enhancement of the effect or prolonged benefit after 5 sessions. More recently, Sayin et al. (2014) observed a reduction of LIDs for only 24 hours after 10 days of 1Hz-rTMS sessions bilaterally applied over the SMAs.

Regarding the M1 target, following a pilot open study of 6 PD patients (Wagle-Shukla et al., 2007), Filipović et al. (2009) reported a significant reduction of LIDs after repeated daily sessions of 1Hz-rTMS of M1 contralateral to the most affected side in a cross-over study of 10 PD patients. Overall the benefit was of short duration. More recently, no change in LIDs was observed after a session of 1Hz-rTMS sequentially applied over the left and right M1 during a levodopa challenge test in 9 PD patients (Flamez et al., 2016). Thus, neither the SMA nor the M1 region appears to be relevant targets for the application of LF-rTMS to impact on LIDs in daily life of PD patients.

Alternative targets are the left DLPFC, using HF-rTMS (Rektorova et al., 2008), the right inferior frontal cortex, using cTBS (Cerasa et al., 2015), and especially the lateral cerebellum, also using cTBS (Koch et al., 2009; Kishore et al., 2014). However, these preliminary results, sometimes obtained with a single session, remain to be further investigated in this clinical context.

3.3. Parkinson's disease: depression

One aforementioned study (Brys et al., 2016) reported the absence of beneficial effects of HF-rTMS of the left DLPFC on mood in a group of 12 PD patients. In this study, a non-significant average reduction of 1.4 point on the Hamilton Depression Rating Scale (HDRS) score was observed after real rTMS of the DLPFC, whereas this reduction was significant in all the other groups, by 6.6, 6.1, and 4.4 points on average in the real M1, sham, and real M1+DLPFC groups, respectively. However, at the same time, another randomized sham-controlled study showed that real HF-rTMS of the left DLPFC performed in 10 PD patients with major depressive disorder (versus sham stimulation performed in 8 patients) was able to improve depression scores on the Montgomery-Asberg

Depression Rating Scale (MADRS) and the HDRS with a beneficial effect persisting for 6 weeks after 10 sessions of real stimulation therapy (Shin et al., 2016). In contrast, no motor change was observed on the UPDRS-III score.

These two studies with opposite results canceled each other, and we propose not to change the level of evidence regarding the antidepressant efficacy of HF-rTMS of the left DLPFC in PD patients, which was B (probable efficacy) in our previous work (Lefaucheur et al., 2014), based on several "positive" Class II studies (Fregni et al., 2004; Pal et al., 2010).

The study of Brys et al. (2016) further showed that real M1 stimulation performed better than DLPFC stimulation to induce antidepressant effects in parkinsonian patients (HDRS score reduction by 40%), although not significantly better than sham stimulation. Makkos et al. (2016) also reported an improvement of depression scores, by 59% on the MADRS and 50% on the Beck depression inventory (BDI) after HF-rTMS of bilateral M1. However, it is too early to draw conclusions about the value of this "motor" procedure for treating depression in PD patients.

3.4. Dystonia

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND dystonia) identified 30 papers, but no original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions.

In our previous work (Lefaucheur et al., 2014), no sufficient evidence has been found to establish a recommendation for the use of any rTMS protocol in dystonia. In most studies, the dorsolateral part of the premotor cortex (dPMC) contralateral to the most affected side was the investigated rTMS target. Clinical improvement of writing abilities and reduction of dystonic symptoms was reported in patients with focal hand dystonia (writer's cramp) following LF-rTMS of the dPMC in 3 sham-controlled studies (Murase et al., 2005; Borich et al., 2009; Kimberley et al., 2013). However, these studies were based on a single rTMS session (Murase et al., 2005) or included less than 10 patients in the group receiving real stimulation (Murase et al., 2005; Borich et al., 2009). The study by Kimberley et al. (2013) consisted of a series of 5 daily sessions performed in 12 patients who received real rTMS, but the sham group only included 5 patients. Overall, improvement was small and of short duration.

Instead of using LF-rTMS, one group assessed the value of cTBS as an "excitability-decreasing" protocol applied to the dPMC in a sham-controlled study of 18 patients with focal hand dystonia (9 real, 9 sham) (Huang et al., 2012). One daily session of cTBS was delivered to the dPMC over 5 consecutive days. At the end of the protocol, the real, but not sham stimulation was able to restore the abnormal PMd-M1 interactions assessed by MEP recordings. However, the clinical benefit on writing abilities was only marginal.

Thus, the dPMC target has not proved its interest in dystonia. At present, more recent studies aimed at investigating the value of cerebellar rTMS in this clinical condition. A sham-controlled Class

III study with parallel-arm design (Koch et al., 2014) enrolled 18 patients (9 real, 9 sham) who underwent 10 sessions (over two weeks) of cTBS delivered to both cerebellar hemispheres. As LF-rTMS, cTBS protocol is considered as "inhibitory", although the cortical plasticity changes induced by this type of rTMS protocol (like the others) have shown a great interindividual variability (Hamada et al., 2013; Hordacre et al., 2017). A small, but significant improvement in cervical dystonia in the Toronto Western spasmodic torticollis rating scale (TWSTRS), but not in the Burke-Fahn-Marsden dystonia rating scale (BFMDRS) was observed in the real cTBS group (Koch et al., 2014). This effect was very short-lasting (a couple of days) and was no more observed two weeks after the last session. Some neurophysiological changes induced by the cTBS protocol were also reported in this study. Further evidence of the value of cerebellar stimulation in dystonia is still needed.

3.5. Essential tremor

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND essential tremor) identified 9 papers, but no original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions.

In this clinical context, the current state of evidence of rTMS efficacy has been recently reviewed and mostly concerned LF-rTMS of the cerebellum (Kang and Cauraugh, 2017; Shih and Pascual-Leone, 2017). As for dystonia, the value of cTBS was also investigated. A crossover study of real versus sham cTBS delivered to the right cerebellar hemisphere, but only as a single session, did not show any change in tremor variables, on either clinical or kinematic analysis (Bologna et al., 2015b). The same group applied the same cTBS protocol in patients with Parkinson's disease and also found no effect on parkinsonian resting tremor (Bologna et al., 2015a).

Two other studies investigated the effect of a single session of cTBS for alleviating essential tremor, but considering left M1 or premotor cortical targets (Hellriegel et al., 2012; Chuang et al., 2014). In the study of Hellriegel et al. (2012), the clinical severity of tremor did not change, despite a reduction in the total power of the tremor signal measured with accelerometry. In the study of Chuang et al. (2014), only a slight reduction of tremor amplitude was observed just after real but not sham stimulation of M1 or premotor cortex. Finally, a pilot study with parallel-arm design, investigated the value of 15 daily sessions (over 3 weeks) of LF-rTMS of the pre-SMA, another premotor target, in a series of 10 patients with essential tremor (5 real, 5 sham) (Badran et al., 2016). A significant reduction of tremor scores was observed after both real and sham rTMS (by 26% and 19%, respectively), but the clinical benefit was maintained at 4- and 8-week follow up only in the real rTMS arm. However, data from the literature remain inconclusive for the use of rTMS in the treatment of essential tremor.

3.6. Miscellaneous: tics and Tourette's syndrome; restless legs syndrome

The potential effects of LF-rTMS of the SMA in Tourette's syndrome were first reported in open-label case reports by Mantovani et al. (2006). A two-centre, sham-controlled, parallel-arm study reassessed the value of 1Hz-rTMS of the SMA in this context (Landeros-Weisenberger et al., 2015). Twenty patients with severe Tourette's syndrome underwent 15 daily rTMS sessions over 3 weeks (9 real, 11 sham). This study did not show any significant reduction in tic severity after real versus sham stimulation. Thus, still no formal recommendation can be made in this indication.

The SMA target was also investigated in the treatment of restless leg syndrome (RLS), but using HF protocol. In a class IV open-label study, Lin et al. (2015a) applied 15Hz-rTMS to the motor cortical leg representation on both hemispheres in 14 patients with RLS, for 14 sessions over 18 days. The international RLS rating scale (IRLS-RS) score decreased by 53% at the end of the rTMS protocol and remained significantly reduced over two months after the intervention. Anxiety scores and the quality of sleep concomitantly improved. However, this study was not sham-controlled, contrary to that of Altunrende et al. (2014), in which 5Hz-rTMS was applied over the SMA, a target rather close to motor representation of the legs. This sham-controlled, parallel-arm study enrolled 19 patients (11 real, 8 sham) who underwent 10 rTMS sessions, each spaced 3 days apart. A significant reduction of the IRLS-RS score was found in the real but not the sham group, up to 78% decrease at the completion of the 10 sessions. In 5 patients who have been not improved by sham rTMS, IRLS-RS scores further decreased after switching to real rTMS. However, no additional follow-up was available, so it is impossible to determine whether this intervention has a clinical relevance or not.

4. Stroke

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND motor stroke) identified 213 papers, including 25 original placebo/sham-controlled studies with at least 10 patients who received real rTMS for several daily sessions over the contralesional and/or ipsilesional hemisphere. Among these studies, 13 studies concerned limb motor rehabilitation at the postacute stage with LF-rTMS of the contralesional M1 and/or HF-rTMS of the ipsilesional M1, 2 studies concerned limb motor rehabilitation at the postacute stage with contralesional cTBS or ipsilesional iTBS, 5 studies concerned limb motor rehabilitation at the chronic stage, 2 studies concerned LF-rTMS or iTBS of the cerebellum, and 4 studies concerned swallowing function rehabilitation. Studies investigating children, central post-stroke pain, depression (e.g., Gu and Chang, 2017), and neuropsychological impairments were excluded from this analysis.

Based on the concept of stroke-induced dysbalanced interhemispheric interactions (Murase et al., 2004; Hummel and Cohen, 2006; Hummel et al., 2008; Volz et al., 2015), "excitatory" HF-rTMS and iTBS protocols are meant to be applied over the lesioned hemisphere, but "inhibitory" LF-rTMS and cTBS over the contralesional hemisphere. In our work, we separately considered the results obtained by using motor cortex rTMS during the postacute (subacute) stage of stroke (here defined as between one week and six months after stroke onset) and the chronic stage of stroke (here defined as

more than six months after stroke onset). The definitions of postacute and chronic stages are based on the fact that after 6 months, spontaneous recovery is very unlikely to take place for the motor system. We are, however, aware that there is an ongoing debate about the different phases post-stroke and that other authors have used different definitions about the periods covered by "acute", "post/subacute" or "chronic" post-stroke phase. Furthermore, our definition of "postacute phase" does not imply that this phase is homogeneous in terms of plasticity and recovery. Only one study (Watanabe et al., 2018) enrolled patients in the hyperacute phase of stroke (here defined as being within one week post-stroke), because of obvious difficulties in applying the technique during this phase. In the study of Watanabe et al. (2018), all the patients started an rTMS protocol within 7 days post-stroke: 8 patients received real iTBS over the affected motor cortex hand area, 7 patients received real 1Hz-rTMS over the unaffected motor cortex hand area, and 6 patients received sham iTBS. The protocol consisted of one daily session for 10 days with 600 pulses per session for ipsilesional iTBS and 1200 pulses per session for contralesional LF-rTMS. Both real conditions improved finger motor function tests evaluated at 12 weeks after stroke onset, compared to the sham condition.

4.1. Contralesional LF-rTMS or cTBS at postacute (subacute) stage of limb motor stroke

In the postacute stage after stroke, most studies concerned LF-rTMS protocols delivered to the "unaffected", contralesional motor cortex. During the 2014-2018 period of this review, 11 sham-controlled studies were published with protocols based on 5 to 30 daily sessions of LF-rTMS (Wang et al., 2014b; Blesneag et al., 2015; Lin et al., 2015b: Lüdemann-Podubecká et al., 2015; Matsuura et al., 2015; Zheng et al., 2015; Du et al., 2016a; Li et al., 2016b; Meng and Song, 2017; Huang et al., 2018b; Long et al., 2018) (Table 3).

One of these studies was not reported in Table 3, since only 8 patients were enrolled in either real or sham group (Blesneag et al., 2015). This study aimed at assessing the changes in motor cortex excitability (TMS motor mapping) between baseline (10 days post-stroke) and one to three months after 10 daily LF-rTMS sessions (45 and 90 days post-stroke). At 45 days after stroke, patients of the real rTMS group showed a better motor recovery on the Fugl-Meyer assessment test of the upper limb (FMA-UL) test and a reduced imbalance between contralesional and ipsilesional hemispheric excitability.

Eight studies aimed at assessing clinical changes produced by a contralesional LF-rTMS protocol on upper limb motor function (Wang et al., 2014b; Lüdemann-Podubecká et al., 2015; Matsuura et al., 2015; Zheng et al., 2015; Du et al., 2016a; Li et al., 2016b; Meng and Song, 2017; Long et al., 2018). In one study (Lüdemann-Podubecká et al., 2015), the impact of rTMS differed according to the location of stroke in the dominant or non-dominant hemisphere: contralesional LF-rTMS was only beneficial for hand dexterity in patients with stroke in the dominant hemisphere.

Clinical improvement was associated with various changes in neurophysiological measures. For example, the movement-related electroencephalographic (EEG) potentials recorded during self-

paced wrist extension of the affected limb were found to be enhanced over the frontocentral electrodes in the ipsilesional hemisphere after contralesional LF-rTMS (Matsuura et al., 2015). In another study (Du et al., 2016a), TMS features of motor cortex excitability were found to be reduced in the contralesional hemisphere (increased RMT and MEP of reduced amplitude and prolonged latency). This study also showed that both clinical improvement and neurophysiological changes were more marked after contralesional LF-rTMS than ipsilesional HF-rTMS performed in another group of patients. Conversely, Li et al. (2016b) compared real contralesional LF-rTMS (42 patients) to either real (43 patients) or sham (42 patients) ipsilesional HF-rTMS and found that both real interventions improved motor performance of the affected hand compared to sham rTMS, but without any difference between the two real interventions.

The most recent study compared a contralesional LF-rTMS protocol performed alone or combined to a protocol of ipsilesional HF-rTMS for 15 consecutive days (Long et al., 2018). Both protocols were effective in improving upper limb motor function assessed by the Fugl-Meyer assessment test of the upper limb (FMA-UL) and the Wolf motor function test (WMFT) up to 3 months after the last session, but the bihemispheric dual protocol was more beneficial than the contralesional LF-rTMS protocol performed alone.

Another study assessed a sequential protocol of 10 daily sessions of contralesional LF-rTMS (900 pulses per session) followed by 10 daily sessions of ipsilesional iTBS (600 pulses per session), or the reverse, performed in patients at 2 to 6 months after stroke (Wang et al., 2014b). In this study, 32 patients received real stimulation (LF-rTMS prior to iTBS in 17 patients and the reverse in 15 patients), whereas 16 patients received sham stimulation. Motor improvement (assessed on FMA-UL and WMFT) was significantly greater in the real condition, especially in patients receiving LF-rTMS prior to iTBS, with a significant benefit persisting for at least 3 months.

One study also combined contralesional LF-rTMS (real or sham, 55 vs. 53 patients) and virtual reality (VR) training for 6 days per week over 4 weeks (24 sessions) (Zheng et al., 2015). At the end of rTMS protocol, FMA-UL and WMFT scores, as well as the modified Barthel index (mBI) were significantly increased in the real compared to the control group.

Finally, two studies aimed at improving lower limb motor function in patients at postacute stage using contralesional LF-rTMS (Lin et al., 2015b; Huang et al., 2018b). One study (Lin et al., 2015b) showed a greater improvement in the postural assessment scale for stroke patients (PASS), the balance subscale of the performance-oriented mobility assessment (POMA), and mBI after real versus sham stimulation. Conversely, the other study (Huang et al., 2018b) did not show any effects on walking abilities following real rTMS (vs. sham condition). Compared to the previous one, a non-focal coil was used (double-cone coil vs. figure-of-8 coil) and stimulation intensity was lower (120% of active motor threshold (AMT) vs. 130% of RMT) in this study.

Taken together the beneficial results reported in at least one Class I study and four Class II studies (Table 3), plus three additional studies published before 2014 (Khedr et al., 2009a; Conforto et al., 2012; Sasaki et al., 2013), it appears that LF-rTMS applied to the contralesional motor cortex

during the postacute stage after stroke has a definite efficacy for promoting rehabilitation and improving residual motor functions at least for the hand (Level A). These beneficial effects were mostly observed when rTMS was used as a priming method before performing 30 to 60 minutes of physical therapy training and may persist up to 6 months after the intervention (Lüdemann-Podubecká et al., 2015).

- Insert Table 3 -

Only one study assessed the impact of repeated cTBS sessions over the contralesional motor cortex (Nicolo et al., 2018). In this study, 41 patients with upper limb paresis persisting at several weeks after stroke were assigned to received 3 sessions per week over 3 weeks (9 sessions) of real cTBS (14 patients), cathodal transcranial direct current stimulation (tDCS) (14 patients), or sham cTBS or tDCS (13 patients). Cortical stimulation was combined with 30 minutes of active functional motor practice but did not produce any significant clinical changes assessed on FMA-UL, Box and Block and 9-Hole Peg test scores, or Jamar dynamometer. Only subtle changes in transcallosal functional connectivity were evidenced after cTBS on high-density EEG.

4.2. Ipsilesional HF-rTMS or iTBS at postacute (subacute) stage of limb motor stroke

In the 2014-2018 period, 5 sham-controlled studies aimed at assessing clinical changes produced by an ipsilesional HF-rTMS protocol on upper limb motor function (Du et al., 2016a; Hosomi et al., 2016; Li et al., 2016b; Guan et al., 2017; Sasaki et al., 2017) (Table 4). As aforementioned, ipsilesional HF-rTMS protocol was compared to contralesional LF-rTMS protocol in two of these studies, showing an equal efficacy of both protocols in one study (Li et al., 2016b) and a superiority of the contralesional LF-rTMS protocol in the other study (Du et al., 2016a). However, in this latter study, HF-rTMS was performed at only 3Hz. Hosomi et al. (2016) applied a 5Hz-rTMS protocol over the lesioned motor cortex and showed significant improvement of various aspects of the paretic hand motor function at the end of a series of 10 daily sessions in the real but not sham condition. These beneficial effects were still present two weeks beyond the last rTMS session. Guan et al. (2017) also performed a 10-day protocol of 5Hz-rTMS applied to the "affected" motor cortex, but in patients at an earlier post-stroke stage (4.6 days after stroke onset on average versus 45 days in Hosomi et al., 2016). During rTMS therapy up to one month after stroke onset, motor improvement was significantly greater in the real vs. sham condition. The difference was no more significant at 3 months post-stroke or thereafter, except for the FMA-UL score that remained improved one year after real HF-rTMS.

Finally, one study showed the value of ipsilesional HF-rTMS targeted with a large double-cone coil over the motor cortical area of leg representation for enhancing lower limb motor functions (Sasaki et al., 2017).

Taken together the beneficial results reported in at least three Class II studies (Table 4), plus four additional studies published before 2014 (Khedr et al., 2005, 2009a, 2010; Chang et al., 2010),

the current level of evidence is in favor of a probable beneficial impact of ipsilesional HF rTMS of M1 in the postacute phase of stroke for promoting motor function recovery, at least for the upper limb (Level B). However, two studies gave evidence for a superiority of the contralesional LF-rTMS protocol in terms of efficacy (Khedr et al., 2009a; Du et al., 2016a).

- Insert Table 4 -

Only one study assessed the impact of repeated iTBS sessions over the ipsilesional motor cortex (Volz et al., 2016). In this study, 26 patients with upper limb paresis due to a first stroke occurred 1 to 16 days before, received 5 daily sessions of real or sham iTBS (13 patients for each condition) at 70% of RMT with 600 TMS pulses delivered per session a few minutes prior to standard physiotherapy performed for 45 minutes. The real stimulation produced significantly stronger recovery of grip strength of the paretic hand compared to control stimulation, with lasting benefit for at least 3 months. Clinical improvement was associated with stronger network connectivity of ipsilesional M1 at functional magnetic resonance imaging (fMRI).

In another study cited above (Wang et al., 2014b), an ipsilesional iTBS protocol was combined with a contralesional LF-rTMS in a sequence of 10 daily sessions of each protocol performed successively. A greater efficacy was found when contralesional LF-rTMS was first applied, prior to ipsilesional iTBS. In fact, bihemispheric dual stimulation was rarely performed, e.g. a protocol combining contralesional LF-rTMS and ipsilesional HF-rTMS for 15 consecutive days (Long et al., 2018) and therefore no recommendation is allowed for such a strategy in the objective of promoting motor function recovery in the postacute stage of stroke.

4.3. Contralesional LF-rTMS at the chronic stage of limb motor stroke

In patients at the chronic stage of stroke (more than 6 months post-stroke), 3 studies addressed the use of contralesional LF-rTMS (Rastgoo et al., 2016; Forogh et al., 2017; Harvey et al., 2018). In series of 15 to 20 patients, two sham-controlled studies (7 to 10 patients in both real and sham groups) showed that focal stimulation (using a figure-of-8 coil) over the leg motor cortical representation of the "unaffected" hemisphere for 5 daily sessions could reduce spasticity (assessed on modified Ashworth scale) and improve lower limb motor function (assessed on FMA-LL) (Rastgoo et al., 2016), with clinical benefits lasting 1 to 3 weeks post-intervention and up to 3 months regarding the impact on balance (measured on Berg balance scale) and static postural stability (Forogh et al., 2017). However, these results on motor recovery and posture remain to be replicated.

An important study on hand motor recovery following 1Hz-rTMS over contralesional M1 was published in the framework of the NICHE trial (Harvey et al. 2018). Remarkable features of this industry-initiated clinical trial were the high number of participants (199 patients) and a multicenter design using a 2:1 randomization strategy (real: 132 patients, sham: 67 patients). Inclusion criteria were patients within 3-12 months post-stroke and with some remaining hand motor function. The protocol consisted of 18 sessions of 1Hz-rTMS over 6 weeks (900 pulses per session at 110% of

RMT), each rTMS session being followed by arm training. The results, obtained in 169 participants who completed all sessions, showed that real rTMS was not superior to sham rTMS, for none of the studied motor parameters (Action Research Arm Test (ARAT), FMA-UL, WMFT). Hence, this study does not support the concept of LF-rTMS of contralesional motor cortex as a beneficial add-on therapy in chronic motor stroke, which was based on several Class II-III studies showing improvement of manual motor abilities for 2 to 12 weeks following rTMS protocols based on 5 to 10 daily sessions (Fregni et al., 2006; Emara et al., 2009, 2010; Avenanti et al., 2012). These recent results significantly weaken our recommendations from Level B (probable effect) to Level C (possible effect) concerning LF-rTMS over contralesional M1 to promote post-stroke recovery of hand motor function in chronic stroke patients. Furthermore, this statement cannot be extended to lower limb rehabilitation or spasticity to date.

4.4. Ipsilesional HF-rTMS or iTBS at the chronic stage of limb motor stroke

In the 2014-2018 period, only one sham-controlled study of 30 patients at the chronic stage post-stroke (4 years post-stroke on average) was based on an ipsilesional HF-rTMS protocol with a real-sham crossover design (Choi et al., 2016). In this study, rTMS was targeted over the thoracic paraspinal muscle representation with a figure-of-8 coil for 10 daily sessions over two weeks and resulted in significant improvement of balance (measured by computerized dynamic posturography) after real vs. sham stimulation.

In contrast, three sham-controlled studies with repeated daily sessions of ipsilesional iTBS were performed in patients at the chronic stage (Lai et al., 2015; Ackerley et al., 2016; Lin et al., 2018) (Table 5). In the first study (Lai et al., 2015), ipsilesional iTBS was able to improve paretic hand motor function (assessed by the WMFT and a finger tapping task) at the end of the 10-day protocol (no follow-up). This motor improvement was positively correlated to the presence and amplitude of MEPs and preserved grip strength in the paretic hand at baseline. In a second study (Ackerley et al., 2016), real or sham ipsilesional iTBS was delivered immediately before a 45-minute session of physical therapy, as a priming procedure. The real stimulation improved paretic upper limb function (measured by the ARAT) at the end of the 10-day protocol, with a significantly lasting effect at one month post-intervention (but not at three months). This functional improvement was correlated to a reduction of interhemispheric asymmetry of cortical excitability (measured on the slope of the MEP recruitment curve) and to an increase in ipsilesional premotor cortex activation during paretic hand grip assessed by fMRI. However, this well-conducted study remains of Class III because of its small sample size (9 patients in both real and sham iTBS groups) and was not reported in Table 5.

The last controlled study used an ipsilesional iTBS protocol to improve lower limb function (Lin et al., 2018). Despite a broad assessment (FMA-LL, National Institutes of Health Stroke Scale (NIHSS), modified Rankin scale, Barthel index, Brunnstorm recovery stage (BRS-leg), Berg balance scale (BBS), timed up-and-go test, 10-meter walking test (10MWT), and computerized dynamic

posturography) and a prolonged stimulation protocol over 5 weeks, only marginal improvement was observed in the real iTBS condition, not significantly different from the sham condition.

Thus, in patients at the chronic stage of motor stroke, the functional benefits provided by ipsilesional stimulation protocols (HF-rTMS or iTBS) were reported by too few studies, also including previously discussed results published by Emara et al. (2009, 2010), to obtain a sufficient level of evidence to make a recommendation.

- Insert Table 5 -

4.5. Ipsilesional cTBS at the chronic stage of limb motor stroke

In the 2014-2018 period of literature search, we found one small study in which cTBS was delivered on the motor cortex of the lesioned hemisphere of chronic stroke patients with severe deficit in order to improve the response to robot-assisted motor rehabilitation (Di Lazzaro et al. 2016). The choice of employing cTBS on the affected hemisphere was based on the results of studies in normal subjects showing that rTMS protocols suppressing cortical excitability strongly facilitate motor learning capacities via an increase in "homeostatic" plasticity (Jung and Ziemann, 2009). In a small previous study of stroke patients with moderate deficits, an enhanced response to physical therapy was observed after ipsilesional cTBS (Di Lazzaro et al., 2013). In a subsequent study of the same research group (Di Lazzaro et al., 2016), 20 chronic stroke patients wtih severe impairment of upper limb motor performances were randomized to robot-assisted therapy associated with real or sham ipsilesional cTBS, delivered for 10 working days. All patients who completed the study (8 real, 9 sham), achieved a small, but significant motor improvement (about 5% on the FMA-UL), but the difference between real and sham cTBS groups was not significant. Thus, this study did not replicate findings obtained in patients with moderate upper limb deficits. The authors suggested that a possible explanation for the discrepancy is that the affected and unaffected hemispheres might play a different role in mild vs. severe strokes, so that the hemisphere mainly responsible for motor recovery in severe stroke is the unaffected one (Di Pino et al., 2014). Thus, a different approach might be needed in patients with severe brain damage. Because there are only two small studies with conflicting results, the level of evidence is not sufficient to make a recommendation and further studies are needed in order to evaluate whether subgroups of patients might respond to a homeostatic modulation of brain plasticity.

4.6. Cerebellar target

Beyond M1, which is the main target considered for rTMS therapy in stroke, recent electrophysiological and imaging evidence underlined that a large motor network includes other key brain areas during the process of post-stroke functional recovery (Grefkes and Fink, 2014; Koch and Hummel, 2017). The cerebellum is one of these alternative targets to M1 for promoting motor

rehabilitation by rTMS in the context of stroke (Wessel and Hummel, 2018). First, Kim et al. (2014a) applied LF-rTMS to the cerebellum in a series of 26 ataxic patients in the subacute stage of a posterior circulation stroke (15 days post-stroke on average). In this sham-controlled protocol of 5 daily sessions (20 patients for the real condition vs. 6 patients for the sham condition), a figure-of-8 coil was used, centered 2cm below the inion and 2cm lateral to the midline, ipsilateral to the ataxic side, with the handle pointing superiorly. The main result was an improvement of walking ability, measured on time and number of steps in the 10MWT, only at 1 month after real rTMS compared to sham condition. Balance, measured on BBS, improved in both conditions, although more significantly in the real rTMS group.

More recently, Koch et al. (2019) applied iTBS over the contralesional lateral cerebellum coupled with physiotherapy (90-minute session of motor and balance therapy) for 3 weeks and also showed an improvement of balance and gait functions (measured on BBS and step width at a walking test) in a series of 34 patients (17 patients in both real and sham conditions) at the chronic stage of middle cerebral artery stroke (6 to 78 months post-stroke).

These approaches appeared to be rather opposite, since LF-rTMS is usually considered as an "inhibitory" protocol and iTBS as an "excitatory" protocol. In fact, such opposition is rather speculative. Thus, these two studies pave the way of future research based on cerebellar stimulation for promoting stroke rehabilitation but are insufficient to provide a level of evidence or make a recommendation.

It is worth mentioning that the clinical impact of motor cortex rTMS is still limited and heterogeneous in stroke patients. These limited effects might be due to the fact that rTMS is not applied in a personalized medicine fashion, tailored to the phase of recovery or individual characteristics of the patient. Understanding biomarkers for targeting stratification will provide elements for precision medicine in order to achieve maximized treatment effects for stroke recovery in each individual patient (Grefkes and Fink, 2014; Morishita and Hummel, 2017; Raffin and Hummel, 2018). In addition, the number and size of most trials is rather small. Larger, multicenter randomized controlled clinical trials are still missing to achieve highest evidence level (Grefkes and Fink, 2016), especially for novel targets (such as the premotor cortex or the cerebellum) (Koch and Hummel, 2017; Wessel and Hummel, 2018), which are going to be evaluated.

4.7. Swallowing and dysphagia

Swallowing dysfunction is a very common symptom, but usually returns to normal over the first weeks after stroke in many patients. Although a minority of patients suffer from persistent dysphagia at 6 months after stroke (Mann et al., 1999), this condition has an important impact on clinical outcome, as dysphagia is a frequent cause of severe adverse events, like aspiration pneumonia which can have lethal consequence. Therefore, accelerating recovery from dysphagia may strongly reduce stroke-related complications. Several studies have investigated the value of rTMS to enhance

swallowing function recovery after stroke on the same concept of interhemispheric rivalry as for limb motor functions, although the control of swallowing is more bilaterally implemented in the brain.

In the 2014-2018 period, 4 sham-controlled studies were published in this field of research, 3 concerning the post-acute stage of stroke (Du et al., 2016b; Park et al., 2017; Zhang et al., 2018) and one the chronic stage (Cheng et al., 2017).

In two studies (Du et al., 2016b; Park et al., 2017), ipsilesional HF-rTMS was applied to the motor cortex representing the swallowing muscles (hot spot of the mylohyoid muscle) in patients in the postacute phase of poststroke dysphagia. In Du et al. (2016b), 13 patients (1.2 week post-stroke on average) received 3Hz-rTMS for 5 days over one week, while in Park et al. (2017), 11 patients (4.2 weeks post-stroke on average) received 10Hz-rTMS for 10 days over 2 weeks. Swallowing function improved after real rTMS when compared with sham rTMS in the first study, but not in the second one (Table 6).

Before 2014, three studies reported beneficial rTMS effects for dysphagia rehabilitation in the post-acute stage (one week to two months post-stroke on average): in two studies from the same group (Khedr et al., 2009b; Khedr and Abo-Elfetoh, 2010) 3Hz-rTMS was applied over the oesophageal representation of the affected motor cortex (300 pulses/session at 120-130% of hand RMT for 5 consecutive days), whereas in the third study (Park et al., 2013a), 5Hz-rTMS was applied over the contralesional pharyngeal motor cortex (500 pulses/session at 90% of hand RMT for 10 days over 2 weeks). Because of this discrepancy (ipsilesional vs. contralesional), no recommendation can be made for the use of HF-rTMS in the context of swallowing dysfunction at the post-acute phase of stroke.

In Park et al. (2017), an additional group of 11 patients received bilateral 10Hz-rTMS over both M1 regions projecting to mylohyoid muscles (500 pulses for 10 minutes over the ipsilesional cortex, followed by 500 pulses for 10 minutes over the contralesional cortex). In contrast to unilateral ispilesional stimulation, bilateral HF-rTMS significantly improved clinical and videofluoroscopic swallowing function at the end of the protocol and also 3 weeks after. This is in line with the aforementioned bilateral cortical control of swallowing. However, this study remains to be replicated.

In Du et al. (2016b), an additional group of 13 patients received contralesional 1Hz-rTMS protocol, which produced similar improvement as ipsilesional 3Hz-rTMS. Both protocols increased cortical excitability of the affected hemisphere (increased amplitude and decreased latency of mylohyoid MEPs).

In another study (Lim et al., 2014), LF-rTMS was applied 5 days/week for 2 weeks over the pharyngeal hotspot of the contralesional motor cortex in a series of 14 patients in the subacute stage of stroke (30 days post-stroke on average). This study was not sham controlled, the other experimental groups being 18 patients treated by 30-minute daily sessions of neuromuscular electrical stimulation (NMES) of the digastric and hyoid muscles and 15 patients with only conventional dysphagia rehabilitation therapy. Both rTMS and NMES improved dysphagia on a functional scale.

A final study on post-stroke swallowing rehabilitation in the postacute stage combined rTMS and NMES performed during the same sessions 5 days/week for 2 weeks (Zhang et al., 2018). In four

groups of 13 to 16 patients in the subacute stage of stroke (21 to 26 days post-stroke on average), NMES was combined to contralesional 1Hz-rTMS, ipsilesional 10Hz-rTMS, both protocols (bilateral rTMS), or sham stimulation (tilted coil). All real rTMS protocols enhanced swallowing function recovery compared with NMES delivered alone, especially bilateral rTMS protocol.

In the chronic phase of stroke, Cheng et al. (2017) found that HF-rTMS delivered to the lesioned hemisphere did not provide any benefit. As post-stroke swallowing dysfunction usually rapidly recover, rTMS should probably be applied early in the history of the disease to achieve more relevant therapeutic effects.

In summary, given the heterogeneity of results and protocols, it is still not possible to conclude that rTMS may be a beneficial therapeutic modality for patients with persisting dysphagia in the postacute or chronic stage of stroke.

- Insert Table 6 -

4.8. Aphasia

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND aphasia) identified 53 papers, including 6 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions.

Before 2014, mostly case reports have been published in this field of research, or studies based on small samples (Barwood et al., 2011a,b; Medina et al., 2012). In our previous work (Lefaucheur et al., 2014), we identified only few studies based on a sufficiently large sample of patients, reporting the effects of repeated daily LF-rTMS delivered over the right inferior frontal gyrus (IFG) followed by 45-min speech and language therapy (Waldowski et al., 2012; Heiss et al., 2013; Thiel et al., 2013; Seniów et al., 2013). These studies mixed patients at the postacute stage with either nonfluent Broca's or fluent Wernicke's aphasia and originated from two research groups. One group used vertex stimulation as control and reported significant improvement in several language functions following real rTMS with no change following sham stimulation (Heiss et al., 2013; Thiel et al., 2013). In contrast, the other group used sham coil as control and did not find any difference in the degree of speech improvement between real and sham conditions (Waldowski et al., 2012; Seniów et al., 2013). Therefore, no conclusion regarding the efficacy of LF rTMS of the right IFG in patients with non-selected type of poststroke aphasia in the postacute phase could be drawn.

In the 2014-2018, only one additional study performed in the postacute phase with a similar design was identified (Rubi-Fessen et al., 2015). In this study, a series of 30 stroke patients in the postacute phase (17 to 94 days post-stroke) with non-selected type of aphasia (one-third nonfluent type) underwent a 10-day protocol of LF-rTMS delivered over the right IFG (15 real, 15 sham consisting of active vertex stimulation). Similarly to previous studies, each rTMS session (1200 pulses/session) was immediately followed by a 45-minute session of speech and language therapy. Real rTMS was found to improve basic linguistic skills and functional communication, measured on

the Aachen Aphasia Test (AAT) and the Amsterdam-Nijmegen Everyday Language Test (ANELT), one day after the treatment peiod. Therefore, conclusion for this particular situation remains the same, with no recommendation for the use of LF-rTMS of the right IFG in patients with non-selected type of aphasia at a postacute post-stroke stage.

However, since 2014, more consistent studes assessing a single type of aphasia in larger samples of patients at the chronic stage of stroke have been published. Most of these studies assessed the value of LF-rTMS for the rehabilitation of nonfluent aphasia, in which the Broca's area is usually damaged by middle cerebral artery infarction (Table 7). Broca's area consists of the pars opercularis and pars triangularis of the IFG of the dominant (left) hemisphere, corresponding to Brodmann areas (BAs) 44 and 45. In most studies, post-stroke aphasia was intended to be treated by LF-rTMS specifically applied to the right BA 45 region, i.e. the contralesional homologue of Broca's area, using image-guided navigation. As it was the case in the studies published before 2014 and also for motor stroke, the rationale for these studies was to down-regulate an increased cortical activity in the contralesional hemisphere, thus reducing the interhemispheric inhibition onto the lesioned cortical regions which was supposed to interfere with successful language recovery.

Yoon et al. (2015) used combination of LF-rTMS of the right IFG with speech and language therapy in 10 patients with nonfluent aphasia at the beginning of the chronic post-stroke phase and compared them with similar group of 10 patients receiving speech and language therapy only. This combined therapy improved repetition and naming performance on the Western Aphasia Battery (WAB, Korean version) at the end of a 4-week protocol in contrast to the control group where no significant improvement was seen.

Hu et al. (2018) further showed that a 10-day protocol of LF-rTMS delivered at 1Hz over the right homologous of Broca's area (defined by F4 site of the 10-20 EEG system) was able to improve some variables of the WAB (Chinese version) in 10 patients with nonfluent aphasia at the beginning of the chronic post-stroke phase. At the end of rTMS protocol, spontaneous speech, auditory comprehension, and aphasia quotients were improved after LF-rTMS, but not HF-rTMS delivered over the same contralesional target. This beneficial effect lasted for at least 2 months.

One research group assessed the value of LF-rTMS of the right IFG in patients with nonfluent aphasia at a more chronic stage. In a first study (Tsai et al., 2014), 31 stroke patients (22 patients in the sham group) underwent 10 sessions of real LF-rTMS applied at 1Hz over the contralesional pars triangularis (right IFG, BA 45). They improved on the Concise Chinese Aphasia Test (CCAT) score, object and action naming accuracy and reaction time after real stimulation, with benefit persisting at 3 months following intervention, at least for the CCAT score. A lower RMT was a predictor of a favorable outcome. The same research group applied LF-rTMS of the right BA 45 during or immediately before a naming training session for 10 daily sessions in 29 stroke patients with nonfluent aphasia (14 patients in the sham group) (Wang et al., 2014a). Patients improved on the CCAT and object and action naming accuracy only when LF-rTMS and speech therapy were concomitantly performed, with benefit persisting at 3 months following intervention.

From all these results, including a duet of Class II studies from one research group (Tsai et al., 2014; Wang et al., 2014a), and two Class III studies from two other independent groups (Yoon et al., 2015; Hu et al., 2018), a level B of evidence (probable efficacy) can now be proposed for LF-rTMS of the right IFG in patients with nonfluent aphasia at a chronic post-stroke stage, especially if combined with speech and language therapy.

- Insert Table 7 -

In our previous work (Lefaucheur et al., 2014), due to the paucity of data (few studies published were all Class IV), no recommendation could be made 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 aphasia. The situation remains the same following the review of the studies published between 2014 and 2018.

A few additional sham-controlled studies deserve to be cited. Firstly, Khedr et al. (2014) applied a dual-hemisphere rTMS protocol in 29 stroke patients (19 real, 10 sham) with nonfluent aphasia at the postacute stage (5 weeks post-stroke on average). Each patient received 1000 rTMS pulses delivered at 1Hz and 110% of RMT over the unaffected IFG (right BAs 44 and 45) and 1000 pulses delivered at 20Hz and 80% of RMT over the affected Broca's area (left BAs 44 and 45) for 10 consecutive days followed by speech and language training. A significantly greater improvement in the Hemispheric Stroke Scale (HSS) and the Stroke Aphasic Depression Questionnaire-Hospital Version (SADQ-H) was observed after real rTMS compared with sham rTMS, which remained significant 2 months after the last session.

Similarly, Vuksanović et al. (2015) 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, followed by 45 minutes of speech and language therapy. Although scarce, these results suggest potential for use of dual-hemisphere protocols in aphasia treatment.

Regarding fluent aphasia, the target is conceivably located in the superior temporal gyrus (STG) (Hamilton et al., 2010). In our previous work, only one Class IV study reporting the effects of LF rTMS applied to the homologue of Wernicke’s area in the right hemisphere in patients with fluent aphasia was found, and consequently no recommendation could be made for this type of aphasia. The situation remains the same following the review of the studies published between 2014 and 2018.

Finally, one study did not address aphasia, but dysarthria (Kwon et al., 2015). Contralesional LF-rTMS was delivered at 1Hz (1500 pulses/session, 5 days/week for 2 weeks) over the orbicularis oris motor hot spot on the non-affected side in a series of 20 stroke patients (10 real, 10 sham) at the postacute stage (26.5 days post-stroke on average). All rTMS sessions were combined with speech therapy for 30 minutes. Dysarthria significantly improved at the end of the rTMS protocol, better after real than sham stimulation in various aspects.

4.9. Neglect

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND neglect) identified 32 papers, including only 3 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions.

Hemispatial neglect preferentially occurs on the left side following stroke in the territory of the right middle cerebral artery, most often related to a lesion of the right posterior parietal cortex (PPC) or the posterior part of the STG. The description of spatial attention deficits following left-hemispheric stroke are scarce (Timpert et al., 2015). The PPC includes the superior parietal lobule (BA 7, above the intraparietal sulcus), corresponding to the P3-P4 sites of the EEG 10-20 System (Homan et al., 1987) and the inferior parietal lobule (below the intraparietal sulcus), with two parts named anteriorly the supramarginal gyrus (BA 40, corresponding to the CP3-CP4 sites of the EEG 10-10 System) and posteriorly the angular gyrus (BA 39, corresponding to the P5-P6 sites).

Most rTMS studies assessed excitability-decreasing paradigms (LF-rTMS or cTBS) applied to the contralesional left PPC following a right-hemispheric stroke. From 2014, only one study assessed the effects of LF-rTMS delivered at 1Hz over the contralesional left PPC (P5 site), 5 days/week for two weeks, in patients with left hemineglect in the postacute stage (about 40 days post-stroke on average) (Yang et al., 2017). Three experimental groups were considered: real LF-rTMS alone (19 patients) or combined with sensory cueing intervention (i.e., a device placed on the left wrist, which emitted vibration every 5 minutes for 3 hours/day to remind the patient to focus on the neglected side) (18 patients) and conventional rehabilitation program alone (19 patients). The combination of LF-rTMS with sensory cueing was better than either rTMS or conventional rehabilitation alone in producing a stronger and long-lasting improvement in unilateral neglect, measured on the Behavioural Inattention Test (BIT).

Conversely, in a sham-controlled study, Cha and Kim (2016) applied LF-rTMS to the right lesioned PPC (P4 site, 1Hz), five days/week for 4 weeks, in 30 patients (15 real, 15 sham) with hemispatial neglect in the late post-acute phase (4 months post-stroke on average). Improvement on Line Bisection test (LBT), Albert test, Box-and-Block test (BBT), and grip strength was significantly greater in the real than the sham rTMS group in this Class II study.

Before 2014, only one sham-controlled study (Kim et al., 2013) compared the respective effects of real LF-rTMS of the contralesional left PPC (P3 site, 1Hz, 9 patients), sham LF-rTMS (tilted coil, 9 patients), and HF-rTMS of the ipsilesional right PPC (P4 site, 10 Hz, 9 patients). Sessions were performed five days/week for 2 weeks in patients with visuospatial neglect in the early post-acute phase (15 days post-stroke on average). This study showed a better improvement of neglect (measured on LBT) in the ipsilesional (right hemisphere) HF-rTMS group than in the contralesional (left hemisphere) LF-rTMS and sham groups.

No recommendation can be proposed regarding the use of conventional LF- or HF-rTMS over parietal regions in the treatment of visuospatial neglect, because of methodological differences in the

two sham-controlled studies: LF-rTMS applied to the contralesional (Kim et al., 2013) or ipsilesional (Cha and Kim, 2016) hemisphere, or ipsilesional HF-rTMS (Kim et al., 2013).

Other studies assessed the value of cTBS delivered to the contralesional left PPC. This was the case of one sham-controlled study based on sessions repeated for several days and published before 2014 (Koch et al., 2012). In this Class II study, 20 patients in the postacute stage of stroke (24-102 days post-stroke) were equally randomized to receive a real or sham cTBS protocol (10 patients in each group) delivered 5 days/week for 2 weeks over the left PPC (P3 site). This study showed that cTBS but not sham stimulation decreased the severity of spatial neglect as assessed by the BIT, with after-effects lasting at least for two weeks after treatment.

A more recent study of Class III (Fu et al., 2015) also assessed the efficacy of cTBS for improving visuospatial neglect (Table 8). The same cTBS protocol was similar to that used as in Koch et al. (2012), i.e. 2 trains separated by 15 minutes and consisting of 3-pulse bursts delivered at 30Hz (not 50Hz) and repeated at 5Hz for 40s at 80% of RMT (not AMT). Patients with right hemisphere stroke and visuospatial neglect at the post-acute stage (17-114 days post-stroke) underwent real or sham cTBS sessions (10 patients in each group) over the PPC (P5 site) of the unaffected left hemisphere, combined with conventional rehabilitation therapy for 2 weeks and were followed up for 4 weeks. The scores for two paper-pencil tests for visuospatial neglect (star cancellation and line bisection tests) significantly improved after real stimulation (but not after sham stimulation) by 21-37% at the end of 2-week rTMS therapy and by 36-47% after 4-week follow-up.

A third research group also reported significant improvement of neglect after cTBS of the left PPC (P3 site) (Nyffeler et al., 2009, 2019; Cazzoli et al., 2012), but they used a large circular coil (MagPro MC-125, 114 mm outer diameter) and a slightly different cTBS protocol, consisting of 4 cTBS trains per session (two cTBS trains separated by an interval of 15 minutes with the third and the fourth trains delivered 60 and 75min after the first one, respectively). In a first study (Nyffeler et al., 2009), they showed that the beneficial effect of a single session of 4 cTBS trains lasting for more than 24 h in 11 patients with left-sided visuospatial neglect at the postacute or chronic stage. Then they assessed the effect of 8 trains of cTBS delivered over 2 consecutive days in 16 patients with left-sided visuospatial neglect at the postacute stage (mean 26.6 days post-stroke) in a randomized, double-blind, sham-controlled crossover study (Cazzoli et al., 2012): cTBS, but not sham stimulation, significantly improved neglect (detection of left-sided visual targets, paper-pencil assessment, and impact on activities of daily living), with benefit lasting for at least 3 weeks. Finally, in a third study of Class II (Nyffeler et al., 2019), they showed that either 8 or 16 trains of cTBS delivered over 2 or 4 consecutive days reduced the impact of spatial neglect-related deficits on the activities of daily life and improved several neuropsychological neglect tests up to 3 months, in a series of 20 patients with left-sided visuospatial neglect at the postacute stage (mean 22.9 to 26.8 days post-stroke), compared to 10 patients stimulated for only 2 days with a sham coil, which was a figure-of-8 coil (MagPro MC-B70, 97 mm outer diameter). Moreover, cTBS significantly improved general functional outcome after stroke and overall no significant difference was observed according to the number of cTBS sessions

(either 2 or 4). Further analyses showed that the variability in the response to cTBS was determined by the integrity of interhemispheric connections within the corpus callosum (parieto-parietal connections). In cTBS responders, in whom neglect and general functional outcome were significantly improved, the corpus callosum was intact, whereas this was not the case in cTBS non-responders.

Thus, three independent research groups have reported beneficial results of the application of cTBS to the contralesional left PPC in the treatment of visuospatial hemineglect in the post-acute phase of stroke, but given various methodological differences (P3 or P5 site of stimulation, 30Hz- or 50Hz-cTBS trains, 2 or 4 trains per session, and especially the use of a figure-of-8 or a circular coil), the recommendation remains at Level C ("possible efficacy") from these three Class II/III studies.

- Insert Table 8 -

5. Multiple sclerosis

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND multiple sclerosis) identified 23 papers in the 2014-2018 period, but only 2 original sham-controlled studies of Class II with at least 10 patients receiving real stimulation for several daily sessions (Table 9).

The first study (Azin et al., 2016) assessed the effect of iTBS delivered over the hand representation of the left M1 in a series of 36 patients with remitting-relapsing multiple sclerosis (RR-MS) (19 real, 17 sham). At the end of iTBS therapy consisting of 10 daily sessions performed over two weeks, there was an improvement of manual dexterity only in the real iTBS group, as revealed by a reduction in the time required to complete the nine-hole peg test (9HPT) and an increased performance in the Box-and-Block test (BBT) when compared to the sham group.

The second study (Korzhova et al., 2019) assessed the effect of iTBS, but also HF-rTMS (20Hz) delivered over the leg representation of both right and left M1 in 34 paraparetic patients with secondary progressive MS (SP-MS). The primary outcome was the degree of lower limb spasticity measured on the Modified Ashworth Scale (mAS) and the Subjective Evaluating Spasticity Scale (SESS). Following 10 daily sessions performed over two weeks, spasticity was reduced up to 12 weeks after stimulation in patients who received a real stimulation, especially iTBS. Conversely, reduction in pain and fatigue was found in the HF-rTMS group.

One additional sham-controlled study (of Class III) was published on the application of iTBS of M1 to treat lower limb spasticity in MS patients (Boutière et al., 2017). However, this study included less than 10 patients in the real stimulation group and therefore did not appear in Table 9. Boutière et al. (2017) assessed the effect of real or sham iTBS targeted to the leg M1 area of one hemisphere using image-guided neuronavigation in 17 patients (9 real, 8 sham) with MS of RR or SP type (4 and 13 patients, respectively). The iTBS protocol was performed during the first 13 working days of a 5-week rehabilitation program. At the end of stimulation period, lower limb spasticity (measured on a VAS) improved greater after real than sham iTBS at the end of the rTMS therapy, with no differential lasting effects two weeks between the two conditions. The beneficial effect on

spasticity was associated with a change in interhemispheric functional connectivity between both motor cortices in resting-state fMRI.

Before 2014, two sham-controlled randomized studies with parallel-arm design also assessed the effect of iTBS on lower limb spasticity in MS patients (Mori et al., 2010, 2011). In the first study, Mori et al. (2010) showed that iTBS applied 5 days a week for 2 weeks significantly improved spasticity assessed on the H/M amplitude ratio and the mAS in the real iTBS group (10 patients), but not in the sham group (10 patients), with benefit lasting for one or two weeks beyond the last iTBS session. In the second study (Mori et al., 2011), a significant improvement of spasticity assessed on the mAS was also found after 10 sessions of real iTBS performed alone (10 patients) or immediately prior to 2 hours of exercise training (10 patients) over 2 weeks. No significant change occurred in a control group of 10 patients who received sham stimulation. In these two studies, issued from the same research group, iTBS was targeted to only one hemisphere, as in Boutière et al. (2017), on the leg representation of M1 contralateral to the most affected limb, since spasticity predominated in one lower limb. In addition, only patients with RR-MS type were enrolled. These were two major differences with the study reported by Korzhova et al. (2019). However, we may also consider a similar pathogenesis of spasticity in all these studies, whether the involvement was predominantly unilateral in RR-MS patients or bilateral in SP-MS patients with a more advanced disease. Therefore, according to the beneficial results reported in Class II studies issued from two independent groups (Mori et al., 2010, 2011; Korzhova et al., 2019), not to mention a positive Class III study of a third group (Boutière et al., 2017), a Level B of evidence (probable efficacy) is reached for the use of iTBS targeted to the leg motor cortex to treat lower limb spasticity in patients with MS. Conversely, no recommendation can be made for iTBS targeted to the hand motor cortex to improve manual dexterity.

- Insert Table 9 -

Finally, one study (Gaede et al., 2017) assessed the efficacy of a non-focal HF-rTMS of the left prefrontal cortex (PFC) using an H6-coil (1800 pulses/session delivered at 18Hz and 120% of RMT) in 19 MS patients (9 real, 10 sham), while a third group of 9 MS patients received a non-focal bihemispheric HF-rTMS over M1 regions using an H10-coil (800 pulses/session delivered at 5Hz and 90% of RMT). In this study, all patients had fatigue related to RR-type of MS, except two patients with SP-MS. The stimulation protocol consisted of 18 consecutive rTMS sessions over 6 weeks, followed by a 6-week follow-up. A significant reduction in fatigue, measured on the Fatigue Severity Scale (FSS), was observed only after M1 stimulation at the end of the stimulation protocol, up to the end of follow-up. Of course no recommendation can be made concerning the use of an H-coil in MS, on the basis of this single study.

6. Epilepsy

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND epilepsy) identified 47 papers, but no original sham-controlled studies with at least 10 patients receiving real stimulation.

From 2014 to date, only one sham-controlled rTMS trial (Class III) has been published in the domain of epilepsy (Seynaeve et al. 2016). In this single-center, crossover study, 7 patients with focal neocortical drug-resistant epilepsy received 3 treatments consisting of 10 sessions of navigated rTMS delivered at 0.5Hz and 90% of RMT over the cortical focus (1500 pulses/session) by means of a figure-of-8 coil, a round coil, or a sham coil. The primary endpoint was the mean daily number of seizures, which did not differ at baseline among the conditions. After LF-rTMS therapy, no difference in mean seizure rate was detected in any of the three coil conditions compared to baseline or between any of these conditions. In one patient, after an initial reduction of seizure frequency, a rebound was even observed up to 20 weeks after the end of the study. Thus, this "negative" study did not confirm positive meta-analytical findings of rTMS in epilepsy treatment (Hsu et al. 2011). However, differences in the paradigm of rTMS interventions, the type and clinical profile of the epilepsy, or the number of antiepileptic drugs taken by each patient (e.g., up to 5 in Seynaeve et al 2016) are confounding factors to be taken into account. Hence, the level of recommendation C for LF-rTMS in epilepsy did not change. Finally, the acute administration of rTMS trains to treat status epilepticus was not considered in the present review because all published studies are case reports, including less than 10 patients (Zeiler et al. 2015).

7. Disorders of consciousness

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND disorders of consciousness OR minimally conscious state OR unresponsive wakefulness syndrome OR vegetative state) identified 19 papers, but only one original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions (Cincotta et al., 2015).

From 2014 to date, several Class III studies assessed the clinical efficacy of rTMS in patients with disorder of consciousness (DOC), including minimally conscious state (MCS) and unresponsive wakefulness syndrome (UWS), which was previously called "vegetative state". They used different approaches and targets; mostly the left M1 (Cincotta et al., 2015; He et al., 2018; Liu et al., 2018) and the left or right DLPFC (Naro et al., 2015; Xia et al. 2017a,b).

In a randomized, crossover, sham-controlled study of 11 chronic UWS patients (9 post-anoxic and 2 post-traumatic), Cincotta et al. (2015) applied rTMS at 20Hz and 90% of RMT to the left M1 for 5 consecutive days. The stimulation pattern was unusual, consisting of 100 blocks of 30-sec (5 trains of 1 sec with 5-sec intertrain), for a total of 1000 pulses/day. Compared to baseline, no improvement was observed on either the JFK Coma Recovery Scale-Revised (CRS-R) or the Clinical Global Impression of Improvement (CGI-I) scale at the end of treatment, real or sham, as well as one week or one month later. No further significant changes were seen on EEG activity.

In two other comparable studies (He et al., 2018; Liu et al., 2018), HF-rTMS of left M1 neither produced significant clinical improvement in patients with DOC at overall group level, but individual patients may have benefited from the procedure. In a sham-controlled, crossover study of 6

patients with MCS or UWS, He et al. (2018) showed that a 5-day protocol of 20Hz rTMS delivered over the left M1 produced a behavioral and neurophysiological improvement in only one patient after the real rTMS stimulation, measured on the CRS-R and EEG reactivity, respectively. The benefit was still present one week after the last rTMS session. In another sham-controlled, crossover study of 7 patients with MCS or UWS, Liu et al. (2018) showed that the same 5-day protocol of 20Hz rTMS delivered over the left M1 also improved only one patient clinically (on the CRS-R score) after the real rTMS stimulation. The clinical benefit in consciousness was associated with an enhanced functional connectivity in a frontotemporoparietal network.

The other assessed target was the DLPFC. In a pilot study, Naro et al. (2015) found that a single session of 10Hz rTMS (10 trains of 10 sec with 60-sec intertrain, for a total of 1000 pulses) delivered over the right DLPFC (F4 site) did not produce any significant clinical change (measured on the CRS-R score) at group level. However, this session may have improved conscious motor behavior in 3/10 post-anoxic UWS patients. This finding was associated with an enhanced cortical excitability (measured by single- and paired-pulse TMS methods) and a partially restored pattern of cortico-cortical interactions (assessed by dual-coil TMS).

Another research group assessed the value of HF-rTMS, but delivered over the left DLPFC in studies with an open-label, not sham-controlled design (Xia et al., 2017a,b). In a series of 16 patients (5 MCS and 11 UWS) who underwent 20 consecutive days of stimulation, the impact of the treatment was clinically significant at overall group level on the CRS-R score measured 10 days after the last rTMS session compared to baseline (Xia et al., 2017a). The clinical benefit was significant from the half of the course of the stimulation protocol in the 5 MCS patients who all improved (although remaining in MCS condition), but not in the UWS patients, of whom only 4 benefited from the procedure, three of them switching to a MCS condition. On a CGI-I scale rated by the caregivers, 10 patients improved (minimally to considerably), 6 patients remained stable, and none worsened (Xia et al., 2017a). In a satellite work, the same authors provided some EEG correlates of the effect of HF-rTMS of the left DLPFC in patients with DOC, i.e. an EEG signal power reduced in the low-frequency bands and increased in the high-frequency bands (Xia et al., 2017b).

Finally, one study was published in which an iTBS protocol (600 pulses/session delivered at 80% of AMT) was delivered over the left DLPFC for 5 consecutive days in a series of 8 patients with MCS or UWS (Wu et al., 2018). At the end of the 5-day iTBS protocol, the CRS-R scores increased in all 4 patients with MCS and in 3 out of 4 patients with UWS, with a level of consciousness rising to emergence and MCS, respectively. The clinical benefit was only at the limit of statistical significance one week after the last rTMS session. On EEG assessment, rTMS was found to increase power in the alpha band, especially in a frontoparietal network. However, this study was not sham-controlled.

In conclusion, although a clinical benefit on the level of consciousness has been reported after HF-rTMS of the left M1 in some individuals or after HF-rTMS or iTBS of the left DLPFC at group level (but in open-label studies), all published series are characterized by a too small sample size to propose any level of evidence or to make any recommendation for the use of rTMS in patients with

chronic DOC. Therefore, the therapeutic efficacy of non-invasive brain stimulation procedures remains matter of debate in this clinical condition and in any case, future studies could benefit from various neurophysiological techniques, such as evoked potentials, event related potentials, or TMS-EEG co-registration to objectively evaluate the impact of the intervention (Ragazzoni et al. 2017; André-Obadia et al., 2018b).

8. Mild cognitive impairment and Alzheimer's disease

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND mild cognitive impairment OR Alzheimer's disease) identified 86 papers, including 6 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions in the context of mild cognitive impairment (MCI) (Drumond Marra et al. 2015) or Alzheimer's disease (AD) (Rutherford et al., 2015; Wu et al., 2015; Lee et al. 2016; Zhao et al. 2017; Koch et al., 2018).

8.1. HF-rTMS of the left DLPFC

In sham-controlled study of Class II including 34 patients with MCI diagnosed for at least one year, Drumond Marra et al. (2015) applied 10Hz rTMS at 110% of RMT over the left DLPFC defined as located 5cm anterior to the hand motor hot spot. It is worth mentioning that this distance is known to be too short to correctly define the anatomical location of the DLPFC (Herwig et al., 2001; Fitzgerald et al., 2009b; Ahdab et al., 2010). The rTMS protocol consisted in 10 sessions over two weeks with 2000 pulses/session, underwent by 15 patients in real condition and 19 patients in sham condition. No adjunctive cognitive rehab was carried out during the trial. The primary objective was the improvement of everyday and episodic memory, assessed by the Rivermead Behavioural Memory Test (RBMT). At the end of the rTMS protocol, up to one month after the last session, the RBMT score improved (i.e., increased) in the real stimulation group more than in the sham group, while secondary variables, such as logical, auditory-verbal, and working memory functions, cognitive functions, assessed by the Mini-Mental State Examination (MMSE), executive functions, assessed by the Trail Making Test (TMT), or verbal fluency did not change after real rTMS.

A second sham-controlled study of Class III with a crossover design (Padala et al., 2018) included only 8 MCI patients who received 10Hz-rTMS at 120% of RMT over the left DLPFC defined as located 5.5cm anterior to the hand motor hot spot (10 sessions over two weeks with 3000 pulses/session). The primary objective was the improvement of apathy, assessed on the Apathy Evaluation Scale-Clinician version (AES-C). At the end of the rTMS protocol, the AES-C score improved (i.e., decreased) in the real stimulation group more than in the sham group and the difference was considered clinically meaningful. In addition, several changes in secondary variables also favored the real rTMS condition, with a benefit observed on cognitive and executive functions, assessed on the MMSE and TMT, respectively.

These results remain insufficient to propose any statement regarding a given level of evidence for HF-rTMS of the left DLPFC in patients with MCI. A similar protocol was also proposed in patients with AD.

In a sham-controlled study of Class II, Wu et al. (2015) applied 20Hz-rTMS at 80% of RMT over the left DLFPC (probably defined according to the 5cm-rule) for a total of 20 sessions (5 sessions/week for 4 consecutive weeks) in 52 patients with AD (26 real, 26 sham). The rTMS protocol (real or sham) was performed concomitantly with the administration of low doses of risperidone, an atypical antipsychotic. The primary objective was the improvement of behavior, assessed on the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). At the end of the rTMS protocol, the BEHAVE-AD score improved (i.e., decreased) in the real stimulation group more than in the sham group, especially on 5 subscale scores, i.e., activity disturbances, diurnal rhythm disturbances, aggressiveness, affective disturbances, and anxiety or fear. In terms of clinically meaningful individual responses (at least 30% reduction of the BEHAVE-AD score), the real rTMS condition provided 73% of responders (19/26 patients), whereas the sham rTMS provided 42% of responders (11/26 patients). Cognitive functions, assessed on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), also improved with a significant decrease of the ADAS-Cog total score after real rTMS.

In a sham-controlled study of Class III with a crossover design (Rutherford et al., 2015), 10 patients with AD received 20Hz-rTMS at 90-100% of RMT over both the right and left DLPFC defined by using measurements from anatomical landmarks (DaSilva et al., 2011). The protocol consisted of 13 sessions over four weeks with 2000 pulses to each of the right and left hemispheres/session. The primary objective was the improvement of cognitive functions, assessed on the Montreal Cognitive Assessment (MoCA) and the ADAS-Cog. No significant difference between the real and sham conditions was observed on these scales at the end of the 4-week rTMS protocol, but the MoCA score improved (i.e., increased) during the rTMS protocol at weeks 2-3, only in the real stimulation condition. Clinical benefit was prolonged by 2 additional weeks of treatment, however performed using an open-label design, and was more marked in patients at an early stage of AD. This latter result is in line with previous studies showing prodromal alteration of cortical excitability early in the course of the disease (Nardone et al., 2013, 2014). In this regard, the degree of grey matter atrophy in AD-related brain regions may contribute to variability of rTMS-induced cognitive after-effects, at least if delivered to the superior temporal gyrus (STG) (Anderkova et al., 2015). Therefore, future studies should focus particularly on early stage of AD, which can be better identified using a combination of various biomarkers (McKhann et al., 2011).

As for patients with MCI, the results reported with HF-rTMS of the left DLPFC remains insufficient to make any recommendation regarding a therapeutic application of such a procedure for patients with AD. Finally, regarding types of dementia other than AD, only preliminary data can be mentioned, i.e. two reports of the beneficial effects on cognitive performance or linguistic skills of bilateral DLPFC HF-rTMS using a figure-of-8 coil in an open-label study of 7 patients with

frontotemporal dementia and 2 patients with primary progressive aphasia (Antczak et al., 2018) or using a H-coil in one patient with primary progressive aphasia (Trebbastoni et al., 2013).

8.2. HF-rTMS of the precuneus

A more recent study (Koch et al., 2018) assessed the value of an rTMS protocol aimed at stimulating the precuneus, i.e. the medial aspect of the superior parietal lobule, involved in episodic memory, visuospatial processing, and various aspects of consciousness, probably through its engagement in large-scale neural networks, such as the default mode network (DMN) and its strong connection with hippocampus. In healthy subjects, a single session of iTBS of the left superior parietal lobule can significantly increase resting-state connectivity in the dorsal attention network and lead to positive cognitive after-effects (Anderkova et al., 2018), while 5 sessions of HF-rTMS targeting another DMN node (the left inferior parietal lobule) can significantly improve a memory association task (Wang et al., 2014c).

In the above mentioned sham-controlled study of Class II with a crossover design (Koch et al., 2018), 14 patients at an early stage of AD received 20Hz-rTMS at 100% of RMT over the left precuneus region defined by image-guided navigation (10 sessions over two weeks with 1600 pulses/session). The primary objective was the improvement of cogntive functions, assessed by the Alzheimer Disease Cooperative Study Preclinical Alzheimer Cognitive Composite (ADCS-PACC) test battery. At the end of the 2-week rTMS protocol, a selective improvement in episodic memory but not in other cognitive domains was found in the real condition, as compared to sham stimulation. A modification of functional connections between the precuneus and medial frontal areas within the DMN, as well as an enhancement of beta-rhythm activity in the precuneus, were revealed by a combined TMS-EEG approach. This original targeting strategy, based on the known alteration of functional connectivity within the DMN and other cognitive networks at very early stages of AD (Palmqvist et al., 2017) remains to be further studied by other research groups.

8.3. Multisite HF-rTMS

In the domain of AD, which includes multiple aspects of cognitive dysfunction and problems with memory, language, temporospatial orientation, motivation, self-care, or behavior, multisite rTMS strategies may theoretically provide more benefits than single-site rTMS strategies. Conversely, one study showed that a simple 5Hz-rTMS protocol targeting only the left DLPFC could produce similar clinical improvement in AD patients compared to a multisite rTMS protocol stimulating six cortical regions of interest (Alcalá-Lozano et al., 2018). In this study, 19 AD patients were randomized to receive one of these protocols (10 patients for single-site rTMS of the left DLPFC vs. 9 patients for multisite rTMS) over 3 weeks. The clinical improvement (measured on the ADAS-Cog and MMSE scores) was similar in both groups and maintained at least for 4 weeks after the intervention. These

authors explained their result by the large-scale structural and functional connectivity of the left DLFPC with a variety of brain structures potentially involved in the pathophysiological progression of AD (Alcalá-Lozano and Garza-Villarreal, 2018).

However, the multisite rTMS procedure performed by Alcalá-Lozano et al. (2018) did not use neuronavigation targeting and was not combined with cognitive training. Indeed, multisite rTMS protocols gain in evidence in the treatment of AD, especially when combined navigated rTMS with cognitive training. A specific approach, usually called rTMS-COG therapy, consists in delivering rTMS trains over different cortical targets for priming cognitive training tasks during a sequential program of treatment. This type of therapeutic protocol has been formalized and structured in the NeuroAD System (Bentwich et al., 2011).

In a sham-controlled study of Class II (Lee et al. 2016), 26 patients with probable AD (18 real, 8 sham) received 5 sessions of rTMS-COG therapy per week for 6 consecutive weeks. Each session consisted of a combination of active cognitive training and rTMS delivered over three different cortical regions targeted using an image-guided navigation system. Thus, on alternate days, either Broca's area, Wernicke's area, and the right DLPFC (days 1, 3, and 5) or the left dlPFC and both parietal somatosensory association cortices (PSAC) (days 2 and 4) are stimulated during the daily session. For each stimulated cortical target, the protocol consisted of a series of 20 trains of 10Hz-rTMS of 2 seconds (20 pulses/train delivered at 90-110% of RMT with a figure-of-8 coil under neuronavigation) followed by 40 seconds of specific cognitive tasks performed between each 2-sec train of 10Hz-rTMS. The patients performed cognitive tasks displayed on a touch screen in front of them, with a level of difficulty adjusted to their cognitive performance assessed on their results in prior sessions. The cognitive tasks differed according to the stimulated cortical region, including syntax and grammar tasks for Broca's area, comprehension of lexical meaning and categorization tasks for Wernicke's area, naming of actions and objects, word recall and spatial memory tasks for both dlPFC areas, and spatial attention tasks for shapes and letters for both PSAC areas. Thus, for each cortical target, the protocol resulted in 400 rTMS pulses priming cognitive training for about 15 min and since each session included 3 targets, the whole session lasted less than one hour with a total of 1200 rTMS pulses delivered per day over the brain. In the study of Lee et al. (2016), no time x group interaction emerged at the end of the 6-week treatment and after 6-week follow-up regarding the ADAS-Cog score (primary endpoint), but the patients who received real rTMS improved significantly more than those who were in the sham group in the domains of memory and language, especially patients with mild AD. The improvement (decrease) in the ADS-Cog score provided by real rTMS-COG therapy in patients with mild AD (-5.5) was twice as much as usually observed with cholinesterase inhibitors in comparable AD patients over 6 months (-2.7).

Before 2014, another sham-controlled study, but including less than 10 patients in the real rTMS group (Class III), had been published using the same procedure (Rabey et al., 2013). In this study, 15 AD patients were randomized to receive real (7 patients) or sham (8 patients) rTMS-COG therapy. The improvement (decrease) in the ADS-Cog score was significantly better in the real

condition group (-3.8) than in the sham group (-0.5) at the end of the 6-week protocol. A maintenance treatment was performed with 2 sessions of one hour per week for 3 months. At the end of follow-up (4.5 months after treatment initiation), the clinical benefit, assessed by the ADAS-Cog score, was still better in the real condition group (-3.5) than in the sham group (+0.4). The Clinical Global Impression of Change (CGIC) was in favor of a mild improvement in the real condition group (3.6 on the 7-point Likert scale) and mild worsening in the sham group (4.3).

Still using the same approach, several open-label studies have been published (Class IV). For example, the same researchers as for the aforementioned sham-controlled randomized study published their experience in 30 patients with mild-to-moderate AD (Rabey and Dobronevsky, 2016). At the end of the 6-week treatment, patients improved regarding both ADAS-Cog (-2.4) and MMSE (+1.7) scores. In 5 patients who were reevaluated at 10 months from treatment initiation and in whom the ADAS-Cog score was returned to baseline, a second rTMS-Cog protocol treatment allowed the same benefit to be obtained as after the first treatment (-2.4).

Another group reported the results obtained by performing real rTMS-COG therapy for 5 consecutive weeks in 10 patients with AD (Nguyen et al., 2017). In addition to the combination of rTMS and cognitive training above described, a short series of 5 trains of 20 pulses at 10Hz (100 pulses/session) was delivered everyday over the left or right DLPFC combined with a ‘‘word recall’’ training, for promoting episodic memory recovery (Rossi et al., 2001). The primary endpoint of the study was improvement of the ADAS-Cog score, which was reached at the end of intervention (-2.9), but not at 6-month follow-up, with the exception of 5 “best responders” in whom the clinical benefit was maintained (ADAS-Cog score: -2.5 compared to baseline). Then, the 5 “poor responders” of this study received two additional weeks of rTMS-COG therapy between 6 and 12 months after the initial treatment and these additional sessions clearly reduced the progression slope of cognitive decline in these patients (Nguyen et al., 2018). Apathy and dependence scores, as secondary endpoints, also improved after rTMS-COG therapy in this work. Conversely, no adverse events occurred, including no seizure, while these patients are known to have a low epileptogenic threshold.

Zhao et al. (2017) also applied multisite rTMS therapy combined with cognitive tasks for 6 weeks (1 session/day and 5 days/week for total of 30 sessions) in 30 patients diagnosed with mild or moderate AD (17 real, 13 sham). However, the protocol was frankly different from that of the NeuroAD System with a lot of ambiguous statements. The authors report a series of 20 trains of 20Hz-rTMS of 10 seconds (200 pulses/train delivered at unknown intensity with unknown coil type) followed by only 20 to 40 seconds of specific cognitive tasks performed between rTMS trains, while intertrain interval was reported to last only 20 seconds. In this article, the cognitive tasks are not described and more importantly, the stimulated areas are reported to include only four parietal and temporal regions, defined as P3/P4 and T5/T6 according to the 10-20 EEG System, while the authors considered "three brain areas" to be targeted and stimulated separately in each session. No significant time x group interaction was observed in the whole series of patients at the end of the 6-week treatment and at 6-week follow-up for any of the neuropsychological tests performed in this study.

However, in the 20 patients with mild AD, defined by a MMSE score ≥21, clinical improvement was significantly better at 6-week follow-up in the real condition group (12 patients) than in the sham group (8 patients), regarding ADAS-Cog (-6.4), MMSE (+4.1), MoCA, and World Health Organization University of California-Los Angeles Auditory Verbal Learning Test (WHO-UCLA AVLT) scores.

In conclusion, taking into account at least one Class II and one Class III study, a Level C of Evidence is reached to consider that multisite rTMS-COG is possibly effective to improve apathy, cognitive function, memory, and language in AD patients, especially at a mild/early stage of the disease. Clinical use of this type of treatment requires additional observational studies to confirm that the long-term effect of multisite rTMS-COG may actually exceed that of rTMS over a given region of interest. In addition, various imaging and/or neurophysiological techniques should be employed to provide an objective readout and improve our understanding of the neural basis of the effects induced by multisite rTMS (Sale et al., 2015; Bergmann et al., 2016).

9. Tinnitus

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND tinnitus) identified 59 papers, including 11 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions (Langguth et al., 2014; Yilmaz et al., 2014; Bilici et al., 2015; Folmer et al., 2015; Schecklmann et al., 2016; Wang et al. 2016b; Cacace et al., 2017; James et al. 2017; Landgrebe et al., 2017a; Sahlsten et al., 2017; Formánek et al., 2018).

9.1. LF-rTMS of the auditory cortex

The usual rTMS procedure to treat chronic tinnitus is to apply LF-rTMS over the auditory temporal cortex of the left hemisphere or contralateral to the most affected ear (Table 10). The rationale of this approach is to reduce a possible hyperactivity of the auditory cortex. Indeed, in one sham-controlled crossover study (Cacace et al., 2017), 25 patients with chronic tinnitus received 5 daily sessions of real and sham 1Hz-rTMS (separated by a wash-out period of 2 to 5 weeks) delivered on the left temporal lobe (halfway between T3 and T5 site of the 10-20 EEG System). The clinical efficacy of real LF-rTMS on tinnitus loudness (measured psychoacoustically) and self-perceived changes in the Tinnitus Handicap Questionnaire (THQ) (including the Social-Emotional-Behavioral subscale), was highly correlated with a down-regulation of excitatory glutamate contents in the stimulated area (left auditory cortex), assessed by single voxel proton magnetic resonance spectroscopy (1H-MRS).

Two large randomized sham-controlled studies (Folmer et al., 2015; Landgrebe et al., 2017a) investigated the effects of 10 days of 1Hz-rTMS delivered over the left temporal lobe, with the figure-of-8 coil centered on a point located 1.5cm posterior to the midline of the T3-C3 line, as initially

described by Langguth et al. (2006). One of these studies was positive (Folmer et al., 2015), but only half of the patients were stimulated on the above described left hemisphere target, whereas the other half were stimulated on the homologous temporal target of the right hemisphere. In this study, 64 patients were equally randomized in the real and sham stimulation groups to receive 2,000 pulses per session on 10 consecutive workdays. Results were analyzed according to the percentage of responders on the Tinnitus Functional Index (TFI) at the end of the treatment, which was higher in the real stimulation group (56%) than in the sham group (22%). In contrast, no significant difference between real and sham rTMS was found in the study of Landgrebe et al. (2017a), including 146 patients with chronic tinnitus, all stimulated over the left auditory cortex. In this study, no significant difference in the change in the sum score of the Tinnitus Questionnaire compared to baseline was found between a group of 71 patients who received the real treatment and 75 patients who were treated by sham stimulation.

As discussed in the literature (Folmer, 2017; Landgrebe et al., 2017b), potential explanations for this discrepancy may be related to differences in: (i) patients' sample characteristics (e.g., regarding age, disease duration, or hearing loss level); (ii) laterality of the stimulation side (left hemisphere only in Landgrebe et al. (2017a) vs. either right or left temporal cortex in Folmer et al. (2015)); (iii) coil orientation (known to be crucial in other rTMS applications, such as in pain domain (André-Obadia et al., 2008; Lefaucheur et al., 2010)); (iv) magnetic stimulator type (efficiency and direction of the current induced in the cortex differ according to manufacturers (Kammer et al., 2001; Thielscher and Kammer, 2004)); (v) outcome measures (TQ sum score in Landgrebe et al. (2017a) vs. percentage of responders on TFI in Folmer et al. (2015)).

A large open-label study with 289 participants aimed at identifying the clinical predictors of LF-rTMS delivered over the left temporoparietal cortex (TPC) (10 sessions over 2 weeks, 1000 pulses/session) for chronic tinnitus treatment (Wang et al., 2016a). Significant tinnitus suppression (reduced loudness on VAS score) correlated with normal hearing level, absence of sleep disturbance, and shorter tinnitus duration (less than one year). Another open-label study even assessed the effects of rTMS in a series of 34 patients with sudden hearing loss and acute tinnitus (Zhang and Ma, 2015). The protocol consisted of 20 sessions of 1Hz-rTMS delivered over 4 weeks (1200 pulses/session) to the temporoparietal junction (TPJ) ipsilateral to the symptomatic ear were performed. Both hearing function and tinnitus perception improved after rTMS, as compared to patients who did not receive rTMS treatment. In this study, rTMS was performed in addition to standard corticosteroid and hyperbaric oxygen therapy. One further sham-controlled trial with limited specifications of methods showed reductions in Tinnitus Handicap Inventory (THI), tinnitus loudness and tinnitus subjective scores for the real stimulation condition (30 patients) but not the sham group (30 patients) (Yilmaz et al., 2014).

Two studies aimed at determining the most efficacious stimulation protocol using LF-rTMS over the left auditory cortex. First, Lo et al. (2014) compared the effect of 5 sessions based on 1000 vs. 2000 pulses/session in 28 tinnitus patients equally randomized. They did not find any difference

related to the number of pulses/session in the reduction of tinnitus assessed on the Tinnitus Handicap Inventory (THI) rating scale, up to 4 weeks after the intervention. Second, Lehner et al. (2015) addressed the issue of maintenance therapy in an open-label study of 55 patients who underwent 2 rTMS protocols over 10 days separated by several months. The more patients worsened between both treatment courses, the more they improved after the second treatment, suggesting that the repeated application of rTMS protocols may be useful in the therapeutic management of patients with tinnitus, regardless of the response to the first treatment course. Long-term efficacy was also assessed in one open-label study of a small sample of 8 patients (Labar et al., 2016). The rTMS protocol consisted of weekly perfomed 1Hz-rTMS sessions applied to the TPJ over 5 weeks and then monthly sessions for the next five months. Significant tinnitus reduction was observed in 4 of 8 patients at week 5, but only in 1 patient at the end of follow-up (7 months).

One important issue is to determine the optimal target location for enhancing the efficacy of LF-rTMS of the auditory cortex. One research group compared the effects of 1 Hz-rTMS (600 pulses per daily session for 5 to 10 days) delivered over the TPC, either contralaterally or ipsilaterally to the symptomatic ear, in 40 to 61 patients with unilateral tinnitus (Kim et al., 2014b,c). These authors found a similar benefit in the THI and VAS scores for tinnitus loudness, awareness, and annoyance for the two approaches both immediately after treatment (Kim et al., 2014b) and at follow-up visits one and six months later (Kim et al., 2014c). Thus, the laterality of LF-rTMS application could be not a decisive factor in relieving tinnitus, as also suggested by the results reported in the study of Folmer et al. (2015).

Another point is to precisely define the target location within the auditory cortex. One randomized study (Noh et al., 2017b) showed that tinnitus was similarly improved by 1Hz-rTMS delivered over the left auditory cortex when anatomically targeted with an image-guided navigation system or defined as posterior to the T3-C3 line, i.e. based on the 10-20 EEG System, according to Langguth et al. (2006). Another randomized study came up with the same conclusion that navigated rTMS was not superior over non-navigated rTMS (Sahlsten et al., 2019). In this latter study, chronic tinnitus improved significantly in both rTMS groups, and treatment response was even better in the non-navigated group regarding tinnitus intensity reduction.

The same research group attempted to optimize rTMS targeting, based on the known tonotopy of the auditory cortex in the superior temporal gyrus (STG), where higher frequencies are represented posteriorly and lower frequencies anteriorly (Sahlsten et al., 2015, 2017). Using an MRI-guided neuronavigation system that visualizes electric field (in V/m) induced by TMS pulses into the brain, these authors determined the location of rTMS target within the left STG roughly according to the tonotopic representation of tinnitus pitch in each individual patient. After an open-label pilot study based on 13 patients with very severe tinnitus symptoms (Sahlsten et al., 2015), a series of 39 tinnitus patients was investigated in a sham-controlled study based on 10 daily rTMS sessions over 2 weeks with a 6-month follow-up (Sahlsten et al., 2017). The session protocol was extraordinarily long, consisting of 4000 pulses delivered at 1Hz over 1 hour. This latter study revealed significant beneficial

effects of rTMS on the THI and VAS scores for tinnitus intensity, distress, and annoyance but no differences between real and sham stimulation groups beyond one month after stimulation period, possibly due to a large placebo effect and wide inter-individual variability.

In contrast, a large, non-focal stimulation was applied in one sham-controlled study for 10 days using a circular coil to deliver 1Hz-rTMS over the left temporal lobe (Billici et al., 2015). This study showed an improvement on the THI score at 1- and 6-month follow-up after real treatment initiation, but not after the sham procedure. No effect of LF-rTMS was observed on the Tinnitus Severity Index (TSI) score, while both THI and TSI scores frankly improved at 6-month follow-up when rTMS was delivered at 10Hz (600 pulses/session), which is an unusual finding.

Finally, one sham-controlled study (Wang et al., 2015) compared the respective efficacy of neuronavigation-guided LF-rTMS protocols delivered over the left TPC and a region defined by high-density EEG source analysis (10 sessions over 2 weeks, 1000 pulses/session). This study enrolled 21 patients with tonal tinnitus and no hearing loss (7 patients in each experimental group: real rTMS of the left TPC or EEG-defined target, or sham rTMS). Significant reduction of tinnitus severity and loudness (measured on the THI and a VAS) was observed at the end of the 2-week rTMS protocol, but significantly more marked in the group of patients stimulated over the target defined by EEG source analysis. This target site was mostly located in the right orbitofrontal cortex (BA 11). Another study further showed that the grey matter volume measured in the orbitofrontal cortex at baseline correlated with clinical improvement observed after LF-rTMS delivered for 10 days over the left temporal cortex in a series of 77 tinnitus patients (Lehner et al., 2014). It was also found that a single session of LF-rTMS over the left temporal cortex (posterior to T3-C3 line, according to Langguth et al. (2006)) was able to modulate resting-state EEG oscillatory activity in frontal cortical regions, increasing the high-to-low frequency power ratio (Schecklmann et al., 2015). The same group, in a large series of 116 patients with chronic tinnitus, showed that the improvement of tinnitus (assessed on the TQ score) induced by a 10-day protocol of LF-rTMS applied to the left auditory cortex was associated with a significant reduction in short-interval intra-cortical inhibition (SICI), reflecting a modulation of GABAergic transmission in the left motor frontal area (Schecklmann et al., 2014b). Thus, LF-rTMS delivered to the auditory cortex is surely able to modulate a large-scale brain network.

- Insert Table 10 -

Two studies assessed methodological variants of the inhibitory stimulation of the left auditory cortex. First, Thabit et al. (2015) studied combination of LF-rTMS of the left TPC and a "peripheral" stimulation, consisting of direct cochlear low-level laser therapy (LLLT) associated with laser acupuncture applied to the affected ear(s) in a 10-day protocol. These authors showed in a series of 30 patients with chronic tinnitus that only this combination of treatment, but not LF-rTMS or LLLT applied alone, was able to reduce tinnitus severity, assessed on THI and a VAS, up to 4 weeks after the end of the treatment.

Second, in a sham-controlled trial, Schecklmann et al. (2016) assessed the value of a cTBS protocol delivered over the left auditory cortex. These authors did not find superior effects of 10 sessions of real cTBS versus sham stimulation in a series of 23 patients (12 real, 11 sham), despite significant changes in sound-evoked brain oxygenation at the site of stimulation measured by near-infrared spectroscopy (NIRS) (Schecklmann et al., 2014a).

Finally, one sham-controlled crossover study aimed at identifying neuronal markers as predictors for treatment outcome of rTMS (4 daily sessions over one week, 1800 pulses/session) delivered to the STG in 12 patients with tinnitus (James et al., 2017). In this study, real rTMS was delivered at 1Hz or 10Hz over the hemisphere opposite to tinnitus or the left hemisphere in case of symmetrical bilateral tinnitus. The greatest clinical effect of rTMS was observed on tinnitus awareness (-16% compared to baseline, assessed on a VAS) after both 1Hz- and 10Hz-rTMS, while tinnitus annoyance and loudness were more slightly reduced (-7/11%, also assessed on a VAS), but only significantly after 1Hz-rTMS. In addition, patients underwent fMRI while performing an attentional conflict task, the Multi-Source Interference Task (MSIT), before and after rTMS treatment. A greater recruitment of bilateral prefrontal and parietal regions by MSIT at baseline corresponded with poorer treatment response, while activity changes in the left DLPFC explained the greatest reduction in tinnitus awareness following 1Hz stimulation. Thus, a predominant effect of LF-rTMS of STG on tinnitus awareness may relate to change in attentional processing due to the connections between the STG and regions of the prefrontal cortex that mediate attention. This study paved the way for considering the left DLPFC as a potential rTMS target to treat tinnitus.

9.3. HF-rTMS of the left DLPFC

The therapeutic value of HF-rTMS of the left DLPFC as a single-site protocol in chronic tinnitus was not supported by one recent study. Noh et al. (2017a) compared HF-rTMS of the left DLPFC performed alone vs. combined with LF-rTMS delivered to the left auditory cortex in a protocol consisting of 3000 pulses delivered per session for 4 days in both conditions. The improvement in THI score was significant for the combined procedure but not for HF-rTMS of the left DLPFC performed alone. However, this study enrolled only 8 and 9 patients in each condition and was not sham-controlled.

The combination of HF-rTMS of the left DLPFC and LF-rTMS of the left auditory cortex was also investigated by several studies before 2014 in the treatment of chronic tinnitus (Kleinjung et al., 2008; Kreuzer et al., 2011; Lehner et al., 2013; Park et al., 2013b). In a series of 32 patients, Kleinjung et al. (2008) first showed that a 10-day protocol of LF-rTMS of the left TPC (1000 pulses/session at 1Hz and 110% of RMT) preceded by HF-rTMS of the left DLPFC (1000 pulses/session at 20Hz and 110% of RMT) could produce the same reduction of tinnitus severity (assessed on TQ score) as LF-rTMS of the left TPC performed alone (2000 pulses/session at 1Hz and 110% of RMT), but with a significantly more prolonged effect at 3-month follow-up. A similar result was obtained in a series of

56 patients, replacing 20Hz-rTMS of the left DLPFC by 1Hz-rTMS of the right DLPFC (Kreuzer et al., 2011). Actually, an open-label study of 7 patients with chronic tinnitus (De Ridder et al., 2013) previously reported that a 10-day protocol of LF-rTMS delivered at 1Hz over the right DFLPC could significantly reduce tinnitus loudness (assessed on a VAS).

In another series of 45 patients, the same research group replaced LF-rTMS of the left TPC by LF-rTMS of both the right and left TPC (Lehner et al., 2013). Such a triple-site rTMS protocol produced similar improvement as single-site LF-rTMS of the left temporal cortex, but, again, with more prolonged significance (clinical benefit being still present at 3-month follow-up only in the multisite group). This study was replicated by the same research group in 49 patients (Lehner et al., 2016). The conclusion was that "no significant superiority of the multisite protocol was observed", but no firm conclusion could be drawn since these studies were not sham-controlled

Only two studies assessed multisite rTMS strategy in tinnitus, including a sham group and more than 10 patients in the real stimulation group (Langguth et al., 2014; Formánek et al., 2018) (Table 11).

First, Langguth et al. (2014) showed that a 10-day rTMS protocol combining 20Hz-rTMS over the left DLPFC, followed by 1Hz-rTMS over the left auditory cortex was able to reduce tinnitus severity (assessed on TQ score) in a group of 46 patients receiving the real stimulation. Overall, the average reduction of the TQ score was not superior in this group than in the groups of patients treated by real or sham LF-rTMS delivered to the left auditory cortex alone. However, the real rTMS protocols provided a higher percentage of individual responders compared to the sham condition.

In a second sham-controlled study, the combined HF-rTMS/LF-rTMS protocol was not found to provide any clinical benefit (Formánek et al., 2018). In this series of 32 patients with chronic tinnitus (20 real, 12 sham), the left DLFPC was stimulated at 25Hz combined with 1Hz-rTMS of the auditory cortex of both hemispheres for 5 consecutive days. No significant effect of rTMS was found at 1- or 6-month follow-up on the Tinnitus Reaction Questionnaire (TRQ) or THQ scores, as well as on the Beck Depression Inventory (BDI). Only a statistical but clinically irrelevant effect on the THI score was observed. This study questioned the value of multisite rTMS protocols in tinnitus, but this protocol may have been less effective because of both auditory cortices were stimulated. Indeed, two previous studies showed no significant treatment effect of real versus sham rTMS following bilateral temporal cortex stimulation (Plewnia et al., 2012; Hoekstra et al., 2013).

The other studies compared two real stimulation protocols, without sham condition. Following a first pilot study (Park et al., 2013b), Park et al. (2015) compared two protocols combining LF-rTMS of the left auditory cortex and HF-rTMS of the left DLPFC with 2000 pulses/session for 3 days vs. 3000 pulses/session for 4 days. Only the latter protocol provided significant tinnitus relief assessed on THI and VAS scores. However, this study only enrolled 6 and 8 patients in each condition.

Kreuzer et al. (2015a) compared the combination of 10Hz-rTMS of the left DLPFC followed by 1Hz-rTMS of the left TPJ to another multisite protocol, combining mediofrontal HF-rTMS over the anterior cingulate cortex (ACC) using a double-cone coil followed by LF-rTMS of the left TPJ with a

figure-of-8 coil. In both protocols, 2000 pulses were delivered to each target per session. In this study conducted in 40 patients with chronic tinnitus, responder rates (assessed on the TQ score) did not differ between both groups.

The combination of rTMS with relaxation techniques was investigated in one pilot study (Kreuzer et al., 2016). Compared to historical control groups having received the same rTMS protocol (active control) and sham treatment (placebo) without relaxation techniques, the 38 patients who listened to relaxation audios during stimulation (10 sessions of rTMS applied to the left DLPFC and TPC targets) tended to have a better outcome (reduction in TQ score) and a significant correlation between deepness of active relaxation and tinnitus improvement

Since chronic tinnitus is often accompanied by comorbid muscular tension, Vielsmeier et al. (2018) studied the value of adding a repetitive peripheral magnetic stimulation (rPMS) of the neck and back muscles before and after rTMS sessions combining HF-rTMS of the left DLPFC followed by LF-rTMS of the left TPC. In a series of 41 patients treated by 10 sessions of such a protocol, no improvement was found in either tinnitus severity (measured on the TQ score) or neck pain.

- Insert Table 11 -

Taken together there has been a substantial amount of new data on different aspects of rTMS application for the treatment of tinnitus in the 2014-2018 period. However, these results still do not allow firm conclusions about the efficacy of rTMS in this clinical condition. Comprehensive analyses of the literature up to 2014 (Soleimani et al., 2016) and since 2014 (Londero et al., 2018) showed a medium-to-large effect size in favor of rTMS therapy, but with a high variability of study design and inter-individual outcomes. However, a definitive conclusion about the efficacy of rTMS for the treatment of tinnitus is still not possible. Some of the available clinical studies are positive, others are negative. Even the available Class I studies based on large samples revealed contradictory results. Folmer et al. (2015, 2017) found a superiority of real versus sham rTMS, whereas Landgrebe et al. (2017a,b) could not detect a significant difference between real and sham rTMS. Thus, systematic meta-analyses are needed for drawing a clearer picture of the effectiveness of rTMS in chronic tinnitus.

To date, there is no robust evidence to prefer a dual- or triple-site rTMS procedure (LF-rTMS over the auditoy cortex of one or both hemispheres combned with HF-rTMS of the left DLPFC) rather than a single-site LF-rTMS procedure over the auditory cortex of the left hemisphere or contralateral to the most affected ear. Therefore the general recommendation remains of Level C ("possible effect of repeated sessions of LF-rTMS of the TPC (on the left hemisphere or contralateral to the affected ear) in tinnitus"). Many questions remain concerning the use of this technique in everyday practice, such as what could be the optimal treatment target(s) and protocol and what could be the role of individual susceptibility to auditory cortex stimulation in influencing outcome or side effects, e.g., related to genetic factors (BDNF genotype, Yang et al., 2016) or the presence of hyperacusis or hearing loss (Lefaucheur et al., 2012b; Tringali et al., 2013).

Therefore, one of the most promising approaches could be to perform a stimulation protocol tailored to the individual patient. A recent pilot study explored this concept (Kreuzer et al., 2017), by delivering rTMS at various frequencies over the left and right DLPFC or TPC targets in a single test session to select the type of protocol subsequently applied for several days. Among 25 tested patients, immediate effect on tinnitus perception was detected in 12 patients who received 9 further treatment sessions with a combined rTMS protocol over the most effective DLPFC and TPC targets found in the test sessions. In the remaining 13 patients, a standard combined protocol (20Hz-rTMS over left DLPFC followed by 1Hz-rTMS over the left TPC) was performed. The responders of the test sessions who received the individualized protocol had a higher benefit than the patients receiving the standard protocol. This result provides a basis for a "tailored" application of rTMS in tinnitus, since usual "standardized" rTMS protocols have shown significant but only moderate efficacy with high interindividual variability in treatment response.

10. Depression

Available therapeutic strategies for depression include medication optimization (by combining antidepressants, add-on therapy or changing their dosage), psychotherapeutic care, augmentation (with lithium, thyroid hormone, and atypical antipsychotics), electroconvulsive therapy (ECT), and rTMS. It is estimated that treatment resistance occurs in 50% of depressed patients who are receiving proper antidepressant medication and over 10% of these patients remain resistant to various psychopharmacological interventions (Fagiolini and Kupfer, 2003). In addition, the risk of relapse (up to 85% of the cases) or chronicization (about 20% of the cases) must also be considered (Ferrari et al., 2013). However, when to apply rTMS in this context and the place of rTMS in the antidepressant treatment algorithm has not been clearly defined yet. Clinical practice shows that rTMS may have a higher chance of success when it is administered in the year of onset of an ongoing depressive episode, to patients below the age of 65 years, and in cases known to have a limited level of resistance to treatment (one or two failed pharmacological trials, with or without additional psychotherapy) (George and Post, 2011). These criteria should be considered as merely indicative as most of rTMS research in the domain of depression has been conducted in MDD patients with some form of treatment resistance. On the other hand, in geriatric samples, beneficial effects of rTMS have been reported on mood (Dardenne et al., 2018), but not on executive functions (Ilieva et al., 2018).

10.1. General results

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND depression) identified 526 papers, including 11 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions. These 11 studies examined the efficacy of HF-rTMS of the left DLPFC (n=3), LF-rTMS to the right DLPFC (n=1), or bihemispheric rTMS over both DLPFC (n=1),

compared right and left DLPFC stimulation (n=1), or evaluated new settings (deep rTMS, TBS, or accelerated rTMS protocol) (n=5)

In the past decades, two different approaches for the treatment of MDD episodes with rTMS emerged: either HF-rTMS of the left DLPFC (aimed at correcting an alleged hypoactivity) or LF-rTMS of the right DLPFC (aimed at reducing an alleged hyperactivity) (De Raedt et al., 2015).

HF-rTMS of the left DLPFC received a recommendation corresponding to a Level A of evidence in our previous guidelines (Lefaucheur et al., 2014). This was also in accordance with the U.S. Food and Drug Administration (FDA) approval, first issued in December 16, 2008 following the report of beneficial results by two large multicenter studies: 301 and 199 patients enrolled in O'Reardon et al. (2007) and George et al. (2010), respectively. In the 2014-2018 period, 4 additional studies were retained for further analysis, one of Class I (Blumberger et al., 2016), one of Class II (Theleritis et al., 2017) and two of Class III (Kang et al., 2016; Li et al., 2016a) (Table 12).

The Class I study (Blumberger et al., 2016) failed to show a significantly differential effect between real and sham HF-rTMS protocols unilaterally delivered to the left DLPFC in terms of remitter or responder rate measured on the 17-item HDRS (HDRS-17) (remission defined as HDRS-17 score $\leq$7, response defined as HDRS-17 score reduction >50%). Conversely, all the other recent sham-controlled studies (Kang et al., 2016; Li et al., 2016a; Theleritis et al., 2017) reported beneficial results of the real stimulation compared to sham control. One of these studies (Theleritis et al., 2017) showed the additional effect of performing rTMS sessions twice a day rather than once a day. The remaining two studies revealed some functional brain changes produced by rTMS or associated with the outcome using fMRI, PET, or EEG assessments (Kang et al., 2016; Li et al., 2016a). Consequently, the Level A of evidence of definite efficacy did not change concerning HF-rTMS applied to the left DLPFC. A recent meta-analysis also concluded to a significant antidepressant effect of HF-rTMS of the left DLPFC (Brunoni et al., 2017).

- Insert Table 12 -

In our previous work, a Level B of evidence (probable efficacy) of LF-rTMS of the right DLPFC was proposed (Lefaucheur et al., 2014), since most studies showed a beneficial antidepressant effect of this procedure compared to placebo, but with lower statistical power than for HF-rTMS of the left DLPFC (Level A). Although the tolerability of LF-rTMS appears better than HF-rTMS, unfortunately, no new sham-controlled studies examined the effects of LF-rTMS applied to the right DLPFC in large MDD samples in the 2014-2018 period. So at this point we can only keep a Level B of evidence for this procedure.

Of note, the published rTMS studies often showed a large variability in the number of sessions proposed (10 to 30) and the number of stimuli per session (120 to 3000), and these variables are usually lower when applying LF-rTMS of the right DLPFC as compared to HF-rTMS of the left DLPFC. One recent meta-analysis (Teng et al., 2017) showed that increasing the number of sessions and the total number of pulses per session (with an optimal value of 1200-1500 pulses/session) was associated with an increased antidepressant efficacy of HF-rTMS of the left DLPFC. A few studies

compared the both types of stimulation (LF-rTMS on the right vs. HF-rTMS on the left) and rather showed a similar antidepressant efficacy, even when rTMS was used in augmentation or as an add-on treatment to antidepressants in pharmacological refractory major depression (Eche et al., 2012; Dell'Osso et al., 2015). One meta-analysis specifically addressed this question and concluded that HF and LF-rTMS had a comparable antidepressant efficacy (Chen et al., 2013). However, other authors pointed out that HF-rTMS might have a greater potential ability to accelerate and improve the clinical response to antidepressants than LF-rTMS, whereas LF-rTMS might have a better tolerability profile than HF-rTMS (Berlim et al., 2013b). Therefore, considering the few studies that have directly compared the efficacy and safety profiles of the two techniques, we prefer to propose only a Level C of evidence to conclude that there is possibly no difference between HF-rTMS of the left DLPFC and LF-rTMS of the right-DLPFC in their therapeutic use for patients with depression.

In our previous analysis of the literature (Lefaucheur et al., 2014), we found that bilateral rTMS of the DLPFC (LF on the right hemisphere and HF on the left one) was compared to unilateral HF-rTMS of the left DLPFC in 7 studies, with only one study showing a superior efficacy of bilateral rTMS and even two studies reporting a lower efficacy of bilateral rTMS. The efficacy of bilateral rTMS was also compared to a sham condition in 7 studies, with a significantly better efficacy of the real stimulation condition observed in only 3 studies. Therefore, no recommendation was made regarding bilateral rTMS of the DLPFC in depression because of highly contradictory results. In the 2014-2018 period, the efficacy provided by the combination of LF-rTMS of the right DLPFC and HF-rTMS of the left DLPFC during the same sessions in the same patients was assessed in 12 studies (2 Class I studies, 6 Class II studies and 4 Class III studies). These studies did not report any superior efficacy of bilateral stimulation, as compared to unilateral stimulation, except one Class I study (Blumberger et al., 2016). In this study, only bilateral rTMS (600 pulses at 1Hz on the right DLPFC followed by 1500 pulses at 10Hz on the left DLPFC), but not unilateral HF-rTMS of the left DLPFC (2100 pulses at 10Hz), produced significantly greater antidepressant effects compared to sham procedure in terms of remission or response (measured on the HDRS-17 score). Therefore, we propose to make a recommendation in favor of a probable antidepressant efficacy (Level B of evidence) of bilateral rTMS protocols over the DLPFC (LF on the right side and HF on the left) in patients with MDD with possibly no differential antidepressant efficacy between bilateral rTMS versus unilateral right LF-rTMS or left HF-rTMS delivered to the DLPFC (Level C of evidence).

Another issue is the relationship between rTMS efficacy and antidepressant pharmacotherapy. In fact, there are two different questions: (i) is there a difference between rTMS and antidepressants in terms of therapeutic efficacy?; (ii) is there an augmenting effect of rTMS when introduced in patients already under stable antidepressant medication or an additive or potentiating effect of rTMS when introduced concomitantly with antidepressant medication ("add-on therapy")?

Since 2014, regarding comparisons between antidepressant effects of rTMS and medication, one large multicenter Class I study of 170 depressed patients (Brunelin et al., 2014) showed that LF-rTMS of the right DLPFC was as effective as venlafaxine administered alone or the combination of

both treatments. This study was in favor of the absence of differential efficacy of rTMS performed alone vs. combined with antidepressants, as was one previous study of Class I (Herwig et al., 2007) and 2 of Class III (Garcia-Toro et al., 2001; Bretlau et al., 2008), whereas 2 studies of class II were in favor of a superiority of an "add-on" effect of the combined procedure (Rossini et al., 2005b; Rumi et al., 2005). More recently, one retrospective Class III study of 32 patients (Verma et al., 2018) showed that HF rTMS of the left DLPFC was an effective add-on treatment strategy in patients with treatment-resistant depression. Regarding the augmenting effect of rTMS, another Class III study (Dell'Osso et al., 2015) showed that either HF-rTMS of the left DLPFC or LF-rTMS of the right DLPFC had comparable rate of efficacy in the treatment of acute unipolar and bipolar MDD episodes in a series of 29 patients with poor drug response or treatment resistance. Therefore, we modify our recommendations to state that there is possibly no differential antidepressant efficacy between rTMS therapy performed alone vs. combined with antidepressants (Level C), although one older meta-analysis concluded to the superiority of combining rTMS and antidepressant medication (Berlim et al., 2013a).

In the 2014-2018 period, no study further compared the efficacy of rTMS vs. ECT. In this domain, as stated in our previous work (Lefaucheur et al., 2014), the main issue is the lack of sham-controlled studies. Several meta-analyses suggested that rTMS has a lower efficacy compared to ECT (Slotema et al., 2010; Berlim et al., 2013b, Ren et al., 2014), especially in depression with psychotic features (Grunhaus et al., 2000). However, one meta-analysis (Chen et al., 2017) suggested that even if ECT was more efficacious, it was less tolerated and bilateral rTMS had the most favorable balance between efficacy and acceptability. On the other hand, the absence of significant differences between ECT and rTMS in some studies may be explained by statistical bias due a small sample size. Regarding bipolar depression, only two studies of Class III with heterogeneous outcomes (Fitzgerald et al., 2016; Hu et al., 2016) were reported in the 2014-2018 period. Although the published data appear to be generally insufficient to draw definitive conclusions, rTMS seems to be ineffective in cases of MDD with psychotic features, a condition which is, on the contrary, a major clinical indication of ECT. Finally, there is currently no evidence to suggest that rTMS is associated with an increased risk of hypomanic switch.

One last issue is the DLPFC targeting method used in rTMS studies to treat depression. To date, most of the rTMS studies, including those that resulted in the FDA clearance for rTMS therapy of medication-resistant MDD and those on which our Level A recommendation was based, were performed with a "standard procedure" of targeting, defining the DLPFC as located 5cm anterior to the hand motor hotspot ("5cm-rule") (Pascual-Leone and Hallett, 1994; Pascual-Leone et al., 1996). However, several studies using image-guided navigation systems demonstrated that such a procedure was anatomically incorrect, the DLPFC being more anterior in a majority of subjects (Herwig et al., 2001; Fitzgerald et al., 2009b; Bradfield et al., 2012; Wall et al., 2016). On average, the DLPFC was found to be located about 7cm in front of the motor hotspot on scalp measurement (Ahdab et al., 2010). In addition, the DLPFC target showed a significantly greater interindividual variability in terms

of anatomical location with the "standard procedure" compared to neuronavigated methods which integrate individual imaging data (Peleman et al., 2010; Rusjan et al., 2010). This could be due to the proper anatomical variability of hand motor hotspot location, which is also large (Ahdab et al., 2016). Thus, on an anatomical point-of-view, the most accurate method for targeting the DLPFC should be to use individual MRI data and a neuronavigation system, as suggest by several neuroimaging studies (Fox et al. 2012; Luber et al., 2017; Dubin et al., 2017). Various neuronavigated algorithms were furthermore proposed to define the DLPFC target at the junction between BA 9 and BA 46 (Mylius et al., 2013) or within BA 46 (Pommier et al., 2017).

However, a navigation system is costly and not available for all rTMS practitioners. Therefore, a non-navigated targeting alternative to the 5cm-rule was suggested as being probably more anatomically accurate. This procedure locates the left/right DLPFC at the F4/F3 sites of the 10-20 EEG System. A simple and dedicated method (the “Beam F3” algorithm) to estimate the scalp location of the F3 site from only three measurements over the skull was then proposed by Will Beam and Jeff Borckardt (Beam et al., 2009) who also developed a free web interface calculator based on their method (http://clinicalresearcher.org/F3/calculate.php). The acccuracy of this method of left DLPFC targeting was confirmed by a comparative study with a neuronavigated approach based on individual MRI data (Mir-Moghtadaei et al., 2015), even if the "Beam F3" target appears to be more anterior than the real F3 site of the 10-20 EEG System (Nikolin et al., 2018). In fact, navigated studies showed that the DLPFC representation could be slightly more lateral than the F3 or "Beam F3" site (Wall et al., 2016), corresponding rather to the F5 site of the 10-10 EEG System (Rusjan et al., 2010). Finally, taken into account the functional relationship between the DLPFC and the autonomic nervous system, another DLPFC target location (FC3/FC4) was recently proposed, based on the site of stimulation where short trains of 10Hz-rTMS produced the largest heart rate deceleration (Iseger et al., 2017).

Actually, definite evidence of a clinical impact of the DLPFC targeting method is still lacking. One study showed that using the "standard procedure" (5cm-rule), rTMS produced a better antidepressant response when the provided target was more anterior and lateral, predicting better efficacy for targeting over F3 or even superior for targeting at the junction between BA 9 and BA 46 (Herbsman et al., 2009). Fitzgerald et al. (2009a) compared the effect of HF-rTMS of the DLPFC targeted with the 5cm-rule (27 patients) vs. at the junction between BA 9 and BA 46 using neuronavigation (24 patients). A significanty better antidepressant outcome was observed in case of neuronavigated approach vs. the "standard procedure". Thus, the use of a more anatomically accurate method of DLPFC targeting appears to enhance the response to rTMS treatment in depression, but this remains to be replicated and confirmed in large clinical trials. Although the 5cm-rule has the best evidence to support its use and is simpler compared to the other targeting methods, the "Beam F3" and MRI-guided navigated procedures may be preferred to reduce interindividual variability of target anatomical location and possibly enhance the efficacy of antidepressant rTMS therapy.

10.2. Novel rTMS protocols to treat depression: deep HF-rTMS over the left DLPFC

Left HF-rTMS and right LF-rTMS delivered to the DLPFC are effective in the treatment of MDD, but the effect size remains quite low (Brunoni et al., 2017), yielding between 30 and 50% of responders, with remission rates even lower. This led to the development of novel forms of rTMS therapy in MDD.

First, we have to mention the use of deep HF-rTMS delivered with the H1-coil to stimulate larger prefrontal cortical regions (Table 13). In several studies, the H1-coil, placed 6 cm anterior to the motor hotspot, was intended to stimulate lateral prefrontal regions bilaterally, but more intensely the left DLPFC, according to electric field models (Parazzini et al., 2017). Following several pilot studies, Levkovitz et al. (2015) reported a multicenter sham-controlled study of Class I initially including 212 patients (101 real, 111 sham) who received such type of deep HF-rTMS protocol (sessions of 1980 pulses delivered at 18Hz and 120% of RMT, daily for 4 weeks (20 sessions) and then biweekly for 12 weeks). From the 212 enrolled patients, 181 completed the primary endpoint assessment (89 real, 92 sham). In this per-protocol analysis sample, a significant reduction of depression scores after real vs. sham treatment (-6.4 vs. -3.3, respectively, on the 21-item HDRS score) at the end of the 5-weeks protocol was observed. Improvement was also significant between real and sham stimulation conditions in terms of response rate (38.4 vs. 21.4%, respectively, defined as HDRS-21 score reduction ≥50%) and remission rate (32.6 vs. 14.6%, respectively, defined as HDRS-21 <10). In addition, the significant benefit of real deep HF-rTMS of the left DLPFC remained stable during the 12-week maintenance phase. Based on these results, the FDA approved the deep rTMS device for the treatment of MDD episodes in patients who have failed to respond to antidepressant medications as substantially equivalent to superficial rTMS systems (January 7, 2013).

A second sham-controlled Class I study (Kaster et al., 2018) assessed the effect of deep HF-rTMS of the left DLPFC in MDD patients, but of older age (between 60 and 85 years vs. less than 68 years in Levkovitz et al. (2015)). In this study, 52 old MDD patients received real (n=25) or sham (n=27) deep HF-rTMS using a H1-coil (20 sessions of 6012 pulses (vs. 1980 in Levkovitz et al. (2015)) delivered at 18Hz and 120% of RMT). The rate of responders (defined as HDRS-24 score reduction >50%) was higher after real vs. sham deep HF-rTMS (44.0% vs. 18.5%, respectively), although the averaged value of HDRS-24 score reduction was not different between both groups. The remission rate was also significantly higher after real vs. sham deep HF-rTMS (40.0% vs. 14.8%, respectively, defined as a score ≤10 on the 24-item HDRS with a reduction ≥60% from baseline).

From these two Class I studies, we propose to retain a Level A of evidence (definite efficacy) for deep HF-rTMS of the left DLPFC in MDD patients, maybe even in the elderly.

A third sham-controlled study (Tavares et al., 2017) assessed the effect of deep HF-rTMS of the left DLPFC in depression, but in a series of 50 patients who had bipolar depression (43 completed the study: 20 real, 23 sham). The parameters of stimulation were the same as in the study of Levkovitz et al. (2015), but the clinical profile of the patients was substantially different. Tavares et al. (2018) found showed a significant reduction of depression score after real vs. sham treatment (-12.3 vs. -7.1,

respectively, on HDRS-17 score) at the end of the 4-week protocol, but not at 4-week follow-up. There was a trend towards a greater response rate between real and sham stimulation conditions (54.6 vs. 26.1%, respectively, defined as HDRS-17 score reduction ≥50%), but no significant difference in terms of remission rate (31.8 vs. 17.4%, respectively, defined as HDRS-17 ≤7). No treatment-emergent mania switch occurred. This study remains to be replicated before providing any recommendation on the efficacy of deep HF-rTMS of the left DLPFC in bipolar disorder.

- Insert Table 13 -

Larger and deeper stimulation than that provided by usual figure-of-8 coils can be produced by coils other than H-coil, such as the double-cone coil. This type of coil was used to bilaterally target the dorsomedial prefrontal cortex (dmPFC) or the dorsal anterior cingulate cortex (dACC) in several rTMS studies for various indications, including tinnitus or craving, for example (Kreuzer et al., 2018). In the context of depression, beyond various open-label studies (e.g., Bakker et al., 2014; Downar et al., 2014; Salomons et al., 2014), only one sham-controlled study was reported using this procedure (Kreuzer et al., 2015b). In this Class II study, 40 depressed patients were randomly allocated to receive 15 sessions of conventional 10Hz-rTMS delivered to the left DLPFC using a figure-of-8 coil (15 patients), 10Hz-rTMS delivered to the dACC using a double-cone coil (13 patients), or sham rTMS (12 patients). The deep HF-rTMS of the dACC produced significantly greater reduction of depression score (assessed on the HDRS-21) than other conditions at the end of the 3-week treatment, but not lasting at follow-up assessments.

10.3. Novel rTMS protocols to treat depression: iTBS over the left DLPFC or cTBS over the right DLPFC

The TBS protocols offer the potential advantage of producing similar (if not larger) effects on cortical excitability and plasticity than conventional HF/LF-rTMS protocols, but for frankly shorter session duration (e.g., 3 minutes for an iTBS protocol vs. more than 20 minutes for a standard rTMS session). Huang et al. (2005) proposed two different TBS protocols, which consisted of 50Hz triplet bursts repeated at 5Hz (600 pulses delivered at 80% of AMT), as an uninterrupted train for 40 seconds (cTBS) or according to 2-second-on/8-second-off cycle (iTBS): the first protocol was thought to reduce cortical excitability and the second one to increase it. In the context of depression therapy, several studies aimed at replacing LF-rTMS by cTBS delivered to the right DLPFC or HF-rTMS by iTBS delivered to the left DLPFC (Table 14).

In 2010, two case series revealed the potential value of TBS in the treatment of depression (Chistyakov et al., 2010; Holzer and Padberg, 2010). Holzer and Padberg (2010) showed that 5 of 7 patients who received a 3-week course of two 600-pulse iTBS sequences delivered per day over the left DLPFC met the criteria of antidepressant response (reduction of the HDRS score ≥50%). Conversely, Chistyakov et al. (2010) found only 2 responders (with the same definition) in a series of 7 patients treated by a similar iTBS protocol for 10 consecutive working days. In this study, 3 of 6

patients (50%) responded to a cTBS protocol delivered to the right DLPFC with the same number of pulses per day (1200 stimuli) for 10 days. An even better response rate (71%) was observed in a series of 14 additional patients who received a cTBS sequence of 1800 stimuli twice daily for 10 days.

However, this prominent antidepressant action of right-sided cTBS was not confirmed by subsequent sham-controlled studies, including a study by the same group that initially reported beneficial results of this procedure (Chistyakov et al., 2015). In this latter study, 29 MDD patients received either real or sham cTBS to the right DLPFC (real 15, sham 14) for 10 consecutive working days. After the 10th session, all patients received real cTBS for additional 10 treatments. Overall, no significant difference in the degree of clinical improvement (assessed on HDRS-21 score) was found between real and sham cTBS groups.

In three studies, another research group assessed the respective efficacy of cTBS of the right DLPFC, iTBS of the left DLPFC, and the combination of both protocols, compared to a sham TBS procedure (Li et al., 2014a, 2018; Cheng et al., 2016). These studies included a series of 60 patients with treatment-resistant MDD episodes (15 patients in each group). After 2 weeks of treatment, depression improved in all groups, but a significantly better antidepressant response was found after real left-sided iTBS and bilateral TBS protocols compared to the sham procedure (Li et al., 2014a). In contrast, the antidepressant effect of right-sided cTBS was similar to sham. Refractoriness to drug treatment was a negative predictive factor for TBS protocol efficacy. In a subsequent analysis, Cheng et al. (2016) showed that only responders to left-sided iTBS protocol improved executive functions assessed by the Wisconsin Card Sorting Test (WCST). Finally, the same authors found that iTBS decreased brain metabolism in the ACC and dmPFC, whereas cTBS increased it (Li et al., 2018).

Overall, with two negative studies of Classes II-III (Li et al., 2014a; Chistyakov et al., 2015), cTBS protocol delivered unilaterally to the right DLFPC appears to be possibly ineffective to produce antidepressant effects (Level C).

Conversely, right-sided cTBS combined with left-sided iTBS was found to produce better antidepressant responses than the sham procedure by Li et al. (2014a) and Plewnia et al. (2014). In this latter study, 32 MDD patients received a sequential TBS protocol combining cTBS of the right DLPFC and iTBS of the left DLPFC or bilateral sham TBS for 6 weeks (30 sessions) in addition to ongoing medication and psychotherapy. Primary outcome measure was the proportion of treatment response defined as depression score reduction ≥50% compared to baseline. As assessed on the Montgomery-Asberg Depression Rating Scale (MADRS), a higher number of responders were found after real vs. sham bilateral prefrontal stimulation.

Another sham-controlled study also assessed bilateral TBS, also compared to bilateral conventional LF-/HF-rTMS protocol (Prasser et al., 2015). In this study, 56 patients received 15 daily sessions of bilateral TBS (cTBS of the right DLPFC + iTBS of the left DLPFC), bilateral rTMS (1Hz-rTMS of the right DLPFC + 10Hz-rTMS of the left DLPFC), or sham TBS. There was no significant effect in the primary outcome measure (change of the HDRS-21 score). However, there was a trend

towards an increased responder rate at the end of the follow-up period for both real TBS and rTMS treatments as compared to sham, and this tendency was most pronounced for the TBS group.

Overall, compared to sham condition, beneficial antidepressant effects were observed after the combination of cTBS of the right DLFPC and iTBS of the left DLPFC in two Class II studies (Li et al., 2014a; Plewnia et al., 2014), with a trend towards higher responder rate in a third study of Class III (Prasser et al., 2015). Thus, according to a recent meta-analysis of Berlim et al. (2017), a Level B of evidence (probable antidepressant efficacy) could be proposed for a sequential bilateral left-sided iTBS + right-sided cTBS protocol applied to the DLPFC in the context of patients with unipolar MDD.

In contrast to the original protocol by Huang et al. (2015), unilateral iTBS over the left DLPFC has often been applied with prolonged or intensified protocols (i.e. 1200-1800 pulses/day for 10 days, instead of 600 pulses/day, at an intensity of stimulation up to 120% of RMT, instead of 80% of AMT). Moreover, few studies compared unilateral iTBS to sham treatment (Li et al., 2014a, 2018; Cheng et al., 2016). Other researchers investigated the antidepressant efficacy of iTBS versus 10Hz-rTMS of the left DLPFC, first in a large, naturalistic, retrospective series of 185 patients (87 versus 98 patients) (Bakker et al., 2015) and then in a controlled study but without comparison with a sham procedure (Blumberger et al., 2018). This latter study showed the efficacy of an iTBS protocol delivered over the left DLPFC (targeted using a neuronavigation system) for 5 weekdays during 4 weeks in a large series of 193 patients with drug resistant MDD episodes. The trial had a non-inferiority design and the iTBS protocol was compared to a standard HF-rTMS protocol delivered over the same left DLPFC target (192 patients), without a control group receiving sham stimulation. At the end of the 4-week treatment, the reduction in depression score (-10 on average on the HDRS-17 score) was similar in both groups, including similar safety and tolerability profiles. Since August 14, 2018, following the report of this study, several companies have received FDA clearance to include iTBS of the left DLPFC as a therapeutic option in adult patients with MDD episode who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode. In addition, the response to either iTBS or 10Hz-rTMS of the left DLPFC could be predicted by similar baseline clinical characteristics (Kaster et al., 2019) or functional and effective connectivity in fronto-insular and salience networks (Iwabuchi et aL, 2019).

However, it is difficult to estimate the value of iTBS delivered unilaterally to the left DLPFC in depressed patients at its current state. On one hand, the large and convincing non-inferiority study of Blumberger et al (2018) showed no difference between left-sided prefrontal iTBS and HF-rTMS in depression, while HF-rTMS of the left DLPFC has established efficacy (Level A in this review). On the other hand, iTBS protocols considerably varied across previous studies, only one group showed the antidepressant benefit of left-sided iTBS in sham-controlled trials, and replication studies are missing. Thus, the evidence for iTBS is still insufficient to make a recommendation according to the methodology of our study. Therefore, sham-controlled studies assessing the antidepressant effect of iTBS delivered unilaterally to the left DLPFC are awaited, although it is difficult to conceive of such a

study from a regulatory and ethical point of view, given the non-inferiority finding published by Blumberger et al (2018).

Finally, another approach using iTBS of the left DLPFC was developed by one group, based on an accelerated protocol consisting of 20 sessions (1620 pulses per session) delivered in 4 days ((Desmyter et al., 2016; Duprat et al., 2016, 2018). This procedure is significantly different from the conventional procedure (one iTBS session per day for 5 weekdays during 2 to 4 weeks) and will therefore be discussed in the next chapter.

- Insert Table 14 -

10.4. Novel rTMS protocols to treat depression: accelerated protocols

To intensify the antidepressant response and to reduce the number of stimulation days, it has been proposed that increasing the number of rTMS sessions performed per day (more than one daily session) could be more effective (Brunoni et al., 2017; Baeken, 2018; Rachid, 2019; Sonmez et al., 2019). These protocols were referred as "accelerated rTMS protocols", after the first open-label report made by Holtzheimer et al. (2010) of a protocol consisting of 15 rTMS sessions administered over 2 days in 14 depressed patients. This accelerated procedure performed over a very limited number of days should not be confused with some studies based on twice-daily rTMS sessions applied for at least two weeks (Loo et al., 2007; McGirr et al., 2015; Desbeaumes Jodoin et al., 2018), closer to conventional once-daily rTMS treatments.

Accelerated rTMS protocol seeming to be safe and well-tolerated in depressed patients (Hadley et al., 2011; Baeken et al., 2017), even in the elderly (Dardenne et al., 2018). The main objective of accelerated rTMS protocols is to reduce the burden for the patients and the operators of repeated sessions over several weeks.

However, only a few sham-controlled studies based on accelerated rTMS protocols for the treatment of depression were published to date, most studies in this domain having an open label. Before 2014, Baeken et al. (2013) reported a crossover sham-controlled study of 20 MDD patients who received 20 sessions of 20Hz-rTMS of the left DLPFC spread over 4 days (5 sessions/day). No significant difference in the reduction of HDRS scores was found between real and sham stimulation conditions, but all responders (HDRS score reduction >50%) were found in the real stimulation condition. In satellite studies, the same research group showed that a higher metabolic activity in the subgenual ACC (sgACC) and a stronger negative functional connectivity with the left superior medial prefrontal cortex at baseline could predict the response to the accelerated HF-rTMS protocol (Baeken et al., 2014, 2015).

George et al. (2014) reported a randomized, sham-controlled study assessing the safety and efficacy of a protocol consisting of 9 sessions of 10Hz-rTMS of the left DLPFC (6000 pulses per session) performed over 3 days (3 sessions per day) in a series of 41 suicidal inpatients. The Suicidal

Ideation score decreased in both real and sham groups, but with a trend for more rapid decline following real rTMS.

One recent study compared the efficacy of an accelerated HF-rTMS (3 sessions per day over 1 to 3 days for 3 weeks) to a standard protocol based on a single daily session (over 5 days per week for 4 weeks) (Fitzgerald et al., 2018). In this study of 115 MDD patients (58 accelerated, 57 standard), no significant difference was found betwen the two treatment groups in terms of remission or response rates or reduction in depression scores. However, this study did not include a sham group.

Finally, one sham-controlled study was published, based on an accelerated iTBS protocol delivered to the left DLPFC (Duprat et al., 2016). In this crossover study, 47 patients received 20 sessions of either real or sham rTMS in 4 days (5 sessions per day). A similar reduction of depression score (measured on the HDRS-17) was observed in both treatment groups, but response and remission rates appeared to primarily increase with some delay (2 weeks) following real stimulation. The same group published several satellite studies based on the same series, showing in particular no differential overall change in the suicidal risk or reward responsiveness following either real or sham accelerated iTBS (Desmyter et al., 2016; Duprat et al., 2018).

In conclusion, although evidence supports a similar efficacy of accelerated rTMS protocols and classical rTMS protocols with only once-daily stimulation session, it is premature to provide any recommendation for the use of accelerated rTMS protocols in the treatment of depression.

10.5. Novel rTMS protocols to treat depression: miscellaneous

Other efforts to increase antidepressant response rates using innovative rTMS protocols are currently under investigation. First, we have to mention a protocol in which a 15-minute train of LF-rTMS delivered at 1Hz over the right DLPFC was "primed" by 20 short bursts of 6Hz-rTMS delivered at low-intensity (Fitzgerald et al., 2008, 2013). In a Class I study performed in 60 MDD patients (30 real, 30 sham), Fitzgerald et al. (2008) showed a significantly greater reduction of depression scores on the Montgomery-Asberg Depression Rating Scale (MADRS) in the real-priming vs. sham-priming group. In a second study, the same research group compared this primed LF-rTMS protocol to a sequential bilateral rTMS protocol (LF-rTMS of the right DLPFC followed by HF-TMS of the left DLPFC) in a large series of 179 patients (Fitzgerald et al., 2013). There was a significant average reduction >50% of the HDRS-17 score (with a response rate of 56% and a remission rate of 40%) in both treatment groups but no difference between groups at the end of the 4-week protocol.

Another innovative protocol was reported in a sham-controlled study published by Leuchter et al. (2015). The protocol was based on low-field TMS synchronized to individual EEG activity recorded prior to the first rTMS session. In a large series of 120 MDD patients who completed the study, a greater reduction of depression score was found after real low-field TMS synchronized to individual alpha-frequency vs. sham stimulation (-9.0 vs. -6.6, respectively, on the HDRS-17 score).

This new modality of stimulation remains to be investigated by other research groups for the treatment of depression.

10.6. Summary

Although rTMS therapy is applied worldwide in depressed patients, there is still a large heterogeneity in the published data concerning the populations included and the stimulation settings. A recent network meta-analysis showed a higher response to real vs. sham stimulation condition for bilateral prefrontal rTMS or iTBS, LF-rTMS of the right DLPFC, and HF-rTMS of the left DLPFC (Mutz et al., 2019). The present recommendations are in favor of a definite antidepressant efficacy of HF-rTMS of the left DLPFC (using either a focal figure-of-8 coil or a deep H1-coil) and a probable antidepressant efficacy of LF-rTMS of the right DLPFC. They mostly apply to patients in an acute phase of a drug resistant MDD episode in the context of unipolar depression. Efficacy does not seem to differ significantly whether patients are concomitantly treated by antidepressant medication. Unfortunately, there are still no robust data or consensus regarding the way of treating depression by rTMS beyond the acute phase with maintenance sessions (Rachid, 2018a; Senova et al., 2019). The issue of how to manage the maintenance phase for the long-term safety and efficacy of rTMS treatment of depression should be a major focus in this field of research for the years to come. Also, additional studies are needed to investigate the efficacy of rTMS in bipolar depression. Our recommendations on the use of rTMS in the treatment of mood disorders are consistent with those of CANMAT (Canadian Network for Mood and Anxiety Treatments) (Milev et al., 2016) that concluded to an evidence level 1 for HF- and LF-rTMS in the treatment of depression. No firm recommendations can be provided yet about new rTMS protocols, such as those based on TBS or accelerated protocols.

11. Schizophrenia

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND (schizophrenia OR hallucinations OR negative symptoms)) identified 147 papers, including 23 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions.

11.1. Auditory-verbal hallucinations

In the treatment of auditory-verbal hallucinations (AVH), most original sham-controlled rTMS studies concerned LF-rTMS or some cTBS protocols applied to the left TPC (including STG and TPJ targets). As emphasized in our previous work (Lefaucheur et al., 2014), highly controversial results were reported concerning the effect of LF-rTMS applied to the left STG/TPJ on auditory hallucinations, with as many "positive" studies showing rTMS efficacy as many "negative" studies showing rTMS inefficacy. However, considering effect size calculated in various meta-analyses,

literature data appeared to be in favor of a possible efficacy of LF rTMS of the left TPC on auditory hallucinations (Level C). Since 2014, the results of only a few additional sham-controlled studies have been published in this setting (Table 15), which were not able to change our previous recommendations. This statement is consistent with two recent meta-analyses investigating the efficacy of 1Hz-rTMS of the left TPC for the treatment of AVH (Slotema et al., 2014; He et al., 2017), which remained slightly positive, despite a decreasing effect size and an increasing placebo effect concerning studies published over time (Slotema et al. 2012, Dollfus et al. 2016). With regard to moderating variables, there is evidence to suggest that the treatment is more effective in young patients and in females (Koops et al. 2018). In addition, it has been suggested that a smaller scalp-to-cortex distance (as measured with an MRI-scan) at the stimulation site is associated with better response (Nathou et al. 2015).

- Insert Table 15 -

For other protocols of stimulation, data are too scarce to give clinical recommendations. Some studies applied LF-rTMS sequentially over temporal regions of both hemispheres. For example, in Hoffman et al. (2013), patients received 1Hz-rTMS for 16 minutes over the left STG (Wernicke's area) or the right homologous region for 5 sessions and then the site of stimulation was switched to the opposite hemisphere for 5 additional sessions. A third block of 5 stimulation sessions was delivered to the site associated with the greatest improvement from the two previous periods. This protocol produced a significant improvement measured on the Hallucination Change Score after real stimulation vs. sham condition. Bais et al. (2014) compared the efficacy of 1Hz-rTMS of the TPJ (defined according to the T3P3 method of targeting) delivered for six consecutive days twice daily to both hemispheres (15 patients), to only the left hemisphere (16 patients), or with a sham procedure (16 patients). No differences were observed between groups on the Positive and Negative Syndrome Scale (PANSS) and Auditory Hallucination Rating Subscale (AHRS) scores, except for a small decrease of hallucination severity on the P3 item of the PANSS in the left treatment group. In Kim et al. (2014d), 22 patients were randomized to one of four conditions: 1Hz-rTMS of both TPJ targets (defined as halfway between T3/T4 and P3/P4), 20Hz-rTMS of both TPJ targets, 20Hz-rTMS of both Broca's areas (defined as the crossing point between T3/T4-Fz and F7/F8-Cz), or sham procedure, with rTMS sessions performed twice daily for 3 to 5 days. No superior effect of the real stimulation protocols over the sham condition was found on AVH severity and frequency.

One study assessed the efficacy of priming a 20-minute train of LF-rTMS of the left TPC by 20 bursts of 6Hz-TMS of 5-second duration delivered at the same site (Ray et al., 2015). Priming LF-rTMS did not result in significantly greater improvement, except for reducing the loudness of AVH.

Other research groups assessed the value of HF-rTMS (rather than LF-rTMS) applied to the left TPC. In three studies (de Weijer et al., 2014; Kimura et al., 2016; Dollfus et al., 2018), 20Hz-rTMS was applied to the left temporal lobe and the effect on the severity of AVH was assessed on the AHRS. Two of these studies were sham-controlled (Kimura et al., 2016; Dollfus et al., 2018) (Table 16) and used the same cortical target, which was precisely defined under MRI-guided neuronavigation

at the crossing between the projection of the ascending branch of the left lateral sulcus and the superior temporal sulcus (Montagne-Larmurier et al., 2009). The identification of this target location resulted from an fMRI study based on a language task and was found to have less interindividual anatomical variability than the classical location of T3P3 based on the 10-20 EEG System (Montagne-Larmurier et al., 2009). No significant change in the AHRS score was observed after 4 sessions (in 2 days) of either real or sham HF-rTMS in the first study (Kimura et al., 2016). Exactly the same rTMS protocol was performed in the second study (Dollfus et al., 2018), in which the primary outcome was negative (no significant reduction of the percentage of patients showing a decrease of more than 30% in the AHRS frequency item at 2 successive ratings between the real and sham stimulation groups). The rTMS-induced change in AHRS total score also did no differ between both groups. However, as secondary outcome, this study showed that the percentage of responders on the AHRS total score (reduction >30%) at day 14 after treatment initiation was greater after real (34.6%) than sham (9.1%) stimulation. The third study was not sham-controlled (de Weijer et al., 2014) and based on small groups of 10 patients who received 1Hz-rTMS and 8 patients who received 20Hz-rTMS for 5 days, followed by a maintenance treatment of one session per week for 3 weeks. Both groups improved (on AHRS score) at the end of the first week of stimulation, but without lasting effects at 4-week follow-up. It is impossible to draw any conclusion from this study, since target location was based on AVH-related activation identified on individual fMRI, which resulted in highly variable stimulation sites, scattered on both right and left hemispheres. In summary, more controlled data are awaited before making recommendation for HF-rTMS delivered over a navigated TPJ target defined as the intersection between the ascending branch of the left lateral sulcus and the superior temporal sulcus.

- Insert Table 16 -

Finally, some studies assessed the value of using cTBS rather than classical LF/HF-rTMS protocols. First, Plewnia et al. (2014) delivered cTBS over the both TPC for 15 sessions in a small series of 16 patients (8 real, 8 sham) and found a beneficial effect of real vs. sham cTBS protocol. A Class II study (Koops et al., 2016), based on a larger sample size (71 patients: 37 real, 34 sham), showed that even unilateral application of an real cTBS protocol over the left TPC for 10 sessions (2/day) was able to significantly reduce AVH (assessed on the Psychotic Symptom Rating Scales (PSYRATS)). Another study did not find any difference in the value of 1Hz-rTMS and cTBS delivered to the left TPC to improve patients with AVH on the same PSYRATS score (Kindler et al., 2013).

11.2. Negative symptoms

In this clinical application, the therapeutic rTMS protocol usually consists of HF-rTMS of the left DLPFC, as for major depression. Since 2014, most sham-controlled studies showed beneficial results of the procedure, excluding the largest and only multicenter trial (Wobrock et al. 2015), in which the patients who received either real (n=76) or sham (n=81) rTMS improved similarly on the

PANSS negative subscale, and also regarding symptoms of depression and cognitive function. Subsequent re-analyses of this study further showed unspecific improvements in the real stimulation group (Hasan et al., 2016; Hansbauer et al., 2018; Wagner et al., 2019), except for the reduction of antipsychotic-induced parkinsonian symptoms (Kamp et al., 2018). In addition, some structural changes in various brain regions quantified on MRI examination before or after the rTMS procedure were associated with negative symptom improvement in the real stimulation group and the baseline MRI pattern was predictive for real treatment response (Hasan et al., 2017; Koutsouleris et al 2018).

Overall, details on the recent sham-controlled studies based on a HF-rTMS protocol delivered over the left DLPFC to treat negative symptoms of schizophrenia are presented in Table 17. Our previous work retained 10 original sham-controlled studies with at least 10 patients who received real HF-rTMS of the DLPFC to treat negative symptoms of schizophrenia (Lefaucheur et al., 2014). Among these studies, there were 3 'positive' Class II studies, 4 'positive' Class III studies, and 3 'negative' Class III studies, leading to a Level B of evidence for the probable efficacy of HF-rTMS of the left DLPFC. In the 2014-2018 period, two additional 'positive' Class II/III studies were published, whereas one Class I and one Class III studies were 'negative' (Table 17). Overall, the final balance to date consists of one 'negative' multicenter Class I study based on a large sample versus four 'positive' smaller Class II studies. Therefore, it seems reasonable to reduce the level of evidence from B to C, in favor of a possible efficacy of HF-rTMS of the left DLPFC on the negative symptoms of schizophrenia. Indeed, there is a wide heterogeneity in the profile of the patients enrolled in these studies and the place of rTMS therapy is not definite regarding its clinical meaningfulness and deserves further investigation. Indeed, meta-analyses found a moderate effect size (Dlabac-de Lange et al., 2010; Slotema et al., 2010; Shi et al., 2014; He et al. 2017; Aleman et al., 2018; Osoegawa et al., 2018), but the total number of studies and patients on which this is based remains relatively limited: 827 patients distributed over 22 studies, in the largest meta-analysis to date (Aleman et al. 2018). Moreover, the control of depressive symptoms was not addressed in most studies, although depressive symptoms may overlap with negative symptoms of schizophrenia. Therefore, in this context, rTMS efficacy may also relate to an antidepressant effect of the rTMS protocol, although this is not necessarily the case (Dlabac-de Lange et al., 2015a). Next, the use of the PANSS scale to evaluate negative symptoms is critically debated (Garcia-Protilla et al., 2015) and future studies must use standardized definitions of a predominant negative syndrome. Finally, the long-term effects of rTMS or the value of a maintenance therapy was not studied yet in this application.

- Insert Table 17 -

In several studies of patients with negative symptoms of schizophrenia, the HF-rTMS protocol differed from focal stimulation of the left DLPFC using a figure-of-8 coil. In one Class I/II study performed on a large sample size (Quan et al., 2015), the left DLPC (defined according to the 5cm-rule) was stimulated using a large circular coil. A series of 117 patients (real 78, sham 39) received 2 courses of 10 daily sessions (800 pulses/session) over two weeks, separated by a 2-week interval. The

clinical benefit on the total and negative subscale scores of the PANSS was significantly superior in the real than the sham stimulation group.

A circular coil was also used in another Class II/III study performed on a large sample size (Zhao et al., 2014), but to deliver an iTBS protocol over the left DLPFC (site not defined) in a group of 24 patients. This protocol was found to be even more efficacious than classical HF-rTMS protocols applied at 10Hz or 20Hz over the same target with a focal figure-of-8 coil to reduce negative symptoms of schizophrenia, assessed on the negative subscale of the PANSS and the Scale for Assessment of Negative Symptoms (SANS). In this study, the sham procedure (10Hz-rTMS performed with a tilted coil at 180°) did not produce any significant clinical effect.

In a third Class III study (Rabany et al., 2014), the stimulated area was even larger, using a H-coil (H1 type) over both DLPFC regions (defined as 5.5cm anterior to the motor hotspot), although the stimulation was rather lateralized to the left hemisphere. A series of 30 patients (20 real, 10 sham) received 20 daily sessions of 20Hz-rTMS over 4 weeks (1680 pulses/session) that produced a significant reduction of negative symptoms (assessed on the SANS) at the end of the real (-7.7) but not the sham (-1.9) stimulation with no significant group differences. However, the difference between real and sham stimulation groups was not significant regarding both the average reduction of SANS total score and the rate of responders (defined as SANS score reduction >20%). Furthermore, no significant change was observed on other clinical scales (such as the PANSS negative subscale or total scores).

A bihemispheric stimulation was also performed over the both DLPFC regions (defined as F3/F4 EEG sites) by Dlabac-de Lange et al. (2015a), but using a figure-of-8 coil. In this Class II study, 32 patients were equally randomized to receive 30 daily sessions of 10Hz-rTMS over 3 weeks (2000 pulses per hemisphere and per session, two sessions per day, only working days). In this study, depression was controlled, but the comparison between the real and sham stimulation groups provided ambiguous results. Indeed, a significant efficacy of the real procedure to improve negative symptoms was found when measured on the SANS but not on the PANSS. In a satellite fMRI study (Dlabac-de Lange et al., 2015b), the same authors found that, compared to the sham procedure, the real bihemispheric stimulation of the DLPFC resulted in an increased activation in right (pre)frontal regions when a cognitive task aimed at assessing planning function was performed. In a second satellite study (Dlabac-de Lange et al., 2017), these authors reported that the clinical benefit of real bihemispheric DLPFC stimulation was associated with an increase in the concentration of glutamine (precursor of glutamate) in the left DLPFC of the treated patients, as measured with ^{1}H-Magnetic Resonance Spectroscopy (1H-MRS).

However, all these studies based on non-focal or bihemispheric stimulation of DLPFC areas are too heterogeneous to make any recommendations concerning the use of such protocols to treat negative symptoms of schizophrenia.

Finally, in a sham-controlled study (Garg et al., 2016), a totally different rTMS protocol was proposed, since the vermal part of the cerebellum was stimulated at 5-7Hz using a double-cone coil. In

this study, 40 patients were equally randomized to receive real or sham stimulation for 10 daily sessions (600 pulses/session). The negative syndrome subscore of the PANSS significantly improved in the real compared to sham stimulation group. This type of cerebellar stimulation protocol was not replicated to date in this clinical context.

12. Substance abuse, addiction and craving

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND (substance abuse OR addiction OR craving)) identified 135 papers, including only 8 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions.

12.1. Alcohol craving

In the 2014-2018 period, only one sham-controlled study of Class III (with at least 10 patients receiving real stimulation) concerned alcohol craving (Del Felice et al., 2016): no effect of 4 sessions of 100 pulses of HF-rTMS delivered over the left DLPFC was observed in both real and sham stimulation groups (10 patients each). In contrast, in patients with alcohol dependence, Jansen et al. (2015) suggested a beneficial effect of LF-rTMS of the right DLPFC on cognitive control for maintaining abstinence by showing a rTMS-induced increased fronto-parietal connectivity on fMRI investigation.

Among other studies, one could also mention that of Mishra et al. (2015), showing a reduction in craving scores in patients with alcohol dependence receiving 10 sessions of 10Hz-rTMS delivered to the right or left DLPFC, without significant difference between both groups. In a sham-controlled study but with small sample size (9 patients in both real and sham stimulation groups) (Ceccanti et al., 2015), 20Hz-rTMS was delivered to the dmPFC using a H1-coil. Ten sessions of real deep HF-rTMS was able to reduce craving and maximum alcohol intake compared to sham stimulation. In an even small study (5 and 6 patients in real and sham stimulation groups, respectively) (Addolorato et al., 2017), four weeks of deep 10Hz-rTMS over bilateral DLPFC region reduced alcohol intake in correlation with a reduction in striatal dopamine transporter availability only in patients of the real stimulation group.

However, there is still insufficient data for making any recommendation regarding LF- or HF-rTMS application to the left and/or right DLPFC in alcohol craving.

12.2. Nicotine craving

Until 2014, two studies (of Class II/III) reported beneficial effects of HF rTMS (10-20Hz) of the left DLPFC on cigarette craving and especially on cigarette consumption and nicotine dependence (Eichammer et al., 2003; Amiaz et al., 2009; Prikryl et al., 2014). From these results, a level C of

evidence (possible effect) was proposed for HF-rTMS of the left DLPFC in the treatment of nicotine craving and consumption. However, these sham-controlled studies were rather heterogeneous regarding various methodological issues, one of these studies being performed in patients with schizophrenia (Prikryl et al., 2014), for example.

Since 2014, a few additional studies have been published. One sham-controlled study was based on a protocol of focal HF-rTMS, but delivered to the right DLPFC and not the left DLPFC (Sheffer et al., 2018). In this study including 29 patients (16 real, 13 sham), HF-rTMS of the right DLPFC (8 sessions with 900 pulses/session over 2 weeks) was combined to the use of a standardized manual for smoking cessation and resulted in an increased abstinence rate in the real vs. sham stimulation group.

Another sham-controlled study was in favor of the efficacy of HF-rTMS of prefrontal regions (Dinur-Klein et al., 2014), but in this study a large H4-coil was used in place of a focal figure-of-8 coil. A lateral prefrontal region was stimulated simultaneously on both hemispheres for 13 daily sessions over 3 weeks (600-990 pulses/session). Compared to two groups of patients who received real 1Hz-rTMS (n=14) or sham rTMS (n=31), the group of patients who received 10Hz-rTMS (n=32) showed a significantly beneficial effect on nicotine consumption.

Conversely, Trojak et al. (2015) applied LF-rTMS to the right DLPFC for 10 sessions over 2 weeks (360 pulses/session) in a series of 37 smokers (real 18, sham 19) and they found reduced craving and more abstinent patients in the real vs. sham stimulation group.

Finally, Dieler et al. (2014) delivered iTBS over the right DLPFC for 4 sessions over 2 weeks (600 pulses/session) in a series of 74 smokers (real 38, sham 36). In this study, rTMS was combined with a cognitive behavioural therapy (CBT) consisting of a smoking cessation program and resulted in a higher abstinence rate in the real iTBS group, but with no change in craving.

In summary, all these recent data showed heterogenous protocols and resulting data, not replicated to date. Therefore, no new recommendation other than that previously proposed for a possible efficacy of HF-rTMS of the left DLPFC (Lefaucheur et al., 2014) can be made for all these alternative rTMS procedures in cigarette craving and consumption.

12.3. Methamphetamine or drug craving

In a study by Su et al. (2017), 30 methamphetamine-addicted patients were equally randomized to receive 5 sessions of real or sham 10Hz-rTMS of the left DLPFC. Real rTMS reduced craving significantly compared to sham and also improved learning and memory capacities. In a more recent open-label study (Liu et al., 2019), 20 sessions of 10Hz-rTMS of the left DLPFC over 4 weeks was performed in a group of 52 methamphetamine users and showed an add-on effect to routine addiction rehabilitation program, lasting for at least 30 days after the last rTMS session.

However, former beneficial results on methamphetamine craving were reported using 1Hz-rTMS (and not HF-rTMS) of the left DLPFC (Li et al., 2013). Liu et al. (2017) conducted a study in

50 metamphetamine users assigned to 1Hz-rTMS of the left or right DLPFC (100% RMT, 600 pulses, 5 days), 10Hz-rTMS of the left or right DLPFC (100% RMT, 2000 pulses, 5 days) or 10Hz-rTMS of the left PPC (P3 site, 100% RMT, 2000 pulses, 5 days) as a control condition, but no sham. All DLPFC interventions reduced craving, but did not differ between each other. Thus, there is still no robust evidence to make any recommendation concerning the use of a specific rTMS protocol in the context of methamphetamine addiction.

In the context of cocaine addiction, one study showed beneficial effects of focal navigated HF-rTMS of the left DLPFC (using a figure-of-8 coil and a navigation system) vs. standard psychopharmacological treatment in 32 cocaine-addicted patients (Terraneo et al., 2016). In another study (Bolloni et al., 2016), a H1-coil was used to stimulate the dmPFC bilaterally at 10Hz. At the end of a protocol of 12 daily sessions of such large and deep rTMS performed over 4 weeks no difference between real and sham stimulation conditions regarding cocaine intake was observed. However, at 3 months after rTMS intervention, the amount of cocaine intake was found to be reduced in the real vs. sham stimulation group, suggesting beneficial effects of this procedure in the long term. Rapinesi et al. (2016) also used a H1-coil, but centred more laterally over the left DLPFC. In this small open-label study of 7 patients with cocaine use disorder, 3 weekly sessions of 15Hz-rTMS over 3 weeks resulted in lasting beneficial effect on craving lasting for several weeks. Finally, in a pilot study of 18 patients with moderate to severe cocaine use disorder, Martinez et al. (2018) used a H7-coil (rather than a H1-coil) to stimulate bilaterally the mPFC-ACC area. The patients were equally randomized to receive 10Hz-rTMS, 1Hz-rTMS, or sham rTMS (6 patients in each group) for 15 sessions over 3 weeks. A reduced choice for cocaine intake was observed over the course of HF-rTMS protocol, but not in the other conditions. However, these heterogeneous results did not allow any recommendation to be made for the indication of a specific protocol of HF-rTMS delivered over prefrontal regions in the context of cocaine use disorders, as for any other type of drug addiction.

12.4. Eating disorders

Before 2014, one sham-controlled study showed that 10Hz-rTMS over the left DLPFC was ineffective to relieve bulimia nervosa (Walpoth et al., 2008): 14 bulimic women were first submitted to one week of sham stimulation, then followed by 3 weeks of real or sham stimulation after excluding placebo responders. The average number of binges per day declined significantly at the end of the 3-week rTMS protocol in both groups with no significant difference between sham and real stimulation. This result was confirmed by Gay et al. (2016) who showed no significant improvement in bingeing and purging symptoms in the 15 days following 10 sessions of 10Hz-rTMS over the left DLPFC in a series of 42 patients with bulimia nervosa.

Finally, Dunlop et al. (2015) showed that 10Hz-rTMS delivered over the dmPFC using a double-cone coil rTMS was able to reduce weekly binge/purge frequency by more than 50% in 16 of 28 patients (57%) who received 20-30 daily sessions. Clinical response was associated an enhanced

frontostriatal connectivity at resting-state fMRI investigation. However, this study was not sham-controlled.

Regarding anorexia nervosa, only one sham-controlled study with repeated sessions performed in a sample size larger than 10 patients has been published to date (Dalton et al., 2018). In this study, 32 patients with anorexia nervosa lasting for at least 3 years were equally randomized to receive 20 sessions of either real or sham HF-rTMS of the left DLPFC. The real stimulation was superior to the sham one especially for mood measures, rather than for eating disorder symptoms or weight gain. Thus, it is still premature to consider rTMS therapy for eating disorders in clinical practice (Rachid, 2018b).

12.5. Gambling disorders

Since 2014, only two sham-controlled crossover studies have been published in this domain, but based on the effect of single sessions. Focal HF-rTMS was assessed, applied to the left DLPFC in 22 patients (Gay et al., 2017) or to the right DLPFC in 30 patients (Sauvaget et al., 2018). In a third study (Zack et al., 2016), two protocols were found to reduce gambling reinforcement in 9 patients with pathological gambling, either a 10Hz-rTMS protocol using a double-cone coil targeting the mPFC or a cTBS protocol using a figure-of-8 coil targeting the right DLPFC. From these sparse and heterogenous data, no conclusion can be drawn.

13. Miscellaneous psychiatric conditions

13.1. Anxiety disorders

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND (anxiety OR panic OR phobia)) identified 120 papers, including only 5 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions.

13.1.1. Generalized anxiety disorder

Since 2014, three sham-controlled studies have evaluated the therapeutic efficacy of rTMS in generalized anxiety disorder (GAD).

In one Class III study, 1Hz-rTMS was applied using a neuronavigation system to the right DLPFC (defined by its stereotactic coordinates) in 25 patients with GAD but only 19 completed the study (9 real, 10 sham) (Diefenbach et al., 2016b). After 30 daily sessions (5 days/week for 6 weeks with 900 pulses/session at 90% of RMT), compared to the sham group, the real stimulation group showed significantly more responders and remitters, defined as a reduction of the Hamilton Anxiety Rating Scale (HARS) score ≥50% and a post-rTMS HARS score <8, respectively. This difference was

found at the end of the rTMS protocol and maintained at the 3-month follow-up. In satellite studies, the same authors showed that the real LF-rTMS of the right DLPFC also significantly improved self-reported emotion regulation (Diefenbach et al., 2016a) and sleep quality (Diefenbach et al., 2019), in correlation with functional connectivity changes in the default mode network. Finally, a "normalization" of functional connectivity between dorsal and subgenual ACC regions was found after real, but not sham rTMS, related to the improvement in worry symptoms (Assaf et al., 2018).

In another study (Dilkov et al., 2017), 20Hz-rTMS was applied at 110% of RMT to the right DLPFC (defined according to 5cm-rule) in 40 patients with GAD, randomized to receive either real (n=15) or sham (n=25) stimulation. After 25 rTMS sessions (over 6 weeks with 360 pulses/session), the real stimulation group showed a significant reduction in anxiety (HARS score) compared to sham group, maintained and even slightly improved up to one-month follow-up.

In a third study (Huang et al., 2018a), the right PPC (P4 EEG electrode site) rather than the DLPFC was the target. A protocol of 1Hz-rTMS was applied to this target for 10 days (1500 pulses/session at 90% of RMT) in 36 patients with comorbid GAD and insomnia equally randomized to a real or a sham procedure. A significant improvement of anxiety (assessed on HARS score) was only observed in the real stimulation group, positively correlated with the improvement in the Pittsburgh Sleep Quality Index (PSQI) score. The rate of responders and remitters, defined on HARS scores as in Diefenbach et al. (2016b), was also significantly higher after real than sham stimulation.

Overall, these three studies did not allow any recommendation to be made for the use of rTMS protocols to treat GAD, given the heterogeneity in targets and stimulation frequencies.

13.1.2. Other anxiety disorders

Since 2014, two randomized sham-controlled trials reported therapeutic efficacy of rTMS for other anxiety disorders, namely panic disorder and a specific phobia (acrophobia, or the fear of heights). Regarding the latter, the single available study (Herrmann et al., 2017) tested only two sessions of 10 Hz-rTMS of the mPFC, and thus was not considered.

For the study on panic disorder, results were reported in two papers (Deppermann et al., 2014, 2017). This double-blind trial was performed in 44 patients, with or without agoraphobia, equally randomized to real or sham iTBS delivered to the left DLPFC for 15 daily sessions in the first third of a 9-week course of Cognitive Behavioral Therapy (CBT). While symptom improvement was reported overall, no differences were found between the two groups (real vs. sham). Previously, two RCTs had described the effects of 1Hz-rTMS delivered at 110% RMT to the right DLPFC for either 10 (Prasko et al., 2007) or 20 days (Mantovani et al., 2013). While the earlier study was smaller (15 patients) and did not result in significant differences between real vs. sham stimulation groups, in Mantovani et al. (2013) a significantly greater improvement was observed in the 12 patients who received real stimulation than in the sham group (13 patients). Nevertheless, heterogeneity between these studies does not allow for a recommendation regarding rTMS to treat panic disorder.

13.2. Post-traumatic stress disorder

In post-traumatic stress disorder (PTSD), the main cortical target that was evaluated was the right DLPFC, stimulated at low or high frequency. Regarding studies published prior to 2014, beneficial effects on the core symptoms of PTSD were found in three Class III sham-controlled studies, including at least 10 patients in the real stimulation group. Two studies showed beneficial effects of HF-rTMS delivered to the right DLPFC in small series of 16 patients (10 real, 6 sham) (Cohen et al., 2004) and 20 patients (10 real, 10 sham) (Boggio et al., 2010). One study showed beneficial effects of LF-rTMS delivered to the right DLPFC in 20 patients (10 real, 10 sham) (Watts et al., 2012). In the study of Cohen et al. (2004), 8 additional patients received real 1Hz-rTMS over the right DLPFC (10 daily sessions with 100 pulses per session), but the protocol was less beneficial than HF-rTMS. Finally, Boggio et al. (2010) also showed a significant decrease in PTSD symptoms after HF-rTMS applied to the left DLPFC, but to a lesser extent than after right-sided stimulation. In this study, mood improved after left-sided HF-rTMS, while anxiety was reduced after right-sided HF-rTMS. The reduction of anxiety following HF-rTMS of the right DLPFC was also found by Cohen et al. (2004). Thus, 10 daily sessions of HF-rTMS of the right DLPFC was found to provide the greatest therapeutic impact in patients with PTSD, with a Level C of Evidence (Lefaucheur et al., 2014). This procedure was able to provide long-lasting improvement in PTSD symptoms, still significant 3 months after the last session (Boggio et al., 2010), while in case of LF-rTMS, therapeutic efficacy was already decreasing at 2-month follow-up (Watts et al., 2012).

Since 2014, only one additional sham-controlled study based on HF-rTMS of the right DLPFC was reported (Ahmadizadeh and Rezaei, 2018). In this study, 58 patients with PTSD were randomized to receive real 20Hz-rTMS over the right DLPFC only (n=19) or the both right and left DLPFC (n=19) or a sham procedure with a sham coil (n=20). The parameters of stimulation consisted of 10 sessions over 4 weeks (3 sessions/week for the first two weeks and 2 sessions/week for the last two weeks) with 2400 pulses/session (all over the right DLPFC, or 1200 pulses over the right DLPFC followed by 1200 pulses over the left DLPFC), performed at 100% of RMT, with the DLPFC target defined according to the 5cm-rule. The proportion of responders (defined as PTSD checklist military version (PCL-M) total score improvement $\geq$ 2 standard deviations) was significantly higher after real unilateral or bilateral rTMS compared to sham rTMS (41.2%, 62.5%, and 0% of responders, respectively). At the end of the 4-week protocol, a greater reduction in the PCL-M total score was found in the real stimulation groups (without significant difference between unilateral and bilateral stimulation) compared to the sham group. The 'positive' results of this Class II study, in addition to those of the two Class III studies previously reported (Cohen et al., 2004; Boggio et al., 2010), allow a Level B of Evidence (probable efficacy) to be reached concerning the application of HF-rTMS to the right DLPFC in the treatment of PTSD.

Regarding LF-rTMS of the right DLPFC, the study of Watts et al. (2012) showed advantage of real stimulation relative to sham on 20 patients (10 real, 10 sham), and that of Cohen et al. (2004) showed no real benefit of the procedure in 14 patients (8 real, 6 sham). Since then, additional sham-controlled studies assessed this procedure only in small samples (less than 10 patients receiving real LF-rTMS protocol). For example, in a series of 16 patients (7 real, 9 sham), Nam et al. (2013) showed a greater improvement over time (up to 5-week follow-up) in the Clinician-Administered PTSD Scale (CAPS) total score and the reexperiencing subscore after real versus sham stimulation. The rTMS protocol consisted of 15 daily sessions (over 3 weeks) of 1Hz-rTMS (1200 pulses per session) delivered at 100% of RMT over the right DLFPC (defined with the 5cm-rule).

Other studies combined LF-rTMS of the right DLFPC and cognitive therapy. First, in a sham-controlled crossover study of 9 patients with PTSD, Osuch et al. (2009) found a moderate improvement in hyperarousal subscore of the CAPS after such a combined protocol. Kozel et al. (2018) applied 1Hz-rTMS to the right DLPFC (defined with the Beam-F4 method) just prior to Cognitive Processing Therapy (CPT) for 12-15 daily sessions (1800 pulses/session at 110% of RMT) in a large series of 62 military veterans (32 real, 30 sham). A 6-month follow-up was completed by 59 patients. The real rTMS+CPT group showed greater improvement (assessed on CAPS and PCL-M) compared to the sham rTMS+CPT group at the end of the rTMS protocol with sustained benefit up to 6 months post-treatment.

Thus, LF-rTMS of the right DLPFC could be an alternative to HF-rTMS of the right DLPFC in patients with PTSD. These two protocols were compared in a recent study (Kozel et al., 2019), including 27 patients (14 patients treated by 1Hz-rTMS and 13 by 10Hz-rTMS for 5 sessions/week during 6 weeks). Both groups significantly improved on various PTSD and depression scores without any advantage for either LF- or HF-rTMS, except the Inventory of Psychosocial Functioning (IPF) score, in which there was significant advantage for 10Hz-rTMS. In conclusion, regarding LF-rTMS of the right DLPFC, one Class III study was positive (Watts et al., 2012), two studies did not meet the requirement of 10 patients receiving real rTMS and showed conflicting results (Cohen et al., 2004; Nam et al., 2013), while two other positive studies assessed the effects of combined cognitive therapy and rTMS (Osuch et al., 2009; Kozel et al., 2018). Thus, and even though one study (Kozel et al., 2019) did not find substantial differences of efficacy for LF-rTMS compared to HF-rTMS of the right DLPFC (which has Level B of Evidence, see above), further work is still required before making a relevant recommendation on the use of LF-rTMS of the right DLPFC in the treatment of PTSD.

Finally, one research group applied a protocol of 20Hz-rTMS in patients with PTSD after a brief exposure to a script of the traumatic event within the same session, for 12 sessions over 4 weeks (Isserles et al., 2013). In this study, a bihemispheric mPFC area (rather than the right DLPFC) was stimulated using a H1-coil. The real stimulation, performed in 9 patients, reduced the Clinician-Administered PTSD Scale (CAPS) total score and various CAPS subscores, while no change was observed in cases of sham stimulation (9 patients) or previous exposure to a non-traumatic script (8

patients). Such larger and more medial HF-rTMS application over prefrontal regions was not replicated to date.

13.3. Obsessive compulsive disorder

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND obsessive compulsive disorder) identified 51 papers, including 9 original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions.

To treat obsessive compulsive disorder (OCD), either LF- or HF-rTMS was applied, using either a focal or a non-focal coil, over various cortical targets, such as the DLPFC (of the right or both right and left hemispheres), the right orbitofrontal cortex (OFC), and more medial regions, including the mPFC-ACC and the (pre-)SMA (Lusicic et al., 2018).

13.3.1. LF-rTMS of orbitofrontal/prefrontal regions

Regarding focal stimulation (using a figure-of-8 coil) delivered at 1Hz over the right DLPFC, two independent sham-controlled studies were published since 2014 (Table 18). One study (Elbeh et al., 2016) showed the superiority of 1Hz-rTMS of the right DLPFC as compared with 10Hz-rTMS or sham rTMS delivered to same target, to improve OCD symptoms, assessed on the Yale-Brown-Obsessive-Compulsive Scale (YBOCS), as well as anxiety, assessed on HARS. In this study, 45 patients were equally randomized to receive 10 session of real LF-rTMS, real HF-rTMS, or a sham procedure. The second study (Seo et al., 2016) also reported the efficacy of 1Hz-rTMS of the right DLPFC, compared to a sham condition, in a series of 27 patients with OCD of at least moderate severity and no comorbid psychiatric disorders other than depression. In contrast, one sham-controlled study performed before 2014 (Alonso et al., 2001) had reported 'negative' results with no significant change in YBOCS score after real LF-rTMS of the right DLPFC. However, this older study was based on a very small sample (10 patients in the real stimulation group and 8 patients in the sham group) and a non-focal stimulation using a circular coil. Focal 1Hz-rTMS of the left DLPFC also did not show any effect on OCD symptoms in an earlier study (Prasko et al., 2006). However, from the two recent sham-controlled Class II/III studies providing 'positive' results, a Level C of Evidence (possible efficacy) can be proposed for focal LF-rTMS of the right DLPFC in OCD.

- Insert Table 18 -

Two studies also performed 1Hz-rTMS, but using a large, non-focal coil. Firstly, in a crossover study of 19 patients with OCD, Nauczyciel et al. (2014) delivered 1Hz-rTMS over the right OFC using a large double-cone coil for 10 daily sessions (1200 pulses/session). Only a trend towards a better improvement was observed after real vs. sham stimulation (19% vs. 6% reduction on YBOCS score, respectively). More beneficial results had been previously published by Ruffini et al. (2009) using 1Hz-rTMS applied to the left OFC using a focal figure-of-8 coil.

Secondly, Carmi et al. (2018) used an H7 coil, designed to stimulate a bihemispheric mPFC area including the ACC. A daily rTMS session was performed for five weeks at 1Hz, but also at 20Hz, or according to a sham procedure. Clinical improvement, measured on the YBOCS, was observed following HF-, but not LF-rTMS, compared to sham. From these results, no conclusion can be drawn for the use of non-focal LF-rTMS of orbitofrontal/prefrontal regions in OCD.

13.3.2. HF-rTMS of prefrontal regions

Other research groups assessed the efficacy of HF-rTMS (rather than LF-rTMS) delivered with either a focal or a non-focal coil over prefrontal regions to improve OCD symptoms.

Before 2014, two sham-controlled studies assessed the value of focal HF-rTMS delivered to the right DLPFC, both showing no significant difference between the real and sham procedures (Sarkhel et al., 2010; Mansur et al., 2011). These results are consistent with those reported by Elbeh et al. (2016) showing the absence of superiority of 10Hz-rTMS of the right DLPFC compared to a sham procedure. Similarly, focal HF-rTMS of the left DLPFC was proved to be ineffective for improving treatment-resistant OCD (Sachdev et al., 2007).

Focal, but bilateral HF-rTMS of DLPFC regions was performed in 3 studies published by the same group of authors (Haghighi et al., 2015; Jahangard et al., 2016; Shayganfard et al., 2016). They delivered bihemispheric 20Hz-rTMS using a figure-of-8 coil over the left then the right DLPFC (targeted according to the 5cm-rule) within the same session (750 pulses per hemisphere and per session at 100% of RMT) for 10 sessions. These 3 crossover studies, including 10 to 21 patients, reported the superiority of real HF-rTMS as compared with the sham procedure (tilted coil) to improve OCD symptoms (30-35% reduction of YBOCS score on average in the real stimulation condition compared to less than 5% reduction in the sham condition). Cognitive, but not executive functions also improved.

In one study (Ma et al., 2014), a circular coil was used to stimulate a more medial region, centered halfway between the right and left DLPFC (defined accoding to F4-P4 and F3-P3 sites, respectively). In this sham-controlled study of 46 patients (25 real, 21 sham), rTMS pulse frequency was synchronized to the alpha frequency (8-12Hz) of EEG activity previously recorded in each individual. Beneficial effects of 10 sessions of HF-rTMS (648-872 pulses/session delivered at 80% of RMT) were reported at the end of 2-week treatment and 1-week follow-up in the real vs. sham stimulation group, both on YBOCS score (32-34% vs. 15-18% reduction, respectively) and HARS score (34-36% vs. 14-22% reduction, respectively).

As aforementioned, Carmi et al. (2018) used an H7 coil to stimulate a large and deep bihemispheric mPFC-ACC region, with individualized symptom provocation preceding rTMS sessions. Clinical improvement was observed after 20Hz-rTMS (n=7), but not LF-rTMS (n=8), compared to sham (n=8), with a significantly higher percentage of responders (defined as YBOCS reduction >30%) for at least one month following the last rTMS session. Due to this interim analysis,

recruitment for the LF group was interrupted, and results from a larger multicenter trial comparing HF-rTMS to sham, coordinated by the same group, were recently published (Carmi et al., 2019). A significant difference in reduction of YBOCS scores was found among patients that completed the trial when comparing HF-rTMS (n=42, 45.2% responders) to sham (n=45, 17.8% responders), which has allowed for FDA clearance of non-focal HF-rTMS for bilateral stimulation of mPFC-ACC regions, combined with individualized symptom provocation, in OCD.

A large and deep HF-rTMS protocol was also assessed in OCD patients using a double-cone coil to stimulate the dmPFC-ACC connectivity, as performed by the same research group in depression (Bakker et al., 2014; Downar et al., 2014; Salomons et al., 2014). In a Class IV study with an open-label design (Dunlop et al., 2016), 20 patients with treatment-resistant OCD received 20 daily sessions (over 4 weeks) of 10Hz-rTMS delivered on the left then the right dmPFC within the same session (3000 pulses per hemisphere and per session) using with a double-cone coil and a navigation system. Target location corresponded to 25% of the total distance from nasion to inion, slightly anterior to the location of pre-SMA target. Ten patients (50%) were responders to the rTMS procedure (improvement ≥50% on YBOCS score). The clinical response correlated to the reduction of a higher dmPFC-ventral striatal connectivity at baseline, assessed on resting-state fMRI.

While there were several positive Class II and III studies for prefrontal HF-rTMS in OCD, the methods used are too heterogenous to make any recommendation on the use of rTMS, delivered focally over the right and/or left DLPFC, or less focally over prefrontal regions using a circular, H7, or double-cone coil. However, as mentioned above, the FDA recently approved the use of deep rTMS as an adjunct for the treatment of adult patients suffering from OCD (on August 16, 2018), according to the protocol described in the study of Carmi et al. (2018) and the subsequent findings reported in a multicenter randomized trial of approximately 100 OCD patients (Carmi et al., 2019). This protocol consists in using an H7 coil to stimulate a bihemispheric mPFC-ACC region at 20Hz.

13.3.3. LF-rTMS of pre-SMA

Before 2014, two sham-controlled studies reported results of 1Hz-rTMS delivered bilaterally to the pre-supplementary motor area (pre-SMA) for 4 weeks in 18 patients (9 real, 9 sham) (Mantovani et al., 2010) or 2 weeks in 22 patients (12 real, 10 sham) (Gomes et al., 2012). Both studies assessed the average reduction of YBOCS score and the rate of responders after real stimulation compared to a sham procedure. Beneficial results were reported, but they were significant compared to sham control only in the study of Gomes et al. (2012).

Since 2014, 3 additional sham-controlled studies investigated the efficacy of LF-rTMS similarly targeted to the pre-SMA (Table 19). When compared to a sham condition, real stimulation was found to be more efficacious to improve OCD symptoms in one study (Hawken et al., 2016). In contrast, bilateral pre-SMA stimulation was found to be ineffective in the other two studies (Pelissolo et al., 2016; Arumugham et al., 2018). In one of these studies (Pelissolo et al., 2016), the pre-SMA

target location was defined on individual MRI using a navigation system and all patients had severe, drug-refractory OCD symptoms. In the second study (Arumugham et al., 2018), patients were less severe, including partial responders to antidepressant medications.

In the meta-analysis of Rehn et al. (2018) rTMS was found to produce overall a modest effect in reducing YBOCS scores and LF-rTMS of the pre-SMA yielded the greatest reductions relative to other cortical targets and stimulation frequency. However, according to our criteria taking into account conflicting results across studies on the significance of the differential effect between real vs. sham stimulation, no recommendation can be made to date for LF-rTMS of pre-SMA in the context of OCD.

- Insert Table 19 -

Other studies have further explored the therapeutic potential of rTMS in OCD, using different approaches. In one study (Kang et al., 2009b), LF-rTMS was sequentially delivered over the right DLPFC and SMA (1200 pulses per site and per session at 100-110% of RMT) in 20 patients equally randomized to receive 10 sessions of either real or sham stimulation. No significant effect of the real procedure was observed on YBOCS and depression scores compared to sham control (tilted coil).

Finally, in a naturalistic open-label study, Singh et al. (2019) targeted either the bilateral SMA (46 patients) or the left OFC (33 patients) using 1Hz-rTMS in medication-resistant OCD. A majority of patients (57%) met criteria for partial clinical response (reduction of YBOCS score >25%) and 40% were 'complete' responders (reduction of YBOCS score >35%). However, there was no significant difference between patients receiving LF-rTMS over bilateral SMA or left OFC. The presence of comorbid depression and higher baseline YBOCS score was associated with lower response to rTMS.

13.4. Autism spectrum disorders

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND autism) identified 29 papers, including only one original sham-controlled study with at least 10 patients receiving real stimulation for several daily sessions (Enticott et al., 2014). In this sham-controlled study, 28 adults with Asperger's disorder (15 real, 13 sham) underwent 10 daily sessions of deep 5Hz-rTMS (1500 pulses/session) using a HAUT-coil (H3-coil), which was designed to stimulate the dmPFC bilaterally. A significant reduction in social relating symptoms (especially self-oriented anxiety during difficult and emotional social situations) was found after real stimulation and not in the sham group.

Another study compared the effect of 1Hz-rTMS of the left DLPFC (F3 site, 20 daily sessions, 1500 pulses/session, 90% of RMT) and anodal tDCS over the same target in 24 children with autism spectrum disorder (Gomez et al., 2017). In this open-label study (Class IV), children <10 years received tDCS, whereas children >11 years received rTMS. A significant improvement of symptom severity in autism-related scores was observed in the rTMS group with no difference between rTMS- and tDCS-induced changes.

To our knowledge, all other rTMS/TBS studies performed in the context of autism had an open-label desing or were based on single sessions and did not meet our study requirements. For

example, one randomized, sham-controlled, crossover trial assessed the value of single sessions of iTBS applied bilaterally over the DLPFC or the posterior superior temporal sulcus (pSTS) in 19 adults with autism spectrum disorder (Ni et al., 2017). Compared to an active sham control (real stimulation over the inion), the reaction time in the Conners' Continuous Performance Test was reduced after the iTBS session delivered over the bilateral DLPFC, but not the STS. An open-label pilot study also showed that 15 sessions of iTBS delivered over the right DLPFC under neuronavigation guidance could improve executive functions, YBOCS score, and repetitive behaviors in 10 patients with autism spectrum disorder (Abujadi et al., 2018).

Overall, the existing evidence concerning the use of rTMS to treat various aspects of autism spectrum disorders is relatively weak taken into consideration the small sample sizes, the heterogeneity in clinical presentation and measures, and the variety of rTMS protocols and targets among the studies (Barahona-Corrêa et al., 2018; Cole et al., 2019).

13.5. Attention deficit hyperactivity disorder

A PubMed search (keywords: (rTMS OR theta burst stimulation) AND attention deficit hyperactivity disorder) identified 11 papers, but no original sham-controlled studies with at least 10 patients receiving real stimulation for several daily sessions. Only one original sham-controlled study deserves to be mentioned, which is the study of Paz et al. (2017). In this study, deep HF-rTMS was performed over bilateral DLPFC areas using an H5-coil (20 sessions of 1980 pulses/session delivered at 18Hz) in 22 adults with attention deficit hyperactivity disorder (9 real, 13 sham), but did not result in any clinical benefit.

13.6. Mental retardation

A single Class IV study performed on 45 right-handed children with mental retardation of various aetiologies is worth mentioning (Qiu et al., 2016). In 24 children aged 2-3 years, a 10-day protocol of non-navigated HF-rTMS of the left IFG (Broca's area) was performed coupled with traditional language training, whereas 21 age-matched children received language training only. The combined procedure (HF-rTMS + language training) produced better clinical improvement than laguage training performed alone, in terms of movement ability and linguistic competence. This result is in line with those above described for the rehabilitation of aphasia.

13.7. Functional neurological disorders

One sham-controlled, crossover Class III study was conducted to verify whether rTMS, without other concomitant therapies, may improve functional flaccid paresis (Broersma et al., 2015). This study enrolled 12 patients with unilateral or asymmetric paresis lasting from 4 weeks to 25 years,

but only 8 of these 12 patients received both real and sham rTMS procedures. These procedures consisted of neuronavigated 15Hz-rTMS delivered over the hand M1 area contralateral to the paretic limb(s) once daily over 10 consecutive weekdays (9000 pulses/session at 80% of RMT). An objective increase in muscle strength of the paretic hand (measured by a dynamometer) was found after real stimulation (+24% on average) but not after realistic sham procedure (+6%). However, subjective ratings showed that patients did not perceive this objectively measured motor improvement. In addition, no long-term follow-up was included in this study, and therefore it remains to be demonstrated that rTMS can have a real therapeutic benefit in patients with functional paresis.

14. Summary of recommendations

This work updates the evidence-based recommendations that were previously established by a group of European experts regarding the potential therapeutic applications of rTMS in the neurological, ENT, and psychiatric domains (Lefaucheur et al., 2014). New recommendations are summarized in Table 20.

Level A evidence (definite efficacy) is still proposed for HF-rTMS of M1 contralateral to pain side in neuropathic pain and for HF-rTMS of the left DLPFC in MDD using a figure-of-8 coil, but also a H1-coil. The same recommendation is now proposed for LF-rTMS of contralesional M1 in hand motor recovery at the postacute stage of stroke.

Level B evidence (probable efficacy) is still proposed for: (i) LF-rTMS of the right DLPFC in MDD; (ii) HF-rTMS of the left DLPFC for treating depression in PD patients. The same recommendation is now proposed in 9 new condtions: (i) HF-rTMS of the left M1 in improving quality of life of patients with fibromyalgia; (ii) HF-rTMS of the left DLPFC in relieving pain in patients with fibromyalgia; (iii) HF-rTMS of bilateral M1 regions in improving motor symptoms of PD patients; (iv) HF-rTMS of ipsilesional M1 in promoting hand motor recovery at the postacute stage of stroke; (v) iTBS of the leg motor cortex in relieving lower limb spasticity in MS; (vi) LF-rTMS of right IFG in promoting nonfluent aphasia recovery at the chronic stage of stroke; (vii) bilateral right-sided LF-rTMS and left-sided HF-rTMS of the DLPFC in MDD; (viii) bilateral right-sided cTBS and left-sided iTBS of the DLPFC in major unipolar depression; (ix) HF-rTMS of the right DLPFC in PTSD.

Level C evidence (possible efficacy) is still proposed for: (i) HF-rTMS of M1 contralateral to pain side in CRPS type I; (ii) cTBS of the contralesional left PPC in visuospatial hemineglect recovery at the post-acute stage of stroke; (iii) LF-rTMS of the epileptic focus to treat chronic epilepsy; (iv) LF-rTMS of the auditory cortex of the left hemisphere (or contralateral to the affected ear) in chronic tinnitus; (v) of LF-rTMS of the left TPC in auditory hallucinations in schizophrenia; (vi) HF-rTMS of the left DLPFC on cigarette craving and consumption. From our previous work, the level of evidence decreased from B to C in three conditions that were: (i) LF-rTMS of the contralesional M1 in hand motor recovery at the chronic stage of stroke; (ii) the differential antidepressant efficacy between:

right LF-rTMS vs. left HF-rTMS, bilateral vs. unilateral rTMS of the DLPFC, and rTMS performed alone vs. combined with antidepressants; (iii) HF-rTMS of the left DLPFC on negative symptoms of schizophrenia. In contrast, the level of evidence increased to C in two other conditions, namely: (i) multisite rTMS-COG to improve cognitive function, memory and language level of AD patients, especially at a mild/early stage of the disease; (ii) LF-rTMS of the right DLPFC in OCD.

- Insert Table 20 -

For conditions in which no recommendation has been proposed, this does not mean that no effect can be obtained in selected responders, taking into account the high interindividual response to rTMS protocols. On the other hand, the current recommendations are based on the differences reached in therapeutic efficacy of real vs. sham rTMS protocols, replicated in a sufficient number of independent studies. This does not mean that the benefit produced by rTMS inevitably reaches a level of clinical relevance.

Compared to meta-analyses, several limitations of the present systematic review must be acknowledged. For instance, in the meta-analyses published in the Cochrane Library (Li et al., 2014b; Pollock et al., 2014; Dougall et al., 2015; Chen et al., 2016; Bath et al., 2018; O'Connell et al., 2018), two important criteria are taken into account in the assessment of the risk of bias that are sample size and study duration. Regarding sample size, Cochrane reviews attribute a high risk of bias for studies with fewer than 50 participants per arm, an unclear risk of bias for studies with between 50 and 199 participants per arm, and a low risk of bias only for studies with 200 or more participants per arm. However, such sample sizes are rarely achieved in rTMS studies and in the present work, we only differentiated the studies according to whether they had more or fewer than 25 or 10 patients in the real stimulation arm (Class I vs. II-III studies).

Regarding study duration, Cochrane reviews attribute a low risk of bias for studies with follow-up of 8 weeks or longer, an unclear risk of bias for studies with follow-up of 2 to 7 weeks, and a high risk of bias for studies with follow-up of less than 2 weeks. The duration of the follow-up was not taken into account in the present work, but it must be admitted that the vast majority of studies involved a follow-up not exceeding a few weeks during or beyond the stimulation time.

A highly structured evaluation of the quality of the evidence provided by studies in controversial literature, such as for rTMS, can also provide answers regarding the therapeutic value of this intervention. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Balshem et al., 2011; Guyatt et al., 2011; Schünemann et al., 2011) integrates multiple aspects of the published studies into a critical rating of the quality of the evidence. In the GRADE system, evidence of the outcome of a study is categorized as high, moderate, low, or very low based on experts' confidence in the estimate of the effect. This assessment takes into account 5 factors that can downgrade the quality level of a set of evidence: (i) limitations in the design and execution of the studies (risk of bias in patients' selection, group allocation, blinding, selective reporting...), (ii) inconsistency (unexplained heterogeneity of results across studies), (iii) indirectness (according to differences in population definition, interventions, outcome measures or comparisons), (iv)

imprecision (small sample size, wide confidence intervals), and (v) publication bias (overestimation of the effect because positive results are most likely to be reported than negative or null findings).

Whether to rate up or down the quality of the body of evidence for each outcome is a matter of judgment. In the present work, the risk of bias related to study limitations was taken into account to downgrade from Class I to Class II the studies including 25 or more patients in the real stimulation arm or from Class II to Class III the studies with a smaller sample. Inconsistency and indirectness were also considered, e.g., regarding the influence of the heterogeneity of rTMS protocol patterns, clinical profiles of patients, types of symptoms treated or outcome measures. On the other hand, we did not estimate the size of the treatment effect, which is usually done by calculating the standardized mean difference (SMD) in the results provided by the active treatment (real rTMS) and placebo comparator (sham rTMS) across studies. This calculation makes it possible to standardize the results and to obtain a pooled effect size regardless of the variability of the intervention effect between the studies combined for the analyses.

We did not perform this quantified evaluation and we focused instead on the fact that results were replicated by independent teams. Indeed, most meta-analyses do not take care that large samples can come from a single team or research network with redundancies in terms of the origin of the published data. In addition, one must always keep in mind that very large studies are more likely to find a statistically significant difference for a trivial effect that does not really make clinical sense (Ioannidis, 2005). Therefore, beyond sample sizes, focusing on the replication of results plays an important role in improving the reliability of research outcomes (Ioannidis, 2014). In our work, for studies based on the same methodology applied to patients with the same clinical profile, only one study was selected per research group at most. The fact that the results were reproduced by independent teams in different articles clearly had more impact in our study than a multicenter study based on a very large sample. This explains why a similar level of evidence could be attributed in this work to the effects of rTMS on pain, stroke and MDD, although sample sizes were largely greater in the latter condition.

In conclusion, differences in the methodology of data analysis lead to differences in the level of evidence across systematic reviews and meta-analyses. As an example, in other systematic reviews based on the GRADE system, the level of evidence of rTMS efficacy was lower than in our work. For example, HF-rTMS of the motor cortex reached a 'weak for' recommendation in neuropathic pain and fibromyalgia (Cruccu et al., 2016) with a low quality evidence for short-term effects on chronic pain and quality of life, due to issues of blinding and precision (O'Connell et al., 2018). Conversely, other meta-analyses reported a significant analgesic efficacy of active rTMS compared to sham rTMS according to effect size measurement based on SMD (Jin et al., 2015) or odds ratios (ORs) up to 4 (Goudra et al., 2017). Regarding therapeutic effects on depression, one meta-analysis reported higher ORs for various rTMS procedures (ranging between 1.7 and 7.4) (Mutz et al., 2018) than what has been shown for most antidepressant drugs (ranging between 1.4 and 2.1) (Cipriani et al., 2018).

Although rTMS was approved or cleared for "safety and efficacy" in various therapeutic indications by regulatory agencies, such as the FDA, there is still a need for substantially larger, rigorously designed studies, particularly including longer courses of stimulation sessions. As emphasized in our previous article, future rTMS studies must gain in rigor and power on the following elements: randomized parallel-group design, sufficient sample size, accurate targeting, especially using neuronavigation and robotic arm systems, realistic sham procedure (Rossi et al., 2007; Mennemeier et al., 2009), double-blinding, and clinically relevant outcome measures.

On the other hand, technical developments include new forms of coils and magnetic field geometry (Deng et al., 2013, 2014; Tendler et al., 2016; Goetz and Deng, 2017; Koponen et al., 2017), and tailored strategies, based on neuroimaging methods (e.g., fMRI or diffusion tensor MRI tractography) (Grefkes and Fink, 2014; Bergmann et al., 2016; Diekhoff-Krebs et al., 2017), on neurophysiological methods (e.g., high-resolution EEG) (Bergmann et al., 2016), on concurrent TMS-EEG method (Tremblay et al., 2019), or on clinical response to single test sessions (Kreuzer et al., 2017). All these data can serve to adapt the rTMS protocol to a personalized medicine approach.

Even personalized, therapeutic applications of rTMS were always performed with an open-loop design to date, while one of the most promising approaches is to consider rTMS in a closed-loop configuration (Gharabaghi et al., 2014; Karabanov et al., 2016; Zrenner et al., 2016, 2018; Mansouri et al., 2018). A closed-loop configuration means that all TMS pulses are delivered at a well-defined time, generally according to EEG activity recorded and analyzed in real-time. Using such a strategy, rTMS could be coupled with neuronal activities for brain-state dependent and adaptive stimulation procedure. New coil design could be developed to offer the possibility to stimulate online at multiple sites of the brain according to the occurrence of specific neural triggers in a feedback-controlled stimulation procedure (Koponen et al., 2018).

Finally, beyond statistical levels of evidence or estimates of effect size and our confidence in these estimates, the clinical importance of the proposed therapeutic efficacy must be considered. The present work only provides arguments to be confident that some rTMS protocols do something that is different from a placebo in some indications, but not that the results obtained are clinically relevant. Clinical relevance in routine practice also requires that rTMS therapy provides beneficial effects in the long term. The optimal time window for applying rTMS treatment should also be specified, i.e. its place in the therapeutic decision tree, especially in the management of MDD and chronic pain. It is probably better defined in other clinical conditions, such as motor stroke, for which the requirements to use rTMS in the postacute or chronic stages are different. However, given the relatively coarse and therefore debatable definitions of the acute, postacute and chronic post-stroke phase, which do not represent uniform periods with sharp boundaries but rather a continuum with different time-sensitive processes, a more systematic assessment of the optimal time window to treat patients with rTMS is needed, ideally based on individual markers of the responsiveness to rTMS. Furthermore, the objective of rTMS as an add-on or priming technique in combination with a rehabilitation therapy for a limited period of time must be differentiated from performing rTMS alone to control a chronic disease. In the

former condition, the timing of rTMS application in the combined strategy must be considered in the foreground to promote functional recovery. In the latter condition, the rhythm of the maintenance sessions is a critical factor for the usefulness of the procedure in the long term. Actually, among the patients with chronic, long-lasting disease, some of them can be considered good or excellent responders and really benefit from rTMS protocols in the dailylife management of their illness. In contrast, the average clinical response to rTMS remains rather modest, short-lasting, and not clincally meaningful and relevant in most of the stimulated patients, although the improvement can be statistically significant on group level. Nevertheless, in spite of present shortcomings, we are convinced that there is a future for rTMS as a therapeutic tool (Terranova et al., 2019). All recent studies have confirmed the good tolerance of this technique, since no severe complication has been reported. It would be interesting if observational studies carried out over long periods (5 to 10 years of follow-up) could confirm this good tolerance. In addition, all efforts should be made towards a precision medicine, which aims at reducing the large interindividual variability in the therapeutic efficacy of rTMS.

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Conflict of interest

Dr. Brunelin received honoraria from Brainsway Inc. for his particpation in the Brainsway European scientific advisory board. Dr. Hasan received paid speakership by Janssen, Lundbeck, and Otsuka and was member of scientific advisory boards of those companies, outside the submitted work. Dr. Langguth received honoraria from Autifony, Boehringer, Decibel Therapeutics, Desyncra, Neurolite, Neuromod, and Servier, outside the submitted work. Dr. Lefaucheur received speaker's fees from Pfizer and Sanofi, outside the submitted work. Dr. Leocani received honoraria for consulting services from Biogen, Merck, Novartis, and Roche, and for speaking activities from Teva, research support from Biogen, Merck, and Novartis, and travel support from Merck and Roche, outside the submitted work. Dr. Oliveira-Maia is the national coordinator for Portugal of a study sponsored by Janssen-Cilag Ltd. and recipient of a grant from Schuhfried GmBH, outside the submitted work. Dr. Padberg is a member of the European Scientific Advisory Board of Brainsway Inc. and has received speaker's honoraria from Mag&More GmbH and the neuroCare Group. Dr. Paulus received consulting

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Table 1. HF-rTMS of M1 contralateral to pain region in neuropathic pain

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Khedr et al., 2015	30 patients with malignant neuropathic pain (real: 15; sham: 15)	Hand M1 contralateral to pain, F8c (anteroposterior orientation)	Tilted coil	20Hz, 80% RMT	2000 pulses, 10 sessions	Reduction of pain score at the end of rTMS protocol (49% on VRS and 37% on VAS), up to 2 weeks after the last session (46% on VRS and 36% on VAS); 87-80% responders (>30% pain relief)	II
Ma et al., 2015	40 patients with postherpetic neuralgia (real: 20; sham: 20)	Homotopic M1 contralateral to pain region, F8c (anteroposterior orientation)	Tilted coil	10Hz, 80% RMT	1500 pulses, 10 sessions	Reduction of pain score (17% on VAS), up to 3 months after the last session; 50% responders (>50% pain relief)	II
Attal et al., 2016	32 patients with neuropathic lumbar radicular pain (real: 21; sham: 11)	Hand M1 contralateral to pain, F8c (anteroposterior orientation)	Sham coil	10Hz, 80% RMT	3000 pulses, 3 sessions	Reduction of pain score at the end of rTMS protocol (#60% on VAS), up to 5 days after the last session (#25% on VAS); 43% responders (>30% pain relief)	II
Nurmikko et al., 2016	27 patients with neuropathic pain of various origins (crossover)	Homotopic M1 contralateral to pain region or an adjacent motor region, F8c (perpendicular to central sulcus)	Occipital stimulation	10Hz, 90% RMT	2000 pulses, 5 sessions	Reduction of pain score compared to control condition one week after the last session (9-11% on VAS); 30% responders (>30% pain relief)	II

Table 2. HF-rTMS of bilateral M1 regions in Parkinson's disease (motor symptoms)

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Kim et al., 2015	17 (crossover)	Bilateral M1, lateralized to the dominant hemisphere (leg representation), DCc	Tilted coil	10Hz, 90% RMT	1000 pulses, 5 sessions	Improvement of UPDRS-III motor score (26%) and freezing of gait, one week after rTMS protocol	II
Brys et al., 2016	29 (real: 14; sham: 15)	Bilateral M1 (hand representation), F8c	Realistic sham coil	10Hz, NR	2000 pulses, 10 sessions	Improvement of UPDRS-III motor score (15%), one month after rTMS protocol	II
Makkos et al., 2016	44 (real: 23; sham: 21)	Bilateral M1 (hand representation), F8c	Tilted coil	5Hz, 90% RMT	2 x 300 pulses, 10 sessions	Improvement of UPDRS-III motor score (23%), one month after rTMS protocol	II

Table 3. LF-rTMS of contralesional M1 in motor stroke at the postacute stage

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Lüdemann-Podubecká et al., 2015	40 patients at 0.5-4 months post-stroke (real: 20; sham: 20)	Hand M1, F8c	0% RMT	1Hz, 100% RMT	900 pulses, 15 sessions (followed by 30-min session of physical motor therapy)	Improved dexterity of the affected hand in patients with stroke of the dominant hemisphere, but not of the non-dominant hemisphere, lasting at least 6 months after the last session	II
Matsuura et al., 2015	20 patients at 4-21 days post-stroke (real: 10; sham: 10)	Hand M1, F8c	Sham coil	1Hz, 100% RMT	1200 pulses, 5 sessions	Improved motor function of the affected hand (FMA-UL and Pegboard test scores), one day after rTMS protocol (no follow-up)	II
Zheng et al., 2015	108 patients at an average of 19 days post-stroke (real: 55; sham: 53)	Hand M1, F8c	Sham coil	1Hz, 90% RMT	1800 pulses, 24 sessions (followed by virtual reality therapy)	Improved motor function of the affected hand (FMA-UL, WMFT, and mBI), at the end of the 4-week rTMS protocol	I
Du et al., 2016a	35 patients at 3-30 days post-stroke (real: 16; sham: 19)	Hand M1, F8c	Tilted coil	1Hz, 110-120% RMT	1200 pulses, 5 sessions (followed by 60-min session of physical motor therapy)	Improved motor function of the affected limbs (FMA-UL/LL and MRC scores), more marked than after ipsilesional HF-rTMS, and lasting at least 3 months after the last session	II
Meng and Song, 2017	20 patients at unknown postacute stage (real: 10; sham: 10)	Hand M1, F8c	Coil away from the head	1Hz, 90% RMT	1800 pulses, 14 sessions (40-minute physical motor therapy twice a day)	Improved motor function of the affected hand (FMA-UL, NIHSS, and BI scores) at the end of the 14-day rTMS protocol	III
Long et al., 2018	62 patients at an average of 19-20 days post-stroke (real LF only: 21; real LF+HF: 21; sham: 20)	Hand M1, Cc	Tilted coil	1Hz (or 1Hz followed by 10Hz), 90% RMT	1000 pulses (or 1000 pulses followed by 1000 pulses at 10Hz), 15 sessions	Improved upper limb motor function (FMA-UL and WMFT score) up to 3 months after the last session, with bihemispheric LF+HF protocol more beneficial than contralesional LF-rTMS protocol alone	II
Li et al., 2016b	84 patients at an average of 1.6-1.9 months post-stroke (real: 42; sham: 42)	Hand M1, Cc	Sham coil	1Hz, 80% RMT	1000 pulses, 10 sessions (followed by 40-min session of occupational therapy)	Improved motor function of the affected hand (FMA-UL), at the end of the 2-week rTMS protocol, with no difference between contralesional LF-rTMS and ipsilesional HF-rTMS protocols	II
Lin et al., 2015b	31 patients at an average of 34-41 days post-stroke (real: 16; sham: 15)	Leg M1, F8c	Sham coil	1Hz, 130% RMT	900 pulses, 15 sessions (followed by 45-min session of physical motor therapy)	Improvement of leg mobility, posture, and gait at the end of the 3-week rTMS protocol	II
Huang et al., 2018b	38 patients at 10-90 days post-stroke (real: 18: sham: 20)	Thigh M1, DCc	Sham coil	1Hz, 120% AMT	900 pulses, 15 sessions (followed by 45-min session of physical motor therapy)	No effect on walking abilities (timed up and go test), balance, motor function, and activity of daily living at the end of the 3-week rTMS protocol	II

Table 4. HF-rTMS of ipsilesional M1 in motor stroke at the postacute stage

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Du et al., 2016a	39 patients at 3-30 days post-stroke (real: 20; sham: 19)	Hand M1, F8c	Tilted coil	3Hz, 80-90% RMT	1000 pulses, 5 sessions (followed by 60-min session of physical motor therapy)	Improved motor function of the affected limbs (FMA-UL/LL and MRC scores) less marked than after contralesional LF-rTMS	II
Hosomi et al., 2016	39 patients at an average of 45 days post-stroke (real: 18; sham: 21)	Hand M1, F8c	Tilted coil	5Hz, 90% RMT	500 pulses, 10 sessions	Improved motor function of the affected hand (Brunnstrom recovery stage (BRS-hand), FMA-UL, National Institutes of Health Stroke Scale (NIHSS) motor score, grip strength, and finger tapping), at the end of the 2-week rTMS protocol, lasting at least 16 days beyond the last session	II
Guan et al., 2017	27 patients at 1-14 days post-stroke (real: 13; sham: 14)	Hand M1, F8c	Tilted coil	5Hz, 120% RMT	1000 pulses, 10 sessions	Improved motor function of the affected hand (FMA-UL, National Institutes of Health Stroke Scale (NIHSS) motor score, and mBI), at the end of the 2-week rTMS protocol, lasting about 1 month beyond the last session, up to 1 year for the FMA-UL score	II
Li et al., 2016b	85 patients at an average of 1.4-1.6 months post-stroke (real: 43; sham: 42)	Hand M1, Cc	Sham coil	10Hz, 80% RMT	1350 pulses, 10 sessions (followed by 40-min session of occupational therapy)	Improved motor function of the affected hand (FMA-UL), at the end of the 2-week rTMS protocol, with no difference between ipsilesional HF-rTMS and contralesional LF-rTMS protocols	II
Sasaki et al., 2017	21 patients at an average of 11 days post-stroke (real: 11, sham: 10)	Leg M1, DCc	Sham coil	10Hz, 90% RMT	1000 pulses, 5 sessions	Improvement motor function of the affected lower limbs (Brunnstorm recovery stage (BRS-leg) and ability for basic movement scale (ABMS II) score)	II

Table 5. iTBS of ipsilesional M1 in motor stroke at the chronic stage

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Lai et al., 2015	72 patients at an average of 9.7-11.4 months post-stroke (real: 55; sham: 17)	Hand M1, F8c	Sham coil	iTBS, 80% AMT	600 pulses, 10 sessions	Improved motor function of the affected hand (WMFT, finger tapping task) at the end of the 2-week rTMS protocol (no follow-up), with better improvement in patients (n=21) with present MEP in the paretic hand at baseline than in patients (n=34) with absent MEP, especially if hand grip strength was also null	II
Lin et al., 2018	20 patients at an average of 12-12.8 months post-stroke (real: 10; sham: 10)	Thigh M1, F8c	Sham coil	iTBS, 100% AMT	1200 pulses, 10 sessions (followed by 45-min session of physical motor therapy) [2 sessions/week over 5 weeks]	Marginal improvement of the affected lower limb (FMA-LL, computerized dynamic posturography), at the end of the 5-week rTMS protocol	III

Table 6. HF-rTMS of ipsilesional M1 in post-stroke dysphagia

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Postacute stage							
Du et al., 2016b	25 patients at 4-26 days post-stroke (real: 13; sham: 12)	Mylohyoid M1, F8c	Tilted coil	3Hz, 90% RMT	1200 pulses, 5 sessions	Improved swallowing function at the end of the rTMS protocol, lasting at least 3 months beyond the last session	II
Park et al., 2017	22 patients at an average of 4.2 to 6.6 weeks post-stroke (real: 11; sham: 11)	Mylohyoid M1, F8c	Tilted coil	10Hz, 90% RMT	500 pulses, 10 session	No effect on swallowing function	II
Zhang et al., 2018	31 patients at an average of 21 to 26 days post-stroke (real: 15; sham: 16)	Mylohyoid M1, F8c	Tilted coil	10Hz, 110% RMT	900 pulses, 10 session combined with digastic muscle electrical stimulation	Improved swallowing function at the end of the rTMS protocol, lasting at least 1 month beyond the last session	III
Chronic stage							
Cheng et al., 2017	14 patients at 19-77 months post-stroke (real: 10; sham: 4)	Tongue M1, F8c	Sham coil	5Hz, 90% RMT	3000 pulses, 10 sessions	No effect on swallowing function, video-fluoroscopic assessment, tongue strength, or swallowing-related quality of life at any time point (up to 2 to 12 months post-rTMS)	III

Table 7. LF-rTMS of right IFG in post-stroke nonfluent aphasia at chronic stage

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Tsai et al., 2014	53 patients at 18 months post-stroke on average (real: 31; sham: 22)	Right IFG (BA45), F8c	Sham coil	1Hz, 90% RMT	600 pulses, 10 sessions	Improved speech on the CCAT, object and action naming accuracy and reaction time at the end of the 2-week rTMS protocol, lasting at least 3 months beyond the last session for the CCAT score	II
Wang et al., 2014a	43 patients at 16 months post-stroke on average (real: 29; sham: 14)	Right IFG (BA45), F8c	Sham coil	1Hz, 90% RMT	1200 pulses, 10 sessions (with concomitant (n=15) or subsequent (n=14) naming task, plus 60-minute speech training twice a week)	Improved speech on the CCAT, object and action naming accuracy at the end of the 2-week rTMS protocol, only in case of concomitant naming training, with benefit lasting at least 3 months beyond the last session	II
Yoon et al., 2015	20 patients at 5.2-6.8 months post-stroke on average (real: 10; sham: 10)	Right IFG (BA45), F8c	No stimulation	1Hz, 90% RMT	1200 pulses, 20 sessions (followed by 45-minute speech and language therapy)	Improved repetition and naming scores of the WAB at the end of the 4-week rTMS protocol	III
Hu et al., 2018	20 patients at 6.8-7.5 months post-stroke on average (real: 10; sham: 10)	F4, F8c	Tilted coil	1Hz, 80% RMT	600 pulses, 10 sessions	Improved aphasia quotients, spontaneous speech and auditory comprehension scores of the WAB at the end of the 2-week rTMS protocol, lasting at least 2 months beyond the last session	III

Table 8. 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	Significant clinical effects of real versus sham condition	Class of the study
Fu et al., 2015	20 (17-114 days after stroke) (real: 10, control: 10)	P5, F8c	Tilted coil	cTBS (3-pulse bursts delivered at 30Hz and repeated at 5Hz for 40s), 80% RMT	4 cTBS trains (15-min interval), 14 sessions	Improvement in tests for visuospatial neglect (star cancellation and line bisection tests) by 21-37% at the end of 2-week rTMS therapy and by 36-47% after 4-week follow-up	III
Nyffeler et al., 2019	30 (12–1080 days after stroke) (real: 20, control: 10)	P3, Cc	Sham F8c	cTBS (3-pulse bursts delivered at 30Hz and repeated at 6Hz for 44s) 100% RMT	4 cTBS trains (15 to 45-min interval), 2 or 4 sessions	Improvement in the impact of neglect-related deficits on the activities of daily life and in various tests for visuospatial neglect up to 3 months after either 2 or 4 cTBS sessions	II

Table 9. iTBS of M1 in multiple sclerosis

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Azin et al., 2016	36 RR patients (real: 19; sham: 17)	Left or right (?) hand M1, F8c	Tilted coil	iTBS, 80% AMT	600 pulses (?), 10 sessions	Improved manual dexterity (9HPT and BBT) at the end of the 2-week rTMS protocol	II
Korzhova et al., 2018	22 SP patients (real: 12; sham: 10)	Bilateral (?) leg M1, F8c	Coil away from the head	iTBS, 80% MSO	1200 pulses, 10 sessions	Improved spasticity (mAS, SESS) at the end of the 2-week rTMS protocol, lasting at least 12 weeks beyond the last session for the SESS score	II

Table 10. LF-rTMS of the auditory cortex in chronic tinnitus

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Langguth et al., 2014	139 (real: 95; sham: 44)	Post-T3-C3-line target (real, n=48) or navigated target on the region of the most increased PET activation within the left auditory cortex (real, n=47 or sham, n=44), F8c	Sham coil	1Hz, 110% RMT	2000 pulses, 10 sessions	No significant reduction of average TQ score between real and sham treatment, but more responders on the TQ score after targeting the post-T3-C3 site only (real: 38%, sham: 13%) at the end of 2-week rTMS protocol	I
Yilmaz et al., 2014	60 (real: 30; sham: 30)	Target not specified, F8c	Sham not specified	1Hz, intensity not specified	1800 pulses, 10 sessions	Significant reduction in THI score and tinnitus loudness one month after real rTMS	III
Bilici et al., 2015	60 (real rTMS alone/+paroxetine: 15/15; paroxetine alone: 15; sham rTMS alone: 15)	Left TPC, Cc	Sham coil	1Hz, 110% RMT	900 pulses, 10 sessions	Improvement of the THI score 2 weeks to 6 months after the end of the 2-week rTMS protocol alone, and only at 6 moths in case of paroxetine intake. No effect on the TSI score, except if combined with paroxetine	III
Folmer et al. 2015	64 (real: 32; sham:32)	Post-T3-C3-line target, F8c	Sham coil	1Hz, 110% RMT	2000 pulses, 10 sessions	More responders on the TFI score at the end of 2-week rTMS protocol (real: 56%, sham: 22%) and significant reduction of average TFI score after real (vs. sham) rTMS at 1 and 2 weeks and especially 26 weeks after rTMS intervention	I
Wang et al. 2016b	24 (real: 14; sham: 10)	Halfway between T5 and C3, F8c	Coil away from the head	1Hz, 110% RMT	1000 pulses, 10 sessions	More responders in terms of reduction in tinnitus annoyance (assessed on a VAS) and loudness (evidenced by gaps in noise detection) at the end of 2-week rTMS protocol (with positive correlation between these score reductions)	III
Cacace et al. 2017	25 (crossover)	Halfway between T3 and T5, F8c	Sham coil	1Hz 110% RMT	1200 pulses, 5 sessions	Reduction in tinnitus loudness level and THQ score at the end of 1-week rTMS protocol	III
James et al. 2017	12 (crossover)	Navigation-defined STG opposite to tinnitus side if unilateral or left STG if bilateral, F8c	Realistic sham coil procedure	1Hz 110% RMT	1800 pulses, 4 sessions	Improved tinnitus awareness, annoyance and loudness at the end of 1-week rTMS protocol	III
Landgrebe et al. 2017a	146 (real: 71; control 75)	Post-T3-C3-line target, F8c	Tilted coil	1Hz 110% RMT	2000 pulses, 10 sessions	No significant difference between real and sham treatment (TQ sum score, quality of life)	I
Sahlsten et al. 2017	39 (real: 19; control 20)	Navigation-defined left STG, targeted roughly according to the tonotopic presentation of tinnitus pitch, F8c	Coil away from the head (a 15-cm plastic block being attached under the coil)	1Hz, 100% RMT	4000 pulses, 10 sessions	No significant difference between real and sham treatment (Tinnitus intensity, annoyance, distress and THI scores). Trend towards more responders (real: 42-37%, sham: 15-10%) at 1 to 3 months after rTMS intervention	II

Table 11. LF-rTMS of the auditory cortex combined with HF-rTMS of the left DLPFC in chronic tinnitus

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Langguth et al., 2014	90 (real: 46; sham: 44)	Post-T3-C3-line target (auditory cortex) and 6cm anterior to the hand motor hotspot (DLPFC), F8c	Sham coil	1Hz (auditory cortex) and 20Hz (DLPFC), 110% RMT	2000 pulses on each target, 10 sessions	No significant reduction of average TQ score between real and sham treatment, but more responders on the TQ score (real: 43%, sham: 13%) at the end of 2-week rTMS protocol	I
Formánek et al., 2018	32 (real: 20; sham: 12)	Auditory cortex of both hemispheres and left DLPFC, F8c	Sham coil	1Hz (auditory cortex), 110% RMT and 25Hz (DLPFC), 80% RMT	1000 pulses on each auditory cortical target and 300 pulses on the left DLPFC, 5 sessions	No significant tinnitus reduction between real and sham treatment (THQ and TRQ scores) at 1 and 6 months after rTMS intervention	II

Table 12. HF-rTMS of the left DLPFC in major depressive disorder

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Blumberger et al., 2016	81 (real: 40; sham: 41), with drug-resistant MDD episode	Navigated BA9/BA46, F8c	Tilted coil	10Hz, 120% of distance-adjusted RMT	2100 pulses, 15 or 30 sessions	No significant difference in the response rate (HDRS-17 score reduction >50%) or remission rate (HDRS-17 score ≤ 7) at the end of 3- or 6-week rTMS protocol between real and sham rTMS groups (real: 15/7.5%, sham: 4.9/2.4%)	I
Kang et al., 2016	24 (real: 13; sham: 11)	Left DLPFC	Sham coil	10Hz, 110% RMT	1600 pulses, 10 sessions	Significant decrease in HDRS-17 scores in real vs. sham rTMS groups at the end of 2-week rTMS protocol, associated with a greater reduction of connectivity strength between bilateral DLPFC regions and left caudate (fMRI)	III
Li et al., 2016a	36 (real: 12; real + cognitive task: 12; sham + cognitive task: 12)	Navigated Left DLPFC	Titled coil	10Hz, 100% RMT	1600 pulses, 10 sessions	Significant decrease in HDRS-17 scores in real vs. sham rTMS groups (real: -40 to 52%, sham: -19%) and significant difference in the response rate (HDRS-17 score reduction >50%) or remission rate (HDRS-17 score ≤ 7) at the end of 2-week rTMS protocol between real and sham rTMS groups (real: 42-58/17-42%, sham: 8/0%), associated with an increase in frontal theta power (EEG) and rostral anterior cingulate cortex metabolic activity (PET)	III
Theleritis et al., 2017	96 (real: 52; sham: 44)	Left DLPFC defined as 5cm anterior to hand motor hotspot (adjusted to 6cm on MRI basis in 35% of patients), F8c	Titled coil	20Hz, 100%RMT	1600 pulses, 15 sessions once a day or twice a day (30 sessions)	Significant difference in the response rate (HDRS-17 score reduction ≥50%) or remission rate (HDRS-17 score < 8) at the end of 3-week rTMS protocol between real and sham rTMS groups (real: 59.2/24.5%, sham: 2.5/0%), with greater HDRS-17 score reduction when rTMS was performed twice a day	II

Table 13. Deep HF-rTMS of the left DLPFC in major depressive disorder

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Levkovitz et al., 2015	181 (real: 89, sham: 92), without bipolar MDD	Left DLPFC, H1-coil	Sham coil	18Hz, 120% RMT	1980 pulses, 20 sessions (and 24 additional sessions for maintenance)	Reduction of depression score (HDRS-21: real: -6.4, sham: -3.3) and higher rates of remission (HDRS-21 score <10: real: 32.6%, sham: 14.6%) and response (HDRS-21 score reduction ≥50%: real: 38.4%, sham: 21.4%) at the end of 5-week rTMS protocol, with benefit maintained after 12-week maintenance therapy	I
Tavares et al, 2017	43 (real: 20, sham: 23), with drug-resistant bipolar MDD	Left DLPFC, H1-coil	Sham coil	18Hz, 120% RMT	1980 pulses, 20 sessions	Reduction of depression score (HDRS-17: real: -12.3, sham: -7.1) and a trend towards higher rate of response (HDRS-17 score reduction ≥50%: real: 54.6%, sham: 26.1%) but not of remission (HDRS-17 score ≤7: real: 31.8%, sham: 17.4%) and at the end of 4-week rTMS protocol, but not at 4-week follow-up	II
Kaster et al, 2018	52 (real: 25, sham: 27), without bipolar MDD	Left DLPFC, H1-coil	Sham coil	18Hz, 120% RMT	6012 pulses, 20 sessions	No reduction of depression score (HDRS-24), but higher rate of remission (HDRS-24 score ≤10: real: 40.0%, sham: 14.8%) and response (HDRS-24 score reduction >50%: real: 44.0%, sham: 18.5%) at the end of 4-week rTMS protocol	I

Table 14. cTBS/iTBS of the right/left DLPFC in major depressive disorder

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Li et al , 2014	60 (real: 15 x3, sham: 15), with unipolar MDD	Left/right DLPFC defined as navigated BA9/BA46, F8c	Titled coil	Left-sided iTBS, right-sided cTBS, combination of both, 80% RMT	1800 pulses on each site, 10 sessions	Reduction of depression score (HDRS-17: bilateral TBS: -52.5%, left iTBS: -42.3%, sham: -17.4%) and higher rates of response (HDRS-17 score reduction ≥50%: bilateral TBS: 66.7%, left iTBS: 40.0%, sham: 13.3%) at the end of the 2-week rTMS protocol	II
Plewnia et al., 2014	32 (real: 16, sham: 16), with unipolar MDD	Left/right DLPFC defined as F3/F4 sites, F8c	Tilted coil	Left-sided iTBS + right-sided cTBS, 80% RMT	600 pulses on each site, 30 sessions	Higher rate of response (MADRS score reduction ≥50%: real: 56%, sham: 25%) and a trend towards higher rate of remission (MADRS/BDI score ≤7/8: real: 44/38%, sham: 19/6%)	II
Chistyakov et al., 2015	29 (real: 15, sham: 14), with unipolar or bipolar MDD	Right DLPFC defined as 5cm anterior to hand motor hotspot, F8c	Sham coil	cTBS, 100% AMT	3600 pulses, 10 sessions (followed by 10 additional real stimulation sessions)	No significant difference in depression score reduction (HDRS-21) between real and sham stimulation groups	III
Prasser et al, 2015	56 (real: 39, sham: 17), with unipolar or bipolar MDD	Left/right DLPFC defined as 6cm anterior to hand motor hotspot, F8c	Sham coil	Left-sided iTBS + right-sided cTBS, 80% RMT	1200 pulses on each site, 15 sessions	No significant difference in depression score reduction (HDRS-21) between real and sham stimulation groups, but a trend towards higher responder rate at the end of the follow-up period	III
Duprat et al., 2016	47 (crossover), with unipolar MDD	Left DLPFC defined as navigated BA9/BA46, F8c	Sham coil	iTBS, 110% RMT	1620 pulses, 20 sessions (in 4 days: 5 sessions/day)	No significant difference in depression score reduction (HDRS-17) between real and sham stimulation groups	II

Table 15: LF-rTMS of the left TPC in auditory hallucinations (schizophrenia)

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Bais et al., 2014	32 (real: 16, sham: 16)	Left TPC (halfway between T3 and P3), F8c	Sham coil	1Hz, 90% RMT	1200 pulses, 12 sessions (2/day)	Trend towards reduction of hallucination (item P3 of the PANSS)	II
Paillère-Martinot et al., 2017	27 (real: 15; sham: 12)	Left superior or middle temporal gyrus (fMRI–based navigation), F8c	Sham coil	1Hz, 100% RMT	1000 pulses, 10 sessions	No significant difference in hallucination reduction (on SAPS) between real and sham stimulation groups	II

Table 16: HF-rTMS of the left TPJ in auditory hallucinations (schizophrenia)

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Kimura et al., 2016	30 (real: 16, sham: 14)	Navigated left TPJ according to Montagne-Larmurier et al. (2009), F8c	Sham coil	20Hz, 80% RMT	2600 pulses, 4 sessions (2/day)	No significant effect on AHRS	II
Dollfus et al., 2018	59 (real: 26; sham: 33)	Navigated left TPJ according to Montagne-Larmurier et al. (2009), F8c	Sham coil	20Hz, 80% RMT	2600 pulses, 4 sessions (2/day)	No significant reduction of AHRS total score between real and sham treatment, but more responders (AHRS decrease >30%) in the real stimulation group (real: 34.6%, sham: 9.1%) at 2 weeks after rTMS protocol	II

Table 17. HF-rTMS studies of the left DLPFC in negative symptoms of schizophrenia

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Wölwer et al., 2014	32 (real 18, sham: 14)	Left DLPFC (5cm anterior to motor hotspot), F8c	Sham coil	10Hz, 110% RMT	1000 pulses, 10 sessions	Similar improvement on the PANSS negative subscale and total scores in the real and sham stimulation groups at the end of the 2-week rTMS protocol. However, facial affect recognition improved significantly more after real rTMS	III
Zhao et al., 2014	69 (real 47, sham: 22)	Left DLPFC (site not defined), F8c	Titled coil	10Hz or 20Hz, 80-110% RMT	1500 pulses, 20 sessions	Decreased PANSS negative subscale and SANS scores at the end of the 4-week real (but not sham) rTMS protocol	II
Wobrock et al., 2015	157 (real: 76; sham: 81)	Left DLPFC (F3 site), F8c	Tilted coil	10Hz, 110% RMT	1000 pulses, 15 sessions	Similar improvement on the PANSS negative subscale and total scores in the real and sham stimulation groups at the end of the 3-week rTMS protocol and up to 12 weeks later	I
Li et al., 2016c	47 (real: 25; sham: 22)	Left DLPFC (site not defined), F8c (?)	Sham coil (?)	10Hz, 110% RMT	1500 pulses, 20 sessions	Decreased SANS total score after real but not sham stimulation, with between-group difference not at the end of the 4-week rTMS protocol but 4 weeks later. No difference on PANSS total	III

						score between real and sham treatments.	

Table 18. LF-rTMS of the DLPFC in obsessive compulsive disorder

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Elbeh et al., 2016	30 (real: 15, sham: 15)	Right DLPFC (5cm-rule), F8c	Tilted coil	1Hz, 100% RMT	2000 pulses, 10 sessions	Significant reduction of YBOCS and HARS scores at the end of the 2-week protocol (YBOCS: real: -45%, sham: -6%; HARS: real: -41%, sham: -6%) and 3 months after YBOCS: real: -41%, sham: -8%; HARS: real: -40%, sham: -11%)	II
Seo et al., 2016	27 (real 14, sham 13)	Right DLPFC (5cm-rule), F8c	Sham coil	1Hz, 100% RMT	1200 pulses, 15 sessions	Significant reduction of YBOCS score at the end of the 3-week protocol (real: -32%, sham: -12%).	III

Table 19. Bilateral LF-rTMS of the pre-SMA in obsessive compulsive disorder

Articles	Number of patients	Target, coil type	Control condition	Stimulation frequency and intensity	Number of pulses/session and number of sessions	Significant clinical effects of real versus sham condition	Class of the study
Hawken et al., 2016	22 (real: 10, sham:12)	Pre-SMA (defined as 15% anterior to Cz, on the nasion-inion line), F8c	Tilted coil	1Hz, 110% RMT	1200 pulses, 25 sessions	Significant reduction of YBOCS score at the end of the 6-week protocol (real: -40%, sham: -5%), with benefit maintained at 6 weeks after the last rTMS session	III
Pelissolo et al., 2016	34 (real: 19, sham: 15)	Pre-SMA (defined using image-guided navigation system), F8c	Sham coil	1Hz, 100% RMT	1500 pulses, 20 sessions	No difference between real and sham stimulation on YBOCS score reduction (real: -13%, sham: -11%) and responder rate (YBOCS reduction >25%: real: 10%, sham: 20%) at the end of the 4-week protocol	II
Arumugham et al., 2018	36 (real: 19, sham: 17)	Pre-SMA (defined as 15% anterior to Cz, on the nasion-inion line), F8c	Sham coil	1Hz, 100% RMT	1200 pulses, 18 sessions	No difference between real and sham stimulation on YBOCS reduction	III

Table 20. Summary of recommendations on rTMS efficacy according to clinical indication

Neuropathic pain	Definite analgesic efficacy of HF-rTMS of M1 contralateral to pain side (Level A), while LF-rTMS is probably ineffective (Level B)
CRPS type I	Possible analgesic efficacy of HF-rTMS of M1 contralateral to pain side (Level C)
Fibromyalgia	**Probable efficacy of HF-rTMS of the left M1 in improving quality of life of patients with fibromyalgia (Level B)**
Fibromyalgia	**Probable analgesic efficacy of HF-rTMS of the left DLPFC in patients with fibromyalgia (Level B)**
Parkinson's disease	**Probable efficacy of HF-rTMS of bilateral M1 regions in motor symptoms of PD patients (Level B)**
Parkinson's disease	Probable antidepressant efficacy of HF-rTMS of the left DLPFC in PD patients (Level B)
Motor stroke	**Definite efficacy of LF-rTMS of contralesional M1 in hand motor recovery at the postacute stage (Level A)**
Motor stroke	**Probable efficacy of HF-rTMS of ipsilesional M1 in hand motor recovery at the postacute stage (Level B)**
Motor stroke	**Possible efficacy of LF-rTMS of contralesional M1 in hand motor recovery at the chronic stage (Level C)**
Post-stroke aphasia	**Probable efficacy of LF-rTMS of right IFG in nonfluent aphasia recovery at the chronic stage (Level B)**
Hemispatial neglect	Possible efficacy of cTBS of the contralesional left parietal in visuospatial hemineglect recovery at the post-acute stage of stroke (Level C)
Multiple sclerosis	**Probable efficacy of iTBS of the leg area of M1 contralateral to the most affected limb (or both M1) in lower limb spasticity (Level B)**
Epilepsy	Possible antiepileptic efficacy of LF-rTMS of the epileptic focus (Level C)
Alzheimer's disease	**Possible efficacy of multisite rTMS-COG to improve cognitive function, memory and language level of AD patients, especially at a mild/early stage of the disease (Level C)**
Tinnitus	Possible efficacy of LF rTMS of the auditory cortex of the left hemisphere (or contralateral to the affected ear) in chronic tinnitus (Level C)
Depression	Definite antidepressant efficacy of HF-rTMS of the left DLPFC in major depression using a figure-of-8 coil or a H1-coil (Level A)
Depression	**Definite antidepressant efficacy of deep HF-rTMS over the left DLPFC in major depression (Level A)**
Depression	Probable antidepressant efficacy of LF-rTMS of the right DLPFC in major depression (Level B)
Depression	**Probable antidepressant efficacy of bilateral right-sided LF-rTMS and left-sided HF-rTMS of the DLPFC in major depression (Level B)**
Depression	**Probable antidepressant efficacy of bilateral right-sided cTBS and left-sided iTBS of the DLPFC in major unipolar depression (Level B), while unilateral right-sided cTBS is possibly ineffective (Level C)**
Depression	**Possibly no differential antidepressant efficacy between: right LF-rTMS vs. left HF-rTMS, bilateral vs. unilateral rTMS of the DLPFC, and rTMS performed alone vs. combined with antidepressants (Level C)**
Post-traumatic stress disorder	**Probable efficacy of HF-rTMS of the right DLPFC in PTSD (Level B)**
Obsessive compulsive disorder	**Possible efficacy of LF-rTMS of the right DLPFC in OCD (Level C)**
Schizophrenia:auditory hallucinations	Possible efficacy of LF-rTMS of the left TPC in auditory hallucinations in schizophrenia (Level C)
Schizophrenia: negative symptoms	**Possible efficacy of HF-rTMS of the left DLPFC on negative symptoms of schizophrenia (Level C)**
Addiction and craving	Possible efficacy of HF-rTMS of the left DLPFC on cigarette craving and consumption (Level C)
In all other conditions, there is "no recommendation", which means the absence of sufficient data to make a recommendation, but not the evidence for an absence of effect. Recommendations that change from our previous work (Lefaucheur et al., 2014) are shown in bold.	