Depressive Disorders

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6.1 Introduction

Major depressive disorder (MDD) is the leading cause of mental health related disability worldwide, with an increase in prevalence of more than 18% in the past decade. Clinical treatment based on pharmacotherapy, psychotherapy, or both is limited in its effectiveness, particularly if therapy-resistance, chronicity, or adverse effects come into play. Repetitive transcranial magnetic stimulation (rTMS) has undergone intensive research, becoming one of the most important nonpharmacological treatment options in MDD. In 2008, rTMS was approved by the FDA as a therapy for treatment-resistant depression (TRD) in the USA and since then it has been approved in other countries, including Canada, Australia, Brazil, and several European countries [1]. Moreover, rTMS is considered a first-line treatment according to current North American and European guidelines. Besides the initial rTMS

treatment protocols, recently, theta burst stimulation (TBS) and H1-coil TMS have been FDA-cleared for the treatment of MDD.

In this chapter, we discuss current state-of-the-art treatment of depression with rTMS and summarize findings from trials focusing on efficacy, maintenance treatment and long-term outcomes in MDD, combinatory treatments, and personalized and stratified treatment, including treatment of MDD subpopulations and vulnerable populations, as an avenue to precision medicine.

6.2 The Rationale of Using rTMS in Depression

The causes of depression are manifold, including neurophysiological dysregulation, genetic vulnerability, and impaired mood regulation. One of the key findings that are relevant for the application of TMS is the observation of distinct changes in the prefrontal cortex (PFC) of patients with depression. The rationale of using noninvasive brain stimulation applied to the PFC for depression is based on the premise that certain stimulation parameters can enhance, or at least modify, brain activity in the targeted brain area. The dorsolateral PFC (DLPFC) has become the most prominent rTMS target area in MDD, not only since early rTMS studies, but also in more recent, pivotal trials [2]. The DLPFC is part of the frontoparietal network (FPN), which is implicated in the regulation of a multitude of processes such as decision-making, working memory, and attention. The DLPFC is thought to be hypoactive in clinically depressed patients [3]. Moreover, hypoconnectivity of the FPN is associated with hyperconnectivity of the default mode network (DMN), which may promote negative emotional bias, dysfunctional self-referential processing, and rumination [4]. Stimulation of the left DLPFC with high-frequency rTMS (HF-rTMS) has been suggested to normalize the functional balance between neural networks, e.g., downregulate connectivity within the DMN, the left DLPFC and insula, and between the salience network and the hippocampus, which has been shown to be associated with an improvement of depressive symptoms. This rationale has been supported, to some extent, by neuroimaging studies in depressed patients receiving rTMS although replication is warranted [5, 6]. Furthermore, reaching a "normal" homeostasis again between cortico-subcortical networks may normalize the known endocrinological disturbances documented in MDD [7].

6.3 The Role of Cognition in rTMS Applications

So far, cognitive outcomes in the context of rTMS depression treatment have primarily been explored to confirm that rTMS is safe. Indeed, with few exceptions, most single session studies showed no adverse cognitive effects of rTMS [8]. Interestingly, MDD itself is often characterized by specific cognitive deficits, including attention, memory, and executive function deficits, and recent meta-analyses not only showed that rTMS techniques are cognitively safe but also that rTMS may even be associated with specific cognitive improvements in MDD

patients. Hence, the rTMS depression treatment targeting the PFC may exert pro-cognitive effects, enhancing cognitive performance specifically in specifically in those functions that are considered vulnerability factors to MDD. Nevertheless, although some studies reported such cognitive improvements in depression after rTMS [9], others failed to find such beneficial cognitive changes [10]. In any case, systematically evaluating and tracking cognitive changes may provide valuable insights into the mechanisms of action by which DLPFC rTMS exerts its antidepressant effects. It may, e.g., be the case that the cognitive changes induced by rTMS drive or, at least, mediate the improvement in depression symptoms, rather than being an independent side effect or a consequence of the antidepressant treatment. In line with this, Harty and colleagues [11] recently described how variability in neural circuits, for example, associated with cognitive functioning, may play a critical role in mediating or moderating the influence of brain stimulation on behavioral changes, such as depression.

6.4 State-of-the-Art rTMS Treatment for MDD

6.4.1 Treatment Recommendations for TMS Therapy

Over the past three decades, two different rTMS approaches for the treatment of major depressive episodes have emerged based on some older theories on the hemispheric lateralization of emotional processes: either high-frequency rTMS (HF-rTMS) delivered to the left DLPFC (aimed at correcting an alleged hypoactivity) or low-frequency rTMS (LF-rTMS) applied to the right DLPFC (aimed at reducing an alleged hyperactivity) [12]. However, current insights into the working mechanisms of rTMS do not follow these lateralization assumptions anymore. Although LF-rTMS or bilateral rTMS (delivering sequentially HF-rTMS over the left DLPFC and LF-rTMS over the right DLPFC) may not have the FDA approval yet or have not reached the Level A in the European guideline recommendations, both rTMS approaches have shown significantly better results than sham in the majority of studies and future large, randomized, controlled studies may indicate similar efficacy as with HF-rTMS over the left DLPFC. Indeed, a recent network meta-analysis showed a higher response to real vs. sham stimulation condition for bilateral prefrontal rTMS (and intermittent TBS or iTBS), LF-rTMS of the right DLPFC, and HF-rTMS of the left DLPFC [13].

Notably, response and remission to rTMS alone have similar efficacy compared to antidepressant medication, and the magnitude of clinical effects remains modest. In a recent network meta-analysis, the efficacy and tolerability of 8 rTMS modalities and sham, including 81 studies and 4233 patients, were evaluated. Some rTMS strategies were more effective than sham [14]. However, none of the active rTMS strategies was significantly superior to another. This highlights the need for identifying subgroups of patients more prone to respond to specific rTMS strategies and better understanding TMS' mechanisms of action.

6.4.2 Intensifying rTMS Protocols

One major drawback of current treatment options is the extended time of up to 2 weeks that is needed for effects to unfold. This has led to the development of accelerated high-frequency rTMS (aHF-rTMS) and accelerated intermittent Theta Burst Stimulation (aiTBS), novel stimulation protocols that apply multiple daily sessions (with at least 600 pulses per session), thereby reducing the total treatment time [15]. From a clinical perspective, the aim was also to challenge response and remission rates as observed with electroconvulsive therapy (ECT). Using excitatory stimulation paradigms over the left DLPFC, aHF-rTMS and aiTBS seem to yield similar remission and response rates as daily rTMS, but still do not reach the remission and response rates of ECT. Increasing the number of rTMS sessions over the left DLPFC may further improve clinical outcomes and reduce treatment time. Furthermore, increasing the number of stimulation sessions over the dorsomedial PFC (dmPFC) is associated with a similar clinical response, adding to a significantly faster onset [16]. This agrees not only with clinical observations using aHF-rTMS [15] and aiTBS [17] but also with a recent pilot study [18] showing that high dose aHF-rTMS (i.e., 10 sessions per day) over the left DLPFC for 5 days results in acute response and remission in high TRD.

These recent findings underline the value of novel protocols in terms of a much faster alleviation of depressive symptoms with respect to time (note that the number of sessions remains the same). The most important clinical challenge will therefore be to validate and further optimize the stimulation parameters while still reaching comparable response and remission rates at or beyond the level that is observed with ECT.

6.4.3 TMS Coil Geometry, Orientation, and Position

The geometry of a coil determines stimulation focality as well as depth of the electric field. Since the beginning of TMS, many different coil geometries have been investigated. For the treatment of depression, the most prevalent coil to date is the figure-of-eight coil; however, recent developments suggest the use of novel coil geometries, including the double cone coil and the H-coil. These latter two coils allow modulation of deeper brain areas such as the dorsomedial prefrontal cortex (dmPFC) or anterior cingulate, albeit also being less focal.

The double cone coil features two windings that are set apart at a defined angle (e.g., 120°): its specific geometry is thought to lead to higher current in the central fissure resulting in a more efficient stimulation targeting the dmPFC and/or the more dorsal parts of the ACC. The rationale behind this approach lies in the involvement of the dmPFC in affective, sensory autonomic, cognitive, and salience regulation. The double cone coil has also been used to target the right orbitofrontal cortex in depression [19], where it was shown that 30% of nonresponders to DMPFC rTMS did respond to stimulation at this target, offering hope for stepped-care approaches in TMS, which could enhance efficacy.

The “H-coil” is thought to stimulate up to a depth of 4–6 cm and was therefore introduced as deep TMS (dTMS). Phantom measurements have shown that while H-coils (e.g., the H1 coil for depression) reach deeper targets, they also provide less focal stimulation, following the well-known trade-off between depth (or intensity) and focality of TMS [20]. In 2013, based on the findings by Levkovitz and colleagues [21], the FDA approved the first dTMS device (featuring an H1-coil) for the use in patients with TRD. In this RCT with 212 MDD outpatients, remission rates were higher in the dTMS (32.6%) compared to the sham group (14.6%), and were stable during the 12-week maintenance phase. Moreover, dTMS appears to be well tolerated and efficacious in late-life depression [22] and showed to be potentially effective as add-on treatment in resistant bipolar depressed patients [23]. To date, there is only one randomized head-to-head comparison of effectiveness between dTMS and standard rTMS using the figure-of-eight coil [24]. Here, the authors demonstrated that, when depressed patients did not respond, or only partly responded, to classical antidepressant medications, neurostimulation add-on or augmentation could be beneficial for the majority of them, with a slightly better outcome for the H1 dTMS coil compared to the more commonly used figure-of-eight coil. Of course, this finding warrants replication.

An often underexplored aspect in the application of rTMS is the orientation of the coil. It is known from primary motor cortex stimulation that a deviation of the 45° orientation of the coil can make a significant difference (“angular sensitivity”), for instance, in observing or not a motor evoked potential (MEP) [25]. Similar research investigating the relevance of coil orientation over the DLPFC using Near Infra-Red Spectroscopy (NIRS) showed that a blood-oxygenation response could only be measured at an angle of 45° to the midline [26], confirming the approach that has been adopted in most clinical trials to date.

The correct positioning of the coil is critical in terms of which underlying brain area is stimulated. Even slight changes in coil positioning can lead to large variations in clinical response. In order to ensure reliable stimulation of the identified targets throughout the treatment period, different coil positioning methods are used, with varying levels of cost versus clinical effectiveness: (1) the 5-cm-rule; (2) stimulation over F3 in accordance with the 10–20 EEG system; (3) the Beam F3 method and (4) MRI-based TMS guided by individual fiducials or neuronavigation. The 5-cm-rule has been the standard approach used for almost two decades. Here, the administrator applies a single TMS pulse to the primary motor cortex to cause an observable muscle twitch or a motor evoked potential (MEP) for indexing the exact coil position within the motor system (the so-called motor hotspot). The TMS depression treatment target is then defined relative to this “functional marker” by simply shifting the TMS coil in the anterior direction, parallel to the midline, by 5 cm (sometimes also 6 cm). However, this approach is critically viewed, as it does not account for interindividual anatomical differences. Stimulation over F3 follows the 10–20 EEG system and therefore considers individual differences in head size. Here, the TMS coil is positioned at EEG electrode position F3, which is thought to correspond to the DLPFC. Recently, the Beam-F3 method has been proposed as a new method [27], which does take individual differences in skull size into account

and is based on the 10–20 EEG location F3 or F4. Free software to easily apply this method can be found at: http://www.clinicalresearcher.org/software.htm. This method has been shown to lead to an adequate determination, with a minimal discrepancy, compared to MRI-neuronavigated location determination [28].

However, MRI-based TMS is thought to be the most precise coil positioning approach, as it is based on the neuroimaging data of individual patients or a template. Frameless stereotactic systems allow precise (online) neuronavigation of a predefined brain area. However, the question of whether higher precision is associated with increased clinical efficacy continues to be discussed.

6.5 Real-Life Outcomes, Durability and Maintenance rTMS (mTMS)

Concerning the effectiveness of clinical outcomes, several large open-label studies have addressed the real-life clinical effects of rTMS. It seems that rTMS can be considered an effective treatment within research and naturalistic settings, with clinical benefits translating well into clinical practice. Additionally, in combination with psychotherapy or other treatment modalities, response and remission rates may have the potential to further increase and lead to sustained and durable effects.

Several large open-label studies have addressed the long-term effects of rTMS. In a large multicenter study with 307 treatment-resistant MDD patients applying HF L-DLPFC TMS, Carpenter and colleagues [29] reported response rates of 58% and 37% remission. Another large open-label study in 1132 patients demonstrated similar effects to Carpenter et al. with 46% response and 31% remission rates using several TMS protocols, mainly HF L-DLPFC and LF R-DLPFC rTMS [30]. In an extension of the Carpenter et al. study, good long-term effects were observed [31], the majority of patients (62.5%) continued to meet response criteria at a 12-month follow-up.

Although guidelines on the topic are lacking to date, maintenance rTMS (mTMS) has been suggested to prolong positive clinical effects. mTMS consists of an ongoing treatment at a lower rate—a similar approach that is used in ECT—and is used after a successful response to an acute course of rTMS. The frequency of mTMS varies from distributed single sessions (weekly, biweekly, bimonthly, or monthly) during the first 2–3 months after the end of the main treatment course, to short treatment periods of daily mTMS (e.g., 1 week per month) or so-called clustered mTMS (e.g., 5 sessions over a two-and-a-half-day period per month or every fifth week) applied over 1, 2, 3, 9, 12 months and up to several years. Studies are highly heterogeneous in terms of design, with rather small sample sizes and lacking placebo controls. Nonetheless, most patients show moderate to clear benefits with mTMS compared to no treatment, achieving remission for up to 3 months to 5 years [32]. While applying clustered mTMS, Wang and colleagues [33] showed significantly reduced relapse rates compared to a previous study that applied clustered mTMS [34]. To date, there are no guidelines for mTMS. Although the protocol should be

individualized clinically, a tentative maintenance protocol following a rTMS taper (4 times weekly for 1 week, 3 times weekly for 1 week, 2 times weekly for 1–2 weeks) could consist of 1 session every 2 or 3 weeks for several months up to several years, depending on the nature of the mood disorder, although this schedule may not be sufficient for certain patients [35].

6.6 Combinatory Treatments

The rationale behind combining rTMS with other treatment approaches lies in the assumption that concomitant stimulation on different levels (i.e., physiological, cognitive, affective, behavioral) may result in synergistic effects.

6.6.1 Combining rTMS with Psychopharmacotherapy

An important issue concerns the relationship between rTMS efficacy and antidepressant intake. In general, patients undergoing rTMS continue to receive antidepressants. However, little is known about the impact of pharmacotherapy on rTMS efficacy. Preclinical studies suggest that antidepressants, anticonvulsants, and benzodiazepines influence cortical excitability. In humans, antidepressants appear to facilitate neuroplastic effects of brain stimulation, whereas anticonvulsants and benzodiazepines seem to have an inhibitory effect [36]. So far, rTMS studies in MDD are very heterogeneous concerning concomitant pharmacotherapy, precluding a comparison. Two questions are imminent: firstly, is there a difference between rTMS and antidepressants in terms of therapeutic efficacy? And secondly, is there an augmenting effect when under stable antidepressant therapy or is there an additive effect when introduced concomitantly as add-on therapy? However, currently, it has not been clearly demonstrated that there is a differential antidepressant efficacy between rTMS therapy performed alone vs. combined with antidepressants or that there is a clear superiority of an “add-on” effect of the combined procedure (Lefaucheur et al., in revision). It has to be noted that while in some studies patients were unmedicated, other studies only allowed benzodiazepines or other specific antidepressant medications to be continued during rTMS treatment, or medication could be freely chosen, but had to be kept stable. As psychopharmacological treatment is known to exert effects on both cortical excitability and neuroplasticity, potential interactions of specific pharmacological regimes and rTMS should be further investigated and henceforward exploited to achieve better clinical outcomes.

6.6.2 Combining rTMS with Psychotherapy

Within a naturalistic setting, rTMS can be considered an effective treatment and clinical benefit appears to translate well into clinical practice. Additionally, in combination with psychotherapy, response and remission rates may have the potential to

increase further and sustain durable effects. In a large naturalistic study, Donse and colleagues [37] reported that the simultaneous application of rTMS and psychotherapy in TRD resulted in a 66% response and a 56% remission rate at the end of treatment with 60% sustained remission at a 6-month follow-up. Though promising, randomized controlled clinical trials, as well as systematic research on combined rTMS-psychotherapy approaches, are needed.

6.6.3 Combining rTMS with Cognitive Training

Cognitive impairments can be observed in over 50% of depressed patients. They are thought to be predictive for poor socio-occupational outcomes and to persist beyond depression symptoms [38]. The persistence of cognitive symptoms and largely lacking effects of pharmacological treatment on cognitive symptoms implies that the two phenomena are dissociated and therefore require a more holistic treatment approach. Cognitive training of working memory used on its own has shown promising effects [39]. However, it might be more effective when used as an add-on to rTMS. This assumes that the application of rTMS during cognitively relevant brain activity induces synergistic effects and therefore enhances cognitive training outcomes. From a perspective of practicability, it appears feasible, as patients are usually unengaged during rTMS treatment.

6.6.4 Combining rTMS with Other (Non)invasive Brain Stimulation Techniques

Although in the field of brain stimulation it is discussed to combine or to prime rTMS treatment with other (non)invasive brain stimulation techniques, for example, (1) in order to increase clinical outcome, or (2) to use it as a maintenance treatment, currently, no systematic studies have been conducted to investigate these assumptions.

6.7 Personalized and Stratified Treatment as an Avenue to Precision Medicine

A general issue in the field is the high interindividual variability of rTMS response not only in clinical applications but also in experimental paradigms. Though not allowing one-size-fits-all approaches, such variability may pave the way to personalized treatment: (1) adjusting rTMS to individualized targets and predictors based on structural or functional connectivity [40, 41], see target engagement below; and (2) applying closed-loop rTMS protocols targeting individual neurophysiological markers. Furthermore, cognitive and clinical indices could be leveraged for several purposes: (1) use as predictors to response to rTMS [42]; (2) cognitive changes can provide insights on rTMS mechanisms of action, for instance, by exploring whether

they mediate depression improvement. Unfortunately, to date, no reliable predictors exist for response to rTMS in a clinically meaningful manner. Many individual studies have reported older age, high MDD severity, high anxiety, etc. to be predictors of poor response; however, a recent large scale study using a strict discovery-replication approach could not replicate any of these associations, albeit only high anhedonia was associated with a lower response, but this did not meet prediction accuracies suitable for clinical practice [42].

A complementary approach for addressing precision in psychiatry is stratification with machine learning approaches and other advanced statistics. In the rTMS field, such approaches have been conducted for symptom clustering and to define subtypes of MDD. Based on clustering according to anxiety and anhedonia dimensions and associated resting-state fMRI connectivity patterns, Drysdale and colleagues [43] identified and validated four biotypes, two of which were more responsive to rTMS than the others. In contrast to standard protocols, however, rTMS was applied over the DMPFC using a double cone coil. Furthermore, a very recent study failed to replicate the biotype solution of the prior report [44]. Kaster et al. [45] published a secondary analysis of a noninferiority trial comparing 10 Hz rTMS and iTBS applying group-based trajectory modeling. Four response trajectories were identified: nonresponse; rapid response; higher baseline symptoms—linear response; and lower baseline symptoms—linear response. The nonresponse trajectory was associated with higher depression scores at baseline, and the rapid response trajectory with older age, lower depression scores (i.e., self-rating) and lack of benzodiazepine use. A recent meta-analysis, investigating EEG predictors for antidepressant treatments, including rTMS, concluded that EEG is not clinically reliable, mainly due to publication bias and lack of replication [46]. In conclusion, while treatment prediction is a promising avenue and in line with notions of personalized medicine and Research Domain Criteria (RDoC), replication and focus on clinical relevance (opposed to "statistical significance" only) need to be further addressed in future studies [42, 46]. Besides true "prediction of response", another possibility is to optimize the stimulation targets by means of a focus on "target engagement".

6.7.1 Target Engagement

Target engagement comprises the use of a direct functional outcome measure as a validation for targeting the optimal TMS location, whereby it can be demonstrated that said location is activated, either directly or transsynaptically. In the same way, as the motor cortex is identified by thumb movement as a demonstration of primary motor cortex activation, such functional outcome measures are thus far lacking for the prefrontal cortex or, more specifically, the DLPFC. One proposed method is by extracting connectivity patterns to frontal areas using the sgACC as a seed region [47]. Other studies hypothesize that the DLPFC could be more accurately targeted with the aid of heart rate, so-called Neuro-Cardiac-Guided TMS (NCG-TMS) [48]. The depression network and the brain–heart axis are interconnected, and a recent

meta-analysis demonstrated that stimulation of the DLPFC systematically resulted in reduced heart rate [49]. Iseger et al. [48] recently demonstrated that rTMS applied to F4 and F3 locations resulted in the most significant heart rate decelerations, followed by FC3 and FC4, whereas heart rate accelerations were found for central sites overlying the primary motor cortex. Individual variation was also found, indicating that the NCG-TMS method could be used to individualize stimulation targets, under the assumption that transsynaptic activation of the sgACC indeed activates the whole DLPFC-sgACC-Vagal nerve pathway that is involved in MDD. However, it remains yet to be established how this correlates with treatment outcome and if such targeting methods result in increased clinical efficacy.

6.7.2 Treatment of MDD Subpopulations and Vulnerable Populations

Knowledge about the relevance of the type of depression for rTMS efficacy is rather limited. In many rTMS studies, patients with both unipolar and bipolar disorder were included, without resulting in any clear indication of differential response. Notably, out of four RCTs [50] that included only patients with bipolar disorder, only one was positive. Regarding bipolar depression, the published data appear to be generally insufficient to draw definitive conclusions about its efficacy for this condition. Albeit a major reason not to include bipolar patients in clinical trials, there is currently no evidence to suggest that rTMS is associated with an increased risk of hypomanic switch. Importantly, rTMS seems to be ineffective in cases of MDD with psychotic features, a condition which is, on the other hand, a major clinical indication of ECT. The application of rTMS in children and adolescents, as well as in the elderly has not been studied extensively. However, the available studies, mostly comprising relatively small samples, do not seem to differ in clinical efficacy nor in tolerability or safety. Another vulnerable population is elderly individuals for whom efficacy of pharmacological treatment is known to be reduced and for whom polypharmacy and interactions of medications pose additional health risks. Some moderating factors possibly influencing clinical response to rTMS in the elderly depressed include but are not limited to: (1) brain atrophy; (2) the intensity and number of pulses (dose–response relationship); and (3) the clinical profile of patients (including treatment resistance, somatic/melancholic and psychotic features, a higher degree of cognitive impairment/dementia and medical comorbidity) [51]. Furthermore, although the current data suggest that the clinical effects, safety, and tolerability of TMS in adolescents may be similar to what has been described in adults, one has to consider neurodevelopmental factors and the unknowns associated with TMS exposure in this particular group [52]. For patients with MDD and Parkinson's disease, a recent meta-analysis has shown clear antidepressant efficacy of rTMS [52], indicating that medical comorbidities have no negative influence on the antidepressant efficacy of rTMS.

rTMS seems especially suited for the treatment of patients with contraindications for pharmacologic treatment, e.g., pregnant and breastfeeding women, or

patients with polypharmacotherapy or comorbid somatic disorders. The application of rTMS in pregnant and breastfeeding women, for whom ECT or pharmacological treatment poses larger risks and side effects than rTMS, is of specific importance. Importantly, no negative pregnancy or fetal outcomes were found except for the potential association with preterm birth and mild headache for mothers [53]. A follow-up study of 30 mothers who had received rTMS for treatment of depression during pregnancy in an open trial setting investigated possible long-term effects of rTMS on offspring neurocognitive development [54]. No impairments were observed in cognitive or motor development in children who were aged 18–62 months at the time of the follow-up. The use of rTMS in postnatal depression was also recently analyzed in a systematic review that extracted data between 1999 and 2018, summing up 49 women [55]. Whereas higher frequencies correspond to increased discomfort and potential increased dropout rates, decreased frequencies seem to lead to less robust results.

6.8 Current Challenges and Future Directions

The main challenge in the treatment of depression lies in the large interindividual variability in treatment response. Researchers worldwide are focused on identifying personalized predictive factors and underlying mechanisms associated with response and remission rates. Further challenges include the extended time it takes for clinical effects to emerge and the lack of successful preventative strategies.

Future clinical research should therefore include large, controlled, noninferiority rTMS treatment studies comparing different stimulation localizations and the further development of novel stimulation patterns, such as accelerated rTMS protocols, that are thought to achieve a faster response. Moreover, our increasing knowledge of underlying neuronal mechanisms of MDD and network interactions should not only fuel the investigation of novel stimulation targets and development of coil designs that allow reaching deeper brain structures but could also be key to the development of more fine-tuned individualized treatment approaches. Future studies should further investigate synergistic effects of combinatory approaches, such as the combination with psychotherapy, cognitive training, and pharmacological treatment, to further enhance clinical outcomes and medium- to long-term antidepressant effects of this technique.

6.9 Conclusions

Despite the worldwide application of rTMS in depressed patients, there is still a large heterogeneity in the published data concerning the populations included and the stimulation settings. They mostly apply to patients in an acute phase of a drug-resistant MDD episode in the context of unipolar depression. A definite antidepressant efficacy of HF-rTMS of the left DLPFC (using either a focal figure-of-eight coil or a deep H-coil) and a probable antidepressant efficacy of LF-rTMS of the

right DLPFC is currently the most evidence-based documented treatment proposal. Efficacy does not seem to differ significantly whether patients are concomitantly treated by antidepressant medication. At this point, it has to be acknowledged that rTMS is an acute antidepressant intervention and that beyond the acute phase data are limited with the exception of maintenance sessions [33].

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