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Repetitive transcranial magnetic stimulation in stroke rehabilitation: review of the current evidence and pitfalls

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***Abstract*:** Acute brain ischemia causes changes in several neural networks and related cortico-subcortical excitability, both in the affected area and in the apparently spared contralateral hemisphere. The modulation of these processes through modern techniques of noninvasive brain stimulation, namely repetitive transcranial magnetic stimulation (rTMS), has been proposed as a viable intervention that could promote post-stroke clinical recovery and functional independence. This review provides a comprehensive summary of the current evidence from the literature on the efficacy of rTMS applied to different clinical and rehabilitative aspects of stroke patients. A total of 32 meta-analyses published until July 2019 were selected, focusing on the effects on motor function, manual dexterity, walking and balance, spasticity, dysphagia, aphasia, unilateral neglect, depression, and cognitive function after a stroke. Only conventional rTMS protocols were considered in this review, and meta-analyses focusing on theta burst stimulation only were excluded. Overall, both HF-rTMS and LF-rTMS have been shown to be safe and well-tolerated. In addition, the current literature converges on the positive effect of rTMS in the rehabilitation of all clinical manifestations of stroke, except for spasticity and cognitive impairment, where definitive evidence of efficacy cannot be drawn. However, routine use of a specific paradigm of stimulation cannot be recommended yet due to a significant level of heterogeneity of the studies in terms of protocols to be set and outcome measures that have to be used. Future studies need to preliminarily evaluate the most promising protocols before going on to multicenter studies with large cohorts of patients in order to achieve a definitive translation into daily clinical practice.

Keywords: neuroplasticity, neurorehabilitation, noninvasive brain stimulation, stroke

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Introduction

Background

Stroke is a common acute neurovascular disorder that causes disabling long-term limitations to daily living activities. The most common consequence of a stroke is motor deficit of variable degree,[1] although nonmotor symptoms are also relevant and often equally disabling.[2] To date, to the best of the authors' knowledge, there is no validated treatment that is able to restore the impaired functions by a complete recovery of the damaged tissue. Indeed, stroke management basically consists of reducing the initial ischemia in the penumbra, preventing future complications, and promoting a functional recovery using physiotherapy, speech therapy, occupational therapy, and other conventional treatments.[3,4]

Ischemic damage is associated with significant metabolic and electrophysiological changes in cells and neural networks involved in the affected area. From a pure electrophysiological perspective, however, beyond the affected area, there is a local shift in the balance between the inhibition and excitation of both the affected and contralateral hemisphere, consisting of increased excitability and disinhibition (reduced activity of the inhibitory circuits).[3,5] In addition, subcortical areas and spinal regions may be altered.[3,5] In particular, the role of the uninjured hemisphere seems to be of utmost significance in post-stroke clinical and functional recovery.

Different theoretical models have been proposed to explain the adaptive response of the brain to acute vascular damage. According to the vicariation model, the activity of the unaffected hemisphere contributes to the functional recovery after a stroke through the replacement of the lost functions of the affected areas. The interhemispheric competition model considers the presence of mutual inhibition between the hemispheres, and the damage caused by a stroke disrupts this balance, thus producing a reduced inhibition of the unaffected hemisphere by the affected side. This results in increased inhibition of the affected hemisphere by the unaffected side. More recently, a new model, called bimodal balance recovery, has been proposed.[3,5] It introduces the concept of a structural reserve, which describes the extent to which the nondamaged neural pathways contribute to the clinical recovery. The structural reserve determines the prevalence of the interhemispheric imbalance over vicariation. When the structural reserve is high, the interhemispheric competition model can predict the recovery better than the vicariation model, and *vice versa*.[3]

Repetitive transcranial magnetic stimulation

One of the proposed interventions to improve stroke recovery, by the induction of neuromodulation phenomena, is based on methods of noninvasive brain stimulation. Among them, transcranial magnetic stimulation (TMS) is a feasible and painless neurophysiological technique widely used for diagnostic, prognostic, research, and, when applied repetitively, therapeutic purposes.[6-9] By electromagnetic induction, TMS generates sub or suprathreshold currents in the human cortex *in vivo* and in real time.[10,11]

The most common stimulation site is the primary motor cortex (M1), that generates motor evoked potentials (MEPs) recorded from the contralateral muscles through surface electromyography electrodes.[11] The intensity of TMS, measured as a percentage of the maximal output of the stimulator, is tailored to each patient based on the motor threshold (MT) of excitability. Resting MT (rMT) is found when the target muscle is at rest, it is defined as the minimal intensity of M1 stimulation required to elicit an electromyography response with a peak-to-peak amplitude $> 50\,\mu V$ in at least 5 out of 10 consecutive trials.[11] Alternatively TMS MTAT 2.0 software (http://www.clinicalresearcher.org/software.htm) is a free tool for TMS researchers and practitioners. It provides four adaptive methods based on threshold-tracking algorithms with the parameter estimation by sequential testing, using the maximum-likelihood strategy for estimating MTs. Active MT (aMT) is obtained during a tonic contraction of the target muscle at approximately 20% of the maximal muscular strength.[11]

The rMT is considered a basic parameter in providing the global excitation state of a central core of M1 neurons.[11] Accordingly, rMT is increased by drugs blocking the voltage-gated sodium channels, where the same drugs may not have an effect on the gamma-aminobutyric acid (GABA)-ergic functions. In contrast, rMT is reduced by drugs increasing glutamatergic transmission not mediated by the N-methyl-D-aspartate (NMDA) receptors, suggesting that rMT reflects both neuronal membrane excitability and non-NMDA receptor glutamatergic neurotransmission.[12] Finally, the MT increases, being often undetectable, when a substantial portion of M1 or the cortico-spinal tract is damaged (i.e. by stroke or motor neuron disease), and decreases when the motor pathway is hyperexcitable (such as epilepsy).[13]

Repetitive (rTMS) is a specific stimulation paradigm characterized by the administration of a sequence of consecutive stimuli on the same cortical region, at different frequencies and inter sequence intervals. As known, rTMS can transiently modulate the excitability of the stimulated cortex, with both local and remote effects outlasting the stimulation period. Conventional rTMS modalities include high-frequency (HF-rTMS) stimulation ($>1\,Hz$) and low-frequency (LF-rTMS) stimulation ($\leqslant 1\,Hz$).[11] High-frequency stimulation typically increases motor cortex excitability of the stimulated area, whereas low-frequency stimulation usually produces a decrease in excitability.[14] The mechanisms by which rTMS modulates the brain are rather complex, although they seem to be related to the phenomena of long-term potentiation (LTP) and long-term depression (LTD).[15]

When applied after a stroke, rTMS should ideally be able to suppress the so called 'maladaptive plasticity'[16,17] or to enhance the adaptive plasticity during rehabilitation. These goals can be achieved by modulating the local cortical excitability or modifying connectivity within the neuronal networks.[10]

rTMS in stroke rehabilitation: an overview

According to the latest International Federation of Clinical Neurophysiology (IFCN) guidelines on the therapeutic use of rTMS,[10] there is a possible effect of LF-rTMS of the contralesional motor cortex in post-acute motor stroke, and a probable effect in chronic motor stroke. An effect of HF-rTMS on the ipsilesional motor cortex in post-acute and chronic motor stroke is also possible.

The potential role of rTMS in gross motor function recovery after a stroke has been assessed in a recent comprehensive systematic review of 70 studies by Dionisio and colleagues.[18] The majority of the publications reviewed report a role of rTMS in improving motor function, although some randomized controlled trials (RCTs) were not able to confirm this result,[19–23] as shown by a recent large randomized, sham-controlled, clinical trial of navigated LF-rTMS.[24] It has also been suggested that rTMS can specifically improve manual dexterity,[10] which is defined as the ability to coordinate the fingers and efficiently manipulate objects, and is of crucial importance for daily living activities.[25] Notably, most of the studies focused on motor impairment in the upper limbs, whereas limited data is available on the lower limbs.[18] Walking and balance are frequently impaired in stroke patients and significantly affect the quality of life (QoL),[26,27] and rTMS might represent a valid aid in the recovery of these functions.[28,29] Spasticity is another common complication after a stroke, consisting of a velocity-dependent increase of muscular tone,[30] and for which rTMS has been proposed as a rehabilitation tool.[31]

Dysphagia is highly common in stroke patients, it impairs the global clinical recovery, and predisposes to complications.[32] It has been pointed out that rTMS targeting the M1 area representing the muscles involved in swallowing may contribute to the treatment of post-stroke dysphagia.[33]

Nonmotor deficit is also a relevant post-stroke disability that negatively impacts the QoL. Aphasia is a very common consequence of stroke, affecting approximately 30% of stroke survivors and significantly limiting rehabilitation.[34] According to the IFCN guidelines, to date, there is no recommendation for LF-rTMS of the contralesional right inferior frontal gyrus (IFG). Similarly, no recommendation for HF-rTMS or intermittent theta burst stimulation (TBS) of the ipsilesional left IFG or dorsolateral prefrontal cortex (DLPFC) in Broca's aphasia has been currently approved.[10] The same is true for LF-rTMS of the right superior temporal gyrus in Wernicke's aphasia.[10]

Neglect is the incapacity to respond to tactile or visual contralateral stimuli that are not caused by a sensory-motor deficit.[35] Although hard to treat, rTMS has been proposed as a tool for neglect rehabilitation.[36] However, the IFCN guidelines state that currently there is no recommendation for LF-rTMS of the contralesional left posterior parietal cortex, or for HF-rTMS of the ipsilesional right posterior parietal cortex.[10] In a recent systematic review, most of the included studies supported the use of TMS for the rehabilitation of aphasia, dysphagia, and neglect, although the heterogeneity of stimulation protocols did not allow definitive conclusions to be drawn.[37]

Post-stroke depression is a relevant complication of cerebrovascular diseases.[38] The role of rTMS in the management of major depressive disorders is well documented,[39,40] and currently, rTMS is internationally approved and indicated for the treatment of major depression in adults with antidepressant medication resistance, and in those with a recurrent course of illness, or in cases of moderate-to-severe disease severity.[39] In major depression disorders, according to the IFCN guidelines, there is a clear antidepressant effect of HF-rTMS over the left DLPFC, a probable antidepressant effect of LF-rTMS on the right DLPFC, and probably no differential antidepressant effect between right LF-rTMS and left HF-rTMS. Moreover, there is currently no recommendation for bilateral stimulation combining HF-rTMS of the left DLPFC and LF-rTMS of the right DLPFC. The mentioned guidelines also state that the antidepressant effect when stimulating DLPFC is probably additive, and possibly potentiating, to the efficacy of antidepressant drugs.[10] However, no specific recommendation currently addresses the use of rTMS in post-stroke depression. Recently, rTMS has been proposed as a treatment option for the late-life depression associated with chronic subcortical ischemic vascular disease, the so called 'vascular depression'.[41–44] Three studies tested rTMS efficacy in vascular depression (one was a follow-up study with citalopram). Although presenting positive findings, further trials should refine clinical and diagnostic criteria to assess its impact on antidepressant efficacy.[45]

Approximately 25–30% of stroke patients develop an immediate or delayed cognitive impairment or an overt picture of vascular dementia.[46] There is evidence of an overall positive effect on cognitive function for both LF-rTMS[47] and HF-rTMS,[48] supported by studies on experimental models of vascular dementia.[49–52] Nonetheless, the few trials examining the effect on stroke-related cognitive deficit produced mixed results.[53–56] In particular, two studies found no effect on cognition when stimulating the left DLPFC at 1 Hz and 10 Hz,[53,54] whereas a pilot study found a positive effect on the Stroop interference test with HF-rTMS over the left DLPFC in patients with vascular cognitive impairment without dementia.[55] However, this finding was not replicated in a follow-up study.[56] To summarize, rTMS can induce beneficial effects on specific cognitive domains, although data are limited and their clinical significance needs to be further validated. Major challenges exist in terms of appropriate patient selection and optimization of the stimulation protocols.[57]

Central post-stroke pain (CPSP) is the pain resulting from an ischemic lesion of the central nervous system.[58] It represents a relatively common complication after a stroke, although it is often under-recognized and, therefore, undertreated.[59] According to the IFCN guidelines for the use of rTMS in the treatment of neuropathic pain, there is a definite analgesic effect of HF-rTMS of contralateral M1 to the pain side, and LF-rTMS of contralateral M1 to the pain side is probably ineffective. In addition, there is currently no recommendation for cortical targets other than contralateral M1 to the pain side.[10] Notably, rTMS might be effective in drug-resistant CPSP patients.[58] A recent systematic review that included nine HF-rTMS studies suggested an effect on CPSP relief, but also underlined the insufficient quality of the studies considered.[60]

Study objective

In this article, we aim to provide an up-to-date overview of the most recent evidence on the efficacy of rTMS in the rehabilitation of stroke patients. Although several studies have been published, a conclusive statement supporting a systematic use of rTMS in the multifaceted clinical aspects of stroke rehabilitation is still lacking.

Methods

Search strategy

A literature review was performed on all the meta-analyses on conventional rTMS protocols in post-stroke rehabilitation studies indexed in PubMed, Cochrane Library, Scopus, and Web of Science, from database inception until 31 July 2019. We focused on the recovery of motor function, manual dexterity, walking and balance, spasticity, dysphagia, aphasia, unilateral neglect, post-stroke depression, vascular depression, cognitive function, and CPSP.

Search queries and results

Pubmed: (("transcranial magnetic stimulation"[MeSH Terms] OR ("transcranial"[All Fields] AND "magnetic"[All Fields] AND "stimulation"[All Fields]) OR "transcranial magnetic stimulation"[All Fields] OR ("repetitive"[All Fields] AND "transcranial"[All Fields] AND "magnetic"[All Fields] AND "stimulation"[All Fields]) OR "repetitive transcranial magnetic stimulation"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])) AND ((Meta-Analysis[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms] AND English[lang]). *Results*: 59.

Cochrane Database of Systematic Reviews: "transcranial magnetic stimulation stroke in Title Abstract Keyword". *Results*: 4.

Scopus: TITLE-ABS-KEY ("repetitive transcranial magnetic stimulation" AND stroke AND meta-analysis) AND DOCTYPE (ar OR re) AND (LIMIT-TO (LANGUAGE, "English"). *Results*: 46.

Web of Science Core Collection: TOPIC: ("repetitive transcranial magnetic stimulation" AND stroke AND meta-analysis) Refined by: LANGUAGES: (ENGLISH) AND DOCUMENT TYPES: (REVIEW OR ARTICLE) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI. *Results*: 30.

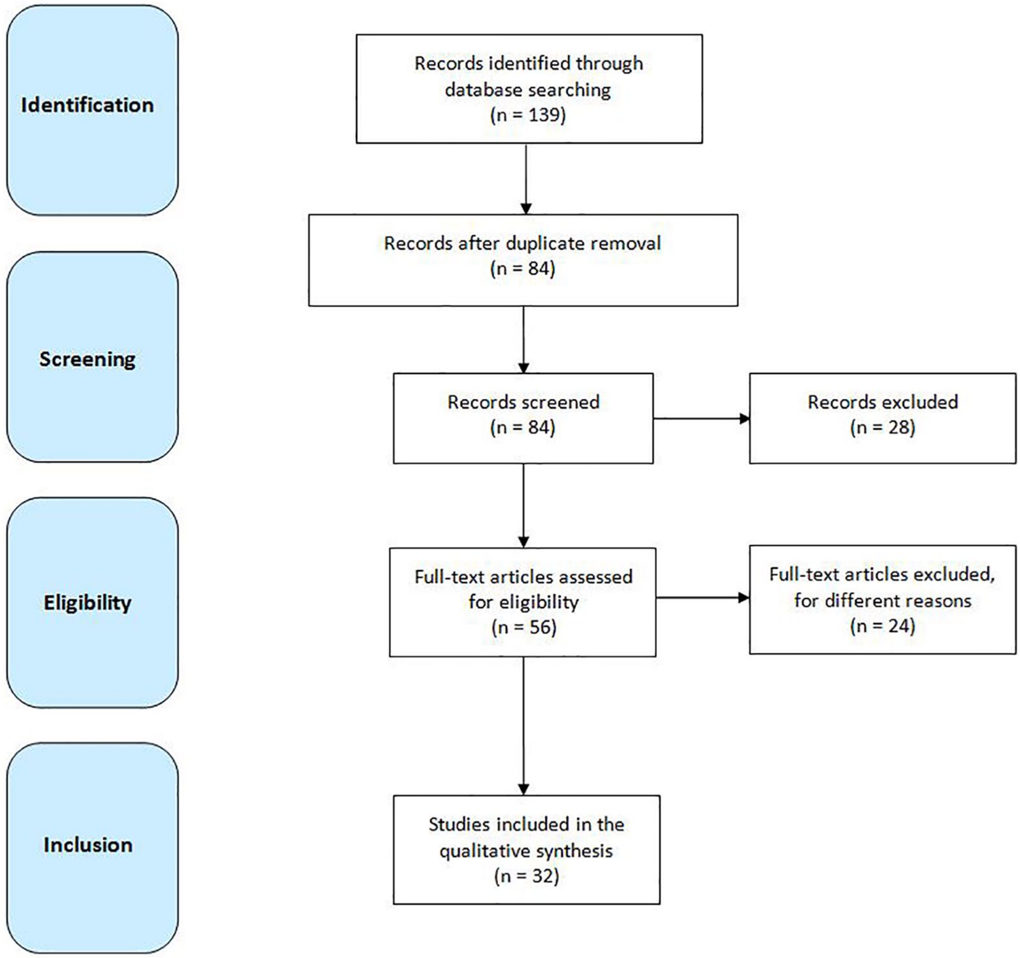

Figure 1. Flow diagram showing the search strategy, the number of records identified, the excluded articles, and the studies eventually included.[61]

Study selection

To be included, a study had to: Use conventional rTMS protocols for post-stroke patients recovery, it is mentioning that studies using other stimulation techniques in addition to rTMS were included only when rTMS data could be independently extracted from the meta-analysis, an exception was made for the studies where data from other techniques (TBS) were pooled in the same meta-analysis but represented only a minority of the total amount of the analyzed studies. Describe a systematic process for searching for and selecting relevant articles. Perform the statistical analysis.

Two independent authors (FF and GL) screened all titles and abstracts of the identified publications. Disagreements were solved by the consensus of a third author (MP). Duplicated entries, retracted publications, studies on other diseases or conditions different from stroke, works on animals, studies without statistical analysis, non-English written papers, publications that are not research studies (i.e. commentaries, letters, editorials, reviews, etc.), and any other study that did not fit within the scope of this review, were excluded. Publications listed in the references were also reviewed in search of more data (Figure 1).

Data extraction

Two authors (RB and GP) independently extracted the following information from the retrieved meta-analyses: type and number of studies included, stimulation parameters and settings, main findings. Disagreements were solved by a third author (AAG). The relevant data are summarized in Table 1.

Table 1. Summary of the main characteristics and findings obtained from the meta-analyses of rTMS and stroke rehabilitation.

Clinical feature	References	Studies included (study design)	Stimulation settings	Main findings
Motor function	Xiang *et al.*[62]	43 RCTs (8 cross-over)	Site: affected M1, unaffected M1, bilateral M1; premotor cortex of the unaffected hemisphere Frequency: 1–25 Hz (7 studies with TBS) Pulses per session: 160–1800 Session number: 1–24 Intensity: 80–130% rMT, 80–120% aMT	Positive effect of rTMS (particularly at 1 Hz) on limb motor recovery and ADL. HF-rTMS modulated MEP. No difference regarding rMT *versus* aMT, stimulation intensity or frequencies, number of pulses, stimulation number and sites. More pronounced effects for 1–7 sessions, early stroke (<30 days), and subcortical lesions.
	Zhang *et al.*[63]	22 RCTs (3 cross-over)	Site: contralesional M1 Frequency: 1 Hz Pulses per session: 600–1800 Session number: 1–24 Intensity: 90–120% rMT	Positive effect on upper limb motor recovery. Short-term efficacy for finger ability, hand strength, and dexterity (in descending order). The long-term effect on finger ability. Enhancing effect of MEPs in the affected hemisphere and suppressing effect in the unaffected hemisphere. Suppressing effect on the rMT of the ispilesional hemisphere and enhancing effect on the rMT of the contralesional hemisphere.
	Graef *et al.*[64]	8 RCTs (1 cross-over)	Site: unaffected M1, affected M1 Frequency: 1 Hz Pulses per session: 240–1500 Session number: 8–22 Intensity: 90–120% rMT	No effect for rTMS combined with upper limb training *versus* upper limb training alone.
	Kang *et al.*[65]	12 RCTs	Site: unaffected M1, affected M1 Frequency: 1–3–10 Hz Pulses per session: 200–1800 Intensity: 90–130% rMT	Positive effect on limb force production for HF-rTMS on ipsilesional M1 and for LF-rTMS on contralesional M1, regardless of the stroke phase (acute, subacute, chronic).
	Hao *et al.*[66]	19 RCTs	Site: unaffected M1, affected M1 Frequency: 0.5–50 Hz Treatment duration: 1 day–4 weeks	No effect on the Barthel Index, motor recovery, HDRS, and cognitive function, regardless of stimulation frequencies or disease duration.
	Hsu *et al.*[67]	18 RCTs	Site: unaffected, affected M1, bilateral Frequency: 1–20 Hz (2 cTBS or iTBS) Pulses per session: 160–2000 Treatment duration: 1–10 days Intensity: 80–130% rMT	Positive effect of on motor function, especially for subcortical strokes. Contralesional LF-rTMS more effective than ipsilesional HF-rTMS. No significant effect on affected side MT. Few adverse events reported.
	Tang[68]	9 (5 RCTs, 4 not specified)	Site: unaffected M1, affected M1. Frequency: 1–20 Hz Pulses per session: 100–1600 Treatment duration: 1–10 sessions Intensity: 80–100% rMT	Positive effect of rTMS on upper limb motor function. Sub-analysis shows a significant effect for acute stroke and LF-rTMS over the unaffected M1.
Manual dexterity	O' Brien *et al.*[69]	11 (not clear which studies have been included in the analysis)	Site: contralateral M1, contralateral dorsal premotor cortex. Frequency: 1–10–20 Hz (1 iTBS – cTBS) Pulses per session: 300–200 Treatment duration: 1–10 sessions Intensity: 80–110% rMT	Positive effect of rTMS on hand dexterity in mild-to-moderate chronic stroke.

(Continued)

Table 1. (Continued)

Clinical feature	References	Studies included (study design)	Stimulation settings	Main findings
	Zhang *et al.*[70]	31 RCTs (8 cross-over)	Site: ipsilesional M1, contralesional M1 Frequency: 1–10–20 Hz (4 studies with cTBS or iTBS) Pulses per session: 160–2000 Treatment duration: 1–26 sessions Intensity: 80–130% rMT	Short- and long-term time-dependent improvement. LF-rTMS to the unaffected hemisphere more effective than HF-rTMS to the affected one. Better results in subcortical stroke. Session number-dependent effect (peak after 5 sessions). Few adverse events reported.
	Le at al.[71]	8 RCTs (3 cross-over)	Site: unaffected M1, affected M1, unaffected premotor cortex Frequency: 1–25 Hz Pulses per session: 150–2000 Treatment duration: 1–10 days Intensity: 80–130% rMT	Positive effect on finger motor ability and hand function. No significant changes in neurophysiologic measures (MEPs amplitude and aMT from the paretic side). Few adverse events observed.
Walking and balance	Tung *et al.*[72]	8 RCTs (7 parallel, 1 cross-over)	Site: affected M1, unaffected M1, left DLPFC, ipsilesional cerebellar hemisphere Frequency: 1–20 Hz Pulses per session: 600–1500 Treatment duration: 5–40 sessions Intensity: 90–130% rMT	rTMS significantly improved lower limb function, walking speed, lower limb scores at the Fugl-Meyer Assessment scale, and MEPs. No difference regarding the stroke phase and the stimulation frequency.
	Vaz *et al.*[73]	3 RCTs	Site: affected hemisphere, unaffected hemisphere Frequency: 1–10 Hz Pulses per session: 600–2000 Treatment duration: 10–30 sessions Intensity: 90% rMT	rTMS combined with other therapies induced positive effects on gait speed and walking cadence compared with the sham procedure; both excitatory and inhibitory stimulation improved gait speed in acute, subacute, and chronic stroke
	Li *et al.*[74]	9 (5 RCTs, 4 cross-over)	Site: affected M1, unaffected M1, bilateral M1 leg area, trunk motor spot Frequency: 1–50 Hz Pulses per session: 600–2000 Treatment duration: 1–40 sessions Intensity: 90% rMT	Significant effect on walking speed for ipsilesional HF-rTMS but not for contralesional or bilateral stimulation; no improvement in balance function and motor function. Significant decrease of MEP amplitude from unaffected hemisphere; no effect on MEP amplitude from the affected hemisphere.
Spasticity	McIntyre *et al.*[75]	10 (1 RCT, 1 cross-over RCT, 8 pre/post studies)	Site: contralesional or bilateral Frequency: LF-rTMS (1 Hz), except for one using ipsilesional HF-rTMS (10 Hz) Session number: 10–15 Pulses per session: 100–2400 Intensity: 90% rMT, apart from 1 (30%)	Uncontrolled studies: significant improvements in spasticity at the elbow, wrist, and finger flexors. RCT: no significant effect on the wrist.
	Korzhova *et al.*[76]	3 (2 RCTs, 1 parallel)	Site: M1 of the unaffected hemisphere Frequency: LF-rTMS (1 Hz)	No difference between real *versus* sham stimulation.
	Graef *et al.*[64]	2 RCTs (1 cross-over)	Site: M1 of the unaffected hemisphere Frequency: LF-rTMS (1 Hz) Pulses per session: 240–1500 Session number: 10–14 Intensity: 90% rMT	No effect for rTMS combined with upper limb training *versus* upper limb training alone.

(Continued)

Table 1. (Continued)

Clinical feature	References	Studies included (study design)	Stimulation settings	Main findings
Dysphagia	Bath *et al.*[77]	9 RCTs	Site: affected, unaffected, bilateral sides Frequency: 1–10 Hz Pulses per day: 300–1200 Treatment duration: 5 days–2 weeks	Positive effect of rTMS on swallowing ability. No effect on case fatality or Penetration Aspiration Scale.
	Chiang *et al.*[78]	6 RCTs	Site: affected, unaffected, bilateral side Frequency: 1, 3, 5 Hz Pulses per day: 300–1200 Treatment duration: 5–10 days Intensity: 90–130% rMT	Positive effect of rTMS on acute and subacute post-stroke dysphagia. rTMS more effective compared with other neuromodulation techniques. No significant adverse events reported.
	Liao *et al.* 2017[79]	6 RCTs	Site: affected hemisphere, unaffected hemisphere, bilateral Frequency: 1, 3, 5 Hz Pulses per day: 300–1200 Treatment duration: 1–2 weeks Intensity: 90–130% rMT	Positive effect on the unaffected hemisphere and bilateral stimulation. HF-rTMS more effective than LF-rTMS. Effect lasting for at least four weeks.
	Pisegna *et al.*[80]	4 RCTs	Site: affected and unaffected hemisphere Frequency: 1, 3, 5 Hz Pulses per session: 250–1200 Treatment duration: 1–10 days Intensity: 90–120% rMT	Positive effect for stimulation of the unaffected side.
	Momosaki *et al.*[81]	5 RCTs	Site: affected hemisphere, unaffected hemisphere, bilateral Frequency: 1, 3, 5 Hz Treatment duration: 5–10 sessions	Positive effect of rTMS on dysphagia measured as improvement at the Dysphagia Outcome Severity Scale and Penetration Aspiration Scale
	Yang *et al.*[82]	3 RCTs	Site: affected hemisphere, unaffected hemisphere, bilateral Frequency: 3–5 Hz Pulses per session: 300–500 Treatment duration: 5–10 days Intensity: 90–130% rMT	Positive effect of rTMS on dysphagia compared with sham stimulation.
Aphasia	Bucur and Papagno[83]	8 (7 RCTs, 1 randomized partial cross-over)	Site: unaffected hemisphere; both sides Frequency: 1–20 Hz Pulses per session: 600–1800 Treatment duration: 10–15 sessions. Intensity: 80–110% rMT	Positive effect of rTMS on naming for both subacute and chronic stroke; the effect maintained over time.
	Shah-Basak *et al.*[84]	8 (4 between subject, 3 within subject, 1 cross-over)	Site: right PTr, left PTr, right POp, left POp, right IFG, left IFG Frequency: 1, 6, 20 Hz (1 iTBS; 1 HF-rTMS followed by LF-rTMS) Treatment duration: 10–15 days Intensity: 90–110% rMT	Positive effect on aphasia in subacute and chronic stroke. Subgroup analysis for trial design: statistically significant effect for between and within-subjects designs, no significant effect for cross-over trial.

(Continued)

Table 1. (Continued)

Clinical feature	References	Studies included (study design)	Stimulation settings	Main findings
	Otal *et al.*[85]	6 RCTs	Site: right IFG Frequency: 1 Hz Treatment duration: 10–15 days Intensity: 90% rMT	Positive effect on aphasia for LF-rTMS over the nonaffected hemisphere.
	Li *et al.*[86]	4 RCTs	Site: right PTr Frequency: 1 Hz Treatment duration: 10–15 days Intensity: 90% rMT	Positive effect of LF-rTMS on naming but not on repetition and comprehension. No adverse effects reported.
	Ren *et al.*[87]	7 RCTs	Site: right PTr Frequency: 1 Hz Treatment duration: 10–15 days Intensity: 90% rMT	Positive effect on severity of aphasia, naming, repetition, writing, and comprehension. No adverse effects reported.
Unilateral neglect	Kashiwagi *et al.*[88]	3 RCTs	Site: Parietal cortex area 3 and 4 Frequency: 1–10 Hz. Pulses per session: 656–1200 Treatment duration: 10–28 sessions Intensity: 80–90% rMT	Positive effect compared with sham on overall USN measured with different scales, more evident at 1 Hz but also present at 10 Hz.
	Fan *et al.*[89]	6 RCTs	Site: Parietal cortex area 3, 4, and 5 Frequency: 0.5, 1, 10 Hz Pulses per session: 656–1200 Treatment duration: 10–28 sessions Intensity: 80–90% rMT	Rapid and long-lasting improvement for both LF- and HF-rTMS applied on ipsilesional or contralesional site. More pronounced effect for ipsilesional stimulation and for HF-rTMS. No serious adverse events reported.
	Salazar *et al.*[90]	6 RCTs	Site: Parietal cortex area 3, 4, and 5 Frequency: 0.5, 1, 10 Hz Pulses per session: 656–1200 Treatment duration: 10–28 sessions Intensity: 80–90% rMT	Positive effect of both LF- and HF-rTMS.
Post-stroke depression and vascular depression	Liu *et al.*[91]	17 RCTs	Site: left DLPFC Frequency: 10 Hz Treatment duration: 2–12 weeks Intensity: 60–110% rMT	Positive effect of HF-rTMS on depression measured by the HDRS; significant response and remission rates; positive effect on ADL; positive effect on NIHSS. Significant incidence of headache in the treatment group reported.
	Shen *et al.*[92]	22 RCTs	Site: right DLPFC, left DLPFC, bilateral DLPFC, bilateral prefrontal cortex, M1, left temporal-parietal Frequency: 0.2–15 Hz Sequence duration: 4–30 s Number of sequences: 20–30 Pulses per session: 1000–1960 Session number: 2–280 Intensity: 60–110% rMT	Primary outcome: significant decrease in HDRS. Secondary outcomes: significant effect on clinical response rate. No effect on remission; positive effect on NIHSS and ADL. No clear relationship with the stimulation site and frequency, disease duration, conventional treatment, type of intervention used as control, and total number of sessions.

(Continued)

Table 1. (Continued)

Clinical feature	References	Studies included (study design)	Stimulation settings	Main findings
	Hao *et al.*[66]	2 RCTs (subanalysis)	Site: bilateral frontal lobes, bilateral prefrontal lobes Frequency: 0.5 Hz. Treatment duration: 1–4 weeks	No effect on HDRS score.
Cognitive function	Hao *et al.*[66]	2 RCTs (subanalysis)	Site: unaffected M1, bilateral frontal lobes Frequency: 0.5–1 Hz. Treatment duration: 2–4 weeks Intensity: 60–100% rMT	No positive effect on cognitive function.
Central post-stroke pain	Leung *et al.*[93]	5 RCTs (1 parallel, 4 cross-over)	Site: M1 Frequency: HF-rTMS (range 5–20 Hz) Session number: 1–5 Pulses per session: 500–2000	Significant analgesic effect of rTMS compared with sham. Greater effect after multiple sessions of stimulation, with a frequency ranging from >1 to ≤ 10 Hz.

ADL, activities of daily living; aMT, active motor threshold; cTBS, continuous theta burst stimulation; DLPFC, dorsolateral prefrontal cortex; HDRS, Hamilton depression rating scale; HF-rTMS, high-frequency repetitive transcranial magnetic stimulation; IFG, inferior frontal gyrus; iTBS, intermittent theta burst stimulation; LF-rTMS, low-frequency repetitive transcranial magnetic stimulation; M1, primary motor cortex; MEPs, motor evoked potentials; NIHSS, National Institutes of Health stroke scale; POp, pars opercularis; PTr, pars triangularis; RCTs, randomized controlled trials; rMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; TBS, theta burst stimulation.

Results

A total of 139 results were originally found. Of these, 32 peer reviewed publications were selected according to the above-mentioned inclusion and exclusion criteria (Figure 1). The publication year ranges from 2009 to 2019.

In detail, the results included the following: seven studies for motor function,[62–68] three for manual dexterity,[69–71] three for walking and balance,[72–74] three for spasticity,[64,75,76] six for dysphagia,[77–82] five for aphasia,[83–87] three for unilateral neglect,[88–90] three for post-stroke depression and vascular depression,[66,91,92] one for cognitive function,[66] and one for CPSP.[93] The study by Graef and colleagues[64] included data on both motor function and spasticity and, therefore, the results were independently considered for both categories. Given that the meta-analyses specifically addressing the treatment of cognitive function were not found, data were extracted from a subanalysis of the study by Hao and coworkers.[66] The same study also included a subanalysis on post-stroke depression.[66]

Motor function

Overall, Tang found a positive effect of rTMS for upper limb motor function, and in particular for LF-rTMS over the unaffected M1 area in acute stroke patients.[68] Hsu and colleagues found an overall positive effect of rTMS on motor function, with more pronounced results in patients with subcortical lesions.[67]

Interestingly, LF-rTMS applied over the unaffected hemisphere appears to be more beneficial than HF-rTMS over the affected hemisphere.[67] A meta-analysis focusing on LF-rTMS applied over the contralesional hemisphere also found a positive short- and long-term effects on upper limb motor recovery.[63] Nevertheless, Kang and colleagues investigated the effect of rTMS on paretic limb strength during the acute, subacute, and chronic phases of the stroke. Their results show a positive effect in all stroke phases, either for HF-rTMS applied over the ipsilesional M1 or for LF-rTMS over the contralesional hemisphere.[65] Recently, Xiang and colleagues reported a positive effect of rTMS (in particular, by using 1 Hz stimulation) on limb motor recovery and activities of daily living (ADL). This effect was more evident for acute and subcortical strokes, as well as after seven sessions of stimulation, whereas it decreased with more prolonged treatments.[62]

Finally, it is worth mentioning that some meta-analyses failed to prove a significant impact of rTMS in stroke recovery. Graef and colleagues did not observe substantial differences when rTMS was combined with upper limb training *versus* upper limb training alone.[64] Hao and colleagues found no effect of rTMS on the Barthel index score, motor function, Hamilton Depression Rating Scale (HDRS), and cognitive status, regardless of different frequencies of stimulation or stroke duration.[66]

Overall, there is currently conflicting evidence regarding the efficacy of rTMS in motor recovery. LF-rTMS applied over the unaffected hemisphere seems to be the most promising protocol, although further studies are required.

Manual dexterity

Le and colleagues found a positive effect of rTMS on finger motor ability and hand function.[71] A meta-analysis of studies using LF-rTMS, HF-rTMS, and TBS for the recovery of the upper limb found a significant short- and long-term improvement in the outcome measures of motor function. Interestingly, the authors reported the time-dependent effectiveness of rTMS, with a descending order from acute to subacute until the chronic phase of a stroke. Finally, they also suggested a number-dependent effect of rTMS sessions on the manual dexterity recovery, with the most beneficial effect obtained after five sessions.

Regarding the stroke location, rTMS seems to be more effective in those patients with subcortical lesions with respect to other cerebral sites.[70] On the other hand, a more recent meta-analysis, focusing exclusively on studies considering manual dexterity as a specific outcome measure after rTMS, shows a significant effect in improving hand dexterity in patients with mild-to-moderate chronic stroke.[69]

To summarize, the evidence available suggests a positive effect of rTMS in manual dexterity recovery, but the optimal timing of administration remains uncertain.

Walking and balance

A recent meta-analysis including nine rTMS studies (seven HF-rTMS and two LF-rTMS) showed a significant treatment effect on walking speed for ipsilesional HF-rTMS but not for contralesional or bilateral stimulation. In addition, no improvement in balance or motor function was observed.[74] Similarly, a further meta-analysis showed a positive effect of rTMS combined with other rehabilitation therapies on gait speed and walking cadence in patients with acute, subacute, and chronic stroke.[73] Conversely, Tung and colleagues found a positive effect of rTMS on lower limb motor function, regardless of the stimulation frequency or stroke phase.[72]

To date, studies specifically addressing the walking and balance recovery are too limited to provide a definitive conclusion, although the effects reported on walking speed are encouraging.

Spasticity

McIntyre and colleagues evaluated the effectiveness of rTMS in improving post-stroke spasticity by taking into consideration the modified Ashworth scale as the main outcome measure.[75] All of the studies included used LF-rTMS (1 Hz) to inhibit the contralesional hemisphere,[75] apart from one, that used bihemispheric stimulation by combining 1 Hz and 10 Hz.[94] Among the 10 uncontrolled studies considered in the meta-analysis, a significant improvement of spasticity at the elbow, wrist, and finger flexors were found. However, the two only RCTs did not show a significant effect for the wrist.[75]

The same two RCTs[31,95] were previously included in a meta-analysis by Graef and colleagues, who did not conclude there was any positive effect on spasticity after rTMS combined with upper limb training *versus* upper limb training alone.[64] Finally, in the meta-analysis of three studies by Korzhova and colleagues, no significant difference between LF-rTMS *versus* sham stimulation over M1 of the unaffected hemisphere was detected.[76]

Based on the limited available data, there is no current evidence to support the role of rTMS in the treatment of spasticity.

Dysphagia

Two meta-analyses found an overall positive effect[82] and a positive effect for the stimulation of the unaffected side,[80] respectively. Momosaki and colleagues observed a positive effect of rTMS on the dysphagia severity rating scale and the penetration aspiration scale.[81] Bath and colleagues found an improvement of swallowing but no effect on case fatality or penetration aspiration scale.[77]

Another recent meta-analysis included six RCTs.[45] The result showed a significant improvement in dysphagia, although HF-rTMS seems to be more effective than LF-rTMS. Regarding the stimulation site, an effect for bilateral or contralesional stimulation was found, but not for ipsilesional stimulation. The therapeutic effect lasts for at least 4 weeks after the procedure.[79] Finally, rTMS seems to be the most effective, among the other neuromodulation techniques (transcranial direct current stimulation, surface neuromuscular electrical stimulation, and pharyngeal electrical stimulation), for the treatment of acute and subacute post-stroke dysphagia.[78]

In brief, rTMS seems to be a promising neuromodulation technique for the treatment of post-stroke dysphagia, although the optimal stimulation setting needs to be defined.

Aphasia

A recent meta-analysis including eight studies (one of which used TBS and another one a combination of HF-rTMS and LF-rTMS) found a pooled positive effect on aphasia after treatment in both subacute and chronic stroke patients.[84] The efficacy of rTMS on naming in subacute and chronic patients is also supported by Bucur and Papagno, who confirmed that the positive effect was maintained over time.[83] In previous work, a positive effect on the accuracy of naming was observed after LF-rTMS over the right IFG.[85] Li and colleagues found a positive effect of LF-rTMS on naming but not on repetition and comprehension,[86] whereas Ren and colleagues showed an effect on severity of impairment, as well as in naming, repetition, writing, and comprehension.[87]

In conclusion, the evidence seems to support the role of LF-rTMS over the unaffected side in the recovery of post-stroke aphasia, with more evident beneficial effects on naming.

Unilateral neglect

A recent meta-analysis including six rTMS studies showed an improvement of unilateral neglect outcome measures, with an immediate and long-lasting effect. Both LF-rTMS and HF-rTMS exerted significant results, either applied on the ipsilesional or the contralesional site, although the effect was more pronounced for ipsilesional stimulation and for HF-rTMS.[89] Similar results after both excitatory and inhibitory stimulation were found by another meta-analysis that considered the same studies.[90] According to the most recent meta-analysis on the same topic, the benefits of rTMS seem to be particularly evident when 1 Hz frequency of stimulation is used.[88]

Although there are promising results, the efficacy of rTMS in the treatment of neglect remains controversial, particularly in terms of the best stimulation parameters to be used.

Post-stroke depression and vascular depression

In their meta-analysis including two RCTs, Hao and colleagues found no effect on the HDRS score.[66] In contrast, a large meta-analysis of 22 RCTs found a significant clinical response after rTMS, as indexed by a significant reduction of HDRS score. However, a clear relationship with the stimulation site and frequency, as well as with the disease duration, the conventional treatment, the type of intervention used as a control, and the total number of sessions, was not found.[92] Regarding the stimulation frequency, the efficacy of 10 Hz stimulation over the left DLPFC was supported by a recent meta-analysis including only HF-rTMS studies.[91]

In short, the evidence seems to support the efficacy of rTMS (particularly HF-rTMS) over the left DLPFC for post-stroke depression. The widely proved efficacy of rTMS for the treatment of major depression disorder encourages further trials.

Cognitive function

In their meta-analysis including two RCTs,[96,97] Hao and colleagues found no significant effect on global cognitive functioning indexed by the Mini Mental State Examination score.[66] Therefore, data regarding the efficacy of rTMS on cognitive functions is currently lacking.

CPSP

A meta-analysis including five HF-rTMS studies found an analgesic effect in terms of a significant decrease of the score at the pain visual analog scale compared with the sham procedure. The effect was greater with multiple stimulation sessions and within a frequency range of 1 and 10 Hz.[93]

To date, given the limited number of low-quality studies available, no recommendation can be made regarding the role of rTMS for post-stroke pain treatment.

Discussion

General considerations

The rationale for using rTMS in stroke recovery is based on the neuroplastic effects that it exerts on altered electrophysiological mechanisms including reduced intracortical inhibition and increased transcallosal inhibition of the healthy hemisphere over the damaged side.[98] Therefore, the therapeutic approaches with rTMS, in accordance with the interhemispheric competition model, are targeted at the normalization of the imbalance between the affected and the unaffected hemispheres.[3,99,100] This can be reached either by delivering HF-rTMS on the ipsilesional hemisphere (to upregulate the level of cortical excitability), or by LF-rTMS to the contralesional hemisphere (thus, downregulating the effect that it exerts on the ipsilesional cortex).[98]

In this context, the selection of the cortical targets is based on the pathophysiological mechanisms that are known to be involved. Functional magnetic resonance imaging (fMRI) studies have demonstrated the role of both ipsilesional and contralesional M1 areas after a stroke, suggesting a reduction of functional connectivity between the areas related to the severity of motor impairment. On the other hand, stronger functional connectivity between M1 and other brain areas is associated with better motor recovery.[101,102] Notably, although conventional fMRI is limited in providing information on cortical locations, which are active during motor movements, sensory stimuli, or cognitive tasks, resting-state fMRI is a recently evolving method from which functional connectivity between distant brain regions is extracted based on low-frequency fluctuations.[101] In particular, Grefkes and colleagues used the dynamic causal modeling, which is a novel approach to capture the intrinsic and task-dependent influences that a particular area exerts over the activity of another area, known as 'effective connectivity'.[102] Based on these assumptions, M1 was confirmed to be the most common stimulation site when aiming to treat motor impairment and spasticity.

The same principle applies to dysphagia, although deglutition is physiologically mediated by bilateral innervation, with a prevalence by the dominant hemisphere. In dysphagia patients, the increasing contralesional activity might help recovery.[33,80] Nevertheless, hemispheric dominance for swallowing can vary among individuals, it is not necessarily the same for language.

Similarly, in patients with aphasia, fMRI demonstrated hyperactivity of the homologous of the Broca's area in the right hemisphere. This activity was associated with poor recovery,[103,104] thus providing the rationale for an rTMS-mediated suppression of the right hemisphere activity.[105]

Hemispatial neglect is typically attributed to a lesion of the right hemisphere, especially involving the parietal cortex. In normal patients, each hemisphere is responsible for the attention toward the contralateral space, a mechanism normally balanced by reciprocal interhemispheric inhibition. Following a stroke, the impaired activity of the right hemisphere favors the disinhibition of the contralateral side. Therefore, the increased activity of the left hemisphere shifts the attention to the right space of the patient, thus further increasing the inhibition over the affected side.[106] Accordingly, patients with neglect show increased cortical excitability of the left parietal regions.[107] In this scenario, inhibitory or excitatory rTMS, applied over the left or right parietal cortex respectively, can modulate the excitability of the regions involved in post-stroke neglect.[89,106]

In depressed patients, many studies pointed out a hypometabolism/hypoexcitability of the left frontal region and a hypermetabolism/hyperexcitability of the right frontal region.[108,109] The DLPFC is easy to access with rTMS, and its crucial involvement in mood/affect regulation and executive functions makes it an ideal target for neuromodulation interventions.[10,110]

Finally, the rationale for the application of rTMS in the treatment of chronic pain is based on the efficacy of the epidural stimulation of the motor cortex in treating drug-resistant neuropathic pain.[111] Repetitive TMS on M1 is capable of modulating pain perception, as demonstrated by experimental models of pain.[112] Although the exact mechanisms are not known, an fMRI study in CPSP patients showed that rTMS can influence the activity of the secondary somatosensory cortex, insula, prefrontal cortex, and putamen, suggesting a more widespread modulation of a complex pain network.[113]

Proposed pathomechanisms

Regardless of the clinical manifestation of the specific neuroanatomical region involved, the human brain typically shows a wide spectrum of innate capacities to react as a dynamic system, in both physiological and pathological conditions, with the final goal to plastically modulate the characteristics of both single cells and neural circuits.[114] These phenomena are recognized under the umbrella term of 'neuroplasticity', defined as the ability of the brain to reorganize itself, with a long-lasting remodeling of neural communication.[115] The recovery of post-stroke motor deficit probably requires long and complex motor learning processes,[116] which are mediated at a molecular level by mechanisms of LTP and LTD.[117] These basically consist in long-lasting modifications of the synaptic activity, mainly mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptors and by GABAergic transmission.

In this context, rTMS is able to reliably mimic the experimental paradigms inducing LTD and LTP phenomena, thus producing changes in MEPs amplitude that outlast the stimulation application.[118] In particular, LF-rTMS inhibits cortical excitability,[119] whereas HF-rTMS produces the opposite effect.[120] The NMDA-dependency of the long-lasting effects of rTMS is suggested by some neuropharmacological studies: memantine, a well-known NMDA antagonist, blocks the effects of TBS.[121]

However, rTMS exerts more diffuse effects, including the induction of specific structural changes within the cortex and the modification of functional connections between different and remote areas of the brain, eventually modulating network oscillations.[15,118] Furthermore, rTMS can trigger the release of different neuromodulators (such as acetylcholine, dopamine, norepinephrine, and serotonin),[122,123] promote the induction of neurotrophic factors,[124–126] and modulate the expression of genes such as c-Fos.[127,128] Of particular interest, a 10 Hz stimulation of the left DLPFC seems to modulate dopamine release, an effect that is not observed during stimulation of the right DLPFC.[129] It is important to note that susceptibility to the neuroplasticity-related modification induced by rTMS might be genetically encoded, thus making the response to treatment customized and possibly predictable.[130–132]

Finally, the modulation of neural activity induced by rTMS might also result from dynamic changes of the blood flow through specific cerebral regions, including those implicated in cognition and mood regulation.[133]

Safety and controversies

Overall, based on the data reviewed, rTMS is shown to be safe, painless, and generally well-tolerated, except for a few patients experiencing mild side effects, such as transient headache and anxiety. Nonetheless, before undergoing any rTMS procedure, candidate patients should always be screened according to the safety guidelines[134] to rule out possible contraindications (e.g. history of seizures, head trauma, syncope, pacemaker, and medical implants or devices, pregnancy). The risk/benefit ratio of the procedure should be carefully evaluated for each patient.

Regarding efficacy, with the exception of spasticity (in which the evidence of benefit is not conclusive yet) and cognitive impairment (for which data are limited), the current literature seems to agree on a positive effect of rTMS for all the other clinical applications of stroke. However, there is still uncertainty regarding the optimal protocols to follow, in terms of patient characteristic and stimulation settings, as briefly summarized in the following and reported in Table 1.

Stroke location. Zhang,[70] Hsu[67] and Xiang[62] reported a more pronounced effect of rTMS on motor function recovery for subcortical stroke. However, it is still unclear whether rTMS should be set for the specific stroke site or not.

Stroke phase. Shah-Basak[84] and Bucur[83] reported a positive effect of rTMS on aphasia in subacute and chronic stroke, whereas O'Brien found a positive effect on fine motor function in chronic stroke only.[69] According to Zhang, the effectiveness of rTMS on manual dexterity recovery follows a descending order from acute to subacute and chronic phase of stroke.[70] On the other hand, Kang described a positive effect on motor function in acute, subacute, and chronic stroke,[65] whereas Tang[68] and Xiang[62] described more pronounced effects for acute stroke compared with chronic stroke, whereas Hao found no effect regardless of the stroke phase.[66] Vaz reported efficacy in walking recovery in all stroke patients.[73] Still, the optimal timing of intervention remains controversial.

Stroke severity. O'Brien described an effect on fine motor function in mild-to-moderate stroke,[69] although data on the correlation between stroke severity and rTMS efficacy are lacking.

Stimulation site. As expected, M1 is the most common site for motor recovery, CPSP, and spasticity, whereas the cortical area representing the muscles involved in deglutition is targeted in post-stroke dysphagia. The DLPFC is the most common target for depression, while the stimulation areas proposed for neglect are parietal cortex areas three, four, and five. In post-stroke aphasia, rTMS is targeted to the pars triangularis, the pars opercularis, and the IFG. The most studied paradigms usually consist of ipsilesional HF-rTMS or contralesional LF-rTMS, although some authors have proposed a combined approach that uses bilateral stimulation. A contralesional HF-rTMS has been also tested in dysphagic patients.[79]

Stimulation frequency. Leung found a positive effect of HF-rTMS in CPSP, particularly in the frequency range > 1 Hz and ≤ 10 Hz.[93] HF-rTMS over the unaffected side seems to be more effective than LF-rTMS for dysphagia.[79] Both HF-rTMS and LF-rTMS seems to be effective in patients with unilateral neglect.[88–90] The most used protocol for aphasic patients is LF-rTMS at 1 Hz over the unaffected side. Ipsilesional HF-rTMS appears to be the more effective for gait recovery,[74] while LF-rTMS over the unaffected side seems to be more beneficial than HF-rTMS over the affected side for gross motor function recovery. HF-rTMS seems to be the most effective protocol for post-stroke depression. Overall, this bulk of heterogeneity does not allow us to draw a definitive conclusion on the ideal stimulation frequency.

Stimulation intensity. As for the stimulation frequency, there is great variability among the studies for the intensity of stimulation to be used, with values oscillating from below to well above the patient's rMT. Suprathreshold upper intensities and frequencies are limited according to the safety guidelines.[134] Therefore, the most appropriate stimulation intensity is still unclear.

Coil type. The type of coil been used in the studies analyzed was not always clearly stated. Moreover, when reported, significant heterogeneity of coil types was noted. These issues make the comparison of the obtained results rather challenging. To date, therefore, a clear recommendation regarding the type of coil to be used cannot be reached.

Stimulation length. Leng found a greater effect of rTMS on CPSP with repeated stimulations.[93] Zhang found a number of dependent effects of rTMS sessions on motor function, with a peak of efficacy after five sessions.[70] Similarly, Xiang describes the best effects on motor function after seven sessions.[62] However, the number of stimulation sessions and the total length of treatment significantly vary among the studies and, to date, there is no conclusive statement about this feature.

Long-term efficacy. Liao observed that the effect of rTMS on dysphagia persisted for at least 4 weeks.[79] A long-lasting positive effect on unilateral neglect was also found by Fan.[89] Zhang described a long-term improvement in motor function.[70] The effects of stimulation seem to be long-lasting for aphasia.[83] Nonetheless, more data is needed to firmly establish the long-term effects of rTMS and to determine the best stimulation parameters to achieve consistent results.

Outcome measures. There is a large heterogeneity of the outcome measures in the studies considered, making the different interventions employed and the expected results difficult to compare. As known, an objective measure of the effectiveness of an intervention is crucial to translate the research results into clinical practice. Therefore, the outcome measures should be selected according to the WHO International Classification of Functioning, Disability, and Health (ICF) in order to ensure comparability, reliability, and validity.[135]

Concomitant treatment. The difference between outcomes from TMS combined with conventional therapy *versus* TMS alone has to be addressed. Indeed, many of the studies reviewed do not report specific results on this aspect, and others do not separately consider the effect of the different therapeutic interventions concomitantly performed.

Strengths and limitations

The strength of this review is that it comprehensively summarizes the evidence from a large number of meta-analyses covering the impact of rTMS on the most common consequences of stroke. The main criticism is of the review is that data were extracted from meta-analyses rather than individual studies, although the meta-analyses provide the highest level of evidence. Another limitation is that, in addition to the conventional HF-rTMS and LF-rTMS, other protocols of repetitive stimulation can be set, such as TBS or the quadripulse stimulation, although this goes beyond the main goal of the present review. When a meta-analysis included both conventional rTMS and TBS, the results on rTMS were in most cases independently extracted, although in some cases data from both techniques were pooled. In these circumstances,[62,67,69,70,84] the meta-analyses were eventually included given that TBS studies represented only a minority of the total results (Table 1). Finally, although the research methodology was systematic, this article cannot be considered as a systematic review because it provides a description of the studies but not a detailed evaluation of the quality of the studies themselves.

Conclusions and future perspectives

In combination, the evidence from the literature reviewed allows us to state that rTMS is a feasible nonpharmacological tool to assist the neurorehabilitation of different motor and nonmotor clinical manifestations of stroke. Integrated with other conventional rehabilitative modalities, rTMS might synergistically act by further enhancing the clinical recovery and the prognostic perspective of stroke survivors.

However, it is not possible to recommend a particular protocol at present. The significant heterogeneity of the studies currently available, especially in terms of the protocol to be set and outcome measures that have to be used, makes it hard to compare the different interventions employed and the expected results. This leads to a lack of consensus on the best clinical and technical settings to be adopted in order to achieve optimal long-lasting results and to expand the use of rTMS into a large-scale application.

To overcome the previously mentioned limitations, future research should preliminarily evaluate the most promising protocols before going on to multicenter studies with large cohorts of patients in order to achieve a definitive translation into daily clinical practice and a reliable group stratification.

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