Review Article

Applications of Transcranial Magnetic Stimulation in Post-Stroke Dysphagia

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ABSTRACT

Objectives: To summarize the main findings of using transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS) in physiologic swallowing response and to review the parameters related to rTMS protocols in post-stroke dysphagia (PSD) treatment.
Study design: English-language literatures published from 1st January 1999 to 20th August 2020 were sought using PUBMED, MEDLINE, and Web of Science; and MeSH terms of transcranial magnetic stimulation, swallowing, deglutition, dysphagia, and stroke. Nineteen randomized control trials (RCT), six non-RCT, and one systematic review article were included.
Setting: Rehabilitation centers and university hospitals in Europe or Asia.
Subjects: Normal population and post-stroke dysphagia patients.
Methods: A narrative review of all the relevant papers related to TMS or rTMS was conducted.
Results: TMS is used to investigate swallowing physiology and to treat dysphagia. Several experiments have shown positive outcomes of swallowing functions without any serious complications. Two parameters: frequency and stimulation side, have different effects. Low-frequency stimulation has an inhibitory effect by decreasing the cortical excitability while high-frequency stimulation has the opposite effect by increasing the excitability. Low-frequency stimulation applied over the unaffected hemisphere inhibits interhemispheric interaction. High-frequency stimulation applied over the unaffected or the affected hemisphere might facilitate the recovery. Bilateral hemispheric stimulation by using high-frequency was shown to improve outcomes. To alter the cortical signal in swallowing, rTMS can be applied on both pharyngeal cortical hemisphere and the cerebellum.
Conclusion: rTMS is one intervention which may facilitate neurological recovery after dysphagic stroke. Although there was weak evidence to support dysphagia treatment, the recent studies showed positive effects. rTMS may be beneficial adjunctive therapy in post-stroke dysphagia treatment if a strong evidence protocol is addressed.

Keywords: transcranial magnetic stimulation, deglutition, dysphagia, stroke

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Introduction

Deglutition is an important process of living and it influences quality of life. Dysphagia is a difficulty in swallowing which in turn, results in malnutrition, dehydration, and aspiration pneumonia. Causes of dysphagia can be categorized into neurological, mechanical, infection, iatrogenic, and neuromuscular disorders. Cerebrovascular accident is one of the important causes.[1]

Nowadays, common therapeutic methods for post-stroke dysphagia (PSD) include, oral-lingual-pharyngeal muscles training, compensatory techniques, and dietary modification.[2] Neurofacilitation is an approach of muscle training. Apart from muscle training, repetitive transcranial magnetic stimulation (rTMS) is an important machine which has been used, successfully, to study deglutition physiology and treatment over a long period of time. Some studies believed it may help accelerate brain recovery.[3]

In the past 20 years, there were many research studies regarding rTMS in swallowing. Therefore, the purpose of this narrative review is to summarize the main findings of using transcranial magnetic stimulation (TMS) and rTMS in physiologic swallowing response and to review the parameters related to rTMS protocols in post-stroke dysphagia treatment; with an appropriate protocol, it could be used as an adjunctive treatment in the future.

Methods

Search strategy

PubMed, MEDLINE, and Web of Science were sought to identify the relevant clinical studies published in English from 1st January 1999 to 20th August 2020. The following MeSH terms: transcranial magnetic stimulation, swallowing, deglutition, dysphagia, and stroke, were used in combinations for database searches.

Inclusion criteria

- Clinical trials associated with usage of TMS and rTMS in protocol finding in physiologic swallowing response.
- Clinical trials, meta-analysis, or systematic reviews

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related to the use of rTMS as an intervention in PSD.

- TMS or rTMS as an intervention in human

Exclusion criteria

- The dysphagia caused from other diseases such as Parkinson's disease, cancer, and traumatic brain injury.
- Reviews, case series, case reports, and preliminary studies
- Other non-invasive brain stimulations such as transcranial direct current stimulation or theta burst stimulation, etc.
- The experiments or the results involved other conditions, for example, communication or hemiparesis.

Quality assessment

The author read the articles in full and analyzed the quality markers by using the Joanna Briggs Institute (JBI)[4] for clinical trials and systematic review articles. This is one of the standard tools for critical appraisal in medical research. Nineteen RCT, six non-RCT and one systematic review article were assessed for quality.

Data extraction

This narrative review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA).[5] There were no specific protocols for this review. The extracted data included the rationales, the processes of the studies, and the outcomes of the experiments.

Results

Five hundred and fifty-one of the literatures were found in the databases. The duplicated articles (n = 322) were excluded. The reviewer assessed the studies (n = 229) following the inclusion and the exclusion criteria. There were eleven articles related to TMS and rTMS in physiologic swallowing response and fifteen studies in post-stroke dysphagia treatment. The experiments were done in the university hospitals or the rehabilitation centers in Europe or Asia. For physiologic swallowing studies, the subjects were healthy. For stroke studies, patients had a unilateral cerebrovascular disease for the first time.

TMS in physiologic swallowing studies

Muscles and nerves can be activated by electrical stimulation. Following Faraday's law, Polsen in 1982 and Barker in 1985 invented a machine called TMS. TMS produces magnetic field via a coil which changes to an electrical field. The electricity passes through the skull, the cortex, subcortical white matter, and neuron projections. The current produced is sufficient to depolarize neural axons and hence, activation of target muscles at last.[6] (Figure 1)

The very first TMS studies were done in motor limbs. Later on, there were researchers who focused more on swallowing. Ertekin was the first researcher who used TMS and needle electromyography (EMG) in cricopharyngeal muscle of the upper esophageal sphincter and found linkage of the cortical pharyngeal cortex to pharyngeal muscles.[7] Paine found the pharyngeal amplitudes were also larger when the intensity was increased.[8] Hamdy and colleagues suggested that the precentral motor cortex plays a major role of deglutition and the pharyngeal motor control in both hemispheres were asymmetrical, showing one side to be more dominant (dominant pharyngeal hemisphere) than one other (non-dominant pharyngeal hemisphere). Moreover, the dominant pharyngeal hemisphere was independent of handedness.[9,10]

rTMS in physiologic swallowing studies

rTMS uses multiple pulses with equal intensity and a specific frequency applied over the brain cortex. The rTMS can produce cortical excitability and cause a prolonged effect for several minutes.[6] Many studies indicate that rTMS can produce excitability from the motor cortex via cortico-bulbar projections to activate pharyngeal musculatures.[3,11]

rTMS in cortical excitability inhibition studies

Mistry et al. established that using the 1 Hz frequency, at 120% of pharyngeal resting motor threshold (PRMT), 600

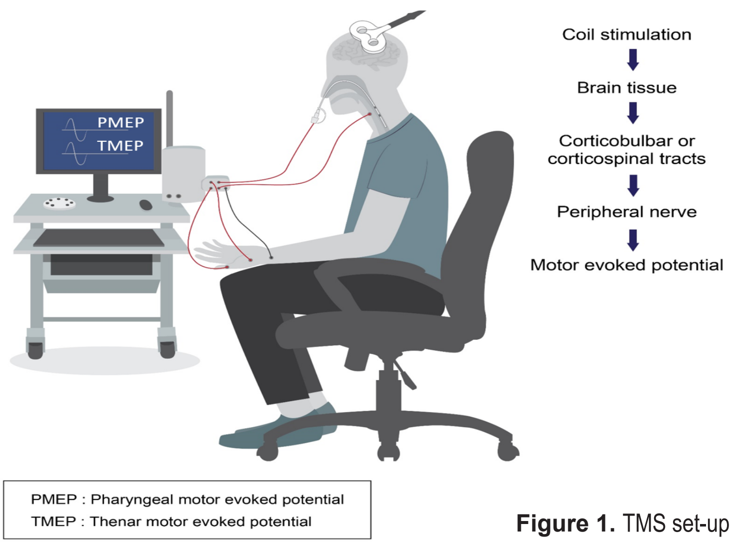

Figure 1. TMS set-up

pulses for 10 minutes over the dominant pharyngeal motor cortex caused a reduced cortical excitability for 45 minutes. The outcomes showed a significant change in pharyngeal motor evoked potential (PMEP) and swallowing behaviors.[12] Verin et al. followed this protocol and found oral transit time (OTT) was delayed and pharyngeal reaction time increased significantly by evaluating from video fluoroscopic swallow study (VFSS).[13] They concluded that the frequency at 1 Hz produced the inhibitory effect. The neurophysiologic effect was called 'virtual lesion' which temporary acted like a true lesion. Furthermore, the virtual lesion occurred only in the dominant pharyngeal hemisphere. If applied this frequency of rTMS over the non-dominant pharyngeal hemisphere, the PMEP and the swallowing behaviors measured from VFSS would not change significantly.[12,13] This finding concurs to what Hamdy et al. found in patients who had brain lesion in the non-dominant swallowing hemisphere but had no dysphagia. It was concluded that oropharyngeal dysphagia might be a result of the damage in the dominant pharyngeal hemisphere only.[1,9]

Additionally, the studies explained more details about the pharynx and the esophagus. In the limbs, they are a predominantly unilateral representation. In contrast to the pharynx and the esophagus, both midline structures are bilateral cortical representation.[9,12] When there is a lesion in one hemisphere, the signal from the contralesional hemisphere inhibits the ipsilesional hemisphere less than what it does in the limbs. This phenomenon implied that transcallosal interactions between the two pharyngeal motor areas were not strongly competitive, and indeed were most likely synergistic.[12]

rTMS in cortical excitability stimulation studies

Gow et al. found that setting frequency at 5 Hz, 80% of PRMT, 100 pulses could increase cortical excitability of pharyngeal motor cortex for the longest duration: 60 minutes, measured by pharyngeal EMG.[11] To use this finding in more clinical setting, Jefferson tried to reverse the virtual lesion in healthy subjects. Several studies had concluded that functional recovery of dysphagia in PSD patients was associated with increased cortical signal only in the unaffected hemisphere.[3,9,14] So, Jefferson applied rTMS over the unaffected hemisphere and found that 250 pulses at 5 Hz frequency were the optimal protocol to reverse the virtual lesion. The effect could last up to two hours.[10] However, in the limbs of stroke patients, more than or equal to 3 Hz of frequency can produce cortical excitability.[6] Therefore, it was also be used by some researchers in swallowing studies.[15,16]

rTMS in cerebellar stimulation studies

Cerebellum is another part which controls the swallowing process. Although the main role is still unclear, it might relate to sequencing, feed-forward control, and internal coordination of oral-lingual and pharyngeal muscles.[1] Impairment in deglutition will occur when stroke lesions are present on this area such as Wallenberg syndrome.[16] One hypothesis indicated that the cerebellum was supplied by vertebrobasilar circulation which was the same branch to the brain stem where the central pattern generator (CPG) was located.[1,16]

Vasant et al. suggested that using 250 pulses at 10 Hz could increase the PMEPs when stimulated over posterior fossa. If the frequency was set to more than 10 Hz, the excitability would not increase anymore due to its ceiling effect.[17] Thereafter, Sasegbon also conducted a study in normal population which was applied to the virtual lesion over the dominant pharyngeal motor cortex. After using 250 pulses at 10 Hz, 90% of thenar resting motor threshold applied over each side of cerebellum (posterior fossa), the cortical inhibition could be reversed when applied over either side compared to sham.[18] A year later, they found that using the same protocols of rTMS applied over both cerebellar hemispheres alternatively could produce the cortical excitability more than only over one side.[19] It could be implied that there were projections from cerebellum passing brain stem to higher brain which control the swallowing processes; neuroplasticity was facilitated by stimulating cerebellar pathways.[18-20]

The advantages of cerebellar stimulation were promoting brain recovery by stimulating at the posterior fossa directly. The anatomical landmark was easy to find and required less intensive training. Serious complications such as seizure also occurred less than stimulating over the cortex.[18]

rTMS in post-stroke dysphagia

rTMS in dysphagia was studied in many experiments. The figure-of-eight coil which released the current focally to the brain was used in all studies. The outer diameter of the coil loop was approximate 70-90 mm. The inclusion and the exclusion criteria were rather similar among of the studies and summarized in the table below.

Table 1. The inclusion and the exclusion criteria to participate the experiments

Inclusion criteria	Exclusion criteria
- Unilateral hemisphere stroke (ischemic stroke mostly) - Varied in time of onset - Age more than 18 years old - Can stay in upright position	- Prior head injury /other neurological disorders/ swallowing problems - Unstable medical conditions such as infection - Severe aphasia or cognitive impairment - Prior administration of tranquilizer - Contraindication for TMS (seizure, implanted pacemaker, medication pump, metal plate in the skull, metal objects in the eye, craniectomy state)

TMS, transcranial magnetic stimulation

Protocols in each experiment were different from each other. However, the influential factors were frequency and stimulation side.[21]

1. The stimulation side and frequency

1.1 Ipsilesional stimulation: When stroke happens, the brain is damaged and loses its neurological control in swallowing. High-frequency stimulation (at least 3 Hz) over this hemisphere can awake the sleep circuits or encourage the coordination of synapses.[15,16] Moreover, the lesional hemisphere might be suppressed from the contralesional side via the transcallosal pathway which was also found in extremity hemiplegia. Enhancing the cortical excitability in ipsilesional side could counteract the suppressive effect.[15] Lee et al. reported that using the 10 Hz frequency of rTMS over the suprahyoid cortical area could significantly improve clinical swallowing assessments.[22]

1.2 Contralesional stimulation can be divided into inhibitory and excitatory effects.

Inhibitory effect: The ipsilesional hemisphere is disrupted from the contralesional hemisphere which is called interhemispheric interaction. Low-frequency rTMS applied over the contralesional side can reduce the inhibition effect.[23,24]

Excitability effect: The recovery from dysphagia stroke involves compensatory changes of the contralesional hemisphere.[9,10] High-frequency stimulation on this side might promote the recovery.[10] Muellbacher et al. supported this hypothesis. They studied acute PSD by using high-frequency rTMS applied over tongue cortical area on the contralesional hemisphere. They found that the cortical excitability increased in bilateral hemispheres which measured by tongue MEP.[14] Moreover, Park et al. suggested to stimulate over the contralesional side; it was easy to find the motor hot spot because in severe cases, the neurons in the lesional hemisphere might remain less than those in the opposite side.[25]

1.3 Bilateral stimulation: The damage on supratentorial areas, when one side is disrupted, the surviving neurons related swallowing functions in the other side will also decrease their activity. Bilateral stimulation might reverse this phenomenon (reverse diaschisis).[26] Following this hypothesis, Park et al. found that the improvements of dysphagia by using high-frequency (10 HZ) of rTMS over bilateral cortical hemispheres were better than those from the unilateral stimulation.[27] The recent study used high-frequency rTMS applied over the lesional hemisphere and used low-frequency on the other side. This protocol could also improve the clinical swallowing assessments but the rationale was unclear.[28]

However, the systematic review in 2017 indicated that the swallowing functions were improved more in contralesional and bilateral hemispheres stimulation. Moreover, both high and low frequency of rTMS could improve the outcomes after treatment.[21]

2. The intensity and the resting motor threshold of the muscles

To calculate the intensity, resting motor threshold (RMT) is needed. RMT is defined as the required minimum stimulation intensity over the motor hot spot to evoke the optimum MEP, 5 out of 10 trials, in the given muscle.[6] There are two groups of muscles which are usually used. The first is hand muscles, abductor pollicis brevis (APB)[25] and first dorsal interossei (FDI)[15,16] muscles, and the second is the pharyngeal muscles.[23,25] The intensity to evoke APB or FDI muscles and achieve at least 50 µV was usually at 30-60% of the maximum stimulating output of the rTMS machine[6] while the intensity to evoke PMEP at least 20 µV is around 70-80%.[12] The intensity to evoke pharyngeal muscles is higher. Therefore, the intensity to activate the cortical excitability after brain damage depends on RMT of which muscle is chosen.

Finding RMT of hand MEP is easier because the cortical area of the upper extremity is large.[25] Some studies chose the intensity following the previous rTMS protocols that were used in unilateral hemiplegia studies.[15,16] Khedr et al. in order to activate more neurons, set high intensity (130%) of FDI RMT because the electricity could spread 2-3 cm over the cortex from the center of coil.[16] However, the safety guideline recommends to use the intensity at < 130% of RMT.[29]

Most problems of PSD are associated with oropharyngeal phase.[1] Most of the experiments used rTMS applied over mylohyoid cortical area because these muscles have the most important role in pharyngeal phase.[22,30] Some

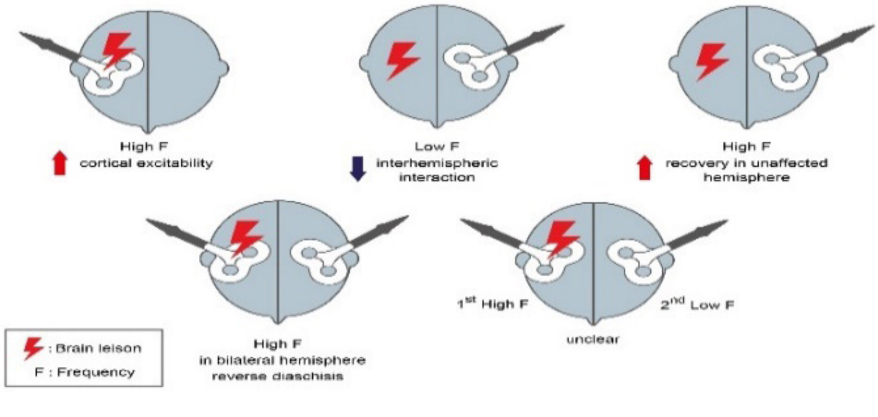

Figure 2. The hypotheses of frequency and stimulation side in rTMS protocols affecting to brain recovery. (F, frequency)

Table 2. Frequencies, intensities, and the cortical motor areas that applied the coil over for rTMS

Frequency and Intensity	Cortical motor area	Position of the coil
- 3 Hz of 120% of FDI RMT over affected side[15] - 3 Hz of 130% of FDI RMT over bilateral hemisphere[16]	Proximal striated muscles of the esophagus[8]	3 cm anteriorly and 6 cm laterally to the vertex[16] In healthy subjects - 3.8±1.4 cm anteriorly and 6.9±1 cm laterally of Rt. side - 3.0±1.7 cm anteriorly and 6.6±0.87 cm laterally of Lt. side[9]
- 3 Hz of 90% of mylohyoid RMT over affected side[30] - 10 Hz of 90% of mylohyoid RMT over bilateral sides[27] - 1 Hz of 100% of mylohyoid RMT over unaffected side[30] - 1 Hz of 90% of mylohyoid RMT over unaffected side[24]	Mylohyoid[24,30]	2-4 cm anteriorly and 4-6 cm laterally from the vertex[24,27,30]
- 5 Hz of 90% of thenar RMT over unaffected side[25]	Pharyngeal muscles[12,25]	Mediolateral and anteroposterior from the vertex 2.5-4 cm from each[12]
- 5 Hz of 90% tongue RMT over affected side[31]	Tongue[31]	0-4 cm anteriorly and 4-6 cm laterally to the vertex[14]
- 10 Hz of 90% thenar RMT[18,19]	Cerebellar hemisphere[18,19]	The central part of coil applied 1 cm below the inion to stimulate the midline, tangentially to the scalp with the handle pointing superiorly[20]

FDI, first dorsal interossei; RMT, resting motor threshold

studies chose tongue muscles because they are mostly involved in oral to initial pharyngeal phase.[14,31] To measure the PMEP directly by transnasal or transoral, pharyngeal intraluminal catheter seemed to be more accurate than surface EMG.[15,16,25] However, some participants felt uncomfortable when the catheter was inserted and wanted to stop the study.[15] Unfortunately, most studies did not describe how the resting motor threshold was determined. This is also important because RMT of any muscle can vary around 20% across studies and across investigators.[8,12] MEP responses also showed a variation according to phase of sleep and intake of ethanol.[8]

3. The duration of effect

Most studies followed up at 3 months and found the effect still lasted.[24,30,32] They hypothesized the long-lasting effect could be from the change of GABAergic circuits in the pharyngeal cortex and enhanced intracortical glutamatergic transmission.[6,25] While some other studies found improved clinical swallowing at 2 weeks,[23,25] 3 weeks,[27] to 4 weeks.[28] However, the systematic review concluded that the results could be maintained over 4 weeks.[21]

4. The outcomes and the adverse effects

Several studies showed positive effects.[21,27,30,32] However, the study of rTMS in chronic PSD did not indicate improvement in swallowing functions (clinical testing, tongue strength, and from VFSS) significantly.[31] Unluer et al. reported that rTMS also improved the quality of life especially in the burden and fear of eating significantly. One hypothesis suggested that diffusing of rTMS signal to prefrontal cortex could affect moods.[24] The small sample size[15,16,21,23,25,31] and the degree of dysphagia (mild to moderate) might impact the exact results in several studies.[22,31] Furthermore, the tools of assessments might have not enough sensitivity to classify the severity of dysphagia clearly.[22,31] Lee et al. reported the clinical rating scale or the Dysphagia Outcome Severity Scale (DOSS). It was used to assess clinical parameters of oral phase more than those of pharyngeal phase whereas the treatment applied over mylohyoid muscles involves more in initial pharyngeal phase.[22] Therefore, the treatments given might not relate well to the parameters assessed.[22] However, rTMS was safe for using in PSD patients due to no serious complications such as seizure. For minor adverse effects, two studies reported dizziness, transient headache,[23,30]and a tingling sensation.[30] Furthermore, pair associated stimulation-combination of rTMS (central stimulation) with neuromuscular or pharyngeal electrical stimulation (peripheral stimulation), might facilitate the speed of neurological recovery.[28,33] More research is still in needed.

Discussion

In the author's aspects, even the protocols were varied and the long-term effects were not clear. However, the results showed the positive effects in both swallowing functions and the swallowing-related quality of life. Using rTMS to promote neuroplasticity in acute and subacute phase combined with traditional therapy might be beneficial. The future study might design a proper methodology including the sample size, outcome assessor blinding, the time of finding RMT, the subtype

Table 3. Recent published studies related to rTMS in post-stroke dysphagia

Study	RCT Participants	Onset	Site of stimulation	Protocol	Duration	Results
Cheng et al, 2017[31]	Double-blinded N = 14	PSD At least 12 months	Affected (active rTMS vs sham)	5 Hz 100 pulses ITI 15 s, 90% RMT of tongue 10 days over 2 weeks	F/U 2,6,12 months	No significant change in VFSS, SAPP and maximum tongue strength
Park et al, 2017[27]	Single- blinded N = 33	Stroke less than 3 months	Bilateral vs affected side vs sham (pre and post treatment)	10 Hz 500 pulses ITI 55 s, 10 min 90% RMT of mylohyoid 10 consecutive days	F/U immediately and 3 weeks	Improved CDS, DOSS, PAS mostly in bilateral stimulation over 3 weeks ($p < 0.05$)
Tarameshlu et al, 2019[32]	Double-blined N = 18	More than 1 month	Unaffected (rTMS + TDT vs TDT vs rTMS)	1 Hz, 1200 pulses + 20% above RMT of mylohyoid 20 min 5 consecutive days	F/U at 5th, 10th, 15th and 18th sessions	MASA: improve all over time ($p < 0.001$) FOIS: improve overall groups ($p < 0.05$), more greater in rTMS+TDT ($p < 0.05$)
Unluer et al, 2019[24]	Single-blinded N = 28	2-6 months	Unaffected (rTMS + TDT vs TDT)	1 Hz, 1200 pulses 90% RMT of mylohyoid 20 min, 5 consecutive days	F/U at after, 1 and 3 months	SAFE: improve all at 1,3 months ($p = .000$) PAS: improve over 1 month ($p < 0.05$), no significant in between group
Zhang et al, 2019[28]	Single-blinded N = 64	Less than 2 months	HF at affected LF at unaffected 1. Sham rTMS + NMES, 2. HF of rTMS + NMES 3. LF of rTMS + NMES 4. Bilateral rTMS + NMES	HF: 10Hz, 900 pulses, 110% RMT of mylohyoid ITI 27 s, 15 min LF: 1 Hz 900 pulses, 80% RMT 15 min, 5 days/ week for 2 weeks	F/U at 2 weeks and 1 month	DD score: improve in bilateral rTMS+NMES at 2 weeks ($p = 0.017$) SSA: decrease all groups at 2 weeks, 1 month ($p < 0.05$), bilateral rTMS + NMES greater > HF/LF of rTMS + NMES > NMES

CDS, Clinical Dysphagia Scale; DD, Degree of Dysphagia; DOSS, dysphagia outcome and severity scale; FOIS, Functional Oral Intake Scale; F/U, follow up; HF, high-frequency; ITI, intertrain interval; LF, low-frequency; MASA, the Mann Assessment of Swallowing Ability; NMES, neuromuscular electrical stimulation; PAS, Penetration-aspiration Scale; PSD, post-stroke dysphagia; RCT, randomized controlled trial; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SAFE, the Swallowing Ability and Function Evaluation; SAPP, the Swallowing Activity and Participation Profile; SSA, Swallowing Assessment; TDT, Traditional Dysphagia Therapy; VFSS, Videofluoroscopic Swallowing Study

Table 4. Advantages and disadvantages of rTMS

Advantages	Disadvantages
- Safe - Painless - Non-invasive procedure - Well-tolerated procedure - Do not need to be actively engaged during treatment	- High cost - Contraindicated in certain patient groups - Varied treatment protocols - Uncertain outcomes - Uncertain long-term effects

of stroke (the recovery is varied in different locations of the lesion) and the tools of assessments. Moreover, the rTMS studies in PSD tend to be increasing so a meta-analyses and systematic review might be done for certain outcomes in the future.

Conclusion

TMS is one intervention which may facilitate neural reorganization after post-stroke dysphagia. Many studies showed several protocols for treatment. The frequency and the stimulation site seem to be crucial. Although there were weak evidences to support the use in PSD treatment, the recent studies showed positive effects. In designing a study, understanding the swallowing physiology, mechanisms of the swallowing recovery, and the limitation of the previous studies is important. rTMS may be beneficial adjunctive therapy in post-stroke dysphagia treatment if a strong evidence protocol is addressed.

Disclosure

The author has no conflict of interest to declare.

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