Review Article

Noninvasive Brain Stimulation for Treatment of Post-Stroke Dysphagia

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Abstract Considerable effort in recent years has been devoted to investigating neurophysiological changes in the brain after stroke and in developing novel strategies to enhance recovery particularly in the limbs and trunk. In contrast, although dysphagia is a severe complication and can be life threatening in a considerable number of stroke patients, it has not yet received the attention devoted to limb control. In this review, we discuss how introduction of (a) transcranial magnetic stimulation (TMS) to test noninvasively the integrity of the cortico-bulbar swallowing system and (b) the plasticity provoking protocols of rTMS and transcranial direct current stimulation have recently stimulated research into dysphagia after stroke and led to new potential avenues for treatment. We discuss the neural control of swallowing and discuss the contributions of TMS to understand how different brain areas are involved in dysphagia. We also consider recent studies using noninvasive brain stimulation to interact with synaptic plasticity in cortex and enhance recovery of dysphagia following stroke. Although further studies are needed, these investigations provide an important starting point to understand the stimulation parameters and patient characteristics that may influence the optimal response to therapeutic noninvasive brain stimulation. These techniques need to be refined further through a multicenter study so that they can become an essential tool that can be used in academic centers of excellence as well as in a general hospital setting.

Keywords post-stroke dysphagia; rTMS; tDCS; natural recovery of post-stroke dysphagia; fMRI; magnetoencephalography

1. Introduction: neurological control and mechanism of swallowing

Swallowing is a highly coordinated process and has been described as the most complex reflex that can be evoked by peripheral stimulation [11]. Much of this is coordinated in the swallowing center of the brainstem which has afferent inputs from peripheral receptors, the cortex, and the respiratory center. Nevertheless, post-stroke dysphagia can occur after either a brainstem or hemispheric stroke [55], suggesting that the representation of swallowing in the cortex is also of some importance in the swallowing process.

1.1. Sensory initiation of swallowing

Sensory input is essential for several aspects of swallowing. In the decerebrate cat, stroking the soft palate, innervated by the trigeminal nerve, will evoke a rhythmic movement of the tongue similar to the oral phase of swallowing [48]. Sensory input from regions of the oropharynx and hypo-pharynx, innervated by the glossopharyngeal (IXth) and internal branch of the superior laryngeal nerve (iSLN), evokes the pharyngeal phase of swallowing which is followed by the esophageal phase. Pharyngeal swallowing can be initiated by electrical stimulation of the fibers in either nerve (in mammals) when the pattern of stimulation is within a particular frequency range [11, 45]. The need for “optimum frequencies of stimulation” suggests that multiple afferents must be activated and with particular patterns to “trigger” the pharyngeal swallow.

1.2. Brainstem

The swallowing center is located at the medullary level and consists of a collection of interneurons within the reticular formation [10, 25, 45] between the posterior pole of the facial nucleus and the rostral pole of the inferior olive [3, 45]. It has relays to and from two regions in the pons, one ventral (part of the afferent system, stimulation of which results in swallowing and mastication) and the other dorsal to the motor trigeminal nucleus (relays sensory information to the ventroposteromedial nucleus in the thalamus) [4].

1.3. Cortex

Swallowing is predominantly a reflex that depends on the swallowing centers of the brainstem; however, the cortex has a role in initiating the reflex on a bolus to bolus basis and is essential for learning motor responses to different bolus characteristics [46, 47]. It seems to initiate activity in brainstem swallowing centers that starts the sequence of muscular contractions in the pharynx and oesophagus which is competed by peristalsis [42]. Transcranial magnetic stimulation (TMS) has been used to study the cortical input to swallowing control [1, 19, 34] and has revealed the presence of a short latency and bilateral projection to the muscles of the upper oesophagus. Khedr et al. [34] found the best site for stimulation to be about 3 cm anterior and 6 cm lateral to...
the vertex, with the site in the right hemisphere marginally anterior to that on the left. This may relate to interhemispheric differences in brain morphology. However, the center of the most effective site for stimulation is very similar to that seen during neurosurgery, being slightly anterior to the best points for obtaining responses in muscles of the hand or arm [43,59].

Hamdy et al. [17,19,21,22,23] reported that although the cortical output to pharyngeal muscles is bilateral, there was a tendency for individuals to have an asymmetry in the strength of the output from each hemisphere. They speculated that this may play a role in determining the severity of dysphagic symptoms after a hemispheric lesion: dysphagia might only occur when there is a lesion of the hemisphere with the largest representation [17]. However, Khedr et al. [34] found that the projections of both hemispheres to the esophageal muscles were of similar magnitude and latency despite asymmetric hemispheric representation. Why this should be is unclear. One possibility is that it represents a sampling bias since there were some individuals in each study who were asymmetric while others were symmetric.

2. Functional magnetic resonance imaging (fMRI) and magnetoencephalographic imaging and swallowing

fMRI studies have found BOLD activation in several distinct cortical loci including the lateral precentral gyrus, the lateral postcentral gyrus, and the right insula during either a naive saliva swallow, a voluntary saliva swallow, or a water bolus swallow [41]. In addition, the inferior frontal gyrus, the cingulate cortex, and the insula may also show activity [60]. Martin et al. [41] found that the anterior cingulate cortex was active almost exclusively during a naive saliva swallow, while the caudal and intermediate cingulate were associated with the voluntary saliva and water bolus swallowing [41]. They suggested that the caudal cingulate was involved with premotor and/or attentional processing that was required during voluntary swallowing. Hamdy et al. felt that the caudal cingulate cortex integrates sensory information during swallowing effectively serving as an association cortex [20].

Watanabe et al.’s magnetoencephalography study indicated that the anterior and posterior cingulate cortices were active bilaterally and well before the swallow of a 3-mL bolus of water on command, suggesting that the cingulate cortex may function in the cognitive process of deciding whether the food is ready to be swallowed [60]. These same investigators showed that the anterior insula and particularly the left insula and inferior frontal gyrus were active before swallowing, and they suggested that they might be essential to initiate a swallow. This would be consistent with the fact that lesions restricted to the anterior insula induce dysphagia with delay in evoking pharyngeal swallowing [9].

Most investigators believe that the sensorimotor representation for activity during pharyngeal swallowing is lateralized and asymmetric [20,24,49]. Dziewas et al. [12] who used magnetoencephalography to monitor activity during swallowing suggested that in most individuals, the left primary sensorimotor cortex was most active during voluntary water swallowing.

3. Dysphagia in stroke patients

Dysphagia or difficulty in swallowing is a frequent consequence of stroke, estimated to occur in up to 76% of patients with acute stroke [32].

3.1. Hemispheric lesions

It is now accepted that, on the basis of clinical and radiographic studies, unilateral hemisphere strokes can result in dysphagia [2,15,53]. Few studies have been conducted looking at precise cortical or hemispheric regions involved in producing dysphagia; the majority have investigated the role of the cortex/brain in general terms, investigating laterality or the lack of a precise center within the supratentorial structures. The majority of cortical lesions that result in dysphagia affect the precentral gyrus [7,8]. Lesions here impair voluntary movement of pharyngeal and laryngeal support musculature on the contralateral side, with spasticity and peristaltic dyssynergia, which may, in turn, lead to aspiration.

3.2. Brainstem lesions

Acute focal brainstem infarct may produce dysphagia with little or no other neurological deficit [31] or in combination with other signs as in the lateral medullary syndrome. Horner et al. [26] found that of the 62.5% of brainstem stroke patients aspirated, most of whom had lesions involving the medulla or pons [55].

4. Natural recovery of post-stroke dysphagia

In many cases, the ability to swallow improves spontaneously and rapidly, but in a percentage, swallowing remains a clinical problem for some time and in a few it is persistently poor for months or years [52]. If swallowing has not improved by 10–14 days, it will take a mean of 69 days to improve [28]. Most patients eventually return to their pre-stroke diet, despite any ongoing abnormalities in the swallow, within 6 months of their stroke [40,56]. Other studies have documented improvements up to 3–4 years after stroke onset [28,29].

This slow recovery of function is thought to be caused by structural changes in the peri-infarct zones around the lesion [6]. In addition, there are areas of hypometabolism at sites not directly affected by the stroke [37]. This reduction in metabolism, in areas with no visible changes on CT,
may explain the presentation and subsequent recovery as the metabolic state returns to baseline. Hamdy's work [18], confirmed by Khedr and Abo-Elfetoh [36], has even suggested that recovery of dysphagia following stroke is due to an improvement in control of swallowing from the pharyngeal representation of the unaffected hemisphere. Unlike hand function, which seems to require restoration of output from the stroke hemisphere for effective functional recovery, bilaterally represented functions such as swallowing might recover by improving output from the non-stroke side.

This reorganization of swallowing areas and the improvement of dysphagia is often independent of recovery from associated hemiparesis [18], and is not associated with any functional change within the brainstem. Indeed, cortical recovery appears to precede any functional change in swallowing. Khedr et al. [35] confirm that both the severity of stroke and neuroplasticity of the unaffected hemisphere have implications in the development of dysphagia.

Can the recovery of swallowing be enhanced? A small number of studies have examined interventions in both the acute phase and chronic phase.

Fraser et al. [13] studied the effect of a single session of electrical stimulation of the pharynx on swallowing and on corticobulbar excitability in a group of patients with dysphagic stroke. They found that 10 min of pharyngeal stimulation at 5 Hz produced long-lasting changes in swallowing function that correlated with increased corticobulbar excitability as assessed using single-pulse TMS. They speculated that sensory stimulation might be a useful therapeutic approach to treat dysphagia. Recently, they have explored the idea that rTMS of the swallowing motor cortex might also be used to treat dysphagia [16]. In a group of healthy subjects, they showed that 100 pulses of rTMS at 5 Hz and 80% motor threshold increased the excitability of corticobulbar projection from both hemispheres for up to 90 min. However, they did not test the effects in dysphagic patients after stroke.

In another study, Jefferson et al. [30] examined if rTMS could reverse the disruption of swallowing functions following a unilateral virtual lesion in the pharyngeal motor cortex in healthy individuals, as a direct test of the idea that rTMS might be developed as a therapy after stroke. Twenty-three healthy subjects were given varying amounts of 5-Hz rTMS over the pharyngeal motor cortex to determine the most effective excitatory parameters. Thereafter, a unilateral virtual lesion was made in the pharyngeal motor cortex using 1-Hz rTMS, followed by contralateral active or sham 5-Hz rTMS. Motor-evoked potentials and serial swallowing reaction times were recorded before and for 60 min post lesion to assess reversibility of the disruption to swallowing. They found that the greatest increase in pharyngeal motor cortex excitability occurred after 250 pulses of 5-Hz rTMS ($P = .008$), an effect that lasted over 2 hours. In contrast to sham rTMS, active contralateral 5-Hz rTMS completely abolished the cortical suppression induced by the virtual lesion, with effects lasting for up to 50 min in both unlesioned ($P = .03$) and lesioned ($P = .001$) hemispheres. Active rTMS also reversed the changes in swallowing behavior ($P = .018$), restoring function to prelesional levels. They concluded that contralumination-targeted neurostimulation modulates brain activity and swallowing motor behavior after experimental disruption and might be usefully applied in stroke-affected patients as a therapy for dysphagia [30].

5. Effect of transcranial stimulation on post-stroke dysphagia (Table 1): 3 Hz rTMS applied to patients in subacute stage of stroke dysphagia

Khedr et al. [33,35] studied dysphagic patients in the subacute stage up to 2 weeks after stroke reasoning that early intervention might maximize the potential benefits. In addition, dysphagia is often most common in the early weeks after stroke, making this the period of greatest clinical need. In their first study [35], they recruited 26 patients with subacute hemispheric stroke and dysphagia in a double randomized trial. Real rTMS was applied for 10 min every day for five consecutive days. A session of stimulation consisted of 10 trains of 3-Hz stimulation, each lasting for 10 s and then repeated every minute given through a figure-of-eight coil (9 cm diameter loop) positioned over esophageal cortical area of the affected hemisphere. The intensity of stimulation was set at 120% of the resting motor threshold for the FDI of unaffected hemisphere. Patients were followed up after the fifth session, and 30 and 60 days after the last session. Five days of rTMS produced substantially greater improvement in dysphagia in the real compared with the sham group and this was maintained over 2 months of follow-up ($P < .001$). In addition, the electrophysiological measures on 10 patients who received real rTMS indicated that the recovery was associated with an increase in the excitability of the corticobulbar projections from both hemispheres (Figure 1). Indeed, almost all patients recovered swallowing almost completely immediately after five sessions of rTMS, while several of the patients in the sham group still had overt dysphagia. Some of the excellent responses may relate to the fact that the rTMS produced an increase in the excitability of the corticobulbar projection from both hemispheres. Nevertheless, it is interesting to speculate that perhaps during natural recovery, the increased excitability of the non-stroke hemisphere might have suppressed function in the stroke hemisphere, as has been proposed for hand and arm function. If so, then the decision to apply rTMS to the stroke hemisphere may not only have encouraged recovery of the affected side but also counteracted any suppressive effect from the non-stroke hemisphere.
Table 1: Clinical trials of rTMS/DCS for treatment of post-stroke dysphagia.

<table>
<thead>
<tr>
<th>Name of author/year</th>
<th>Onset of stroke</th>
<th>Type of trial</th>
<th>Number of patients</th>
<th>Frequency of rTMS/DCS application</th>
<th>Site and side of rTMS/DCS application</th>
<th>Assessment test/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verin and Leroi 2009 [58]</td>
<td>More than 6 month</td>
<td>Noncontrolled pilot study</td>
<td>7 patients with hemispheric or subhemispheric ischemic stroke</td>
<td>1 Hz rTMS, 20% above the threshold value, 20 min per day every day for 5 days</td>
<td>The mylohyoid cortical area of the healthy hemisphere</td>
<td>Dysphagia handicap index and videofluoroscopy initially, the score was 43 ± 9 of a possible 120 which decreased to 30 ± 7 (P = .05) after rTMS; there was an improvement of swallowing coordination, with a decrease in swallow reaction time for liquids</td>
</tr>
<tr>
<td>Khedr et al. 2009 [35]</td>
<td>Subacute ischemic stroke 2 weeks after the stroke</td>
<td>Double blind randomized trial real (n=14) or sham (n=12) rTMS</td>
<td>Twenty-six patients with post-stroke dysphagia</td>
<td>3 Hz, 300 rTMS pulses at an intensity of 120% hand motor threshold for 5 consecutive days</td>
<td>Affected hemisphere/oesophageal motor area</td>
<td>Clinical ratings of dysphagia and motor disability were assessed before and immediately after the last session and then again after 1 and 2 months. The amplitude of the motor-evoked potential (MEP) evoked by single-pulse TMS was also assessed before and at 1 month in 16 of the patients. Real rTMS led to a significantly greater improvement compared with sham in dysphagia and motor disability that was maintained over 2 months of follow-up. This was accompanied by a significant increase in the amplitude of the esophageal MEP evoked from either the stroke or non-stroke hemisphere</td>
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<tr>
<td>Khedr and Abou-Elfereid 2010 [33]</td>
<td>Subacute ischemic stroke Within one to three months</td>
<td>Double blind randomized trial real (n=6) or sham (n=5) rTMS</td>
<td>11 patients with lateral medullary syndrome</td>
<td>3 Hz, 300 TMS pulses at an intensity of 130% hand motor threshold for 5 consecutive days</td>
<td>Both hemispheres affected and unaffected hemisphere</td>
<td>Clinical ratings of dysphagia and motor disability were assessed before and immediately after the last session, and then again after 1 and 2 months. Active rTMS improved dysphagia compared with sham rTMS (P = .001)</td>
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<tr>
<td>Michou et al. 2012 [44]</td>
<td>Chronic dysphagia from stroke (mean of 38.8±24.4 weeks post stroke)</td>
<td>Uncontrolled trial</td>
<td>6 patients with severe, chronic dysphagia from stroke (mean of 38.8±24.4 weeks post stroke)</td>
<td>Ten minutes of PAS to the unlesioned pharyngeal cortex/PAS was delivered by pairing a pharyngeal electrical stimulus (0.2-millisecond pulse) with a single TMS pulse on the pharyngeal MI at the intensity of motor threshold (MT) plus 20% of stimulator output with an interstimulus interval of 100 milliseconds</td>
<td>With an interstimulus interval of 100 milliseconds, based on previous investigations</td>
<td>Significantly increased the cortical excitability of the un-affected hemisphere, which was accompanied by a decrease in penetration aspiration scores and changes in bolus transport timings, with corresponding decreases in the pharyngeal response times and transit times of bolus flow. There was also a small but significant increase in the affected hemisphere when compared with the hemispheric baseline pharyngeal representation excitability</td>
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<tr>
<td>Kumar et al. 2011 [38]</td>
<td>24–168 hours after their first ischemic stroke</td>
<td>Randomized control trial anodal versus sham stimulation</td>
<td>14 patients with subacute unilateral hemispheric infarction</td>
<td>Anodal transcranial direct current stimulation (tDCS) over 5 consecutive days (2 mA for 30 min)</td>
<td>Sensorimotor cortical representation of swallowing in the unaffected hemisphere/mid-distance between C3 and T3 on the left or C4 and T4 on the right hemisphere</td>
<td>Swallowing scale, dysphagia outcome and severity scale (DOSS), patients who received anodal tDCS gained 2.60 points improvement in DOSS scores compared to patients in the sham stimulation group who showed an improvement of 1.25 points (P = .05) after controlling for the effects of other aforementioned variables. 6 out of 7 (86%) patients in tDCS stimulation group gained at least 2 points improvement compared with 3 out of 7 (43%) patients in sham group (P = .107)</td>
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<tr>
<td>Yang et al. 2012 [61]</td>
<td>25.9±10.2 days after stroke</td>
<td>Randomized control trial anodal versus sham</td>
<td>Sixteen patients with post-stroke dysphagia</td>
<td>Anodal tDCS group (1 mA for 20 min), or (2) sham group (1 mA for 30 s)</td>
<td>Over the pharyngeal motor cortex of the affected hemisphere during 30 min of conventional swallowing training for 10 days</td>
<td>Functional dysphagia scale (FDS) scores based on VFSS were measured at baseline and immediately and 3 months after the intervention. FDS scores improved in both groups without significant differences. However, 3 months after the intervention, anodal tDCS elicited greater improvement in terms of FDS compared to the sham group (β = −7.79, P &lt; .041)</td>
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Figure 1: Cortical map area (number of stimulation points) and peak-to-peak amplitudes of esophageal MEPs evoked from the stroke and non-stroke hemispheres in the 10 subjects who received real rTMS before and 1 month after treatment. Note the increase in the area of the cortical map in the stroke but not in the non-stroke hemisphere, and the increase in MEP amplitude in both hemispheres after rTMS treatment. Data are expressed as mean ±SE; see Khedr et al. [35].

In the second study, Khedr and Abo-Elfetoh [33] recruited patients with lateral medullary syndrome and other brainstem infarctions in a double randomized trial (real versus sham stimulation). They applied rTMS over both hemispheres, with the hypothesis that bilateral stimulation of the cortical swallowing motor areas would increase excitability of corticobulbar projections to brainstem swallowing nuclei and improve swallowing.

They found that effect of rTMS on dysphagia was clear in both patient groups and was greater than the effect on other measures of general motor function. Indeed, almost all patients who received real rTMS recovered swallowing to different degrees immediately after the fifth session and this improvement was maintained for at least 2 months, while patients who received sham rTMS still had overt dysphagia at the end of 2 months (Figures 2 and 3). They proposed that the effect might be related to the fact that control of swallowing is usually bilateral whereas the lesion in LMI is usually unilateral. Thus, the remaining intact ipsilateral premotor neurons and the contralateral center in the medulla oblongata may eventually begin to operate and overcome the severity and long-term persistence of dysphagia. If so, the functional recovery that was observed in the patients could be due to rTMS speeding up this natural process of recovery. However, it cannot exclude other effects on less direct pathways from the cortex to the brainstem that could contribute to recovery, particularly those in the brainstem infarct subgroup in which lesions were bilateral.

6. 1 Hz rTMS applied to patients with chronic dysphagic stroke

Interestingly, the use of neurostimulation in patients with chronic dysphagic stroke has been reported before; in one recent study [58], 1 Hz rTMS (an inhibitory stimulation paradigm) was applied, in a specific regimen, over the intact hemisphere in stroke-affected patients with very mild chronic dysphagia who were a mean of 56 weeks post...
Figure 3: Changes in mean different rating scores of dysphagia (a), Barthel index (b), NIHSS (c), and hand grip strength (d) at the four assessment points for the patients with brainstem infarction. The first assessment was immediately prior to commencing repetitive transcranial magnetic stimulation (rTMS) treatment (Pre), the second (Post session) was immediately after the end of the first and the fourth assessment at the end of the second month. Each group separately shows significant improvement. However, the mean scores of the patients who received active rTMS are significantly better than sham group in dysphagia rating score only over the course of the treatment, while no significant differences in the other scales were recorded between groups. Data are expressed as mean ±SE; see Khedr and Abo-Elfetoh [33].

stroke. Even though the study was not controlled and the patients were not severely dysphagic, immediate behavioral effects were observed.

7. Paired associative stimulation (PAS) applied to patients with chronic dysphagic stroke

PAS is a technique that induces heterosynaptic plasticity in the motor and somatosensory cortical areas by combining peripheral stimulation of the targeted muscle with cortical stimulation over the representational area of that muscle in the MI. Long-term changes in MI excitability can be produced by repeatedly combining these two modalities, peripheral and central, and by separating them with a specific time interval [44].

The effectiveness of facilitatory PAS to the contralesional cortex in brain injury was explored in a pilot study of patients with severe dysphagic stroke (mean time post-stroke, 38.8 ± 24.4 weeks), 5 of which were tube fed [44]. Although the number of patients (6 patients) was small, application of PAS over the contralesional pharyngeal MI significantly increased cortical excitability of the same hemisphere. This was accompanied by reduced aspiration penetration scores and changes in bolus transport timings, with corresponding decreases in the pharyngeal response times and transit times of bolus flow. There was also a small but significant increase in excitability of the pharyngeal representation in the affected hemisphere when compared with baseline.

8. Transcranial direct current stimulation (tDCS) and acute stroke dysphagia

tDCS is another noninvasive brain stimulation technique that utilizes weak, direct current to produce shifts in neuronal excitability [50,51] and can be combined with swallowing maneuvers or exercises. It has generated great interest recently because of its ease of use, patient tolerability, and safety profile which is of particular importance during the acute/subacute phases of a stroke. It has been shown to improve motor functions in chronic stroke patients [27, 54]. Moreover, the presence of a sham mode makes it possible to examine effects in a blinded trial paradigm [14]. Recent work has shown that application of anodal tDCS to the pharyngeal motor cortex in healthy human subjects increases pharyngeal excitability in an intensity-dependent manner [30].

Kumar et al. [38] investigated whether anodal TDCS in combination with swallowing maneuvers facilitates swallowing recovery in dysphagic stroke patients during early stroke convalescence (acute/subacute unilateral hemispheric infarction). They randomized fourteen patients with subacute unilateral hemispheric infarction to tDCS or sham stimulation of the sensorimotor swallowing representation in the unaffected hemisphere for five consecutive days with concurrent standardized swallowing maneuvers. Severity of dysphagia was measured using a validated swallowing scale, the dysphagia outcome and severity scale (DOSS), before the first and after the last session of tDCS or sham. They found that patients who received anodal tDCS improved by 2.60 points compared to patients in the sham stimulation group who improved by 1.25 points (P = .019) after controlling for the effects of other variables. Six out of 7 (86%) patients in the real tDCS group gained at least 2 points improvement compared with 3 out of 7 (43%) patients in the sham group (P = .107). They concluded that since brainstem swallowing centers receive a bilateral cortical innervation, measures that enhance cortical input and sensorimotor control of brainstem swallowing may be beneficial for dysphagia recovery.

Another study using tDCS undertaken by Yang et al. [61] recruited 16 patients with post-stroke dysphagia, who were diagnosed using video fluoroscopic swallowing (VFSS). They were randomly assigned into two groups: (1) anodal tDCS (1 mA for 20 min), or (2) sham (1 mA for 30 s) over the pharyngeal motor cortex of the affected hemisphere.
During 30 min of conventional swallowing training daily for 10 days. Functional dysphagia scale (FDS) scores based on VFSS were measured at baseline, immediately, and 3 months after the intervention. They found that immediately after the intervention, FDS scores had improved to the same extent in both groups. However, 3 months later, the group that had received anodal tDCS showed greater improvement in terms of FDS compared to the sham group ($P = .041$) after controlling for age, National Institutes of Health Stroke Scale (NIHSS) score, lesion size, baseline FDS score, and time from stroke onset. They concluded that anodal tDCS applied over the affected pharyngeal motor cortex can enhance the outcome of swallowing training in post-stroke dysphagia.

9. Mechanism of action of noninvasive brain stimulation (rTMS and tDCS) on post-stroke dysphagia

Repetitive transcranial magnetic stimulation can produce long-lasting effects on the excitability of the motor cortex that in some instances have been shown to disappear after taking drugs that interfere with NMDA receptor function [14]. This suggests that some of the effects may be mediated by changes in synaptic function in the cortex that are analogous to long-term potentiation or depression demonstrated in experiments on animals. In addition, it is also known from both physiological and imaging studies that the effects of rTMS occur not only at the site of stimulation but also in connected structures, presumably via activation of synaptic inputs at those sites. Gow et al. [16] and Khedr et al. [35] showed that rTMS over the swallowing cortex of one hemisphere increases the excitability of the output from both hemispheres. Indeed, it seems likely that the functional recovery that they observed was due to this change in corticobulbar input to the brainstem swallowing centers. It is interesting to note that the physiological pattern of recovery after rTMS may differ from the natural course of recovery as described by Hamdy et al. [21]. Both Hamdy et al. [16] and Khedr et al. [35] found that patients who were initially dysphagic after stroke had very inexcitable projections from the stroke hemisphere. Nevertheless, it is interesting to speculate that perhaps during natural recovery, the increased excitability of the non-stroke hemisphere might have suppressed function in the stroke hemisphere, as has been proposed for hand and arm function. If so, then the decision to apply rTMS to the stroke hemisphere may not only have encouraged recovery of the affected side, but also counteracted any suppressive effect from the non-stroke side [36].

Therapies that combine swallowing practice with rTMS/TDCS usually consider that the important mechanism of action is linking motor outputs with brain stimulation. However, such interventions also link sensory inputs with stimulation. Sensory input from the pharynx in stroke patients is known by itself to increase the excitability of the swallowing motor cortex of the unaffected hemisphere [13]. When paired with rTMS/TDCS, this effect may be enhanced and focused topographically onto the pharyngeal motor representation via the mechanisms of paired associative stimulation [57]. Perhaps a similar effect occurs when training is paired with brain stimulation, and this improves performance beyond levels reached by each intervention alone [5,39].

10. Recommendation and future directions for rTMS studies in dysphagia

Together, these studies represent important first steps in understanding how rTMS can be used to reorganize motor areas of stroke patients. However, much work is still required to optimize the way rTMS is utilized to affect motor recovery, performance, and learning in stroke patients. These investigations will also need to address many different contributing factors that might affect the response to brain stimulation from patient characteristics to rTMS dosing. Even the optimal site of stimulation is not settled. It is highly possible that patients will need to be assessed prior to application of brain stimulation in order to understand how their brain has been reorganized between injury and the time of the intervention.

The direction of future research lies in detailed understanding of the natural recovery of post-stroke dysphagia and of the ability to enhance this recovery.

11. Conclusion

The use of transcranial magnetic stimulation has helped improve our understanding of the mechanisms underlying recovery of motor function after stroke. This in turn has opened an opportunity to test repetitive TMS as well as other interventions to affect motor behavior. At this point, it is clear that it is possible to modulate TMS as well as other interventions to affect motor behavior. At this point, it is clear that it is possible to modulate TMS as well as other interventions to affect motor behavior. At this point, it is clear that it is possible to modulate TMS as well as other interventions to affect motor behavior. At this point, it is clear that it is possible to modulate TMS as well as other interventions to affect motor behavior. At this point, it is clear that it is possible to modulate TMS as well as other interventions to affect motor behavior. At this point, it is clear that it is possible to modulate TMS as well as other interventions to affect motor behavior.

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