The role of non-invasive Brain stimulation in Neurorehabilitation of Post- Stroke Dysphagia

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Keywords: Stroke, Dysphagia, Neurorehabilitation, Non-invasive brain stimulation TMS, tDCS

Abatract: Post stroke dysphagia has been related to an increased risk for pulmonary complications and higher rate of morbidity and mortality. A developing body of evidence has pointed to noninvasive brain stimulation techniques as efficient neurorehabilitation approaches in treatment of post-stroke dysphagia. Transcranial magnetic stimulation (TMS) depending on frequency and transcranial direct current stimulation (tDCS) depending on the duration and polarity of stimulation can activate or suppress activity in cortical regions. Enhancement of cortical excitability in the undamaged hemisphere has been related to the improvement of swallowing function in post stroke dysphagia. Developing data suggest that adjunct of cortical stimulation and following reorganization of the intact swallowing cortex augmented the speed of improvement of oropharyngeal dysphagia after a unilateral hemispheric stroke. This Review aims to evaluate the effects of the role of noninvasive brain stimulation techniques including TMS and tDCS as facilitators of recovery from post stroke dysphagia.

Introduction: Stroke is among the main causes of death worldwide and permanent adult disability in Europe and the USA, despite of occurring some spontaneous recovery in most stroke survivors [1-3]. It has reported that 50-81% of patients with stroke experience dysphagia or swallowing problems as a frequent consequence of stroke that leading to more cost implications and morbidity, more complications with worse outcomes and higher rate of mortality [4-8]. Oropharyngeal dysphagia has recognized as a major risk factor for aspiration pneumonia, malnutrition, and dehydration following stroke [9]. In addition, it has reported a very little evidence related to effectiveness of various intensive compensatory manipulation therapies for treatment of chronic dysphagia that usually are employed by speech and language pathologists [10]. Hence, post-stroke dysphagia needs to a more efficient and quick rehabilitation for improving swallowing functions because natural recovery or compensatory strategies are slow and incomplete approaches [6]. Multiple randomized controlled trials have investigated on effectiveness of application of noninvasive brain stimulation techniques in rehabilitation of stroke-related dysphagia but larger and clinically heterogeneous randomized-controlled trials are needed to providing reliable estimates of efficacy of non-invasive brain stimulation techniques in treatment of post- stroke dysphagia [6]. The brain stimulation might by augmentation of changes that naturally occur in the unaffected swallowing cortex results in beneficial effects [11]. Although swallowing is mediated principally by brain stem areas, the cerebral cortex especially inferior peri-rolandic sensorimotor cortex also has implicated in the initiation and regulation of swallowing and cortical dysfunction has been reported to causing various impairments of swallowing [12]. Stimulation of restricted regions of the cortex can lead to triggering or regulation of swallowing [12]. Cerebral cortex bilaterally innervate brain stem swallowing centers, therefore enhancing cortical input and sensorimotor control of brain stem swallowing centers may be useful for improvement of dysphagia [13]. Dysphagia after unilateral hemispheric stroke is a result of disrupted projections from cortical regions to the "swallowing centers" of the brain stem and recovery of swallowing functions is related to magnitude of pharyngeal representation and cortical excitability in the intact hemisphere, suggesting a role for undamaged hemisphere reorganization in recovery [11,14,15]. In stroke patients with intact brain stem and peripheral structures but impaired cortical regions of swallowing, application of brain stimulation techniques may through facilitation of pharyngeal representation expansion in the unaffected hemisphere result in recovery of swallowing functions [13]. The primary aim of this review is to evaluate the effectiveness of non-invasive stimulation techniques including repetitive TMS and tDCS for improvement of post- stroke dysphagia.

Neurophysiology of swallowing and post stroke dysphagia

Swallowing functions are initiated by a central pattern generator (CPG) situated in the rostral brainstem and cortical centers for controlling of swallowing are localized bilaterally in the frontal cortex anterior to the sensorimotor cortex [16,17]. The many pharyngeal muscles role playing in swallowing function have bilaterally and asymmetrical cortical control [18]. It is well known that the cerebral cortex implicate in functional regulation of swallowing and brainstem centers control reflexive component of swallowing and integrity of cortical motor areas is necessary for the initiation of swallowing as a voluntary action [12,18]. Contraction and inhibition of swallowing muscles is regulated by three levels of brain stem neural structures including afferent or descending input related to termination sites of central and peripheral swallowing afferent fibers, efferent level related to motoneurons of the cranial motor nuclei that innervate swallowing muscles and one organizing level that comprises of an interneuronal network of premotor neurons that has connections with both afferent and efferent levels [19]. Initiation or organization of the swallowing motor sequence is performed by these interneurons or premotor neurons that are described as the swallowing CPG [16]. The presence of swallowing premotor neurons and interneurons has reported in principal regions of brain stem including ventral swallowing group (VSG) just above the nucleus ambiguus (NA) and the dorsal swallowing group (DSG) in and around nucleus of the solitary tract (NTS) [16,19]. It has suggested that premotor neurons of swallowing probably are involved in bilaterally rostrocaudal coordination of several groups of motoneurons [16]. All swallowing motoneurons in the V, VII, IX, X, and XII driven by the premotor neurons of the VSG and DSG neurons within the medullary swallowing network activate VSG neurons [16]. In according to the developing clinical evidence, unilateral hemispheric

damage to the cerebral cortex may produce dysphagia in stroke patients and occurrence of a stroke result in bilateral redistribution of swallowing networks [15,20-23]. In accordance to neurofunctional adaptation theory related to post stroke brain plasticity, dominant hemisphere lesion would result in cortical activation to shift to the intact hemisphere [15,24]. Left hemispheric patients with Post stroke dysphagia demonstrated bilateral increased activation in the cingulate gyrus, insula and precentral gyrus in compared to healthy subjects and right hemispheric patients with Post stroke dysphagia showed overactivation compared with control subjects especially in superior cingulate gyrus, temporal gyrus and the precentral and postcentral gyri [15]. It has shown that stroke patients during volitional swallowing have overactivation in the left medial frontal gyrus, insula and left precentral and postcentral gyri of all of the stroke patients compared with healthy subjects [15]. Right hemispheric patients with post stroke dysphagia frequently have exhibited pharyngeal dysmotility and post stroke dysphagic patients with left hemispheric damage often display reduced oral coordination suggesting left and right hemispheric stroke patients may have different dysphagic characteristics [14,15,25,26]. Left hemispheric stroke patients compared with right hemispheric damage have shown more severe dysphagia and smaller cerebral activation during swallowing task, supporting this hypothesis that damage to the left hemisphere probably causes more severe swallowing dysfunction because left hemisphere plays a more important role in mediating function swallowing [15]. Asymmetry of cortical representation may lead to variability in degree and duration of post stroke dysphagia development, suggesting that compensatory reorganization of contralateral hemisphere might be accountable for recovery from dysphagia after unilateral stroke [15]. The anatomical regions including primary motor, somatosensory areas, anterior cingulate and insular cortices have shown highly activation during swallowing in healthy adult subjects and recovery of swallowing after a stroke is dependent to a compensatory activation of cerebral cortex regions in the unaffected hemisphere [15]. Accordingly, targeting enhancement of the swallowing improvement by the future rehabilitation therapies is required to aim reorganization of the intact hemisphere [15]. In addition, sensory feedback from peripheral structures including nerves and muscles, brainstem and cortex and subcortical regions plays an important role in swallowing movements and increasing sensory input from peripheral nerves or strengthen the swallowing muscles by traditional swallowing trainings are effective in improvement of swallowing function [17].

Non-invasive brain stimulation techniques

Noninvasive brain stimulation techniques include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) [27]. Noninvasive brain stimulation (NIBS) is progressively applied to increase the functional recovery after stroke and NIBS might generate an improvement of function in patients with stroke [28]. It has hypothesized that NIBS through induction of shifts in regional excitability or modifying the distributed activity and connectivity in functional brain networks may induce the beneficial therapeutic effects in stroke [29,30]. In addition, it has hypothesized that abnormal interhemispheric inhibition result in maladaptive neural activation pattern after stroke and adjuvant use of noninvasive brain stimulation techniques may by modulation of cortical excitability produce synaptic plasticity and improve the efficacy of rehabilitative strategies employed after stroke [31]. Post stroke recovery is dependent to a balanced activity of neural network involving both the damaged and the undamaged brain hemispheres. Enhanced activity in the damaged hemisphere can lead to promotion of recovery while hyper activity of undamaged hemisphere may induce maladaptive effects [32]. Application of NIBS techniques in neurorehabilitation needs to safe stimulation protocols [33]. TMS directly and depending on the specific stimulation parameters can induce activation or suppression of activity in cortical regions and consequently increases or decreases neuronal excitability [34-36]. Similarly, tDCS depending on the duration and polarity of stimulation can upregulate or downregulate excitability in the stimulated brain regions through long term potentiation (LTP) and long term depression (LTD) like mechanisms, changing of sodium and calcium-dependent channels and altered activity of N-methyl- D-aspartate-receptor [37-39]. Induction of excitation and inhibition by tDCS within the cortex is dependent on the direction of current flow between anode and cathode electrodes. Excitation is induced by anodal tDCS typically when anode electrode is located on the motor cortex and the cathode on the supraorbital ridge whereas inhibition occurs by reversed current flow [40]. In regard to comparing two noninvasive brain stimulation techniques, rTMS is more expensive but provides better temporal resolution and focal stimulation whereas tDCS compared with rTMS is inexpensive and is easier to concurrently employ with other rehabilitative approaches [41]. Moreover, performing of sham tDCS for double-blind studies is easier than sham rTMS [37].

Transcranial magnetic stimulation (TMS)

Investigation on the excitability of swallowing motor cortex following rTMS in healthy subjects showed that repetitive cortical stimulation increased the excitability of the corticobulbar projection from both hemispheres to the pharynx for up to 90 min, suggesting rTMS might be a beneficial method in the motor rehabilitation of post stroke dysphasia induced by impairment of sensory projections to the swallowing cortex [42]. Momosaki et al. investigated on the safety and feasibility of a Six days protocol of 10 sessions of rTMS at 3 Hz applied to the pharyngeal motor cortex bilaterally combined with 20 min of intensive swallowing rehabilitation exercise in 4 patients with chronic poststroke dysphagia [43]. Their results confirmed that all patients completed the treatment protocol without obvious adverse effects and bilateral cerebral rTMS combined with intensive swallowing rehabilitation resulted in improvement of swallowing function [43]. Khedr et al. reported that applying 3 Hz-rTMSduring 5 consecutive days over the oesophageal motor cortex of the affected hemispheres improved significantly swallowing performance in acute stroke patients with dysphagia in patients with acute stroke [44]. Importantly, this recovery was related to increased excitability of the corticobulbar projections from both hemispheres and was continued for at least 2 months compared with the sham group [44]. Jefferson et al. found increased excitability of the contralateral cortex and improved function of pharyngeal muscle after treatment with 5 Hz-rTMS [45]. Verin and Leroi reported that 5 days of treatment with rTMS at a frequency of 1 Hz applied to undamaged hemisphere significantly improved swallowing performance in 7 patients with stroke that is probably due to a decrease in interhemispheric inhibition

induced by low-frequency rTMS [46]. Similarly, Kim et al. demonstrated that applying of 10 consecutive low frequency rTMS sessions over the pharyngeal motor area improved swallowing function compared to high-frequency or sham stimulation in patients with a unilateral hemispheric brain injury [47]. In a hypothetic view, increasing of cortical excitability of affected hemisphere by applying high-frequency rTMS and lowering the excitability of the non-affected hemisphere by applying low-frequency rTMS, both reduce Interhemispheric inhibition that occurs in patients with unilateral hemispheric brain injury [47]. However, it has reported that applyinghigh-frequency rTMS to affected hemisphere in order to increasing excitability of the damaged hemisphere and reduction of interhemispheric inhibition could not improve swallowing function [47]. Hamdy et al. believed that dominant hemisphere plays a principal role in swallowing function and consequently stroke patients with unilateral lesions in the dominant hemisphere might experience a severe dysphagia. In addition, they assumed that improvement of dysphagia depends on the role of non-affected hemisphere in reduction of interhemispheric inhibition [48]. An association has appeared between the smaller pharyngeal representation on the intact hemisphere and oropharyngeal dysphagia in patients with unilateral hemispheric stroke which enhances in size following improvement of swallowing, suggesting implication of reorganization of unaffected hemisphere in recovery [11,14]. Based on this hypothesis, Park et al. reported that by 2 weeks of a 5 Hz high-frequency rTMS applied to contra-lesional pharyngeal motor cortex in order to increasing excitability of the pharyngeal motor cortex on the undamaged hemisphere leads to clinical improvement of dysphagic patients and maintained for up to 2 weeks, suggesting a new method for treatment of post-stroke dysphagia [49]. The findings reported by park is completely in contrast to Verin and Leroi's hypothesis that employed inhibitory 1 Hz rTMS for 20 min for suppression of the intact hemisphere and reducing transcallosal inhibition and observed recovery from oropharyngeal dysphagia in stroke patients [46]. It has believed that excitatory stimulation of unaffected hemisphere is more effective than inhibitory stimulation because an association has reported between recovery from dysphagic stroke and an increased pharyngeal representation in the intact hemisphere [11,49]. Michou et al. investigated on application of 5 Hz single-pulse rTMS over the pharyngeal motor cortex before, immediately, and 30 min, after both real and sham neurostimulation in 18 patients with chronic dysphagic stroke and founded that corticobulbar excitability of unaffected hemisphere but not affected hemisphere appeared to increase [9]. In addition, a significant correlation was observed between increases in excitability of unaffected hemisphere and improvement in swallowing safety (reductions in aspiration) however, compared to sham, this change was not statistically significant [9]. In summary, almost all included trials have reported that application of either high-frequency or low-frequency rTMS stimulation over unaffected hemisphere could induce beneficial effects compared to sham stimulation.

Transcranial direct current stimulation (tDCS)

Another noninvasive brain stimulation technique is transcranial direct current stimulation (tDCS) that employs weak direct current to induce changes in neuronal excitability and can be used in combination with swallowing maneuvers or exercises [13,40,50]. It has paid particular attention to use of tDCS during the acute/subacute phases of stroke Because of its easy application, tolerability and safety profile [13]. Jefferson et al. found that anodal tDCS could change excitability of pharyngeal motor cortex which might affect swallowing center in the brainstem [51]. It has reported that in healthy human subjects anodal tDCS can increase excitability of pharyngeal motor cortex in an intensity-dependent manner and therefore anodal stimulation may promote recovery in patients with dysphagia [51]. One pilot study performed by Kumar et al. revealed that repeated application of anodal tDCS versus sham stimulation of the undamaged swallowing cortex in combination with timed effortful swallowing maneuvers facilitated swallowing recovery in dysphagic stroke patients [13]. Brain stimulation of the unaffected hemisphere concurrent with swallowing maneuvers may through combining of sensorimotor input derived from sensory stimulation of pharynx with brain stimulation effect augment increase in the excitability of the swallowing sensorimotor cortex in dysphagic stroke patients [11,15,42,52]. Studies investigating paired-stimulation protocol have hypothesized that cortical stimulation paired with peripheral stimulation of the somatosensory afferents may induce more increased excitability and enduring changes in plasticity of the human motor cortex [53]. It has reported that dextromethorphan prevented this enhanced excitability probably by blocking of long term-potentiation development [54]. Combination of peripheral sensorimotor actions or peripheral nerve stimulation with stimulation noninvasive brain techniques such as tDCS can potentiate beneficial effects of training on learning and consolidation of motor skills compared to each intervention alone in patients with subacute or chronic stroke [13,55,56]. Fregni et al. investigated on the effect of reduced excitability of intact hemisphere induced by cathodal tDCS on the improvement of motor function compared to increased excitability of damaged hemisphere induced by anodal tDCS and sham tDCS in stroke patients [32]. It has found that both stimulation of damaged hemisphere by anodal tDCS and stimulation of undamaged hemisphere by cathodal tDCS but not sham tDCS significantly improved motor function, suggesting crucial role of appropriate modulation of bihemispheric brain structures in promotion of motor performance improvement [32]. Yang et al. investigated on the effects of simultaneous combination therapy with tDCS and 30 min of conventional swallowing training on the post-stroke dysphagia in sixteen stroke patients that received anodal tDCS or sham over the affected pharyngeal motor cortex during for 10 days [57]. The results of their study showed that application of anodal tDCS over the pharyngeal motor cortex of the affected hemisphere can increase the effect of swallowing training on the recovery from post-stroke dysphagia [57]. It has shown that transracial application of weak electrical currents in the healthy human subjects probably lead to selectively enhancement of motor cortex excitability by anodal stimulation and selectively reduction of excitation by cathodal stimulation [40]. The probably reason for this finding is that anodal stimulation generates neuronal depolarization and enhancing neuronal excitability while cathodal stimulation induces opposite effects [40]. Shigematsu et al. in one prospective, single-center, single-blind trial investigated on the effects of 1- mA anodal tDCS or a sham procedure to the to the cortical motor and sensory pharyngeal

areas combined with intensive conventional swallowing therapy on improvement of dysphagia [17]. Their results suggested that anodal tDCS to the ipsilesional pharyngeal motor cortex combined with simultaneous peripheral sensorimotor activities significantly improved poststroke dysphagia as compared with swallowing training alone [17]. evidence from animal studies also have revealed that cortical electrical stimulation combined with rehabilitative training causes increased functional improvement and enhanced dendritic plasticity following unilateral focal ischemic lesions in sensorimotor cortex of rats [58]. Generally, it has suggested that the transcranial application of weak electrical stimulation provides a painless, selective, focal, noninvasive and reversible modulation of the cortical excitation and therefore seems to be a promising tool for clinical neuroplasticity research [40] (Table 1).

Type of Stimulation	Size and Schedule	Location of Stimulation	Duration of Stimulation	Design	Main Result	Reference
rTMS	frequency of 5 Hz, intensity 90% of resting thenar Motor Threshold (MT) in train of 250 pulses, in 5 blocks of 50 with 10 s between-blocks pause	Undamaged pharyngeal motor cortex (MI)	1 day	Measuring corticobulbar excitability before, immediately, and 30 min after real and sham 5 Hz single-pulse rTMS in 18 patients with unilateral stroke	rTMS did not achieve significant increases in brain excitability compared to sham. Both real and sham rTMS showed visible increase in brain excitation	Michou et al. [10]
rTMS	5 Hz rTMS or sham stimulation for at 90% of the thenar motor threshold	unaffected pharyngeal motor cortex	10 days	In 18 patients received rTMS for 10 min per day for 2 weeks. Asession of stimulation consisted of 10 trains of 5 Hz stimulation, each lasting for 10 s	Two weeks of a 5 Hz excitatory rTMS improved unilateral stroke dysphagia and the effect lasted up to 2 weeks	Park et al. [50]
rTMS	20 blocks of 50 pulses at 5 Hz high frequency rTMS, 1 block of 1200 pulses at 1 Hz low frequency rTMS and sham stimulation at 100% of motor evoked potential (MEP) threshold	Affected and Unaffected Mylohyoid cortical "hot spot"	10 days	In 30 patients High frequency rTMS applied to ipsilesional hemisphere hot Spot for 10 sec, and repeated every minute for 20 minutes (total, 1,000 pulses) and low frequency on the contralesional hemisphere hot spot.rTMS delivered for 20 minutes (total, 1,200 pulses)	only low-frequency rTMS but not high frequency and sham stimulation improved dysphagia in patients with a unihemispheric brain injury	Kim et al. [48]
tDCS	10 blocks of 30 pulses at 3 Hz. The intensity was set at 120% of the resting motor threshold for the first dorsal interosseous muscle (FDI)	Esophageal motor cortex of Affected hemisphere	5 days	each stimulation lasting for 10 s that repeated every minute for 10 min every day	rTMS in 26 patients with mono hemispheric stroke generated significantly greater improvement in dysphagia in the real compared to the sham group and this was sustained for at least 2 months	Khedr et al. [45]

tDCS	1-mA anodal tDCS, 20 min/day	ipsilesional pharyngeal motor cortex of Affected hemisphere	ipsilesional pharyngeal motor cortex of Affected hemisphere	10 days	20 patients with post stroke dysphagia randomly received anodal tDCS or a sham procedure combined with intensive swallowing therapy	Shigematsu [18] et al.
tDCS	1-mA anodal tDCS, 20 min/day	pharyngeal motor cortex of the affected hemisphere	10 days	16 patients with post- stroke dysphagia randomly received anodal tDCS or sham stimulation combined with 30 min of conventional swallowing training	16 patients with post- stroke dysphagia randomly received anodal tDCS or sham stimulation combined with 30 min of conventional swallowing training	Kumar et al. [14]
DCS	2 mA anodal, 30 min/day	unaffected swallowing motor cortex	5 days	14 patients with subacute unilateral hemispheric infarction randomly received anodal tDCS or sham stimulation in conjunction with standardized swallowing maneuvers	14 patients with subacute unilateral hemispheric infarction randomly received anodal tDCS or sham stimulation in conjunction with standardized swallowing maneuvers	Kumar et al. [14]

Table 1. Characteristics of the included non-invasive brain stimulation trials for treatment of post stroke dysphagia.

Conclusion: Combination therapy with swallowing training and non- invasive cortical stimulation has suggested an important adjuvant strategy in treatment of patients with post-stroke dysphagia. Some evidence has reported that applying anodal tDCS over the both affected and unaffected hemispheres in combination with sensorimotor effects of swallowing training might result in more improvement in swallowing function in stroke patients. Bilaterally cortical innervations of brain stem swallowing centers make possible that enhancement of cortical input and sensorimotor control of brain stem swallowing may result in dysphagia improvement. Both high-frequency and low-frequency rTMS applied to undamaged pharyngeal motor cortex has demonstrated beneficial effects in recovery from post stroke dysphagia. Theoretically stimulation of both ipsilesional and contralesional hemisphere may be useful in recovery from post stroke dysphagia because swallowing musculature is represented bilaterally. However, developing data support the notion that functional behavioral recovery from dysphagic unilateral stroke are mostly driven by improvements in the unaffected cortex and targeting and promotion of compensatory alterations in the undamaged circuitry are required for successful neurorehabilitation approaches. More longitudinal studies in patients with post stroke dysphagia are necessary for providing further evidence on how the undamaged cortex facilitates recovery

from dysphagia several months after stroke or to what extent the conjunctive activity of the damaged and undamaged hemispheric corticobulbar projections might be involved in the compensation of adaptive function. Neurostimulation studies mostly have applied NIBS techniques to both damaged and undamaged hemispheres without strong rationale due to presence of restricted findings about the exact physiologic mechanisms underlying recovery from stroke. High-frequency rTMS applied to the damaged hemisphere increases cortical excitability, whereas applying low frequency rTMS to the intact hemisphere reduces cortical excitability. Improvement of dysphagia after a unilateral hemispheric stroke needs to reduction of interhemispheric inhibition through regulation of the intact hemisphere. Interhemispheric inhibition happens in patients with a unilateral hemispheric stroke, and high- frequency rTMS by enhancing the excitability of the damaged hemisphere or low-frequency rTMS by decreasing the excitability of the intact hemisphere reduces this inhibition. However, there is some evidence that applying high frequency rTMS to the damaged hemisphere to reduce interhemispheric inhibition by enhancing excitability of the damaged cortex does not result in recovery from dysphagia. There is developing data that rTMS may be beneficial therapeutic method in both acute and chronic stroke patients. Generally, muscles of pharynx have asymmetrical representation in both cortical hemispheres, and applying anodal tDCS to both hemispheres may be useful in improvement of swallowing function.

Conflict of Interest

All authors declare they have no conflicts of interest.

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