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Neurorehabilitation strategies for poststroke oropharyngeal dysphagia: from compensation to the recovery of swallowing function

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Oropharyngeal dysphagia (OD) is very prevalent among poststroke patients, causing severe complications but lacking specific neurorehabilitation treatment. This review covers advances in the pathophysiology, diagnosis, and physiologically based neurorehabilitation strategies for poststroke OD. The pathophysiology of oropharyngeal biomechanics can be assessed by videofluoroscopy, as delayed laryngeal vestibule closure is closely associated with aspiration. Stroke may affect afferent or efferent neuronal circuits participating in deglutition. The integrity of oropharyngeal–cortical afferent pathways can be assessed by electroencephalography through sensory-evoked potentials by pharyngeal electrical stimulation, while corticopharyngeal efferent pathways can be characterized by electromyography through motor-evoked potentials by transcranial magnetic stimulation. Dysfunction in both cortico-mediated evoked responses is associated with delayed swallow response and aspiration. Studies have reported hemispherical asymmetry on motor control of swallowing and the relevance of impaired oropharyngeal sensitivity on aspiration. Advances in treatment include improvements in compensatory strategies but are mainly focused on (1) peripheral stimulation strategies and (2) central, noninvasive stimulation strategies with evidence of their clinical benefits. Characterization of poststroke OD is evolving from the assessment of impaired biomechanics to the sensorimotor integration processes involved in deglutition. Treatment is also changing from compensatory strategies to promoting brain plasticity, both to recover swallow function and to improve brain-related swallowing dysfunction.

Keywords: oropharyngeal dysphagia; swallowing disorders; neurorehabilitation; stroke; therapy

Introduction, prevalence, and risk factors of poststroke oropharyngeal dysphagia

Oropharyngeal dysphagia (OD) is a major complaint following stroke. A systematic review on the prevalence of OD following acute stroke found that the reported incidence of OD was lowest using bedside screening techniques (37–45%), higher using clinical testing (51–55%), and highest using instrumental testing (64–78%).[1] OD is specifically classified in the latest editions of the International Classification of Diseases (ICD) and Related Health Problems promoted by the World Health Organization ICD-9 and ICD-10 (787.2, R13).[2]

Despite its enormous impact on functional capacity, quality of life, and survival, OD is both underestimated and underdiagnosed as a cause of major nutritional and respiratory complications in stroke patients. OD may occur with cerebral lesions affecting both anterior and posterior circulation territories, as a consequence, for instance, of a single stroke situated in the hemispheres, posterior fossa, or brain stem, or as the result of more diffuse

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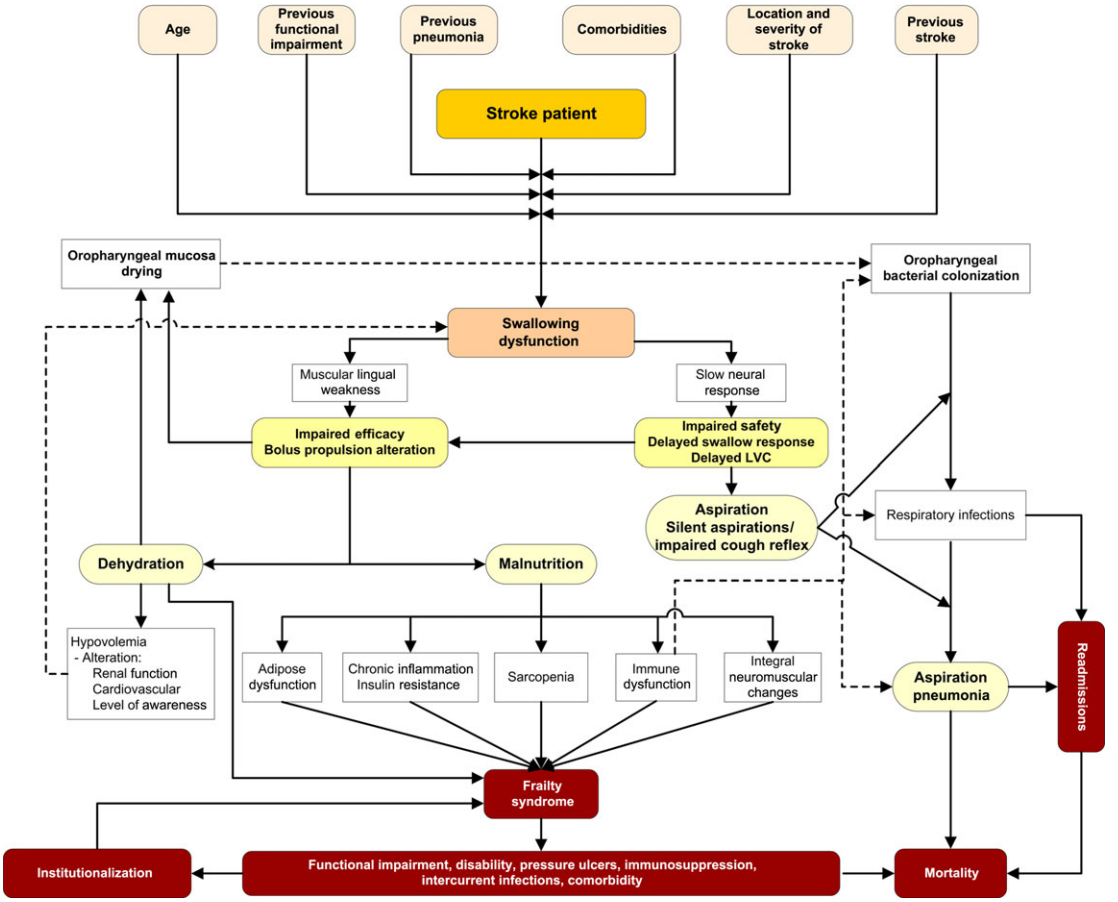

Figure 1. Complications of oropharyngeal dysphagia in poststroke patients. Adapted from Ref. 119.

cerebral disease.[3–5] There may be little or no other neurological deficit,[6] and it can result in impaired pharyngeal contraction, delayed laryngeal vestibule closure (LVC), vallecular pooling, vocal fold palsy, and incomplete relaxation of the upper esophageal sphincter (UES).[7,8] From a neuroanatomical perspective, unilateral hemispheric stroke leads to OD in 40% of cases, bilateral hemispheric stroke lesions lead to OD in 56%, brain stem stroke in 67%, and combined lesions in 85% of cases.[9] The natural history of OD in stroke patients is not fully understood, and, although an improvement of OD can be observed during the first weeks, it persists in as many as 50% of patients, and complications frequently arise.[5] A recent study from our group found that the incidence of poststroke swallowing dysfunction was 45.1% on admission, and prevalence of those who came at the 3-month follow-up visit was still 42.1%.[10]

OD can produce two types of severe complications in stroke patients (Fig. 1): (1) alterations in the efficacy of deglutition, which cause malnutrition or dehydration in up to 25% patients, and (2) impaired safety of swallow in 40% and aspiration in up to 21%,[11] which may lead to aspiration pneumonia (AP) and high mortality rates. There is increased risk for AP in patients with dysphagia (relative risk (RR), 3.17) and an even greater risk in patients with aspiration (RR, 11.56); the predictive odds ratio for death is 9.2, showing that OD is a major predictor for the development of AP and mortality in stroke.[1,12] Recent data from European populations 3 months after a first stroke showed that more than 40% of patients had a poor outcome (death, dependency, or institutionalization), and the risk of death was 21.8%.[13] The severity of OD following stroke varies from moderate difficulty to complete inability to swallow. Choking and tracheobronchial aspiration

result in pneumonia in 50% of cases, with an associated mortality of up to 50%.[12] In a stroke unit, up to 20% of patients with stroke suffer from early AP, and AP is one of the major causes of mortality during the first year after discharge.[14] A very recent study from our group on 400 consecutive stroke patients clearly showed OD to be an independent risk factor for prolonged hospitalization, complications, and mortality during hospital stay and 1-year follow-up.[15] Other studies found that stroke mortality at 2-year follow-up correlated with signs of aspiration in the initial videofluoroscopy (VFS) study.[16] The pathogenesis of AP presumes the contribution of risk factors that alter the swallow response, cause aspiration, and predispose the oropharynx to bacterial colonization. Impairment of cough reflex and silent aspiration—up to 50% of aspirations in stroke patients[11]—further increase the risk of AP in stroke patients.[17] In addition, consequences of malnutrition for stroke patients with OD can be a very serious prejudice outcome,[18] impair ventilatory drive and immune function, increase morbidity, delay recovery from illness, and decrease functional status.[19] A strong relationship between in-hospital and long-term mortality rates and oropharyngeal aspiration and AP has been found in several studies, and the introduction of specific programs for early management of OD in stroke patients has reduced the rate of AP and improved survival.[20] However, the current standard of care for the majority of European citizens with stroke suffering from OD is very poor, as 80% of patients are not even diagnosed and do not receive any treatment for this condition.[21]

This review provides an overview of advances in the pathophysiology, diagnosis, and novel neurorehabilitation strategies for poststroke OD. These are exciting times, with increasing awareness and progressive recognition of its clinical relevance and complications by healthcare providers from many fields. In addition, the emergence of new methods to screen and assess both swallow and brain function impairments associated with OD and the marked advances in understanding the pathophysiology of this condition are opening a new era with new professional domains in deglutology, which includes the enhancement of cortical plasticity to provoke and accelerate swallowing recovery. Therapeutic strategies are developing away from compensation of biomechanical swallowing deficits and toward new approaches in neurorehabilitation aimed at the restoration of impaired swallow and brain function.

Advances in the pathophysiology of poststroke OD

Normal swallowing is a complex and well-coordinated process that requires the appropriate interaction between several areas of the central nervous system (CNS), sensory and motor cranial nerves (CNs), and peripheral receptors of pressure, temperature, chemical stimuli, and water. It also requires the anatomical integrity of the oropharynx and larynx and the preserved neuromuscular function of up to 30 pairs of cervical striated muscles, including the UES, and close coordination with the respiratory system.[22] Our knowledge of the pathophysiology of poststroke swallowing dysfunction has greatly improved with better understanding of the four biomechanical phases of normal swallow (oral preparatory, oral propulsive, pharyngeal, and esophageal), the mechanisms of swallow control in the CNS, and the peripheral sensory and motor components involved in the oropharyngeal swallow response (OSR) (Fig. 2).

Pathophysiology of poststroke OD: motor control at the CNS

Central mechanisms controlling the motor aspects of deglutition lie in a complex network involving cortical and subcortical areas. Lower brain stem motorneurons from trigeminal motor, facial, ambiguous, and hypoglossal nuclei are controlled by corticonuclear pathways (probably monosynaptic) originating in both hemispheres, which run down bilaterally[23,24] to guarantee accurate and fine control of the voluntary phases of swallowing. Accurately timed activation of several components of the central pattern generator (CPG) situated in the lower brain stem is crucial to achieve a good outcome of swallow response in the pharyngeal phase and depends, among other factors, on the sensory feedback from the oropharynx to the trigeminal sensory and tractus solitarius nuclei.[25,26] Ischemic and hemorrhagic stroke may randomly affect any site of this complex circuit and cause variable clinical degrees of OD.

Supranuclear control of swallowing is somatotopically organized in several areas of the brain, involving primary and secondary sensorimotor

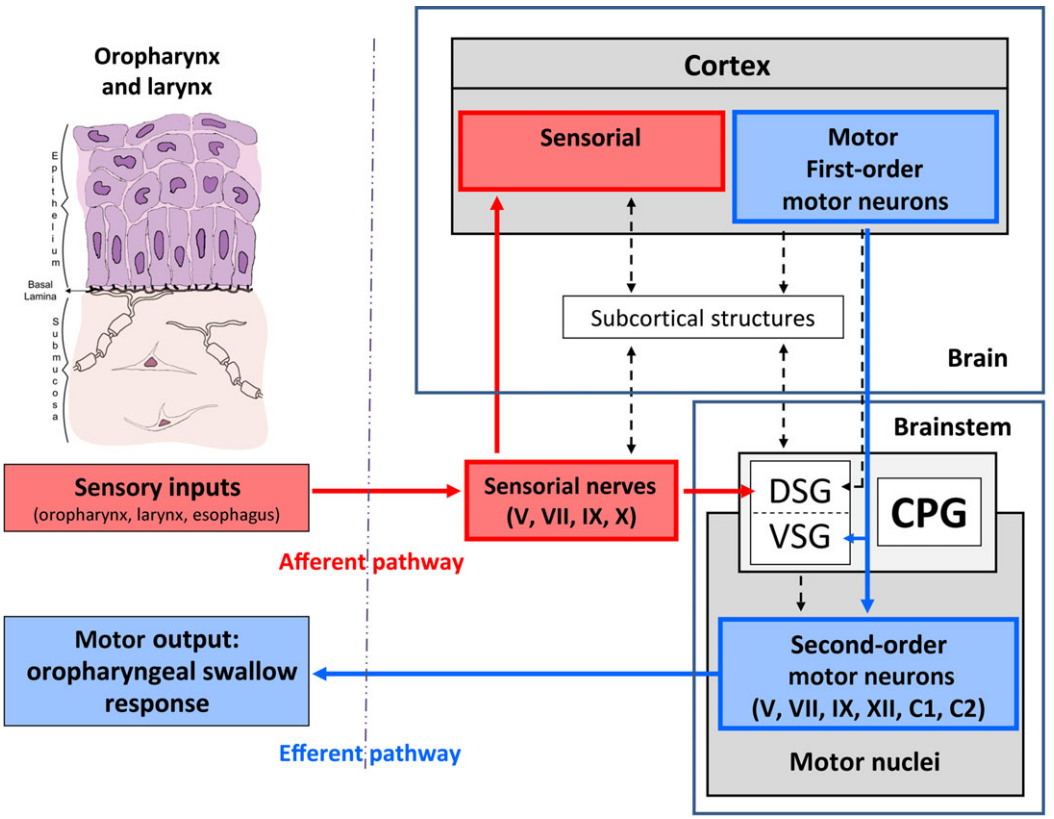

Figure 2. Pathophysiology of poststroke oropharyngeal dysphagia (OD). Scheme of the multidimensional neuronal network of the central nervous system controlling the oropharyngeal swallow response (OSR). The OSR is triggered by the swallowing center, an interneuronal network located in the medulla oblongata at the brain stem called the central pattern generator (CPG), receiving both central inputs from the cortex and peripheral sensory inputs from the pharynx and larynx. Poststroke OD can arise from the damage of first- or second-order motorneurons, sensorial neurons, and/or structures involved in sensorimotor integration (dashed lines). DSG, dorsal swallowing group; VSG, ventral swallowing group.

cortices as well as associative cortical areas, such as the frontal operculum, orbitofrontal cortex, and insula.[27] Specifically, there is a bilateral cortical representation of the muscles involved in deglutition (e.g., mylohyoid, pharyngeal, and upper esophagus muscles), as demonstrated by studies using transcranial magnetic stimulation (TMS) and brain imaging.[28–30] TMS studies of cortical mapping have located the "hotspot" of the pharynx musculature (i.e., the site with largest representation) at the lateral precentral motor strip, slightly anterior and lateral to the primary motor cortex of the hand and close to the inferior precentral gyrus and premotor area. Further studies have shown that dominance of either pharyngeal or esophageal muscles is variable between subjects and is not necessarily related to handedness.[24,31] The asymmetry in such representation is fundamental to understanding different dysphagia outcomes in patients after acute unilateral hemispheric stroke lesions. In these patients, the involvement of the dominant swallowing area causes dysphagia, while swallowing function is preserved when only the nondominant pharyngeal swallowing cortex is affected. Moreover, patients with poststroke OD who recover successfully show an enhanced contralesional (healthy) cortical pharyngeal representation,[32] as a likely surrogate of cortical plasticity related to dysphagia recovery. This compensation phenomenon differs from that found in other cortical functions represented exclusively in one hemisphere, such as language, where recovery after focal lesion only correlates with increased function in the region surrounding the stroke site in the ipsilesional hemisphere.

The location of the stroke may lead to different clinical outcomes of dysphagia. Impairment of cortical or supranuclear structures (first-order motorneurons) would affect the control and modulation of swallowing function, whereas direct damage to swallowing nuclei at the lower brainstem would lead to lack of motor output to swallowing musculature (second-order motorneurons). Plasticity mechanisms involved in brain stem stroke are largely unknown. Contrary to hemispheric lesions, poorer outcome on dysphagia of lower brain stem strokes may be related to the lack of proper plasticity mechanisms when second-order motorneurons are affected. For instance, lateral medullary stroke (Wallenberg's syndrome) frequently occurs with severe dysphagia, palatal weakness, and decreased gag reflex, as it affects either motor (e.g., ambiguous) or sensory (e.g., tractus solitarius and trigeminal) nuclei.[7] While it is not clear whether sensory or motor arc circuit impairment is more relevant for the clinical appearance of dysphagia in this disorder, it is well known that cephalic and vertical spread lesions are related to severe dysphagia.[33] In contrast to hemispheric lesions, where plasticity mechanisms play an important role in recovery of function, it is highly possible that primary damage to the motor output of the brain stem motorneurons, as found in Wallenberg's syndrome, prevents the manifestation of compensatory mechanisms occurring at higher cerebral levels.

Pathophysiology of poststroke OD: peripheral sensory inputs

Appropriate oropharyngeal sensory feedback is essential for safe and efficient swallowing. The potential role of sensory function in the pathophysiology of swallowing disorders has attracted less attention than motor impairments. However, the impaired pharyngeal sensitivity of poststroke patients could play a fundamental role in the pathophysiology of swallowing dysfunction associated with stroke. In the 1980s, Jean[26,34] indicated the relevance of sensory feedback during swallowing to adapt the swallow motor response to bolus characteristics, making the swallow response dependent on peripheral sensory inputs. Some years later, Aviv *et al.*[25] reported impaired pharyngeal sensitivity in poststroke dysphagic patients associated with increased risk of aspiration and poor prognosis and demonstrated its fundamental role in the physiopathology of swallowing dysfunction.

Pharynx–cortical bidirectional signaling seems critical to achieving a proper timing and extent of swallow response. Timed synergic rostrocaudal activation of brain stem nuclei is achieved through sensorimotor integration of sensory pharyngeal inputs and swallowing motor output. Theoretically, this process may occur at cortical or subcortical levels. Sensory nerve branches are responsible for carrying afferent inputs from the oral–pharyngeal cavity to the sensory cortex through transcortically mediated long-loop circuits. These participate mainly during voluntary swallows, although the short-loop circuits subcortically integrated at the CPG also participate to enable automatic swallowing responses, such as spontaneous swallows.[35] The most effective afferent areas to trigger the swallow response are the anterior faucial pillars, the palatopharyngeal arch, and the posterior pharyngeal wall (innervated by the pharyngeal branch of the glossopharyngeal nerve, GPNph, CN IX), and the epiglottis and the aryepiglottic arch (innervated by the superior laryngeal nerve, SLN, branch of CN X). Despite discrepancies, only studies using electronic microscopy show sensory nerve terminals trespassing the basal lamina and contacting the epithelial cells at the deepest layers of the epithelium; most sensory nerve terminals remain below the basal lamina. Sensory nerves express transient receptor potential (TRP) channels. TRPV1 is expressed in the oropharynx, with higher levels in the CN V region (tongue) than in the CN X region (epiglottis), and was localized at epithelial cells and nociceptive fibers in all studied regions. TRPA1 was also expressed in all studied regions but was always localized below the basal lamina. No immunoreactivity for TRPA1 was found on epithelial cells.[36] Preliminary studies from our group show that the cortical activation of stroke patients with OD in response to pharyngeal electrical stimulus is delayed compared with healthy volunteers. This sensorial impairment might be a critical pathophysiological element and a potential target for treatment of swallowing dysfunction in older patients.[37]

Poststroke swallowing dysfunction: VFS signs of impaired motor swallow response and mechanisms of aspiration

VFS studies have shown that the physiology of the OSR is severely impaired in stroke patients. The main signs of impaired efficacy during the oral stage in stroke patients include apraxia and

reduced control of bolus propulsion by the tongue. VFS signs of impaired safety during the pharyngeal stage include penetrations and/or aspirations. Penetration refers to the entering of contrast into the laryngeal vestibule within the boundaries of the vocal cords. Aspiration occurs when the contrast goes beyond the cords into the tracheobronchial tree.[38] VFS studies after the acute phase of stroke revealed some swallowing abnormality in up to 87% of patients: 53% in the oral phase and 84% in the pharyngeal phase (aspiration in 66%, half being silent).[39]

The potential of VFS regarding image digitalization and quantitative analysis allows accurate swallow-response measurements in patients with stroke and dysphagia. Delayed LVC and slow UES are the most characteristic aspiration-related parameters in patients with poststroke OD (Fig. 3).[11,40] The overall duration of OSR in stroke patients is significantly longer than that in healthy subjects. This increase in duration of OSR is mainly due to a delay in the early phase of oropharyngeal reconfiguration from a respiratory to a digestive pathway (time to LVC and UES opening (UESO)).[11,41,42] These results are consistent with an early study by Kahrilas *et al.*[40] that found that prolonged intervals from glossopalatal junction opening (GPJO) to LVC and from GPJO to UESO were the key abnormalities of OSR leading to unsafe deglutition in neurological patients. Our results also agree with other studies that showed that the strongest predictor of aspiration was the pharyngeal delay time.[43] Time to LVC is the time interval during which the potential penetration or aspiration occurs, and a delay in UESO increases the bolus volume held in the hypopharynx, thereby increasing the potential for bolus overflow into the LV. We agree with other authors that the length of this interval of vulnerability was inversely proportional to the safety of deglutition. Oropharyngeal residue was caused by impaired tongue bolus propulsion.[11,44]

Advances in the assessment of poststroke OD

Recent advances in the pathophysiology of poststroke OD strongly rely on the assessment of impairments in pharyngeal afferent pathways providing sensory information to the CNS and impairments in the cortical areas controlling oropharyngeal motor response.

Pharyngeal sensory-evoked potentials

Aged and stroke dysphagic patients present impaired pharyngeal sensitivity in the mucosa of the pharynx and larynx, demonstrated by increased sensory thresholds to mechanical stimulation,[45,46] which is associated with the altered swallow response and aspiration found in this disorder. However, little is known about how the pharyngeal sensory information is processed at the cortical level, either in healthy people or dysphagic patients. In this line of research, for instance, the application of topical anesthesia to the pharyngeal mucosa reduces not only the sensory but also the pharyngeal motor cortex excitability,[47–49] suggestive of disruption in sensorimotor integration processes. Thus, the study of pharyngeal sensory-evoked potentials (SEPs) may increase our knowledge of swallowing control networks, as well as provide a tool to monitor the effects of different therapies on pharyngeal sensory function.

SEPs to stimulation of swallowing structures are usually obtained by using the standard electroencephalographic (EEG) electrode arrangement (10–20 system). SEP relies on the recording of cortical EEG activity, which is synchronized by sensory stimuli applied repetitively on the afferent pathway. Early, middle, and late waves are characterized depending on their latency from the stimulus application. In normal subjects, SEPs have been elicited by mechanical stimulation of several structures involved in deglutition (e.g., lips, buccal cavity mucosa, tongue, palate, nasopharynx, oropharynx, larynx, and esophagus).[50–53] As a general pattern for the normal population, the waves generated on swallowing evoked-related potential show four well-characterized peaks, two negative and two positive, at latencies between 60 and 160 milliseconds. While early-wave peaks (N1 and P1) are mainly distributed in frontoparietal scalp regions, mid-latency waves (N2 and P2) show a more extended scalp peak distribution[54] (Fig. 4). Similar findings on sensory patterns of swallow distribution have been obtained using other noninvasive brain techniques, such as magnetoencephalography and functional magnetic resonance imaging.[55–57] Specifically, the integration and process of the pharyngeal sensory stimuli also shows bilateral representation on sensory cortical areas.[58–60]

Studies using SEP in dysphagic subjects are scarce. Data from our laboratory showed that, in older OD

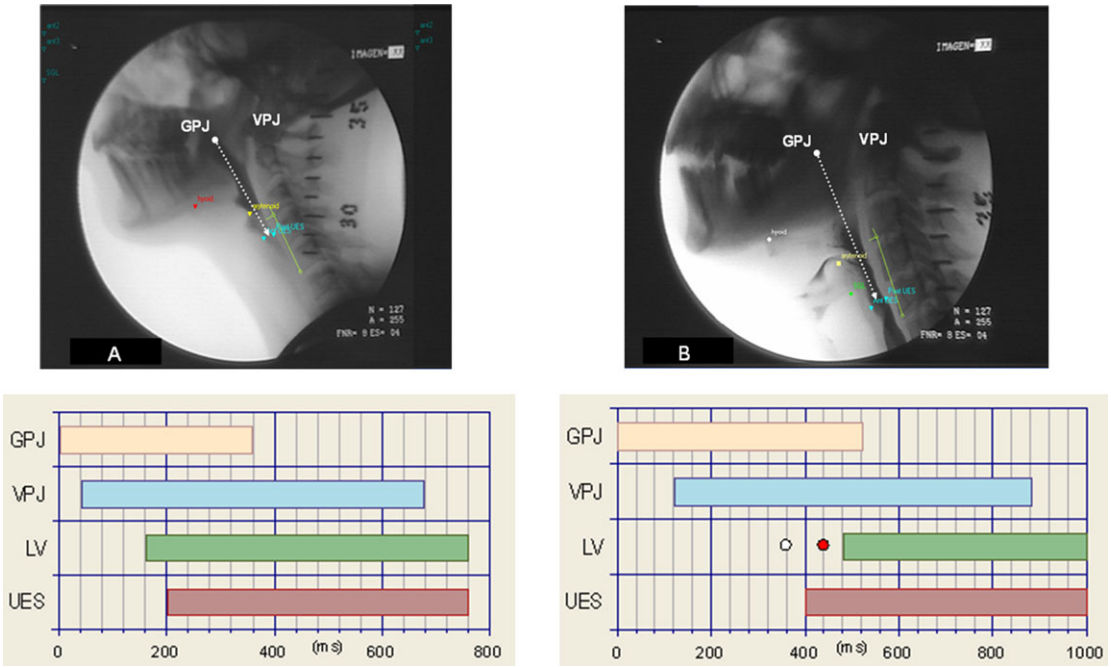

Figure 3. **Videofluoroscopic images and oropharyngeal swallow response (OSR) during the swallow of 5-mL nectar bolus. (A) Safe swallow in a healthy individual. (B) Penetration and aspiration in an older patient with neurogenic dysphagia and aspiration associated with stroke. An increased total duration of the OSR is seen, as well as delayed laryngeal vestibule closure and upper esophageal sphincter opening. The white dot indicates the time when contrast penetrates into the laryngeal vestibule and the red dot indicates the passage into the tracheobronchial tree (aspiration). GPJ, glossopalatal junction; VPJ, velopalatal junction; LV, laryngeal vestibule; UES, upper esophageal sphincter. Reprinted from Ref. 44.**

patients who underwent pharmacological therapy with capsaicin for 2 weeks, there was a significant correlation between latency shortening of SEP and improvement of biomechanical events, such as timing of LVC and upper esophageal opening,[61] suggesting that a disrupted pattern of cortical activation to pharyngeal inputs is associated with this disorder. These findings highlight the crucial role of appropriate oropharyngeal sensory feedback to achieve a safe and efficient swallow response. We suggest that dysphagic poststroke patients show impaired cortical activation to sensory stimuli in the ipsilesional hemisphere, as shown in Figure 5A from a representative patient.

Motor-evoked potentials

TMS is a painless, noninvasive method for stimulation of the human cortex through the intact skull.[62] TMS uses a rapidly changing magnetic field to induce brief electric pulses in the brain that can trigger action potentials in superficial cortical neurons, such as giant pyramidal motorneurons (Betz cells) and excitatory interneurons. The motor-evoked potential (MEP) is the resulting muscle EMG response obtained from activation by TMS of pyramidal tract neurons, mainly formed by corticobulbar and corticospinal pathways[63] and represents the muscle activity brought about by temporal and spatial summation of multiple descending volleys (D-wave and I-waves). MEP amplitude and onset latency are the most consistent parameters used in clinical and research settings.

In order to investigate the cortical excitability of projections directed to the muscles involved in swallowing, MEPs have been successfully recorded in several studies from submental muscles,[28,64] pharyngeal muscles,[24,28,35,64–67] and esophageal muscles,[24,48,68,69] among others (such as the cricopharyngeal muscle). Pharyngeal MEPs are usually recorded with an intraluminal catheter that houses bipolar ring electrodes placed just above the UES.[64,70] In general terms for the normal population, MEPs from swallowing musculature show much lower amplitude (ranging about 50–100 μV)

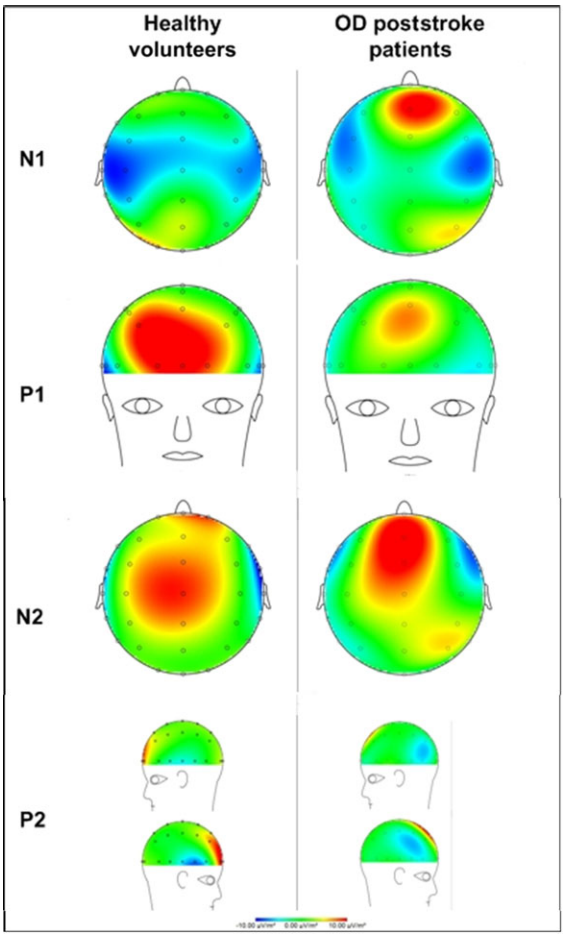

Figure 4. Current scalp density maps at each evoked-related potential peak time point for pharyngeal electrical stimulation are shown for representative healthy subjects and poststroke patients with OD. The study of evoked potentials allows the construction of distribution maps representing cortical areas with larger pharyngeal representation to sensory inputs. Note that these maps are built for each of the relevant components of the pharyngeal SEP (N1, P1, N2, and P2) corresponding to the synchronized timed EEG activation of sensory volleys at different moments of the arrival in sensory pharyngeal cortex. SEPs are a reliable neurophysiological methodology to study scalp distribution in time of afferent volleys from pharyngeal stimulation.

than MEPs recorded from limb muscles (larger than 1 mV). This is partly explained by the spatial features of the recording catheter, an arrangement where both electrodes are placed over electrically active muscle fibers, which may lead to phase cancellation of action potentials, reducing MEP amplitude.[71] In healthy subjects, onset latency of pharyngeal and esophageal MEP ranges from 7 to 10 ms, which represents the overall conduction time of synchronized descending volleys between excitation of swallowing cortex and muscle recording, including both central (first-order motorneuron activation of pyramidal tract) and peripheral (from second-order motorneuron activation to axonal conduction and muscle activation) pathways. MEP of *submentalis*-complex musculature is typically recorded with surface electrodes,[72] and therefore reflects collective activation of the anterior belly of the digastric, the mylohyoid, and the geniohyoid muscles, rather than being specific to any one of these muscles. Other muscles involved in swallowing, such as masticatory (masseter), periorial (orbicularis oris), and tongue (hypoglossal) have also been studied with TMS in healthy populations.[73–75]

Most MEP studies have increased understanding of the plasticity mechanisms of corticobulbar

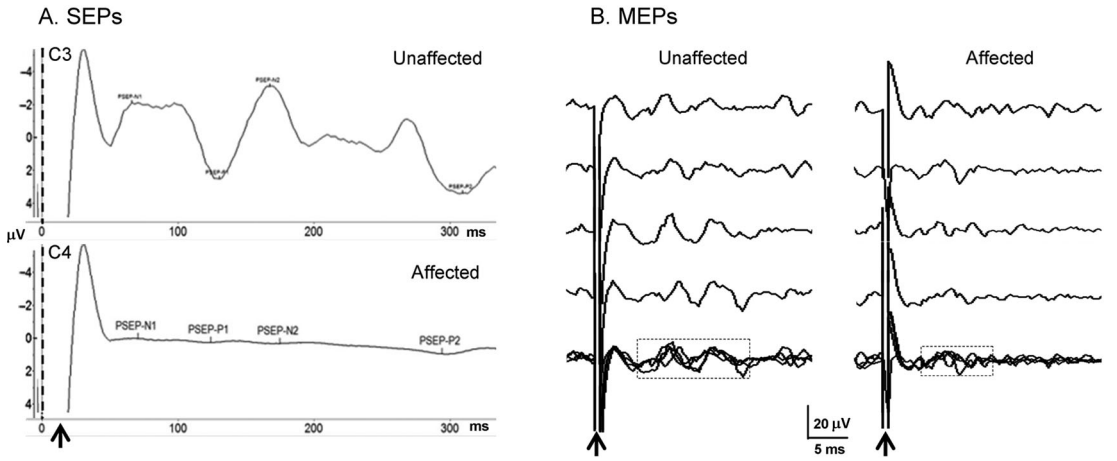

Figure 5. Representative recordings of sensory and pharyngeal motor-evoked potentials from electrical stimulation of the pharynx wall (SEPS) and from transcranial magnetic stimulation (MEPs) of a dysphagic patient affected by a right hemisphere stroke. (A) SEP wave recordings were obtained after averaging 190 traces for either the right affected (C4) or the left unaffected (C3) hemisphere. Note that four main peaks (N1, P1, N2, and P2) can be clearly identified in C3 but not in C4. (B) Four traces of MEPs are shown in a raster manner (superimposed at the bottom of the figure) obtained by TMS of the pharyngeal hotspot of either hemisphere. Note that amplitude of MEPs is significantly lower following stimulation of the affected compared with the unaffected hemisphere (motor response is highlighted within a dashed-line rectangle), with no significant differences on latency. Stimulus artifact is marked with an arrow in both panels.

function associated with swallowing, as well as differential hemispheric function of swallowing,[24,32] cerebellar contributions to swallowing motor pathways,[76] recovery of dysphagia following stroke,[24] and the effects of rehabilitation techniques on cortical excitability.[28,32,69] In a study, Ertekin *et al.*[68] failed to elicit MEPs from cricopharyngeal muscles in patients with corticobulbar tract involvement, such as patients with amyotrophic lateral sclerosis or pseudobulbar palsy, a significant difference from healthy volunteers, who all showed MEPs. Specifically, a few characteristic alterations have been observed in MEPs of poststroke patients in comparison with healthy individuals. As expected, lower amplitude but no differences in latency of MEPs have been found with TMS of the affected hemisphere compared with the unaffected hemisphere in stroke patients.[24,28] Representative recordings of pharyngeal MEPs from a stroke patient are shown in Figure 5B. The presence of dysphagia has been also correlated with lower MEPs to stimulation of the intact hemisphere, suggesting that the cortical plasticity mechanisms in the healthy side are responsible for compensation of swallowing dysfunction and may prevent the manifestation of dysphagia.[28] Interestingly, in patients with chronic unihemispheric stroke, the severity of dysphagia has been correlated with abnormally long MEP latency in the ipsilateral mylohyoid musculature to the affected hemisphere.[77]

Advances in treatment

Compensatory strategies

Treatment for OD has tended to focus on compensating for the swallow dysfunction by adopting different postures and maneuvers during swallowing and modifying bolus consistency. These treatments are widely accepted in clinical practice, but evidence supporting their effectiveness is limited.[78] Diet modification, such as the increase of fluid viscosity, has been successful in reducing aspirations and penetrations and in preventing AP. However, thickeners do not improve the physiology of the swallow response, and they may modify the palatability of some beverages, leading to poor compliance by patients. We found that increasing bolus viscosity greatly improves swallowing function in poststroke patients, providing a viscosity-dependent therapeutic effect for OD.[11] In addition, we recently compared the therapeutic effects of modified starch and xanthan gum thickeners on swallow safety and efficacy in chronic poststroke OD patients using clinical

and VFS assessment. We found that penetration–aspiration scale score was significantly reduced with increased viscosity with both thickeners. Modified starch increased oral and pharyngeal residues at nectar and spoon-thick viscosities but xanthan gum did not[79] (i.e., we have seen that the prevalence of pharyngeal residue seems to be dependent on the composition of the thickening agent used, in part also explained by the different intrinsic properties of the fluids). Timing of airway protection mechanisms (LVC) and bolus velocity were not affected by either thickener. As such, increasing bolus viscosity with modified starch and xanthan gum thickeners strongly and similarly improved safety of swallow in chronic poststroke OD by a compensatory mechanism; in contrast, only modified starch thickeners increased oropharyngeal residue.[79]

We also specifically analyzed the effectiveness of the chin-down posture in patients with neurogenic OD and found that only half the patients with acquired brain injury avoided aspiration during cervical flexion; 48% of silent aspirators continued to aspire in this position and that persisting aspiration in the chin-down posture was significantly related to delay-time pharyngeal residue, cricopharyngeal dysfunction, and bolus volume (patients with aspiration at larger volumes responded better to the chin-down posture). Patients with more severe biomechanical swallowing alterations responded more poorly to chin-down posture.[80]

Behavioral strategies focused on exercise and swallow rehabilitation have also been developed. These exercises aim to increase muscle strength and improve the motion of oropharyngeal structures, and may promote modest neuroplastic changes in the CNS. The translation of principles and concepts of neural plasticity into the clinical science of exercise rehabilitation for oropharyngeal swallowing disorders is a very recent issue, with as yet little evidence to support it.[81,82]

Effects of sensory-stimulation strategies

Several strategies have been used to modulate the swallow response by modifying the sensorial properties of the bolus (either chemically or physically) or by stimulation of sensory and motor pathways at the pharynx and larynx. The swallowing center receives strong afferent inputs, so sensory feedback is crucial to the initiation and modulation of the swallow response. A recent review by our group on the effects of sensory stimulation in the treatment of poststroke OD suggests that enhancing the sensorial stimuli by electrical or pharmacological oropharyngeal stimuli may increase the sensorial input to the swallowing center of the brain stem, thus triggering the swallow response earlier and protecting the respiratory airway. Moreover, there is increasing evidence that sensorial stimuli may promote brain plasticity, facilitating the recovery of poststroke OD.[83] Further randomized controlled trials are needed to confirm the initial findings of all these proof-of-concept studies.

Electrical stimuli. *Intrapharyngeal electrical stimulation.* Studies have found that adjunctive PES reverses swallowing disability after brain lesions.[84] The application of electrical stimuli on the pharynx of acute poststroke dysphagic patients, using intrapharyngeal electrodes (5 Hz, 10 min), showed a significant reduction in the pharyngeal transit time, swallowing response time, and prevalence of aspirations. These effects were associated with a marked increase in pharyngeal corticobulbar excitability and topographic representation in the undamaged hemisphere. A clinical study showed that 3-day treatment (10 min/day, 5 Hz) improved airway protection compared with controls, reduced aspirations, improved feeding status, and resulted in a shorter time to hospital discharge 2 weeks after the intervention.[84] Our experience with PES shows that it is a safe technique, and a very recent randomized control trial in patients with subacute stroke and dysphagia also found that PES was safe but did not improve dysphagia. Undertreatment of patients receiving PES may have contributed to the neutral result of this study.[85] Finally, a recent meta-analysis of randomized controlled trials showed that PES was associated with fewer aspirations on VFS, lower clinical dysphagia, and possibly shorter length of stay in hospital across three small trials.[86]

Surface electrical stimulation. Transcutaneous electrical stimulation is used to activate muscles involved in swallowing function through stimulation of axonal motor nerve endings and muscle fibers (neuromuscular electrical stimulation (NMES)). However, its effectiveness and safety in the treatment of dysphagia is still under discussion, and studies evaluating NMES therapy present inconsistent results. Transcutaneous electrical stimulation has also been used as a sensory strategy,

avoiding muscle contraction during the treatment by using a lower intensity of electrical stimulus. Sensory strategy has shown significant improvement in several swallow parameters, such as delayed swallow response time and prevalence of aspirations, in chronic poststroke dysphagic patients.[87,88] We recently compared both strategies of stimulation and found that surface electrical stimulation was a safe and effective therapy for chronic OD associated with stroke.[88] Surface electrical stimulation improved the swallow response and safety of swallow at both sensory and motor intensities and the efficacy of swallow at the motor level of stimulation. In addition, the therapy demonstrated an excellent safety profile, as no serious adverse events related to the study product were detected. A National Institute for Health and Care Excellence interventional procedure overview on NMES states that current evidence on the efficacy of NMES for OD is limited in quality. The evidence on safety is limited in both quality and quantity, but there were no major safety concerns.[89] Also, very recently, submental sensitive transcutaneous electrical stimulation was found to be effective in increasing cortical plasticity for mylohyoid muscles and reversing oropharyngeal cortical inhibition in healthy subjects, suggesting it could be a noninvasive treatment for poststroke OD.[89]

Pharmacological stimuli. Pharmacological/chemical stimulation of swallow involves the use of substances or drugs that modulate the swallow response by modifying the sensory properties of the bolus or stimulating the sensory neural pathways of deglutition.[83] Although there are limited targets, compounds, and studies evaluating them,[90] promising results are arising. The use of pungent ingredients, such as capsaicin (TRPV1 agonist) or piperine (dual TRPV1/TRPA1 agonist), or menthol (dual TRPA1/TRPM8 agonist) in acute and mid-term studies improved OD by reducing the latency of the swallow response[91–94] and the prevalence of penetrations into the laryngeal vestibule (LV) through shortening the time to LV closure and improving the speed and extent of hyoid movement.[37,95] In our studies, we found significant therapeutic effects at 150 μM for piperine (and maximal therapeutic effect at 1 mM)[95] and at 150 μM for natural capsaicinoids.[37] In addition, capsaicin boluses also improved the efficacy of swallow by reducing the prevalence of oropharyngeal residue via increasing the tongue propulsion force,[37] and the midterm use of these strategies seem to improve brain plasticity.[94] All of these studies included groups of patients with poststroke OD, where these agonists showed significant effects on VFS signs of swallow response. We also recently studied the expression of TRPV1/A1 receptors in the human oropharynx, further confirming that these receptors are promising therapeutic targets to develop active treatments for OD patients.[36]

Effects of noninvasive brain stimulation and other CNS stimulation strategies

Repetitive TMS. TMS is governed by the principles of electromagnetism. Trains of single magnetic pulses, known as repetitive transcranial magnetic stimulation (rTMS), can induce changes in cortical excitability at the site of stimulation and transsynaptically at distant sites, which can last for minutes or even hours.[96,97] It is generally accepted that high-frequency rTMS (>1 Hz) increases cortical excitability, whereas low-frequency rTMS (≤ 1 Hz) decreases cortical excitability.[96,97] Repetitive TMS appears to lead to sustained changes in cortical activity lasting well beyond the duration of the TMS application. This can be explained by several mechanisms, including synaptic changes resembling long-term potentiation and long-term depression mechanisms, as well as shifts in network excitability, activation of feedback loops, activity-dependent metaplasticity, and other mechanisms.[97]

Repetitive TMS can inhibit or facilitate the excitability of the pharyngeal M1 representation in unimpaired swallowing and alter swallowing function. Investigators have gone further in this aspect by investigating the role of rTMS applied to one or both hemispheres as a single intervention[69,98–101] or in comparison and combination with other central or peripheral neuromodulation strategies used for dysphagia recovery.[65,102] Thus, rTMS therapy is being used to provoke swallowing recovery after unilateral hemispheric stroke by means of two main strategies: by the disinhibition/excitation of neighboring ipsilesional cortical areas or, as proposed by Park *et al.*,[99] by increasing the excitability of contralesional healthy pharyngeal motor cortex, or by a combination of both excitatory strategies (bihemispheric stimulation). Theoretically, the approach of Park *et al.* might promote a better reorganization of neural connections similar

to that found during spontaneous recovery of swallow function after stroke. Considering the first approach, two studies have investigated the effects of 3-Hz rTMS applied over the esophageal M1 representation. In one study, real or sham rTMS was applied over the lesioned motor cortex over 5 days in 26 patients with dysphagia related to unihemispheric stroke. Real rTMS led to a significant increase in corticoesophageal excitability and a greater overall improvement in dysphagia, measured by the Dysphagic Outcome and Severity Scale (DOSS).[69] In a second study performed to investigate the effects of bihemispheric excitatory rTMS, the same authors found a significant improvement in DOSS scores in 22 patients with dysphagia related to brain stem infarction (1–3 months after stroke) after receiving real rTMS over both esophageal cortical motor areas for 5 days.[103] Taken together, these studies suggest that the excitability enhancement of esophageal M1 representation related to rTMS may benefit patients with infarction at either the cortical or brain stem level.[69,103]

Following the second therapeutic strategy, Park *et al.*[99] applied 5-Hz rTMS to the contralesional pharyngeal motor cortex in 18 patients presenting with unilateral hemispheric stroke. Significant improvement in swallowing functions, assessed by videofluoroscopic DOSS and the penetration–aspiration scale, was observed with real rTMS. Excitatory rTMS over both pharyngeal motor cortices has also been investigated, as in the study of Rhee *et al.*,[100] by applying 5-Hz rTMS for 2 weeks on one patient with a lateral medullary infarct, who showed a qualitative improvement in swallowing function.

Finally, some authors have proposed a third strategy using rTMS therapy, the inhibitory approach, and seek to restore the pharyngeal cortex functionality of the affected hemisphere by inhibiting the intact hemisphere to decrease transcallosal inhibition.[101] Verin and Leroi investigated the effect of inhibitory 1-Hz rTMS applied for 5 days to the contralesional M1 representation of the mylohyoid musculature in seven patients with chronic hemispheric or subhemispheric infarcts. With rTMS, mean clinical scores of swallowing function were increased, assessed by a Dysphagia Handicap Index incorporating physical, functional, and emotional aspects of swallowing. Average aspiration scores for liquids and penetration scores for paste were also reduced following 1-Hz rTMS.[101]

It is interesting to note that current rTMS strategies for dysphagia have mainly focused on targeting motor cortical hotspots commanding swallowing musculature.[98–102] However, there has been less research on the likely role of sensory cortical areas on deglutition. Indeed, there is evidence from neuroimaging studies that supports strong activation of primary sensorimotor cortices and other cortical areas during deglutition, indicating that swallowing involves the recruitment of an extended brain network requiring sensorimotor-integration processes.[29,30,104] We therefore believe that high-frequency rTMS applied over other cortical areas, such as the primary sensory cortex (S1), might be a promising strategy to induce dysphagia recovery. This is an interesting question currently under investigation.

Combined neuromodulation strategies and paired associative stimulation. The above-mentioned strategies may be used as single or combined interventions. Paired associative stimulation (PAS) is a promising therapeutic approach to enhance cortical excitability and improve motor function.[105] In PAS, two stimuli are applied with a known interval between to ensure the synchronized arrival of afferent volleys to the motor cortex, the sequence being repeated over an extended period of time. The first is an electrical stimulus applied for tens of milliseconds over a peripheral nerve in advance of the second, a magnetic stimulus applied over contralateral M1. PAS has been used recently in a few studies using varying paradigms to improve swallowing function. Michou *et al.*[65] studied 18 patients with unilateral or bilateral stroke. Patients were assigned to receive a single session of PES, a combination of PES and single-pulse TMS, or rTMS at 5 Hz over the contralesional pharyngeal motor representation. The authors reported increased pharyngeal MEPs and reduced penetration–aspiration score. Momosaki *et al.*[98] studied the effect of 3-Hz rTMS applied to the pharyngeal motor cortex bilaterally, combined with intensive swallowing rehabilitation, in four chronic stroke patients. Over 6 days, each patient received 10 sessions of rTMS, followed by 20 min of intensive swallowing rehabilitation exercises. The authors reported improved laryngeal elevation delay time with the combined treatment. In another study,[103] 10 days of 1-Hz rTMS or NMES was applied to 47 patients with subacute unilateral

hemispheric stroke, which was compared with conventional dysphagia therapy alone. Functional Dysphagia Scale and the penetration–aspiration scale showed improvement in rTMS and NMES groups without differences between them.

Transcranial direct current stimulation, techniques, and strategies. Another promising noninvasive brain-stimulation technique is transcranial direct current stimulation (tDCS), which uses low-intensity continuous currents (1–2 mA) applied to broad cortical areas to modify resting membrane potential of cortical neurons. Easier to apply and cheaper than rTMS, tDCS is usually delivered throughout a pair of electrodes, one anode and one cathode.[106] Depending on the electrical stimulus features, tDCS can facilitate or reduce cortical excitability: anodal stimulation enhances the excitability of the motor cortex, whereas cathodal stimulation reduces it.[107,108] In addition to these effects, short- and long-term effects have been found in several cortical domains associated with the use of tDCS,[109] in accordance with phenomena similar to long-term potentiation and long-term depression. The change in membrane resting threshold and neuronal firing pattern generated by tDCS is probably due to up- and/or downregulation of membrane receptors.[110,111] As with rTMS, the potential tDCS-related effects on swallowing function have been only investigated in a few studies. In these studies, a standard bipolar tDCS montage has been used, in which the anode is used as active electrode and placed over the primary swallowing cortex (near the centroparietal area in the 10–20 EEG system), and the cathode is used as reference electrode and placed on the contralateral supraorbital area. In healthy volunteers, anodal tDCS enhances the cortical excitability of the pharyngeal representation[112] and accelerates swallowing,[113] suggesting that swallowing cortical centers are susceptible to be modulated with tDCS applied in this arrangement.

At present, there are only a few studies investigating the possible beneficial effects of tDCS on the recovery of dysphagic patients after stroke. Kumar *et al.*[114] showed that anodal tDCS applied over the contralesional hemisphere improved the scores of dysphagia in patients affected by stroke at least 1 month before. More recently, Shigematsu *et al.*[115] demonstrated that dysphagia scores were also improved when tDCS was applied over the ipsilesional hemisphere in a group of early-suffering stroke patients (within a week of onset). In summary, tDCS has been used with different paradigms to stimulate either hemisphere: anodal tDCS to the nonaffected hemisphere induced swallow recovery after treatment and anodal tDCS to the affected hemisphere did not produce significant swallowing improvement after the intervention but improved swallow 3 months after the intervention.

Summary of noninvasive brain-stimulation strategies

Two recent reviews summarize the current evidence of central strategies on brain plasticity in dysphagic poststroke patients. The meta-analysis of Yang *et al.*[116] included six studies exhibiting significant heterogeneity with respect to dysphagia assessments, study population, stroke etiology and characteristics, brain site of therapy application, and the time to intervention after stroke onset. While no significant improvement of dysphagia was found with application of tDCS, subgroup analyses showed that significant benefit on dysphagia was found when high-frequency rTMS was applied over the contralesional hemisphere. Similarly, the systematic revision of Pisegna *et al.*[117] including dysphagic poststroke patients receiving tDCS or rTMS showed that dysphagia improved to a larger extent when noninvasive brain stimulation (NIBS) was applied on the contralesional hemisphere. Although the exact neuronal plasticity mechanisms involved in these findings are only a matter of speculation, altogether the results suggest that NIBS applied in the contralateral side to unilateral stroke induces and/or facilitates cortical reorganization, playing a key role in functional recovery of dysphagia.

Clinical applicability and future perspectives

Diagnostic approach of poststroke OD is evolving from the assessment of impaired biomechanics of the swallowing function, mainly through the study with VFS, to the characterization of dysfunctional sensorimotor integration processes involved in deglutition through the study of evoked potentials. Taken together, the new technologies allow the individual study of either afferent or efferent pathways, as well as cortical responses and biomechanical integration with the VFS analysis of the swallow response. In the last decades, neurophysiological

studies have been positioned as diagnostic tools to investigate the pathophysiology of impaired function of swallow cerebral centers in detail in patients with OD. The main advantage of this approach, with respect to characterization of the biomechanics of the swallow response, relies on the understanding of the specific pathways involved in OD and how each of them may contribute to variable clinical presentations of dysphagia. While videofluoroscopic assessment supplies a big (and also accurate) picture of the biomechanical dynamics of swallowing in dysphagic patients, neurophysiological assessment explores the underlying neural mechanisms of the disorder and the potential targets for specific treatments.

The potential applicability of the neurophysiological study of swallow is extensive for clinical and research settings. Although the high costs of TMS equipment contrast with cheaper SEP equipment, MEPs seem faster to perform than SEPs. In clinical settings, evoked potentials may be used for monitoring recovery in OD patients undergoing rehabilitation therapy, an aspect currently under research. With regard to knowledge of the specific mechanisms involved in OD, there is a broad field of research not yet explored in depth in poststroke dysphagic patients. For instance, SEPs and MEPs might distinguish between isolated pharyngeal dysfunction of afferent and efferent pathways, to be further correlated with specific lesions found in stroke. Neurophysiological and structural correlation studies may furnish interesting data on the relationship between the source of altered evoked potentials and neuroimaging lesion localization, implying sensory or motor swallowing brain areas. In the future, this strategy could help answer several questions regarding the exact locations, size, and number of lesions, among many others aspects associated with clinically relevant OD in acute or chronic poststroke patients. This approach could also help identify patients with particular affectation of pharyngeal neural circuits (e.g., afferent and efferent pathways or sensorimotor integration centers) in order to select specific treatments. Indeed, focal targeting of neural structures implied in the pathophysiology of OD is the main goal of therapeutic interventions, such as rTMS, currently under investigation. In this review, we have shown significant evidence that NIBS techniques are an emerging strategy to improve cerebral function related to disordered deglutition.

Summary

It is well recognized that OD is a major complaint in patients following stroke and is also underestimated as a cause of malnutrition and respiratory complications. The state of the art (endorsed by scientific societies such as the European Society for Swallowing Disorders) is for systematic screening for OD to be performed on every stroke patient before starting oral feeding, followed by clinical and instrumental (VFS or fiberoptic endoscopic evaluation of swallowing) assessment.[118] First, bolus modification with adaptation of bolus volume and viscosity of solids and fluids and postural adjustments should be part of the minimal treatment protocol, but they do not change the impaired swallow physiology or promote recovery of damaged neural networks in stroke patients. Second, there is a growing interest in elucidating the main role of sensory impairment in the pathophysiology of OD. We and others have shown that several peripheral stimulation strategies (including pharmacological) may induce significant improvements in several biomechanical parameters of the swallow response, in particular reducing the rate of aspirations. This indicates that the swallow response is not a fixed reflex and that mid-term use of this strategy seems to have plastic effects on brain function, in particular using pharmacological strategies. Third, there is evidence that enhancement of pharyngeal cortical representation in the contralesional hemisphere of poststroke patients (i.e., neuroplasticity reorganization occurring in cortical undamaged swallowing areas) plays a significant role in dysphagia recovery, supporting the use of NIBS as an emerging strategy to directly improve cerebral function related to disordered deglutition. It is clear, therefore, that future implications of this kind of approach are sound.

The two main results of this review are (1) diagnosis of poststroke OD is developing from the assessment of impaired biomechanics of swallowing function to the characterization of dysfunctional sensorimotor integration processes involved in deglutition, and (2) the paradigm of treatment is also changing from compensatory strategies to the promotion of brain plasticity aiming at the recovery of both impaired swallow and brain-related swallowing dysfunction. We believe that these two strong tendencies and the results of new randomized control trials will induce, in the near future,

a lot of changes in the management of poststroke OD, and future treatment for stroke will look very different from how it looks today. This has a strong implication for healthcare professionals involved in the care of these patients, as education and research in these new technologies is a cornerstone allowing maximal potential recovery of stroke patients with OD. Therefore, combining the new pathophysiological and therapeutic tendencies may achieve specific neurorehabilitation treatment for these patients.

Emerging neurophysiologic strategies are providing the basis to better understand the pathophysiology of poststroke swallowing dysfunction, paving the way for new neurorehabilitation strategies for poststroke OD from compensation to the recovery of swallowing function.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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