Treatment of dysphagia after stroke

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Abstract:

Dysphagia following stroke affects a majority of patients and can lead to aspiration pneumonia, malnutrition and adverse functional outcomes. Currently, protective interventions aimed at reducing these complications remain the cornerstone of treatment. Dietary adjustments and oral hygiene help mitigate the risk of aspiration pneumonia, while nutritional supplementation, including tube feeding, may be necessary to prevent malnutrition. Rehabilitative interventions aim to enhance swallowing function, with different behavioural strategies showing promise in small-scale studies. Recent investigations have explored the use of pharmaceutical agents like capsaicin and other TRPV-1-receptor-agonists, altering sensory perception in the pharynx. Neurostimulation techniques, including transcranial direct current stimulation, repetitive transcranial magnetic stimulation, and pharyngeal electrical stimulation, promote neuroplasticity within the sensorimotor swallowing network. Neuromuscular electrical stimulation is employed to strengthen swallowing muscles. Further advancements in comprehending central and peripheral sensorimotor mechanisms in dysphagia after stroke and its recovery will contribute to optimising treatment protocols.

Introduction:

Dysphagia refers to the impairment of the transport of food, drink, and saliva from the oral cavity to the gastric entrance. As swallowing requires central control in an extensive cortical, subcortical, and brainstem network, dysphagia after stroke frequently occurs in the acute phase of the disease, with prevalence rates of up to 75% when instrumental diagnostics are used[1]. Dysphagia not only compromises quality of life, but also leads to serious complications. The association with aspiration pneumonia due to bolus intrusion into the airway has been well established for many years[2–5]. In addition to pneumonia, post-stroke dysphagia contributes to malnutrition by impairing oral intake[6]. As a result of these severe complications, dysphagia is associated with increased in-hospital mortality[7] and additional costs to the healthcare system[8].

Complications of dysphagia often occur early in the course of the disease making timely dysphagia management important[9]. A combination of clinical screening protocols and instrumental dysphagia assessments, such as Flexible Endoscopic Evaluation of Swallowing (FEES) and Videofluoroscopic Swallowing Study (VFSS) as diagnostic gold standards[10] play a decisive role in stepwise diagnosis. In our previously published review, diagnostic aspects of post-stroke dysphagia were described and discussed in detail[11]. This review now focuses on therapeutic strategies for dysphagia.

Despite its clinical relevance, dysphagia management has been neglected for many years, possibly due to previously scarce and heterogeneous study data. This has changed markedly, as there are now a large number of studies providing evidence for the treatment of post-stroke dysphagia (Panel 1 provides an overview of treatment recommendations derived from international guidelines identified during the specified search-period). Therapeutic strategies include protective measures aimed at reducing complications without targeting swallowing function itself, and restitutive approaches aimed at improving swallowing physiology. To support evidence-based implementation of treatment, this review provides a comprehensive summary of available therapeutic strategies for dysphagia after stroke. We begin by proposing a universal minimum standard of care, suitable even for resource-constrained settings. Then, we delve into advanced add-on therapies that build upon current knowledge. Lastly, we outline future directions in the field.

Panel 1: International guideline recommendations on treatment of post-stroke dysphagia published since 2017:

- European Stroke Organisation (ESO) and European Society for Swallowing Disorders (ESSD) guideline for the diagnosis and treatment of post-stroke dysphagia[12]. Texture-modified diets are recommended based on an appropriate assessment of swallowing. Behavioural swallowing exercises, acupuncture, oral nutritional supplementation or enteral feeding in patients with risk of malnutrition together with oral health-care interventions are recommended for dysphagia management. Pharmacological and neurostimulation treatments are recommended within a clinical trial setting.
- European Society for Clinical Nutrition and Metabolism guideline on clinical nutrition in neurology[13]. Oral nutritional supplementation is recommended for patients at risk of malnutrition. The guideline states that data on the effect of texture-modified diets and thickened liquids on outcome parameters are insufficient. It therefore recommends the use of texture modification and fluid thickening only after swallowing assessment and when fluid balance and nutritional intake are monitored. Early enteral tube-feeding is recommended for patients with anticipated prolonged severe dysphagia. In case of enteral feeding >28 days percutaneous endoscopic gastrostomy (PEG) tube insertion is recommended.

Search Strategy and selection criteria:

We searched for articles published in English on PubMed between 12/2017 and 1/2024 with the search terms "Dysphagia" AND "Stroke". We selected articles that reported on therapeutic aspects of dysphagia after stroke. We also considered publications cited in these articles that did not appear in the search algorithm. Further, we included articles published at an earlier date, if we considered them still relevant to the field, e.g., if the previously selected articles cited a respective article frequently. The final selection of cited articles reflects our subjective assessment of their relevance with respect to the reported results and the methodological quality of the reported work.

Dietary interventions

Food and liquid texture modification has become a therapeutic cornerstone in addressing dysphagia and is based on the principle that aspiration risk may vary between different bolus consistencies. Evidence for dietary interventions has previously been hampered by the use of non-standardised consistencies across studies. Therefore, in recent years, the International Dysphagia Diet Standardisation Initiative has provided a framework with standardised definitions and terminology of bolus textures[14]. It defines a continuum of eight consistency levels, ranging from low to high viscosity. Levels 0 to 4 are used to describe drinks, while levels 3 to 7 are assigned to foods. Levels 3 and 4 represent overlapping consistencies. The framework also includes user-friendly test procedures to determine the appropriate consistency level (for more information, visit https://iddsi.org/).

Texture modification, such as thickening liquids and pureeing solid foods, is commonly used in dysphagia management. In a recent study with 120 stroke patients from Spain, the aspiration rate decreased steadily with increasing viscosity by liquid thickening[15]. A further study recruiting 454 stroke patients from Japan demonstrated that individualised dietary intervention including texture modification was associated with improved nutritional status, physical function, and shorter hospital stay[16]. A systematic review summarising earlier studies on texture modification for oropharyngeal dysphagia concluded that thickening of liquid may reduce the aspiration rate but, as a negative consequence, also lead to an increase in pharyngeal residue[17]. In a recent retrospective study of 443 stroke patients from Japan, the administration of decreased food-texture-levels was associated with malnutrition and sarcopenia[18]. This association may be attributed to decrease in appetite due to texture-modified diets[19] and subsequent reduced patient acceptability.

Due to the potential adverse long-term effects, texture modifications are best suited as a short-term early intervention during the acute phase of the disease. Thus, training of swallowing function can be started early in dysphagia rehabilitation (e.g., also if tube-feeding is still required). Dietary interventions should be implemented as part of an individualised approach based on case-by-case assessment, preferably with instrumental testing.

Nutritional interventions

The goal of nutritional intervention is to prevent the negative effects of malnutrition. In cases of severe dysphagia, where patients are unable to swallow an adequate amount of calories, fluids, or required medication, tube-feeding becomes necessary to ensure sufficient protein-calorie intake. The FOOD family of trials, published in 2005, consisted of three multicentre randomised controlled trials (RCTs) focused on nutritional interventions for stroke. In the FOOD-2 trial in 859 stroke patients from 15 countries, there was a statistically non-significant reduction of 5.8% (p=0.09) in deaths in the early tube-feeding group compared to delayed tube-feeding after more than 7 days[20]. In reality, tube insertion is often needed for drug administration whether or not feeding is to be commenced immediately. However, tube-feeding does not reduce the rate of aspiration pneumonia[21,22], as salivary aspiration with oral pathogens still occurs. This is also reflected in the increased long-term mortality of patients on enteral nutrition[23]. It is subject of debate which caloric regimen is most appropriate in patients with tube-feeding. A recent RCT involving a total of 315 severe stroke patients from China suggested that hypocaloric enteral nutrition is associated with increased mortality when compared with a modified total enteral protocol where sufficient caloric intake was administered together with prokinetic agents[24]. In two RCTs (from United Kingdom and Iran), the use of metoclopramide or domperidone as prokinetic drugs reduced the rate of pneumonia in stroke patients[25,26] although this was not seen with metoclopramide in the large and recently presented European PRECIOUS trial (European Stroke Organisation Conference, May 2023). In a retrospective observational study from China, protein intake but not caloric intake was associated with reduced mortality at 30 days and 6 months, suggesting that adequate protein intake in particular may be relevant[27]. The question of whether and when exactly enteral nutrition should be provided via a nasogastric tube or via a percutaneous endoscopic gastrostomy (PEG) cannot be conclusively answered on the basis of the available studies to date. In the FOOD-3 trial in 321 stroke participants from 11 countries, there was an increase in the absolute risk of death and poor functional outcome of 7.8% (p=0.05) in the study group that received an early PEG compared with nasogastric tube patients. As a limiting factor, it should be noted that the tube was placed considerably later in the 162 PEG patients than in the 159 patients with nasogastric tubes[20]. In contrast, a 2012 Cochrane review concluded that nasogastric and PEG nutrition are not associated with differences in case fatality and dependency; indeed, PEG nutrition was associated with fewer treatment failures, less gastrointestinal bleeding, and higher feed delivery[28]. For pragmatic considerations, it seems reasonable not to perform the more invasive PEG insertion immediately after stroke, since oral intake recovers within 30 days in a substantial numberof patients[29]. Accordingly, there is a broad consensus among experts that PEG placement should be performed if tube-feeding is anticipated to be required for more than 28 days in a stable phase after stroke[13].

Given the detrimental effect of malnutrition after stroke, providing extra energy in form of oral supplements has been considered as further nutritional intervention. Regarding unselected stroke patients on oral nutrition, the FOOD-1 trial found no benefit of supplemental oral nutrition therapy on death or functional outcome in 4023 stroke patients from 15 countries[30]. However, in selected patient groups, oral nutritional supplementation is assumed to have a beneficial effect. In a prospective observational study on 454 stroke patients from Japan, dietary interventions including oral energy and protein supplementation within an individualised approach based on nutritional assessment was investigated. This approach was independently associated with an increase in muscle mass, improved physical function and a shortened hospital stay[16]. A recent RCT from China evaluated individualised nutritional support in 173 stroke patients, including an individualised nutrition plan in which caloric requirements were calculated. After the intervention, the body composition of the intervention group showed higher lean mass and phase angle, and serologically higher protein, albumin, and haemoglobin levels[31]. Thus, the results suggest that individualised nutritional support, including monitoring of caloric intake, may improve the nutritional status of selected patients.

In conclusion, the available data suggest that early tube-feeding with adequate caloric intake should be performed in patients with severe dysphagia. PEG placement should be considered in patients who are assumed to require tube-feeding for more than 4 weeks. Further, caloric intake should be closely monitored and individually managed. Oral supplemental nutrition therapy should only be used in selected patients with risk for malnutrition if oral intake is sufficiently safe.

Oral hygiene

Aspiration of saliva contaminated with oral pathogens is considered a critical mechanism for the development of aspiration pneumonia in acute stroke patients. In line with this, PCR analysis in a recent study from New Zealand showed that oral bacterial levels of non-physiological pathogens such as Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa increased after stroke and that the combined bacterial level was associated with pneumonia[32]. Conversely, the aim of oral hygiene interventions is to diminish colonisation with oral pathogens. In a recent RCT with 84 stroke patients from China, pneumonia rates showed a statistically non-significant reduction from 32% to 14% (p=0.052) when an intensified oral hygiene program, including swabbing teeth and oral soft tissues with chlorhexidine 3 times daily[33]. In a retrospective observational study involving 2,771 acute stroke patients from Japan, the implementation of systematic dental oral care was associated with a statistically significant reduction in pneumonia rates compared to a period without such care. The odds ratios for pneumonia reduction ranged from 0.24 to 0.49 across different care periods, each characterised by varying levels of enhanced dental care[34]. However, other older RCTs reported either no statistically significant effects[35,36] or an improvement in oral hygiene without effects on respiratory complications[37]. In a recent meta-analysis, studies of oral hygiene interventions showed a statistically non-significant reduction of pneumonia (p=0.06) and improved oral health outcomes[12]. Therefore, oral hygiene should be optimised as much as possible within the available nursing capacity.

Behavioural therapy

Behavioural exercises and manoeuvres are the most widely used therapeutic approach for dysphagia with several different procedures available to Speech & Language Therapists. Compensatory procedures are based on changing the body and head position during swallowing and aim to achieve immediate improvement by optimising physiological swallowing aspects and bolus flow. Rehabilitative swallowing exercises, aim to achieve a long-term effect through muscle training or optimisation of swallowing mechanics. However, in recent years many behavioural procedures are now considered to have both short-term compensatory and long-term altering effects, depending on their administration within an exercise program.

Some studies have addressed the overall efficacy of behavioural dysphagia therapies, e.g., in the context of an individualised approach. A retrospective study on 2994 stroke patients from Taiwan using propensity score matching associated swallowing therapy with a lower incidence of pneumonia and improved long-term survival[38]. Within the group of patients who received swallowing therapy, a treatment duration of more than 1 month was again associated with a decreased pneumonia rate, suggesting an intensity-dependent effect. An older but methodologically high-quality RCT involving a total of 306 stroke patients from Australia compared usual dysphagia therapy with standard low-intensity swallowing therapy (swallowing compensation strategies and dietary modifications) and standard high-intensity swallowing therapy (high-frequency direct swallowing exercises and dietary modifications). There was a statistically significant decrease in chest infections and death or institutionalisation in both standard swallowing therapy groups. The high-intensity group additionally showed an increase of patients who were able to return to a normal diet or recover swallowing function[39]. Further, in a 2018 Cochrane meta-analysis, various behavioural interventions considered together were associated with improved swallowing ability and reduced the proportion of stroke patients with dysphagia[40].

Numerous studies assessed the therapeutic effects of specific manoeuvres or exercise protocols. One of those techniques is the modified chin-tuck manoeuvre. In the original chin-tuck manoeuvre, patients tilt their head to their chin. This is intended to improve swallowing mechanics due to the change in posture. More recently, this technique has been modified into a long-term effect exercise against resistance protocol. A recent meta-analysis summarising 8 RCTs concluded that chin-tuck against resistance leads to improvements in swallowing-safety (5 studies) and oral intake (3 studies) compared with control interventions[41]. In a subgroup analysis, the chin-tuck-against-resistance intervention was more effective in improving swallowing safety compared with Shaker exercise (4 studies)[41], a head-lifting exercise aimed at increasing laryngeal elevation and upper oesophageal sphincter opening. In a recent RCT with a total of 32 stroke patients from Korea, there was improvement in the penetration-aspiration scale and functional oral intake in the Shaker exercise group compared with conventional dysphagia therapy[42]. Finally, exercise protocols are in use with the aim of strengthening oral, facial or breathing muscles. A RCT on 19 stroke patients conducted in Sweden with oral neuromuscular training revealed positive effects on swallowing rate and lip strength; however, no statistically significant differences were found in the VFSS analysis [43]. A further RCT comparing tongue-to-palate resistance training with conventional therapy in 35 Korean stroke patients demonstrated an improvement of tongue strength and oral and pharyngeal parameters on VFSS[44]. A RCT with 19 stroke patients from the USA suggested an increase in functional oral intake associated with device-facilitated lingual exercises[45]. The effect of resistive jaw opening was investigated in 29 Korean stroke patients in a further RCT in which liquid penetrations and aspirations were reduced in the intervention group but not in the control group in the pre-post comparison, however there was no statistically significant difference between the groups[46]. Training of inspiratory and expiratory muscles is hypothesised to improve cough reflexes and swallowing function. In a RCT with a total of 109 stroke patients from Spain, inspiratory and expiratory muscle training was able to strengthen the respective muscles and reduce respiratory complications[47]. Furthermore, a RCT with a total of 27 stroke patients from Korea suggests that expiratory muscle strength training (EMST) contributes to a reduction in penetrations and aspirations of fluids and an improvement in oral intake[48]. Consistent with this, a meta-analysis summarising 11 RCTs concluded that respiratory muscle training decreases the risk of respiratory complications and reduces penetrations and aspirations with fluid consistency[49]. In addition, electromyographic or visual biofeedback with instrumental visualisation of swallowing impairment can be used to optimise swallowing mechanics or to increase the myographic amplitude of the swallowing muscles[50,51]. Further, various recent meta-analyses suggested a positive therapeutic effect of acupuncture[12,52–54]. However, despite several, often large studies, due to a lack of high-quality methodology and heterogeneity, the evidence for acupuncture remains of low quality[55], and the therapeutic mechanism of this procedure is largely unknown.

In summary, there are several protocols available for behavioural dysphagia therapy. Easy-to-implement exercise protocols that have been shown to improve dysphagia after stroke include chin-tuck against resistance, shaker exercises, and EMST (these exercises-protocols are illustrated in figure 1). Behavioural therapy should be based on the individual dysphagia pattern and its effectiveness should be evaluated on a case-by-case basis during the course of therapy.

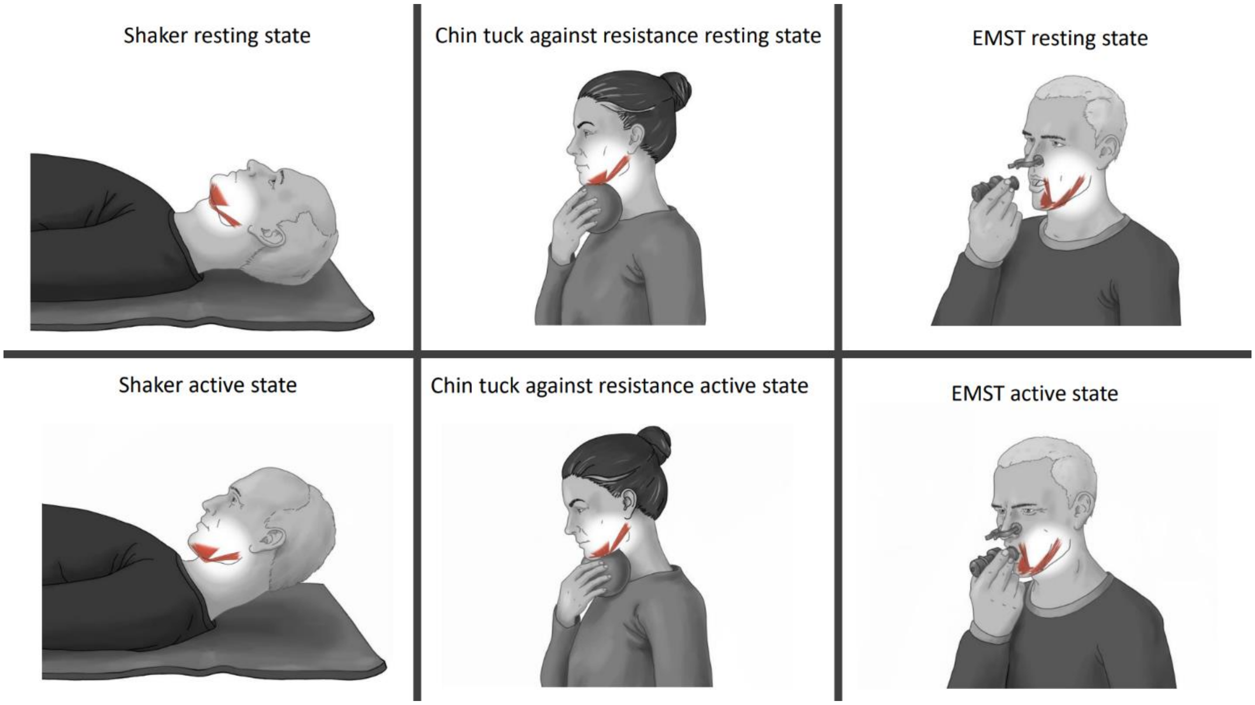

Figure 1: Illustration of behavioural swallowing exercises to treat dysphagia after stroke: Shaker-exercise: The patient lies flat on the floor and holds the head up for one minute using the supra- and infrahyoid muscle groups. This is repeated 3 times for 1 minute, following 30 head lifts, 3 times a day for 6 weeks. Chin-tuck against resistance: The patient bends the head against a resistance on the chin, involving the supra- and infrahyoid muscle groups. This procedure is repeated several times. Expiratory-Muscle-Strength-Training (EMST): The patient blows air against a resistance into a corresponding EMST device with the participation of pharyngeal muscle groups. This process is repeated several times.

Pharmacotherapy

Despite promising study results, pharmacological treatment should currently be used primarily in the context of clinical studies due to a lack of clear evidence in recent meta-analyses[12]. Pharmacological treatment options for dysphagia consist of medications that have a neuromodulatory effect on swallowing, either at the peripheral sensory level or at various levels of the central nervous system.

A peripherally acting substance used to treat dysphagia is capsaicin, which can be considered a pharmacological sensory stimulus. Capsaicin is an agonist of the Transient-Receptor-Potential-Vanilloid-1-sensory-receptor (TRPV-1-receptor) and mediates the release of the neuropeptide substance-P from sensory nerve endings. In nature, capsaicin is found in chili peppers, where it causes the spicy taste. In a recent RCT with a total of 92 stroke patients from China, capsaicin together with ice was compared with ice stimulation alone. The ice stimulation consisted of using an ice swab to stimulate specific areas, including the soft palate, palatine arch, posterior pharyngeal wall, and posterior part of the tongue. This stimulation was administered twice a day before lunch and dinner. The intervention group showed a greater improvement in dysphagia as assessed by a water swallowing test and clinical swallowing assessment. In addition, the intervention group showed higher serum substance-P levels after the intervention compared to the control group[56]. Another RCT with a total of 60 stroke patients from China investigated the effect of capsaicin in addition to tactile thermal stimulation. Tactile thermal stimulation involved applying a 4°C solution to the oropharyngeal mucosa using a cotton swab. Here, the intervention group showed a greater improvement in swallowing function, as measured by a questionnaire and clinical assessment by water swallow tests[57]. The results of another RCT involving 53 patients with haemorrhagic stroke from China suggest that administration of a capsaicin solution nebulisation regimen resulted in improvement in cough function and pharyngeal residue[58]. In contrast, in a further study from Spain in which the effect of capsaicin was evaluated immediately after the intervention using VFSS, no effect on swallowing physiology was detected, although enhanced excitability of the motor cortex was observed[59]. Besides capsaicin, piperine and menthol also stimulate TRPV-1 or functionally comparable subgroup receptors and were associated with improved swallowing function in etiologically heterogeneous groups of patients with dysphagia[60,61]. Other classes of pharmacological agents under investigation with inconclusive results include angiotensin converting enzyme (ACE) inhibitors, which inhibit the degradation of substance-P and sensitise the cough reflex (also known as side effects), and dopaminergic agents, which are assumed to shorten the latency of swallowing response[12,62].

Neurostimulation

In recent years, different peripheral and central neurostimulation procedures have been developed with the aim of inducing neuroplastic changes of the swallowing network to improve swallowing function after stroke (illustrated Panel 2 and Panel 3).

Panel 2: Non-invasive brain stimulation:

Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) are non-invasive brain stimulation methods. In tDCS, electrical current is applied over the skull via electrodes, reversibly affecting cortical excitability. The specific effects depend on the polarity of the electrode placement. Anodal stimulation increases cortical excitability, while cathodal stimulation decreases it.

In rTMS, a magnetic field is generated using a coil placed on the scalp. The application of the magnetic field promotes or decreases cortical excitability depending on the stimulation frequency. High-frequency rTMS (e.g., >5 Hz) typically enhances cortical activity, while low-frequency rTMS (e.g., 1 Hz) tends to reduce it.

Besides dysphagia rehabilitation, these approaches are used in modulating brain activity in various neurological and psychiatric conditions.

Panel 3: Methods of peripheral oropharyngeal stimulation:

Pharyngeal electrical stimulation (PES) and neuromuscular electrical stimulation (NMES) involve peripheral stimulation of the pharynx and swallowing muscles.

In PES, an electric current is applied to the hypopharyngeal mucosa via a catheter providing a sensory stimulus.

NMES is applied to the cervical region to activate nerves or muscles involved in swallowing function through stimulation of axonal motor and/or sensory nerve endings and muscle fibres transcutaneously.

Although the exact mechanisms of peripheral neurostimulation procedures have not been fully elucidated, it is believed that these techniques may exert secondary modulatory effects on the entire swallowing network at various levels.

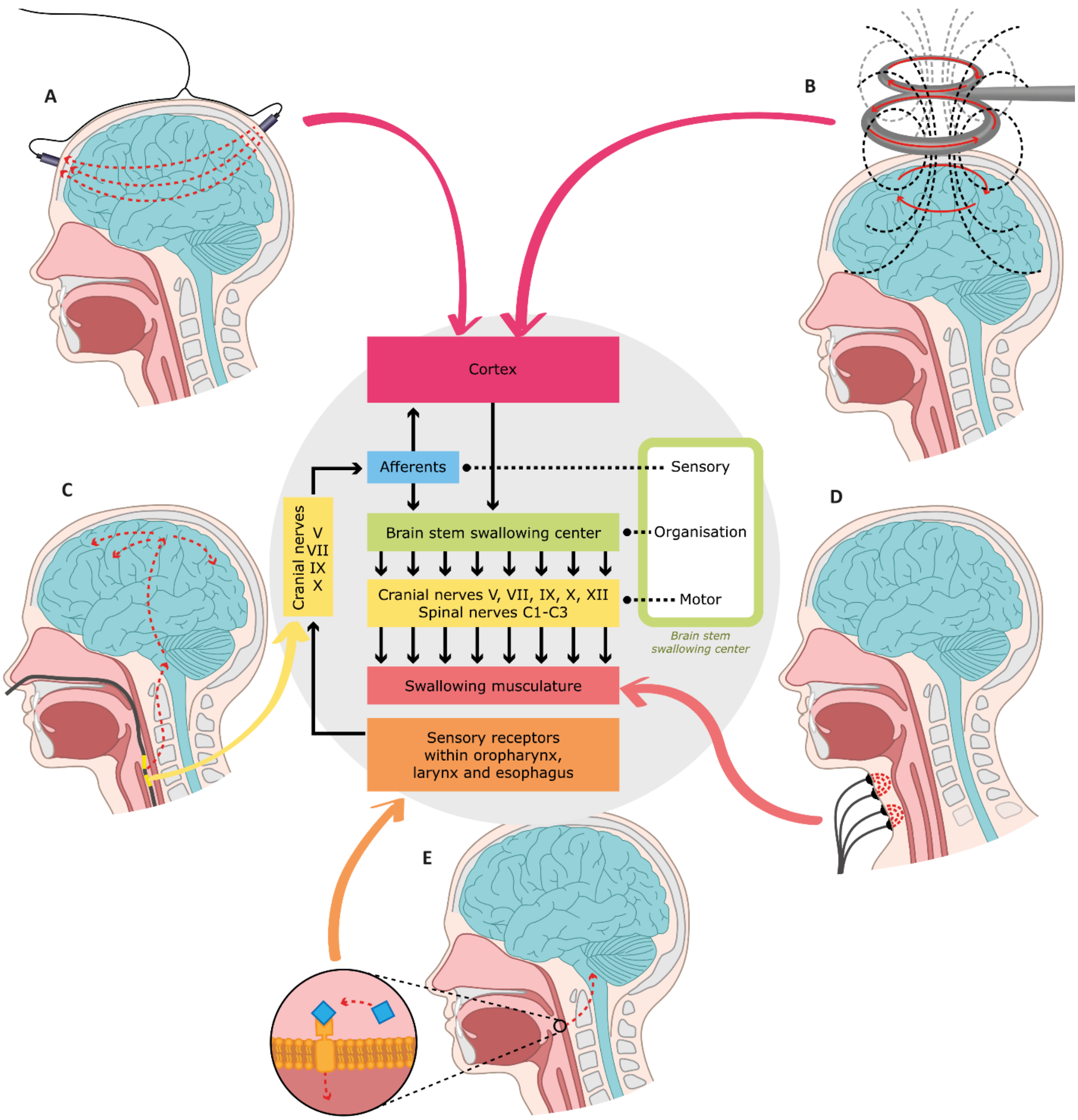

Figure 2: Illustration of innovative neuromodulatory dysphagia therapies and their mechanistic targets in the neuromuscular process of swallowing. A: Transcranial direct current stimulation: A direct current is applied to the brain inducing neuroplasticity. B: repetitive transcranial magnetic simulation: A strong, pulsating magnetic field and the associated electric field affect cortical excitability and induces neuroplasticity. C: Pharyngeal electrical stimulation: A sensory stimulus is set by electrical stimulation in the pharynx. This is transmitted via the sensory cranial nerves and triggers secondary neuroplasticity processes and modulates motor swallowing. D: Neuromuscular Electrical Stimulation: The swallowing muscles are electrically stimulated. E: Pharmacological treatment with capsaicin: Via stimulation of the TRPV-1 sensory receptor, sensory nerves are stimulated, which is centrally transmitted via the cranial nerves and triggers secondary neuroplasticity processes that modulate motor swallowing. For a comprehensive depiction of the neuromuscular process of swallowing, encompassing the anatomy of the central swallowing network, we refer to the following article[11].

Transcranial direct current stimulation (tDCS): TDCS in stroke swallowing-rehabilitation was addressed by various recent meta-analyses that all suggest a positive effect of tDCS on swallowing function[12,63–73]. Partially different results were found in subgroup analysis of stimulation localisations. In one meta-analysis, positive effects were found for ipsilesional, contralesional, or bilateral anodal (excitatory) stimulation, with a greater effect when the contralesional side was stimulated[63]. In another meta-analysis, only contralesional excitatory stimulation was reported to improve dysphagia[68]. In contrast, a further meta-analysis concluded that stimulation of the ipsilesional side showed a more pronounced effect[65]. Yet another meta-analysis found no differences between groups[64]. Individual studies suggest that tDCS also has a positive effect on dysphagia in brainstem strokes[74,75] and thus improvement in swallowing function in these patients may also be mediated by promoting cortical neuroplasticity.

Repetitive transcranial magnetic stimulation (rTMS): Various recent meta-analyses conclude that rTMS improves swallowing function[12,40,66–70,76–82]. Within the subgroup analysis, they report either no differences for specific stimulation locations or the hemisphere[76,78,80] or a tendency to a better effect with high-frequency stimulation on the ipsilesional side[68,82]. In addition, results from recent RCTs suggest that stimulation of the cerebellum also leads to an improvement in dysphagia[83–85] and that the therapeutic effect of rTMS may be moderated by the structural integrity of the corticobulbar tract[86].

Neuromuscular electrical stimulation (NMES): Recent meta-analyses suggested a therapeutic effect of NMES on swallowing function[12,66,70,72,87,88]. In a RCT with a total of 31 stroke patients from Korea, different electrode placement schemes were investigated. The results suggest that horizontally placed electrodes on the suprahyoid and infrahyoid muscles achieved the best therapeutic effects compared to vertical placement of the electrodes[89]. In another RCT involving 26 stroke patients from Korea, there was a tendency toward reduced penetration and aspiration in those with suprahyoid compared to infrahyoid electrode placement[90]. No differences in overall dysphagia severity as determined by VFSS were observed in a further RCT with a total of 40 stroke patients from Korea and additionally stimulation of the masseter muscle in the intervention group[91].

Pharyngeal electrical stimulation (PES): A recent meta-analysis summarising 6 RCTs revealed an improvement in swallowing function and an increased rate of nasal feeding tube removal associated with PES[92]. Another recent meta-analysis comprising 5 studies narrowly missed the statistical significance threshold for a positive effect of PES on swallowing function[12]. Nevertheless, a favourable impact on tracheostomy tube removal was observed in the analysis of tracheotomised patients, summarising 2 studies[12]. Two additional meta-analyses, each summarising 2 studies, did not identify therapeutic effects for PES (whereas decannulation was not considered)[66,70]. Conversely, in another meta-analysis that evaluated 8 studies with tracheotomised and non-tracheotomised patients combined, a statistically significant improvement of dysphagia with PES was reported, whereas decannulation success was considered a therapeutic effect[68]. Differentiating between critically ill, tracheotomised patients, and less severely affected non-tracheotomised patients may thus be crucial when assessing the therapeutic effect of PES. In line with this, a multicentre RCT involving 69 tracheotomised stroke patients from various European countries demonstrated a statistically significant higher decannulation rate of 49% in the intervention group compared to 9% in the control group[93]. In another RCT involving 60 post-extubation stroke patients from Germany who received stimulation within 4 hours after extubation, PES was associated with improved post-extubation dysphagia, reduced pneumonia incidence, decreased tube-feeding requirements at discharge, and a shorter hospital stay[94].

In summary, many RCTs are available for neurostimulation procedures, suggesting positive effects on swallowing function. Effects on other important outcome parameters such as aspiration pneumonia, tube-feeding or mortality are uncommonly reported. Furthermore, the question remains which of the methods used is most suitable for which patient groups. Two meta-analysis comparing the effects of the different neurostimulation methods conclude that rTMS has the greatest effect on swallowing function, ahead of NMES and tDCS, while no statistically significant effect was shown for PES[66,70]. Consistent with this, another meta-analysis focussing on tDCS and rTMS showed the best treatment effect for rTMS[67]. A further meta-analysis also showed the largest effect size for rTMS, followed by PES and tDCS, whereas NMES was not analysed[68]. One potential reason for the variation in the evaluation of PES is that, in addition to focusing on swallowing scores, the latter meta-analysis also took decannulation into account as an outcome parameter. In the same meta-analysis, the effect of non-invasive brain stimulation methods was examined depending on the stimulation localisation. Here, the greatest effect was seen with bilateral stimulation. For unilateral stimulation, the results differed between tDCS and TMS, with a larger effect on the ipsilesional side for TMS and a statistically significant effect for tDCS only on the contralesional side. A recent RCT involving a total of 40 stroke patients from Turkey further suggests that the combined use of rTMS and NMES may result in an additional positive therapeutic response[95]. Possible reasons for the partially contradictory study results are differences in stimulation frequency, localisation of the application, stimulation targets, duration and repetitions of the study protocols and variations in the patient cohorts. Moreover, there are different and partly contradictory theoretical models of compensatory neuroplasticity as a recovery mechanism of dysphagia, leading to different stimulation protocols (illustrated in figure 2). Due to the partially conflicting data, further studies are needed to obtain conclusive results on the detailed stimulation protocols regarding the central stimulation strategies.

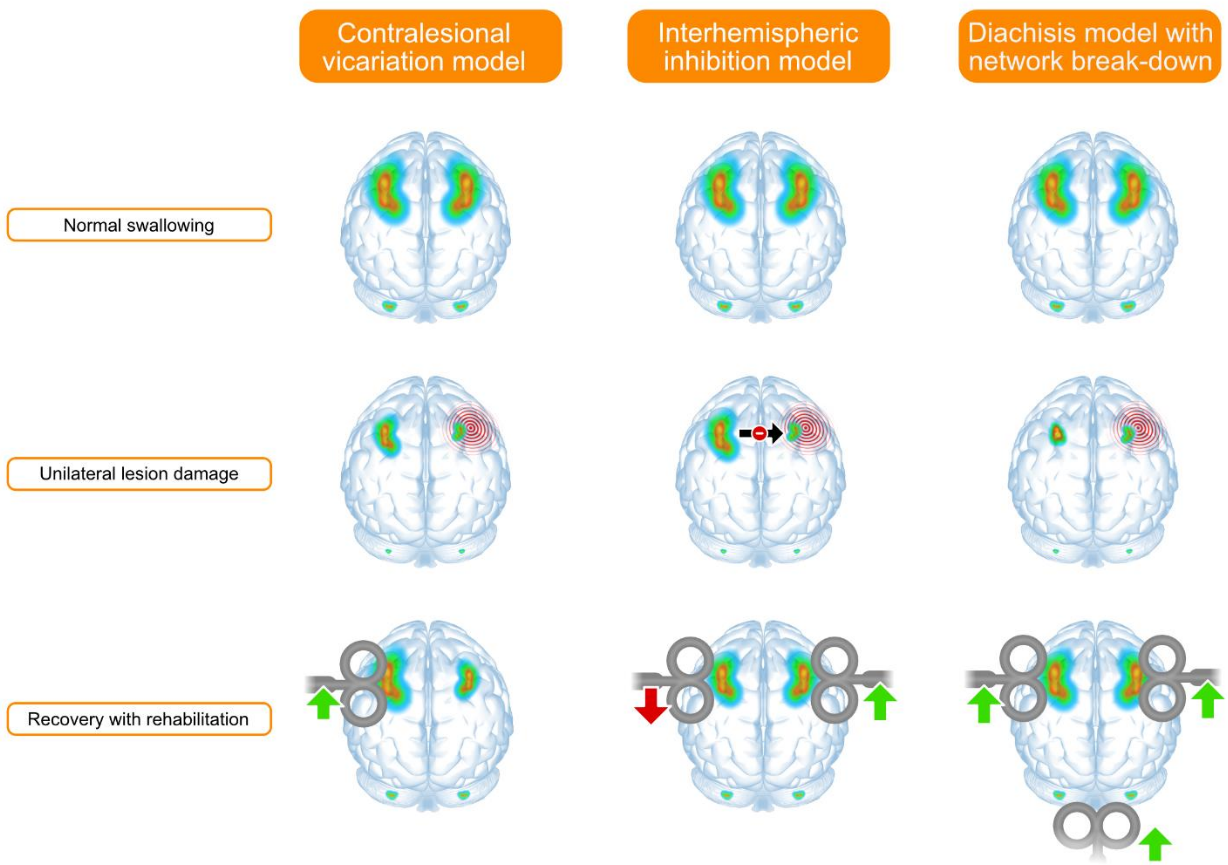

Figure 3: Different models of recovery of dysphagia after unilateral stroke and the corresponding non-invasive brain stimulation protocols to promote neuroplasticity. In the healthy brain, swallowing is represented bilaterally in the sensorimotor cortex and the cerebellum (coloured area with increasing activity from green to yellow). Contralesional vicariation model: After unilateral stroke (red circles), the swallowing network is disrupted. According to the model,

recovery of swallowing function is essentially driven by neuroplasticity in the contralateral hemisphere. Therefore, excitatory contralesional stimulation promotes rehabilitation of dysphagia. Interhemispheric inhibition model: The contralesional hemisphere exerts inhibition over the ipsilesional hemisphere. Therefore, according to the model, inhibitory stimulation in the contralesional hemisphere or excitatory stimulation in the ipsilesional hemisphere may promote recovery of dysphagia. Diaschisis model with total network break-down: The stroke lesion causes extensive breakdown of the swallowing network. According to the model, bilateral excitatory stimulation or excitatory stimulation of the cerebellum can support the restoration of the swallowing network.

From a pragmatic point of view and considering the methodological advantages and disadvantages of the various procedures, further conclusions can be drawn about their suitability for certain patient groups: PES, without the need for patient cooperation, is particularly suitable for tracheotomised and severely affected stroke patients with pharyngeal hypoaesthesia and delayed swallowing reflex. TDCS and NMES work well as adjunctive treatments with behavioural interventions, requiring patient cooperation. In contrast, rTMS, while suitable for non-cooperative patients in principle as well as in adjunct to behavioural interventions, is technically demanding and typically requires transport to a specialised facility. It may therefore be considered for patients with limited cooperation but stable conditions.

Conclusions and future directions:

Dysphagia is highly prevalent in stroke patients and associated with severe complications. Therefore, early management of post-stroke dysphagia is mandatory to reduce mortality and improve patient's quality of life. Currently, there are various basic therapies available that should be applied on a large scale. In addition, there are add-on therapies with increasing evidence that should currently be used particularly within a clinical trial setting.

Therapeutically, the established basic interventions aim primarily at avoiding the complications of dysphagia, without targeting swallowing function itself. These include interventions to improve oral health and reduce the load of respiratory pathogens in the oral cavity. Dietary interventions to adjust bolus consistencies target swallowing safety, aiming to prevent aspiration and are used to start early swallowing training. Monitoring nutritional status and supplemental or substitutive oral or enteral nourishment can prevent malnutrition. In addition, there are several behavioural therapeutic exercise methods with either a compensatory mechanism or aiming to improve swallowing function in the long term. In recent years, different stimulation procedures have emerged that aim to trigger and promote neuroplasticity processes. These include direct brain stimulation methods such as tDCS or rTMS, but also peripheral stimulation interventions such as PES and NMES. Several studies have shown promising results with evidence of improvement in swallowing function for all these procedures. However, high-quality studies showing effects on other more clinically relevant outcome parameters such as pneumonia, functional outcome or mortality are widely lacking. Besides neurostimulation, pharmacological agents, particularly capsaicin, have shown promising study results suggesting improvement of swallowing function or cough facilitated by pharmacological sensory stimulation. Figure 3 outlines the recommended key points and time periods for utilising the different dysphagia therapies as part of holistic dysphagia management.

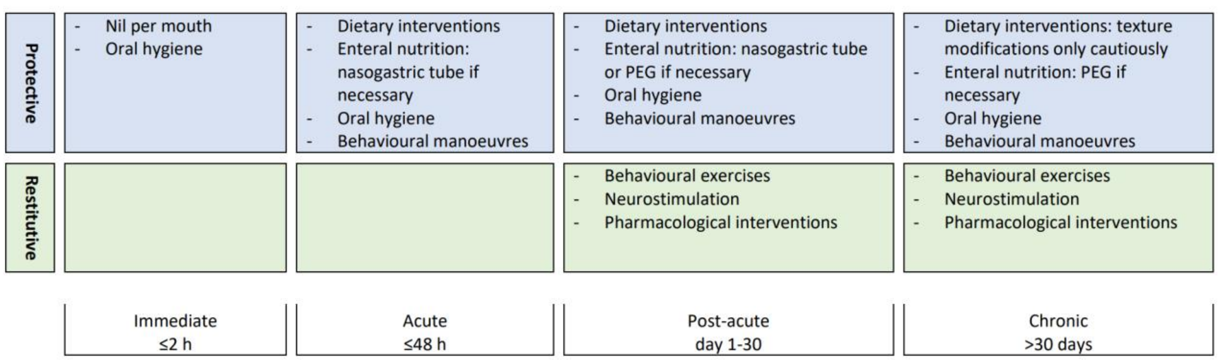

Figure 4: Periods in the course of the disease with appropriate dysphagia therapies as part of holistic dysphagia management: In the acute phase of the disease, protective measures with a focus on complication prevention prevail due to the high complication rate in the early course of the disease. Enteral nutrition should be provided with a nasogastric tube, as dysphagia may recover. In the post-acute and chronic stages, the full armamentarium of dysphagia therapies, including restitutive measures to improve swallowing function, should be used. Enteral nutrition for chronic dysphagia should be provided via percutaneous endoscopic gastrostomy (PEG). Dietary measures should be used with caution in the chronic phase due to the risk of adverse effects with long-term use.

The localisation, directionality, and hemispheric coordination of the swallowing network in the context of dysphagia rehabilitation is not yet fully understood. To date, this limits the optimisation of neuromodulation procedures, leading to a variety of stimulation protocols and thus to non-comparable or inconsistent study results[96]. In addition, factors such as the lack of clearly defined responsibilities regarding who can or should perform these applications, concerns related to recognised risks such as induced epileptic seizures with tDCS and rTMS, regulatory barriers, and lack of industry interest have hindered further dissemination. Nevertheless, from a mechanistic perspective, the rehabilitation potential mediated by neuroplasticity is particularly high given the bilateral central representation of swallowing. Increasing and detailed understanding of central control and neuroplasticity in dysphagia rehabilitation will drive further improvement of neurostimulation. To this end, combined clinical and neuro-imaging studies will be crucial in the future.

Furthermore, it is important that evidence-based therapeutic methods find their way into clinical practice. In this context, the increasing implementation of instrumental diagnostics allows to characterise the dysphagia phenotype, providing insights into the mechanistic patterns of swallowing impairment[97]. Notably, dysphagia observed in medulla oblongata stroke, in contrast to supratentorial infarcts, often presents with clustered residue in the piriform sinus[97]. This distinctive feature may be attributed to hypercontractility of the upper oesophageal sphincter. For patients falling within this subgroup exhibiting such a specific pathology, targeted interventions aimed at mitigating the hypercontractility of the upper oesophageal sphincter, such as surgical interventions[98], could potentially yield relevant clinical benefits. In addition to incorporating the dysphagia phenotype, future advancements will likely lead to a more detailed characterisation of the individual etiological factors contributing to dysphagia. This nuanced understanding will play a crucial role in tailoring appropriate therapeutic interventions. Thus, age-related changes in swallowing function may occur in the form of presbyphagia[99]. Accordingly, in stroke patients, sarcopenia and/or reduced swallowing muscle volume have been identified as crucial mechanisms of dysphagia and its recovery in various studies[100–103]. Specifically, in cases of delayed onset of dysphagia occurring more than 7 days after stroke, sarcopenia could possibly represent the leading dysphagia mechanism[100]. For patients with (additional) sarcopenic aetiology of dysphagia, whole-body muscle programs may be effective in dysphagia rehabilitation, as suggested by a retrospective Japanese study that found an association between improved food intake levels and the frequency of chair-stand exercises in 148 stroke patients[104]. Thus, future studies will consider the phenotypic and etiologic subset of dysphagia and help to promote individualised and mechanistic therapies. The outlined progress will enhance dysphagia therapy, leading to a reduction in the serious complications, decreased mortality, and improved quality of life for patients.

Contributors

BL: conceptualisation, literature search, visualisation, writing the original draft; EM: literature search, writing (review & editing); MTG: literature search, writing (review & editing); SSK: writing (review & editing); PM: writing (review & editing); PB: literature search, writing (review & editing); RD: conceptualisation, literature search, visualisation, writing (review & editing).

Declaration of interests

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