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REVIEW

The Cortical and Subcortical Neural Control of Swallowing: A Narrative Review

Kuo-Chang Wei[2,3] · Tyng-Guey Wang[1,2] · Ming-Yen Hsiao[1,2]

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Abstract

Swallowing is a sophisticated process involving the precise and timely coordination of the central and peripheral nervous systems, along with the musculatures of the oral cavity, pharynx, and airway. The role of the infratentorial neural structure, including the swallowing central pattern generator and cranial nerve nuclei, has been described in greater detail compared with both the cortical and subcortical neural structures. Nonetheless, accumulated data from analysis of swallowing performance in patients with different neurological diseases and conditions, along with results from neurophysiological studies of normal swallowing have gradually enhanced understanding of the role of cortical and subcortical neural structures in swallowing, potentially leading to the development of treatment modalities for patients suffering from dysphagia. This review article summarizes findings about the role of both cortical and subcortical neural structures in swallowing based on results from neurophysiological studies and studies of various neurological diseases. In sum, cortical regions are mainly in charge of initiation and coordination of swallowing after receiving afferent information, while subcortical structures including basal ganglia and thalamus are responsible for movement control and regulation during swallowing through the cortico-basal ganglia-thalamo-cortical loop. This article also presents how cortical and subcortical neural structures interact with each other to generate the swallowing response. In addition, we provided the updated evidence about the clinical applications and efficacy of neuromodulation techniques, including both non-invasive brain stimulation and deep brain stimulation on dysphagia.

Keywords Deglutition disorder · Cerebral cortex · Neurophysiology

Introduction

Swallowing is a sophisticated process involving the precise and timely coordination of the central and peripheral nervous systems, along with the musculatures of the oral cavity, pharynx, and airway [1]. Basic physiological research has demonstrated that the swallowing central pattern generator (sCPG) and cranial nerve nuclei at the brainstem are critical to controlling and coordinating the swallowing process [2]. However, the role played by cortical and subcortical neural components in swallowing is less clearly understood when compared with the sCPG in the brainstem.

Clinical physiological research among stroke patients has further emphasized the importance of the brainstem's sCPG in normal swallowing. Stroke patients with brainstem lesions were found to have poorer outcomes in terms of safe oral feeding, possibly due to delayed or absent swallowing reflex leading to impaired airway protection and passage of food from the pharynx to the esophagus [3, 4]. Impaired sCPG and cranial nerve nuclei delays the swallowing reflex, with the oropharyngeal musculatures unable to contract with normal strength, timeliness, and coordination. However, the sCPG not only plays major role in involuntary swallowing by initiating the swallowing reflex but also receives various feedback and inputs from the supranuclear regions, including the somatosensory cortex, basal ganglia (BG), and thalamus [2]. Furthermore, clinical studies have revealed

✉ Ming-Yen Hsiao
myferrant@gmail.com

1 Department of Physical Medicine and Rehabilitation, College of Medicine, National Taiwan University, No. 7, Zhongshan South Road, Zhongzheng District, Taipei 100, Taiwan

2 Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, No. 7, Zhongshan South Road, Zhongzheng District, Taipei 100, Taiwan

3 Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital Jinshan Branch, New Taipei City, Taiwan

that patients with neurological diseases including cortical or subcortical stroke and Parkinson's disease have altered swallowing patterns, although the sCPG should be intact [5, 6]. While Albert et al. disclosed no significant correlation between stroke location and the occurrence of aspiration, the majority of lesion-symptom mapping studies found the correlation between the lesion sites and the presentation or prognosis of swallowing disturbance among patients with cortical or subcortical stroke [4, 5, 7–22]. Lesions including somatosensory and motor cortices, basal ganglia, insula, and internal capsules have been reported to cause dysphagia [23, 24]. These findings indicate the role of various cortical and subcortical neural structures in swallowing, in addition to sCPG.

In recent years, rapid advances in functional neuroimaging and neuromapping modalities have allowed researchers to further investigate how the human brain processes sensory and motor information. The development of modalities including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetoencephalography (MEG), electrocorticography (ECoG), and transcranial magnetic stimulation (TMS) has enabled a more comprehensive exploration of the neuroanatomy and neurophysiology of swallowing mediated by both cortical and subcortical structures [23–40]. fMRI and PET detect hemodynamic and metabolic changes correlating to neural activation triggered by swallowing [23, 27]. MEG captures the magnetic fields generated by synchronized neuronal currents [32]. ECoG detects the cortical potential generated by neural oscillatory activities and has disclosed the role of the cerebral cortex in both the motor and sensory components of voluntary swallowing [41, 42]. TMS enables direct activation of cortical neurons and was used to investigate the integrity of the corticospinal and corticobulbar tracts [43]. These developments have driven enhanced understanding of how these supranuclear neural structures interact in both normal swallowing and dysphagia. Therefore, this review article aims to provide a comprehensive summary of the functions of cerebral cortices, subcortical gray matter, and subcortical white matter in swallowing control based on results from clinical studies of various central nervous system disorders and neurophysiological studies investigating the neural control of swallowing.

Role of Cerebral Cortex in Swallowing

Information about the cortical control of swallowing was derived from animal studies, functional imaging studies of normal subjects, and, to a large extent, lesion studies of stroke patients. These lesion studies provide indirect indications of the role of cortical structures by demonstrating their impact on swallowing performance when damaged. However, further neurophysiological studies are necessary to precisely delineate the physiological functions of the cerebral cortex. This review article illustrates the potential contribution in swallowing of commonly reported cortical areas including sensorimotor cortices, insular cortex, parieto-temporal cortex, and cingulate cortex. These cortical regions are connected with subcortical structures including BG and the thalamus through white matter tracts, like periventricular white matter (PVWM) and corona radiata (CR). In addition, the internal capsule (IC) contains the corticobulbar tract connecting the cortical regions with the brainstem. Table 1 summarizes the main results of both neurophysiological and clinical lesion studies investigating the impact of the cerebral cortex in swallowing control, while Fig. 1 shows a schematic presentation of central nervous system (CNS) control in swallowing, with emphasis on the interplay between cortical and subcortical structures. Table 2 summarizes the potential roles of the cerebral cortex in swallowing based on the knowledge of neurophysiology.

Sensorimotor Cortices

The sensorimotor cortex is composed of primary motor and primary sensory cortices. The topographic organization of the sensorimotor cortex, called the motor and sensory homunculus, contains motor or sensory representations of certain body parts, including those used in swallowing, such as the face, lips, teeth, gums, jaw, tongue, larynx, and pharynx [87–91]. Through the corticobulbar tract, which connects the cortical regions with the brainstem, the sensorimotor cortex initiates voluntary swallowing by activating and providing cortical inputs to the sCPG and receives afferent inputs from cranial nerve nuclei at the brainstem. [92–95]

Sensory inputs from the oral, laryngeal, pharyngeal, and esophageal areas have been shown to activate the primary sensory cortex, and this sensory information is important in providing biofeedback to ensure safe swallowing [79]. Among patients with impaired cortical sensory input due to oropharyngeal anesthesia, swallowing could still be generated by the brainstem but the swallowing response was less coordinated due to loss of cortical modulation to the sCPG [58]. Several studies have found a relationship between impaired somatosensory cortices in stroke patients and the occurrence of dysphagia [5, 10, 11]. Wilmsskoetter et al. found that impaired laryngeal vestibular closure and excessive pharyngeal residue are associated with lesions in the postcentral gyrus, while impaired laryngeal elevation is associated with lesions in the precentral gyrus [5]. In addition, lesion mapping analysis revealed that the only region that was predictive for severe dysphagia was the right postcentral gyrus, the primary sensory area for swallowing. [10]

One 2007 study investigated the influence of primary motor cortex inhibition on swallowing, using TMS to create

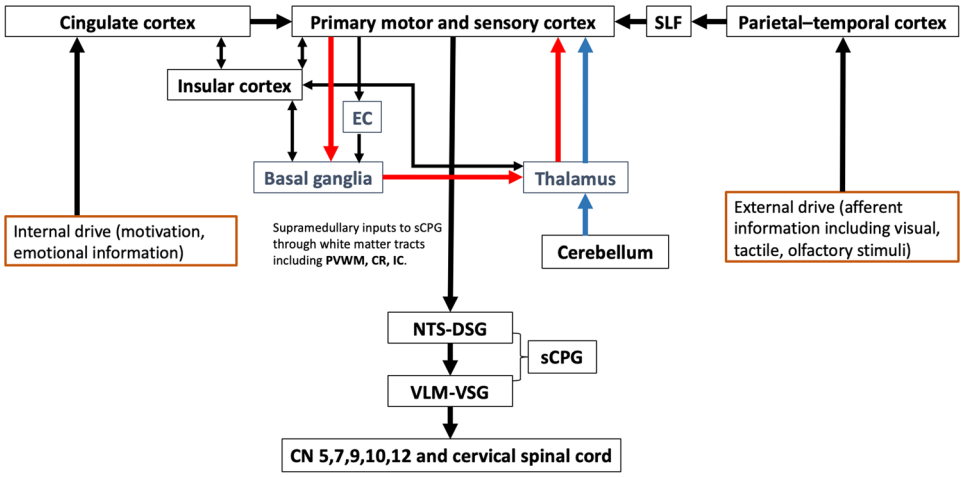

Fig. 1 A schematic figure showing the interplay between cortical and subcortical neural structures and the sCPG. Note the sCPG could be divided into dorsal (NTS-DSG, nucleus tractus solitarius-dorsal swallowing group) and ventral (VLM-VSG, ventrolateral medulla-ventral swallowing group) parts [44]. The NTS-DSG receives supramedullary inputs and further activates the VLM-VSG [44]. The VLM-VSG further controls motor neurons of cranial nerve nuclei at brainstem [44]. Also note that the cortico-striato-thalamo-cortical loop was presented with the red arrows and the cerebello-thalamo-cortical pathway was presented with the blue arrows

an artificial lesion on the primary motor cortex [57]. Investigators applied an inhibitory repetitive TMS protocol to both the stronger and weaker pharyngeal motor cortex of 13 healthy volunteers. A stronger pharyngeal motor cortex was defined as the pharyngeal motor cortex producing the largest consistent motor-evoked potential at the lowest stimulus threshold, while the contralateral pharyngeal cortex was defined as the weaker one. Each participant performed voluntary swallowing tasks following electrical cues. The timing of initiation of swallowing and change of pressure wave was recorded by a pressure transducer placed at the pharynx. The time from the electrical cue to the onset of swallowing was the swallow reaction time. Results showed that the swallowing reaction time decreased significantly if inhibitory TMS stimulation was applied to the stronger pharyngeal motor cortex. The authors asserted that the reduction of swallowing reaction time might be indicative of less controlled swallowing, causing poorer manipulation of bolus and higher risk of consequent aspiration [57]. More importantly, the results indicated that the pharyngeal motor cortex produces important inhibitory inputs to the brainstem that influence swallowing initiation and modulate voluntary swallowing behavior asymmetrically [57]. A recent study used intracranial electroencephalography to record the cortical oscillatory changes induced by swallowing at the orofacial motor cortex [41]. High-gamma activity bursts coincided with voluntary swallowing and soon decreased with the completion of voluntary swallowing, indicating that the motor cortex plays a crucial role in the initiation of voluntary swallowing [41]. Similarly, several other studies also found that the motor cortex participates in swallowing initiation, as do other cortical regions including the insular cortex, cingulated cortex, and supplementary motor area, and provide significant inhibitory input to the brainstem. [26, 39, 46, 48, 49, 57, 59, 96]

Based on findings from neurophysiology studies and studies of stroke patients, the sensorimotor cortices are in charge of the initiation and coordination of the swallowing process.

Parietal–Temporal Cortex

Despite the association between lesions in the posterior parietal and temporal lobes and dysphagia, the actual role of parietal–temporal cortex in swallowing has yet to be clearly identified [10–13]. These regions, including the supramarginal gyrus and angular gyrus, are traditionally known as sensory-motor integration areas, and process and relay afferent information to generate movement planning [97]. The temporal lobe was found to have a rich connection with the frontal lobe, occipital lobe, and thalamus, suggestive of its potentially integrative role for these regions [98].

Previous studies have reported the right parietal–temporal regions are related to impaired swallow response, indicated by aspiration or penetration or by poor cough reflex found during fiber-optic endoscopic evaluation of swallowing (FEES) and oropharyngeal residue [10, 11]. The results of these studies revealed the possible importance of parietal–temporal regions in relaying afferent sensory information to the swallowing motor network [10, 11]. In 2009, Steinhagen et al. found that patients with parieto-temporal infarction of either side were prone to attention deficits and those with left-side parieto-temporal infarction were more likely to have buccofacial apraxia, causing disturbance of orofacial movement during the oral stage of swallowing

Table 1 Summary of demographic data and results of studies

Author, year	Study groups	Neuroimaging or neurophysiological modality	Swallowing assessment	Main results
Neurophysiological studies in healthy volunteers				
Levine, 1992 [45]	49 healthy subjects	MRI	VFSS	Longer total swallowing duration and OTT for semisolids were found in subjects with more severe white matter lesions
Hamdy, 1999 [26]	8 healthy subjects	PET/TMS	NA	Increased regional cerebral blood flow was detected at bilateral caudolateral SMC, right ant. insula, right orbitofrontal and temporopolar cortex, left mesial premotor cortex, left temporopolar cortex, amygdala, left superiomedial cerebellum, and dorsal brainstem during swallowing process TMS mapping showed interhemispheric asymmetries in the motor representation for pharynx supported PET findings
Hamdy, 1999 [39]	10 healthy subjects	fMRI	NA	ACT of caudal SMC, ant. insula, premotor cortex, frontal operculum, ant. cingulate and prefrontal cortex, anterolateral and posterior parietal cortex, and precuneus and superiomedial temporal cortex was observed during swallowing
Mosier, 1999 [46]	8 healthy subjects	fMRI	NA	Bilateral ACT of primary motor cortex, primary somatosensory cortex, SMA, prefrontal cortex, superior temporal gyrus, insular cortex, transverse temporal gyrus, cingulate gyrus, thalamus, and internal capsule was observed during swallowing 63% of subjects showed left hemispheric dominance of cortical activation
Mosier, 1999 [47]	8 healthy subjects	fMRI	NA	ACT was observed in primary motor and sensory cortices, motor processing and association areas, including insular cortex and subcortical sites More subjects showed left hemispheric dominance, while stronger lateralization was seen in subjects with right hemispheric dominance
Martin, 2001 [48]	14 healthy females	fMRI	NA	Automatic and volitional swallowing produced ACT at lateral precentral gyrus, lateral postcentral gyrus, and right insula

Table 1 (continued)

Author, year	Study groups	Neuroimaging or neurophysiological modality	Swallowing assessment	Main results
Mosier, 2001 [49]	8 healthy subjects	fMRI	NA	ACT of SMC, cingulate gyrus, inf. frontal gyrus, corpus callosum, BG, thalamus, premotor cortex, post. parietal cortex, cerebellum, and insula was recorded while performing swallowing tasks The insular loop and cerebellar loop are two parallel pathways controlling voluntary swallowing
Kern, 2001 [50]	14 healthy subjects	fMRI	NA	ACC, motor/premotor cortex, insula, and occipital/parietal regions were activated with swallowing
Hartnick, 2001 [51]	2 healthy adults and 4 healthy children	fMRI	NA	ACT at pre- and postcentral gyrus, superior motor cortex, insula, inf. frontal cortex, Heschl's gyrus, BG and sup. temporal gyrus was observed during swallowing
Kern, 2001 [52]	8 healthy subjects	fMRI	NA	Reflexive swallowing showed ACT at bil. primary SMC Volitional swallowing showed ACT at bil. insula, prefrontal, cingulate and parietooccipital regions and bil. primary SMC During volitional swallowing, the total activated volume in the right hemisphere was significantly larger than left hemisphere
Dziewas, 2003 [30]	10 healthy subjects	MEG	NA	Left-side ACT of primary SMC was observed during volitional water swallowing Act of left insula and frontal operculum was observed with preparation and execution of volitional water swallowing
Suzuki, 2003 [53]	11 healthy subjects	fMRI	NA	ACT induced by swallowing was observed at SMC, insula, cerebellum, putamen, globus pallidus, thalamus, ACC, SMA, superior temporal gyrus, substantia nigra
Watanabe, 2004 [33]	9 healthy subjects	MEG	NA	ACT at insular cortex was long lasting before the initiation of swallowing
Martin, 2004 [54]	14 healthy subjects	fMRI	NA	Left pericentral and ant. parietal cortex, rostral ACC, precuneus and right parietal operculum/insula were activated by swallowing Greater ACT at ACC, SMA, right precentral and postcentral gyri, premotor cortex, right putamen, and thalamus was induced by tongue elevation compared with swallowing

Table 1 (continued)

Author, year	Study groups	Neuroimaging or neurophysiological modality	Swallowing assessment	Main results
Toogood, 2005 [55]	8 healthy subjects	fMRI	NA	ACT of the precentral gyrus, postcentral gyrus, and ACC and insula were specifically related to the act of swallowing ACT associated with voluntary swallowing was located at the intermediate and caudal regions of ACC
Daniels, 2006 [56]	38 healthy subjects	NA	VFSS	The left hemisphere task induced a decrease in swallowing volume, while the right hemisphere task reduced swallowing rate
Mistry, 2007 [57]	13 healthy subjects	rTMS	Swallow reaction time obtained by pressure transducer	Inhibited pharyngeal motor cortex leads to quicker but less controlled swallowing process
Teismann, 2007 [58]	10 healthy subjects with or without topical oropharyngeal anesthesia	MEG	NA	Normal swallowing induced bilateral ACT of the mid-lateral primary SMC Oropharyngeal anesthesia led to a pronounced decrease of both sensory and motor ACT
Malandraki, 2009 [59]	10 healthy subjects	fMRI	NA	Areas activated during throat clearing included post. insula and small portions of post- and precentral gyri bilaterally
Peck, 2010 [60]	10 healthy subjects	fMRI	NA	ACT at inferior frontal gyrus, inferior parietal lobe, insula, middle frontal gyrus, pre- and postcentral gyrus, supramarginal gyrus, and superior temporal gyrus was noted during dry, Mendelsohn and effortful swallowing tasks with differing degrees of symmetry between two hemispheres
Mistry, 2011 [61]	13 healthy subjects	fMRI	NA	Asymmetric pharyngeal motor representation (lateralised dominance) was found according to TMS data Right lateralized ACT of primary motor cortex was observed with water swallowing Left-lateralized ACT of premotor cortex and SMA was observed with tongue elevation and saliva swallowing
Clinical lesion studies				
Logemann, 1993 [62]	8 patients with left basal ganglion/internal capsule infarction and 8 normal objects	CT	Clinically and VFSS	Stroke patients were found to have longer PTT compared with normal objects

Table 1 (continued)

Author, year	Study groups	Neuroimaging or neurophysiological modality	Swallowing assessment	Main results
Robbins, 1993 [63]	40 ischemic stroke patients	CT/MRI	VFSS	More significant dysphagia was found among patients with right MCA stroke or lesions at superior branch of MCA A lack of labial, lingual, and mandibular coordination caused an extremely prolonged oral stage in a subset of patients with left hemispheric stroke
Daniels, 1996 [64]	16 ischemic stroke patients	CT/MRI	VFSS	Dysphagia was more severe in patients with right hemispheric stroke due to more prevalent delayed pharyngeal swallow and pharyngeal stasis
Daniels, 1997 [65]	4 stroke patients	CT	Clinically and VFSS	Ant. insula may be an important cortical substrate in swallowing
Satow, 2004 [38]	8 healthy subjects and 6 epilepsy patients	Scalp and epicortical EEG	NA	Bereitschaftspotentials for swallow was maximal at the midline vertex and asymmetrically distributed between two hemispheres
Gonzalez-Fernandez, 2008 [8]	29 acute stroke patients	MRI	Clinically	Adjusted odds ratio of dysphagia for patients with lesions at IC was significantly increased
Steinhagen, 2009 [12]	60 acute stroke patients	CT/MRI	Clinically or FEES	Frontal and parieto-temporal infarctions were associated with increased risk of attention deficits, buccofacial apraxia, and orofacial paresis BG and IC infarctions were associated with attention deficit and buccofacial apraxia Lateral medullary infarction caused impaired UES opening
Cola, 2010 [15]	20 acute subcortical stroke patients	MRI	VFSS	Lesions at left PVWM has more impact on swallowing behavior than right PVWM
Suntrup, 2012 [66]	30 patients with acute striatocapsular hemorrhage	CT	FEES	Swallowing impairment was observed in 76.7% of patients Predominant finding of FEES exam was impaired oral motor control
Lin, 2012 [67]	25 Parkinsonism patients	NA	VFSS	Significantly longer PTT and delayed onset of pharyngeal swallowing were found among patients with Parkinsonism dysphagia and aspiration
Galovic, 2013 [20]	94 acute stroke patients	MRI	Clinically	Lesions at insular cortex and IC were associated with acute risk of aspiration after stroke

Table 1 (continued)

Author, year	Study groups	Neuroimaging or neurophysiological modality	Swallowing assessment	Main results
Maeshima, 2014 [68]	113 patients with thalamic hemorrhage	CT	Clinically	Abnormal bedside swallowing assessment was found among 55% of the enrolled patients
Suntrup, 2015 [10]	200 acute stroke patients	CT/MRI	FEES	Right precentral and postcentral gyri, opercular region, SMG, and SLF were associated with dysphagia, especially right postcentral gyrus
Ellerston, 2016 [69]	34 PD patients	NA	VFSS	VFSS showed reduced pharyngeal constriction and delay in airway closure
Kim, 2015 [70]	33 PD patients and 33 healthy subjects	NA	VFSS	PD patients showed reduced ant. hyoid displacement It took longer time for hyoid bone, epiglottis, and vocal folds to reach maximal displacement More peaks were observed at the velocity curves of hyoid bone
Galovic, 2016 [71]	119 acute stroke patients	MRI	Clinically and tube-dependent state	Stroke lesions at ant.insular cortex was associated with tube dependency Stroke lesions at Rolandic operculum, insular cortex, sup. CR, putamen, SLF, and EC were associated with impaired oral intake (indicated by FOIS scale)
Suntrup, 2017 [11]	200 acute stroke patients	CT/MRI	FEES	Right parieto-temporal area associated with increased residue and delayed or absent triggering of swallowing response Right limbic structures and left sensory areas associated with cough reflex disturbance
Jang, 2017 [18]	82 chronic stroke patients	MRI	VFSS	Delayed OTT was associated with lesions at left inf. frontal lobe and precentral gyrus Delayed pharyngeal transit time was associated with lesions at right BG and CR Aspiration was associated with lesions at putamen
Galovic, 2017 [72]	62 acute stroke patients	MRI	Clinically and FEES	Prolonged impaired oral intake (indicated by FOIS scale) > 4 weeks was associated with lesions at ant. insula Impaired oral intake (indicated by FOIS scale) lasting > 1 week was associated with lesions at sup. CR and SLF, EC, and putamen to a lesser extent, with fibers connected with thalamus, primary motor, and SMA and the BG

Table 1 (continued)

Author, year	Study groups	Neuroimaging or neurophysiological modality	Swallowing assessment	Main results
Moon, 2017 [73]	63 older patients with mild stroke	MRI	VFSS	OTT increased as severity of white matter lesion (Fazekas grade) increased Presence of penetration could be predicted by severity of white matter lesion (Fazekas grade)
Fandler, 2017 [74]	332 patients with subcortical stroke	MRI	Clinically	Risk factors for swallowing dysfunction included higher NIHSS score, pontine infarction, and more severe white matter hyperintensities
May, 2017 [75]	18 ischemic stroke patients	MRI	VFSS	Pharyngeal swallowing mechanics differed more significantly in patients with right hemispheric stroke compared with left hemispheric stroke
Wilmskoetter, 2018 [22]	46 ischemic stroke patients	MRI	VFSS	Worse pharyngeal impairment and PAS score were found in patients with right hemispheric stroke
Wilmskoetter, 2019 [5]	68 ischemic stroke patients	MRI	VFSS	Significant correlation between lesion at thalamus and ant. hyoid excursion was found Right precentral gyrus, right ant. and post. insula, right sup. CR, and right SLF were associated with impaired laryngeal elevation Left postcentral gyrus, left SMG, right ant. and post. insula, right sup. CR, and right EC were associated with impaired laryngeal vestibular closure Right postcentral gyrus, right SMG, right AG, right sup. temporal gyrus, right sup. CR, right post. CR, right tapetum, post. limb of right IC, retrolenticular part of right IC, right SLF, right post. insula, and right post. sup. temporal gyrus were associated with increased pharyngeal residue Lesions at right precentral gyrus, right postcentral gyrus, right SLF, and right SMG were associated with higher PAS scale
Moon, 2019 [16]	88 ischemic stroke patients	MRI	VFSS	Involvement of corticobulbar tract in white matter lesion was associated with prolonged PTT

Table 1 (continued)

Author, year	Study groups	Neuroimaging or neurophysiological modality	Swallowing assessment	Main results
Kim, 2019 [21]	59 stroke patients with dysphagia	MRI	Clinically and VFSS	Lesions at both post. limb of IC and caudate nucleus were associated with longer recovery time from dysphagia
Lee, 2019 [76]	23 PD patients, 23 elderly healthy subjects, 23 young subjects	NA	VFSS	PD patients were found with decreased horizontal HD and HV during the initial backward and forward motions
Schiffer, 2019 [77]	68 PD patients and 48 healthy subjects	NA	VFSS	Slower initiation of airway closure and a delay in relaxation of hyoid elevation during swallow were found in PD patients
Lee, 2020 [19]	137 stroke patients	MRI	Clinically and VFSS	Initial dysphagia severity and bil. lesions at CR, BG, and IC were found to be prognostic factors for 6-month swallowing recovery
Lapa, 2020 [78]	12 patients with ET and bil. VIM-DBS reporting dysphagia	NA	Clinically and FEES	With DBS turned on, all patients had dysphagia. While with DBS turned off, the swallowing function of all patients improved
Hashimoto, 2021 [41]	8 epileptic participants	EEG	NA	High-gamma activity bursts were found with voluntary swallowing and the bursts soon decreased with the completion of voluntary swallowing
Kim, 2022 [17]	100 acute or subacute stroke patients	MRI	VFSS	Lesions at right lentiform nucleus of the BG and right CR beneath right mid. frontal gyrus were associated with the development of cricopharyngeal dysfunction

ACC anterior cingulate cortex; *ACT* activation; *AG* angular gyrus; ant., anterior; *BG* basal ganglia; bil., bilateral; *CR* corona radiata; *CT* computed tomography; *DBS* deep brain stimulation; *EC* external capsule; *EEG* electroencephalography; *ET* essential tremor; *fMRI* functional magnetic resonance imaging; *FEES* fiber-optic endoscopic evaluation of swallowing; *IC* internal capsule; *MCA* middle cerebral artery; *MEG* magnetoencephalography; Mid, middle; MRI, magnetic resonance imaging; NA, not available; OTT, oral transit time; *PAS* penetration-aspiration scale; *PD* Parkinson's disease; *PET* positron emission tomography; post., posterior; *PTT* pharyngeal transit time; *PVWM* periventricular white matter; sup., superior; *SLF* superior longitudinal fasciculus; *SMA* supplementary motor area; *SMC* sensorimotor cortex; *SMG* supramarginal gyrus; *TMS* transcranial magnetic stimulation; *VIM* ventral intermediate nucleus

Table 2 Summarized information about the role of cerebral cortices, subcortical gray matter, and subcortical white matter in swallowing

Summarized information about the role of cerebral cortices in swallowing		
Cortical regions	Potential roles in swallowing	Reference
Primary motor cortex	Initiation of voluntary swallowing	[26, 39, 41, 57, 48, 49, 59, 46]
Primary sensory cortex	Provides cortical modulation to the sCPG and biofeedback to ensure safe and coordinated swallowing	[79, 58]
Parietal–temporal cortex	Relays afferent sensory information to swallowing motor network to generate movement planning of swallowing	[10, 11]
Insular cortex	Acts as the central integration hub of the swallowing network and participates in motivation and initiation of swallowing and motor planning	[13, 33, 47–50, 81, 82, 54, 50, 47, 80–82]
Cingulate cortex	The ACT of ACC might be indicative of visceromotor activity such as digestive function or affective/attentive response of swallowing The PCC integrates sensory information via reciprocal connection with the thalamus and might further modulate the swallowing motor response	[39]
Summarized information about the role of subcortical gray matter and white matter in swallowing		
Subcortical regions	Potential roles in swallowing	Reference
Basal ganglia	Movement control and coordination during swallowing	[83, 67, 69, 76, 77, 70]
Thalamus	Processes both sensory and motor inputs via the thalamo-cortical or the thalamostriatal pathways in swallowing	[5, 47, 72, 84, 85]
Periventricular white matter	Connects the cerebral cortex and cranial nerve nuclei at brainstem	[16]
Corona radiata	Coordinates the sCPG of the bulbar swallowing center through integration of both central and peripheral afferent signals	[17]
Internal capsule	Connects the cerebral cortex and the cranial nerve nuclei and the sCPG at brainstem via the corticobulbar tract at genu of IC	[8, 20]
Superior longitudinal fasciculus	Connects the temporal–parietal swallowing regions to the frontal motor areas	[13]
External capsule	Connects the SMC with the BG and therefore plays a role in motor control	[86]

ACC anterior cingulate cortex; *ACT* activation; *BG* basal ganglia; *IC* internal capsule; *PCC* posterior cingulate cortex; *sCPG* swallowing central pattern generator; *SMC* sensorimotor cortex

[12]. Furthermore, swallowing deficits including delayed or absent swallowing response, impaired laryngeal vestibular closure, and reduced hyolaryngeal excursion were more frequent among patients with parietal–temporal lesions. [13]

Insular Cortex

The insular cortex contains the primary gustatory cortex that encodes chemosensory information of food and may play a role in food preferences [80]. Moreover, insular cortex has abundant connectivity to both the cortical and subcortical brain regions [81]. Connections among the olfactory bulb, limbic system, sensory cortex, thalamus, frontal cortex, nucleus tractus solitarius, and insular cortex are both directly and indirectly related to swallowing and are implicated in functions including taste, the motivation, and initiation of swallowing and motor planning [81, 82]. For multifaceted involvement in swallowing, the insular cortex is considered to be a central integration hub of the swallowing network [13].

Several fMRI studies have shown the participation of the insular cortex in swallowing. Insular activation was found to be either bilateral or more significant in the right hemisphere [47–50, 53, 54]. The exact location of insula activated during swallowing has also been investigated but without definite conclusions. While Daniel et al. reported that the anterior insula (which directly connects to cortical and subcortical regions participating in the swallowing process) is particularly important in normal swallowing compared with posterior part, others have reported the posterior insula is activated during swallowing [48, 65]. Malandraki et al. suggested that the entire insular cortex plays a role in swallowing, with the posterior insula possibly being more activated in less voluntary and more autonomic actions, such as laryngeal closure [59]. The role of insular cortex in initiation of voluntary swallowing was suggested by Watanabe et al. [33]. In this study, long-lasting activation of insular cortex was detected by MEG before initiation of swallowing, suggesting that the activation of insular cortex might be crucial for initiation of swallowing. [33]

Clinically, stroke patients with impaired insular cortex might have prolonged dysphagia and thus be restricted from oral feeding. According to Galovic et al., stroke patients with impaired insular cortex were more often feeding tube

dependent within the first 48 h after stroke onset [71]. In 2017, a lesion mapping study investigated the severity of swallowing impairment using Functional Oral Intake Scale (FOIS) among stroke patients with a follow-up period up to 4 weeks after stroke [72]. This study demonstrated that lesions of the anterior insula are associated with impaired oral intake during the second to fourth week after stroke [72]. The impact of the integrity of the insular cortex on swallowing could be explained by its integrative nature, as the insula is connected to key regions involved in the initiation and execution of swallowing, including the sensorimotor cortices, thalamus, and nucleus tractus solitarius. [72, 81, 82]

Cingulate Cortex

Different parts of the anterior cingulate cortex (ACC) have different functions related to swallowing. The rostral part of the ACC can process painful stimuli, while the affective part processes emotion and attention to volitional actions [33]. On the other hand, the more dorsal and caudal parts are considered to be involved in movement regulation, response selection, and performance of willed action [99]. However, the exact role of the ACC in swallowing is not yet fully understood and the exact site of activation in the ACC during voluntary and involuntary swallowing remains unconfirmed. In 1999, two studies from the same research team reported that both the rostral and caudal ACC could be active during water swallowing [26, 39]. Martin et al. found the rostral ACC was activated during naïve saliva swallowing, while activation of the intermediate and caudal ACC was associated with voluntary saliva and water bolus swallowing [48]. This is consistent with a subsequent study by Toogood et al. [55]. Although not conclusive, these results suggest a functional partition of the ACC corresponding to voluntary versus involuntary aspects of swallowing tasks [59].

Malandraki et al. also found the posterior cingulate cortex (PCC) is active during throat clearing [59]. In addition, PCC was activated with a volitional swallowing task [39]. The PCC integrates sensory information via reciprocal connection with the thalamus [100]. Therefore, activation of this area in conjunction with other sensory areas (including the primary somatosensory cortex, thalamus, and precuneus) during swallowing might indicate that sensory information from the oropharyngeal area and esophagus is received and processed in these areas. Furthermore, these sensory information would modulate the motor response via connections with the motor cortex and the insula. [39]

Subcortical Regions Related to Swallowing

Daniels et al. created a neural anatomic model of swallowing involving the bilateral sensorimotor cortex with descending input to the medullary swallowing center [14]. Theoretically, disruption of the connection between cortical and subcortical structures like periventricular white matter (PVWM) would lower inputs to the brainstem. Clinical observations of post-stroke dysphagia have shown that impaired neural structures including the basal ganglia, internal capsule, thalamus and PVWM led to significant swallowing disturbance [15, 94]. Also, studies investigating the swallowing disturbance of Parkinson's disease (PD) noted the importance of the intact cortico-striatal-thalamic-cortical loop in normal swallowing [84]. The following text illustrates the potential contribution to swallowing of commonly reported subcortical structures, including BG, thalamus, PVWM, internal capsule, superior longitudinal fasciculus (SLF), and external capsule. Table 1 summarizes the main results of both neurophysiological and clinical lesion studies investigating the impact of subcortical neural structures in swallowing control. Table 2 summarizes the potential roles of subcortical neural structures in swallowing based on the knowledge of neurophysiology. Figure 1 presents the connection between the subcortical and cortical regions and the sCPG.

It should be stressed again that these lesion studies offer indirect evidence regarding the involvement of subcortical structures by showcasing the effects of their damage on swallowing performance. However, additional neurophysiological investigations are required to accurately outline the physiological functions of these structures.

Basal Ganglia

The basal ganglia (BG) is composed of interconnected nuclei including striatum, globus pallidus, subthalamic nucleus and substantia nigra located at midbrain. The BG plays a significant role in movement control, movement coordination, cognitive tasks, and limbic functions via integrating information from the cortical regions and conveying this information back to the cortical regions [101].

BG activation during swallowing has been demonstrated in several functional imaging studies [39, 51]. The brain activity of 10 healthy volunteers was recorded via fMRI, while drinking water in a study done by Hamdy et al. [39]. Although less consistent than that of the cerebral cortex, swallow-related activation was still detected at the putamen and caudate nucleus [39]. A study of pediatric brain activity found increased brain activity in both the putamen and globus pallidus when swallowing [51]. A 2004 study found activation of the right putamen and thalamus with voluntary tongue elevation [54].

Stroke patients with BG lesion were reported to have high incidence of swallowing disturbance and altered swallowing features. Suntrup et al. reported that 76.7% of patients with acute striatocapsular hemorrhage suffer from dysphagia [66]. The predominant feature of dysphagia was an impaired oral swallowing phase with premature leakage to the valleculae and piriform sinus [66]. Similarly, Steinhagen et al. found that basal ganglion infarctions were associated with buccofacial apraxia, leading to oral-phase dysphagia [12]. Logemann et al. found significantly prolonged pharyngeal transit time and less efficient swallowing among those with left basal ganglion infarction and noted increased oral residue and prolonged oral transit time [62]. Thus, impaired oral motor control may be a feature of swallowing disturbance among patients with BG lesions.

Dysphagia is highly prevalent among advanced PD patients, whose swallowing disturbance is possibly caused by BG dysfunction due to neuronal loss in the substantia Nigra [6]. VFSS findings of PD patients were consistent with the hallmark features of bradykinesia, hypokinesia, and difficulty in movement initiation [83], including reduced velocity of hyoid movement, prolonged swallowing time, and delayed airway closure [67, 69, 76]. Schiffer et al. reported prolonged hyoid elevation, possibly caused by delayed relaxation of suprahyoid muscle due to rigidity [77]. Moreover, increased peaks in the velocity curves of hyoid movement were found by Kim et al., which might represent incoordination of pharyngeal contractions [70]. While several studies showed decreased hyoid displacement among PD patients, the causal relationship between decreased hyoid displacement and aspiration was not significant [69, 70, 76]. On the other hand, sluggish and incoordinate hyoid movement might lead to aspiration in PD patients. [67, 83]

To sum up, BG controls and coordinates normal swallowing and its dysfunction might cause swallowing disturbance in both oral and pharyngeal phases.

Thalamus

The thalamus is responsible for relaying both sensory and motor information between cortical and subcortical neural structures and it is seen as contributing to sensory-motor integration during swallowing [47]. In the BG-thalamo-cortical loop, the sensory information of the swallowing process is conveyed by thalamus, while the BG monitors movement accuracy and progression [84, 85]. In a lesion-symptom mapping study using repetitive saliva and modified water swallowing tests, Maeshima et al. found that more than half of patients with thalamic hemorrhage had impaired swallowing efficiency or safety [68]. In 2017, Galovic et al. found an association between impaired oral intake (indicated by FOIS) lasting more than 7 days and the disrupted white matter tract, especially the projections fibers connecting thalamus and superior corona radiata [72]. Owing to the possible sensory-motor disintegration caused by disrupted thalamo-cortical fibers, prolonged oral phase of swallowing occurred [72]. Wilmskoetter et al. further investigated the relationship between acute stroke lesion locations and impairments of specific events in oropharyngeal swallowing evaluated by Modified Barium Swallow Study Impairment Profile (MBSImP) in VFSS [5]. Significant association between thalamic lesions and impaired anterior hyoid excursion was found, possibly due to sensory-motor disintegration caused by thalamic stroke [5].

In addition to the cortico-striato-thalamo-cortical loop, the thalamus might also affect the swallowing process through its connection with the cerebellum. The thalamus and the cortical areas were connected with the cerebellum via the cerebello-thalamo-cortical pathway. Deep brain stimulation (DBS) to the ventral intermediate nucleus could affect movement control of extremities and articulation, leading to gait ataxia and ataxic dysarthria [102–104]. In addition, a recent study found that DBS of the ventral intermediate nucleus could lead to dysphagic presentations including poor bolus control and early bolus transition from oral stage to pharyngeal stage [78]. These dysphagic presentations were attributed to a lack of coordination of the muscles of the oral cavity, possibly caused by stimulation of cerebellar-thalamic afferent fibers. [78]

Periventricular White Matter

PVWM are white matter tracts lying adjacent to the lateral ventricles of the brain. Bundles of white matter tracts that convey both motor and sensory information to cerebrum and spinal cord are contained in PVWM [105]. Currently, the role or significance of PVWM in swallowing remains unclear and there are few relevant studies. In 1992, Levine et al. investigated the impact of PVWM lesion on swallowing physiology, with VFSS showing significantly longer total swallowing duration and oral transit duration for semisolids in subjects with more severe white matter lesions [45]. In 2010, Cola et al. reported PVWM lesions among more than half of left subcortical stroke patients suffering from dysphagia [15]. Furthermore, Moon et al. suggest that PVWM lesion could be a prognostic predictor of swallowing function in elderly patients with mild stroke [73]. The severity of white matter lesions were graded using the Fazekas scale to build a prediction model using linear logistic regression analysis, with results indicating that Fazekas grade could effectively predict prolonged oral transit time and presence of penetration [73]. In a similar study including 332 patients, Fandler et al. found a higher Fazekas grade and pontine lesions to be risk factors for dysphagia [74]. Furthermore, Moon et al. found that PVWM lesions involving

the corticobulbar tract (CBT) are associated with insufficient laryngeal elevation and prolonged pharyngeal transit time [16]. Based on these study results, the location and severity of PVWM lesions may determine the type of swallowing disturbance. The abnormal VFSS findings of the pharyngeal phase of swallowing are possibly caused by the disrupted connections between the cortex and cranial nerve nuclei at the brainstem.

Corona Radiata (CR)

The corona radiata is composed of both ascending and descending fibers connecting the cortical area and internal capsule. Several studies of stroke patients have shown that an injured corona radiata could cause swallowing disturbance. In 2016, Galovic et al. found that the superior corona radiata was significantly associated with impaired oral intake [71]. A later another lesion mapping analysis done by the same team found that CR lesions are associated with prolonged impaired oral intake status as assessed by the FOIS scale [72]. In addition, patients with a larger proportion of damaged corona radiata were more likely to have impaired oral intake, specifically, the majority of patients had impaired oral intake when more than 50% of corona radiate were involved in stroke [72].

Several studies have suggested a possible association between the locations of CR lesions and specific impairments in swallowing physiology as determined by VFSS. However, the results of these studies have not been consistent [5, 17, 18]. Wilmskoetter et al. reported that impaired right superior CR was associated with impaired laryngeal elevation and laryngeal vestibular closure, while right superior and posterior CR was associated with increased pharyngeal residue [5]. Lesions at the anterior corona radiata beneath the right middle frontal gyrus were found to correlate significantly with cricopharyngeal dysfunction according to Kim et al. [17]. Jang et al. analyzed the relationship between brain lesion location and chronic dysphagia in patients with supratentorial stroke, finding that delayed pharyngeal transit time correlated with lesions in right corona radiata [18]. These findings could be explained by the potential role of the CR in coordinating the sCPG of the bulbar swallowing center through integration of both central and peripheral afferent signals [17].

In terms of prognosis, Lee et al. found that stroke lesions at the bilateral corona radiata, along with bilateral BG and internal capsules, were an indicator to predict 6-month swallowing recovery [19]. The authors' assumptions included diminished compensatory reorganization from the undamaged brain side and disruption of bilateral corticobulbar tracts, leading to possible severe pharyngeal paralysis [19].

Internal Capsule (IC)

Ascending and descending fibers, including the corticospinal tract and corticobulbar tracts extending caudally from the corona radiata, were contained in a somatotopical arrangement in the IC, with corticospinal tract localized at posterior limb and corticobulbar tract at genu of IC [106]. Stroke patients with IC lesions were reported to have a higher risk of swallowing disturbance. Gonzalez-Fernandez et al. discovered a strong correlation between IC stroke and dysphagia [8]. Galovic et al. reported that damage at the internal capsule leads to increased risk of acute aspiration after stroke [20]. In 2019, a MRI-based lesion mapping analysis done by Wilmskoetter et al. found an association between lesions at the right posterior limb and retrolenticular part of the internal capsule and increased pharyngeal residue [5]. Furthermore, as mentioned in the subsection Corona Radiata, bilateral lesions at the internal capsule, basal ganglia, and corona radiata significantly prognosticate 6-month swallowing recovery [19]. Similarly, Kim et al. reported that stroke patients with lesions at the posterior limb of the IC and caudate nucleus required longer recovery time from dysphagia [21]. Based on these data, the IC should be considered an integral part of the complex swallowing neural network. The connection between the cortex and cranial nerve nuclei at the brainstem is disrupted with a lesioned internal capsule, leading to dysphagia.

Superior Longitudinal Fasciculus (SLF)

The SLF is an association tract connecting the frontal, occipital, parietal, and temporal lobes and transmitting cortical neural signals across long and short distances [107]. Through the connection between different cortical sensorymotor regions (e.g., the supramarginal gyrus and premotor and prefrontal regions) it might play a significant role in motor control, including swallowing [13]. Currently, few studies have examined the role of SLF in the swallowing process. In 2015, Suntrup et al. evaluated the swallowing function of 200 stroke patients with FEES within 96 h from admission. 165 were diagnosed with dysphagia, with a significant correlation with lesion at the SLF [10]. Galovic et al. used voxel-based lesion-symptom mapping to investigate the association between lesion pattern and dysphagia [71, 72]. Lesion at the SLF was found to be significantly associated with both acute tube dependency (within 48 h of stroke onset) and persistence of impaired oral intake based on FOIS scale after 7 days of stroke onset [71, 72]. More recently, Wilmskoetter et al. investigated the relationship between stroke lesions and swallowing physiology assessed by VFSS using Modified Barium Swallow Study Impairment Profile

(MBSImP). Voxels at the right SLF were associated with impaired laryngeal elevation, increased pharyngeal residue, and higher penetration–aspiration scale (PAS) score. [5]

Although the exact underlying mechanism is unclear, dysphagia caused by impaired SLF might be the result of disrupted signal transmissions from the temporal–parietal swallowing regions to the frontal motor areas. [13]

External Capsule (EC)

The EC is composed of white matter fibers and is located between the putamen and claustrum, with potentially diverse physiological functions. Both cortico-cortical association fibers and striatal fibers connecting the primary sensorimotor cortex with the putamen were found in EC [86]. Therefore, EC is considered to be a key connection between the cortical motor regions and the basal ganglia, and it might contribute to the engagement of the basal ganglia in motor control. Several lesion-symptom mapping studies showed the relationship between damaged EC and swallowing impairment [5, 71, 72]. Galovic et al. found that lesion at the EC was significantly associated with impaired oral intake within 2 days or lasting more than one week [71, 72]. In addition, Wilmskoetter et al. used VFSS to identify an association between injured EC and impaired laryngeal elevation and impaired laryngeal vestibule closure [5].

Hemispheric Dominance of Swallowing Control

Hemispheric dominance, or functional lateralization, plays a crucial role in the efficient and rapid access of neural resources for variable tasks, including swallowing, by preventing interhemispheric neural conduction delay [108]. Studies using EEG, functional neuroimaging, and TMS have reported hemispheric dominance of swallowing control, with interhemispheric asymmetry of cortical representation of mylohyoid, pharyngeal, and esophageal musculature on the motor and premotor cortex [90, 109]. Both right and left hemispheric dominance have been reported by functional neuroimaging studies and the side of hemispheric dominance was different among individuals [26, 30, 38, 47, 48, 52, 54, 60]. Furthermore, the presentation of hemispheric dominance seemed related to the cortical regions activated during swallowing [39]. Hamdy et al. found a clear asymmetric activation of the right premotor cortex and insula during volitional swallowing but a more bilateral activation of sensorimotor areas [39]. Nonetheless, one functional near-infrared spectroscopy study displayed no lateralization effect during motor execution or in swallowing imagery [110].

Additionally, task-dependent hemispheric dominance of swallowing control was revealed by several neuroimaging studies [30, 47, 48, 56, 61, 111]. Kristine et al. showed that the hemispheric dominance noted during dry or wet swallows shifted alternatively between 6 out of 8 subjects [47]. In another study, right hemispheric dominance of insula activation was found only during voluntary saliva swallowing but not during naïve saliva and water bolus swallowing [48]. Mistry et al. showed that the primary motor cortex, predominantly right lateralized, was strongly activated during water swallowing [61]. By contrast, the activation of the premotor cortex and supplementary motor cortex was predominantly detected at the left hemisphere during tongue elevation and saliva swallowing [61]. Lastly, Daniels et al. used a modified dual-task paradigm to investigate whether the swallowing performance would be affected by left hemisphere- or right hemisphere-specific tasks [56]. The results showed that different components of swallowing showing differential lateralization [56]. Left hemisphere tasks reduced the volume of swallowing while right hemisphere tasks reduced the rate of swallowing [56]. These results indicate a task-dependent hemispheric dominance of swallowing control.

Furthermore, lesion-symptom mapping studies of stroke patients have shown that the side of the lesioned hemisphere is associated with the features or severity of dysphagia [5, 10, 11, 22, 63, 64, 75]. Right hemispheric stroke was possibly associated with impaired pharyngeal phase of swallowing and more severe dysphagia while left hemispheric stroke was associated with impaired oral phase [5, 63, 64, 75]. Nonetheless, impaired pharyngeal phase of swallowing could still be detected in a right hemispheric stroke, including increased pharyngeal stasis, delayed pharyngeal swallow, and reduced hyoid elevation [63, 64, 75], suggesting that both right and left cerebral networks are crucial for neural control of swallowing [5].

Plastic Change Induced by Non-invasive Brain Stimulation (NIBS) and Deep Brain Stimulation (DBS) and the Corresponding Clinical Implication

Neuroplasticity refers to the brain's ability to adaptively change its structure or function in response to intrinsic or extrinsic stimuli [112]. Plastic change of the motor cortex at the damaged hemisphere in stroke patients has been found to enable the recovery of swallowing function [113]. Available evidence indicates that non-invasive brain stimulation including repetitive TMS (rTMS) and transcranial direct current stimulation (tDCS) could induce neural plastic change in the pharyngeal motor cortex of normal subjects [57, 114, 115]. Furthermore, recently published meta-analysis has disclosed the positive effect induced by NIBS on recovery of dysphagia in stroke patients [116, 117]. Nonetheless, at present there is no available standard protocol or guideline

to provide the best treatment practices for patients suffering from post-stroke dysphagia. High-frequency rTMS stimulating the affected or unaffected motor cortex could improve swallowing function of patients with post-stroke dysphagia [118–121]. In addition, some studies have revealed that bilateral hemisphere high-frequency rTMS stimulation outperforms unilateral stimulation in terms of improving swallowing function [122, 123]. More specific investigation about the effect of stimulation frequency and stimulation hemisphere of unilateral rTMS for post-stroke dysphagia was done by Cheng et al. in a recently published meta-analysis [124]. The effect size of high-frequency rTMS over ipsilesional hemisphere was larger than low-frequency rTMS over contralesional hemisphere and high-frequency rTMS over contralesional hemisphere [124]. tDCS can improve swallowing in post-stroke dysphagia but may be inferior to rTMS in reducing aspiration risk [117]. The meta-analysis done by Cheng et al. disclosed that the anodal stimulation on contralesional hemisphere was superior to stimulation on ipsilesional hemisphere [124]. The discrepancy of the stimulation protocol between rTMS and tDCS could be explained by the bimodal balance recovery model of post-stroke neural plasticity [125]. In this model, if the damaged hemisphere has low structural reserve due to more severe damage, the input from the unaffected hemisphere is crucial to compensate for the lost function. Therefore, stimulatory NIBS applied on the unaffected hemisphere could lead to better functional outcome in this scenario [125]. On the other hand, it is possible that stimulatory NIBS applied on the damaged hemisphere or inhibitory NIBS applied on the contralesional hemisphere will lead to better outcome if the structural reserve is high [125, 126].

DBS has been applied in the treatment of various kinds of CNS diseases, including PD, essential tremor, and Alzheimer disease [126]. In addition to immediate response, DBS also produces persistent effects by inducing neuroplasticity [127, 128]. However, few studies have investigated the effects of DBS on swallowing function. A narrative review summarized the effects of DBS on swallowing function in PD patients [129], with a majority of the recruited studies showing positive effects of subthalamic nucleus (STN) DBS [129]. Improvements in both oral and pharyngeal phases were found. The possible underlying mechanism might be direct activation of the nigrostriatal dopaminergic pathway through activating the glutamatergic neurons in the STN and subsequent stimulation of substantia Nigra [130]. Other mechanisms, such as reversing the phenomenon of excessive beta oscillations and extinction of theta and gamma rhythms in the striatum through STN DBS, have also been reported [131]. Furthermore, Agarwal et al. showed that low-frequency STN DBS could disrupt the pathological oscillations observed in the STN of PD patients, leading to a more reliable relay of cortical input to thalamic neurons [132]. The impact of different DBS locations and frequencies on swallowing function of patients with different movement disorders was investigated by Yu et al. [133]. While contradictory effects were found with high-frequency STN DBS [133], a more consistent improvement was found with low-frequency STN DBS in PD [133]. Xie et al. firstly found that low-frequency bilateral STN DBS could reduce aspiration frequency in PD and the beneficial effect could last for an average of 6 weeks [134]. Nonetheless, when the follow-up period was extended to approximately one year, the beneficial effect of low-frequency STN over routine 130-Hz stimulation in reducing aspiration frequency or swallowing difficulty perception was not observed [135]. The effect of globus pallidus internus (GPi) DBS on swallowing function was compared with STN DBS in 2 studies of PD patients [136, 137]. The retrospective chart review from Troche et al. showed that the PAS worsened significantly in STN DBS group but not in GPi DBS group [136]. Robertson et al. found that STN DBS decreased voluntary jaw velocity in PD patients, whereas GPi DBS had the opposite effect [137]. It is important to note that DBS did not generate significant beneficial effect on PD patients with dysphagia according to a recently published meta-analysis [138]. However, only 3 DBS randomized controlled trials were recruited in the subgroup analysis [138]. Therefore, further larger numbers of randomized controlled trials are needed to elucidate the effect of DBS on swallowing function of PD patients.

Both NIBS and DBS could induce neural plasticity. Providing more precise and individualized brain stimulation requires the establishment of brain stimulation protocols based on a comprehensive understanding of the neurophysiology of swallowing and the pathophysiology of dysphagia, given the variability of lesion patterns and the corresponding clinical deficits in stroke patients and in patients with movement disorders.

Conclusion

Swallowing is a sophisticated process relying on coordination and participation of various neural structures, including the cerebral cortex, subcortical white and gray matters, sCPG, brainstem nuclei, and peripheral cranial nerves. Although the roles of both the cerebral cortex and subcortical neural structures are less well studied than brainstem structures, understanding of the participation and specific contribution of these neural structures in swallowing is gradually improving with accumulating data from analysis of altered swallowing performance in multiple neurological diseases, especially the lesion mapping studies of stroke patients, and the advancement of both structural and functional neural image modalities [139]. However, the inconsistent results of lesion mapping studies have led to a poor

definition of the relationship between lesion location and specific impaired components of the swallowing process. A more thorough understanding of the neurophysiology of swallowing will help clinicians develop more individualized and precise treatment protocols via non-invasive brain stimulation, for example, rTMS or transcranial direct current stimulation, or deep brain stimulation to induce neuroplasticity and further improvement of swallowing performance.

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Conflict of interest The authors declare that they have no conflicts of interest.

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Kuo-Chang Wei MD

Tyng-Guey Wang MD

Ming-Yen Hsiao MD, PhD