Review Article

Cerebral control of swallowing: An update on neurobehavioral evidence

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ABSTRACT

This review aims to update the current knowledge on the cerebral control of swallowing. We review data from both animal and human studies spanning across the fields of neuroanatomy, neurophysiology and neuroimaging to evaluate advancements in our understanding in the brain's role in swallowing. Studies have collectively shown that swallowing is mediated by multiple distinct cortical and subcortical regions and that lesions to these regions can result in dysphagia. These regions are functionally connected in separate groups within and between the two hemispheres. While hemispheric dominance for swallowing has been reported in most human studies, the laterality is inconsistent across individuals. Moreover, there is a shift in activation location and laterality between swallowing preparation and execution, although such activation changes are less well-defined than that for limb motor control. Finally, we discussed recent neurostimulation treatments that may be beneficial for dysphagia after brain injury through promoting the reorganization of the swallowing neural network.

1. Introduction

Swallowing is one of the most primitive yet complex functions in mammals. In humans, the swallowing process requires precise coordination of kinematics of approximately 50 pairs of muscles [1]. It is mediated by the central nervous system, involving the brainstem, cerebral cortex, cranial nerves and motoneurons supplying the swallowing musculature [2,3]. Studies with animals offer valuable insights into the neurophysiology of swallowing in mammals. These studies have shown that swallowing and related orofacial movements can be elicited through electrical stimulation of the cerebral cortex, brainstem, and peripheral nerves including glossopharyngeal cranial nerve and superior laryngeal nerve in anaesthetized or awake mammals [2]. Importantly, several cortical regions, such as the cortical masticatory area (CMA), are found to be involved in the neural control of swallowing, but these regions differ across species. Implanted electrode recordings have shown that neurons in primary motor (M1) and sensory (S1) cortices are specialized for swallowing, mastication or tongue movements in primates [4–6].

In humans, early understanding of the neurological control of swallowing mainly comes from lesion studies, which allow indirect deduction of the function of the lesioned regions considered to be responsible for swallowing. However, such deduction can be problematic, because lesion data can only infer the remaining functionality of brain control systems in the absence of the lesioned sites rather than its intact normal function. Traditionally, the brainstem was thought to be the primary center for swallowing and the cerebral cortex was not essential for swallowing, based on the observation that encephalic babies with an intact brainstem have retained the ability to suckle [7]. Such perception has been displaced by clinical reports of dysphagia resulting from supratentorial lesions of a single hemisphere. Since then, growing attention has been given to the cerebral cortex in the investigation of the whole brain neural basis of swallowing. With the advancement in functional neuroimaging technologies, cortical activation during swallowing can be examined in detail with high levels of spatial and temporal resolution. However, there remains considerable uncertainty particularly around how different cerebral regions are functionally connected. Therefore, this review aims to update the current knowledge on the cerebral control of swallowing and the functional connectivity within the cerebral cortex. Evidence from neurophysiological, neuroanatomical and functional neuroimaging studies will be discussed. Finally, we will discuss the therapeutic value of recent treatments in facilitating the rehabilitation of neurogenic dysphagia.

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Table 1
Cortical areas that are involved in swallowing and/or orofacial (mainly tongue and jaw) movements as identified by studies with animals across species.

Study	Animal	Methods	Anaesthetized / Awake	Areas for swallowing	Areas for orofacial (e.g. jaw, tongue) movements	Findings on laterality
Sumi, 1969 [14]	25 rabbits	Open skull electrical stimulation	Anaesthetized	· Anterolateral frontal lobe · Rostral to insular cortex and lateral to S1 *Overlapping is great, but areas for swallowing are narrower and more rostrolateral*	· Anterolateral frontal lobe · Rostral to insular cortex and lateral to S1	· Bilaterally controlled even after separation of hemispheres
Sumi, 1972 [27]	53 rabbits	Open skull electrical stimulation	Lightly anaesthetized	· Concurrent stimulation of anterolateral frontal cortex facilitates swallowing evoked by poutine stimulation		
Baldwin et al., 2016 [20]	10 treeshrews (*Tupaia belangeri*)	ICMS	Anaesthetized		· Lateral M · Lateral S (areas 3a and 3b)	
Bieger & Hockman, 1976 [28]	38 cats	Open skull electrical stimulation	Anaesthetized	· Concurrent stimulation of caudal half of the orbital gyrus, internal capsule, caudate nucleus and entopeduncular nucleus, anterior substantia nigra, and rostral pons facilitates SLN elicited swallowing		
Jean & Car, 1979 [10]	22 sheep	Open skull electrical stimulation	Anaesthetized	· Orbitofrontal cortex		
Miller and Bowman, 1977 [15]	13 rhesus monkeys (*Macaca Mulatta*)	Open skull electrical stimulation	Anaesthetized	· Anterolateral M1 *More posteriorly than the areas for chewing*	· Anterolateral M1	
Huang et al., 1989 [21]	2 monkeys (*Macaca fascicularis*)	ICMS	Awake		· Face-M1 · Face-S1 · CMAp · CMAd	
Stepniewska et al., 1993 [23]	11 owl monkeys (*Aotus trivirgatu*)	ICMS	Anaesthetized		· Lateral M1 · Lateral and ventral PMC	
Martin et al., 1999 [16]	2 monkeys (*Macaca fascicularis*)	ICMS	Awake	· Face-M1 · Face-S1 · CMA · Area ventral to CMAd	· Lateral face-M1 · Lateral face-S1 · Lateral CMA and the region ≥5 mm deep into cortical surface	· Area for swallowing were greater on the left hemisphere than the right · Areas for orofacial movements were greater on the right hemisphere than the left
Hatanaka et al., 2005 [24]	7 monkeys (*Macaca fuscata*)	ICMS	Anaesthetized		· CMA · Orofacial area of M1 · Orofacial area of SMA	
Burish et al., 2008 [22]	5 marmosets (*Callithrix jacchus jacchus*)	ICMS	Anaesthetized		· Lateral M1 · Lateral S (areas 3a and 3b)	

Abbreviations: CMA: cortical masticatory area; CMAp: principal part of cortical masticatory area; CMAd: deep part of cortical masticatory area; ICMS: intracortical microstimulation; M: motor cortex; M1: primary motor cortex; PMC: premotor cortex; SLN: superior laryngeal nerve; S: sensory cortex; S1: primary sensory cortex; SMA; supplementary motor area

2. Cerebral control of swallowing in animals

Animal studies have contributed significantly to our understanding of the swallowing mechanism because they facilitate dissection of individual components of the swallowing control system that would otherwise be restricted in research with humans. In early 1900s, Sir Charles Sherrington and Professor Albert S. F. Grünbaum pioneered the first maps of cortical localization of motor functions in primates [8,9]. Since then, direct electrical stimulation has been used to stimulate various levels of the corticofugal pathways and the cortex of anesthetized or awake animals to elicit swallowing or swallowing-related movements [2]. Microelectrode recordings in sheep and rats have identified that interneurons responsible for swallowing are mainly located in the brainstem, including the solitary tract nucleus (NTS) and the reticular formation surrounding the nucleus ambiguous (NA), and have shown that stimulation of the superior laryngeal nerve can trigger swallowing activity [10–13].

While the brainstem is often regarded as the most important structure for swallowing, studies have also identified the vital role of the cerebral cortex in mediating swallowing (Table 1). Early studies with anaesthetized sheep found that swallowing can be evoked by repeated stimulation of the orbitofrontal cortex [10]. Activation of "early" NTS neurons, which fire before or during the oropharyngeal stage of swallowing, following cortical stimulation suggested that this region might be responsible for triggering of swallowing in sheep. In anaesthetized rabbits, Sumi [14] found that the cortical regions for swallowing were located in the anterolateral frontal cortex. Similar findings have been reported in primates. In anaesthetized monkeys, Miller and Bowman [15] found that swallowing can be elicited in posterior regions of the anterolateral primary motor cortex (M1). In awake monkeys, intracortical microstimulation (ICMS) of distinct regions of the cerebral cortex, including the lateral region of face primary somatosensory cortex (face-S1), cortical masticatory area (CMA; *see below for descriptions*) and frontal operculum, could elicit swallowing [16]. Studies have shown that "cold-block" of the face-S1 of awake monkeys significantly affects swallowing and tongue-jaw coordination and movements [17–19].

Among all orofacial movements, cortical control of tongue and jaw movements have been studied most extensively given their relevance to swallowing (Table 1). Cortical regions for these movements and those for swallowing are found to be largely overlapping [14,15]. Studies with small mammals such as treeshrews and rabbits showed that jaw movements can be evoked by stimulating the lateral regions of motor and sensory cortices and frontal lobe [14,20]. In primates, the cortical areas involved in tongue and jaw movements, including M1, S1 and CMA, appear to be more distinct compared to small mammals [15,16,21–24]. The CMA, of which repetitive stimulation evokes rhythmic jaw movements, comprises two parts: the principal part (CMAp) which is located in the precentral gyrus anterolateral to M1, and the deep part (CMAd) which is located in the inner face of frontal operculum [21]. Single neuron recording studies have shown that neurons in the orofacial sensory (S1o) and motor (M1o) cortex are specialized for swallowing, mastication, or tongue protrusion [4–6]. Using chronically implanted multi-electrode arrays, Arce et al., [25] investigated the activation patterns of populations of neurons in the orofacial sensorimotor cortex during directional tongue protrusion tasks in 2 monkeys. They found that over 70% of neurons modulate their spiking activity according to the direction of tongue movements (task-modulated neurons). These neurons showed concurrent but different firing patterns in which S1o neurons showed peak activity on or before force onset whereas M1o neurons showed peak activity when peak force was reached. Importantly, this study also found that the direction of tongue-protrusion can be accurately predicted by decoding the firing patterns of M1o and S1o neurons. The finding of distributed population of neurons for directional information processing suggests that direction is likely an important feature for cortical control of tongue movements.

Of particular interest is the interaction among cortical structures, subcortical structures and brainstem for masticatory movements and swallowing. Histological studies have shown that several cortical regions are interconnected to enable the complex flow for sensory inputs and motor outputs for cortical control of jaw or masticatory movements [21,24,26]. Hatanaka et al., [26] found that the CMAp receives direct projections from the amygdala in primates, suggesting that the amygdala may be involved in modulation and generation of masticatory patterns. A further study by Hatanaka et al., [24] found that the CMA, primary orofacial masticatory area (M1o) and supplementary orofacial masticatory area (SMAo) are key cortical components of a dynamic neural network for distinctive masticatory movements. These areas receive projections from the sensory and motor thalamic nuclei, as well as intracortical projections from the frontal, parietal and orbital cortices, and send motor commands to the lateral tegmental field (LTF) in the brainstem directly or indirectly via basal ganglia. This complex network enables execution of the masticatory motor sequence with concurrent modulation through sensory feedback. In anaesthetized rabbits, Sumi [14] found that swallowing and mastication responses were facilitated by stimulation of both hemispheres and such facilitation remained after splitting of the two hemispheres, indicating that swallowing was bilaterally mediated and interhemispheric pathways were absent or dormant for swallowing control. Another study showed that brainstem-evoked swallowing was enhanced by repeated stimulation of the anterolateral frontal cortex in rabbits [27]. Moreover, reflexive swallowing evoked by peripheral stimulation of superior laryngeal nerve was found to be facilitated by concurrent stimulation to structures along the corticobulbar pathway, including caudal half of the orbital gyrus, internal capsule, caudate nucleus and entopeduncular nucleus, anterior substantia nigra, and rostral pons [28].

These animal studies examined the organization of neural networks for swallowing and swallowing-related orofacial movements using electrical stimulation. While some may argue that swallowing evoked by electrical stimulation in a laboratory setting is artificial, and that electrical currents may stimulate all types of nerve fibers (excitatory and inhibitory; sensory and motor) and elicit activity that is not normally seen in a functional central nervous system, this technique allows perturbating the system to obtain a visible outcome (the swallow). Therefore, electrical stimulation to the central nervous system remains a valuable technique for understanding the neurophysiology of swallowing. Although some techniques used in animals such as ICMS are invasive and not applicable to human subjects, advances in magnetic and electrical stimulation technology, for example the development of transcranial magnetic stimulation (TMS), have made similar investigations in humans a realistic possibility. Taken together, these findings highlight the involvement of cerebral cortex in the control of complex swallowing process, which provide valuable implications for the organization of neural networks for swallowing in humans.

3. Neurodevelopment of swallowing in human brain: from fetus to adolescent

In humans, neonates at birth have developed the ability to swallow, which is essential for the intake of life-sustaining nutrients. A recent embryology study using real-time ultrasound imaging found that most fetuses displayed swallowing behavior as early as 15 weeks of gestation and showed consistent swallowing by 22 to 24 weeks of gestation [29]. Fetal swallowing is important for the regulation of amniotic fluid homeostasis and the development of somatic and gastrointestinal functions [30]. Neurologically, the developmental maturation of cerebral and brainstem pathways involved in swallowing determines the readiness for oral feeding after birth [31]. Myelination in the brainstem and cranial nerves including facial (VII), glossopharyngeal (IX) and hypoglossal (XII) occurs at 18 to 24 weeks of gestation, and the development of brainstem interneuron network for pharyngeal swallow reaches a functional level before full-term of gestation [31].

The cerebral cortex plays an important role in swallowing, as

suggested by findings from studies with anencephalic fetuses and infants. Studies have found that swallowing was absent during fetal stages for anencephalic children despite the presence of largely intact medulla, pons and cerebellum [32]. Although swallowing was seen in an older anencephalic child, this was accompanied by the presence of cerebral tissues with unknown intactness [33]. Interestingly, an fMRI study found that a 9-year-old child who suffered an anoxic injury at birth and had no normal oromotor control or prior oral feeding experience showed activities in cortical areas identical to age-matched controls while attempting to perform a swallowing task [34]. It is possible that abnormal or damaged neural circuits included those beyond the cortical level, such as the cerebellum or brainstem, which were not detected by the fMRI paradigm used in the study. This finding suggested that the integrity of both brain structures and functional connectivity of neural circuits are essential for normal swallowing. In healthy adolescents, it is found that the regions of cortical activation during swallowing, including S1, M1, superior motor cortex, insula, inferior frontal cortex, Heschl's gyrus, putamen, globus pallidus, and the superior temporal gyrus, were comparable to adults, suggesting that maturation of neurological control of swallowing has largely completed [34].

Taken together, these findings highlighted the importance of cerebral cortex for the development of swallowing from the gestation of the fetus to adolescent with much of this completed by mid-childhood.

4. Clinical lesion studies in humans

Numerous studies and clinical reports have demonstrated the impacts of cortical lesions on swallowing in humans. Based mainly on animal data, the early concept around the brain's role in swallowing was that there was bilateral hemispheric control. It was thus believed that lesions in the supratentorial regions must be bilateral to cause neurological disturbances of swallowing [7]. This belief was questioned by a clinical report of six cases of dysphagia associated with unilateral cerebral stroke [7]. This report began to change the conventional perception on the role of cerebral cortex in swallowing and triggered further investigation into the functions of supratentorial structures. Indeed, much of the recent advancements in neuroimaging technology allowing detailed investigation on the relationship between lesion characteristics, including location, lateralization and size, and dysphagia, has consolidated this contention. Here, we will first discuss the observations obtained from neuroanatomical data ensuing from clinical lesion studies.

4.1. Lesion location and dysphagia

It is now well-established that damage to the cerebral hemispheres, such as following cerebral vascular disease (CVA or stroke), can result in dysphagia [35,36]. The relationship between lesion location and dysphagia is of particular interest as it indirectly informs the roles of lesioned regions in swallowing, and it can potentially be used to predict the likelihood of dysphagia and its recovery. Given the relatively focal nature of ischemic infarction, studies on this relationship are predominantly based on retrospective review of the magnetic resonance imaging (MRI) and computerized topography (CT) scans of ischemic stroke patients. Although an early study by Albert et al., [37] failed to identify significant relationship between lesion location and occurrence of aspiration in acute stroke patients, the majority of studies in the literature have reported significant correlations [38–48] (Table 2).

Cortical regions that have been found associated with dysphagia include, primary and secondary somatosensory and motor (SM1 and SM2) cortices, supplementary motor area, inferior frontal gyrus, anterior cingulate cortex, orbitofrontal cortex and supramarginal gyrus [38–42]. Among these regions, lesions to the somatosensory and motor areas are most frequently identified and associated with dysphagia. However, the correlation between these regions and dysphagia is inconsistent across studies, potentially due to differences in analysis methods and patient characteristics. Daniels et al., [38] found that lesions to the M1 were associated with higher risks of aspiration than lesions to the S1. The involvement of SM1 in swallowing is further suggested by a large study with 200 stroke patients [39], which found that among several cortical and subcortical regions, the SM1 was associated with severe swallowing impairments. Studies have also attempted to correlate specific dysphagia symptoms with lesion location. Lesions to the SM1 and SM2 were associated with aspiration, residues, and delayed or missing swallowing response which increased the risk of aspiration, whereas sensory regions and limbic structures were associated with impaired cough reflex [39,40]. More detailed spatial segmentation of the SM1 with fMRI showed that S1 lesions were related to impaired laryngeal vestibule closure and pharyngeal residues whereas M1 lesions were related to impaired laryngeal elevation [41].

Apart from cortical lesions, other studies have reported relatively strong associations between dysphagia and deep brain lesions, including the insula, basal ganglia, corona radiata, thalamus, internal capsule, and periventricular white matters [38,39,41–48]. Recent studies have suggested that subcortical lesions are associated with higher rate of dysphagia than cortical lesions [42]. Among all subcortical structures,

Table 2
Relationship between lesion location and dysphagia symptoms.

Lesion location		Dysphagia symptoms	References
Supratentorial	Primary somatosensory cortex	• Aspiration • Pharyngeal residue • Impaired swallowing response • Impaired cough reflex • Poor laryngeal vestibule closure	[39,40]
	Primary motor cortex	• Aspiration • Pharyngeal residue • Impaired swallowing response • Impaired laryngeal elevation	[39,40]
	Limbic structure	• Impaired cough reflex	[39,40]
	Insula	• Elevated risk of aspiration • Prolonged pharyngeal transit time • Impaired laryngeal elevation • Impaired laryngeal vestibule closure • Prolonged risk of aspiration (with the presence of opercular lesion)	[41,42,45,48]
	Operculum	• Elevated risk of aspiration • Prolonged risk of aspiration (with the presence of insular lesion)	[48]
	Basal ganglia	• Elevated risk of aspiration	[38,48]
Infratentorial	Brainstem	• Impaired laryngeal elevation • Prolonged pharyngeal delay time	[49,50]

the insula is the most consistently identified region to be associated with dysphagia. Daniels et al., [47] first reported that damage to the insular cortex is most common among the 16 stroke patients studied. In a further study with 4 patients with insular lesions, they found that all three patients with dysphagia had a lesion in the anterior insula, whereas the non-dysphagic patient had lesions restricted to the posterior region [46]. This finding suggests that the anterior portion of insula may be more important for swallowing than the posterior insula. Other studies also found that lesions to the insula and operculum were associated with elevated risk of aspiration [48] and that the association was strongest among all the supratentorial regions assessed [42]. Importantly, infarction of the frontal operculum in addition to insula increased the likelihood of extended risk of aspiration due to impaired recovery in the subacute phase [48]. However, a negative correlation between insula and dysphagia was reported by Gonzalez-Fernandez et al., [44]. With respect to dysphagia symptoms, lesions to the insula are associated with prolonged pharyngeal transit time [45], impaired laryngeal elevation and laryngeal vestibule closure [41].

When comparing the likelihood of dysphagia between supratentorial and infratentorial lesions, Jeon et al., [49] found that dysphagia was associated with brainstem lesions, but not with cortical or subcortical lesions. In particular, brainstem lesions are associated with pharyngeal phase dysfunction, including reduced laryngeal elevation and prolonged pharyngeal delay time. A similar relationship was reported by Daniels et al., [50]. Using diffusion-weighted imaging, they revealed that lesions to the infratentorial structures are associated with more severe penetration and aspiration, whereas lesions to the supratentorial structures have no such association. However, these findings were challenged by a recent study which reported no association between dysphagia and infratentorial lesions [42].

In summary, damage to supratentorial structures can result in dysphagia. However, the relationship between lesion location and dysphagia symptoms remains poorly defined. This is unsurprising given the distributed neural circuits related to swallowing, the likely compensation mechanisms that exist in preserving swallowing after brain injury and the variability in stroke manifestations. Nonetheless, understanding the impacts of lesions to these regions can provide insights into potential swallowing difficulties that may occur in patients prior to swallowing assessments.

4.2. Side of lesion, hemisphere and dysphagia

The effects of a unilaterally lesioned hemisphere have been the center of debate in studies of cerebral control of swallowing. Some studies have reported no association between the side of the lesioned hemisphere and dysphagia severity or characteristics [37,38,48–50], while others have reported hemispheric bias [39–41,47,51–53]. Most of these studies report that right hemispheric lesions result in more severe dysphagia involving pharyngeal impairments [47,51,52]. The symptoms associated with right hemispheric lesions include altered swallowing mechanics characterized by prominent pharyngeal dysmotility and reduced hyolaryngeal elevation [47,52], prolonged pharyngeal events [51], increased pharyngeal residue, impaired swallow response, increased risk of aspiration [39–41,51,53]. Moreover, Li et al., [54] reported that right hemispheric lesions were associated with pharyngeal dysfunction whereas left hemispheric lesions were associated with oral dysfunction. It should be noted that while these associations are significant at group level, inconsistency has been reported across individuals [41,53].

Other studies suggested that the effect of hemisphere is region-specific, such that lesions to certain structures in the left hemisphere may be more strongly associated with dysphagia than in the right or vice versa [40,42]. For example, Cola et al., [43] found that left hemispheric lesions in periventricular white matter was associated with dysphagia but right hemispheric lesions were not. Therefore, given the inconsistencies in reported effects of sidedness for each hemisphere, it

remains difficult to draw any definitive conclusions on the relationship between lesion laterality and dysphagia.

4.3. Lesion size and dysphagia

Compared to lesion location and hemisphere, fewer studies have investigated the relationship between lesion size and dysphagia severity. Similar to the other two stroke characteristics, the reported relationship is mixed, with both positive [55,56] and negative [42,47,57] findings. A recent study by Hess et al., [42] found that the size of hemorrhage is independent of risk of dysphagia as small lesions in the subcortical area could result in substantial dysphagia. By contrast, Lee et al., [56] found that the hemorrhage size in patients with subcortical stroke is positively correlated with the severity of dysphagia. Several indicators of dysphagia, including, presence of tracheostomy, inadequate lip sealing, tongue protrusion and/or laryngeal elevation, and absence of reflex coughing, were found to be correlated with the size of hemorrhage. Another study by Power et al., [55] showed that patients who aspirate had larger stroke lesion volume than those who did not aspirate. Although these data did not show definitive relationship between size and dysphagia severity, those positive findings suggest that lesion size may be associated with certain dysphagia symptoms, and such relationship should not be overlooked.

5. Neurophysiologic and functional imaging of the cerebral cortex for swallowing in healthy humans

The structure of the human cerebral cortex was first studied in the mid-19th century and the most notable work was done by Korbinian Brodmann who classified the human brain into 52 discrete areas based on its cytoarchitectonic features [58,59]. Since then, the functional organization of human cerebral cortex was initially investigated using direct electrical stimulation during open brain surgery [60]. Penfield and Boldrey [60] first reported findings from systematically mapping of cortical areas during neurosurgery in over 120 cases. They showed that electrical stimulation of anterolateral M1 could induce rhythmic swallowing movements. This type of study is invasive and can only be done when there is a justified medical need for brain mapping. With the introduction of transcranial magnetic stimulation (TMS) in 1985 [61], mapping studies of the human brain have become more amenable. TMS is a non-invasive brain stimulation technique that induces electric current within the brain through electromagnetic induction [62]. When applied over the motor cortex, TMS can trigger electromyographic (EMG) responses, termed motor evoked potential (MEP), in the corresponding muscles [62]. Different characteristics of MEP, such as amplitude, latency, or intracortical inhibition, can inform different properties of the central nervous system, hence it has been used extensively to study human motor neurophysiology pathways [62,63]. Using TMS, Aziz et al., [64] found that stimulation of the face-associated area of the M1 or vagal cranial nerve could elicit early and late EMG responses from esophageal muscles. The early responses were thought to result from direct stimulation of motor fibers whereas the late responses were likely mediated by polysynaptic extrapyramidal pathways that were involved in swallowing control [64]. A further study by Hamdy et al., [65] demonstrated that cortical representation of mylohyoid, pharynx and esophagus were organized somatotopically in the motor and premotor cortex. Specifically, mylohyoid muscles are represented in the lateral precentral and inferior frontal gyri, pharyngeal muscles are represented in the anterolateral precentral and middle frontal gyri and esophageal muscles are represented in the anterolateral precentral and superior frontal gyri [65].

Functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetoencephalography (MEG), functional near-infrared spectroscopy (fNIRS), electroencephalogram (EEG) and electrocorticography (ECoG) are functional neuroimaging/ neuromapping techniques that have been used to study cortical activation during

swallowing. Each of these techniques has its own unique advantages and disadvantages, such that their findings can be complementary. FMRI measures changes in cerebral blood oxygenation which reflects the underlying neural activity during tasks [66]. It has good spatial resolution of 3-4 mm but relatively low temporal resolution (seconds) [67]. PET detects radioactive tracers such as carbon-11, oxygen-15, nitrogen-13, and fluorine-18 within the region of interest [68]. It has lower spatial (5-10 mm) and temporal (minutes) resolution than fMRI but it is useful for imaging the subcortical structures [67]. MEG detects changes in electrical current induced by the varying neuromagnetic field related to brain (mainly cortex) activation [67,69]. The spatial resolution of MEG is limited to 10-20 mm, but it has excellent temporal resolution (milliseconds) [67,69]. FNIRS measures changes in the concentration of oxygenated and deoxygenated hemoglobin molecules in the blood within the brain, but the measurement is restricted to the cortex due to limited probing depth (3 cm) [70]. It has low spatial (10-20 mm) and temporal (seconds) resolutions, but it is more portable compared to fMRI, allowing flexibility in studying various swallowing protocols [67]. Recently, researchers have explored the use of EEG and ECoG in detecting swallowing-related cortical activations and reported encouraging findings [71–73]. EEG measures brain electrical activity through scalp electrodes. Similar to MEG, although EEG has poor spatial resolution, it offers excellent temporal resolution (1–5 milliseconds), making it a suitable candidate for measuring timing-related neural activity [74]. Finally, ECoG measures cortical electrical potentials directly from the exposed brain. Although invasive in nature, ECoG offers better spatial and temporal resolution compared to EEG [75].

The imaging protocols used in functional neuroimaging studies have been diverse and increasingly complex. Early studies tended to only investigate cortical activation during two conditions, swallow versus rest [76–86]. More recent studies have attempted to explore activations during saliva swallow versus water swallow [87–89], oral and jaw muscles movement versus swallow [90–94], swallowing imagery versus swallow execution [95–97], swallow versus oral stimulation (or anesthesia) [98,99], as well as voluntary versus reflexive swallowing [91,98,100].

Despite the diversity in imaging techniques and protocols, studies have collectively shown that swallowing, whether reflexive or volitional, is represented in spatially and functionally distinct cortical and subcortical foci. The areas that have been reported to be activated during swallowing include (in descending order of occurrence in studies): M1, S1, insula, cingulate cortex, supplementary motor area, premotor cortex, auditory cortex, inferior frontal gyrus, parietooccipital and prefrontal cortex, operculum, putamen, thalamus, global pallidus, internal capsule, cerebellum, corpus callosum, basal ganglia, caudate, pons and midbrain, inferior parietal lobule [34,54,76–79,81–94,96–106] (Fig. 1). Most of these regions have been identified in lesion studies. Interestingly, motor imagery of swallowing appears to activate similar regions as swallowing execution [97]. The following discussion will not cover all brain regions purported to have been involved in swallowing control but focuses on the most consistently reported (> 50% of all studies; Fig. 1) regions, including M1, S1, insula, cingulate cortex and basal ganglia. Table 3 presents a summary of findings from neuroimaging and neurophysiology studies on the involvement of these areas during swallowing.

5.1. Primary motor cortex (M1) and primary somatosensory cortex (S1)

Primary motor and somatosensory cortices, often known together as primary sensorimotor cortex (SM1), are well-recognized cortical regions involved in swallowing. These regions are often found activated together during swallowing or oral sensory stimulation [98] or reduced in activation during oropharyngeal anesthesia [99], suggesting that both M1 and S1 function in synchrony. Separately, M1 has been suggested to be responsible for swallowing initiation and execution [76,77,88,89,93,103]. The activation of M1 during swallowing is in accordance with animal studies which found that ICMS of the face-M1 could induce swallowing [16], "cold-block" applied to this area could disrupt food preparatory phase [18], and that single neuron firing of tongue-M1 is related to swallowing [107]. In humans, studies have reported that electrical stimulation of M1 could induce rhythmic swallowing movements [60]. Cortical mapping studies using TMS have demonstrated efferent projections from the M1 to swallowing musculature, including mylohyoid, pharyngeal and esophageal muscles [64,65]. A virtual lesion (induced by 1 Hz repetitive TMS) of the M1 seems to result in temporary disruption of swallowing behavior,
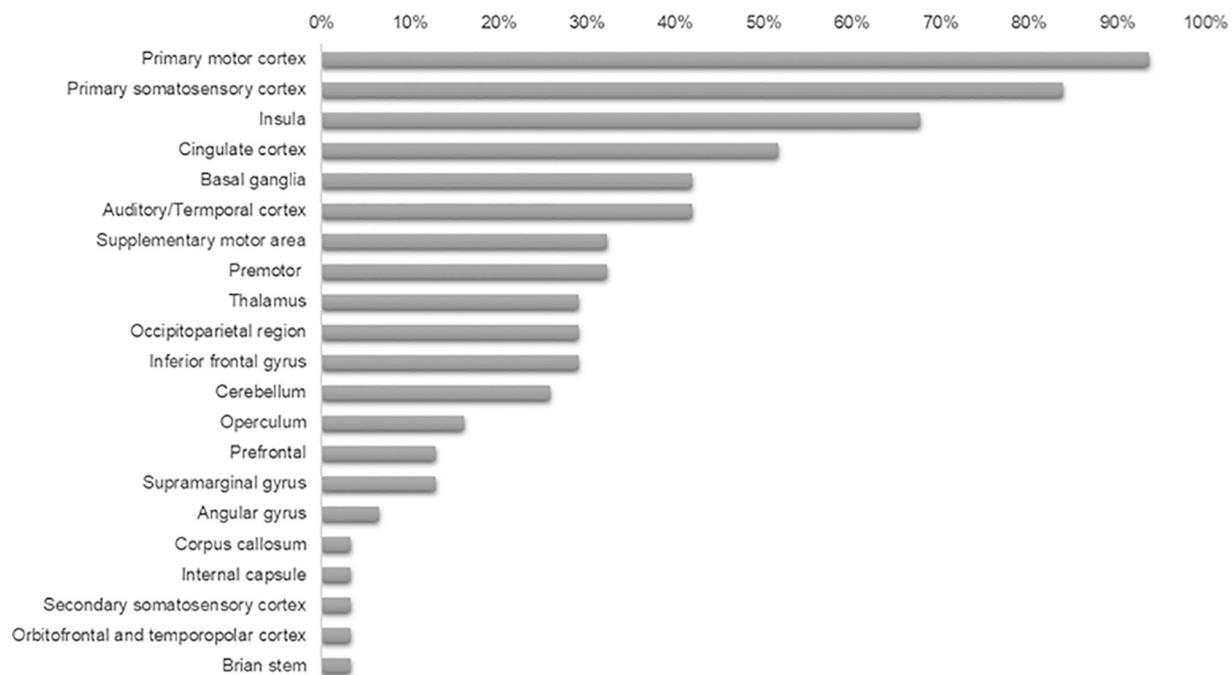

Fig. 1. Summary of cerebral regions found to be activated during swallowing. The percentage represents the frequency of occurrence across 30 functional neuroimaging studies.

Table 3

Summary of findings from neuroimaging and neurophysiology studies in healthy humans on the involvement of sensorimotor cortex, insula, frontal operculum, cingulate cortex and basal ganglia during swallowing.

Brain regions	Neuroimaging / neurophysiology technique	Stimulation / swallowing task	Main findings	Proposed roles in swallowing	Reference
SM1	fMRI	Air-pulse stimulation of posterior oral area Volitional saliva swallow Imaginary swallow	Increased activation Larger activation during volitional saliva swallow than imaginary swallow	M1 and S1 may function in synchrony	[98]
	MEG	Volitional water swallow Oral anaesthesia	Increased activation during oral stimulation Reduced activation after anaesthesia		[99]
	fMRI	Automated saliva swallow Volitional saliva swallow Volitional water swallow	Increased activation during swallowing		[76,88,89,93,103]
	PET	Volitional water swallow	Increased activation during swallowing		[77]
M1	TMS	Cortical mapping: Elicits EMG responses by stimulating M1	Mylohyoid: lateral M1 and inferior frontal gyrus Pharynx: anterolateral M1 and middle frontal gyrus Esophagus: anterolateral M1 and superior frontal gyrus	Initiation and execution of swallowing	[64,65]
	–	Direct electrical stimulation during open-skull surgery	Elicits rhythmic swallowing		[60]
	–	"Virtual lesion" of pharyngeal M1 induced by 1 Hz rTMS	Decreased oral transit time, increased swallow response time and reduced swallowing accuracy		[108,109]
	fMRI	Pleasant and unpleasant taste stimulation	Increased activation of inferior S1		[111]
	fMRI	Retention of room temperature water in oral cavity	Increased activation		[92,112]
S1	fMRI, MEG	Air-pulse stimulation of posterior oral area, laryngeal mucosa	Increased activation	Processing of sensory information during swallowing	[98,113,114]
	MEG	Electrical stimulation of pharyngeal mucosa	Increased activation		[115]
	PET	Balloon distention of lower esophagus	Increased activation, increase further with painful stimulation		[116]
	PET, fMRI, MEG	Gustatory stimulation	Increased activation		[111,120–124]
Insula and frontal operculum	PET	Balloon distention of lower esophagus	Increased activation during both painful and non-painful stimulation	Processing and perception of taste information (Taste centre)	[116]
	MEG	Volitional water swallow	Increased activation before swallowing	Initiation of swallowing	[80]
	–	Electrical stimulation of right inferior posterior insula using deep electrodes	Delayed and irregular swallowing		[127] (single case study)
Cingulate cortex	fMRI	Balloon distention of lower esophagus	Increased activation in left mid-ACC with increasing pain Reduced right mid-ACC activation when pain is distracted, but no changes with left mid-ACC activation	Higher order cognitive processing and attention to swallowing	[130,131]
	fMRI	Automate saliva swallow Volitional saliva swallow Volitional water swallow	ACC activation is more likely associated with volitional saliva and water swallow than automated saliva swallow		[88]
	MEG	Volitional water swallow	Increased ACC and PCC activation before swallowing		[80]
Basal ganglia	fMRI, PET	Automated saliva swallow Volitional saliva swallow Volitional water swallow	Increased activation during swallowing	Largely unknown, but it is proposed to be part of a neural circuit for swallowing which comprises the inferior frontal gyrus, S2, corpus callosum, basal ganglia and thalamus	[76,79,82,89,90,95,96,98]

Abbreviations: ACC: anterior cingulate cortex, EMG: electromyography, fMRI: functional magnetic resonance imaging, MEG: magnetoencephalography, M1: primary motor cortex, PCC: posterior cingulate cortex, PET: positron emission tomography, rTMS: repetitive transcranial magnetic stimulation, S1: primary sensory cortex, S2: secondary sensory cortex, SM1: primary sensorimotor cortex

characterized by decreased oral transit time, increased swallow response time and reduced swallowing accuracy [108,109].

Processing of sensory information is an integral part of swallowing. It is essential to provide biofeedback on the texture of bolus and dynamics of bolus passage to ensure swallow safety [110]. Studies have shown that S1 is activated when different forms of sensory input are presented to the oral, laryngeal, pharyngeal or esophageal areas. Faurion et al., [111] showed that the inferior regions of S1 were activated when healthy volunteers were presented with liquids of pleasant and unpleasant tastes. Moreover, mechanical sensory inputs from the oral cavity, including retention of room temperature pure water in the oral cavity [92,112] and air-pulse stimulation of right posterior oral area [98,113], are also processed in the S1. Apart from the oral cavity, bilateral activation of S1 is observed during air-pulse stimulation of the laryngeal mucosa [114], electrical stimulation of the pharynx [115] and sensory stimulation of the lower esophagus through balloon inflation [116]. The activation was noted to increase during painful lower esophageal stimulation [116].

5.2. Insula

Studies with primates have identified the insula and frontal operculum as the primary taste cortex [117,118]. Single neurons located in these regions were found to be responsive to sensory (olfactory, gustatory and visual) stimulation [119]. Some of these neurons responded to combined modalities, allowing processing of sensory information of different modalities simultaneously [119]. In humans, convergent findings of increased activation in the insular-opercular region during gustatory stimulation have been reported in studies using PET [120,121], fMRI [111,122,123] and MEG [124]. Moreover, Aziz et al., [116] found that the insula was activated during both painful and non-painful esophageal stimulation, suggesting that it may also be involved in processing mechanical sensory information transmitted from both vagal and/or spinal afferents. Apart from being the primary taste cortex, the insula is also thought to be a primary integrative area for volitional swallowing [125] and is responsible for coordinating visceral sensory and motor information [126]. A case report showed that electrical stimulation of the right inferior posterior insular cortex using deep electrodes resulted in irregular and delayed swallows [127]. This finding is contradictory to that reported by Daniels et al., [46] which suggested that lesions in the posterior insula was not associated with dysphagia. However, given that these were single case reports, cautions should be taken when interpreting these results. Watanabe et al., [80] found that the insula was activated before swallowing, indicating that this region may be essential for the initiation of swallowing.

5.3. Cingulate cortex

The cingulate cortex is part of the limbic system. Within this region, the anterior cingulate cortex (ACC) is frequently identified in functional neuroimaging studies for swallowing. The ACC is considered to be a multifunctional region that is involved in the initiation and motivation of goal-directed behaviors, anticipation of and attention to action, and error detection [128,129]. Moreover, ACC may be involved in the processing of visceral pain. Several fMRI studies have found that the level of activation in the left mid-ACC increased with increasing intensity of pain resulted from esophageal electrical stimulation [130,131]. Interestingly, Coen et al., [131] found that the activation in the right mid-ACC was reduced when the attention to the pain was distracted, whereas the activation in the left mid-ACC remained unchanged. This finding suggested the potential role of the right ACC in attention or cognition. The PCC is an association area with abundant connections to the thalamus and is suggested to be responsible for attentional focus [132]. An MEG study found that both ACC and PCC were activated before swallowing [80]. Furthermore, using fMRI, Martin et al., [88] found that ACC activation is more likely associated with volitional saliva and water

swallow than automated saliva swallow. Taken together, these findings suggest that the cingulate cortex may be responsible for higher order cognitive processing of and attention to swallowing.

5.4. Basal ganglia

The basal ganglia are a group of subcortical nuclei consisting of the striatum, the globus pallidus, the subthalamic nucleus, and the substantia nigra [133]. They are involved in a number of cortical-subcortical neural circuits that supports sensorimotor, cognitive and emotional-motivational brain functions [134]. Their main roles are thought to be learning and selection of appropriate motor programs [134]. Basal ganglia dysfunction can lead to a number of movement disorders, including Parkinson's disease (PD) and Huntington's disease (HD), in which dysphagia is common [133,135–137]. Although functional neuroimaging studies have demonstrated activation of basal ganglia during swallowing [76,79,82,89,90,95,96,98], little is known regarding their specific roles in the control of swallowing [135]. Functional connectivity studies have shown that basal ganglia are part of a neural circuit for swallowing [89] (See section 5.6).

5.5. Hemispheric dominance for swallowing

Hemispheric dominance or functional lateralization is thought to be a result of brain size expansion during evolution [138]. It is important for rapid access of neural resources for complex functions like swallowing by avoiding excessive conduction delays between the hemispheres. Hemispheric dominance for swallowing has been extensively reported, albeit inconsistently, in several TMS and functional neuroimaging studies. Early TMS studies reported unilateral dominance of cortical representation of mylohyoid, pharyngeal and esophageal musculature [64,65,139] and such dominance is independent of handiness [65]. Findings from functional neuroimaging studies are mixed. Both left [87,100,102,104] and right [88,101] hemispheric dominance has been reported. However, some studies noted that hemispheric dominance is inconsistent across individuals [76,77,105], while other studies did not find significant lateralization [91,97]. One possible explanation for the lack of lateralization in these studies is the averaging of individual data, such that the lateralization effects may be lost at the population level.

Furthermore, lateralization of swallowing control appears to be task-dependent [87,88,100,140]. Mosier et al., [87] found that the hemispheric dominance for swallowing appeared to change depending on the swallowing task. In this study, eight healthy volunteers performed 3 tasks, including 10 s of dry swallow, 10 s of water swallows and 15 s of dry swallows, during fMRI scanning. The results showed that 6 out of the 8 subjects had inconsistent hemispheric dominance and degrees of laterality during the 3 tasks. There was no discernible pattern of hemispheric dominance for each task across subjects. Moreover, consistent with early TMS studies, there was no relationship between hemispheric dominance and handedness. Similarly, Mistry et al., [139] also reported task-specific lateralization. They found that during water swallow, M1 activation was the strongest and lateralized to the right whereas during tongue elevation and saliva swallowing, premotor cortex and supplementary motor cortex activation was lateralized to the left. Martin et al., [88] demonstrated that there was greater activation of right insula than the left during volitional swallow but not reflexive swallow and there was no significant lateralization for the M1 or S1. Finally, a dual task study by Daniels et al., [141] found that specific swallowing components may be preferentially mediated by one hemisphere versus the other. They showed that the left hemisphere task induced a decrease in volume swallowed whereas the right hemisphere task reduced swallowing rate. Therefore, depending on the tasks used in functional neuroimaging studies, the findings on hemispheric dominance may vary.

Although findings on hemispheric dominance in healthy swallowing remains inconclusive, lesion studies have reported differences in both

dysphagia severity and characteristics between right and left hemispheric strokes. Therefore, it is likely that lateralization exists in swallowing control, and it is highly complex such that cortical structures are differentially lateralized according to different components of swallowing. Cortical structures that are functionally connected may be clustered within the same hemisphere for efficient access and processing of neural information.

5.6. Functional connectivity of brain regions

Although cortical activation during swallowing and swallowing-related tasks have been well studied, the functional connectivity among different activated regions remains largely underexplored. Mosier et al., [89] first attempted to analyses the interactions among cortical regions that were activated during swallowing. Using principal component analysis, they found that there were 5 major modules in the swallowing network, including the sensorimotor areas and cingulate gyrus (SM-CINGYR); inferior frontal gyrus, S2, corpus callosum, basal ganglia and thalamus (IFG-S2-CC-BGTHAL); premotor cortex and posterior parietal cortex (PREMOTOR-PCC); cerebellum; and insula. The connections of these components are best described by a parallel loop model which comprised two functional loops. The first loop involved the PREMOTOR-PCC, SM-CINGYR and insula modules while the second loop involved the IFG-S2-CC-BGTHAL, SM-CINGYR and cerebellum modules. The insular loop was thought to be responsible for synchronizing swallowing movement, whereas the cerebellar loop was responsible for modulation of internal representation of swallowing and coordination of swallowing related events such as respiration. Other functional connectivity studies have shown that insular region appeared to be the primary integrative region in the cerebral cortex. Lowell et al., [125] found that the insula had significantly greater connected voxels than other seed regions, which included inferior frontal gyrus, S1 and M1. Functional connectivity was also reported between sensorimotor regions, between insular and prefrontal operculum [84], as well as between hemispheres [142].

These findings suggest that both cortical and subcortical structures activated during swallowing are functionally connected. A common finding among these studies is that the insula acts as an important center that integrates sensorimotor information within the cerebral cortex. Nonetheless, the organization of the human swallowing network remains incompletely understood and poorly explained. Future studies using neuroimaging techniques with high temporal and spatial resolution and carefully designed study protocols should help to further elucidate the dynamic functional organization of cortical structures and their roles in swallowing.

5.7. Temporal dynamics of human swallowing control: preparation vs execution

While cortical activation data provides important information on the involvement of individual brain regions in swallowing, the temporal dynamics of activated regions allows understanding of their roles at different stages of the swallow sequence. Some studies have attempted to segregate swallowing into several events, including swallowing preparation and initiation, which are thought to be voluntary; versus swallowing execution, which is thought to be predominantly reflexive so as to identify the differences in cortical activation among these processes. However, the findings are highly inconsistent partly due to the differences in study methodologies and partly due to the complex nature of swallowing. Unlike limb motor control, in which cortical activations during preparation and execution can be segregated into distinct regions [143,144], activations during these two processes in swallowing share overlapping regions that are distinguishable by the degree of activation. Malandraki et al., [93] reported a change in degree of activation, in which bilateral SM1, ACC, insula, thalamus, basal ganglia and cerebellum were less significantly activated during swallowing preparation

than execution. A study using ECoG reported activation of face/tongue SM1 during the preparatory phase of volitional swallowing, but such activation was less pronounced during swallowing, suggesting that the cerebral cortex may be more involved in preparation than execution of swallowing [105].

Other studies have reported a shift in activation sites within the cortex [82,86,92,100] or from predominantly cortical to predominantly subcortical structures [72,145]. Using MEG, Furlong et al., [92] found that activation shifted from caudolateral sensorimotor cortex during swallowing preparation towards more superior sensorimotor cortex during swallowing execution and related tongue movement. By contrast, Dziewas et al., [100] reported a posterior-to-anterior shift in the S1 and sensorimotor integration areas from swallowing preparation to execution. Mihai et al., [145] revealed that there was a sequential activation of cortical regions throughout the swallowing process in which the premotor cortex, supplementary motor area and bilateral thalamus were first activated, followed by SM1, insula, cerebellum and pons. Recently, Toogood et al., [82] found that swallowing preparation preferentially activates bilateral ACC, left premotor and M1, bilateral thalamus and basal ganglia. During swallowing execution, both bilateral insula and left dorsolateral pericentral cortex were activated [82]. The finding that thalamus and basal ganglia were activated during swallowing preparation differs from that reported by Malandraki et al., [93] which reported preferential activation of these areas during swallowing execution. The authors speculated that this discrepancy may be due to differences in the nature of swallowing tasks. In an event-related fNIRS study, Karmarunas et al., [86] found that swallowing preparation showed predominantly activation of S1, possibly due to the sensation of saliva accumulating in the oral cavity, whereas swallowing execution showed both activation of S1 and M1.

Some studies reported changes in cortical oscillations in relation to different stages of swallowing. Using simultaneous EEG and EMG, Koganemaru et al., [71] studied corticomuscular coherence (CMC), which is the coherence between cortical rhythm and electrical activity produced by skeletal muscles, during swallowing. They found that in the early stage of swallowing CMC in the low-frequency (alpha: 8-14 Hz) band was more prominent while in the late stage of swallowing CMC in the beta (15-25 Hz) frequency band was more prominent. This suggested that different neural networks maybe recruited for early and late stages of swallowing. A recent electrocorticogram (ECoG) study by Hashimoto et al., [146] found that high gamma (HG) (75–150 Hz) band activity in the orofacial cortex increased before swallowing and peaked at the junction between voluntary and involuntary stages of swallowing, implying that the driving force of swallowing may have switched from the cerebral cortex to the brainstem during the transition. Furthermore, this group of researchers also investigated the relationship between high-frequency and low-frequency cortical oscillations using phase-amplitude coupling (PAC) methods [72]. They found that during motor tasks (mouth opening and swallowing), HG activities were coupled with alpha band (10–16 Hz) before motor-related HG power increase, whereas for the sensory task (water injection into the mouth), HG activity was coupled with theta band (5–9 Hz) during sensory-related HG power increase. This suggested that the patterns of cortical oscillations during sensory and motor neural processing are distinctive. While not surprising, these findings provided novel evidence around the dynamics of swallowing neural control.

Apart from changes in the degree and regions of activation and cortical oscillations, changes in laterality have also been reported. Dziewas et al., [100] reported bilateral activation of SM1 during the preparation stage and strong left lateralization of mid-lateral SM1 during swallowing execution. The authors suggested that sensory processing was accomplished by both hemispheres whereas lateralization occurs only with the motor output system. Teismann et al., [147] reported more detailed changes during swallowing execution. They reported a shift in activation of SM1 from left to bilateral in early stages, and finally to right during the late stage. Similarly, Mihai et al., [57]

found that the activations are located mainly in the left hemisphere early in the sequence, which shifted to the right over time.

Although findings on temporal dynamics of cortical activation remain inconsistent, these findings have shown that the brain regions are functionally specialized for different stages of swallowing. Importantly, the cerebral cortex is intimately involved even in the reflexive stage of swallowing in addition to the brainstem. It is possible that the swallowing network directs muscle recruitments necessary for the execution of swallowing sequences and this drive continually compares and contrasts the sensory input from the food bolus regarding its size, texture, and direction of bolus flow as it moves along the oral and pharyngeal regions. This integration between descending signals and afferent inputs may occur in the cortex and cerebellum, within which multiple synaptic connections that are responsible for different functions are present. Some cortical regions may be responsible for integrating mastication with swallowing while others compare the descending signals to the brainstem with sensory feedback as the bolus moves along the swallowing tract. It is also possible that the primary swallowing pathway may expand to recruit other regions within the central nervous system depending on additional factors such voluntarily eliciting swallowing, chewing and swallowing, swallowing on different types of foods, and chemical properties of food like calories, sugar and other factors that the central nervous system evaluates as we eat. Moreover, changes in lateralization suggest that the swallowing process involves dynamic interhemispheric control and coordination which may reflect hemispheric specialization. Although data from these studies do not allow conclusive identification of the functional roles of each hemisphere in swallowing, they suggest that each may be responsible for different components of the swallowing process. Further studies on the sequential cortical activation during swallowing will provide more insights into the possibility of hemispheric specialization for swallowing. Finally, it would be intriguing to investigate the interactions between the homologous cortical areas of the two hemispheres when bilateral muscles are recruited during swallowing. Given the strong bilateral connections at the brainstem level, it is reasonable to expect that similar level of bilateral connections would be present at the cortical level.

6. Changes in cerebral control of swallowing after stroke

Incidence of dysphagia is high (up to 78%) following stroke [148], yet most patients recover within first 2 weeks of stroke onset [149]. Such recovery is thought to be, in part, driven by neuroplasticity, which is the reorganization of function, structure, and connections of the nervous system in response to intrinsic and extrinsic stimuli [150]. The neurological differences between persistent dysphagic patients and patients who have recovered from initial dysphagia may provide insights into the underlying neurological changes essential for functional recovery. Neurophysiological studies have showed that dysphagia is associated with reduced pharyngeal cortical representation in the undamaged hemisphere and recovery of swallowing is likely to be driven by an increase in cortical representation of the undamaged hemisphere [151]. This suggests that compensatory recruitment of intact neural networks may be key for dysphagia recovery.

Functional neuroimaging studies have suggested differences in cortical activation during swallowing between patients with post-stroke dysphagia and healthy controls, but the findings were not conclusive across studies. Increased cortical activation in recovering patients and correlations between dysphagia severity and degree of activation have been reported in some studies [54,57]. This is in accordance with previous TMS findings that showed compensatory redistribution of swallowing network. However, contradictory observations on the degree of activation have also been reported in these studies. Li et al., [54] found increased activation in patients than healthy controls, whereas Mihai et al., [57] found an overall reduction in activation in patients. This difference in observation may be due to differences in the time of studies from ictus (acute vs. sub-acute vs. chronic), dysphagia status (dysphagia

versus recovered) of patients and in swallowing trial protocols.

The pattern of cortical activation during swallowing execution and motor imagery of swallowing has been found to be dependent on lesion location [95]. Using fNIRS, Kober et al., [95] found that dysphagic patients with unilateral cerebral lesions showed greater activation in the affected hemisphere than the unaffected one and prolonged hemodynamic changes compared to healthy and brainstem stroke patients. Previous TMS study showed that patients with persistent dysphagia for 3 months post-stroke did not show increased cortical representation in the undamaged hemisphere [151]. The post-stroke period of the patients studied in Kober et al.,'s [95] study ranged from 2.5 to 8 months. It is possible that the lack of increase in the activation of the unaffected hemisphere may reflect an insufficient compensatory recruitment of intact neural networks essential for recovery, and hence explain the poor prognosis and persistence of dysphagia in these patients.

Taken together, neurophysiological and functional neuroimaging data have provided insights into the neurological changes in patients with post-stroke dysphagia. The increase in cortical representation and activation in the unaffected hemisphere appears to play an important role in the recovery of swallowing following stroke.

7. Changes in cerebral control following other neurogenic diseases

Dysphagia is a common and one of the most severe complications experienced by patients with neurodegenerative diseases, such as Parkinson's disease (PD), Kennedy disease (KD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). The prevalence of dysphagia in PD patients is estimated to be 35% based on objective measurements and up to 85% based on subjective outcomes [152]. However, the underlying pathophysiology of dysphagia in PD patients is poorly understood. It is thought to be related to degeneration of the substantia nigra disturbance of non-dopaminergic systems and neuronal loss in the medullary swallowing central pattern generator [136,153]. Suntrup et al., [154] studied cortical activation during swallowing in 20 PD patients using whole-head MEG. They found that PD patients, particularly those with dysphagia, showed a remarkable decrease in overall activation when compared to healthy controls. Non-dysphagic PD patients showed specific activation patterns, including a shift of peak activation towards lateral premotor, motor and inferolateral parietal cortex during initiation of swallowing and reduced and delayed activation in supplementary motor area. This finding indicated a compensatory mechanism in PD patients with preserved swallowing function.

KD is a rare progressive motor neuron disorder characterized by the degeneration of spinal and bulbar motor neurons [155]. A functional neuroimaging study by Dziewas et al., [156] found that KD patients with dysphagia showed increased bilateral activation in the SM1. Furthermore, their activation patterns during volitional swallowing are different from that of age-matched healthy controls. While healthy controls demonstrated a shift in activation from left to right hemisphere during swallowing execution, KD patients showed predominantly right hemispheric activation throughout the whole process.

ALS is another neurodegenerative disease that is associated with progressive degeneration of upper and lower motor neurons [157]. Studies have shown that patients with ALS began to show dysphagia symptoms, predominantly caused by tongue muscle deficits, approximately 2 years after onset of other symptoms [158]. Using MEG, Teismann et al., [159] found that ALS patients showed reduced activation in sensorimotor cortices during swallowing when compared to healthy controls. Moreover, cortical activation in patients with severe dysphagia was lower than those with mild dysphagia, suggesting a progressive deterioration in cortical activation with the progression of the disease. This study also found that, similar to KD patients, ALS patients showed predominantly right hemispheric activation during swallowing, in contrast to the slightly stronger left hemispheric activation in healthy controls. This right hemispheric lateralization may be related to cortical

reorganization in ALS patients such that pharyngeal phase swallowing deficits may be compensated by increasing the number of active neurons in the right hemisphere.

HD is associated with motor dysfunction, cognitive decline and psychiatric symptoms [160]. Neuropathologically, HD is characterized by progressive striatal degeneration and cortical atrophy throughout the course of the disease. HD patients may experience difficulties at all stages of swallowing, including lingual dysfunction, reduced soft palate elevation, delayed pharyngeal swallow initiation, difficulties in clearing pharyngeal residue and compromised airway protection [137]. A recent neuroimaging study found that dysphagia in HD patients is associated with atrophy in the left S1, the right inferior temporal lobe, bilateral thalamus and cerebellum [160]. Using functional 18F-fluorodeoxyglucose Positron Emission Tomography (FDG PET), Trender-Gerhard et al., [161] found that HD patients with mild dysphagia showed different cortical activation patterns compared to healthy controls. They showed reduced activation in the frontal cortex than other brain regions and pronounced activation in precentral and anterior cingulate cortices during swallowing and at rest.

Taken together, these findings showed that different neurogenic disorders exhibit different cortical activation patterns during swallowing, suggesting that each neurogenic disorder may have unique adaptive mechanisms. As such, it would be inappropriate to assume that damage to particular structures would always result in certain adaptive behaviors.

8. Neurostimulation treatments for dysphagia following stroke

Dysphagia is commonly managed by compensatory and/or rehabilitative approaches. Compensatory strategies include modifications of diet texture, feeding posture, or feeding route to minimize the risk of aspiration whereas rehabilitative treatments include exercises that aim to recover oromotor and swallowing functions. Recent systematic reviews suggested that the clinical efficacy for existing rehabilitative exercises is limited and controversial [162,163]. The growing understanding of neurological changes in patients with neurogenic dysphagia has led to the development of novel treatment approaches, including central and peripheral neurostimulation, that target at promoting reorganization of swallowing neural network. Central neurostimulation refers to stimulation techniques that target at the brain, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Both rTMS and tDCS can be used to non-invasively modulate cortical excitability and induce long-lasting neuroplasticity changes [164]. In the human swallowing system, studies have shown that high frequency rTMS or anodal tDCS increases cortical excitability whereas low frequency rTMS or cathodal tDCS reduces cortical excitability [164]. These changes in cortical excitability were accompanied by improvement (high-frequency rTMS or anodal tDCS) or suppression (low-frequency rTMS) of swallowing performance. Low-frequency rTMS has been used to induce "virtual lesion" in healthy subjects as a powerful tool to test feasibility of novel treatment protocols given its ability to temporarily disrupt the swallowing system [110,111,165–168]. Peripheral neurostimulation refers to stimulation of peripheral nerves and muscles that result in long term changes in neuroplasticity of the swallowing system. Such stimulation can be electrical [115], thermal [169], or chemical [170]. Mechanical stimulation such as air-pulse stimulation may increase cortical activation during swallowing [113], yet further studies are needed to establish its capacity in inducing neuroplasticity.

The effects of both central and peripheral neurostimulation on swallowing have been studied extensively over the past two decades. Recent meta-analysis showed that these treatments are beneficial for improving dysphagia severity and reducing risk of aspiration in stroke patients [171]. However, certain limitations, such as individual variability in responsiveness, uncertainties on the safety in patients with comorbidities and insufficient evidence from large-scale clinical trials,

have hindered the translation of these treatments into the mainstream clinical practice [172]. Several studies have proposed strategies to maximize the beneficial outcomes of these treatments. Raginis-Zborowska et al., [173] reported that the individual's genetic predisposition may affect the responsiveness to rTMS and suggested that it may be one of the selection criteria for who will likely to be benefited from rTMS treatments. In a recent study, Cheng et al., [174] derived a preconditioned rTMS protocol that resulted in greater excitation in cortical excitability and improvement in swallowing accuracy than conventional rTMS. This protocol involves preconditioning of the M1 with low frequency rTMS prior to high frequency rTMS. Future development of neuromodulation treatments for dysphagia may build on this theoretical basis of preconditioning of the swallowing motor system.

9. Conclusions

We have reviewed animal, human clinical, neurophysiological, neuroanatomical and functional neuroimaging data on the cerebral control of swallowing. Functional neuroimaging studies have collectively shown that multiple distinct regions within the cerebrum are involved in swallowing. The primary sensorimotor cortex, insula and cingulate cortex are regions that have been most consistently identified. These regions are functionally connected; however, further studies are warranted to fully elucidate their functional organization in the swallowing system. Hemispheric dominance of swallowing has been reported in most studies, yet the laterality is inconsistent across individuals. Moreover, studies have found that cortical activation patterns shift in both location and laterality throughout the swallowing preparatory to execution process, although such activation changes are less well-defined than that for limb motor control. Finally, several neuromodulation technologies that can promote neuroplasticity have shown promise as therapies for post-stroke dysphagia, based on a fundamental understanding of the cerebral control of swallowing and brain areas to be targeted to achieve optimal neurorehabilitative outcomes.

Statements and Declarations

All authors declare no conflicts of interest.

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