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REVIEW ARTICLE

Neuroplasticity and Swallowing

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Abstract Recent research has suggested that the central nervous system controlling swallowing can undergo experience-dependent plasticity. Moreover, swallowing neuroplastic change may be associated with behavioural modulation. This article presents research evidence suggesting that nonbehavioural and behavioural interventions, as well as injury, can induce swallowing neuroplasticity. These studies indicate that while swallowing and limb neuroplasticity share certain features, certain principles of swallowing neuroplasticity may be distinct. Thus, an understanding of swallowing neuroplasticity is necessary in terms of explaining and predicting the (1) behavioural effects of injury to the swallowing nervous system and (2) effects of swallowing interventions applied in rehabilitation.

Keywords Neuroplasticity · Swallowing · Cerebral cortex · Rehabilitation · Experience · Oropharyngeal · Deglutition · Deglutition disorders

Neuroplasticity, which refers to the ability of the central nervous system (CNS) to alter itself morphologically or functionally as a result of experience, is one of the major frontiers of neuroscience today (for reviews, see [34, 65]). Over the past two decades, there has been tremendous growth in research on neuroplasticity. A recent PubMed search identified a tenfold increase in published papers on neuroplasticity between 1985 and 2005. Yet, the concept of neuroplasticity is not new. In the 1960s, Hubel and Weisel demonstrated the effects of visual experience on ocular dominance columns in kittens (for review, see [12]). At about the same time, enrichment studies showed that rats raised in an enriched environment had larger brains, with increased cortical thickness, compared with rats raised in standard environments, and that while these brain changes were more pronounced if the enrichment occurred during development, they also occurred if the exposure occurred during adulthood (for review, see [29, 60]). Merzenich and colleagues [96, 98] subsequently documented persistent functional changes within the sensorimotor cortex following transient sensory or motor manipulations. These seminal studies laid the early foundation for the current view that neuroplasticity is a fundamental property of the CNS through which it is continually remodeled across the life span in response to experience [67]. Similar mechanisms may underlie neuroplasticity in the developing and the adult brain [70]. For example, the concept of developmental "critical periods," during which given experiences have particularly robust influences on the organization of brain and behaviour, bears similarity to the enhanced receptivity to modulation that can be induced in the adult brain by training, stimulation, and injury [60].

One of the most compelling aspects of recent neuroplasticity research is the emerging understanding that neuroplastic change can be associated with behavioural alteration [67]. That is, experiences that drive neuroplasticity may also give rise to behavioural change through their effects on brain morphology and/or function. Experiences that appear to have the potential to affect neuroplastic and associated behavioural change include peripheral or central injury [61, 78], as well as a broad range of external interventions, including sensory

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stimulation or deafferentation [21, 80, 96], motor skill acquisition [62], and electrical [7] or magnetic stimulation [79]. Correlated neuroplastic and behavioural changes that occur in response to experience may be adaptive modifications that benefit the organism or maladaptive changes that give rise to impaired function [24].

Aims of the Review

This review article examines neuroplasticity as it relates to swallowing (for discussion, see [44, 72, 75]). The principal motivation for exploring neuroplasticity in the context of swallowing is the mounting evidence that (1) swallowing neural substrates can undergo plastic changes as a function of experience, and (2) these swallowing neuroplastic changes may be associated with modulated swallowing behaviour. Given the possibility of an association between swallowing neuroplasticity and behavioural change, neuroplasticity may provide a "*mechanistic rationale*" [60] for *explaining* and *predicting* (1) swallowing impairment and swallowing recovery following injury, and (2) the effects of therapeutic interventions employed in swallowing rehabilitation. Such a mechanistic rationale would be of great value, both theoretically and clinically, since current understanding of swallowing neuropathophysiology and swallowing modulation as a function of rehabilitation is incomplete.

A second motivation for examining neuroplasticity in relation to swallowing is that the vast majority of the literature on sensorimotor neuroplasticity is based on studies of limb function [34]. Yet, there are reasons to question whether principles of neuroplasticity derived from limb studies will hold for swallowing. In contrast to limb movements, oropharygneal functions, including swallowing, involve the coactivation of paired, midline muscles. There is less lateralization of brain function for oral and oropharygneal functions compared to limb function, with contralateral and ipsilateral contributions [15, 58]. Swallowing and other oropharyngeal sensorimotor behaviours involve the contraction of a number of specialized muscles, for example, tongue muscles that lack a bony skeletal framework [89]. Also, because the oral/oropharyngeal sensorimotor system gives rise to a broader range of autonomic and volitional behaviours (e.g., swallowing, mastication, respiration, speech, phonation, volitional oral movements) than the limb, the oral system provides a greater opportunity to explore how, for example, voluntary sensorimotor training might influence the neural and behavioural correlates of autonomic behaviours that recruit the same end organs and overlapping cortical sensorimotor representations (e.g., voluntary tongue movement versus oropharyngeal swallowing; see [52]).

This article reviews the research evidence that (1) neuroplasticity within the swallowing/oral nervous system occurs as a function of (a) external interventions or (b) injury, and (2) this neuroplasticity is associated with swallowing/oral behavioural change. Principles of neuroplasticity within the swallowing system are discussed. Experimental approaches for exploring the potential neuroplastic correlates of swallowing modulation and challenges involved in testing the neuroplastic effects of various classes of swallowing interventions are discussed.

Plasticity has been demonstrated within multiple levels of the nervous system (for review, see [100]) mediating swallowing, including the cortex, nucleus tractus solitarius (for review, see [4]) and the dorsal vagal complex [3]. However, the focus of this review will be on cortical plasticity since the majority of the human swallowing neuroplasticity literature has addressed cortical plasticity in particular.

Neuroplasticity as a Function of External Interventions

A variety of external interventions such as sensory experience, motor skill acquisition, and electrical or magnetic stimulation have been shown to affect neuroplasticity. These interventions can be conceptualized as nonbehavioural or behavioural (Fig. 1). Nonbehavioural interventions refer to those in which the subject is a passive recipient, with no overt immediate response being required of the subject in response to the application of the intervention in order for it to have a modulatory effect. Three types of nonbehavioural interventions have been examined in terms of swallowing neuroplasticity: (1) peripheral electrical stimulation, (2) peripheral sensory (nonelectrical) stimulation, and (3) transcranial magnetic stimulation (TMS).

These nonbehavioural interventions can be contrasted with behavioural interventions that require a motor response as an integral part of the intervention protocol. These include motor training and muscle strengthening exercises. To date, very few studies have examined the potential effects of behavioural interventions on

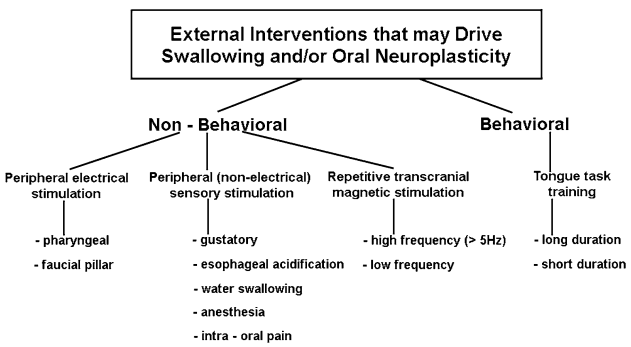

Fig. 1 Experiences that may drive swallowing neuroplasticity

swallowing neuroplasticity. However, a number of studies have examined the effects of oral task training in animal models and humans, as reviewed below.

Effects of Nonbehavioural Interventions

Peripheral Electrical Stimulation

Hamdy et al. [25] have reported a series of studies that focused on the neuroplastic and behavioural effects of electrical stimulation applied to the pharynx or oropharynx. In 1998, Hamdy et al. [25] showed that a 10-min application of a 10-Hz electrical pharyngeal "sensory" stimulation increased the amplitude of pharyngeal electromyographic (EMG) responses to transcranial magnetic stimulation (TMS) but reduced the amplitude of esophageal EMG responses to TMS in eight healthy control subjects. This increased excitability of the pharyngeal motor cortex was observed immediately and at 30 min after the pharyngeal stimulation. EMG responses returned to baseline levels by 60 min post-stimulation. The pharyngeal stimulation was also associated with an increase in the size of the pharyngeal motor cortical representation and a decrease in the size of the esophageal representation such that the pharyngeal representation appeared to have expanded into the suppressed esophageal area. The authors concluded that the organization of the "swallowing motor cortex can be altered in a sustained manner after sensory stimulation of the pharynx [25]."

A subsequent study by Fraser et al. [19] showed that, in eight healthy volunteers, the neural reorganization associated with pharyngeal electrical stimulation depended on certain parameters of the pharyngeal stimulation, where the greatest increase in pharyngeal EMG responses to TMS occurred following stimulation at 5 Hz, 75% maximum tolerated amplitude, for 10 min. Stimuli of 10 Hz and higher were reported to have the opposite effect, reducing excitability of the pharyngeal motor cortex. The maximal facilitatory effect occurred at 60 and 90 min after pharyngeal stimulation, but not following sham. Functional MRI (fMRI) of swallowing showed an increase in the area of swallow-related activation within the sensorimotor cortex 1 h after pharyngeal stimulation. Furthermore, in a group of 16 patients with dysphagia secondary to acute hemispheric stroke (mean 4 days post-stroke), 10 randomized to pharyngeal stimulation and 6 to sham, videofluoroscopic studies compared before and 1 h after stimulation revealed reduced pharyngeal transit times, swallowing response times, and aspiration scores post-treatment in the stimulation group only. Cortical excitability and pharyngeal motor representation size were correlated with change in aspiration scores.

Power et al. [68] examined the effects of electrical faucial pillar stimulation in healthy controls. They reported that stimulation at 5 Hz produced cortical inhibition and had a negative effect on swallowing, while low-frequency (0.2 Hz) stimulation increased cortical excitability at 60 min post-stimulus and had no effect on swallowing. In a subsequent study of 16 patients with dysphagia following stroke who were randomized to stimulation or sham group, however, 0.2-Hz electrical stimulation of the faucial pillar failed to produce effects on swallowing [69]. Thus, the authors questioned the clinical utility of faucial pillar stimulation in the rehabilitation of swallowing following stroke.

The finding that faucial pillar electrical stimulation at 0.2 and 5 Hz induced opposite effects on cortical excitability warrants further investigation. As Power et al. [68] noted, previous animal studies have shown that stimulation of swallowing afferent pathways can have either excitatory or inhibitory effects, depending on the stimulus intensity and frequency. They further suggested that the 5-Hz stimulus may have been perceived as noxious, with the result that it activated inhibitory circuits. In support of this possibility, noxious electrical stimulation has been shown to induce long-term depression (LTD) of oral somatosensory processing. For example, Ellrich [17] showed that low-frequency (i.e., 0.1 Hz) stimulation of the tongue induced a sustained decrease in the jaw-opening reflex (JOR), while high-frequency tongue stimulation induced a transient JOR increase for less than 10 min in mice. In humans, LTD of the blink reflex by noxious electrical low-frequency stimulation of the forehead and of the masseter inhibitory reflex by noxious stimulation of mental nerve afferents has been reported [83]. Furthermore, LTD of spinal field potentials was switched to long-term potentiation (LTP) following spinalization [42], suggesting that central mechanisms contribute to the excitatory versus inhibitory effects of peripheral electrical stimulation.

Peripheral Sensory Stimulation

The finding that pharyngeal electrical stimulation is associated with swallowing neuroplastic and behavioural change suggests the possibility that other, nonelectrical sensory stimuli may have similar effects. The potential for such neuroplastic change is further supported by the extensive animal literature showing that peripheral orofacial manipulations such as whisker trimming in the rat can give rise to experience-dependent neuroplastic changes in adult animals [94]. A number of studies have suggested that mechanical, thermal, and gustatory stimuli, and combinations of these, as well as deafferentation, may modulate swallowing behaviour in healthy controls and patients with dysphagia [6, 29, 40, 76]. Thus, these sensory

interventions are logical targets of neuroplasticity research. However, few studies have examined the neuroplastic effects of peripheral sensory stimulation applied to the swallowing mechanism.

Mistry et al. [54] used TMS mapping of the pharyngeal motor cortical representation before and after a 60-min infusion of neutral, sweet, or bitter liquids that were swallowed or delivered directly to the stomach in healthy controls. They found that the amplitudes of motor evoked potentials (MEPS) were reduced at 30 min following tastant application in the swallowing condition; however, no changes in MEP amplitude were seen with the stomach delivery condition. Thus, gustatory stimulation during swallowing appeared to have lasting effects on the excitability of the pharyngeal motor cortex.

Paine et al. [64] examined the effects of esophageal acidification on the swallow-related cortical activation using fMRI. They found that, following a 30-min acid infusion to the distal esophagus, there was a significant reduction in swallow-related activation within the precentral gyrus. Thus, esophageal acidification appeared to inhibit motor and association cortical areas during a swallowing task.

Fraser et al. [20] reported that a 10-min period of water swallowing (5 ml per swallow; swallowing frequency = 0.2 Hz) was associated with an immediate, transient increase in pharyngoesophageal corticobulbar and craniobulbar excitability, as measured by EMG responses to TMS in healthy controls. In contrast, pharyngeal electrical stimulation produced a delayed increase in corticobulbar excitability that reached a maximum at 60 min poststimulation but had no effect on craniobulbar excitability. Following anesthesia, the excitability of both corticobulbar and craniobulbar pathways decreased, with the greatest decrease occurring 45 min following anesthesia. Thus, swallowing appeared to give rise to an early facilitation of corticobulbar and craniobulbar pathways, while deafferentation caused a delayed inhibition of both pathways. Based on these findings, Fraser et al. [20] suggested that both volitional swallowing and pharyngeal stimulation might be employed in dysphagia rehabilitation as methods of driving cortical excitability. However, based on the finding that pharyngeal stimulation produced a longer and somewhat larger effect than swallowing and the challenge of volitional swallowing for dysphagic patients, they favored stimulation techniques over volitional exercises.

Repetitive Transcranial Magnetic Stimulation

Whereas single-pulse TMS can alter cortical excitability for a short period, trains of magnetic pulses, called repetitive TMS (rTMS), can have longer-term effects on neural circuits [34, 43]. Indeed, positive effects of rTMS in depressed patients have been reported to last for several weeks [18]. Effects can be excitatory or inhibitory depending on rTMS frequency, with low-frequency stimulation inducing inhibition and high-frequency stimulation (i.e., 5 Hz and higher) generally producing excitatory effects [66]. Recently, motor cortex stimulation with theta-burst patterns resulted in more intense and longer-lasting modulation of MEPs [32]. rTMS-induced modulatory effects have been documented not only at the locus of simulation, but also at a distance of one or more synapses [97]. While rTMS is believed to alter the excitability of cortical neurons by changing the effectiveness of synaptic interactions through mechanisms similar to long-term depression (LTD) and long-term potentiation (LTP), the underlying physiology is not fully understood [43].

While the vast majority of the rTMS literature has focused on the limb, recent studies have examined the effects of rTMS on swallowing and its neural representation. Gow et al. [22] showed, in healthy controls, that rTMS at 5 Hz applied over the swallowing motor cortex increased the excitability of the corticobulbar projection to the pharyngeal musculature, with the greatest increase occurring 60 min following rTMS. Mistry et al. [55] subsequently showed that only high-intensity 1-Hz rTMS consistently suppressed pharyngeal motor cortex excitability immediately and for up to 45 min after TMS. Furthermore, when 1-Hz rTMS was applied unilaterally to each hemisphere, rTMS applied to the pharyngeal motor representation that had evoked the stronger MEPs altered normal and fast swallowing response times. These results show that the suppression of the pharyngeal motor representation by rTMS is intensity- and frequency-dependent and they support the view of a hemispheric functional asymmetry in the control of swallowing. In a subsequent study, Jefferson et al. [35] showed that the inhibitory effect of unilateral 1-Hz rTMS, which could be seen as a "virtual lesion," could be reversed by excitatory 5-Hz rTMS applied to the opposite hemisphere, with cortical excitability increasing in both the lesioned and the contralesional hemisphere. Thus, they suggested that rTMS might be useful as a therapeutic intervention for dysphagia.

Significance of Neuroplasticity Studies on Nonbehavioural Interventions

These studies on sensory neuroplastic effects are highly significant because they provide the first evidence that sensory experience can drive plasticity within the neural system that mediates swallowing. These neuroplastic effects may be correlated with swallowing behavioural modulation, suggesting that peripheral sensory stimulation may be an important therapeutic intervention in swallowing rehabilitation.

Kleim and Jones [38; see also 44, 73] have discussed ten principles of experience-dependent plasticity: (1) use it or lost it, (2) use it and improve it, (3) plasticity is experience-specific, (4) repetition matters, (5) intensity matters, (6) time matters, (7) salience matters, (8) age matters, (9) transference, and (10) interference. The findings of Hamdy et al. [25] suggest that several of these principles apply to the swallowing system. The finding that pharyngeal stimulation gives rise to alterations in the excitability and size of the pharyngeal motor cortex suggests that the principles of "use it and improve it" and specificity hold for the pharyngeal system. The findings that the effects of pharyngeal electrical stimulation and rTMS are frequency-dependent, with cortical excitatory effects peaking at specific times following stimulation, support the importance of repetition, intensity, and time as factors in the neuroplastic processes observed. The associated finding that pharyngeal stimulation gave rise to a decrease in the excitability and size of the esophageal motor cortex indicates that transference of neuroplastic effects across motor cortical representations is also possible.

Future studies should be aimed at replicating and extending the work on the neuroplastic effects of sensory stimulation applied to the swallowing system. One remaining question relates to the frequency-dependent effects of pharyngeal electrical stimulation. Hamdy et al. [25] found that pharyngeal electrical stimulation at 10 Hz had an excitatory effect on pharyngeal motor cortex, whereas Fraser et al. [19] reported a decrease in pharyngeal cortical excitability. The temporal profile of the neuroplastic effects also deserves further study in that Hamdy et al. [25] reported that the greatest neuromodulatory effect was seen immediately and at 30 min after stimulation, whereas Fraser et al. [19] found the greatest effects at 60 and 90 min after stimulation. Another question relates to the possible motor effects of pharyngeal electrical stimulation, given that twitch contractions of the pharynx were reported in two subjects during pharyngeal stimulation at larger stimulus amplitudes [25]. The possibility that transcutaneous electrical stimulation excites not only sensory endings but also motor nerve endings, at higher stimulus intensities, is also supported by a study by Ludlow et al. [44]. The possible contribution of habituation (i.e., adaptation) in swallowing sensory stimulation is another relevant question.

Effects of Behavioural Swallowing Interventions

In contrast to the literature reviewed above on the neuromodulatory effects of nonbehavioural swallowing interventions, to date no studies have addressed the neuroplastic effects of swallowing behavioural training. There is, however, evidence on the neuroplastic effects of oral motor training in both awake primates and humans.

Sessle et al. [48, 85] have reported a series of studies aimed at characterizing the properties and functional organization of the orofacial sensorimotor cortex in the awake primate. They employed intracortical microstimulation (ICMS) to map the input-output properties of neurons in the face sensorimotor cortex, cortical masticatory area (CMA), and cortical swallowing area. Swallowing could be evoked by ICMS applied to four discrete cortical regions: the face primary motor cortex (face MI), face primary somatosensory cortex (face SI), the CMA, and a deep area below the CMA [50]. Many neurons in the swallowing cortical area had somatosensory receptive fields on the tongue surface. Behavioural biting and tongue protrusion tasks were employed to further document the activity-related patterns of neurons in these cortical regions [41, 49, 59]. In the tongue protrusion task, the monkey was trained to protrude its tongue against a force transducer, thereby moving a cursor, which was displayed on a monitor in front of the monkey, from a baseline to a target area. A successful tongue task trial, achieved when the monkey maintained the cursor within the target area for a predetermined time period, was rewarded with juice that was delivered from the force transducer.

Recently, Sessle et al. [85, 86] have used the same experimental paradigm to study the neuroplastic effects of tongue task training on the primate face sensorimotor cortex. They reported that following a 1–2-month period of training on the novel tongue protrusion task, the region of sensorimotor cortex from which tongue protrusion movements were evoked by ICMS expanded and shifted, while the cortical region from which lateral tongue movements were evoked was reduced. They also showed that the proportion of MI neurons and SI neurons showing tongue protrusion-related activity increased significantly following training, as did the proportion of neurons with mechanosensory inputs from the tongue. In contrast, similar neuroplastic changes were not observed within CMA or the swallow cortex following tongue task training, suggesting differential expression of task-related neuroplasticity in these three cortical areas. These findings suggest a degree of specificity in orofacial and swallowing neuroplastic effects and beg the general question of the relative potency of (1) nonswallowing task training versus (2) swallowing-specific task training (e.g., chewing and swallowing), in terms of driving swallowing behavioural change and swallowing neuroplastic effects.

Svensson et al. [90, 91] have employed the same tongue protrusion task paradigm in the context of TMS mapping studies to investigate the neuroplastic effects of tongue task training on the tongue motor cortex in humans. They

mapped the cortical representation of the tongue with TMS before and after tongue training. They reported that following 1 week [90], and as little as 1 h [91], of tongue task training, the amplitude of tongue MEPs was increased at 1 and 7 days post-training. The thresholds for evoking tongue MEPs were decreased at 30 min, 1 day, and 7 days post-training. They also showed that the size of the TMS-defined tongue cortical map was increased at 1 day post-training over baseline levels. Furthermore, success rate on the tongue protrusion task was significantly correlated with net increases in tongue MEPs at 1-day follow-up. Their use of a hand muscle control condition strengthens the findings.

More recently, Boudreau et al. [5] examined the effects of an even shorter period of tongue training (15 min) and the effects of intraoral pain on tongue MI neuroplasticity. In nine healthy adults who participated in two crossover training sessions in which capsaicin cream or vehicle cream was applied to the tongue in random order at the onset of tongue training, 15 min of a novel tongue-training task was associated with an immediate increase in TMS-evoked tongue MEPs and reduced MEP threshold after the vehicle session but not after the capsaicin session. Furthermore, subjects' mean performance scores were significantly higher in the vehicle session than in the capsaicin session. Thus, tongue motor cortical neuroplasticity occurred after a very short period of tongue motor training, and oral pain altered this neuromodulatory process.

Significance of Neuroplasticity Studies of Behavioural Interventions

Like the studies by Hamdy et al., [25] the findings of Sessle et al. and Svensson et al. demonstrate several neuroplasticity principles. The effect of tongue protrusion task training on the tongue motor cortex and tongue motor performance provides support for the principle of "use it and improve it." Expansion of the cortical region from which tongue protrusion movements were evoked by ICMS and the associated reduction in the cortical region from which lateral tongue movements were evoked in the primate [48] are consistent with the concept of specificity and with the view, derived from limb studies, that body regions compete for cortical representation, and the use of a body part can enhance its representation [24]. The finding of Sessle et al. [85] that the neuromodulatory effects of tongue task training were observed within the tongue motor cortex, but not within the CMA or swallow area, also suggests a degree of specificity and supports the view that voluntary tongue training may not give rise to swallowing neuromodulation or behavioural change. That the effects of tongue training were observed at specific times following training [90, 91] suggests the importance of time. In addition, the study by Boudreau et al. [5] provides support for the view that sensory applications can interfere with experience-dependent plasticity.

By showing that a short period of tongue motor training is associated with improved tongue motor performance and neuroplastic change within the tongue motor cortex, these studies also provide a basis for future research that examines the neuroplastic effects of other behavioural interventions on oropharyngeal function and swallowing in particular. Robbins et al. [73] have conceptualized these interventions as (1) compensations, (2) motor training with swallow, and (3) motor training without swallow. This classification scheme is consistent with the limb-training literature that has differentiated two types of training: direct training in which training is aimed specifically at modifying the motor response under study, e.g., training the H-reflex in attempts to modulate the H-reflex. This is contrasted with indirect training, such as strength training, in which the motor behaviour to be modified is not, itself, the object of training; rather, its change occurs "en passant" as part of the broader context of the training [100].

Given the broad range of swallowing behavioural interventions that have been considered in terms of their potential neuroplastic effects, one early challenge is to select a subset of interventions for study based on a number of considerations, including the following:

(1) What is the evidence that the behavioural intervention under consideration modifies swallowing in a lasting manner? While treatment studies have examined many behavioural approaches, randomized controlled trials (RCTs) documenting efficacy are few (for review, see [73]).
(2) What is the likelihood that the behavioural treatment under consideration will drive neuroplastic change, given the principles of neuroplastiticy that have emerged from limb, swallowing, and orofacial neuroplasticity studies? For example, limb studies have shown that while repetitive use of an effector is unlikely to drive long-term cortical change, training that results in increasing motor skill drives cortical neuroplasticity [60]. A related issue is the evidence that attention to sensory features of a training protocol plays a role in regulating cortical plasticity and learning [56]. A number of swallowing behavioural interventions are, or could be, designed within the context of a skill-training paradigm to meet these criteria of skill acquisition and attention. These interventions include direct training such as the effortful swallow [13, 31, 33, 95] and indirect training such as the Shaker head-raising exercise protocol [87, 88], Lee Silverman Voice Treatment [16], tongue-strengthening exercises [39, 72], and expiratory

muscle strength training (EMST) [82]. The neuroplasticity literature suggests that these behavioural interventions will have a greater likelihood of driving neuroplasticity if they employ a precisely defined target motor behaviour (i.e., movement pattern) for which task performance is initially low but gradually increases as the subject repeatedly executes the behaviour to criterion in a consistent fashion.

(3) Are pilot data available to provide an understanding of the behavioural intervention and neural subsystem under study? Neuroplasticity research that is based on a solid foundation of pilot data should be more straightforward to interpret than studies lacking such background. The tongue is a system about which there is substantial background knowledge from cortical electrophysiology in primates [85], functional brain-imaging studies of tongue motor cortex [36, 52], effects of tongue training on tongue motor behaviour and tongue motor cortex [90, 91], and the effects of tongue-strengthening exercises on swallowing and dysphagia [39, 72]. Thus, interventions involving the tongue should be one logical focus of future swallowing neuroplasticity studies.

The tongue-training studies are also significant because they, like the Hamdy et al. studies, provide an experimental model for future neuroplasticity studies of behavioural swallowing interventions. For example, it would be instructive to replicate the tongue task studies of Svensson et al. [90, 91], incorporating outcome measures of swallowing behavioural change and swallowing neuroplasticity such as swallow-related fMRI, to address the question of transference of tongue protrusion training to swallowing. There are challenges to consider, however, such as muscle fatigue. Even 15 min of tongue training may induce tongue fatigue that could affect MEP thresholds and cortical maps. Perhaps muscle fatigue can be addressed in future neuroplasticity studies by employing tasks that require movement accuracy with low levels of muscle force. Other strengths of the studies by Hamdy et al., Sessle et al., and Svensson et al. include the use of the thenar muscle and a sham condition as controls. In considering optimal experimental models for studying swallowing neuroplasticity, an important question relates to the definition of "swallowing neuroplasticity" because it will contribute to determining the study outcome variables. Does an alteration of the TMS-defined tongue motor cortex, as reported by Svensson et al. [90, 91], constitute "swallowing neuroplasticity" given that studies have shown that the sensorimotor cortical representations of the tongue and swallowing overlap [36, 52]? Or, is a change in swallow-related cortical activation per se required as evidence of swallowing neuroplasticity? Similarly, does a change in pharyngeal MEPS and the size of the TMS-defined pharyngeal motor cortex [25, 28] provide evidence of swallowing neuroplasticity, or is swallow-related functional reorganization required to show neuroplastic change of swallowing?

Combining Nonbehavioural and Behavioural Interventions

There is increasing evidence that nonbehavioural and behavioural neuromodulatory experiences can be combined in ways that can maximize the positive functional and neuroplastic changes associated with each experience individually [7, 45]. For example, Butefisch et al. [8] tested the view that use-dependent plasticity could be enhanced with the synchronous application of rTMS to the motor cortex that is engaged in the motor training. They showed, in controls, that training plus synchronous rTMS applied to the contralateral hemisphere enhanced coding of a motor memory, while rTMS applied to the ipsilateral hemisphere blocked this effect. Kim et al. [37] showed that high-frequency rTMS over the contralateral MI increased the amplitude of finger MEPs, and this plastic change was positively associated with increased accuracy in finger motor task performance. These studies suggest that one neuromodulatory experience may give rise to an experimentally induced critical period during which the effects of a second neuromodulatory experience are enhanced. Thus, nonbehavioural interventions that have been shown to drive neuroplasticity within the swallowing system, such as pharyngeal electrical stimulation and rTMS, might be combined with behavioural approaches such as task training to potentiate the neuromodulatory and behavioural effects of these interventions.

Injury

Studies in both animals and humans have shown that injury to the central or peripheral nervous system can induce neuroplastic effects (for reviews, see [9, 11, 78, 81]). While the majority of injury studies have examined limb function, there is an emerging literature on the neuroplastic effects of central and peripheral injury to the orofacial, oropharyngeal, and swallowing systems.

Central Injury

Abnormal patterns of brain activation associated with motor behaviour have been reported to arise early after stroke and also several weeks after stroke. These patterns include increased bilateral activation, recruitment of

additional sensory and secondary motor cortical areas that are not normally involved in the motor task, expansion of one primary sensorimotor representation into an adjacent area, and peri-infarct activation (for reviews, see [9, 78, 92]). Functional brain changes following stroke appear to occur via two types of reorganization. Rapidly occurring brain alterations appear to reflect the increasing efficacy and unmasking of pre-existing synaptic connections [77]. In contrast to these rapid neuroplastic effects, longer-term changes that occur over days and weeks are believed to reflect the formation of new synaptic connections [70, 77]. Several factors contribute to these patterns of reorganization. For example, as discussed previously, unmasking may reflect the phenomenon whereby body regions compete for cortical representation, with the use of a body part potentially enhancing its representation [24]. Another related concept is interhemispheric inhibitory dynamics. In health, the two hemispheres function in a state of balance through interhemispheric inhibition [65, 67]. Following stroke, there is release of the intact hemisphere due to reduced inhibition by the lesioned hemisphere. Thus, one approach to improving function after stroke involves decreasing the excitability of the intact hemisphere with low-frequency rTMS (for review, see [101]) in an attempt to decrease the inhibition of the lesioned hemisphere by the intact hemisphere. Studies have shown that low-frequency rTMS applied to the intact motor cortex following stroke is associated with improved performance of the paretic hand in a variety of hand motor tasks [46]. Interhemispheric inhibition also forms the conceptual basis for constraint-induced therapy (CIT) that aims to improve upper-extremity paresis following stroke by involving the paretic limb in intensive practice of function tasks while restraining the less-affected arm [47]. CIT has been associated with expansion of the affected hand's representation and behavioural improvements in upper-extremity function (for review, see [10]).

Neuroplastic Effects of Stroke on Swallowing

Hamdy et al. [27] compared the TMS-defined pharyngeal motor cortical representation in two patients with unilateral hemispheric stroke, one with and one without severe dysphagia. While both patients had reduced pharyngeal responses from the affected hemisphere, the cortical representation of the pharyngeal musculature in the unaffected hemisphere differed between the two patients, with a large pharyngeal representation identified in the nondysphagic patient and a much smaller area in the dysphagic patient. Moreover, the size of the representation in the unaffected hemisphere increased as swallowing improved in the dysphagic patient. A subsequent study by Hamdy et al. [26] reported that dysphagic patients who recovered swallowing function had an increase in the pharyngeal motor cortical representation in the unaffected hemisphere at 1 and 3 months poststroke, without a change in the representation within the affected hemisphere. In contrast, the thenar cortical representation increased in the affected hemisphere but not in the unaffected hemisphere at 1 and 3 months poststroke. These findings suggested (1) a role for the intact hemisphere in swallowing recovery and (2) the importance of return of function in the lesioned hemisphere in limb recovery following stroke.

The finding of Hamdy et al. [26] suggesting the importance of the lesioned hemisphere in recovery of limb function is consistent with previous studies. Investigations of limb recovery following stroke have shown that a return of finger-movement-related activation in MI and SI towards the lesioned hemisphere is associated with better finger motor recovery [10]. The distinction between the neuroplastic processes of swallowing and limb motor recovery following stroke reported by Hamdy et al. [26] is also consistent with a study by Muellbacher et al. [57] in which TMS was used to study the tongue motor representation following unilateral stroke. In patients with unilateral lingual paralysis, TMS of the intact hemisphere produced contralateral and ipsilateral lingual compound muscle action potentials (CMAPs), with those in the contralateral tongue being of greater amplitude and shorter latency. In contrast, TMS applied to the lesioned hemisphere failed to produce any CMAPs bilaterally. (Controls showed bilateral CMAPs following TMS applied to either hemisphere.) Following recovery of tongue function, TMS applied to the lesioned hemisphere still failed to evoke lingual CMAPs, leading the authors to conclude that the recovery of lingual movements must have been mediated by the intact hemisphere. Thus, they suggested that "…the intact hemisphere is responsible for restoration of normal lingual movements most likely by potentiating the effects of pre-existing uncrossed motor pathways" [57]. Taken together, these studies suggest that motor systems in which the cortical sensorimotor representation is largely contralateral may require activation of the lesioned hemisphere for motor recovery because the ipsilateral representation is insufficient to support function. In contrast, in motor systems of paired, midline muscles that have contralateral and substantial ipsilateral cortical sensorimotor representations, descending cortical inputs from the unaffected (i.e., ipsilateral) hemisphere play a major role in mediating functional recovery.

Oh et al. [63] reported that a 2-week program of electrical stimulation applied to the neck over the anterior digastric and thyrohyoid muscles in eight dysphagic stroke patients was associated with increased amplitudes of TMS-evoked cricothyroid muscle MEPs and an expansion of the

cortical motor representation. These neural changes were correlated with improvement in swallowing as determined from videofluoroscopy up to 12 h after stimulation. The study did not report a sham or control condition.

As noted above, Ludlow et al. [44] have suggested that transcutaneous electrical stimulation at higher stimulus amplitudes may excite both sensory and motor nerves. Thus, the mechanism through which neck stimulation induced swallowing effects in the study by Oh et al. [63] remains open to question.

Peripheral Injury

Peripheral injury also appears to have the potential to induce neuroplastic changes, not only within the limb system but also within the orofacial system (for review, see [84, 86]). The majority of studies have examined the effects of oral manipulations in animal models, although studies in humans have recently been reported.

Sessle et al. [86] have reported a series of animal studies in which the effects of a variety of oral manipulations on face MI have been investigated. Adachi et al. [1] showed that lingual nerve transection was associated with time-dependent changes in the ICMS-defined genioglossus and anterior digastric representations within the primary motor cortex. Trimming of the rat mandibular incisors so as to modify their contact with the maxillary teeth was associated with a decrease in the anterior digastric (AD) representation in the face MI [86], while tooth extraction increased the cortical AD representation 1 week after extraction [2]. These various outcomes across studies led Adachi et al. [2] to conclude that specific types of peripheral manipulations induce different forms of neuroplasticity within MI.

A small number of studies have examined the effects of deafferentation on human orofacial or pharyngeal neuroplasticity. Halkjaer et al. [23] examined the effects of lingual nerve anesthesia on tongue MEPs evoked by TMS applied over the tongue motor cortex. They reported a delayed facilitation of lingual MEPs approximately 50 min following nerve block. As discussed earlier, Fraser et al. [20] reported that oropharyngeal anesthesia led to a delayed decrease in the excitability of both the pharyngeal and esophageal corticobulbar and craniobulbar pathways.

The neuroplastic effects of peripheral paralysis have also been examined. Peripheral facial paralysis is associated with an expansion in the adjacent TMS-defined hand motor cortex representation [71]. More recently, Yildiz et al. [99] reported a TMS mapping study of face MI in patients with unilateral peripheral facial paralysis (PFP). They showed that the mean amplitude of intact perioral MEPs elicited by TMS applied to the ipsilateral hemisphere was significantly higher in patients than in controls, suggesting a cortical reorganization in the hemisphere contralateral to the paralytic side leading to increased corticofugal output to the intact perioral muscles. Similarly, Rodel et al. [74] found evidence of bilateral tongue motor cortex reorganization in PFP patients.

The neuroplastic effects of paralysis of the swallowing musculature were recently examined in a magnetencephalography (MEG) study by Teismann et al. [93]. They studied cortical activation associated with water swallowing in a patient with wound botulism, a muscle-paralyzing disease that causes severe dysphagia. MEG of water swallowing performed at a time when the patient showed severe dysphagia revealed reduced swallow-related sensorimotor cortical activation but strong activation of the right insula and left posterior parietal cortex (PPC). In contrast, MEG performed 5 days later, after clinical recovery of swallowing, showed reduced activation of the right insula and PPC but bilateral activation of the primary and secondary sensorimotor cortex, similar to that seen in a group of healthy controls. In terms of rehabilitation, these studies suggest that the management of patients with dysphagia secondary to peripheral injury should take into account not only the impact on swallowing of the peripheral injury per se, but also its potential effects on the central cortical representation of swallowing [51–53].

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