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Organization and reorganization of human swallowing motor cortex: implications for recovery after stroke*

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ABSTRACT
Swallowing problems can affect as many as one in three patients in the period immediately after a stroke. In some cases this can lead to serious morbidity, in particular malnutrition and pulmonary aspiration. Despite this, swallowing usually recovers to a safe level in the majority of patients within weeks. This propensity for recovery is likely to relate to how the swallowing motor cortex is organized and then reorganized after cerebral injury. In this review, we examine present knowledge on the cortical control of swallowing in humans, and examine the aspects of its organization that are important for compensating for recovery after damage. In addition, we examine approaches which may be useful in speeding up the process of recovery. Swallowing may turn out to be a useful model for studying central nervous system plasticity.

CENTRAL NERVOUS SYSTEM (CNS) NEUROPLASTICITY
CNS plasticity refers to the ability of neuronal systems to alter function in response to changes in input, both physiological and pathophysiological [1]. The precise role of neuroplasticity in modelling and remodelling behaviour is still unclear, although over the last two decades a number of studies have improved our understanding both of the mechanisms responsible and of its relationship with injury [2]. These studies have demonstrated that neuroplasticity may be both beneficial, as in recovery of function after cerebral injury [3], and also maladaptive, for instance in the development of pain syndromes, e.g. phantom limb pain after amputation [4]. At present, while there is increasing evidence that neuroplasticity plays a substantial role in central remodelling of human function after cerebral injury, understanding of how it relates both to pathophysiology and functional recovery remains limited.

CEREBRAL INJURY AND RECOVERY
Cerebral injury is a common consequence of a number of disease processes, such as trauma, infection and stroke. Stroke, one of the commonest causes of brain injury (e.g. following intra-cerebral haemorrhage or ischaemia), often results in a catastrophic cerebral insult, leading to significant disability or even death [5]. Nonetheless, stroke is of interest in that it represents a definable neural insult, in terms of both CNS location and resulting...
disability, and is easily identifiable by non-invasive imaging, making it a useful human model for studying neuroplasticity after cerebral injury.

Postulated mechanisms for recovery after stroke have included restoration of function within viable cortex in the damaged hemisphere and/or functional reorganization within cortex of the undamaged hemisphere [6–8]. Most current neuro-rehabilitative treatments available for stroke lack objective scientific evidence to support their efficacy [5]. Furthermore, while neuroprotective agents in the acute phase of the stroke have shown promise [9], the majority of stroke victims are unlikely to benefit from such interventions due to the limited ‘time window’ for therapeutic effect. There is, therefore, a clear need to develop novel approaches to neuro-rehabilitation, based on objective scientific methods, and centered around an understanding of how human neuroplasticity can be manipulated.

CNS CONTROL OF SWALLOWING

It is now well established that the cerebral cortex plays an important functional role in the regulation of swallowing [10]. While the reflexive component of swallowing depends on swallowing centres in the brainstem, the initiation of swallowing is a voluntary action that involves the integrity of motor areas of the cerebral cortex [11]. In anaesthetized animals, electrical stimulation of either hemisphere can induce swallowing [12]. This might be interpreted as indicating that both hemispheres have an equal role in controlling the swallowing process [10]. Analogous neurosurgical studies of the motor cortex in humans [13,14] have usually been confined to one hemisphere, so that a direct comparison with animal data has not been possible. However, these human data show that the locus of the cortical control of swallowing lies within and antero-caudal to the face area of primary motor cortex [13].

THE PROBLEM OF DYSPHAGIA AFTER STROKE

Injury to swallowing areas of motor cortex and/or their connections to the brainstem will usually result in problems with swallowing (dysphagia). The commonest reason for dysphagia in the U.K. is now stroke [15]. Up to half of all stroke patients experience dysphagia, which is associated with the life-threatening complications of pulmonary aspiration and malnutrition [15,16]. Dysphagia leads to increased length of stays in hospital and greater demands on health service resources, estimated to be an extra £400 million per year in the U.K. [17]. Diagnosing dysphagia in stroke (and other neurological diseases) can be difficult and therefore requires a high level of clinical suspicion. The pattern of disordered swallowing in stroke is usually a combination of oral and pharyngeal abnormalities [15], a typically delayed swallowing reflex with pooling or stasis of residue, reduced pharyngeal peristalsis and weak tongue control, but occasionally oesophageal abnormalities may be apparent. Clinical suspicion of swallowing difficulty should be followed up by a thorough bedside swallowing assessment and, where appropriate, videofluoroscopy. The bedside examination incorporates a number of clinical measures, including assessment of the patient’s feeding status, posture, breathing and co-operation levels, before examining the patient’s oral musculature, oral reflexes, pharyngeal swallow and a trial feed with a 5–10 ml water bolus. While the bedside assessment is cheap, easy to perform and involves no radiation exposure, it does not give detailed information on the pharyngeal stage of swallowing, making it prone to missing significant aspiration, especially silent aspiration. By comparison, videofluoroscopy gives a detailed anatomical assessment of the pharyngeal swallow, but is expensive, involves radiation and uses a non-physiological medium, i.e. barium, which may not give a true picture of the patient’s swallowing performance.

The management of dysphagia after stroke is therefore critical. With severe dysphagia the risk of aspiration is high and the patient is therefore kept nil by mouth, with early commencement of parental fluids. With less severe dysphagia, based upon videofluoroscopic and bedside swallowing assessment outcomes, therapeutic interventions may be tried. These interventions often include changes in diet, posture and food placement adjustments, as well as methods for sensitizing or desensitizing the oro-pharynx to alter the swallow reflex, although their efficacy is a matter of some controversy. At present there have been no randomized controlled trials of these interventions to show proven efficacy in improving swallowing after stroke [18]; consequently patients require nasogastric tube or gastrostomy feeding until swallowing improves spontaneously [19].

STUDIES OF DYSPHAGIA AFTER STROKE AND CEREBRAL INJURY

Despite inferential animal evidence for bilateral control, studies after brain damage tend to suggest that, at least in humans, one or other hemisphere may be dominant [20–24]. Indeed, one of the earliest observations of a unilateral cerebral lesion producing dysphagia was in 1898, when Bastian [24] reported on the case of a man who had been admitted to hospital with a hemiplegia and aphasia, but who also had transient ‘difficulty in deglutition’. Later necropsy revealed that, apart from two limited lesions in the left hemisphere, the brain was healthy. More recently, Meadows [23] reported on six
cases of dysphagia. All of them had confirmed unilateral lesions of the cerebral cortex, five of which affected the right hemisphere. Since then a number of studies [10,15–17,22–27] have confirmed that perhaps 40% or more of patients with unilateral hemispheric stroke may have swallowing difficulties. There was an increased tendency for the pharynx to be involved if the damage was limited to the cortex, and was on the right hemisphere [22,27].

ORGANIZATION OF HUMAN SWALLOWING MOTOR CORTEX

The data missing from these studies has been a lack of information about the normal pattern of cortical projections to swallowing muscles in normal humans. Recently, the technique of transcranial magnetic stimulation (TMS) has been able to fill the gaps in our knowledge. This technique uses a very short, rapidly changing magnetic field to induce electric current in the brain beneath the stimulator [28,29]. The site of stimulation is less well localized compared with an electrode applied directly to the surface of the brain, so that the effective area of stimulation is larger than that obtained in acute experiments on anaesthetized subjects or animals. However, the centre of the most effective site for stimulation is very similar to that seen during neurosurgery, being slightly anterior to the best points for obtaining responses in muscles of the hand or arm [30,31]. One important difference between the techniques is that, in previous work, the brain has been stimulated with a train of several hundred stimuli at a rate of 50–60 Hz. Such stimuli can induce a full swallowing cycle visible to the experimenter [13]. However, because of the risk of...
inducing epileptic seizures in awake subjects, TMS studies usually employ only single shocks given several seconds apart. The consequence is that a full swallow is never evoked. Instead, the response has to be monitored by recording the EMG (electromyograph) of pharynx and oesophagus from an intraluminal catheter inserted into the oesophagus [32,33].

The type of response that can be observed is illustrated in Figure 1. A single stimulus evokes a simple EMG potential that has a latency of about 8–10 ms, compatible with a fairly direct and rapidly conducting pathway from cortex via brainstem to the muscle. Mapping these projections demonstrates that the various swallowing muscles are arranged somatotopically, with the oral muscles (mylohyoid) lateral and the pharynx and oesophagus more medial. However, the most important finding from a large group of subjects [33] was that, in the majority of individuals, the projection from one hemisphere tended to be larger than that from the other, i.e. there was asymmetric representation for swallowing between the two hemispheres, independent of handedness. This difference in projection was observed to be discordant in a pair of identical right-handed twins, suggesting little genetic contribution to its development.

**FUNCTIONAL NEUROANATOMY OF HUMAN SWALLOWING**

While information gathered from TMS has helped to delineate in greater detail the organization of projections from motor cortex to swallowing muscles, this approach does not allow an assessment of cerebral activity associated with functional swallowing. The recent technological advances in functional imaging of the human brain have revolutionized our understanding of how the cerebral cortex operates in processing sensory and motor information. In particular, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have become established as useful methods for exploring the spatial localization of changes in neuronal activity during tasks, within both cortical and subcortical structures. Both techniques have been applied to the study of human swallowing [34–36] and, broadly speaking, the results have been similar. A number of brain regions with increased activation were detected with PET [34], and these are shown in Figure 2 as integrated projections through sagittal, coronal and transverse views of the brain. These loci included: right orbito-frontal cortex; left mesial prefrontal cortex and cingulate; right...
Swallowing motor cortex reorganization and stroke

Figure 3 Swallowing motor cortex mapping changes with swallowing recovery after dysphagic stroke

The mapped cortically evoked EMG responses recorded from the pharynx are shown in one recovered dysphagic stroke patient, at presentation, 1 month and 3 months. Each grid pair represents the right and left hemispheres as viewed from above, with the vertex marked with an X. Traces are shown only at the grid sites where an EMG response was obtained. It can be seen that pharyngeal responses from the right hemisphere (unaffected) show a marked increase both in amplitude and in area of representation over time, whereas there is little change in responses from the left hemisphere (affected). Reproduced, with kind permission, from [38].

caudo-lateral sensorimotor cortex; left caudo-lateral sensorimotor cortex; right anterior insula; left temporo-polar cortex merging with left amygdala; right temporo-polar cortex; left medial cerebellum, which merged across the mid-line with the right medial cerebellum; and dorsal brainstem. Strongest activations were found to be in the sensorimotor cortices, insula and cerebellum. Therefore swallowing recruits multiple cerebral regions, often in an asymmetrical manner, particularly in the insula, which is predominantly on the right, and in the cerebellum, being mainly on the left. These latter observations are in keeping with the earlier observations with TMS that motor cortex representation for swallowing musculature displays degrees of asymmetry.

MECHANISMS OF DYSPHAGIA AFTER UNILATERAL CEREBRAL STROKE

The results from patients with dysphagia also tend to confirm this idea of inter-hemispheric asymmetry in the cortical representation of swallowing. In a TMS study [37] the projections from both hemispheres to the swallowing muscles were examined in a large series of pure unilateral stroke patients. Half of the patients had dysphagia, whereas the other half did not. The authors of this study reasoned that, if there were a true asymmetry of swallowing representation in normal subjects, then perhaps dysphagia would occur if the damage had affected the side of the brain with the largest (‘most
dominant’) projection. The results showed that, although stimulation of the damaged hemisphere produced little or no response in either group of patients, stimulation of the undamaged hemisphere tended to evoke a much larger response in the non-dysphagic than in the dysphagic subjects. Thus the size of the hemispheric projection to swallowing muscles may have determined the presence or absence of dysphagia.

CORTICAL REORGANIZATION AND SWALLOWING RECOVERY AFTER STROKE

Given sufficient time, many dysphagic stroke patients eventually recover their ability to swallow. However, the mechanism for this recovery, seen in as many as 90% of initially dysphagic stroke patients [16], has remained controversial. In a detailed study of stroke using TMS, both dysphagic and non-dysphagic patients were serially mapped over several months while swallowing recovered [38]. The findings of the study showed that the area of pharyngeal representation in the undamaged hemisphere increased markedly in patients who recovered (Figure 3), while there was no change in patients who had persistent dysphagia or in patients who were non-dysphagic. No changes were seen in the damaged hemisphere in any of the groups. These observations imply that, over a period of weeks, the recovery of swallowing after stroke depends on compensatory reorganization in the undamaged hemisphere. The situation appears to differ from that for the limb muscles, where some TMS studies have indicated that limb recovery after hemiparesis is more likely to result from an increase in the activity of remaining viable cortex in the damaged hemisphere [7]. In such cases, the scope for expansion of a normal connection from the undamaged part of the brain may be a limiting factor in recovery.

DRIVING REORGANIZATION IN HUMAN SWALLOWING MOTOR CORTEX

Given that the intact hemisphere plays an important role in the recovery of swallowing after stroke, we are provided with an interesting opportunity for studying the plasticity of an intact (normal) pathway. Indeed, it could be suggested that any future therapies aimed at enhancing swallowing recovery should be targeted towards manipulating reorganization on the intact side. One potential candidate for such a therapy might be the manipulation of sensory input to the cortex. Sensory input from the gut not only has a major influence on the activity of brainstem swallowing centres, but also converges on to cortical sensory and motor areas [11]. Furthermore, it has been shown that the excitability of the cortical projection to swallowing muscles can be influenced by stimulation of afferent fibres in the vagal and trigeminal nerves [39]. Single stimuli, used in those studies, had a very short-lasting effect, but recent work has shown that prolonged electrical stimulation of the pharynx can induce changes in cortical excitability that outlast the stimulus by up to 30 min [40] (Figure 4). If this approach could be adopted in dysphagic stroke patients, then it could prove to be a potential mechanism for speeding the recovery of function from the intact representation in the undamaged hemisphere.

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