Brain Research Bulletin 84 (2011) 88–93

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

# Task-dependent differences in corticobulbar excitability of the submental motor projections: Implications for neural control of swallowing

Sebastian H. Doeltgen [a,b,c,*], Michael C. Ridding [c,1], John Dalrymple-Alford [b,d,2], Maggie-Lee Huckabee [a,b,3]

[a] Swallowing Rehabilitation Research Laboratory, Department of Communication Disorders, University of Canterbury, Christchurch, New Zealand
[b] Van der Veer Institute for Parkinson's and Brain Research, University of Canterbury, Christchurch, New Zealand
[c] Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, Australia
[d] Department of Psychology, University of Canterbury, Christchurch, New Zealand

ARTICLE INFO

*Article history:*
Received 7 May 2010
Received in revised form 7 November 2010
Accepted 8 November 2010
Available online 18 November 2010

*Keywords:*
Deglutition
Motor evoked potentials
Transcranial magnetic stimulation
Motor control
Swallowing

ABSTRACT

It has been suggested that the primary motor cortex plays a substantial role in the neural circuitry that controls swallowing. Although its role in the voluntary oral phase of swallowing is undisputed, its precise role in motor control of the more reflexive, pharyngeal phase of swallowing is unclear. The contribution of the primary motor cortex to the pharyngeal phase of swallowing was examined using transcranial magnetic stimulation (TMS) to evoke motor evoked potentials (MEPs) in the anterior hyomandibular muscle group during either volitional submental muscle contraction or contraction during the pharyngeal phase of both volitionally, and reflexively, initiated swallowing. For each subject, in all three conditions, TMS was triggered when submental surface EMG (sEMG) reached 75% of the mean maximal submental sEMG amplitude measured during 10 volitional swallows. MEPs recorded during volitional submental muscle contraction were elicited in 22 of the 35 healthy subjects examined (63%). Only 16 of these 22 subjects (45.7%) also displayed MEPs recorded during volitional swallowing, but their MEP amplitudes were larger when triggered by submental muscle contraction than when triggered by volitional swallowing. Additionally, only 7 subjects (of 19 tested) showed MEPs triggered by submental muscle contraction during a reflexively triggered pharyngeal swallow. These differences indicate differing levels of net M1 excitability during execution of the investigated tasks, possibly brought about by task-dependent changes in the balance of excitatory and inhibitory neural activity.



## 1. Introduction

Swallowing is a complex neuromuscular task that requires the precise coordination of up to 32 paired muscles controlled by up to 7 cranial nerves. Central pattern generators (CPGs) in the brainstem orchestrate the contraction of the pharyngeal musculature during the largely reflexive, pharyngeal phase of swallowing [8]. Using fMRI, previous studies have revealed activation of a number of cortical areas, including the primary motor area (M1) during volitional swallowing [6,11,12,15,16,27]. Although M1 involvement in the more voluntary oral phase of swallowing is undisputed, the precise role of M1 in the motor control of the pharyngeal phase of swallowing has not yet been clearly defined. Research has linked M1 activation to volitional oral movements such as those required for bolus preparation [12]. In this study, signal intensity, representing the degree of cortical activation, was similar for volitional oral preparatory movements and volitional swallowing. This finding is contrasted by reports of greater activation of M1 during volitional tongue elevation compared to volitional swallowing [16]. Similarly, M1 activation was found to be greater during volitional swallowing than during reflexive swallowing [11]. These findings suggest a progressive decrease in M1 activation associated with an increase in the level of reflexive motor control during swallowing related motor activity. Because subjects were not specifically instructed to limit tongue movements during swallowing tasks and in light of the limited temporal resolution of fMRI in the order of at least one second, cortical activation documented in these studies may largely relate to voluntary movements in the oral preparatory phase, rather than the pharyngeal phase of swallowing. In addition, blood oxygen level dependent fMRI cannot determine whether detected neural activity is excitatory or inhibitory in nature.

* Corresponding author. Current address: Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, DX 650-515, Adelaide, SA 5005, Australia. Tel.: +61 8 8313 1303; fax: +61 8 8313 1355.
*E-mail addresses:* sebastian.doeltgen@adelaide.edu.au (S.H. Doeltgen), michael.ridding@adelaide.edu.au (M.C. Ridding), john.dalrymple-alford@canterbury.ac.nz (J. Dalrymple-Alford), maggie-lee.huckabee@canterbury.ac.nz (M.-L. Huckabee).
[1] Tel.: +61 8 8303 7592.
[2] Tel.: +64 3 378 6090.
[3] Tel.: +64 3 378 6070; fax: +64 3 364 2401.

0361-9230/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.brainresbull.2010.11.006

Using electroencephalography (EEG), Huckabee et al. [7] investigated cortical motor planning prior to a task in which subjects were instructed to inhibit orolingual movements before volitional onset of pharyngeal swallowing. This research documented a relative quiescence of M1 during this task, based on an absence of the second component of the Bereitschaftspotential (BP, or readiness potential) that is known to correlate with transfer of the motor plan to M1. The authors hypothesized that this relative inactivity represented direct transmission of the neural command generated by the supplementary motor area (SMA) to the swallowing pattern generators in the brainstem. In a similar study of cortical potentials, Satow et al. [25] reported lower post-movement potentials for volitional swallowing compared to a tongue protrusion task, suggesting that excitatory networks in M1 may not contribute as substantially to movement processing for volitional swallowing.

Based on these reports, differences may exist in the level of excitability of motor cortical networks during voluntary oral muscle contraction and more reflexive contraction during the pharyngeal phase of swallowing. The submental musculature offers the opportunity to assess M1 excitability during different motor components of swallowing as it plays a central role in both the oral and pharyngeal phases of swallowing. We hypothesized that corticobulbar activation would be largest during a volitional contraction condition because of a stronger activation of direct corticobulbar projections and least robust during a reflexive swallowing condition due to primary brainstem modulation of swallowing. To test this hypothesis, we evaluated corticobulbar excitability using transcranial magnetic stimulation (TMS) elicited motor evoked potentials (MEPs) recorded during three conditions of submental muscle activation: volitional contraction, contraction during the pharyngeal phase of volitional swallowing and, in a smaller subgroup of subjects, contraction during the pharyngeal phase of reflexive swallowing. MEP amplitude is a reliable measure of the excitability of the tested neural pathway and can be facilitated by pre-activation of these pathways [3,14,21,23]. In addition, the level of corticobulbar excitability, as identified by pharyngeal MEP amplitude, has previously been shown to relate to functional measures of swallowing [4]. When triggered at the same level of muscle activation, differences in MEP amplitude, reflecting differing levels of corticobulbar excitability, provide new insights into the relative role of M1 during volitional and reflexive components of swallow-related muscle activation.

A secondary aim of this study was to investigate a potential relationship between handedness and hemispheric dominance in the motor control of the submental musculature. This investigation is based on previous studies of the pharyngeal musculature, which is thought to be represented bilaterally, but asymmetrically, suggesting hemispheric dominance in the motor control of these muscles [19]. Similar hemispheric differences in motor cortical activation have previously been reported for swallowing and voluntary tongue elevation tasks using fMRI [16]. Using logistic regression analysis, we investigated whether handedness could predict (i) which hemisphere produced the largest MEP during voluntary contraction and (ii) presence or absence of MEPs during swallow-related muscle activation.

## 2. Materials and methods

### 2.1. Subjects

Thirty-five healthy community volunteers were recruited (24 females, 11 males; group mean age 30.1 yrs (SD 8.4s), 26 right handed, as determined by the Edinburgh Inventory [20]). Subjects provided written informed consent and reported full understanding of the research tasks they were asked to perform. Subjects were neurologically unimpaired and reported no contraindications on the TMS Safety Screen [10]. This study was approved by the appropriate Institutional Health Ethics Review Board and was in compliance with the Declaration of Helsinki.

### 2.2. Data acquisition

Data acquisition procedures used in this study have been shown to provide a reliable recording of task-related MEPs [3]. Two surface electrodes (BRS-50K, Blue Sensor™, Ambu, Denmark) were placed at midline over the submental muscle group. The two electrodes were centered in the mid-sagittal plane, midway between the anterior bony aspect of the mandible and the superior palpable edge of the thyroid cartilage, with an inter-electrode distance maintained at 1 cm. Both electrodes overlapped midline laterally by 1 cm. Surface electromyographic (sEMG) activity was therefore recorded collectively from left and right portions of the mylohyoid muscles, anterior belly of digastric muscles and geniohyoid muscles. A ground electrode was attached to the bony mandibular prominence at the base of the vertical ramus. All three electrodes were connected to an amplifier (Dual Bio Amp, ML 135™, ADInstruments, Castle Hill, Australia) and recording system (Powerlab 8/30™, ML 870, ADInstruments). The sampling rate for data acquisition was 10 kHz and data were high pass filtered at 10 Hz. sEMG activity was recorded for a period of 200 ms when the magnetic stimulator (Magstim 200™, Magstim Company Limited, Whitland, Wales) was discharged, recording 50 ms pre- and 150 ms post-trigger.

### 2.3. Muscle contraction conditions

In all subjects, data were recorded in counterbalanced order for two conditions of submental muscle pre-activation: volitional contraction and volitionally initiated pharyngeal swallowing. In a subset of 19 subjects (14 females, 5 males; group mean age 27.4 yrs (SD 6.9), 16 right handed [20]), MEPs were additionally recorded during reflexive swallowing. In this subset, MEP recordings were randomized across the three tested conditions. For the volitional contraction task, subjects were instructed to "contract the muscles under your chin as if stifling a yawn". For volitional swallowing, subjects were asked to "swallow your saliva". During performance of the two volitional conditions, subjects were instructed to limit volitional oral movements; in particular they were instructed to keep their tongue as relaxed as possible. Subjects practiced the contraction tasks, alternating between swallows and contractions, guided by the verbal feedback of the investigator and visual sEMG feedback, for approximately 5 min prior to data collection.

For the reflexive swallowing condition, a small, flexible tube (2 mm diameter) was placed into the posterior aspect of the subject's oral cavity, with the opening of the tube resting approximately at the level of the base of the tongue. Subjects were asked to close their eyes to deter visual cuing and 1 ml of room temperature water was infused slowly onto the base of tongue at random intervals, eliciting a reflexive swallow. Trials that did not elicit a swallow or induced coughing or throat clearing were discarded and repeated.

In a subgroup of 15 subjects (11 females, 4 males; group mean age 26.3 yrs (SD 7.4), nine right handed [20]), MEPs were also assessed at rest in order to investigate whether the excitability of corticobulbar motor projections varied between the tested muscle contraction conditions and rest. The intensity of the magnetic stimulus was increased from 80% of maximal stimulator output in 2% increments until MEPs were measurable or maximal stimulator output was reached.

### 2.4. Transcranial magnetic stimulation of submental motor cortex

Focal cortical stimulation was achieved with a figure-of-8 coil with an outer wing diameter of 90 mm and a maximal output of 2.2 Tesla. Submental surface EMG (sEMG) activity was monitored by a custom-built triggering system, which discharged the magnetic stimulator when a pre-set trigger threshold was breached. The trigger threshold was determined for each individual prior to data collection by calculating 75% of the mean maximal sEMG amplitude recorded during 10 volitional saliva swallows that were executed with minimized volitional orolingual movements. Setting the threshold to this value ensured that the stimulator was discharged at the onset of a volitionally initiated pharyngeal swallow in the absence of volitional oral movements. All trials were inspected visually for sEMG activity associated with voluntary orolingual movements immediately prior to the onset of swallowing related sEMG activity. Infrequently, TMS was not triggered during pharyngeal swallowing and these trials were discarded and repeated. The same trigger threshold was maintained in the volitional contraction and reflexive swallowing conditions to ensure that the underlying degree of muscle activation at the time of TMS discharge was matched across all conditions. The trigger device was automatically disabled for 10 s after each stimulus to minimize triggering not associated with target motor behavior.

Prior to data collection, the optimal scalp site for consistently eliciting the largest submental MEP amplitude (peak to peak) was identified for both hemispheres. An area approximately 4 cm anterior and 8–10 cm lateral to the cranial vertex was searched systematically for this location. During this procedure, subjects were asked to minimize movement, particularly of the head and shoulders. Subsequent to identification of the optimal scalp location, the position of the coil was marked on the scalp with a water-soluble pen to ensure consistent coil positioning throughout the research session. Then, maximal MEP amplitude was identified for this site on each hemisphere by increasing TMS intensity until no increase in MEP amplitude was observed or 100% stimulator output was reached. Data were collected from the hemisphere over which largest MEPs could be evoked. Stimulator output for subsequent data collection was set to the value at which MEPs of 50% of maximal

**Table 1**
Average MEP areas (μV ms) of all subjects displaying significant MEP responses during the volitional contraction condition ($N = 22$).

| MEP size (μV ms) | | | |
|---|---|---|---|
| Subject | Volitional contraction | Volitional pharyngeal swallowing | Reflexive pharyngeal swallowing |
| 1 | 4136.2 | 2955 | Not tested |
| 2 | 902.4 | 639.3 | Not tested |
| 3 | 1890 | 2114.1 | Not tested |
| 4 | 2283.1 | 988.9 | Not tested |
| 5 | 1943.4 | 1179.6 | Not tested |
| 7 | 1065.4 | 936.7 | Not tested |
| 8 | 1675 | 545.4 | Not tested |
| 9 | 2197.9 | 2617.4 | 2630.9 |
| 10 | 1162.7 | 0 | 0 |
| 11 | 1994.5 | 1204.1 | 1627 |
| 12 | 1773 | 673.7 | 656.8 |
| 14 | 1758.3 | 336.7 | 0 |
| 15 | 3355.9 | 0 | 0 |
| 16 | 943.7 | 920 | 815.9 |
| 18 | 1685.9 | 0 | 0 |
| 20 | 2306 | 3193.3 | 2160.6 |
| 21 | 1321.4 | 833.7 | 0 |
| 25 | 1381.9 | 689.4 | 1074.1 |
| 27 | 607.3 | 0 | 0 |
| 28 | 2292.2 | 1515.8 | 1188.5 |
| 31 | 1452.5 | 0 | 0 |
| 34 | 3861.7 | 0 | 0 |

MEP amplitude during volitional contraction were elicited. For each muscle pre-activation condition, 15 MEPs traces were recorded from each subject.

### 2.5. Data preparation and analysis

For each of the 15 individual MEP trials in each pre-activation condition, presence of an MEP was judged based on statistical analysis of the rectified post-stimulus sEMG using a similar approach as reported previously [28]. An MEP was accepted as present if the post-stimulus sEMG exceeded the average pre-stimulus sEMG level of 50 ms (−55 ms to −5 ms) by more than two standard deviations (SD) for at least 5 ms. This was considered the MEP detection threshold. Trials that did not meet these criteria were judged as producing no valid MEP response. Overall, a subject was accepted to display an MEP in any of the conditions if at least 50% of trials within that condition satisfied the criteria for a significant MEP.

### 2.6. Quantification of MEP responses

In order to quantify the size of motor responses during the three pre-activation conditions, the MEP area (ΔEMG, in μV ms) exceeding the MEP detection threshold was calculated as:

$$\Delta\text{EMG} = (\text{MEP} - \text{pre-stimulus sEMG}) \times \text{duration of MEP}$$

The duration of the MEP was defined as the duration of the period during which the post-stimulus sEMG exceeded the MEP detection threshold. MEP onset latency was defined as the point in time at which the post-stimulus sEMG first exceeded this threshold. The MEP area was calculated for each individual trial that was accepted to represent a statistically significant MEP response and averaged for each condition in each subject. Trials that did not display an MEP were assigned "0 μV ms" and were included in the average MEP area.

### 2.7. Statistical analysis

Chi-squared analyses were used to determine whether the likelihood of detecting MEPs varied as a function of muscle pre-activation condition. A paired samples *t*-test was used to determine whether MEP areas differed between the volitional submental contraction condition and the volitional pharyngeal swallowing condition in the overall group of 22 subjects that displayed MEPs in the volitional contraction condition. In the subgroup of 19 subjects that additionally performed the reflexive pharyngeal swallowing condition, MEP areas, and in addition MEP onset latencies, were compared across all three conditions using one-way repeated measures analyses of variance (ANOVA) with the within subject variable of Condition (volitional contraction, volitional swallowing, reflexive swallowing). Post hoc paired samples *t*-tests were undertaken on the condition of a significant main effect. Logistic regression analysis of the volitional contraction data of the 22 subjects that displayed MEPs during this condition was used to determine whether handedness predicted which hemisphere produced largest MEPs. Logistic regression analysis of the volitional pharyngeal swallowing MEP data of all subjects was used to determine whether handedness or hemispheric dominance for volitional contraction predicted presence of MEPs during the volitional pharyngeal swallowing condition.

## 3. Results

Pre-stimulus sEMG levels did not differ between the three contraction conditions ($F_{(2,28)} = 1.43$, $P = 0.256$). Trigger thresholds used for eliciting TMS during all three conditions were identical within each subject. Mean trigger threshold across subjects was 0.16 mV (SD 0.05). In 15 subjects, corticobulbar excitability was tested in the resting condition. In these individuals, MEPs could only be elicited in one subject at a stimulator output of 98%.

### 3.1. MEP occurrence across conditions

Of the overall group of 35 subjects, no MEPs could be elicited during pre-activation for any contraction condition in 13 subjects (38%). In the remaining 22 subjects (62%), discernable MEPs could be recorded during the volitional contraction condition; MEPs were recorded during the volitional swallowing condition in only 16 of these subjects (46%). Chi-squared analysis revealed no significant difference between occurrences of MEPs between the volitional submental contraction condition and the volitional pharyngeal swallowing condition ($\chi^2 = 2.07$, $P = 0.23$).

Motor evoked potentials during reflexive swallowing were additionally investigated in 19 subjects but could only be recorded in seven of these subjects (37%). In this sub-sample, MEPs could be recorded during volitional contraction in 15 subjects (79%) and in nine subjects (47%) during the volitional pharyngeal swallowing task. Chi-squared analysis revealed that there was a significant association between swallowing contraction conditions and whether or not significant MEPs could be recorded ($\chi^2 = 7.35$, $P = 0.026$). Based on odds ratios, MEPs were 4.17 times more likely to occur during the volitional contraction condition compared to the volitional pharyngeal swallowing condition, 6.42 times more likely to occur during the volitional contraction condition compared to the reflexive swallowing condition and 1.27 times more likely to occur during the volitional pharyngeal swallowing condition compared to the reflexive pharyngeal swallowing condition.

### 3.2. MEP Size

In the overall group of subjects who displayed MEPs in the volitional contraction condition ($N = 22$) (Table 1), MEP

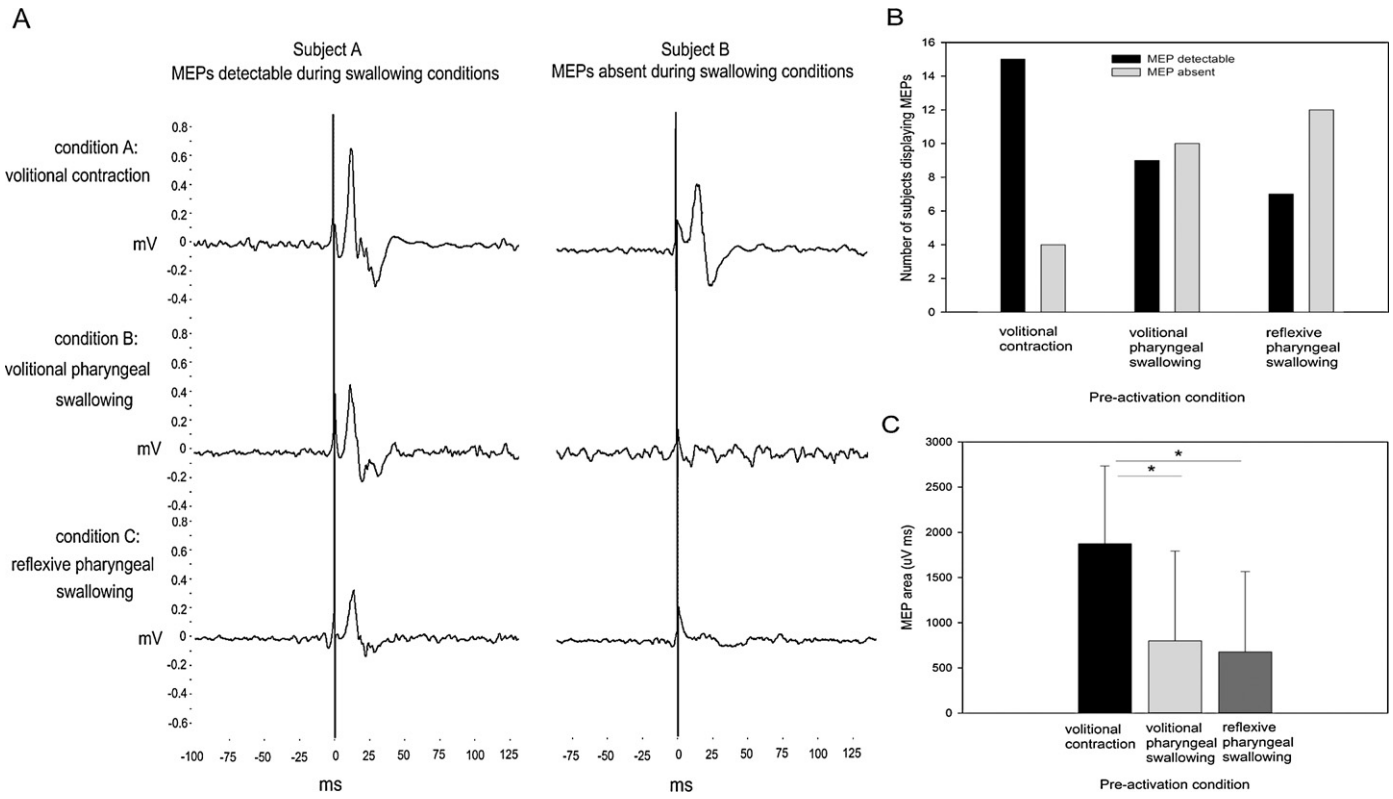


**Fig. 1.** (A) Averaged motor evoked potential (MEP) waveforms of two representative subjects. MEPs were triggered from submental sEMG during a volitional contraction condition (condition A), and muscle contraction at the onset of the pharyngeal phase of volitional (condition B) or reflexive swallowing (condition C). The vertical line at 0 ms displays the magnetic stimulus artifact. Note a rise in sEMG activity just prior to TMS and similar sEMG profiles across conditions prior to TMS triggering. (B) Distribution of MEP observations in a subgroup of 19 subjects in whom MEPs were assessed during all three muscle pre-activation conditions and (C) average MEP area (+1 SD) during all three muscle pre-activation conditions recorded in the 15 subjects of this subgroup that displayed MEPs during the volitional contraction condition. $^{*}p < 0.05$.

areas were smaller during the pharyngeal swallowing condition (970 μV ms, SD 972) compared to the volitional contraction condition (1908 μV ms, SD 907) ($t_{(21)} = 4.06$, $P = 0.001$).

In the subgroup of subjects that were examined in all three pre-activation conditions ($N = 19$), there was a significant main effect of Condition ($F_{(2,28)} = 12.72$, $P = 0.002$). Post hoc paired samples $t$-tests revealed that MEP areas were larger when recorded during the volitional contraction condition (1872 μV ms, SD 861) compared to the volitional swallowing condition (799 μV ms, SD 993) ($t_{(14)} = 3.34$, $P = 0.005$) or the reflexive swallowing condition (677 μV ms, SD 888) ($t_{(14)} = 3.96$, $P = 0.001$). There was no significant difference between the two swallowing conditions ($t_{(14)} = 1.22$, $P = 0.242$) (Fig. 1).

### 3.3. MEP onset latency

Repeated measures ANOVA comparing onset latencies across all three pre-activation conditions revealed no significant differences between conditions [($F_{(2,12)} = 0.544$, $P < 0.594$), voluntary contraction condition: 10.47 ms (SD 2.38); volitional pharyngeal swallowing: 10.11 ms (SD 1.75); reflexive pharyngeal swallowing: 11.03 ms (SD 2.05), Table 2].

### 3.4. Predictability of hemispheric dominance and swallowing MEP occurrence

Logistic regression analysis revealed that handedness did not predict which hemisphere produced largest MEPs (dominant hemisphere) during the volitional contraction condition ($R^2$: 0.11, $p = 0.14$). Neither handedness ($R^2$: 0.12, $p = 0.54$), nor the dominant hemisphere for volitional contraction ($R^2$: 0.017, $p = 0.46$) predicted presence of MEPs during the volitional swallowing condition.

## 4. Discussion

In order to determine the contribution of M1 to the motor control of the pharyngeal phase of swallowing, we evaluated the excitability of submental corticobulbar projections during execution of three swallowing-related tasks. In 13 subjects, no discernable MEPs could be recorded during any of the tasks. This finding is in line with previous reports of high motor thresholds and small or absent MEPs recorded from the masseter muscles, which may be related to an unfavorable angle between the induced magneto-electric field and the stimulated neurons, or an overall small number of crossed connections originating from the motor cortex [13]. In the remaining subjects, MEPs were detected most consistently during the voluntary muscle contraction task, a task that would recruit excitatory neural circuits in M1 [22]. They were less frequently detected, and were smaller in amplitude, during the volitional swallowing condition. Furthermore, MEPs were infrequently detected during reflexive swallowing, a task that is thought to be primarily governed by brainstem central pattern generators [8]. MEP amplitude is a reliable measure of the excitability of the tested neural pathway and can be facilitated by pre-activation of these pathways [3,14,21,23]. Therefore, differences in MEP amplitude provide new insights into the relative role of M1 in the volitional and reflexive components of swallowing.

One important factor when comparing MEP amplitudes across different active conditions is that background EMG levels are matched. In the present study TMS was triggered for discharge at

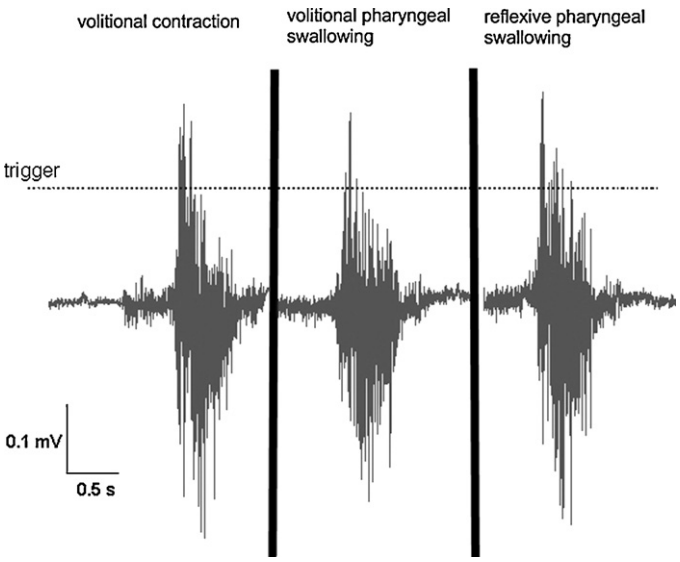


**Fig. 2.** Single sweep, raw sEMG recordings during three muscle pre-activation conditions (volitional contraction, volitional pharyngeal swallowing, reflexive pharyngeal swallowing) without transcranial magnetic stimulation in one representative subject. Note that the trigger threshold for transcranial magnetic stimulation, set to the individual's 75% of the mean maximal submental sEMG measured during 10 volitional swallows, is kept consistent across pre-activation conditions.

the same EMG amplitude across conditions. This was confirmed by analysing pre-trigger EMG levels. Likewise, differences in the performance of the examined motor tasks might influence motor cortical excitability. For example, subjects that displayed MEPs during the swallowing conditions may not have been as effective in inhibiting oral phase movements as those that did not display MEPs in this condition, thus activating M1. While we cannot absolutely rule out slight inter-individual differences in the performance of these tasks, we minimized false triggering by allowing subjects to train the volitional motor tasks at the beginning of the experimental sessions and repeated any trials in the swallowing conditions that were triggered prior to the pharyngeal phase of the swallow. Additionally, visual inspection of pre-trigger sEMG profiles revealed no obvious differences in sEMG profiles of those subjects that displayed MEPs in the swallowing conditions and those that did not (Fig. 2). Therefore, we consider differences in sEMG levels across the conditions and potential variations in the performance of the examined motor tasks unlikely explanations for the difference in MEP amplitudes evoked during the three conditions.

Although CPGs in the brainstem have been shown to play a central role in the motor control of pharyngeal swallowing [8], a growing body of research suggests that M1 may have a role in volitionally initiated [6,15,16,26,27] and also reflexively initiated swallowing [11]. fMRI has documented that M1 is activated during volitional swallowing, although the degree of cortical activation is debated. Lower cortical activation than during a tongue elevation task was reported by Martin et al. [16], whereas Kern et al. [12] reported similar signal intensities during volitional swallowing and non-deglutitive motor tasks such as jaw clenching, lip pursing and tongue rolling. However, large voxel size and the limited temporal resolution of fMRI may have obscured differentiation between tasks in these studies and failed to rule out the contribution of volitional oral phase movements to M1 activation. Further, fMRI is of limited use for determining the specific nature of motor cortical involvement, as blood-oxygen level dependent measurement of cortical activation cannot discriminate between activation of excitatory or inhibitory neural networks. In this context, a study employing inhibitory rTMS over the pharyngeal motor representation in M1 has documented a decrease in swallowing onset time, suggesting that inhibitory neural networks may play a substantial role in the control of pharyngeal swallowing [19]. Other studies employing single pulse TMS have demonstrated that pharyngeal electrical stimulation can enhance or inhibit corticobulbar excitability, with important implications for swallowing function [4]. Together, these data provide evidence for functionally relevant M1 involvement in the control of pharyngeal swallowing.

We propose that the presented data support the notion that M1 has a role in the control of pharyngeal swallowing. In keeping with previous reports [2,17] we could not evoke MEPs at rest in 14 of the 15 tested subjects. In one subject, a small response could be evoked at 98% of maximal stimulator output. However, it was possible to evoke MEPs albeit of smaller amplitude than those evoked during voluntary contraction, in some of the subjects during both pharyngeal swallowing conditions, indicating that the corticobulbar pathways were more excitable during swallowing than at rest. This finding provides some evidence that M1 plays a role in the pharyngeal phase of both voluntary and reflexive swallowing in some subjects.

However, the finding that MEP amplitudes were smaller during the pharyngeal swallowing condition suggests a difference in net corticobulbar excitability between the evaluated muscle contraction conditions. There are different possibilities that might explain this finding. Firstly, there may be less excitatory drive from M1 during swallowing than during a voluntary contraction. This would be in keeping with a reduced role of M1 in the control of swallowing. Alternatively, the reduction in MEP amplitude during the swallowing conditions may be due to a shift in the balance of activation of excitatory and inhibitory neural circuits during the contraction conditions. For example, it is plausible that the smaller MEPs evoked during the pharyngeal swallowing conditions are seen due to an up-regulation of inhibitory neural network excitability in M1. Indeed, it has previously been hypothesized that inhibition of cortical motor output might ensure uninterrupted execution of reflex swallowing [5,19].

Studies employing EEG techniques provide support for the notion that the excitability of the motor cortex varies between different motor tasks. For example, Huckabee et al. [7] have shown that the second component of the Bereitschaftspotential (BP, or readiness potential) that is known to correlate with transfer of the

**Table 2**
Average MEP onset latency (ms) of all subjects ($N = 7$) displaying significant MEP responses during all three muscle contraction conditions (volitional contraction, volitional pharyngeal swallowing and reflexive pharyngeal swallowing).

| MEP onset latency (ms) | | | |
|---|---|---|---|
| Subject | Volitional contraction | Volitional pharyngeal swallowing | Reflexive pharyngeal swallowing |
| 9 | 10.5 | 11.7 | 13.2 |
| 11 | 8.0 | 9.1 | 8.7 |
| 12 | 11.7 | 13.2 | 12.9 |
| 16 | 8.1 | 9.8 | 12.5 |
| 20 | 14.8 | 10.0 | 11.2 |
| 25 | 11.0 | 8.8 | 8.0 |
| 28 | 9.2 | 8.2 | 10.7 |

motor plan to M1 was absent prior to volitionally initiated pharyngeal swallowing. This finding suggests a reduced role of M1 in the execution of this motor task. In fact, the authors hypothesized that motor planning networks of the SMA may be directly linked to swallowing CPGs, essentially bypassing M1 [7]. Similar direct connections between the SMA and hand motoneurons in the cervical spinal cord have been reported in monkeys [24]. Further evidence for reduced net excitability of M1 during swallowing comes from a study reporting lower post-movement potentials for volitional swallowing compared to a tongue protrusion task [25].

The observed differences in task-dependent MEP facilitation are in line with the notion that an increase in the level of reflexive motor control is associated with a decrease in net M1 excitability. It is plausible that a shift in the balance of excitatory and inhibitory neural activation is induced by reciprocal sensory feedback loops as peripheral sensory input is crucially important for the initiation and modulation of pharyngeal swallowing. For instance, electrical stimulation of the superior laryngeal nerve has been shown to initiate reflex swallowing [18] and varying levels of sensory feedback, modified through different bolus sizes, have been demonstrated to affect swallowing biomechanics differentially [9]. Sensory feedback, therefore, is a probable candidate mechanism for ensuring that cortical excitability is continuously adapted so that it provides just the right amount of descending modulation to CPGs in the brainstem.

Interestingly, previous research has demonstrated that the pharyngeal musculature is represented bilaterally, but asymmetrically, suggesting hemispheric dominance in the motor control of these muscles [19]. Similar hemispheric differences in motor cortex activation were reported for swallowing and tongue elevation tasks using fMRI [16]. The present data corroborate these findings and demonstrate that the asymmetry in motor cortical activation observed for the volitional contraction condition was not related to handedness, and that neither handedness nor the dominant hemisphere for volitional submental muscle contraction could predict the occurrence of MEPs during volitional pharyngeal swallowing. The relationship between cortical motor networks active during the volitional contraction condition and the swallowing conditions tested in this study is unclear and warrants further investigation.

It is likely that the many volitional and reflexive motor components of the different phases of swallowing are governed by distinct but inter-related neural networks. Activation of excitatory circuits in M1 is required for volitional bolus manipulation in the oral stage of swallowing [12]. Our data provide evidence that the execution of the more reflexive, pharyngeal phase of swallowing does not rely as heavily on excitatory cortical motor control. It is possible that the observed decrease in cortical excitability is related to down-regulation of excitatory neural networks, up-regulation of inhibitory neural networks, or a combination of both. At the present stage, these interpretations are inevitably tentative and are not intended to comprehensively define the role of M1 in swallowing motor control. Nevertheless, on balance our data support the notion that M1 is involved in the motor control of pharyngeal swallowing. Further research is warranted to investigate the precise role of M1 in the control of swallowing. In particular, studies examining intracortical inhibitory function during swallowing might prove enlightening. A better understanding of the role of M1 in swallowing would be helpful in designing rehabilitative interventions targeting specific neural networks that underlie disordered swallowing.

## References


[2] G. Cruccu, A. Berardelli, M. Inghilleri, M. Manfredi, Functional organization of the trigeminal motor system in man, Brain 112 (1990) 1333–1350.

[3] S.H. Doeltgen, M.C. Ridding, G.A. O'Beirne, J. Dalrymple-Alford, M.L. Huckabee, Test–retest reliability of motor evoked potentials (MEPs) at the submental muscle group during volitional swallowing, J. Neurosci. Methods 178 (2009) 134–137.

[4] C. Fraser, M. Power, S. Hamdy, J. Rothwell, D. Hobday, I. Hollander, P. Tyrell, A. Hobson, S. Williams, D. Thompson, Driving plasticity in the human adult motor cortex is associated with improved motor function after brain injury, Neuron 34 (2002) 831–840.

[5] S. Hamdy, Q. Aziz, J.C. Rothwell, A. Hobson, D.G. Thompson, Sensorimotor modulation of human cortical swallowing pathways, J. Physiol. 506 (1998) 857–866.

[6] S. Hamdy, D.J. Mikulis, A. Crawley, S. Xue, H. Lau, S. Henry, N.E. Diamant, Cortical activation during human volitional swallowing: an event-related fMRI study, Am. J. Physiol. Gastronintest. Liver Physiol. 40 (1999) G219–G225.

[7] M.L. Huckabee, L. Deecke, M.P. Cannito, H.J. Gould, W. Mayr, Cortical control mechanism in volitional swallowing: the Bereitschaftspotential, Brain Topogr. 16 (2003) 3–17.

[8] A. Jean, Brain stem control of swallowing: neuronal network and cellular mechanisms, Physiol. Rev. 81 (2001) 929–969.

[9] P.J. Kahrilas, J.A. Logemann, Volume accommodation during swallowing, Dysphagia 8 (1993) 259–265.

[10] J.C. Keel, M.J. Smith, E.M. Wassermann, A safety screening questionnaire for transcranial magnetic stimulation, Clin. Neurophysiol. 112 (2001) 720.

[11] M. Kern, S. Jaradeh, R.C. Arndorfer, R. Shaker, Cerebral cortical representation of reflexive and volitional swallowing in humans, Am. J. Physiol. Gastrointest. Liver Physiol. 280 (2001) G354–G360.

[12] M. Kern, R. Birn, S. Jaradeh, A. Jesmaniwicz, R. Cox, J. Hyde, R. Shaker, Swallow-related cerebral cortical activity maps are not specific to deglutition, Am. J. Physiol. Gastrointest. Liver Physiol. 280 (2001) G531–G538.

[13] G.M. Macaluso, G. Pavesi, M. Bonanni, D. Mancia, P. Gennari, Motor-evoked potentials in masseter muscle by electrical and magnetic stimulation in intact alert man, Arch. Oral Biol. 35 (1990) 623–628.

[14] A. Maertens de Noordhout, J.L. Pepin, P. Gerard, P.J. Delawaide, Facilitation of responses to motor cortex stimulation: effects of isometric voluntary contraction, Ann. Neurol. 32 (1992) 365–370.

[15] R.E. Martin, B.G. Goodyear, J.S. Gati, R.S. Menon, Cerebral cortical representation of automatic and volitional swallowing in humans, J. Neurophysiol. 85 (2001) 938–950.

[16] R.E. Martin, B.J. MacIntosh, R.C. Smith, A.M. Barr, T.K. Stevens, J.S. Gati, R.S. Menon, Cerebral areas processing swallowing and tongue movement are overlapping but distinct: a functional magnetic resonance imaging study, J. Neurophysiol. 92 (2004) 2428–2443.

[17] A.S. McMillan, C. Watson, G. Walshaw, Improved reproducibility of magnetic stimulation-evoked motor potentials in the human masseter muscle by a new method for locating stimulation sites on the scalp, Arch. Oral Biol. 43 (1998) 665–668.

[18] A.J. Miller, Significance of sensory inflow to the swallowing reflex, Brain Res. 43 (1972) 147–159.

[19] S. Mistry, E. Verin, S. Singh, S. Jefferson, J.C. Rothwell, D.G. Thompson, S. Hamdy, Unilateral suppression of pharyngeal motor cortex to repetitive transcranial magnetic stimulation reveals functional asymmetry in the hemispheric projections to human swallowing, J. Physiol. 585 (2007) 525–538.

[20] R.C. Oldfield, The assessment and analysis of handedness: the Edinburgh inventory, Neuropsycholigogica 9 (1971) 97–113.

[21] E.K. Plowman-Prine, W.J. Triggs, M.P. Malcolm, J.C. Rosenbek, Reliability of transcranial magnetic stimulation fro mapping swallowing musculature in the human motor cortex, Clin. Neurophysiol. 119 (2008) 2298–2303.

[22] C. Reynolds, P. Ashby, Inhibition in the human motor cortex is reduced just before a voluntary contraction, Neurology 53 (1999) 730–735.

[23] J.C. Rothwell, P.D. Thompson, B.L. Day, S. Boyd, C.D. Marsden, Stimulation of the human motor cortex through the scalp, Exp. Physiol. 76 (1991) 159–200.

[24] E.M. Rouiller, V. Moret, J. Tanne, D. Boussaoud, Evidence for direct connections between the hand region of the supplementary motor area and cervical motoneurons in the macaque monkey, Eur. J. Neurosci. 8 (1996) 1055–1059.

[25] T. Satow, A. Ikeda, J.I. Yamatomo, T. Begum, D.H. Thuy, M. Matsuhashi, T. Mima, T. Nagamine, K. Baba, T. Mihara, Y. Inoue, S. Miyamoto, N. Hashimotot, H. Shibasaki, Role of the primary sensorimotor cortex and supplementary motor area in volitional swallowing: a movement-related cortical potential study, Am. J. Physiol. Gastrointest. Liver Physiol. 287 (2004) G459–G470.

[26] M. Suzuki, Y. Asada, J. Ito, K. Hayashi, H. Inoue, H. Kitano, Activation of cerebellum and basal ganglia on volitional swallowing detected by functional magnetic resonance imaging, Dysphagia 18 (2003) 71–77.

[27] J.A. Toogood, A.M. Barr, T.K. Stevens, J.S. Gati, R.S. Menon, R.E. Martin, Discrete functional contributions of cerebral cortical foci in voluntary swallowing: a functional magnetic resonance (fMRI) "Go, No-Go" study, Exp. Brain Res. 161 (2005) 81–90.

[28] U. Ziemann, K. Ishii, A. Borgheresi, Z. Yaseen, F. Battaglia, M. Hallett, M. Cincotta, E. Wassermann, Dissociation of the pathways mediating ipsilateral and contralateral motor-evoked potentials in human hand and arm muscles, J. Physiol. 518 (3) (1999) 895–906.