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Remote effects of intermittent theta burst stimulation of the human pharyngeal motor system

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Abstract

Intermittent theta burst stimulation (iTBS) is a novel, non-invasive form of brain stimulation capable of facilitating excitability of the human primary motor cortex with therapeutic potential in the treatment of neurological conditions, such as multiple sclerosis. The objectives of this study were to evaluate the effects of iTBS on cortical properties in the human pharyngeal motor system. Transcranial magnetic stimulation (TMS)-evoked pharyngeal motor responses were recorded via a swallowed intra-luminal catheter and used to assess motor cortical pathways to the pharynx in both hemispheres before and for up to 90 min after iTBS in 15 healthy adults (nine male/six female, 22–59 years old). Active/sham iTBS comprised 600 intermittent repetitive TMS pulses, delivered in a double-blind pseudo-randomised order over each hemisphere on separate days at least 1 week apart. Abductor pollicis brevis (APB) recordings were used as control. Hemispheric interventional data were compared with sham using repeated-measures ANOVA. iTBS was delivered at an average intensity of 43 ± 1% of stimulator output. Compared with sham, iTBS to the hemisphere with stronger pharyngeal projections induced increased responses only in the contralateral weaker projection 60–90 min post-iTBS (maximum 54 ± 19%, $P \leq 0.007$), with no change in stronger hemisphere responses. By contrast, iTBS to weaker projections had no significant effects ($P = 0.39$) on either hemisphere. APB responses similarly did not change significantly ($P = 0.78$) across all study arms. We conclude that iTBS can induce remote changes in corticobulbar excitability. While further studies will clarify the extent of these changes, iTBS holds promise as a potential treatment for dysphagia after unilateral brain damage.

Keywords

deglutition; dysphagia; healthy volunteers; neurostimulation; transcranial magnetic stimulation

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Disclosure
No conflicts of interest to declare.

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Introduction

Non-invasive transcranial magnetic stimulation (TMS) studies demonstrate that swallowing musculature is bilaterally and often asymmetrically represented within the brain (Hamdy *et al.*, 1996). The importance of the cortex in the regulation of swallowing (including coughing, gasping and gagging, etc.) is often clinically highlighted in patients with dysphagia following neurological disorders such as stroke where cortical damage to either hemisphere can result in oropharyngeal dysfunction (Hamdy *et al.*, 1997). The presence of dysphagia as a major complication following stroke is also now well recognised as a significant contributor to malnutrition, aspiration pneumonia and premature death (Kumar *et al.*, 2010). However, despite such high morbidity, our understanding of the mechanisms underlying both the development and variable recovery of dysphagia after stroke remains poor.

Fortunately, novel forms of rehabilitative treatments targeting the brain's natural compensatory strategies for functional recovery are attracting lots of interest, with studies of human corticobulbar pathways demonstrating that the pharyngeal motor cortex is capable of reorganisation after brain lesions (Hamdy *et al.*, 1998b), and in response to experimental neurostimulation both directly (Gow *et al.*, 2004; Jefferson *et al.*, 2009a,b) and indirectly (Fraser *et al.*, 2002; Mistry *et al.*, 2006; Jayasekeran *et al.*, 2010). Moreover, they suggest that effective recovery of swallowing function after unilateral stroke is associated with increased corticobulbar excitability and cortical map size of the unaffected hemisphere (Hamdy *et al.*, 1998b).

Recently, novel neurostimulation protocols capable of probing long-term potentiation and depression-like synaptic plasticity in the human motor cortex have been developed. One such technique, theta burst stimulation (TBS), uses a high-frequency repetitive TMS regimen of three stimulation pulses delivered at 50 Hz and repeated every 200 ms (5 Hz). Originally developed to replicate hippocampal theta rhythms observed in rodent and human brains, TBS is becoming an increasingly common method of conditioning the brain (Oberman *et al.*, 2011). When delivered intermittently (2-s trains of stimuli repeated every 10 s for 190 s) or continuously (40-s trains of stimuli; total of 600 pulses for both), this short and powerful protocol is capable of inducing facilitation or inhibition of cortical excitability, respectively (Huang *et al.*, 2005, 2009; Agostino *et al.*, 2008; Di Lazzaro *et al.*, 2008). In the pharyngeal motor system, the inhibitory effects of continuous TBS have been explored with limited success (Mistry *et al.*, 2007); however, the effects of facilitatory intermittent TBS (iTBS) in this system have not been assessed.

Importantly, iTBS studies in stroke patients with motor (Talelli *et al.*, 2007) and language (Szaflarski *et al.*, 2011) deficits demonstrate beneficial effects on rehabilitation. Moreover, low-intensity iTBS represents a potentially safe and useful therapeutic intervention for the treatment of dysphagia after stroke since seizure risk from motor cortical stimulation is primarily associated with high stimulation intensities (Wassermann, 1998; Bezard *et al.*, 1999; Rossi *et al.*, 2009).

We aimed to assess the effects of iTBS on human corticobulbar pathway excitability as measured by TMS, and hypothesised that iTBS would be capable of modulating cortical excitability within the pharyngeal motor system.

Materials and methods

Participants

Healthy adult volunteers (n = 15, nine male/six female, 22–59 years old) participated in this study. All volunteers were in general good health and met previously established TMS inclusion criteria (Wassermann, 1998). Exclusion criteria included people with a history of epilepsy, cardiac pacemaker, previous brain or ear, nose and throat surgery, previous swallowing problems, pregnancy, metal in the head or eyes, or use of medication that acts on the CNS. Ethical approval was granted by the Salford and Trafford Local Research Ethics Committee. All studies were conducted in the clinical laboratory of the University of Manchester, Inflammation Sciences Research Group located at Salford Royal Hospital (Salford, UK), in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All subjects gave informed written consent.

Pharyngeal electromyographic measurements

Corticobulbar electromyographic responses evoked by TMS, known as motor-evoked potentials (MEPs), were recorded from the pharynx using a pair of bipolar ring electrodes built into a 3.2-mm diameter intra-luminal catheter (Gaeltec Devices; Isle of Skye, UK) passed into the oropharynx either 11–14 cm trans-orally or 13–17 cm trans-nasally according to subject preference. A corresponding earth was also attached to a skin electrode sited over the upper portion of one of the sternocleidomastoid muscles in the neck. Electrodes were connected to a preamplifier and amplifier (Headstage and 1902; Cambridge Electronic Design, Cambridge, UK) with high- and low-pass filter settings of 200 Hz and 2 kHz, respectively, via connecting cables. Response signals were processed through a 50/60 Hz noise eliminator (HumBug; Quest Scientific, North Vancouver, Canada) to remove any unwanted electrical interference, and collected through a laboratory interface (Micro 1401; Cambridge Electronic Design) at a sampling rate of 5 kHz and recorded using SIGNAL software (v4.08; Cambridge Electronic Design).

Hand electromyographic measurements

Solid gel, cloth-backed skin electrodes (H69P; Tyco Healthcare, UK) were sited 1.5 cm apart over the abductor pollicis brevis (APB) muscle in the hand contralateral to the hemisphere receiving the active iTBS treatment. A corresponding earth was also attached to a skin electrode on the wrist. Electrodes were connected to the recording system as per pharyngeal MEP recording.

Transcranial magnetic stimulation

Magnetic stimulation (single monophasic pulses) was performed using a hand-held (custom) figure-of-eight coil (70 mm outer diameter) connected to a Magstim Bistim^2 magnetic stimulator (The Magstim Company, Whitland, Wales) producing a maximum output of 2.2 Tesla. From previous studies, the optimal orientation was known to be in an antero-posterior

direction, with the plane of the coil parallel to the scalp surface and the handle/axis of the coil approximately 45 ° to the mid-sagittal line (Hamdy *et al.*, 1996).

Repetitive TMS

Repetitive stimulation was performed using the iTBS protocol as first described by Huang *et al.* (2005). Briefly, this consisted of three pulses of stimulation delivered at 50 Hz, repeated every 200 ms and delivered in 2-s trains repeated every 10 s for a total of 190 s (total 600 pulses). The iTBS protocol was manually configured using signal software and delivered using a Magstim super rapid stimulator (The Magstim Company) through a standard figure-of-eight coil with an outer diameter of 70 mm and a maximum output of 1.8 Tesla. Sham iTBS was given using a 90 ° tilt of the same coil, producing the same noise as active stimulation, but without motor cortical stimulation (Loo *et al.*, 2000).

Experimental protocol

To elucidate the neurophysiological effects of iTBS on the pharyngeal motor cortex excitability, volunteers attended on three occasions with studies performed at least 1 week apart in a double-blind, pseudo-randomised order incorporating the active and sham components.

For each session that the participant attended, they were seated in a comfortable chair with the catheter *in situ* and their eyes open. A disposable cap was taped over their head with the cranial vertex identified according to the international 10–20 system for electrode placement (Jasper, 1958), which was then marked on the cap. The optimal location of the coil in both hemispheres was determined through cortical mapping by discharging the coil at suprathreshold intensities over regions of interest on the scalp, as described previously by Hamdy *et al.* (1996) and Mistry *et al.* (2007). Briefly, this location, known as the ‘motor hot spot’, was characterised as the scalp site where magnetic stimulation produced the largest MEPs from the target muscle when the subject was relaxed. Pharyngeal MEP responses were then recorded from each hemisphere. The hemisphere evoking the largest consistent responses at the lowest threshold was described as the ‘*stronger*’ pharyngeal projection. Consequently, the contralateral pharyngeal motor cortex was described as the ‘*weaker*’ pharyngeal projection. APB responses were recorded from the motor hot spot in the hemisphere receiving iTBS to determine the specificity of the intervention. The resting motor threshold for each motor hot spot was subsequently determined using single-pulse TMS at incremental (1–5%) intensities starting at 30%. For the pharynx, resting motor threshold was defined as the intensity that produced MEPs of at least 20 μV on 50% of occasions. For the APB, resting motor threshold was defined as the intensity producing MEPs of at least 50 μV on 50% of occasions. All stimulation sites were marked onto the cap worn by the participants. Cranial measurements for each location were made to the point underlying the anterior bifurcation of the coil. To reduce any confounding variability through the identification of the optimal stimulation sites across multiple sessions, in subsequent sessions the same cap was worn by the individual participant with the cranial vertex position confirmed to be in the same location in each session. Motor hot spot identification and thresholding was conducted in the same manner in each session. This included identification of the optimal stimulation sites; however, this was not found to be

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different across sessions. Catheter and electrode positions were similarly noted and replicated across sessions.

Baseline measurements of cortical excitability were made using single-pulse TMS stimuli delivered in blocks of 10 stimuli (resting motor threshold +10% and +20% of stimulator output) at each of the three sites (stronger and weaker pharyngeal motor cortices and APB motor cortex), with a 5-s interval between each stimulus (60 stimuli in total). During each set of stimuli, subjects were asked to relax and to try to avoid swallowing, talking, coughing or making hand and arm movements in order to minimise any potential facilitation or contamination of MEP responses. The resulting traces were recorded and saved for off-line analysis.

Following baseline measurements of cortical excitability, participants received one of the three iTBS interventions – iTBS over the stronger pharyngeal motor cortex (iTBS-Strong); iTBS over the weaker pharyngeal motor cortex (iTBS-Weak); and sham iTBS (over the stronger pharyngeal motor cortex but with the coil tilted away from the cortex). As the magnetic output differs between the single-pulse and rapid-pulse magnetic stimulators, the APB resting and active motor thresholds were also measured with the repetitive TMS system at the APB motor hot spot. These values were then used to define the intensity of repetitive TMS to be delivered so that paradigms complied with current safety guidelines (Wassermann, 1998; Rossi *et al.*, 2009). All iTBS interventions were delivered at 80% of the active motor threshold of APB.

Following the intervention, cortical excitability was reassessed, as per baseline, immediately (time 0), and every 15 min for up to 90 min post-intervention. Each study took place on separate days, at least 1 week apart, with the intervention order randomly assigned for each participant in a double-blind manner and delivered by an independent member of the research team.

Data analysis

The peak-to-peak amplitude of MEPs evoked by magnetic stimulation was used as a measure of motor cortex excitability. Response latency was described as the interval between the onset of the stimulus and the onset of the MEP. Individual MEPs were reviewed using SIGNAL software. The amplitudes and latencies of individual MEPs in each group of 10 traces (for each muscle group and intensity) were determined and then averaged. To minimise the inter-individual variability in the amplitude of MEPs, data were normalised to baseline and expressed in the results as a percentage change from baseline. Inter-individual factors such as age and sex, which might conceivably alter these results, were therefore equalised.

Statistical methods

Statistical analyses were performed using spss 16 (SPSS, Chicago, Illinois, USA). Based on previous studies (Mistry *et al.*, 2006, 2007; Jefferson *et al.*, 2009a,b; Singh *et al.*, 2009; Jayasekeran *et al.*, 2010; Michou *et al.*, 2012), raw baseline MEP data for all interventions were first compared using non-parametric Friedman tests to rule out any results bias due to

conducting the studies on separate days. Changes in the excitability of the normalised MEP data (as reflected in increases or decreases in the MEP amplitude) over time between the different interventional groups were then compared with sham using a general linear model repeated-measures analysis of variance (ANOVA), including each time point except baseline. When a significant interaction was present, separate ANOVAs with time as a within-subject factor were performed to characterise the time-dependent changes. *Post hoc* paired-sample *t*-tests were then performed to explore the strength of the main effects and patterns of interaction between the experimental factors. The above analyses were also performed for the MEP latency data using the raw values. *P*-values of < 0.05 were taken as a measure of statistical significance, and data are expressed as mean [± standard error of the mean (SEM)] unless stated otherwise.

Results

Both TMS and repetitive TMS were well tolerated by all the participants, with no reported adverse events. Of the 15 participants studied, eight were judged to have stronger responses from the pharyngeal motor cortex in the right hemisphere and seven in the left hemisphere. The group mean scalp positions (referenced to the vertex) of the pharyngeal motor cortex in each hemisphere were 2.8 ± 0.17 cm medio-lateral and 3.7 ± 0.18 cm antero-posterior. For the APB, scalp positions were 3.7 ± 0.17 cm medio-lateral and 4.3 ± 0.2 cm antero-posterior from the vertex. The mean resting motor threshold values of the pharynx (stronger and weaker hemisphere) and APB were 63 ± 2%, 64 ± 2% and 46 ± 3% of stimulator output, respectively. The mean intensity of cortical stimulation for the iTBS was 43 ± 1% of the repetitive stimulator output. Representative MEP data traces from one individual of the mean effects of all iTBS interventions on the pharyngeal and APB motor cortex excitability are shown in Fig. 1. Figures 2-4 show the group mean effects of all iTBS interventions on the pharyngeal and APB motor cortex excitability.

Effects of iTBS on the pharyngeal motor cortex

Amplitude—The mean percent (%) change effects of all iTBS interventions on the pharyngeal motor cortex excitability are shown in Figs 1 and 2. Friedman tests comparing the raw baseline response amplitude values for each of the treatments (iTBS-Strong, iTBS-Weak and sham iTBS) for both the stronger (group mean values of 102 ± 11, 93 ± 18 and 99 ± 10 μV, respectively) and weaker (group mean values of 69 ± 11, 71 ± 13 and 66 ± 10 μV, respectively) pharyngeal motor projections did not reveal any significant differences across study days ($P = 0.25$ and $P = 0.70$, respectively).

A three-way repeated-measures ANOVA on the pharyngeal MEPs with factors of Treatment (iTBS-Strong, iTBS-Weak, sham iTBS), Site (stronger and weaker pharynx) and Time (0, 15, 30, 45, 60, 75 and 90 min post-iTBS) revealed a significant effect of Site ($F_{1,14} = 5.99$, $P \leq 0.028$), a Treatment × Site interaction ($F_{1,14} = 3.51$, $P \leq 0.013$), a Site × Time interaction ($F_{1,14} = 5.56$, $P \leq 0.033$) and a Treatment × Site × Time interaction ($F_{1,14} = 7.59$, $P \leq 0.015$).

To determine the Site (stronger or weaker pharynx) of the significant interactions as determined by the three-way ANOVA, separate two-way repeated-measures ANOVAs were

calculated. Factors of Treatment (iTBS-Strong, iTBS-Weak, sham iTBS) and Time (0, 15, 30, 45, 60, 75 and 90 min post-iTBS) were used, and revealed a significant effect of Treatment ($F_{1,14} = 6.68$, $P \leq 0.022$) and a Treatment × Time interaction ($F_{1,14} = 5.26$, $P \leq 0.038$) for the weaker pharynx MEP responses. No significant interactions were detected for the stronger pharynx MEP responses.

Separate one-way ANOVAs with Time as a within-subject factor were then performed to characterise the time-dependent changes in the pharyngeal MEPs, and revealed that responses were significantly increased only after the iTBS-Strong but within the unstimulated hemisphere ($F_{6,84} = 2.13$, $P \leq 0.05$). *Post hoc t*-tests then revealed responses in the unstimulated hemisphere were significantly increased 60–90 min post-iTBS-Strong (maximum = 54 ± 19%, $P \leq 0.007$), implying that the neurophysiological effects of the iTBS intervention built-up over time and were not present immediately after the stimulation.

Latency—The mean response latencies at baseline and each time point for the pharyngeal MEPs following iTBS are shown in Table 1. Friedman tests comparing the raw baseline response latency values for each of the treatments (iTBS-Strong, iTBS-Weak and sham iTBS) for both the stronger and weaker pharyngeal motor projections did not reveal any significant differences across the study days ($P = 1.0$ and $P = 0.53$, respectively). Repeated-measures ANOVA also did not reveal any significant effects of Treatment ($F_{2,28} = 1.49$, $P = 0.24$), Site ($F_{1,14} = 0.62$, $P = 0.44$) or Time ($F_{7,98} = 2.16$, $P = 0.10$).

Effects of iTBS on APB motor cortex

Amplitude—The mean percent (%) change effects of all iTBS interventions on the APB motor cortex excitability are shown in Fig. 3. Friedman tests comparing the raw baseline values for each of the Treatments (iTBS-Strong, iTBS-Weak and sham iTBS) for the APB motor cortex (group mean values of 87 ± 11, 106 ± 14 and 81 ± 14 mV, respectively) did not reveal any significant differences across the study days ($P = 0.16$). A two-way repeated-measures anova analysis of the APB MEPs with factors of Treatment (iTBS-Strong, iTBS-Weak, sham iTBS) and Time (0, 15, 30, 45, 60, 75 and 90 min post-iTBS) did not reveal any significant effects of any iTBS intervention on the APB muscle responses [Treatment ($F_{1,14} = 3.49$, $P = 0.83$), Time ($F_{1,14} = 0.48$, $P = 0.50$), Treatment × Time ($F_{1,14} = 0.19$, $P = 0.74$)]. No further analyses were therefore considered.

Latency—The mean response latencies at baseline and each time point for the APB MEPs following iTBS are shown in Table 1. As with response amplitudes, latencies were unchanged and therefore no further analyses were considered.

Discussion

Our study explored the excitation properties of the pharyngeal motor cortex to high-frequency repetitive cortical stimulation, and demonstrated that stimulation of the pharyngeal area of primary motor cortex with the iTBS pattern of repetitive TMS can excite corticobulbar pathways. However, in contrast to previous studies of iTBS in the hand motor cortex (Huang *et al.*, 2005), this excitation appeared to manifest primarily in the contralateral unstimulated hemisphere while conditioning the stronger pharyngeal motor

cortex projection. Moreover, conditioning the weaker projection directly did not significantly alter excitability of either pharyngeal motor cortex when compared with sham. This observation of increased excitability, contralateral to the stimulated site without significant ipsilateral changes in excitability, is a relatively unexpected finding and therefore warrants further discussion.

In some respects, the present data are similar to those in a previous study by Gow *et al.* (2004). They also applied 5-Hz regular repetitive TMS to the stronger hemisphere and observed facilitation of the contralateral projection. We suggest that these contralateral effects result from activation of interhemispheric connections between the pharyngeal motor cortices. Unlike the situation in hand muscles where interhemispheric interactions at rest are predominantly inhibitory (Ferbert *et al.*, 1992), those between the pharyngeal motor representations are mainly facilitatory (Hamdy *et al.*, 1998a; Gow *et al.*, 2004; Singh *et al.*, 2009; Michou *et al.*, 2012). Moreover, bilateral stimulation of the pharyngeal motor cortex has been shown to generate spatial summation of responses from each hemisphere at specific interstimulus intervals that are larger than when stimulating unilaterally, indicating that cortical efferents likely project onto a shared population of target neurons (Hamdy *et al.*, 1998a).

Behavioural evidence is also consistent with this interpretation of facilitatory interhemispheric interaction. Recent functional brain imaging data also suggest that these interhemispheric transcallosal pathways are actively used when performing swallowing behaviours (Mistry *et al.*, 2011). Experimentally disrupting the pharyngeal motor cortex activity through ‘virtual-lesions’ can also affect reflexive swallowing behaviours, but only when disrupting the stronger projection. However, when performing more complex swallowing tasks such as the challenged swallow reaction task, virtual-lesions to either pharyngeal motor cortex projection can affect swallowing behaviours (Mistry *et al.*, 2007). We conclude that an excitatory influence from iTBS to the stronger pharyngeal motor cortex facilitated the unstimulated pharyngeal motor cortex via activity in transcallosal pathways. This is in contrast to the interaction between hand muscle representations where the main effects are inhibitory (Harris-Love *et al.*, 2007). In stroke patients, inhibitory TBS of the unaffected hemisphere’s hand motor cortex has also been shown conversely to excite the homologous area of the affected hemisphere through a reduction in interhemispheric inhibition.

Why were these after-effects seen only in the weak projection from the contralateral hemisphere, whereas there was no effect on the excitability of the stronger projection from the hemisphere receiving iTBS? Interestingly Gow *et al.* (2004) noted a similar asymmetry in their experiments when they applied 5-Hz repetitive TMS to the hemisphere with the stronger projection – facilitation of the pharyngeal projections appeared larger in the contralateral hemisphere than in the stimulated hemisphere. One possibility is that the balance of control from the two hemispheres is maintained within a certain range in order to preserve stability of control. This might prevent excitatory iTBS from increasing excitability in the hemisphere with the stronger pharyngeal projection beyond a certain ‘ceiling’ level.

To date, the majority of studies utilising iTBS have primarily focused on conditioning the motor cortical representations of peripheral muscles, sometimes demonstrating immediate changes in the excitability of the targeted brain regions (Oberman *et al.*, 2011). However, the greatest changes in the pharyngeal motor cortex excitability only becomes evident in the unstimulated hemisphere 60–90 min after iTBS of the stronger projection – why? This is most likely a consequence of the intensity of iTBS used for conditioning the pharyngeal motor cortex, and although the effects of the iTBS only begin to become significant 60 min after stimulation, there appears to be a slow and continuous build-up of excitability throughout the post-intervention recording period. International safety guidelines for the use of repetitive TMS in humans (Wassermann, 1998; Rossi *et al.*, 2009) limit the intensity of iTBS interventions to 80% of the active motor threshold of the hand motor cortex in the stimulated hemisphere. In this study, this equates to 43 ± 1% (group mean threshold) of the repetitive stimulator output, which is well below the pharyngeal resting motor threshold (group mean average thresholds; stronger = 63 ± 2%, weaker = 64 ± 2% of stimulator output). Interestingly, a similar, albeit shorter (usually < 10 min), build-up period for excitability is also commonly seen in the hand motor cortex, where the intervention intensity and hand motor cortex thresholds are more closely aligned.

Finally, iTBS to the hemisphere with the weaker projection had no effect on the excitability of either hemisphere. Plasticity in the weaker hemisphere has not been examined in previous trials in swallowing. One possible reason for the lack of effect in the present case is that the intensity for iTBS may have been lower than optimal. The values were the same for the stronger and weaker hemispheres despite the much smaller MEPs evoked from the latter. It may therefore have been necessary to increase slightly the intensity of iTBS in order to recruit a sufficient proportion of the corticobulbar output to produce detectable changes in MEP.

Of importance, evidence in dysphagic patients suggests that effective recovery of swallowing function after unilateral stroke is associated with increases in the cortical excitability and cortical map size of the unaffected hemisphere (Hamdy *et al.*, 1998b). Pre-clinical studies on the development of neurostimulation therapies for the treatment of swallowing disorders have also shown that reversal of the neurophysiological and behavioural effects of virtual-lesion-induced cortical disruption (Mistry *et al.*, 2007) can be achieved through contralesional neurostimulation (Jefferson *et al.*, 2009a; Jayasekeran *et al.*, 2010; Michou *et al.*, 2012). Importantly, these potential therapeutic benefits of contralesional neurostimulation are further supported by more recent evidence in stroke patients with chronic dysphagia (Jefferson *et al.*, 2009a; Jayasekeran *et al.*, 2010; Michou *et al.*, 2012). Moreover, these studies demonstrate changes in the excitability of both the stimulated and unstimulated pharyngeal motor cortices, postulating that transcallosal pathways may act as the intermediate by which this excitation is spread. It is therefore possible that iTBS may be acting along these exact same pathways but targeting different neuronal populations. Future studies assessing the effects of iTBS after virtual-lesion-induced cortical suppression may help to answer some of these questions. Interestingly, the changes in cortical excitability observed in these earlier studies of neurostimulation in the pharyngeal motor cortex are of similar magnitude to those observed in the current study

(maximum = 54 ± 19%), suggesting that iTBS is potentially as effective at inducing cortical plasticity within the pharyngeal motor cortex, albeit indirectly, but has a dramatically shorter treatment time. Moreover, with further refinement of the treatment parameters and neural targets, the benefits of iTBS in certain patient populations may outweigh those of other types of neurostimulation.

In summary, we demonstrate for the first time modulation of pharyngeal primary motor cortex excitability using the iTBS pattern of repetitive TMS. However, in contrast to all previously published studies of iTBS, this excitation appeared to manifest primarily in the contralateral unstimulated hemisphere whilst conditioning the stronger pharyngeal motor cortex projection. We conclude that iTBS therefore has potential novel therapeutic value in the treatment of dysphagia and other oro-motor dysfunctions commonly seen after stroke. However, more work is needed to determine the optimal parameters of stimulation required, the number of doses to use, the mechanism by which these changes in cortical excitability are being driven and, through virtual-lesion studies, identify which hemisphere to target for maximum therapeutic benefit.

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Abbreviations

APB	abductor pollicis brevis
iTBS	intermittent theta burst stimulation
MEP	motor-evoked potential
TBS	theta burst stimulation
TMS	transcranial magnetic stimulation

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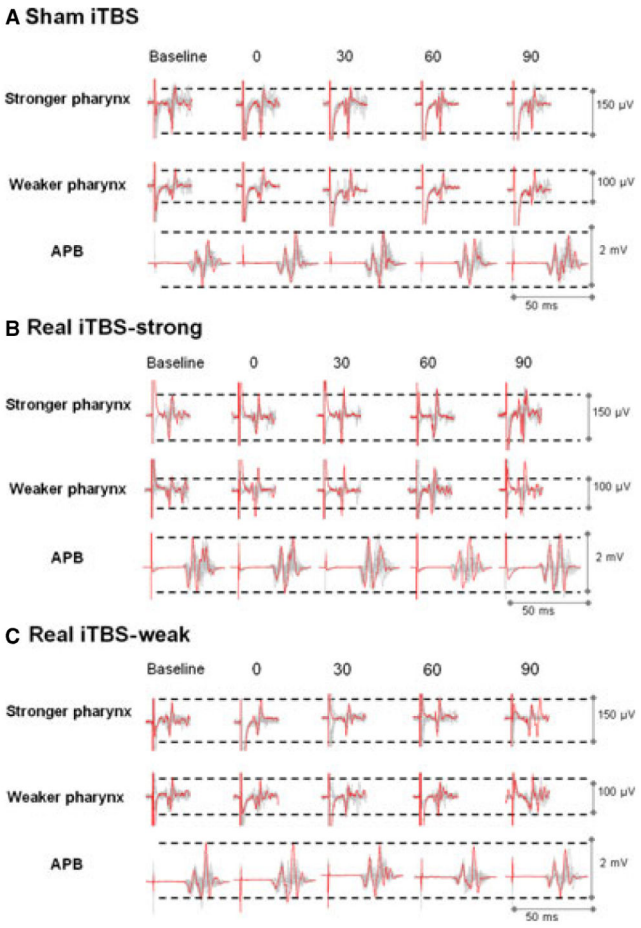

Fig. 1.

Representative pharyngeal and abductor pollicis brevis (APB) data traces. Representative data traces from an individual trial participant for all muscle groups after (A) sham intermittent theta burst stimulation (iTBS) over the stronger pharyngeal projection. (B) Real iTBS over the stronger pharyngeal projection (iTBS-Strong). (C) Real iTBS over the weaker pharyngeal projection (iTBS-Weak). For simplicity, responses from the intermediate time points 25, 45 and 75 min post-iTBS have been removed. Trace clusters for each recording site are comprised of 20 overdrawn responses with the highlighted trace representing the average response at that time point. Compared with sham iTBS, significant increases in response amplitudes are only seen 60–90 min post-iTBS-Strong, but only in the contralateral unstimulated weaker hemisphere for pharynx (maximum = 54 ± 19%, $P \leq 0.007$).

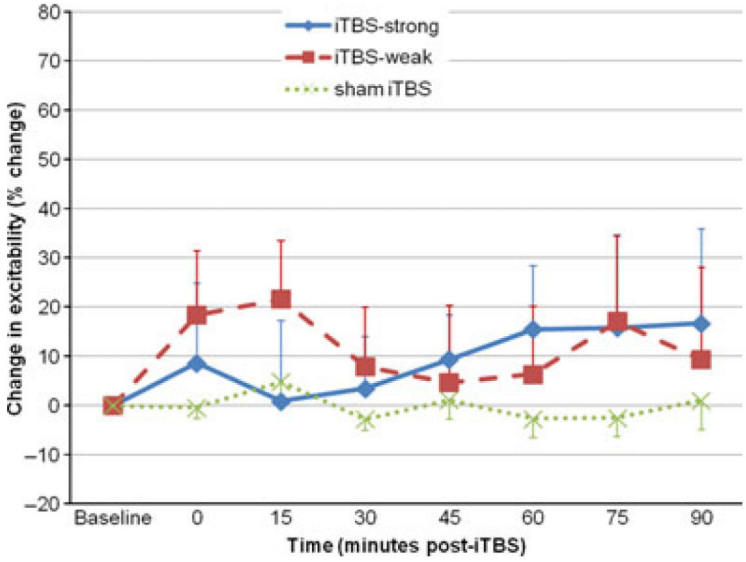

Fig. 2.

Effects of intermittent theta burst stimulation (iTBS) on the stronger pharyngeal motor cortex responses. Group mean ± SEM (%) change in the stronger pharyngeal motor cortex response amplitudes from baseline following iTBS-Strong (◆), iTBS-Weak (■) and sham iTBS (X). Despite modest increases in the pharyngeal MEP response amplitudes after iTBS-Weak (maximum = 22 ± 16%), response amplitudes were not significantly different to sham [Treatment ($F_{1,14}$ = 1.09, P = 0.32)].

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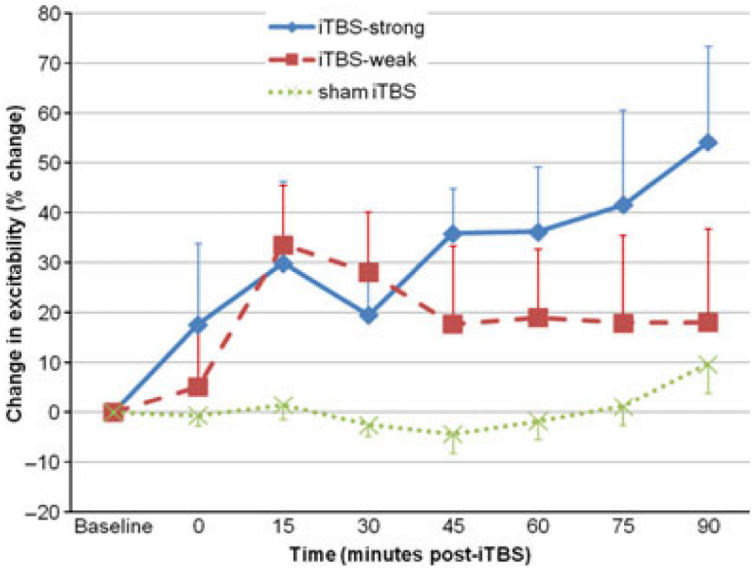

Fig. 3.

Effects of intermittent theta burst stimulation (iTBS) on the weaker pharyngeal motor cortex responses. Group mean ± SEM (%) change in the weaker pharyngeal motor cortex response amplitudes from baseline following iTBS-Strong (◆), iTBS-Weak (■) and sham iTBS (**X**). Compared with sham iTBS, significant increases in the weaker pharyngeal MEP response amplitudes are only seen 60–90 min after iTBS over the contralateral stimulated stronger hemisphere for pharynx (maximum = 54 ± 19%, $P \leq 0.007$). Despite an early increase in response amplitudes after iTBS-Weak, responses were not significantly different to sham [Treatment ($F_{1,14} = 3.4$, $P = 0.09$)].

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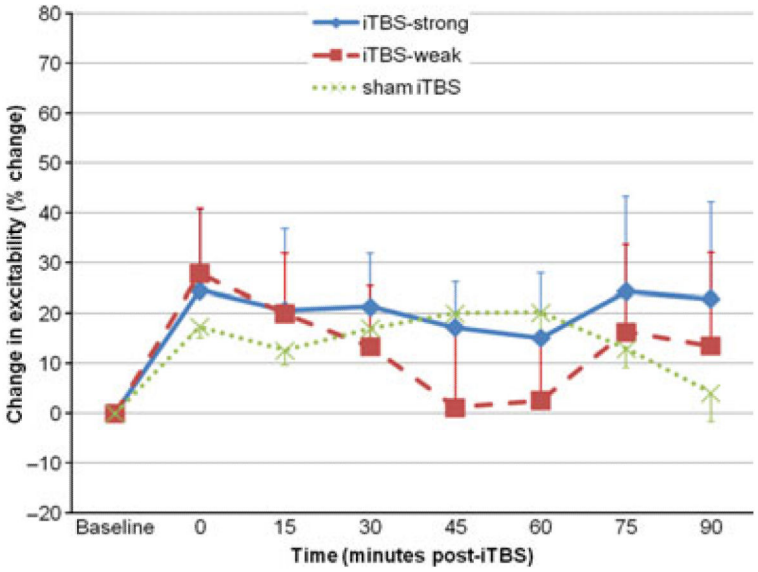

Fig. 4.

Effects of intermittent theta burst stimulation (iTBS) on the abductor pollicis brevis (APB) motor cortex responses. Group mean ± SEM (%) change in the hand motor cortex response amplitudes from baseline following iTBS-Strong (◆), iTBS-Weak (■) and sham iTBS (**X**). Despite modest increases in responses amplitudes after all iTBS interventions, the APB response amplitudes were not significantly different to sham [Treatment ($F_{1,14}$ = 0.47, P = 0.51)].

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Table 1

Response latencies for each site, across each time point before and after all iTBS interventions

Cortico-pharyngeal and APB response latencies									
Intervention	**Site**	**Baseline**	**0 min**	**15 min**	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**
iTBS-Strong	Stronger pharynx	8.3 ± 0.2	8.5 ± 0.2	8.2 ± 0.2	8.0 ± 0.3	7.9 ± 0.2	8.2 ± 0.2	8.3 ± 0.2	8.1 ± 0.2
	Weaker pharynx	8.5 ± 0.3	8.4 ± 0.3	8.1 ± 0.2	7.9 ± 0.2	8.0 ± 0.3	7.9 ± 0.3	8.2 ± 0.3	8.0 ± 0.2
	APB	21.8 ± 0.3	21.7 ± 0.3	21.7 ± 0.4	21.9 ± 0.4	21.9 ± 0.4	22.0 ± 0.3	22.2 ± 0.4	22.3 ± 0.4
iTBS-Weak	Stronger pharynx	8.2 ± 0.2	8.1 ± 0.2	8.2 ± 0.3	7.8 ± 0.3	7.8 ± 0.2	8.2 ± 0.3	8.1 ± 0.2	8.1 ± 0.2
	Weaker pharynx	8.0 ± 0.2	8.1 ± 0.3	8.1 ± 0.3	8.0 ± 0.3	7.8 ± 0.2	7.6 ± 0.2	7.9 ± 0.2	8.1 ± 0.2
	APB	21.5 ± 0.3	21.6 ± 0.3	21.4 ± 0.3	21.9 ± 0.3	21 ± 0.3	21.8 ± 0.4	22.0 ± 0.3	22.0 ± 0.3
sham iTBS	Stronger pharynx	8.3 ± 0.3	8.6 ± 0.4	8.1 ± 0.3	8.3 ± 0.3	8.4 ± 0.3	8.2 ± 0.3	8.4 ± 0.3	8.3 ± 0.3
	Weaker pharynx	8.1 ± 0.3	8.5 ± 0.3	8.2 ± 0.3	8.2 ± 0.2	8.2 ± 0.3	8.4 ± 0.2	8.3 ± 0.3	8.3 ± 0.3
	APB	22.0 ± 0.4	22.2 ± 0.4	22.2 ± 0.4	22.1 ± 0.4	21.9 ± 0.5	22.3 ± 0.4	22.2 ± 0.4	22.1 ± 0.4

APB, abductor pollicis brevis; iTBS, intermittent theta burst stimulation. Data (ms) are presented as mean ± SEM.