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The effect of swallowing treatments on corticobulbar excitability: A review of transcranial magnetic stimulation induced motor evoked potentials

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HIGHLIGHTS

- MEPs are used with increasing frequency in swallowing research.
- The link between cortical excitability and functional swallowing behaviour is unclear.
- Large standard deviations are typical of MEPs recorded from swallowing muscles.
- Analysis characteristics need to be clearly defined for comparison between studies.
- A review of considerations specific to swallowing related MEPs is provided.

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ABSTRACT

Transcranial magnetic stimulation (TMS) has been used extensively as a method of investigating the corticomotor physiology of many motor tasks, including healthy and disordered swallowing. Changes in excitability of cortical projections to various swallowing muscles have been documented in response to treatments with TMS induced motor evoked potentials (MEPs). These studies have provided valuable insight into CNS response to swallowing impairment, and more importantly, the adaptations associated with functional recovery. However, unique obstacles are presented when investigating corticobulbar neurophysiology associated with the complex task of swallowing. Stringent methodological control and supplementary outcome measures are required to ensure robust and clinically applicable findings. This article offers a tutorial for the researcher who may be considering the use of TMS for investigating changes in cortical excitability associated with various swallowing paradigms. Included is a review of the mechanisms of TMS and what can be measured with this technique, a summary of existing research using MEPs to investigate swallowing, a review of methodological factors that may influence outcomes, and proposed directions for new areas of research.

Contents

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1. Introduction

Transcranial magnetic stimulation (TMS) has been used extensively as a method of investigating neurophysiology and connections between brain and muscles. TMS has emerged into swallowing research as a neurophysiologic measure of healthy and disordered swallowing, as well as a measure of treatment response. This article offers a tutorial for the researcher who may be considering the use of TMS for investigating changes in cortical excitability associated with various swallowing paradigms. Included is a review of the mechanisms of TMS and what can be measured with this technique, a summary of existing research using TMS induced motor evoked potentials (MEPs) to investigate swallowing, a review of methodological factors that may influence outcomes, and proposed directions for new areas of research.

1.1. What is TMS and what does it measure?

TMS was first described by Barker et al. (1985) as a non-invasive technique for stimulating the motor cortex in humans. This technique has been used extensively to investigate organization and physiology of the motor cortex, as well as excitability of corticomotor projections. Researchers have used TMS in healthy participants to investigate factors that influence these physiologic parameters (see Jacobs et al., 2012 for a review), and to provide guidelines on TMS research (Chipchase et al., 2012). These parameters have been investigated in various neurological disorders (see Badawy et al., 2012 for a review), including stroke (Badawy et al., 2012; Bembenek et al., 2012; Cortes et al., 2012). TMS involves the generation of a transient stimulating electric current in the brain by discharging a high intensity electrical current through an external coil held parallel to the scalp surface and overlying the motor cortex. This current induces a transient magnetic field perpendicular to the coil (Hallett, 2000) that penetrates the scalp, skull, and brain tissue. This changing magnetic field, in turn, induces a circulating secondary electrical current perpendicular to the magnetic field and, therefore, parallel to the primary electric current, but in the opposite direction to that in the coil (Epstein, 2008). The intermediary magnetic field means that the electric current is induced in the underlying brain with minimal sensation and minimal attenuation of the magnetic field (Barker, 1999). A propagating action potential will be initiated if the depolarization exceeds the activation threshold (Mills, 1999). Magnetic stimulation preferentially activates fibres that lie parallel to the stimulating coil (usually parallel to the brain surface) such as intracortical fibres, rather than perpendicularly oriented pyramidal neurons (Kapogiannis and Wassermann, 2008; Rothwell, 1997; Stefan et al., 2000).

The motor evoked potential (MEP, measured by electromyography [EMG]) is the resulting electrical potential that signifies the muscle's response to stimulation of the corticobulbar or corticospinal pathways (Griskova et al., 2006). The MEP represents the muscle activity brought about by temporal and spatial summation of multiple descending volleys, caused by magnetic stimulation of the corticospinal or corticobulbar tract (i.e., pyramidal tract neurones (PTNs)). When a TMS stimulus is of high intensity and/or the coil orientation is such as to induce a lateral to medial current in the brain, PTNs can be stimulated directly (Di Lazzaro et al., 1998). This results in a D-wave (direct) in the MEP. Conversely, when low stimulus intensities are used, activation of the PTNs occurs indirectly via monosynaptic, corticocortical connections, eliciting an I-wave (indirect), which occurs approximately 1 ms after the D-wave (Di Lazzaro et al., 1998). When TMS intensities are increased beyond MEP threshold intensity, further indirect waves resulting from PTN activation via multi-synaptic corticocortical connections can occur (Di Lazzaro and Ziemann, 2013). The D- and I-waves activate alpha motor neurons in the spinal or bulbar segment (Kapogiannis and Wassermann, 2008; Lissens, 2003). In turn, this neural activity stimulates motor units in muscles, which can be seen via electromyography (EMG). Coil orientation influences the characteristics of I-waves, suggesting that modification of the induced currents in the brain can result in differential activation of the same cortical neurons, or activation of different neurons altogether. Because of lower TMS intensities and coil orientation, parameters typically used for investigation of cortical excitability generally evoke I-waves (Rothwell, 1997; Terao and Ugawa, 2002). Therefore, the MEP measured via EMG at the muscle reflects the accumulation of motor neuron activation resulting from the summation of I-waves. Because TMS preferentially activates corticocortical fibres, TMS can stimulate a range of neural structures directly (i.e., immediate and surrounding tissues) or indirectly (i.e., through corticocortical connections).

Phase is the term used to describe the portion of the electrical discharge cycle that has elapsed in relation to its origin. When two waves of similar frequency occur together, the resulting output is a sum of their magnitude. If these two waves are in phase, the result is increased magnitude of the electrical discharge cycle. If the two waves are out of phase, the desynchronization results in neutralization of electric potential due to the negative phase of one motor unit

coinciding with the positive phase of another (Rosler and Magistris, 2008). The MEP is an amalgamation of potentials and it therefore incorporates this inherent phase cancellation, which explains, in part, the large trial-to-trial variability in MEP measures (Darling et al., 2006; Ellaway et al., 1998; Thickbroom et al., 1999).

Because the MEP is measured at the target muscles, the response latency of the MEP (Fig. 1A) represents the time from initiation of motor cortex stimulation to the first sign of the associated EMG response in the peripheral muscle. The amplitude of the MEP (Fig. 1B) represents the overall level of excitation of the corresponding pathways between the motor cortex and the peripheral muscle (Chen, 2000). The amplitude of the MEP is calculated as the largest distance between consecutive positive and negative peaks. If the EMG activity is rectified, the MEP magnitude can also be calculated by determining the area of the response, and thus is influenced by the duration of the EMG activation. MEP amplitude reflects the state of the excitatory corticocortical axons, corticospinal or corticobulbar neurons, spinal or bulbar motor neurons, and muscle fibres, as well as the effectiveness of all intermediary excitatory synapses (Kapogiannis and Wassermann, 2008). Excitatory and inhibitory inputs to each neuron along this pathway determine its efficiency in transmitting excitatory activity (Kapogiannis and Wassermann, 2008). Therefore MEP amplitude signifies the overall excitability of the corticomotor system being investigated, incorporating phase cancellation and amalgamation of multiple volleys. The intensity required to elicit a MEP in target muscles is known at the *motor threshold*. Changes in the motor threshold also reflect overall changes in the excitability of the complex system of inputs along the system under investigation. Despite the contribution of multiple neurons and synapses to the MEP, when stimulating parameters remain unchanged, increases in MEP amplitudes are considered to reflect greater excitability in the corticocortical neurons rather than subcortical structures (Devlin and Watkins, 2008; Fraser et al., 2002). This is based on studies that document less variable EMG responses when stimulation occurs at structures further along the corticomotor pathway than the motor cortex (Kiers et al., 1993; Moosavi et al., 1999). Changes in MEP latency suggest alterations in the conduction time of the neural command from the motor cortex to the muscle (Chen, 2000; Misulis, 1994), through more or less rapid depolarization of neurons within the corresponding pathway. MEPs recorded from proximal muscles often exhibit shorter response latencies than those recorded from distal muscles, reflecting reduced distance between the cortex and motor unit in the former.

2. TMS-induced MEPs for the investigation of swallowing

TMS of the human cortex has been used to investigate motor physiology for numerous movements executed by humans. Because MEP recordings have high temporal resolution (Ilmoniemi, 2002), they have the sensitivity to detect corticobulbar activations associated with the very rapidly occurring swallowing process. TMS has been used for mapping the cortical areas that project to the muscles involved in swallowing (Gallas et al., 2009; Hamdy et al., 1996; Khedr et al., 2008; Michou et al., 2014a; Oh et al., 2007; Plowman-Prine et al., 2008). Cortical mapping involves determining the number and collective size of the scalp positions that successfully elicit a MEP response in a target muscle when stimulated. Cortical mapping is also used to determine which scalp locations elicit the largest MEPs in target muscles. Other investigations quantify response latency and amplitude of MEPs (described above) from submental muscles (Abdul Wahab et al., 2010; Al-Toubi et al., 2010; Doeltgen et al., 2009, 2010, 2011; Gallas et al., 2007, 2009; Hamdy et al., 1997; Plowman-Prine et al., 2008; Verin et al., 2012), pharyngeal muscles (Fraser et al., 2002, 2003; Gow et al., 2004a,b; Hamdy et al., 1996, 1997, 1998a; Jayasekeran et al., 2010, 2011; Jefferson et al., 2009a,b; Michou et al., 2012, 2013, 2014b; Mistry et al., 2006, 2007; Plowman-Prine et al., 2008; Power et al., 2004; Singh et al., 2009; Vasant et al., 2014), esophageal muscles (Ertekin et al., 2001; Fraser et al., 2003; Hamdy et al., 1996; Khedr et al., 2008, 2009) and other muscles involved in swallowing (Ertekin et al., 2001) to investigate cortical excitability of projections to these muscles. MEPs have also been recorded following cortical TMS in animals, to elucidate the relationship between the cortex and physiological swallowing events (Hamdy et al., 2001; Valdez et al., 1993).

The focus of this paper is to discuss issues pertinent to quantifying response latency and amplitude of MEPs in humans, as this is the most common use of MEPs for investigation of swallowing neurophysiology. These studies have shed light on many pertinent issues relating to plasticity of corticobulbar function associated with swallowing, including differential hemispheric (Hamdy et al., 1996, 1998b) and cerebellar contributions to swallowing motor pathways (Jayasekeran et al., 2011), recovery of dysphagia following stroke (Hamdy et al., 1996), and the effects of rehabilitation techniques on cortical excitability (Doeltgen et al., 2010; Fraser et al., 2002, 2003; Gow et al., 2004a,b; Hamdy et al., 1997, 1998a; Jefferson et al., 2009a,b; Khedr et al., 2009; Mistry et al., 2006, 2007; Power et al., 2004).

2.1. Specificity of MEP recordings from muscles involved in swallowing

The tools used to record MEPs are worthy of discussion in this review of MEP methods. For the swallowing investigations above, submental muscle EMG response is typically recorded with surface electrodes. Surface electromyography (sEMG) uses electrodes placed on the skin surface overlying the muscles of interest (Crary and Groher, 2000), providing an approximate measure of the collective electrical activity of muscles in the vicinity of the electrodes (Palmer et al., 1999). MEPs recorded with sEMG from the submental muscle region therefore reflect collective activation of the anterior belly of the digastric, the mylohyoid, and the geniohyoid muscles. While the genioglossus sits deeper than the floor of mouth muscles, it may also contribute to muscle activation measured in this vacinity. EMG responses recorded with sEMG must therefore be interpreted as a collective signal from these muscles, rather than being specific to any one of these muscles. Pharyngeal MEPs are recorded with an intraluminal catheter that houses bipolar ring electrodes to record EMG responses. The pharyngeal catheter is passed transnasally or transorally, and has a diameter of approximately 3 mm (Michou et al., 2013; Power et al., 2004; Mistry et al., 2007; Plowman-Prine et al., 2008; Vasant et al., 2014; Jayasekeran et al., 2010). Because this method of EMG recording utilizes a surface electrode, the issues of muscle specificity are also a consideration when interpreting pharyngeal MEPs. In addition to the issue of muscle specificity, the use of a catheter that is not fixed to a specific muscle region poses greater limitations for interpretation. Pharyngeal catheters are known to move during swallowing (Brasseur and Dodds, 1991; Olsson et al., 1995), creating uncertainty regarding the muscles responsible for recorded MEP signals. One must remain mindful of these limitations when interpreting findings of MEPs recorded from swallowing muscles.

2.2. Treatment effects

2.2.1. Healthy subjects

Healthy participants are often engaged to determine differential treatment effects on corticobulbar excitability and optimal treatment parameters for patient populations. These studies have used various treatment paradigms in an attempt to induce facilitation or inhibition of corticomotor excitability. Inhibitory treatment effects

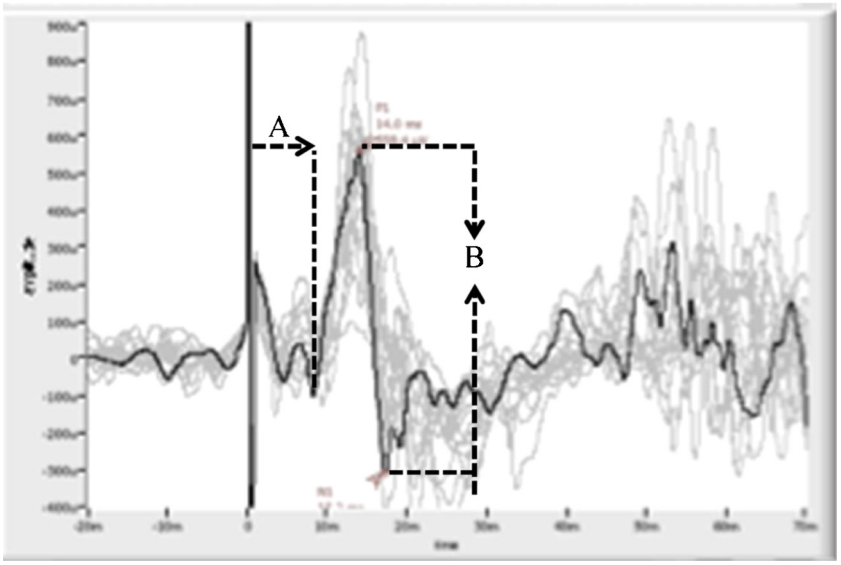

Fig. 1. MEP onset latency (A) and peak-to-peak amplitude (B).

reduce the overall excitability of the pathways connecting the cortex to the target muscles. Such effects are evidenced by a decrease in amplitude of MEPs, or an increase in motor threshold required to register activation in the target muscle. Excitatory paradigms facilitate corticomotor excitability, and result in an increase of MEP amplitude, or a decrease in motor threshold, signifying a heightened state of 'readiness' of involved neurons. A number of investigations have utilized MEPs to show both excitatory (Abdul Wahab et al., 2010; Doeltgen et al., 2010; Fraser et al., 2002, 2003; Gow et al., 2004a,b; Hamdy et al., 1997, 1998a; Jayasekeran et al., 2011, 2010; Jefferson et al., 2009a,b; Khedr et al., 2008, 2009; Michou et al., 2012, 2013; Mistry et al., 2006, 2007; Power et al., 2004; Singh et al., 2009; Vasant et al., 2014) and inhibitory effects (Fraser et al., 2003; Jefferson et al., 2009b; Mistry et al., 2006, 2007; Power et al., 2004) of treatment techniques on healthy cortical projections to muscles involved in swallowing. An increase in healthy MEP response amplitude has been documented following treatment protocols including repetitive transcranial magnetic stimulation (rTMS) (Gow et al., 2004b; Jefferson et al., 2009a; Khedr et al., 2008, 2009), transcranial direct current stimulation (tDCS) (Jefferson et al., 2009b), neuromuscular electrical stimulation (NMES) (Doeltgen et al., 2010; Fraser et al., 2002, 2003; Gow et al., 2004a; Hamdy et al., 1998a; Power et al., 2004), cranial nerve stimulation (Hamdy et al., 1997, 1998a), water swallowing (Fraser et al., 2003), and swallowing exercise (Gallas et al., 2009). Many of these investigations have utilized sham stimulation conditions as a control to show that changes in corticomotor excitability are specific to the treatment being applied (Gow et al., 2004a; Jayasekeran et al., 2011, 2010; Jefferson et al., 2009a,b; Michou et al., 2012, 2013; Singh et al., 2009; Vasant et al., 2014).

2.2.2. *Patients with dysphagia*

Four studies have examined changes in corticobulbar excitability as a result of intervention using dysphagic patients (Fraser et al., 2002; Khedr et al., 2009; Michou et al., 2012, 2014b). These studies have investigated the effects of rTMS (Khedr et al., 2009; Michou et al., 2014b), paired associative stimulation (PAS) (Michou et al., 2012, 2014b) and electrical stimulation (Fraser et al., 2002; Michou et al., 2014b) on corticomotor projections to the oesophagus (Khedr et al., 2009), and pharynx (Fraser et al., 2002; Michou et al., 2012, 2014b). All of these studies employed sham conditions in an attempt to control for differences unrelated to treatment. Unfortunately, the sham group in the study by Khedr and colleagues did not participate in the outcome MEP assessment and, therefore, the possibility that changes in MEPs resulting from factors unrelated to treatment remains unknown (Khedr et al., 2009). Regardless of the cause of increased MEP amplitudes in the treatment group, the coincident improvement in blinded clinical ratings of dysphagia documented by Khedr et al. (2009) may offer some insight into the possibility that corticomotor adaptations may be associated with modifications of swallowing function, as a result of treatment.

The remaining studies (Fraser et al., 2002; Michou et al., 2012, 2014b) are therefore the only investigations of changes in cortical excitability as a result of treatment with a sham group for comparison. In the study by Fraser and colleagues, the effect of real stimulation on response amplitudes and cortical map areas did not differ to the sham condition. The significant improvement in swallowing function and aspiration scores documented for the real-stimulation group but not the sham group may suggest changes in corticobulbar excitability were not the mechanism responsible for functional improvements. This study also shows that excitability of projections from the unaffected hemisphere in dysphagic patients was influenced to a greater extent following treatment than the affected hemisphere, with a significant difference documented between the responses of the hemispheres. This finding supports previous research showing that recovery of dysphagia is associated with plasticity of the unaffected hemisphere (Barritt and Smithard, 2009; Hamdy et al., 1998b, 2000). In further support of this notion, Michou et al. (Michou et al., 2012, 2014b) found increased corticomotor excitability in the unaffected hemisphere of their dysphagic patients. However, unlike Fraser and colleagues, Michou et al. (2012) and Michou et al. (2014b) documented significantly increased cortical excitability for the real stimulation, compared with the sham group. Increased cortical excitability in both studies by Michou et al. (2012, 2014b) was also accompanied by decreases in penetration and aspiration scores, suggesting some consistency in a positive relationship between functional modifications of swallowing physiology and corticobulbar excitability. However, the small number of studies investigating patient corticomotor response to treatment highlights the need for more research in this area. Our understanding of how corticomotor function coincides with improved swallowing function will be enhanced with such investigations.

2.3. Comparison of healthy and dysphagic MEP characteristics

Despite the lack of evidence of corticobulbar response to intervention in a patient population, some studies have used MEP measures to describe differences in corticomotor function between patient populations and healthy controls (Ertekin et al., 2001; Gallas et al., 2007; Khedr et al., 2008). These studies offer important advances in understanding changes in corticobulbar function associated with impaired swallowing function. UES MEPs (Khedr et al., 2008) and mylohyoid MEPs (Gallas et al., 2007) induced from the affected hemisphere of dysphagic patients are of smaller amplitude (Gallas et al., 2007; Khedr et al., 2008) and longer latency (Khedr et al., 2008) than those recorded from healthy controls. Of interest in these studies is the comparison of dysphagic stroke patients to not only control participants but also to non-dysphagic stroke patients. MEPs from the affected hemisphere in non-dysphagic patients were larger than the equivalent from dysphagic patients, and mimicked those seen in healthy controls (Gallas et al., 2007; Khedr et al., 2008). This reinforces that TMS-induced MEPs quantify activation of neural pathways pertinent to functional swallowing control. This is further supported by comparison of UES MEPs between dysphagic patients, non-dysphagic patients, and healthy controls (Ertekin et al., 2001). This comparison revealed that while all participants had MEPs in response to peripheral vagal nerve stimulation, cortically evoked MEPs were absent in patients with a hyper-reflexive UES and clinical signs of pseudobulbar palsy (Ertekin et al., 2001). These findings suggest that MEPs have the sensitivity to detect impairment in cortical projections to swallowing musculature. These differences between MEPs from healthy and impaired participants suggests normative temporal and magnitude values may prove useful in detecting disorder in corticobulbar projections.

One study utilized pharyngeal MEPs to compare cortical excitability during on- and off-medication states in patients with Parkinson's disease (Michou et al., 2014a). This study found that levadopa increased the bilateral excitability of pharyngeal projections in patients whose dysphagia was present both on and off medication and in patients whose dysphagia was only present when on medication. This increase in excitability was not present for patients with no evidence of dysphagia. Increased MEP measures were accompanied by a decrease in swallowing safety, as assessed by penetration and aspiration ratings. The authors suggest that subcortical injury or degeneration could be responsible for a lack of functional improvements associated with increased cortical excitability (Michou et al., 2014a). These findings highlight the complex relationship between excitatory and inhibitory mechanisms of neural substrates involved in swallowing, as well as caution the interpretation that increased excitability is synonymous with improved swallowing function.

2.4. Duration of swallowing treatment effects documented with MEPs

MEPs of both healthy participants and dysphagic patients are typically recorded at several time points following completion of treatment protocols to describe fluctuations in excitability across given time frames. These time points are typically spaced 15–30 min apart over 2–3 h (Abdul Wahab et al., 2010; Doeltgen et al., 2010; Fraser et al., 2002, 2003; Gow et al., 2004b; Jefferson et al., 2009a,b; Mistry et al., 2006, 2007; Power et al., 2004). Only one study has investigated adaptation of MEPs over a longer timeframe, measuring MEPs before and after 1 week of behavioural swallowing treatments (Gallas et al., 2009). This paucity of evidence for long-term modifications highlights the need for more investigations of cumulative response of corticomotor excitability to treatments. Investigating multiple timeframes of response is an important component of MEP studies, as it provides insight into the optimal period for maximized corticomotor excitability following treatments. While changes in MEPs do not provide direct evidence for cellular changes associated with long-term potentiation (LTP), they offer insight into cortical plasticity mechanisms which may be related to such learning processes (Vorel and Lisanby, 2008). Investigations of enduring changes in MEPs also provides information regarding differential effects of dose and frequency manipulations. Because adaptations to corticomotor excitability following many dysphagia treatments appear transient in nature (Abdul Wahab et al., 2010; Doeltgen et al., 2010; Fraser et al., 2002, 2003; Gow et al., 2004b; Mistry et al., 2006, 2007), it is imperative to couple these neural changes with modifications in swallowing function. This is particularly important for studies that have documented inhibitory effects of treatments on the excitability of swallowing pathways (Fraser et al., 2003; Jefferson et al., 2009a,b; Mistry et al., 2006, 2007). If it is shown that an increase in MEP amplitude and a decrease in MEP latency positively influence functional response to treatment (and the reverse negatively influences the response), MEPs can provide evidence of treatment efficacy at the corticomotor level, with changes indicative of one of the possible mechanisms responsible for improvements in swallowing function.

2.5. How do changes in MEPs represent changes in swallowing physiology and function?

MEPs do not reflect swallowing biomechanical processes and, therefore, do not provide a direct functional measure of swallowing per se. However, documenting modification of corticomotor function may provide insight into the underlying mechanisms behind altered biomechanics. Several studies have shown increased MEP amplitude to be associated with increased activation in the sensorimotor cortex as seen in functional magnetic resonance imaging (fMRI) (Fraser et al., 2002) and magnetoencephalography (MEG) (Gow et al., 2004a), indicating that MEPs measured at the muscles of swallowing are associated with cortical changes as measured by other imaging techniques. To link changes in corticomotor excitability with swallowing function, some studies have concurrently quantified other swallowing measures after treatments. Temporal measures of swallowing such as swallowing reaction time (SRT, also know as pharyngeal response time, PRT) (Fraser et al., 2002; Jayasekeran et al., 2010; Jefferson et al., 2009a; Michou et al., 2012, 2014b; Mistry et al., 2007; Power et al., 2004; Vasant et al., 2014), oral transit time (OTT) (Jayasekeran et al., 2010; Michou et al., 2014b; Power et al., 2004), pharyngeal transit time (PTT) (Fraser et al., 2002; Jayasekeran et al., 2010; Michou et al., 2014b; Power et al., 2004), UES opening duration (Jayasekeran et al., 2010; Michou et al., 2014b; Power et al., 2004), and laryngeal closure duration (Jayasekeran et al., 2010; Michou et al., 2014b; Power et al., 2004) have been used to monitor kinematic/physiologic adaptations that occur alongside fluctuations in MEPs.

The relationship between cortical excitability and functional swallowing events may be clarified by modifications of MEPs. However, a number of studies have found no changes in several temporal measures when MEPs are modified (Jayasekeran et al., 2010; Michou et al., 2014b; Power et al., 2004) or vice versa (Fraser et al., 2002). Additionally, discrepant results between studies investigating the same temporal measures further complicates the picture of how cortical excitability relates to swallowing physiology (Fraser et al., 2002; Power et al., 2004). Some studies even differ on their interpretation of the same observation in these temporal measures. For example, a decrease in swallowing response time (SRT), as measured by either videofluoroscopy or pharyngeal manometry, has been described as both desirable (Fraser et al., 2002) and detrimental (Jefferson et al., 2009a; Mistry et al., 2007)

to swallowing function. These issues may be related to the fact that temporal and spatial measures of swallowing kinematics are highly variable, even for investigations of healthy participants (Molfenter and Steele, 2011, 2012). The functional impact of these physiological measures therefore requires attention prior to conclusions being drawn about the relationship they have with cortical excitability.

One must also remain cognizant that documenting change in temporal measures alone does not provide insight into changes in accuracy (Reis et al., 2008). A more rapid progression of oral to esophageal transport does not necessarily equate to a more effective ingestive process, i.e., increased efficiency and safety of bolus transport from the mouth to the stomach. Therefore, measures with less ambiguity are required. The inclusion of functional measures of swallowing performance in dysphagic patients, such as decreased aspiration scores, have been investigated in conjunction with MEP measures in a small number of studies (Fraser et al., 2002; Michou et al., 2014b). These measures provide a crucial link for determining the functional relevance of changes in cortical excitability. However, it should be noted that Fraser et al. (2002) found no difference between MEPs in their treatment and control group, indicating that changes in corticomotor excitability are not a prerequisite for improved functional outcome. Conversely, Michou et al. (2014b) saw decreased penetration and aspiration in their treatment group only, which occurred in conjunction with increased cortical excitability. While this suggests a link between functional swallowing behaviours and cortical excitability of projections to the muscles involved in these behaviours, more studies are required before we can confirm functional sequelae of corticomotor adaptations on swallowing. Additionally, another study by Michou et al. (2014a), comparing PD patients on an off medication, found increased MEPs were associated with decreased swallowing safety. This suggests that the relationship between MEP measures and swallowing function is not necessarily the same for different disorders and situations.

3. Methodological considerations for using TMS-induced MEPs in swallowing research

3.1. Reliability of MEPs

3.1.1. Submental MEPs

The reliability of submental MEPs (Al-Toubi et al., 2010; Doeltgen et al., 2009; Gallas et al., 2009; Plowman-Prine et al., 2008), pharyngeal MEPs (Plowman-Prine et al., 2008) and esophageal MEPs (Paine et al., 2006) have been assessed by a small number of studies. Of the four studies looking at submental MEPs, two have used intraclass correlation coefficients (ICCs) and two have used repeated-measures ANOVA. Therefore, integration of results is limited to two studies in each group. When five trials were recorded at each session, across-session reliability over two sessions is reportedly .78 (Plowman-Prine et al., 2008), and decreases slightly to .66 across four sessions (Doeltgen et al., 2009). When Doeltgen et al. (2009) compared 10 with 5 trials, their across-session reliability increased to .72, still slightly lower than those reported by Plowman-Prine et al. (2008) using 5 trials. Interestingly, Doeltgen et al. (2009) found a decrease in across-session reliability when 15 trials were used in each recording block, with ICCs dropping to .69. However, with regards to within-session reliability, 15 trials elicited the highest ICC (.92), with the authors citing a reduction in ICCs with a reduction in MEP trials. Plowman-Prine et al. (2008) classified ICCs of .75 and over as high (Portney and Watkins, cited in Plowman-Prine et al., 2008, p. 2301). Doeltgen et al. (2009) used a more stringent classification of .90, with ICCs ranging between .70 and .80 as "good" (Atkinson and Nevill, 1998, cited in Doeltgen et al., 2009). The two studies utilizing ANOVA revealed no differences in MEP amplitudes or latencies when no treatments were executed between recording blocks (Al-Toubi et al., 2010; Gallas et al., 2009).

The placement of electrodes poses one limitation in generalizing the reliability estimates of submental MEPs to future studies. While most studies use surface electrodes for submental musculature, whether these are placed to measure activity of the right and left muscles separately (Plowman-Prine et al., 2008), collectively (Doeltgen et al., 2009), or of one side only (Gallas et al., 2009) varies from study to study. Therefore, reliability differences may be due to measurements being obtained from differential components of the submental muscle group. Reliability estimates of MEPs utilizing electrode placements that differ from these studies therefore require further investigation.

3.1.2. Pharyngeal and esophageal MEPs

One study has investigated the reliability of pharyngeal MEPs (Plowman-Prine et al., 2008). This study used five MEP trials and report high reliability across two testing sessions, with an ICC of .76. A single study has documented the reliability of esophageal MEPs (Paine et al., 2006). This study included 20 trials at each of three sessions, evaluating mean values after each trial. Additionally, this study assessed the difference in reliability across five different stimulus intensities. As found by Doeltgen and colleagues' investigation of submental MEPs (2009), within-session reliability of esophageal MEPs improves over the first 10 trials, and declines with more than 15 stimuli (Paine et al., 2006). This study also concludes that reliability of esophageal MEPs improves with higher stimulus intensities (Paine et al., 2006). Paine and colleagues discuss the concern that even the best reliability estimates for amplitude indicate that variance as large as double the amplitude is within the inherent variability.

3.2. Stimulus intensity

Higher stimulus intensities also heavily influence MEP size, the two increasing together (Paine et al., 2006). Stimulus intensity is typically determined on an individual basis, influenced by motor threshold (Paine et al., 2006), or MEP response size (Abdul Wahab et al., 2010; Al-Toubi et al., 2010; Doeltgen et al., 2010). Because of the variation in stimulus intensities applied, large variation is seen across participants and within participants when lower stimulus intensities are used, resulting in large standard deviations for group values (Wassermann, 2002). This variation is important to consider when investigating changes in the excitability of cortical projections (Paine et al., 2006). While reliability studies have documented no significant changes in MEP measures across sessions (Al-Toubi et al., 2010; Gallas et al., 2009), or moderate ICCs (Doeltgen et al., 2009; Plowman-Prine et al., 2008), the variability reported in these studies indicates that relatively large group effects are required to override the inherent variability of swallowing MEPs. Studies of submental MEP reliability report standard deviations of 50–80% of the mean (Al-Toubi et al., 2010; Doeltgen et al., 2009; Plowman-Prine et al., 2008). Standard deviations of 90–140% of the mean have been reported (Plowman-Prine et al., 2008), suggesting that MEPs from varying muscle groups may render different variability estimates. While variance estimates at the group level provide an idea of the size of effects required across-participants, within-participant variance estimates are not generally reported. Therefore, the magnitude of within-participant treatment effects required to supersede change as a result of simply repeating the measure in the absence of treatment remains unknown.

3.3. Background muscle activation

3.3.1. Magnitude of muscle contraction

In addition to stimulus intensity, investigations of MEPs from limb muscles have shown that level of background muscle contraction influences MEP amplitude (Darling et al., 2006; Devanne et al., 1997). As MEP amplitude increases with magnitude of background muscle contraction, the variability of the MEP decreases (Darling et al., 2006). Some level of muscle contraction also reportedly reduces MEP onset latency compared with MEPs taken from a resting muscle (Andersen et al., 1999). As stimulus intensity and contraction levels have a cumulative effect on the amplitude (Darling et al., 2006), a balance between facilitating the MEP amplitude to reduce variability and avoiding saturation needs to be achieved (Aranyi et al., 1998) if fluctuations in amplitude are to be considered reflective of treatment effects. Furthermore, higher levels of contraction do not necessarily reduce variability over minimal levels of contraction (Darling et al., 2006). However, these factors considered together indicate that MEPs taken from muscles during some level of contraction are less variable and allow lower TMS intensities to achieve quantifiable MEP amplitudes. As older participants require increased stimulus intensities to reach the same MEP amplitudes as younger counterparts (Pitcher et al., 2003), some level of contraction may facilitate recording cortical excitability in this population.

In further support of recording MEPs during muscle contraction, motor cortex excitability has been shown to increase during inactivity of hand muscles (Todd et al., 2006). Obtaining MEPs from muscles at rest requires participants maintain relaxed, inactive muscles for the duration of the investigation. It is proposed that a decrease in cortical inhibition associated with such restriction causes these fluctuations in motor cortex excitability (Todd et al., 2006). However, one caution to consider when recording MEPs from a contracted muscle is that small fluctuations resulting from intervention may be masked (Andersen et al., 1999). As small increases in background contraction have been shown to have a large impact on MEP amplitude when recorded from hand muscles (Darling et al., 2006), pre-stimulus background EMG should be monitored to confirm consistent number of supra-threshold neurons across trials and tasks (Aranyi et al., 1998). Studies have coupled the TMS discharge with a pre-set EMG trigger threshold in an attempt to maintain uniformity in the number of supra-threshold neurons (Abdul Wahab et al., 2010; Al-Toubi et al., 2010; Doeltgen et al., 2010). Additionally, analysis of MEPs from pre-contracted muscles requires some restriction on the duration of the MEP analysis window to ensure volitional EMG activity is not included as MEP response.

3.3.2. Nature of muscle contraction

If recording MEPs from pre-contracted muscles, the type of contraction performed at the time of cortical stimulation also has a bearing on the amplitude of the resulting MEP (Aranyi et al., 1998). When triggering of TMS was kept at a consistent EMG level between tasks, dynamic contraction (of increasing force) of a shoulder muscle showed increased MEP amplitude compared with steady contraction (Aranyi et al., 1998). The authors proposed that more neurons sit in a 'ready' state just below threshold in the dynamic condition, in anticipation of unexpected force requirements. This study found that changes in the length of the muscle during stimulation did not influence MEP amplitudes when EMG triggers were controlled (Aranyi et al., 1998), suggesting that whether the goal of the movement was force or motion was irrelevant to fluctuations in cortical excitability.

Specific to swallowing, significant differences in MEPs from the submental muscles have been documented across three tasks: volitional contraction, volitional swallowing, and reflexive swallowing (Doeltgen et al., 2011). The authors reported a progressively larger MEP area from reflexive swallowing, to volitional swallowing, to volitional contraction, and proposed that this reflects increased M1 input for the contraction task over the brainstem-modulated tasks of swallowing. This assumption fits with the belief that the cortex plays a modulatory role in the primarily brainstem-generated swallowing response (Robbins et al., 2008). A consideration of the comparison of these tasks is the use of area for quantification of the MEP size. While the authors controlled pre-stimulus activation of the target muscles across tasks using an EMG trigger system, they do not report if the duration of volitional EMG or the MEP analysis window was restricted. When utilizing rectified area of the EMG response for MEP analysis of contracted muscles, control of the post-stimulus EMG is required and can be achieved by subtracting pre-stimulus EMG or an isolated EMG trial (Pearce et al., 2003; Sowman et al., 2009; Tunstill et al., 2001; van Hedel et al., 2007). Additionally, as area of the MEP is influenced by the magnitude and temporal characteristics of the EMG response, the duration of the analyzed response must also be controlled to ensure differences in the duration of muscle activation across tasks does not produce differences in MEP area (Pearce et al., 2003; Sowman et al., 2009). Furthermore, integration of the findings by Doeltgen and colleagues with those reported by Ariyani and colleagues (discussed above) (Aranyi et al., 1998) suggests differences in the type of muscle contraction may also need to be considered when assessing amplitude differences across tasks.

3.4. Coil orientation

While changes in the orientation of the coil, and therefore the flow of the underlying current, heavily influence MEP amplitude (Brasil-Neto et al., 1992; Kammer et al., 2001; Mills et al., 1992), fixing the head and coil position has not shown any advantages over hand-held coil positioning (Ellaway et al., 1998). While hand-held coil positioning involving stabilization of the coil against the head and scalp marking has been suggested to be sufficient to elicit reproducible MEPs (Al-Toubi et al., 2010), comparison of standard deviations from studies utilizing head and coil fixation with those obtaining MEPs via hand-held methods would elucidate any advantages of the former. Paine and colleagues (Paine et al., 2006) utilized head and coil stabilization to record esophageal MEPs. This study reports similar standard deviations for MEP amplitudes as investigations that have not utilized such controls, ranging from around 60% to 100%, raising uncertainty about the advantages of such measures. While variation may not decrease with such stabilization efforts, movement of the head and coil should be minimal to ensure that the site of stimulation is consistent throughout assessment. While coil orientation affects amplitude, it has no impact on the variability of MEPs (Ellaway et al., 1998), indicating that as long as coil angle is kept constant for repeated measures, no orientation is advantageous over others. However, for accessing greater amounts of underlying cortical projections to target muscles, a coil orientation of approximately 45 degrees towards the mid-sagittal plane on both hemispheres is recommended (Mills et al., 1992).

3.5. Filtering and analysis

An external influence on the quantification of MEPs is the filtering and analysis methods used. Various processes have been used to quantify MEPs, including averages from single-trial rectified EMG data (Doeltgen et al., 2011; Ziemann et al., 1999), averages of single-trial unrectified EMG data (Doeltgen et al., 2009, 2010; Gow et al., 2004b; Jefferson et al., 2009a; Mistry et al., 2007), maximal MEP response (McDonnell et al., 2004), peak-to-peak amplitude and area of ensemble-average waveforms (Bastings et al., 2002; McDonnell et al., 2004; Pitcher and Miles, 2002; Pitcher et al., 2003),

median value of single-trial unrectified data (Awiszus, 2005; Wolf et al., 2004), and peak-to-peak values from an ensemble-median waveform (Awiszus, 2005). Quantifying MEPs from contracted muscles using area of rectified EMG data requires some control of volitional EMG (mentioned above) to minimize its influence on the MEP. Details of how MEP onset, peak-to-peak amplitude, or duration of MEP is defined are generally not reported in the literature (Doeltgen et al., 2010; Jefferson et al., 2009a; Mistry et al., 2007). Additionally, filtering at levels that influences the amplitude of the evoked potential is reported in some studies (Mistry et al., 2007; Verin and Leroi, 2009). As filter settings often differ across studies, the effect of these settings on the size of the MEP must be considered when comparing results.

3.6. Inherent variability of MEPs

Even when the many factors influencing MEPs are controlled, large variability in amplitudes is still evident when measuring MEPs from limb muscles (Darling et al., 2006; Ellaway et al., 1998; Thickbroom et al., 1999). Comparison of the variability of cortical MEPs from hand muscles to reflexes induced at the spinal neurons shows variation in the former is much larger than the latter (Kiers et al., 1993), lending to the hypothesis that intrinsic fluctuations of cortical projections are largely responsible for the unexplained 'noise' (Darling et al., 2006; Pitcher et al., 2003). The unpredictable nature of cortical excitability is highlighted by the finding that activation of facial muscles facilitates MEPs recorded from hand muscles (Andersen et al., 1999). The authors propose that increased excitability of cortical areas that represent the face influence cortical areas in close proximity, such as the hand, and therefore serve to facilitate excitability of projections to both. The proximity of the cortical representations of hand and facial muscles may be the rationale for many swallowing studies utilizing MEPs from hand muscles as a control condition (Michou et al., 2012, 2013; Mistry et al., 2007; Vasant et al., 2014). However, the findings from Andersen and colleagues (1999) suggest that this proximity may result in facilitation of both areas and, therefore, true treatment effects may be dismissed due to common facilitation.

Another issue relating to the variability of MEPs measured from muscles involved in swallowing was raised by Doeltgen et al. (2011). This study reports a large number of participants (between approximately 40% and 50% when recording MEPs during volitional and reflexive swallows) for whom MEPs from the submental muscles cannot be recorded. The inability to record measurable MEPs from muscles involved in swallowing is rarely discussed in the literature. This aspect of variability is crucial to consider, and indeed report, when completing investigations of cortical excitability of projections to muscles involved in swallowing.

4. Future directions for using MEPs to document the effects of treatment for dysphagia

While MEPs recorded from swallowing muscles have been used to document changes in excitability of cortical projections, how these changes correlate with peripheral swallowing physiology and functional outcomes remains uncertain. Future studies need to concurrently monitor changes in peripheral physiology and functional measures of swallowing if the mechanisms responsible for improved function following treatment techniques are to be understood.

MEPs of swallowing muscles in healthy participants are sensitive to effects of various treatments. Studies to date have observed changes in cortical excitability over a relatively short period of time, typically over a duration of 2–3 h, with only one study observing changes over 1 week (Gallas et al., 2009). To elucidate whether changes in cortical excitability play a role in long-term adaptations of swallowing function, it is necessary to document both functional and corticobulbar outcomes over extended periods, such as days, weeks, and months.

If lasting effects are investigated over repeated sessions, parameters that affect MEPs must be controlled to ensure changes can be attributed to treatments rather than methodological error. If recording MEPs from active rather than resting muscles, levels of activation at the time of stimulation need to be consistent across sessions, with consideration given to the types of activation being executed during MEP recording. Stimulus intensity, as well as coil orientation and hot spot location must be kept constant across sessions, a methodological struggle for any researcher. Integration of the findings from studies investigating submental MEP reproducibility suggests between 10 and 15 trials are required at each time point to ensure the maximum level of within- and across-session repeatability is achieved for MEPs from the submental and esophageal muscles.

Because of the large variability seen in responses within and across individuals, the size of response variability needs to be taken into account when assessing changes in the excitability of cortical projections (Paine et al., 2006). Methods of analysis need to incorporate this variance to ensure findings reflect true changes in the relatively noisy data sets that are inherent to MEP investigations. Comparison of estimated effect sizes and their 95% confidence intervals with within- and across-participant variance allows insight into such issues.

As many steps in MEP analysis are not reported in the literature – for example, definition of how onset of MEP is selected, which peaks are used when calculating peak-to-peak amplitude, or how duration of rectified MEPs is determined – how these issues affect MEP quantification needs to be investigated to enhance comparison of results across studies. As increased levels of filtering affects the amplitude of the MEP, this information must also be considered when comparing across studies. When the level of filtering used imposes substantially on the MEP signal, how these values reflect true physiology must also be called into question.

5. Conclusion

TMS-induced MEPs offer a painless, non-invasive, and effective way to document neural adaptations associated with swallowing treatment techniques, injury, and recovery. As researchers continue to utilize MEPs to contribute to the crucial body of literature that provides this information, we must be mindful of reviewing our technique to ensure methodological error is minimized. It is also imperative that future studies are designed with the aim of providing either immediate or eventual evidence for clinical application. Understanding the functional implications of changes in cortical excitability is an important aspect of this continued research. Given the large variance in MEP measures, treatment effects of smaller magnitude are especially in need of such functional verification. Many of these fundamental issues need to be addressed before swallowing research attempts to complete comprehensive treatment studies in patient populations. Once the role of cortical excitability in recovery of functional swallowing impairment is elucidated, MEPs can provide robust neurophysiologic evidence for dysphagia rehabilitation techniques.

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