1 **Title:**

2 Transcranial Magnetic Stimulation (TMS) and Motor Evoked Potentials (MEPs) in

3 Speech Perception Research

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1 **Abstract:**

2 Transcranial Magnetic Stimulation (TMS) has been employed to manipulate brain

3 activity and to establish cortical excitability by eliciting Motor Evoked Potentials

4 (MEPs) in speech processing research. We will discuss the history, methodological

5 underpinnings, key contributions, and future directions for studying speech processing

6 using TMS and by eliciting MEPs. Furthermore, we will discuss specific challenges

7 that are encountered when examining speech processing using TMS or by measuring

8 MEPs. We suggest that future research may benefit from using TMS in conjunction

9 with neuroimaging methods such as functional Magnetic Resonance Imaging (fMRI)

10 or electroencephalography (EEG), and from the development of new stimulation

11 protocols addressing cortico-cortical inhibition/facilitation and interhemispheric

12 connectivity during speech processing.

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14 **Keywords:**

15 Speech, Perception, TMS, MEP

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1. Historical background

Brain stimulation using magnets is based on the work of Michael Faraday (1831, cf. (Cowey, 2005), who discovered that moving a magnet in and out of a wire coil induced a voltage, and therefore produced a current; a process known as electromagnetic induction. Applying this concept to human subjects, Arsene d'Arsonval (1896) reported the induction of magnetophosphenes (perceived flashes of light in absence of a light source) when the participant was placed inside a magnetic field generated by wire coils. D'Arsonval thus illustrated for the first time that electrical functioning of the human brain could be altered non-invasively by the application of magnetic pulses. An important advancement of this technique occurred in the early 20th century, when alternating currents instead of direct currents were introduced, making it easier to generate alternating magnetic fields. D'Arsonval's findings were replicated several times using alternating currents, notably by Thompson (1910), who attributed the evoked magnetophosphenes to the direct stimulation of low-level visual areas of the brain. Finally, Barker, Jalinous, and Freeston (1985) were the first to stimulate the hand area in primary motor cortex (M1) and elicited movements in the contralateral arm, using a simple round coil. The work by Barker et al. represented an important step in the development of the method, as they directly targeted a specific cortical area using a simple and effective design that could be applied to other cortical areas. In subsequent years, it was demonstrated that behaviour in a wide variety of cognitive tasks, including speech tasks, could also be affected by directing the coil to areas outside M1.

Since publication of Barker et al., TMS has been refined further by the introduction of new coils: e.g., the figure-of-eight coil, H-coils, or butterfly coils, which all allow for more focal stimulation than the original round coil. The stimulator

has improved as well, and modern setups include double, or even triple, linked stimulators that can discharge paired stimuli from the same coil or from two independent coils targeted to two different brain areas, simultaneously or with a time-delay (Epstein, Wassermann, & Ziemann, 2008). These setups enable the design of sophisticated experiments, for instance those in which TMS pulses are applied simultaneously using two coils, or experiments in which the interaction between brain areas can be studied. For in-depth reviews of the history of TMS, see Walsh, Pascual-Leone, and Kosslyn (2003), or Rotenberg, Horvath, and Pascual-Leone (2014). This review will focus on how TMS and MEPs have been used to elucidate the neurobiological basis of speech processing by discussing their underlying principles and method, before highlighting key papers in the field, focusing mostly on studies on speech perception, and finally suggesting future directions for the use of TMS and MEPs in speech processing research.

2. Principles and Method

TMS works on the following principles: magnetic fields are generated by a rapidly alternating current passing through the TMS coil. The TMS coil is connected to a capacitor that delivers the electrical current to the coil. The coil is placed on the scalp of an awake participant, who is stimulated with a brief (~100-200 μs), but relatively strong (~1-2 Tesla) magnetic field. This magnetic field induces an electrical current in the (conductive) neural tissue under the scalp. TMS can be administered using single, paired, or with trains of pulses; a type of protocol often referred to as repetitive TMS (rTMS). Pulses either occur 'online': at the same time as a task, or 'offline': before a task. Effects of TMS on task performance can be varied using different protocols to induce an inhibitory or facilitatory effect, which lasts for either the same length of

time as the stimulation, or longer. It should be noted that TMS, in principle, always results in excitation of the cortex, but that the overall effect on the task can be inhibitory or excitatory depending on the duration, frequency, and timing of stimulation, and the area of cortex stimulated (Fitzgerald, Fountain, & Daskalakis, 2006). Inhibitory/excitatory effects of specific TMS protocols can be established by measuring Motor Evoked Potentials (MEPs) from specific skeletal muscles following TMS to areas of primary motor cortex (M1) linked to these muscles, such as the First Doral Interosseus muscle in the hand (FDI). A decrease in the size of MEPs is interpreted as an inhibitory effect of TMS to M1, and an increase as a facilitatory effect. A 1Hz paradigm that lasts 15 minutes delivers 900 pulses and the effect of stimulation is generally found to outlast the time during which stimulation was applied. For instance, (Romero, Anschel, Sparing, Gangitano, & Pascual-Leone, 2002) applied 10 minutes of 1Hz TMS to right hand motor cortex and reported a decrease in the amplitude of MEPs for 10 minutes after delivery of the pulse train. A 5Hz paradigm, on the other hand, delivers 300 pulses per minute, and the effect of stimulation has also been found to outlast the time of stimulation. For instance, (Peinemann et al., 2004) delivered 1800 pulses at 5Hz to right hand motor cortex and recorded an increase in corticospinal excitability as measured using hand Motor Evoked Potentials, for up to 30 minutes. Most protocols deliver pulses at frequencies between 1 and 10Hz, and thus deliver between 1 and 10 pulses per second. The duration of the effects of inhibitory and excitatory protocols has been found to differ greatly between paradigms (Chen et al., 1997; Muellbacher, Facchini, Boroojerdi, & Hallett, 2000; Nyffeler et al., 2006; Wassermann et al., 1996). Alternative protocols, such as theta-burst stimulation (TBS), have recently been developed, whereby three TMS pulses are given at 50Hz every 200ms. If this paradigm is applied continuously

for 20-60 seconds (300-900 pulses), depending on the specific protocol used it has an inhibitory or excitatory effect on neural processing (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). The effects of theta-burst stimulation have been shown to last from 10 minutes (Ishikawa et al., 2007; Valero-Cabre, Payne, & Pascual-Leone, 2007), up to one hour (Gamboa et al., 2011; Huang et al., 2005; Ji & Hilgetag, 2008; Nyffeler et al., 2006).

Slow (<5Hz) offline TMS is assumed to inhibit cognitive functioning, while fast (5Hz and above) offline TMS protocols are assumed to facilitate cognitive functioning (Sack, 2006), but note that certain protocols using high-frequency stimulation, such as TBS (Huang et al., 2005), are also capable of inducing inhibition. The suppressive effect of TMS has been attributed to a variety of factors, including the activation of inhibitory (GABAergic) interneurons (Mottaghy et al., 2003), or the introduction of 'neural noise' into the neurons being stimulated that is asynchronous with task-related activity and therefore results in poorer performance (Harris, Clifford, & Miniussi, 2008; Walsh & Cowey, 2000). The effects of excitatory TMS have been related to optimisation of long-term potentiation at apical and dendritic synapses in animal models (Capocchi, Zompolini, & Larson, 1992) but little is known about the precise mechanism of action. See Moliadze et al. (2003), Rothwell (1997), Siebner et al. (2009), and Wagner et al. (2009) for a detailed discussion of physical/neurophysiological mechanisms.

Some TMS protocols allow for inferring causality between induced changes in cortical functioning and behavioural task performance. Tasks used in speech TMS experiments vary widely, and include, for example, semantic or phonological decision tasks (Krieger-Redwood, Gaskell, Lindsay, & Jefferies, 2013) or categorical

1 perception tasks (Möttönen & Watkins, 2009), and the associated dependent variables

2 are therefore reaction times in milliseconds, percent correct, or accuracy.

3   Finally, single or paired pulses of TMS applied to M1 can also be used to elicit

4 MEPs in contralateral target muscles. MEPs can be recorded in conjunction with or

5 without a task. They reflect activation of the primary motor system and depolarisation

6 of neurons in the descending motor tract, and are recorded using electromyography

7 (EMG). MEPs occur at specific muscle-dependent latencies, which are in part

8 dependent upon the length of motor tract to a particular muscle. Elicitation of MEPs

9 can be used, as discussed in section 2, to establish the effect of TMS stimulation

10 protocols on the excitability of M1 (Fitzgerald et al., 2006; Peinemann et al., 2004;

11 Romero et al., 2002). Moreover, MEPs can use used for indexing changes in

12 activation of the associated underlying cortical motor representation of the muscle

13 (Baldissera, Cavallari, Craighero, & Fadiga, 2001; Strafella & Paus, 2000). When

14 using pairs of TMS pulses to elicit MEPs, the first pulse acts as a conditioning pulse

15 to the stimulated cortex. The second pulse constitutes the test stimulus, and elicits the

16 MEP. Pairs of pulses can also be applied to different regions in the same hemisphere

17 to measure cortico-cortical inhibition or facilitation, or to regions in different

18 hemispheres to measure interhemispheric inhibition or facilitation. The intensity of

19 the conditioning pulse, test pulse, and the inter-pulse interval need to be carefully

20 considered to induce facilitation or inhibition (Tokimura, Tokimura, Oliviero,

21 Asakura, & Rothwell, 1996; Ziemann, Tergau, Wischer, Hildebrandt, & Paulus,

22 1998).

23 **3. Challenges and solutions**

24   One challenge for TMS and MEP study design relates to the timing of

25 stimulation. For online protocols, it is often difficult to determine precisely when the

TMS should be administered, or the MEP elicited, during the stimulus or task. This is particularly the case if the length of TMS will last less than the duration of the stimulus; for example, a single TMS pulse during a word stimulus. An issue that is specifically problematic for speech processing research is the fact that the discharge of the coil is accompanied by a high-intensity auditory artefact, or click sound. The click has been shown to cause permanent threshold shifts in (unprotected) ears of experimental animals (Counter, Borg, Lofqvist, & Brismar, 1990). Pascual-Leone et al. (1992) and Loo et al. (2001) report that a small proportion of participants experience a transient increase in auditory thresholds, and a permanent shift has only been reported in one individual, who did not wear hearing protection (Zangen, Roth, Voller, & Hallett, 2005). Therefore, subjects should always wear ear protection, and it is recommended that experimenters also wear earplugs. If TMS accompanies an auditory stimulus, the TMS click will inevitably result in some degree of partial masking, which needs to be considered when designing an experiment and interpreting its results. Magnetically shielded insert headphones attenuate external sound by approximately 30 dB (SPL), and can at least reduce the perceptual effect of the click (Hartwigsen, Price, et al., 2010).

The sensation of the magnetic field can also negatively affect task performance if present during stimulus presentation, as TMS often causes peripheral nerve innervation, resulting in muscle twitches in the scalp, face, or neck. TMS to areas in the temporal and frontal lobes, which are areas of the brain usually stimulated when studying speech processing, may be especially uncomfortable for participants (Rossi, Hallett, & Group., 2012). For MEP protocols, there is often obvious muscle twitching, for instance in hand muscles such as FDI, as a result of the central stimulation to M1. Therefore, thorough piloting and the selection of a control area (see below) that is

likely to be equally (un)comfortable to stimulate are crucial for TMS experimental design in speech processing research.

When designing TMS experiments, it is important to include of an appropriate control site not hypothesised to be involved in the task, in order to demonstrate the specificity of the effect of TMS. A typical control site is the vertex, which is defined as the intersection between 50% of the nasion-inion distance, and 50% of the left to right pre-auricular distance. However, it is advisable to choose a different control site, e.g., the Occipital Pole (OP) (Krieger-Redwood et al., 2013), when targeting premotor or motor cortex, as the effect of TMS might spread to the motor area of interest, and there is also M1 cortex at the vertex point. Alternatively, one can also decide to use a sham (placebo) condition. If no sham TMS or control site is included, it cannot be concluded that any behavioural effects of TMS are specific to the targeted site(s), and not due to general effects of TMS, e.g., the acoustic artefact or cutaneous sensations linked to TMS, including face twitches. It is also appropriate to include a control task, which is ideally matched in terms of duration and difficulty, but does not involve the process under study. If stimulating a target area significantly affects task performance relative to the control task, this indicates that the stimulated area is necessary to perform the task. Examples of a control task are matching tasks of scrambled faces to control for semantic or processing tasks (Krieger-Redwood et al., 2013), or a colour matching task to control for a phonetic decision task (Meister, Wilson, Deblieck, Wu, & Iacoboni, 2007).

An advantage of using an offline protocol is that the delivery of speech stimuli and stimulation are separated in time, thus issues with the TMS artefact and magnetic field are avoided during the task. Yet, offline TMS is not without its challenges, but these are issues that apply to TMS in general and that are not specific to studying

speech (Fecteau & Eldaief, 2014). For instance, there is considerable debate about when the effect of stimulation is maximal and for how long it lasts. For example, the inhibitory effects of (40 seconds) TBS have been found to differ by as much as 40 minutes depending on the region of M1 receiving stimulation (Gamboa et al., 2011; Ishikawa et al., 2007). In addition, prolonged continuous TBS (of 80 seconds or more) results in neuronal excitation rather than a longer state of inhibition (Gamboa et al., 2011). It is also challenging to determine the intensity at which to stimulate, particularly for non-motor brain regions where there may not be an obvious 'correlate' of the stimulation.

MEP experiments face similar challenges as TMS studies, but also have their own considerations. First, the main muscles of interest when studying motor excitability during speech processing are lip, tongue, and hand muscles. Measurements from different muscles require standardisation before comparison, such as conversion into site-specific z-scores, as hand and articulatory muscles are considerably different; (sub-)cortically and in the muscle configurations themselves. Cortically, the amount of cortex contributing to the hand representation is more extensive than for lips and tongue, making it easier to localise hand muscles. Also, the skull tends to be thicker over the lip than over the hand area. Moreover, the lip area on the precentral gyrus is often located more within the sulcus than the hand representation (Devlin & Watkins, 2007). As a consequence of these three factors, hand representations tend to be more sensitive to TMS than lip representations (Möttönen, van de Ven, & Watkins, 2014). Sub-cortically, hand and lip MEPs arise via different descending motor pathways. The hand response involves the corticospinal pathway, which travels via the spinal cord where axons synapse with motor neurons at the vertebral level of muscle control. Conversely, axons of

1   pyramidal neurons in speech M1 synapse with motor neurons in the brainstem, which

2   go on to innervate muscles controlled by the facial nerves via the corticobulbar

3   pathway. These pathway differences contribute to latency differences between hand

4   and speech muscles, as hand muscles typically have a longer latency of around 20ms

5   due to the longer corticospinal motor pathway compared to lip and tongue MEPs,

6   where amplitude peaks approximately 10ms after the TMS pulse. Additionally, motor

7   pathway differences also affect the silent period (SP) of MEPs, as additional

8   inhibitory spinal mechanisms contribute to the SPs of hand muscles. The SP therefore

9   tends to be longer for hand muscles than for speech muscles. The SP represents a

10 period of cortical silence immediately after receiving electric or magnetic stimulation

11 (Fuhr, Agostino, & Hallett, 1991). The SP reflects the behaviour of inhibitory

12 neurons, which act to automatically suppress the excitatory activity facilitated by the

13 external stimulation. During the SP, neurons cannot fire, and even during voluntary

14 contraction, the background EMG signal will be silenced. Finally, the different

15 arrangement of motor units in hand and lip muscle may also contribute to MEP

16 morphology, with lip MEPs often demonstrating multiple peaks, whereas hand MEPs

17 largely consist of a single peak (cf. Figure 2).

18   *--- Insert Figure 2 about here ---*

19   Notably, MEP metrics are significantly affected by the intensity of the TMS, the

20 extent of background muscle contraction, and the direction of the induced current,

21 thus several experimental factors must be considered during experimental design.

22 Firstly, motor thresholds defined based on monophasic stimulation are not

23 comparable to those defined on biphasic stimulators due to the different effect of the

24 pulse shape on the underlying cortical tissue. Moreover, it is necessary to define

25 criteria to standardise TMS intensities across subjects and stimulation sites; usually

established by identifying a motor threshold. Different threshold criteria have been employed in the literature (Möttönen et al., 2014; Murakami, Kell, Restle, Ugawa, & Ziemann, 2015; Rossi et al., 2012; Rossi, Hallett, Rossini, Pascual-Leone, & Group, 2009), with one common criterion: comprising five out of 10 MEPs that exceed a pre-defined amplitude level, when the muscle is at rest (resting Motor Threshold, rMT) or activated (active Motor Threshold, aMT). Physiological differences between hand and facial muscles result in smaller lip than hand responses (Möttönen et al., 2014), which is why participants are often found to have higher thresholds for lip representations. Estimating a motor threshold per participant is essential to standardise TMS intensities in MEPs research, but also serves to determine the appropriate stimulator output for online and offline TMS protocols. For online and offline protocols, participants are often stimulated at 100%, 110%, or 120% aMT (Walsh et al., 2003). For TBS protocols, 80% aMT is often used (Oberman, Edwards, Eldaief, & Pascual-Leone, 2011).

Finally, the physiological differences outlined between hand and speech muscles need to be considered when analysing MEP data. For example, area under the curve (Nuttall, Kennedy-Higgins, Hogan, Devlin, & Adank, 2016; Watkins, Strafella, & Paus, 2003) measures can be used to promote objectivity over subjectively picking MEP peak-to-peak measurements when multiple peaks can make this difficult, as is often the case for lip muscles. Identifying peaks and troughs in hand MEP complexes, however, is more straightforward, and further assisted by the longer SP. Using running averages online when locating the motor hot spot for speech muscle MEPs, and using overall averages when analysing data offline, can both help the researcher to judge which peaks are most prominent and robust in MEPs.

4. Key empirical contributions

Research using TMS to study structure-function links in speech processing has illuminated neural substrates involved in phonological, lexical, and semantic processing, which we will briefly evaluate in turn. Many TMS studies have contrasted phonological against semantic processing, while many MEP studies contrast speech sounds produced by different articulators (e.g., lips: /ba/ versus tongue /da/ sounds) in phonological designs. These contrasts represent powerful ways to design TMS and MEP studies in speech processing, as it allows one to test for double dissociations of areas involved in processing different dimensions of speech. We will discuss TMS studies establishing the causal role of key brain areas in the speech peception network, namely left and right STG, left Premotor Cortex (PMC), left Inferior Frontal Gyrus (IFG), left and right Supramarginal Gyrus (SMG), and left and right Angular Gyrus (AG) and MEP studies examining the response of areas of M1.

Krieger-Redwood et al. (2013) sought to establish the causal role of left posterior STG and left PMC in phonological and semantic processing of spoken words. They asked participants to perform a semantic and a phonological judgement task in a typical double dissociation design, using the same stimuli in both tasks. They asked participants to perform either a two-alternative forced choice (2AFC) phonological task (decide whether a word ends in a given sound or not, e.g., does 'cart' end with a /t/?) or a semantic task (decide whether a word referred to a manmade or natural object, e.g., is 'cart' manmade?). Participants also completed a control task, in which they were presented with a probe image of a scrambled face plus two additional images of scrambled faces shown below. Participants were asked which of the two scrambled images was identical to the probe. Participants performed all tasks before and after application of 10 minutes of offline 1Hz rTMS (thus

delivering 600 pulses) to either the left posterior STG, left Premotor Cortex (PMC) or the Occipital Pole (OP; control site). The behavioural results for the three tasks consisted of percent correct responses. Results indicated a causal role of left posterior STG in semantic and phonological processing, as accuracy scores for both tasks decreased after TMS to left posterior STG. Moreover, left PMC is causally involved in processing phonology, as accuracy scores decreased for the phonological task, but not the semantic task, after TMS to left PMC. Accuracy scores for both tasks did not change following stimulation to the control area (OP).

Hartwigsen et al. (2010) tested the effect of real or sham online 10Hz TMS to left, right, or bilateral SMG and AG, during phonological, semantic, and perceptual decisions. Participants received four TMS pulses 100ms apart (10Hz), 100 ms after word onset from one TMS coil positioned over the left or right pIFG or aIFG, or simultaneously from two coils positioned over left and right SMG or AG. In three sham control conditions (left, right, and bilateral), participants received sham TMS with the coil(s) placed rotated 90 degrees (perpendicular) to the head and the stimulation intensity turned up 15% to allow for the generation of an acoustic TMS artefact comparable to the TMS conditions. Participants performed the same 2AFC tasks on sets of auditory or visual word stimuli in a phonology-semantics double dissociation design. In the phonological task, subjects categorised words as having two or three syllables, and in the semantic task, the same stimuli were used in a natural/man-made decision task. Two perceptual tasks were included as control tasks. In the control task, participants decided whether or not there had been a decrease in pitch toward the end of the word (auditory task) or whether or not font size had decreased toward the end of the word (visual task). The accuracy and reaction times of phonological decisions were selectively disrupted relative to semantic and

perceptual decisions when real TMS was applied over the left, right, or bilateral SMG. These effects were not observed for TMS over both AG sites, nor for the sham or control conditions. These findings indicate that the right SMG causally contributes to accurate and efficient phonological decisions in the healthy brain, with no evidence that left and right SMG compensate for each other during online TMS.

Alba-Ferrara, Ellison, & Mitchell (2012) examined the role of left and right STG and sham TMS in prosodic and semantic aspects of sentence processing in a 2AFC double dissociation design. Participants heard sentences that were either happy or sad in content (semantic task), and were either happy or sad in tone of voice (prosody task) with equal congruency/incongruency. Participants were asked to focus on one dimension of the stimuli (e.g., the semantic form) and ignore the other elements. No control task was included. Participants received offline 1Hz rTMS for 10 minutes to either left or right STG in the TMS conditions, and in the sham TMS condition, a non-discharging coil was held to one of the target areas for 10 minutes, while a discharging coil was in close proximity resulting in similar conditions to TMS application (i.e., the auditory artefact noise) but without the magnetic pulse and related effects. Slower behavioural responses were observed after both left and right STG stimulation relative to the sham TMS control condition for semantic content, in agreement with the results of Krieger-Redwood et al. (2013). However, on the prosody task, reaction times were only affected after rTMS to the right STG. No effect was found for either the left STG or control sham stimulation. Alba-Ferrera et al. conclude that bilateral STG is crucial for semantic comprehension, but only right STG is crucial for prosodic decoding.

Recent MEP paradigms are starting to examine intracortical and interhemispheric functional and anatomical connectivity during different aspects of

speech processing. Using fMRI-navigated rTMS, Murakami et al. (2015) found that speech-related MEP facilitation was disrupted by rTMS of the posterior Superior Temporal Sulcus (STS), the sylvian parieto-temporal region SPT, and by double-knock-out, but not individual stimulation, of left Pars Opercularis and dorsal PMC. Repetitive TMS of these regions, but not left anterior STS, implicated in speech comprehension, or the occipital control site, caused deficits specifically in phonological processing of fast transients of the speech signal. Furthermore, all stimuli were degraded in a noise-dependent manner.. Murakami et al.'s findings are important for understanding how, and when, the motor system is involved in speech perception, and confirm that the left dorsal stream targets the articulatory M1 through pSTS and SPT, and via frontal parallel pathways through POp and dPMC. However, as this brief synopsis exemplifies, there is considerable variability in the speech tasks and protocols used in TMS speech research.

Only in the last decade or so have studies been conducted that used MEPs to quantify activity of articulatory M1 during speech perception. For instance, Watkins, Strafella and Paus (2003) report that listening to and viewing speech enhanced the size of lip, but not hand, MEPs generated in the left hemisphere. These results indicated that both auditory and visual speech perception facilitates excitability of speech production motor system. Murakami, Restle and Ziemann (2011) replicated and extended Watkins et al.'s findings, confirming that M1 lip, but not hand, excitability and intracortical inhibition increased when viewing speech-related lip movements or listening to speech. Furthermore, the increase in lip MEP amplitude correlated inversely with accuracy of speech perception. Murakami et al. interpreted their MEP findings as evidence of observation-execution matching in the human mirror neuron system, which is potentially fundamental for the evolution of language.

1   Further work has built upon these findings to establish that speech articulators

2   activate in a highly specific somatotopic way (for instance, Sato, Buccino, Gentilucci,

3   & Cattaneo, 2009). Sato et al. showed that exposure to syllables incorporating visual

4   and/or acoustic tongue-related phonemes is associated with enhanced excitability of

5   the tongue area in M1 as early as 100–200 ms after the consonantal onset of the

6   acoustically presented syllable. Furthermore, these MEP findings have been

7   corroborated, first, by behavioural data in which TMS over tongue and lip motor

8   representations appears to somatotopically alter the reaction time to speech,

9   particularly in background noise (D'Ausilio et al., 2009). The current state of thinking

10   is that motor activity observed during speech perception fits into a distributed neural

11   framework for spoken language understanding. Namely, motor activations reflect

12   auditory-motor mapping via a left-hemispheric dorsal speech-processing stream

13   (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009).

14

15   **5. Future directions**

16   Results from neuroimaging studies using functional Magnetic Resonance

17   Imaging (fMRI) have resulted in the description of networks associated with speech

18   processing at pre-lexical (Turkeltaub & Coslett, 2010) and post-lexical levels (Adank,

19   2012) and associated models of the network (Hickok & Poeppel, 2007; Rauschecker

20   & Scott, 2009). TMS offers the opportunity to complement fMRI and patient studies

21   by establishing the causal role of nodes in these networks. Indeed, recent years have

22   seen an increase in TMS studies aiming to elucidate the role of cortical areas in

23   temporal (Krieger-Redwood et al., 2013), frontal (Krieger-Redwood et al., 2013;

24   Meister et al., 2007; Möttönen & Watkins, 2009) and parietal lobes (Hartwigsen,

25   Price, et al., 2010).

Moreover, the great majority of TMS studies on speech processing focus solely on speech perception, as outlined in section 4. Only a handful of papers have used TMS to investigate speech production, and most of these examined picture naming in patient populations, for example Naeser et al. (2005) and Naeser et al. (2011). However, there is a paucity of studies that used TMS and/or elicited MEPs in conjunction with a speech production task, using an articulatory or semantic speech generation task) in healthy participants, with the exception of so-called 'speech arrest' protocols, in which speech production is distorted in a general sense (i.e., interrupted or stopped altogether) following online TMS to left frontal areas (e.g., Stewart, Walsh, Frith, & Rothwell, 2001). Nevertheless, one way to capitalise on the advantages of offline TMS protocols would be to stimulate just prior to the speech task. Such a paradigm would allow for precise timing of the stimulation, without unwanted interference with task performance due to the TMS artefact or cutaneous sensations. While such protocols have been used in cognitive neuroscience (de Graaf, Cornelsen, Jacobs, & Sack, 2011; Mottaghy, Gangitano, Krause, & Pascual-Leone, 2002; Romei, Driver, Scyns, & Thut, 2011), a similar paradigm has been trialled only once before in speech science in a speech production study (Berent et al., 2015). This type of protocol would provide a more controlled approach to study speech perception and production.

Current TMS methodologies offer further opportunities, for instance by combining TMS with neuroimaging methods such as Electroencephalography (EEG) (Möttönen, Dutton, & Watkins, 2012) or fMRI (Andoh, Matsuhita, & Zatorre, 2015) using functional connectivity to outline neural circuits supporting spoken language comprehension (Pascual-Leone, Walsh, & Rothwell, 2000). For example, Andoh et al. (2015) demonstrated that TMS to the right auditory cortex, but not the left, resulted in

widespread connectivity decreases in auditory- and motor-related networks in the resting state network. Furthermore, advanced designs such as paired-pulse TMS protocols offer great potential to start to establish the relationship between nodes in the speech perception network (Murakami, Restle, & Ziemann, 2012). More research combining MEPs, behaviour, and inhibitory forms of TMS applied to various neural hubs associated with speech processing, such as employed by Murakami et al. (2011, 2015), is essential for a deeper knowledge of how the neural substrates implicated in processing phonology, semantics, and lexical status, work together in concert to achieve successful perception and comprehension of speech, particularly in challenging listening environments.

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13

1   **Figure Captions**

2
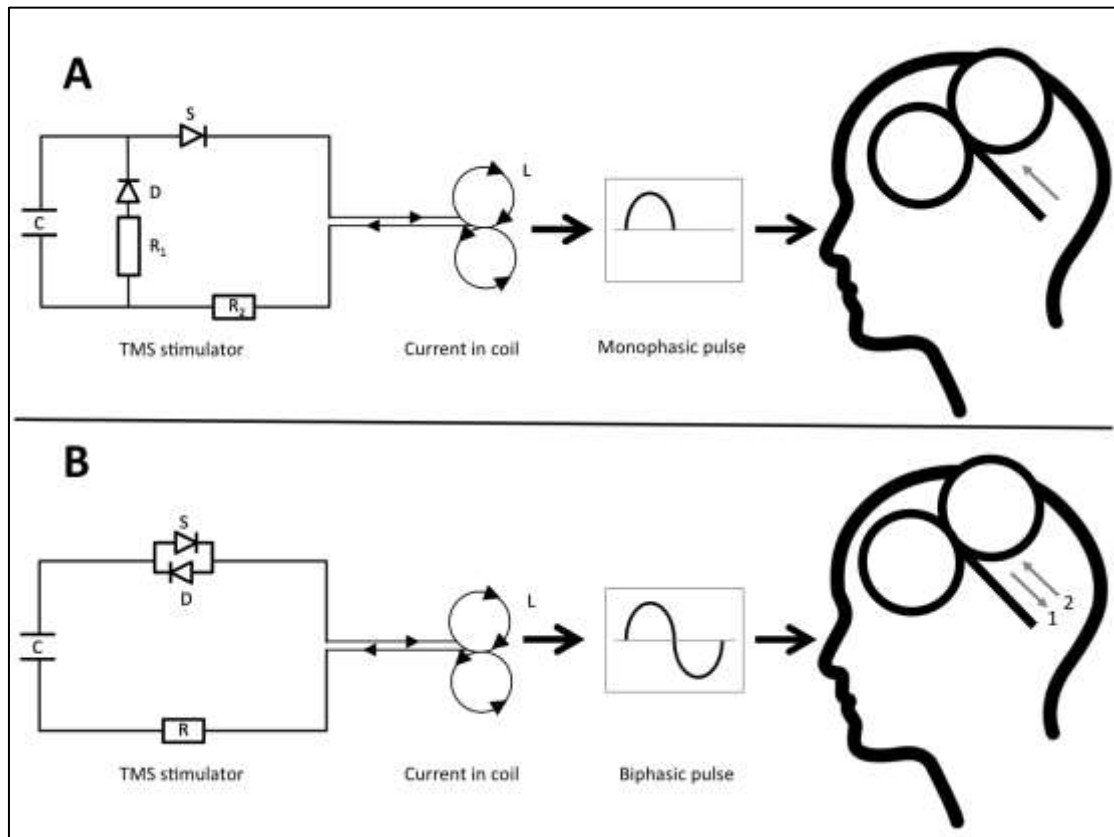
3

4   *Figure 1.*

5   Schematic representation physical processes, current flow in the coil, and the induced

6   current flow in the brain under the coil (Sommer et al., 2006). A: simplified diagram

7   of a TMS stimulator producing a monophasic pulse. S = switch, D = diode, R_i =

8   resistor, C = capacitor, L = left.   The stimulator invokes a current in the coil, the

9   current loops through both wings of the standard figure-of-eight coil, resulting in a

10   monophasic pulse shape consisting of a rise plus fall shape (simplified). This pulse

11   invokes a current running posterior to anterior (grey arrow) in the neural tissue under

12   the coil, when the coil is held at 45 degrees to the midline (coil handle posterior,

13   wings anterior). B: diagram of a TMS stimulator producing a biphasic pulse. The

14   stimulator invokes a current in the coil, the current loops through both arms of the

1   standard figure-of-eight coil, resulting in a biphasic pulse shape costing of a rise plus

2   fall shape (simplified), followed by second fall and a subsequent rise (simplified).

3   This pulse invokes a first current running anterior to posterior (grey arrow 1),

4   followed by a current running posterior to anterior (grey arrow 2) in the neural tissue

5   under the coil.
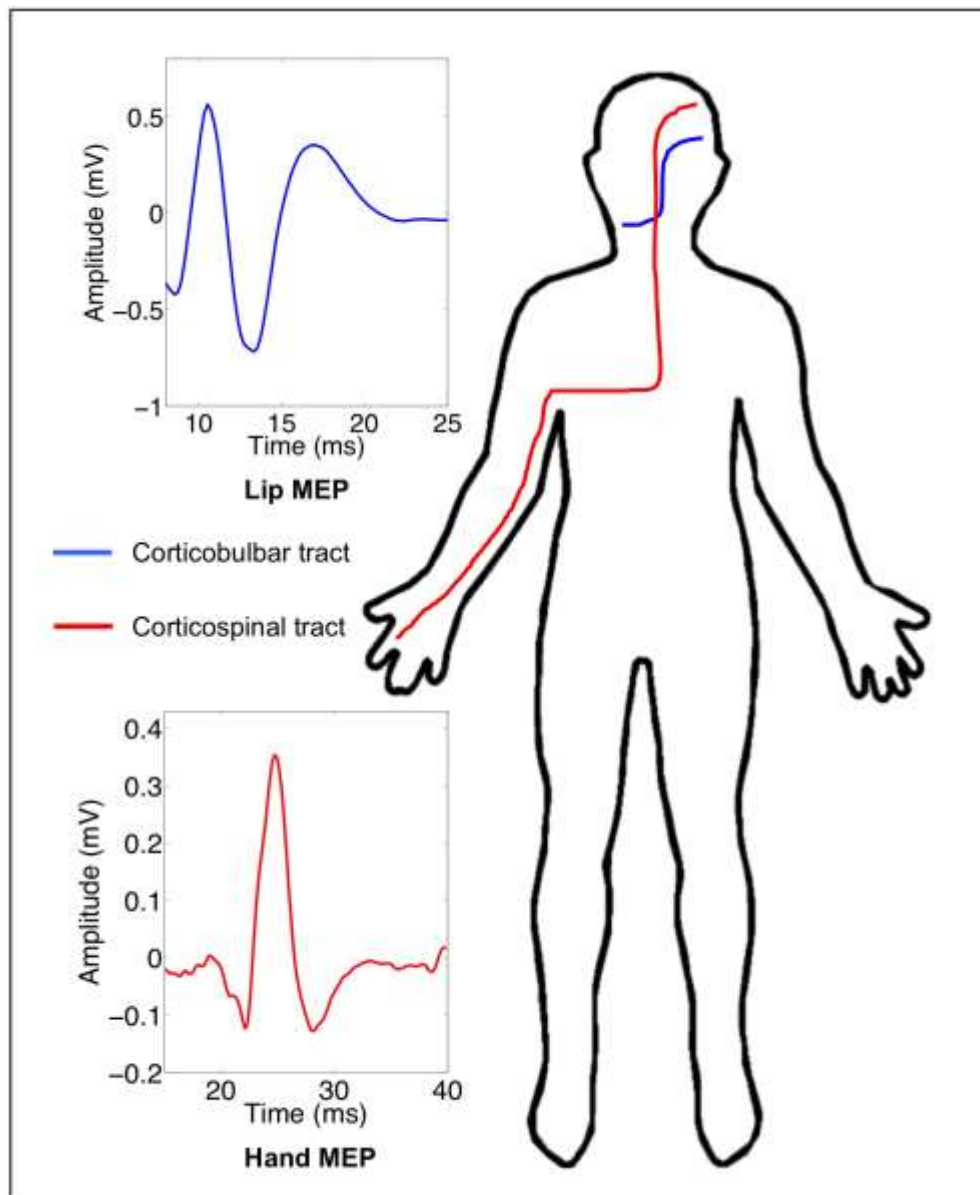
6

7   *Figure 2.*

1   Schematic representation of descending motor pathways for hand and lip Motor

2   Evoked Potentials (MEPs), including typical morphology of each type of MEP (mV:

3   millivolt; ms: milliseconds.

4