

1 Modulation of intra- and inter-hemispheric connectivity between primary and
2 premotor cortex during speech perception

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27 Abstract

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29 Primary motor (M1) areas for speech production activate during speech perception. It has been
30 suggested that such activation may be dependent upon modulatory inputs from premotor cortex
31 (PMv). If and how PMv differentially modulates M1 activity during perception of speech that is easy
32 or challenging to understand, however, is unclear. This study aimed to test the link between PMv
33 and M1 during challenging speech perception in two experiments. The first experiment investigated
34 intra-hemispheric connectivity between left hemisphere PMv and left M1 lip area during
35 comprehension of speech under clear and distorted listening conditions. Continuous theta burst
36 stimulation (cTBS) was applied to left PMv in eighteen participants (aged 18-35). Post-cTBS,
37 participants performed a sentence verification task on distorted (imprecisely articulated), and clear
38 speech, whilst also undergoing stimulation of the lip representation in the left M1 to elicit motor
39 evoked potentials (MEPs). In a second, separate experiment, we investigated the role of inter-
40 hemispheric connectivity between right hemisphere PMv and left hemisphere M1 lip area. Dual-coil
41 transcranial magnetic stimulation was applied to right PMv and left M1 lip in eighteen participants
42 (aged 18-35). Results indicated that disruption of PMv during speech perception affects
43 comprehension of distorted speech specifically. Furthermore, our data suggest that listening to
44 distorted speech modulates the balance of intra- and inter-hemispheric interactions, with a larger
45 sensorimotor network implicated during comprehension of distorted speech than when speech
46 perception is optimal. The present results further understanding of PMv-M1 interactions during
47 auditory-motor integration.

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56 1. Introduction

57 After decades of research, the neurobiological network subserving speech perception
58 remains unclear. Without this knowledge, we are limited in our ability to understand how humans
59 perceive and use language (Skipper, Devlin, & Lametti, 2017). The role of motor regions in the
60 speech perception network, in particular, is still hotly debated. Involvement of motor areas in
61 speech perception is based on the observation that speech perception activates speech production
62 brain regions (Silbert, Honey, Simony, Poeppel, & Hasson, 2014; Skipper, Nusbaum, & Small, 2005;
63 Wilson, Saygin, Sereno, & Iacoboni, 2004). However, discussion continues as to whether observed
64 motor activity during situations requiring auditory-motor integration really is essential to speech
65 processing (Meister, Wilson, Deblieck, & Wu, 2007), complementary (Möttönen & Watkins, 2009), or
66 epiphenomenal (Hickok, Houde, & Rong, 2011). This has led to the division of ‘fractionated’ and
67 ‘integrated’ views of speech perception (Schomers & Pulvermüller, 2016). In the fractionated view,
68 the temporal speech perception network is key to recognising speech, but does not significantly
69 depend on fronto-parietal speech production circuits. The ‘integrated’ view, however, postulates
70 strong reciprocal links between temporal and fronto-parietal areas, yielding multimodal distributed
71 neuronal circuits capable of reciprocal influence that are causally involved in language
72 understanding, and provide the neuronal basis for speech perception and production.

73 The evidence for the latter ‘integrated’ network view has been proposed based largely on
74 Transcranial Magnetic Stimulation (TMS) studies. TMS research has demonstrated that primary
75 motor (M1) areas for speech production activate during speech perception. This has been
76 established using single-pulse TMS to the left hemisphere to generate Motor Evoked Potentials
77 (MEPs) in speech articulators such as the lips or tongue, which serve to index the excitability of the
78 underlying motor pathway. Such studies have identified that activity in the corticobulbar motor
79 pathway from left hemisphere M1 lip and tongue regions to the respective speech muscles is
80 facilitated when perceiving speech relative to non-speech sounds (Fadiga et al., 2002; Murakami,
81 Kell, Restle, Ugawa, & Ziemann, 2015; Murakami, Restle, & Ziemann, 2012; Watkins, Strafella, &
82 Paus, 2003). This speech-specific increase in motor pathway excitability is further modulated by
83 listening difficulty, whereby speech-internal distortions, such as unfamiliar manner of speaking, as
84 well as speech-external distortions, such as background noise, have both been found to affect the
85 excitability of the left hemisphere motor pathway for speech production (Murakami, Restle, &
86 Ziemann, 2011; Nuttall, Kennedy-Higgins, Hogan, Devlin, & Adank, 2016). TMS studies have also
87 been used to disrupt activation in M1 lip area, which was found to impair perception of speech
88 sounds produced by the lips, suggesting a potentially causal role for lip M1 under ambiguous
89 listening conditions (Möttönen & Watkins, 2009). Both types of effects of TMS to articulatory speech

90 regions have been found to be muscle-specific, with no corresponding effects on speech perception
91 or MEPs after TMS to M1 hand area (Möttönen & Watkins, 2009; Nuttall et al., 2016).

92 Although such findings are striking, articulatory M1 is not known to receive direct inputs
93 from auditory areas, raising the question of how is auditory information able to influence activity in
94 M1, when M1 is not connected to auditory temporal cortex. One candidate possibility is that effects
95 observed at M1 during speech perception are mediated by ventral premotor cortex (PMv), which is
96 thought to receive auditory inputs and is linked to temporal auditory association areas via the
97 superior longitudinal and arcuate fasciculi. Using fMRI multivariate analysis in conjunction with
98 probabilistic fibre tracking based on diffusion tensor imaging data, Saur and colleagues (2010)
99 identified that the posterior Superior Temporal Gyrus (pSTG) exhibits extensive direct interactions
100 with PMv nodes, mediated via the dorsal arcuate fasciculus/superior longitudinal fasciculus system
101 (Frey, Campbell, Pike, & Petrides, 2008; Saur et al., 2008). This temporo–premotor interaction via
102 the dorsal pathway is suggested to be important for a rapid, automated conversion of acoustic
103 representations into motor representations (Vigneau et al., 2006).

104 It has also been suggested that right PMv mediates mirror facilitation effects observed in left
105 M1 hand area, where it is thought that learned associations between multi-modal inputs at PMv
106 contribute to facilitation of the corticospinal motor pathway to the hand (Catmur, Mars, Rushworth,
107 & Heyes, 2011). In humans, the motor system governing the fingers of the hand has been found to
108 be specifically facilitated by mirror facilitation. Mirror facilitation refers to the idea that an MEP from
109 a finger muscle will be greater in size when a subject observes a movement performed involving that
110 muscle, relative to a movement involving a separate muscle. Indeed, Catmur et al (2011) observed
111 that inter-hemispheric PMv-M1 connections modulate the M1 corticospinal response to observed
112 actions, and suggest that MEP mirror facilitation may be governed by PMv. This finding also raises
113 the question of the role of inter-hemispheric connectivity in action observation. It stands to reason,
114 therefore, that articulatory M1 facilitation measured during perception of speech may be
115 underpinned by a similar PMv mechanism, if Catmur et al.'s observation can be generalised to the
116 corticobulbar motor system. However, the intra- and inter-hemispheric significance of activity in
117 articulatory motor networks during speech perception is not clear, as it has not been explored.

118 Consistent with the possibility of a (intra- or inter-hemispheric) mediating connection
119 between PMv and M1 during speech perception, a body of neuroimaging evidence indicates that
120 frontal brain areas involved in the planning and execution of speech gestures, i.e., the posterior part
121 of the left inferior frontal gyrus and the PMv are activated during passive speech perception
122 (Pulvermüller et al., 2006; Skipper et al., 2005; Wilson & Iacoboni, 2006; Wilson et al., 2004).

123 Disruptive TMS to left hemisphere PMv has indeed indicated a mediating role for PMv in
124 understanding speech, particularly during phonemic segmentation (Sato, Tremblay, & Gracco, 2009)
125 and syllable discrimination in background noise (Meister et al., 2007). This has led to the hypothesis
126 that PMv, during language learning, may mediate the comparison of sensory representations of
127 speech against stored articulatory productions held in repertoire, and similarly, these comparisons
128 may further assist listening in difficult environments by helping to disambiguate auditory
129 information (Sato et al., 2009) in line with M1 observations (D'Ausilio, Bufalari, Salmas, & Fadiga,
130 2012).

131 However, if, and how, PMv differentially modulates M1 activity during perception of speech
132 that is easy or challenging to understand is unknown. Correlational evidence from PET and MEPs
133 (Watkins & Paus, 2004) suggests that increased excitability of the left articulatory M1 during speech
134 perception is significantly related to an increase in blood flow to left hemisphere frontal brain area
135 BA 44 (Watkins & Paus, 2004). This led the authors to propose that BA 44 (pars opercularis of Broca's
136 area) may directly, or indirectly via PMv, 'prime' the motor system during speech perception, even
137 when no speech output is required.

138 Taken together, the role of PMv in speech perception remains unclear, particularly the intra-
139 and inter-hemispheric association between PMv and articulatory M1. During effortful listening,
140 accumulating evidence from TMS, fMRI, and PET studies has demonstrated that PMv is active
141 relative to control conditions (Meister et al., 2007; Sato et al., 2009; Watkins & Paus, 2004; Wilson et
142 al., 2004). Relatedly, evidence from hand MEP studies has indicated a mediating role of PMv on M1
143 during hand action observation, indicating that PMv may govern activity in M1 during hand
144 perception. To further understand the role of PMv in speech perception, two outstanding issues
145 need to be resolved. Firstly, how does disrupting activity in PMv affect speech perception
146 behaviourally, and what effect does this disruption have on articulatory M1? Secondly, what is the
147 significance of inter-hemispheric PMv-M1 connectivity during speech perception?

148 The present study aimed to build on and extend observations from Watkins and Paus (2004),
149 by examining connectivity between left articulatory M1 and left and right PMv in two experiments.
150 The first experiment investigated intra-hemispheric connectivity between left hemisphere PMv and
151 M1 lip area during comprehension of speech under clear and distorted listening conditions. To this
152 end, continuous theta burst stimulation (cTBS) was applied to PMv to directly manipulate brain
153 activity in that region. Post-cTBS, participants performed a sentence verification task on distorted
154 (imprecisely articulated), and clear speech, whilst also undergoing single-pulse stimulation of left M1
155 lip area to elicit MEPs. In a second experiment, we investigated the role of inter-hemispheric
156 connectivity between right hemisphere PMv and left hemisphere M1 lip area using an inter-

157 hemispheric inhibition TMS protocol to moderate lip MEPs, whilst subjects listened to clear and
158 distorted speech, and a no-speech control. Taken together, these experiments allowed us to assess
159 how manipulating the influence of ipsilateral and contralateral PMv impacted left hemisphere M1 lip
160 when listening to speech.

161

162 2. Method

163 2.1. Subjects

164 In Experiment 1, twenty-two subjects took part (eight males; average age: 22 years 8 months (\pm
165 SD 3 months); age range: 18–28 years). Four subjects could not tolerate cTBS to PMv and withdrew
166 from participation. Twenty-one subjects took part in Experiment 2 (seven males; average age: 22
167 years 6 months (\pm SD 3.8 months); age range: 18–30 years), two of whom had also participated in
168 Experiment 1. Three subjects could not tolerate the dual-pulse protocol to right PMv and left M1 lip,
169 and withdrew from participation. All subjects in Experiments 1 and 2 were right-handed,
170 monolingual, native speakers of British English, with normal language function and hearing
171 thresholds. Handedness was established via self-report. Pure-tone audiometric hearing thresholds
172 were established using a diagnostic audiometer (AD229b, Interacoustic A/S, Denmark) in accordance
173 with The British Society of Audiology Recommended Procedure (The British Society of Audiology,
174 2011), across 0.25, 0.5, 1, 2, 4, and 8 kHz bilaterally. All subjects had clinically normal thresholds (\leq 20
175 dB HL). Subjects presented no TMS contraindications as assessed by the University College London
176 TMS safety screening form. All subjects had a minimum high school-level education, with the
177 majority currently studying at University level. Experiments were undertaken with the understanding
178 and written consent of each subject, according to Research Ethics Board of University College
179 London.

180

181 2.2. Speech stimuli

182 For Experiment 1, 160 unique sentences were recorded from the Speed and Capacity of
183 Language Processing (SCOLP) stimuli set (Baddeley, Emslie, and Nimmo-Smith, 1992). The SCOLP
184 sentences are not matched for psycholinguistic variables. However, SCOLP sentences have been
185 found to be a sensitive and reliable measure of the speed of language comprehension, as errors tend
186 to be low across patient and control groups (Adank, Evans, Stuart-Smith, & Scott, 2009; Baddeley,
187 Emslie, & Nimmo-Smith, 1992; Bayre, Geffen, & McFarland, 1997). These comprised two sets of clear
188 sentences, and two sets of distorted sentences based on motor distortion (40 sentences for each
189 set), to ensure unique sentences were tested at baseline and post-cTBS. The average duration of

190 clear sentences was 2008 ms (SD 351 ms), and for distorted sentences was 2585 ms (SD 516 ms).
191 These durations reflect the natural articulation of both types of speech, with the distorted sentences
192 being more difficult and taking longer to articulate. Stimuli were presented in blocks of clear and
193 distorted sentences, with one block of each stimulus type. The order of stimulus block type was
194 counter-balanced across subjects. The SCOLP sentences are designed to be used for semantic
195 verification; are all obviously true or are false, with false sentences being based on a mismatch of
196 subject and predicate from true sentences, i.e., *'Melons are people'*. For each subject, and for each
197 stimulus type and time point (baseline or post-cTBS), a stimulus list containing forty stimuli was
198 randomly permuted, and stimuli were presented according to this order in each condition.

199 In Experiment 2, twenty vowel-consonant vowel (VCV) syllables containing an equal
200 distribution of lip- (/apa/, /aba/) tongue-articulated (/ata/, /ada/) syllables were recorded. Two sets
201 of the same twenty syllables were created: a clear set based on natural articulation, and a set based
202 on motor distortion. All stimuli were naturally produced to be of approximately the same duration
203 (mean 2864 ms) but were not synthetically manipulated to be precisely the same length. Stimuli
204 varied by a standard deviation of 573 ms. For each subject, and for each condition, a stimulus list
205 containing five occurrences of /apa/, /aba/, /ata/ and /ada/ stimuli was randomly permuted, and
206 stimuli were presented according to this order (20 stimuli in total per condition).

207 Distorted stimuli were always based on a motor distortion, where the speaker produced the
208 stimuli whilst speaking with a tongue depressor. The tongue depressor was a flat wooden spatula
209 with rounded ends, and was five inches long and one inch wide. A tongue depressor was specifically
210 chosen so as to introduce a motor-based distortion into the speech signal, to relate the speech
211 perception challenge to a speech production difficulty (for further information about these stimuli,
212 and how they are perceived, please see Nuttall et al., 2016). This enabled us to contrast clear speech
213 against distorted speech produced by the same speaker, in contrast to imposing synthetic
214 manipulations upon the spectral characteristics of the original clear speech. Clear speech comprised
215 naturally articulated, normal speech.

216 Stimuli were produced by a female British English speaker aged 27 years old for Experiment
217 1, and by a male British English speaker aged 23 for Experiment 2. Stimuli were recorded in a sound-
218 attenuated room and audio digitized at 44.1 kHz with 16 bits. All stimuli were amplitude root-mean-
219 square normalized offline using Praat (Boersma and Weenink, 2016), and then presented using
220 Matlab (The Mathworks, Inc., Natick, MA) through ultra-shielded insert earphones (ER-3A; Etymotic
221 Research, Inc., IL), at a comfortable listening level of around 65 dB SPL.

222

223 2.3. Design

224 Two separate experiments were undertaken to assess how PMv-M1 interactions are modulated
225 when listening to clear and distorted speech, as shown in Figure 1. In Experiment 1, continuous theta
226 burst stimulation (cTBS) TMS was applied to modulate cortico-cortical interactions between left PMv
227 and left M1 lip. This allowed us to test the contribution of left PMv to lip MEPs evoked during speech
228 perception, as well as perception of the associated speech. Subjects were instructed to semantically
229 verify the sentences at baseline and post-cTBS as quickly as possible without compromising
230 accuracy. Subjects were asked to respond using the index finger of the left hand, and to press the
231 left arrow key '<' if a sentence was true, and the right arrow key '>' if a sentence was false. The left
232 hand was used instead of the dominant right hand in order to avoid any motor preparation and
233 execution effects affecting global motor activity in left hemisphere M1. The order of experimental
234 conditions in Experiment 1 was counter-balanced. The following two experimental conditions were
235 tested:

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- 237 1) Distorted: Listening to motor-distorted speech produced using a tongue depressor.
- 238 2) Clear: Listening to naturally articulated clear speech.

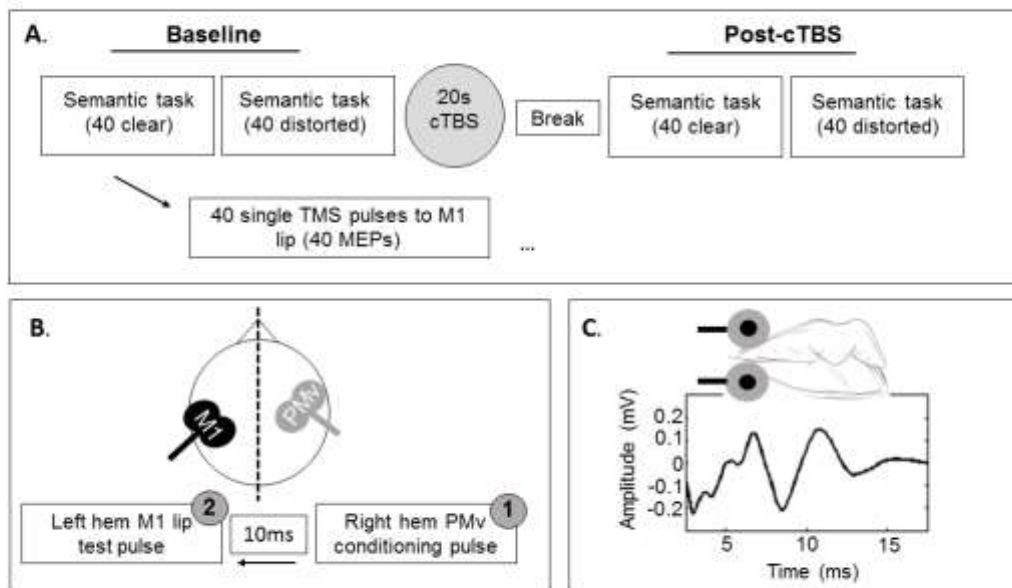
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240 In Experiment 2, an inter-hemispheric TMS protocol was used to modulate inter-hemispheric
241 connectivity between right PMv, and left M1 lip (Chen, 2004; Ni et al., 2009). This allowed us to
242 examine if right hemisphere PMv exerts an influence over left M1 lip during speech perception.
243 Subjects were instructed to listen passively to the speech stimuli. The order of experimental
244 conditions in Experiment 2 was randomised. The following three experimental conditions were
245 tested in the inter-hemispheric double-pulse protocol and were all expressed relative to the single-
246 pulse control condition, which was measured using single-pulse stimulation to left M1 lip, without
247 any auditory stimulation:

248

- 249 1) Distorted: Listening to motor-distorted speech produced using a tongue depressor.
- 250 2) Clear: Listening to naturally articulated clear speech.
- 251 3) No-speech Control: No auditory stimulation.

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253

254 Figure 1. A. Schematic of the cTBS design in Experiment 1. Subjects semantically verified 40 clear
 255 sentences and 40 distorted sentences at baseline. At the same time, subjects received single-pulse
 256 TMS to M1 lip area. Each sentence was accompanied by one TMS pulse, generating one lip MEP per
 257 sentence (example MEP given in C.). Subjects received 20 seconds of cTBS. After a 5 minute break,
 258 subjects then performed the semantic verification task again with MEP measurement, as described
 259 at baseline. Note that baseline measurements were performed before cTBS, as shown in A., or at the
 260 end of the experiment. B. Schematic of inter-hemispheric TMS design in Experiment 2. One
 261 conditioning pulse was applied at 120% aMT to right PMv (1). A test pulse was then applied after 10
 262 ms at 0.5mV threshold intensity to left M1 lip area (2), generating an MEP. This procedure was
 263 performed during perception of clear speech, distorted speech, and without auditory stimulation
 264 (no-speech control).

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267 2.4. Transcranial magnetic stimulation

268 2.4.1 MRI acquisition and co-registration

269 T1-weighted structural magnetic resonance imaging (MRI) scans were acquired using a
 270 Siemens Avanto 1.5T MRI scanner and a 32 channel head coil (Siemens Healthcare, GmbH, Germany)
 271 at the Birkbeck-UCL Centre for Neuroimaging (BUCNI). A structural image for each participant was
 272 obtained using an MP-RAGE sequence [repetition time (TR) = 2730ms; echo time (TE) = 3.57ms;

273 voxel size = 1x1x1mm; slices = 176]. Once obtained, the structural scans were later used in the main
274 TMS session in conjunction withBrainsight frameless stereotaxy (Rogue Research, Montreal,
275 Canada). For each participant, we performed co-registration between the participant's head and
276 MRI using four anatomical landmarks (tip of the nose, bridge of the nose, and intertragal notch on
277 the left and right ears), which were first identified and marked on the participant's MRI. Accuracy of
278 co-registration was assessed visually using an infrared tracking system (Polaris, Northern Digital,
279 Waterloo, Canada). Upon successful co-registration, infrared tracking was used throughout the
280 experiments in order to maintain coil position during the stimulation.

281

282 2.4.2. Motor thresholds

283 In both Experiments 1 and 2, monophasic single TMS pulses were generated by a Magstim
284 200² unit and delivered to left M1 by a 70mm diameter figure-of-eight coil (Magstim, Dyfed, UK) set
285 to simultaneous discharge mode (inter-pulse spacing of 1 ms). The coil was placed tangential to the
286 skull at a 45 degree angle such that the induced current flowed from posterior to anterior under the
287 junction of the two wings of the figure-of-eight coil. The lip area of M1 was found by using the
288 functional 'hot spot' localization method, whereby application of TMS elicits an MEP from the
289 contralateral muscle. Here, the coil position on the precentral gyrus is adjusted in millimetre
290 movements to ascertain the location on the scalp at which the most robust MEPs are elicited. This
291 location was then marked on a cap and the motor threshold (MT) determined. Before finding the lip
292 area, we first located the hand area by asking subjects to perform a pinching action where the index
293 finger was held against the thumb to activate first dorsal interosseous. Following this, the lip area
294 'hot spot' was identified by moving the coil ventrally and slightly anterior until an MEP was observed
295 in the contralateral lip muscle. In Experiment 1, the active MT was identified, which constitutes the
296 intensity at which TMS pulses elicited 5 out of 10 MEPs with an amplitude of at least 0.2 mV during
297 20% of maximum voluntary muscle contraction (Möttönen, Rogers, & Watkins, 2014). The intensity
298 of the stimulator was then set to 120% of aMT for the single-pulse stimulations applied during the
299 experiment. The mean stimulator intensity (120% aMT \pm SD) used to elicit lip MEPs in Experiment 1
300 was 51.4% (\pm 4).

301 In Experiment, 2 a dual-pulse inter-hemispheric inhibition protocol was utilised, which
302 comprised a conditioning pulse to right PMv followed by a test pulse to left M1 lip (Chen, 2004; Ni et
303 al., 2009). First, aMT was established as detailed above in right M1 lip area, though a 50mm
304 diameter figure-of-eight coil (Magstim, Dyfed, UK) was used in thresholding, which was the same coil
305 used for delivering TMS to the right hemisphere in the dual-pulse protocol (please see section

306 2.4.3.2 for further details). However, we were unable to record robust lip MEPs from right M1 lip in
307 three subjects, who did not continue on with the study. The intensity of the TMS pulse to right PMv
308 (conditioning stimulus) was subsequently set to 120% of right M1 lip aMT (mean 61.5% \pm 5.7). For
309 left M1 lip, we found the hot spot using the method detailed above using a 70mm diameter figure-
310 of-eight coil (Magstim, Dyfed, UK), and then set the intensity such that the TMS pulse elicited a lip
311 MEP of on average 0.5 mV in 5 out of 10 MEPs (test stimulus), without any conditioning pulse
312 stimulation, in line with inter-hemispheric inhibition protocols based on M1 hand (Di Lazzaro et al.,
313 1999; Mochizuki, Huang, & Rothwell, 2004). The mean stimulation intensity for the test pulse was
314 67.6% (\pm 5.6) of maximum stimulator output. All test pulses were applied using the 70mm coil that
315 had been used for left M1 lip thresholding.

316

317 2.4.3. TMS protocols

318 2.4.3.1. Experiment 1

319 After establishing TMS test intensity, half of the subjects then received two blocks of single-
320 pulse TMS to the lip area of M1 in the left hemisphere to measure baseline MEPs during perception
321 of blocks of clear and distorted speech. This was followed immediately by 20s cTBS to PMv, and then
322 two more test blocks of single-pulse TMS to measure MEPs during perception of clear and distorted
323 blocks of speech, post-cTBS. The other half of the subjects received cTBS first, and then two test
324 blocks of single-pulse TMS during perception of clear and distorted speech to record post-cTBS
325 MEPs. This was followed by a break, and then repeated in order to record baseline MEPs during
326 perception of clear and distorted speech. The baseline MEP measurements were always performed
327 at least 30 minutes after administering cTBS to ensure that baseline performance had returned, as
328 20s of cTBS is thought to affect the brain for around 20 minutes (Huang, Edwards, Rounis, Bhatia, &
329 Rothwell, 2005). The order of baseline testing was counter-balanced to control for order effects.
330 This design mitigates against post-TMS results being confounded by practice effects. Baseline order
331 showed no significant interactions with any of the experimental variables (all $p > 0.1$), which
332 suggests that it is highly unlikely that cTBS contaminated the baseline data for subjects who
333 performed baseline measurements after cTBS.

334 During the single-pulse TMS test blocks, subjects were presented with the speech stimuli
335 (see Methods section 2) and were asked to semantically verify the sentences. During the
336 presentation of each speech stimulus, Matlab was used to externally trigger the TMS system at a
337 jittered time point towards the middle or end of the sentence to avoid intersensory facilitation

338 effects, i.e., where reaction times to the auditory stimuli is primed due to the sensation of a TMS
339 pulse occurring at a predictable time. All speech stimuli were accompanied by a TMS pulse;
340 therefore, all trials were presented with TMS. The timing of the single-pulse TMS delivery was not
341 manipulated to coincide specifically with a particular phoneme; therefore, MEPs did not represent
342 specific time-locked phoneme-based MEPs. TMS test blocks lasted for approximately 3-4 minutes,
343 allowing for the application of 40 TMS pulses per block. Single-pulse TMS was always performed
344 using a Magstim 200² unit and delivered by a 70mm diameter figure-of-eight coil (Magstim, Dyfed,
345 UK).

346 For cTBS to PMv, a Rapid² stimulator and 70mm diameter figure-of-eight coil (Magstim,
347 Dyfed, UK) was always used. The intensity of cTBS was fixed for all subjects at 40%, as it is not
348 feasible to record robust lip MEPs using a biphasic pulse, as delivered by the Rapid², and nor is it
349 possible to extrapolate motor thresholds obtained using a monophasic stimulator (Magstim 200²
350 unit), to a biphasic stimulator. The stimulation site for cTBS to left PMv was based on the average
351 MNI space co-ordinate from Meister et al., 2007: -53, -4 and -49, which fell within the superior
352 portion of the PMv. This was marked in each subject's anatomical scan using Brainsight software
353 (Rogue Research Ltd, Montreal, Canada). Across subjects, the co-ordinate fell within premotor
354 cortex, but not always within superior PMv. For the stimulation, we used 20s of cTBS in one offline
355 train of 300 pulses. cTBS is a patterned form of repetitive TMS. The standard theta burst pattern
356 consists of three pulses given in a 50 Hz burst and repeated every 200 ms (5 Hz). We allowed for a 5
357 minute interval immediately after stimulation to allow for stimulation effects to stabilise, in line with
358 published literature (Huang et al., 2005), after which the single-pulse protocol was administered.

359

360 2.4.3.2 Experiment 2

361 In Experiment 2 a dual-pulse inter-hemispheric inhibition protocol was utilised involving a
362 conditioning pulse to right PMv and a test pulse to left M1 lip. Test pulses in the dual-pulse TMS
363 conditions, and the single-pulse control TMS condition were always performed using a Magstim 200²
364 unit and delivered by a 70mm diameter figure-of-eight coil for left hemisphere stimulation. A 50mm
365 diameter figure-of-eight coil was always used for the conditioning pulses to the right hemisphere in
366 the dual-pulse conditions (Magstim, Dyfed, UK). It was necessary to use the 50mm coil on the right
367 side of the head as two 70mm coils will not fit when both are positioned at a 45° angle tangential to
368 the skull, which we did not wish to compromise as different coil orientations target different
369 populations of neurons (D'Ostilio et al., 2016; Hannah & Rothwell, 2017). The stimulation site for the
370 conditioning pulse to right PMv was based on the MNI space co-ordinate from Catmur et al., (2011):

371 57, 12, and 23. This was marked in each subject's anatomical scan using Brainsight software (Rogue
372 Research Ltd, Montreal, Canada). We used a 10ms inter-pulse-interval after the conditioning pulse
373 before administering the subsequent test pulse to left M1 lip area, consistent with inter-hemispheric
374 inhibition protocols (Di Lazzaro et al., 1999; Mochizuki et al., 2004). This dual-pulse protocol was
375 always administered by two experimenters who held one coil each, as it is not feasible for one
376 experimenter to hold both coils at the same time.

377

378 2.4.4 Electromyography

379 In both Experiments 1 and 2, electromyographic (EMG) activity was recorded from the lip
380 muscle, orbicularis oris, using surface electrodes (Ag/AgCl; 10-mm diameter) in a non-Faraday caged,
381 double-walled sound-attenuating booth. Electrodes were attached to the orbicularis oris on the right
382 side of the mouth in a bipolar belly-belly montage, with an electrode placed at the right temple
383 serving as a common ground. To stabilize background EMG activity, subjects were trained for
384 approximately five minutes to produce a constant level of contraction (approximately 20% of
385 maximum voluntary contraction) of the lip muscles by pursing, which was verified via visual feedback
386 of the ongoing EMG signal (Möttönen et al., 2014; Watkins et al., 2003). Contraction of the lip
387 muscle also facilitates a lower motor threshold relative to when the muscle is at rest, enabling the
388 use of lower levels of stimulation during the experiment. The raw EMG signal was amplified by a
389 factor of 1000, band-pass filtered between 100–2000 Hz, and sampled at 5000 Hz online using a
390 1902 amplifier (Cambridge Electronic Design, Cambridge), and analog-to-digital converted using a
391 Micro1401-3 unit (Cambridge Electronic Design, Cambridge). Continuous data were acquired and
392 recorded using Spike2 software (version 8, Cambridge Electronic Design, Cambridge).

393

394 2.5. Data analysis

395 In Experiment 1, the proportion of correct responses and associated relative reaction times
396 for the distorted and clear speech pre- and post-cTBS were calculated for each individual. Reaction
397 times were expressed relative to the end of each stimulus, which shows how long after the end of
398 the stimulus a response was made. This is in contrast to expressing the response from the onset of
399 the stimulus, which does not take into account differences in stimulus length. The end of each
400 stimulus was visually identified from the waveform and spectrogram by a trained phonetician using
401 Praat software, who located the final voicing cycle of a vowel, release of a consonant, or cessation of
402 frication, for example, in the spectrogram. In Experiments 1 and 2, for the MEP data, individual EMG

403 sweeps starting 40 ms before the TMS pulse and ending 1000 ms post-stimulation were exported
404 offline from the recording software into Matlab. Individual MEPs were identified in each trial and
405 rectified. The integrated area under the curve (AUC) of the rectified EMG signal of each individual
406 mean MEP was then calculated. In Experiment 2, dual-coil MEP ratios were calculated for by dividing
407 each dual-coil condition MEP (clear, distorted, and no-speech control) by the MEPs in the single-
408 pulse no-speech control condition, to express the influence of the dual-coil protocol on MEPs
409 relative to the single-pulse baseline measure. MEP AUCs were then converted into standard scores
410 within subjects, to control for inter-subject variability. The standardized AUCs of MEPs were used in
411 the statistical analyses. The average height of the pre-TMS baseline EMG activity was also computed,
412 and paired t-tests confirmed that there were no significant differences between baseline activity
413 levels between any conditions in Experiment 1 nor 2, indicating that baseline activity did not
414 influence MEPs across conditions.

415 Statistical analyses were carried out using SPSS (version 22.0, IBM). In Experiment 1, two-
416 way repeated measures analysis of variance (RMANOVA) were conducted on reaction time,
417 accuracy, and standardised MEP AUC as the dependent variables, with stimulus type (clear,
418 distorted), and time (baseline, post-cTBS), as within-subjects factors. In Experiment 2, a one-way
419 RMANOVA was conducted on standardised MEP AUC ratio, with stimulus type (clear, distorted, no-
420 speech control) as the within-subject factor. Planned comparisons were subsequently computed
421 where appropriate (alpha level = .05).

422

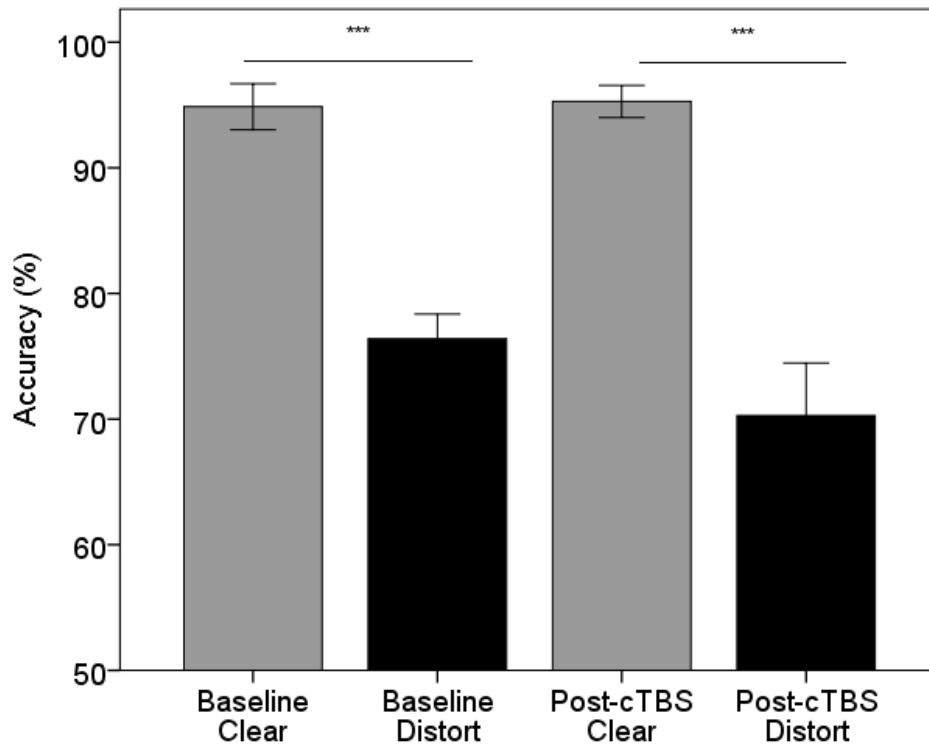
423 3. Results

424 3.1. Experiment 1

425 3.1.1. Accuracy

426 Experiment 1 tested how cTBS to left PMv affected behaviour and MEP responses from left
427 M1 lip during perception of clear and distorted speech. The mean difference in accuracy as a
428 function of time and stimulus type is shown in Figure 2. On average, there was a difference in the
429 accuracy of responses to clear and distorted speech at baseline and after cTBS. A two-way repeated
430 measures ANOVA demonstrated a significant main effect of stimulus type on accuracy ($F(1,17) =$
431 $117.68, p < 0.001, \text{partial } \eta^2 = .87$), confirming that subjects were less accurate in identifying
432 distorted stimuli (73.3%, SE 2.8%) relative to clear (95.1%, SE 1.15%). The main effect of time was
433 not significant ($F(1,17) = 2.9, p = .10$), nor was the time x stimulus type interaction ($F(1,17) = 2.1, p =$

434 .16), indicating that cTBS did not modulate the accuracy of subjects' responses to clear and distorted
435 stimuli.



436

437

438 Figure 2. Average percent correct performance for clear (grey) and distorted (black) stimuli at
439 baseline and after cTBS to left PMv. Error bars represent +/- 1 SE.

440

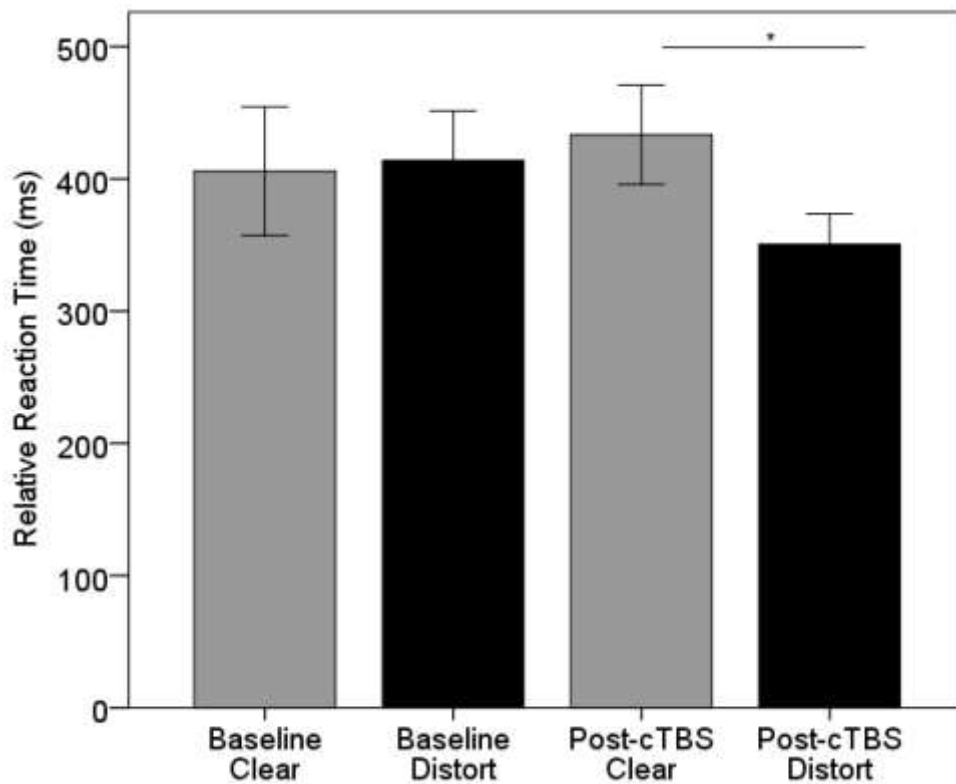
441 3.1.2. Reaction time

442 The mean difference in reaction time as a function of time and stimulus type is shown in
443 Figure 3. On average, there was little difference between reaction times to clear and distorted
444 speech at baseline. The difference between reaction times to clear and distorted speech increased
445 after cTBS. A two-way repeated measures ANOVA found that the interaction between stimulus type
446 and time was significant ($F(1,17) = 5.35$; $p = 0.033$), suggesting that cTBS affected reaction times
447 differently depending on the type of speech stimulus perceived. Paired t-tests (two-tailed)
448 confirmed a significant difference between reaction times post-cTBS to clear and distorted speech
449 ($t(17) = 2.13$, $p = 0.048$ [clear = 433.37 ms, SE 37.45 ms; distorted = 350.43 ms, SE 23.16 ms]), which
450 was not present at baseline ($t(17) = -0.22$, $p = 0.83$ [clear = 405.82 ms, SE 48.57 ms; distort = 413.94,
451 37.52]). No main effects were significant: time = $F(1,17) = 0.37$, $p = 0.55$; stimulus type = $F(1,17) =$

452 1.29, $p = 0.27$. There was a trend towards a significant reduction in reaction times post-cTBS relative
453 to baseline for distorted speech ($p = 0.08$ [baseline: 413.94 ms, 37.52 SE ms, post-cTBS: 350.43 ms,
454 SE 23.16 ms]), which was not evident in reaction times to clear speech post-cTBS ($p = 0.4$). These
455 data indicate, therefore, that the significant interaction is driven by cTBS to PMv reducing response
456 time to distorted speech specifically, without changing response time to clear stimuli.

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461 Figure 3. Average relative reaction time to clear (grey) and distorted (black) stimuli at baseline and
462 after cTBS to left PMv. Error bars represent +/-1 SE.

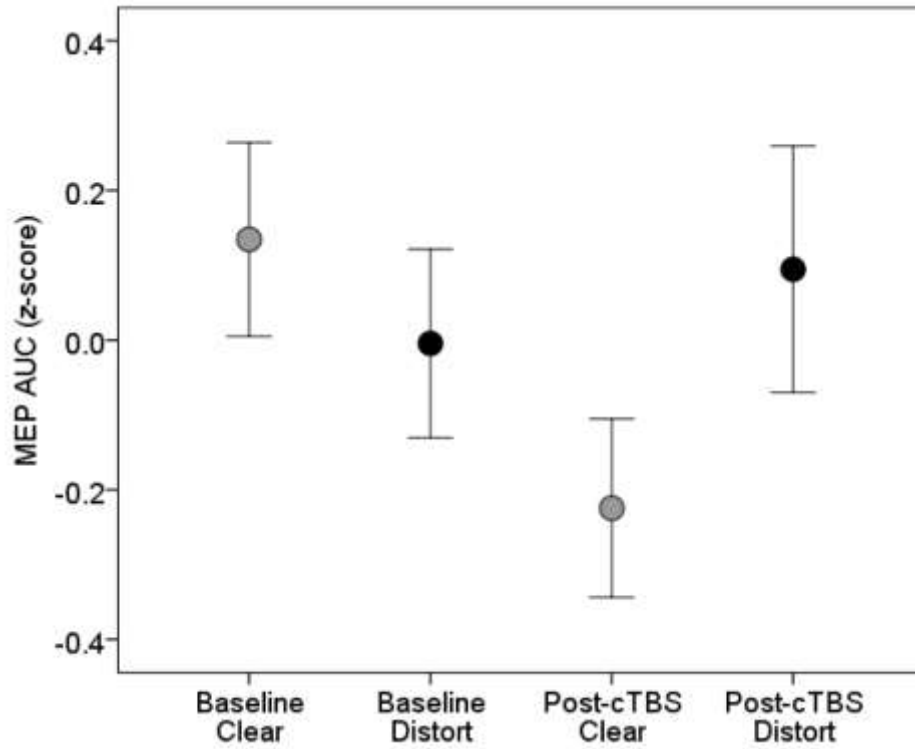
463

464 3.1.3. Effect of cTBS on Lip MEPs

465 The mean difference between MEPs elicited during perception of clear and distorted speech
466 at baseline and post-cTBS is shown in Figure 4. Two-way RMANOVA indicated that MEPs were not
467 modulated by stimulus type ($F(1,17) = 0.27$, $p = 0.61$) or by time ($F(1,17) = 0.30$, $p = 0.44$). The

468 interaction was also not significant ($F(1,17) = .94, p = .17$). These data confirmed that cTBS to PMv
469 did not influence MEPs during perception of clear or distorted stimuli.

470



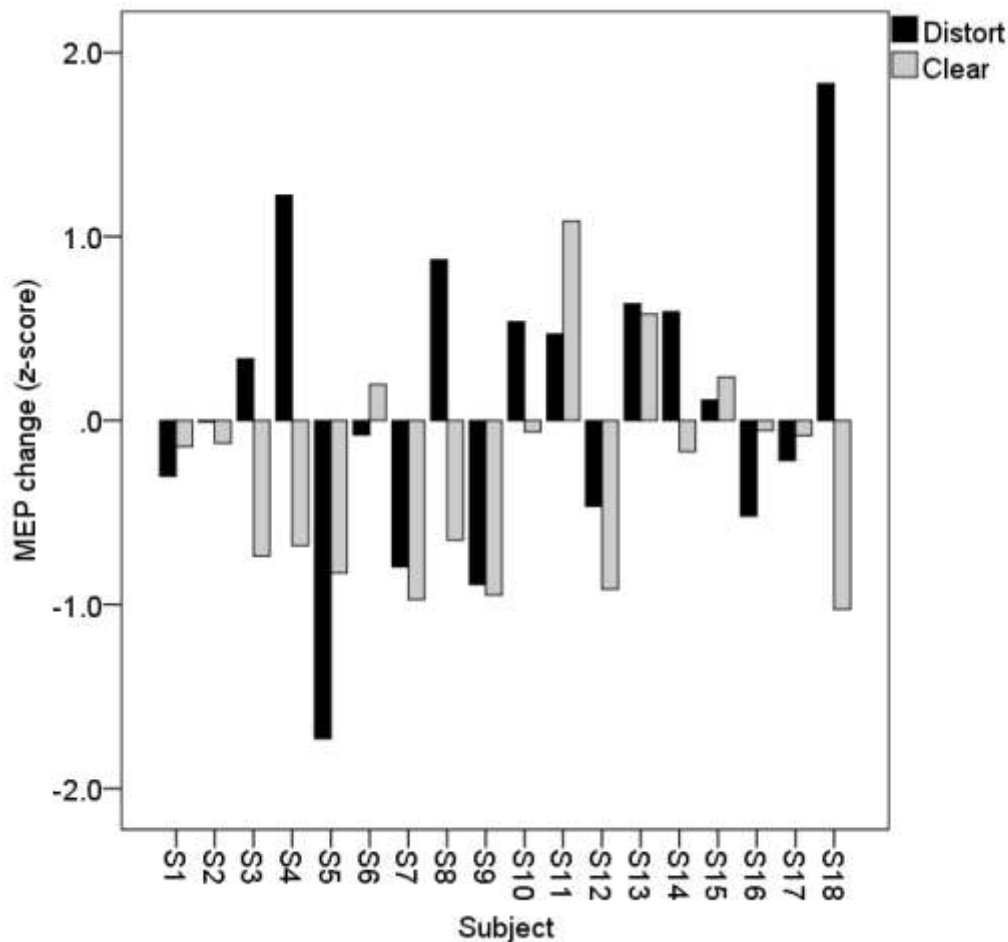
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473 Figure 4. Average MEP area during perception of clear (grey) and distorted (black) speech at baseline
474 and after cTBS to left PMv. Error bars represent +/-1 SE.

475

476 Notably, there was considerable variability in the effect of cTBS on motor excitability. Individual
477 subject's responses to cTBS for each condition are shown for in Figure 5. In some subjects, cTBS
478 caused MEP facilitation, whereas in other subjects, cTBS caused MEP inhibition. The direction of the
479 effect was also not consistent across speech conditions.



480

481 Figure 5. Bars express individual participant's change scores (Δ) in MEP area from baseline, to post-
 482 cTBS, in both Distorted (black) and Clear (grey) conditions.

483

484

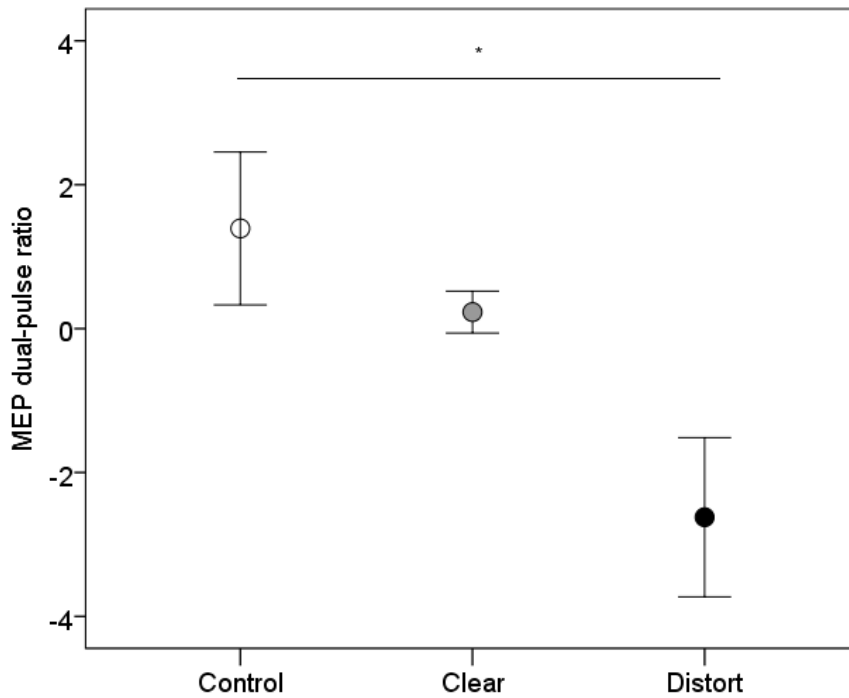
485 3.2. Experiment 2

486 3.2.1. Motor Evoked Potentials

487 Experiment 2 tested how a dual-pulse inter-hemispheric inhibition protocol to right PMv
 488 affected MEP responses from left M1 lip during perception of clear and distorted speech, as well as
 489 during the no-speech control condition. Mean MEP data are shown in Figure 6, where it can be
 490 observed that distorted MEP data are further away from the mean than either clear or control MEP
 491 data. A one-way RMANOVA indicated that there was a significant effect of stimulus type on the
 492 extent of the inter-hemispheric MEP inhibition resulting from disruption of right PMv ($F(1,14) = 3.5$,
 493 $p = 0.044$, partial eta squared 0.2). Planned comparisons confirmed a significant difference between
 494 MEPs during perception of clear and distorted speech elicited after dual-pulse TMS ($p = 0.035$). The

495 difference between control and distorted MEPs showed a trend towards a significant difference ($p =$
496 0.08). There was no significant difference between control MEPs and MEPs elicited during
497 perception of clear speech ($p = 0.3$). These data indicate that when listening to distorted speech,
498 inhibiting right PMv inhibits MEPs from left M1 lip area. These findings suggest that right PMv may
499 play a role during perception of distorted speech specifically

500



501

502

503 Figure 6. MEP ratios following dual-pulse inter-hemispheric TMS to right PMv and left M1 lip area,
504 during perception of clear (grey) and distorted (black) speech, and no-speech control (no auditory
505 stimulation, open circle) conditions. MEP ratios were calculated by dividing each dual-coil condition
506 MEP (clear, distorted, and no-speech control) by the MEPs in the single-pulse no-speech control
507 condition, to express the influence of the dual-coil protocol on MEPs relative to the single-pulse
508 baseline measure.

509

510 4. Discussion

511 The present study aimed to investigate the intra- and inter-hemispheric influence of PMv on
512 left M1 during speech perception. Experiment 1 showed that disruption to PMv causally affected
513 reaction time to speech under distorted listening conditions specifically, but did not affect responses

514 to clear speech. Effects were specific to reaction times and not accuracy. This is in keeping with
515 previous reports of behavioural changes post-TMS, which predominantly manifest in a change in
516 response time (Devlin, Matthews, & Rushworth, 2003; Krieger-Redwood, Gaskell, Lindsay, &
517 Jefferies, 2013; Pobric, Jefferies, & Ralph, 2007; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies,
518 2011). Surprisingly, MEPs were not modulated by distorted sentences, despite this form of distortion
519 modulating MEPs to pre-lexical stimuli (Nuttall, Kennedy-Higgins, Devlin, & Adank, 2017; Nuttall et
520 al., 2016). MEPs were not affected by cTBS when considered at group level. In Experiment 2, we
521 found an inter-hemispheric influence of PMv on left M1 lip MEPs. This finding was specific to the
522 distorted listening condition only, in line with the behavioural findings from Experiment 1, with no
523 modulation of control MEPs, or MEPs elicited during perception of clear speech, by right PMv.
524 However, we used syllables instead of sentences in Experiment 2, meaning that different patterns of
525 connectivity were potentially evaluated in both experiments. As such, data should be interpreted in
526 light of this methodological difference.

527 Our observation in Experiment 1 that PMv influences behavioural responses to distorted but
528 not clear speech resonates with previous findings regarding the role of PMv in speech perception.
529 Specifically, PMv may be causally involved in accurate identification and discrimination of speech
530 that is difficult to understand (Meister et al., 2007; Sato et al., 2009). Here, we demonstrate that
531 PMv also plays a role in higher-level speech comprehension. The task employed in Experiment 1
532 involved the semantic verification of sentences, relative to lower-level phonetic identification or
533 discrimination tasks that have previously been used in some PMv studies (D'Ausilio et al., 2012;
534 Krieger-Redwood et al., 2013; Meister et al., 2007; Sato et al., 2009). This is in line with previous
535 findings that point to a role of motor areas in speech comprehension (Fadiga et al., 2002; Murakami
536 et al., 2015; Schomers, Kirilina, Weigand, Bajbouj, & Pulvermüller, 2015; Watkins et al., 2003).

537 Importantly, however, previous studies that used TMS to disrupt PMv found that
538 behavioural performance became worse and not better after the stimulation, as our data might
539 suggest. One reason for this difference may be due to the effect of the TMS paradigm used, as the
540 effect of cTBS appears to vary considerably across people (Hannah, Rocchi, Tremblay, & Rothwell,
541 2016; Hordacre et al., 2016; Volz, Hamada, Rothwell, & Grefkes, 2014). In our subject sample, five
542 participants showed increased reaction times, whereas thirteen showed decreased reaction times,
543 leading to a reduction in reaction time on average. These different effects may reflect the highly
544 variable response profile associated with cTBS. Future studies should seek to replicate involvement
545 of PMv in speech comprehension paradigms using alternative TMS protocols, to further clarify the
546 role of PMv in speech perception. Furthermore, it would also be informative to pre-screen subjects
547 to investigate the nature of their response profile; i.e., whether they show an inhibitory response to

548 cTBS, or a facilitatory response to cTBS. This would allow for response profile to be included in the
549 design and analysis, and the influence of cTBS to be accurately measured. It cannot necessarily be
550 assumed that the same form of stimulation will affect all subjects equally,

551 Surprisingly, however, we did not observe facilitation of lip MEPs to the complex sentential
552 stimuli used. One reason for this may be that the complexity of the task, and/or stimulus type, did
553 not draw on resources from articulatory M1 in the same way that distorted syllables modulate M1
554 activity. Indeed, MEP studies observing facilitation to speech stimuli are largely based on passive
555 protocols, or low-level pre-lexical speech stimuli (Fadiga et al., 2002; Möttönen & Watkins, 2009;
556 Roy, Craighero, Fabbri-Destro, & Fadiga, 2008; Watkins et al., 2003). Therefore, it may be the case
557 that M1 is not recruited to the same extent when this type of perceptual ambiguity can be resolved
558 using other mechanisms and resources, or resolution is not solely dependent upon phonetic analysis
559 by the subject. Indeed, presence of extensive semantic top-down information, as in the semantic
560 verification task, may render phonetic analysis unnecessary. However, it should be noted that Dial &
561 Martin's (2017) data suggest that pre-lexical access may also occur in spite of such semantic
562 information being available. Nonetheless, the lack of MEP changes by cTBS of left PMv indicates no
563 modulation of intra-hemispheric PMv-M1 connectivity on lip motor excitability, under the conditions
564 used in this experiment.

565 We also did not observe any effect of cTBS on group-level lip MEPs. This is line with previous
566 findings regarding cTBS effects on M1 lip, where MEPs were found to reveal no measurable change
567 in motor excitability following 40 seconds of cTBS (Rogers, Mottonen, Boyles, & Watkins, 2014).
568 However, in accordance with our results, Rogers and colleagues also observed an influence of cTBS
569 on behaviour, despite finding no effect of cTBS on MEPs, the lack of which they attribute to inter-
570 individual variability. Indeed, we also found highly variable MEP responses to cTBS, to both types of
571 speech stimuli. This is in line with recent observations of highly variable MEP response profiles
572 following cTBS (Goldsworthy et al., 2016; Hannah et al., 2016; Hordacre et al., 2016; Vallence et al.,
573 2015; Vernet et al., 2014). Whilst progress has been made in understanding the causes of MEP
574 variability (for review see Ridding & Ziemann, 2010), a large component of this variability remains
575 unexplained, and may contribute to non-significant group results after cTBS. Identifying additional
576 factors contributing to response variability is important for improving understanding of the
577 physiology underpinning MEP responses to cTBS.

578 In Experiment 2, we found that disruption of right PMv interacted with the type of speech
579 stimulus being perceived during lip MEP recording. Specifically, during perception of speech that was
580 difficult to understand, we observed that disrupting right PMv inhibited left M1 lip MEPs. This may
581 indicate that inter-hemispheric connectivity between right PMv and M1 lip is therefore modulated

582 for distorted listening conditions, such that right PMv may be recruited when speech perception is
583 challenging.

584 Context-dependent modulation of PMv-M1 interactions has been observed intra-cortically in
585 hand action observation and execution literature. During hand action observation, PMv facilitates
586 grip-specific representations in M1, but only while grip formation is observed (de Beukelaar, Alaerts,
587 Swinnen, & Wenderoth, 2016). These findings suggest that PMv and M1 interact temporarily to
588 facilitate grip-specific representations in M1, but no sustained input from PMv to M1 seems to be
589 required to maintain action representations that are anticipated based on contextual information or
590 once the grip is formed. These findings are also in line with the intra-hemispheric relationship
591 between PMv and M1 during hand action execution, where it is known that PMv-M1 interactions are
592 selectively modulated during specific types of grasp (Davare, Lemon, & Olivier, 2008). Considerably
593 less, however, is known about modulation of inter-hemispheric PMv-M1 interactions during action
594 observation.

595 Taken together, data from Experiments 1 and 2 highlight several findings with regards to the
596 intra- and inter-hemispheric influence of PMv during speech perception. With respect to intra-
597 hemispheric effects, we observed a reduction in reaction time to distorted speech specifically in
598 Experiment 1. There was no corresponding effect on clear speech. TMS timing was jittered
599 substantially for both types of stimuli, which should mitigate against a general inter-sensory
600 explanation for this TMS effect, though we cannot rule it out completely. The influence of cTBS to
601 PMv on lip MEPs appeared to be bidirectional; i.e., for some subjects, cTBS suppressed MEPs,
602 whereas for other subjects, cTBS facilitated MEPs. Due to this difference in response profile, the net
603 effect of the cTBS influence is obscured when considered at group-level. With regards to the inter-
604 hemispheric influence of right PMv on left M1, we observed a specific pattern of results that
605 indicated an involvement of right PMv in the sensorimotor network only under distorted listening
606 conditions. This differed from the MEP results from Experiment 1, where there was no difference
607 between clear and distorted speech, and suggests the PMv-M1 intra-hemispheric interactions may
608 be relevant for both clear and distorted speech perception, but PMv-M1 inter-hemispheric
609 interactions are influential only during perception of distorted speech. In other words, the entire
610 system for speech perception works harder when listening becomes more difficult. As we did not
611 measure behavioural responses in Experiment 2, we cannot attest to the necessity of right PMv in
612 perception of distorted speech. It must be noted, however, that our interpretation of PMv is based
613 on two protocols that use different speech stimuli. For a full understanding of the role of PMv in
614 speech perception, future work should seek to use different types of speech stimuli within the same
615 protocol, in order to determine how speech stimulus type affects involvement of PMv.

616 Data presented within this paper feed into speech perception models that are characterised
617 by reverberant, bilateral speech-motor circuits, which adapt dynamically based on context. As
618 emphasised by Skipper and colleagues (Skipper et al., 2017), it is not the case that the
619 neurobiological network for speech perception should be conceived of as fixed, as one might
620 interpret from dual stream models (Hickok, 2012). It is indeed unambiguous that the brain is
621 adaptable and highly plastic. Likewise, we are in agreement with Skipper and colleagues that it is
622 equally possible that multiple permutations of different speech perception and speech production
623 brain networks exist. The specifics of which particular network is brought online will be most likely
624 moderated by context demands. For example, the engagement of a particular speech perception
625 network is highly dependent on listening difficulty. This is evidenced by how clear and distorted
626 speech differentially modulate intra-cortical and inter-cortical PMv-M1 interactions, which may
627 reflect the influence of PMv operating within two different types of neurobiological networks,
628 dependent upon the auditory stimulus.

629 The functional role of PMv and articulatory M1 regions in speech perception and language
630 comprehension is likely to help disambiguate auditory information that is hard to understand. Under
631 this interpretation, motor regions provide a supportive, but perhaps not essential role, relative to
632 how they have been measured in the present study. The size of the effects reported here may also
633 corroborate the suggestion that motor regions play a supportive, but non-essential role. However,
634 given that the involvement of motor regions is likely to adapt dynamically in response to situational
635 demands, the role of motor regions should not be considered fixed, and may increase in influence
636 depending on the listening context. Neurobiological interactions, of course, do not map neatly onto
637 behavioural relevance, which we believe poses a different question (for extensive treatment see
638 Schomers & Pulvermüller, 2016).

639 In summary, the present study explored whether PMv exerts an influence intra-cortically,
640 and inter-cortically, during perception of speech that is easy or challenging to understand. Data
641 indicated that left PMv may exert online influence over perception of distorted speech. We also
642 found evidence to suggest that right PMv influences left M1 lip only when listening conditions are
643 challenging. These data support bilateral models of speech perception, where sensorimotor
644 interaction is adaptive depending upon context and stimulus (Schomers & Pulvermüller, 2016;
645 Skipper et al., 2017).

646

647

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651

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