Amplitude Modulation detection ability can be differentially affected using state-dependent Transcranial Magnetic Stimulation

Abbreviated title: TMS differentially affects sensitivity to AM

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1 Abstract

2 Temporal changes in the speech envelope are crucial for intelligibility, and humans
3 are particularly sensitive to amplitude modulations (AM) at frequencies commensurate
4 with the syllabic rate (4Hz). Some asymmetric models of auditory processing
5 have attempted to explain observed functional asymmetries between left and right
6 auditory cortices in terms of temporal integration windows of differing lengths. In
7 this paper we use an fMRI-localised, state-dependent, dual-pulse TMS paradigm to
8 investigate auditory processing as exemplified by detection of sinusoidal amplitude-
9 modulation of a broadband noise carrier. The effect of left and right hemisphere
10 TMS on accuracy levels for detection of such modulations at rates of 4 and 40Hz
11 under conditions of behavioural adaptation were examined. Effects of TMS on AM
12 detection were found only in the 40Hz detection task when TMS was applied to the
13 left hemisphere. Further, this effect showed a dissociation based on the modulation
14 used during behavioural adaptation, with a facilitation shown when participants
15 were behaviourally adapted to 4Hz AM whereas a disruption was shown when participants
16 were behaviourally adapted to 40Hz AM, contrary to initial predictions
17 based on state-dependent TMS theory. These results show for the first time that
18 it is possible to differentially affect AM detection ability using TMS and further
19 emphasise the importance of subtle timing factors in TMS studies. The novel use
20 of this technique in the auditory domain has implications for further elucidating
21 auditory processing mechanisms in health and disease.

22 Highlights

- 23 • Detection of amplitude modulation in auditory stimuli can be perturbed using
24 TMS
- 25 • An interaction is found between hemisphere of stimulation and AM rate of the
26 stimulus

- 27 • An explanation based on neural coding mechanisms and timing of TMS is
28 considered

29 **Keywords**

- 30 • Amplitude modulation
- 31 • Behavioural adaptation
- 32 • Human behavioural
- 33 • fMRI
- 34 • TMS

35 Introduction

36 The structure of human speech is highly dynamic, consisting of continuous changes
37 in both amplitude and frequency content. Slow temporal amplitude modulations
38 (Rosen 1992), are known to be crucial to speech intelligibility (Drullman et al.
39 1994a,b). Indeed, intelligibility remains high even under conditions of severely de-
40 graded spectral content, provided that these amplitude modulations are preserved
41 (Shannon et al. 1995).

42 Psychophysical work has shown that humans are particularly sensitive to detect-
43 ing AM at rates commensurate with the speech envelope and that AM detection
44 can be characterised as a low-pass (Viemeister 1979; Rees et al. 1986; Kohlrausch
45 et al. 2000) or band-pass process (Edwards and Chang 2013). It has been proposed
46 that AM is extracted by a bank of filters, each tuned to different modulation rates
47 (Dau et al. 1997a,b; Jepsen et al. 2008; Simpson et al. 2013; Xiang et al. 2013).
48 The exact anatomical locus of such a modulation filterbank is currently unclear,
49 although it is known that progressively higher areas of the auditory pathway show
50 peak responsivity for lower AM rates (Harms and Melcher 2002; Harms et al. 2005),
51 behaviour which has been compared to a cascade of modulation filters (Giraud et
52 al. 2000).

53 In addition to differential sensitivity from lower to higher auditory areas, several
54 hypotheses have been proposed to account for observed asymmetries in auditory
55 processing. One hypothesis holds that the left hemisphere preferentially processes
56 temporal structure whilst the right hemisphere is more sensitive to spectral cues
57 (Zatorre and Belin 2001; Zatorre et al. 2002) whilst an alternative (‘Asymmetric
58 Sampling in Time’; Poeppel 2003) proposes that the right hemisphere integrates
59 over longer timescales ($\sim 250\text{ms}$) than the left hemisphere ($\sim 25\text{ms}$). The longer
60 of these timescales ($\sim 250\text{ms}$) corresponds closely with the syllabic rate of speech
61 ($\sim 4\text{Hz}$). The shorter timescale ($\sim 25\text{ms}$) corresponds to a frequency of 40Hz , which
62 is around the phonemic rate of speech. Dichotomous accounts of asymmetric pro-

63 cessing have, however, been challenged - both due to a of lack of empirical support
64 for left hemisphere temporal selectivity as well as the fact that such a division does
65 not account for the true structure of the speech signal (McGettigan and Scott 2012).

66 In the current study, TMS was used to further investigate the behavioural detec-
67 tion of sinusoidal amplitude modulation of broadband noise. The study was designed
68 with specific reference to asymmetric models of auditory processing.

69 A state-dependent, dual-pulse, TMS method was used to perturb judgements in
70 a sinusoidal AM detection task at modulation rates of 4Hz and 40Hz. When TMS
71 is delivered to neuronal populations in different activation states, state-dependent
72 differential effects have been observed (Silvanto and Pascual-Leone 2008; Silvanto
73 2008; Cattaneo and Silvanto 2008). In this context, state-dependent TMS essen-
74 tially refers to the fact that the impact on behaviour caused by the TMS pulse is
75 altered by the nature of the processing being performed by the neuronal population
76 at the time at which the pulse is administered. These effects include behavioural
77 facilitations for detection of adapted stimuli, suggesting that the common concep-
78 tualisation of TMS as a purely disruptive tool is inadequate (Romei et al. 2016).
79 An overall framework has recently been proposed that can explain classic ‘virtual
80 lesion’ inhibitory effects of TMS and state-dependent effects (Silvanto and Cattaneo
81 2017). Combining state-dependent TMS with behavioural adaptation is a prom-
82 ising method for investigating AM detection for three principal reasons. Firstly, the
83 perceptual effects of adaptation to amplitude and frequency modulated sounds are
84 well characterised (Regan and Tansley 1979; Tansley and Suffield 1983; Bacon and
85 Grantham 1989; Houtgast 1989; Wojtczak and Viemeister 2005; Kleinschmidt and
86 Jaeger 2015). Secondly, state-dependent TMS potentially allows the dissociation
87 of cortical functioning in brain areas with overlapping populations responsible for
88 processing different rates of AM, as may be expected based on previous localisation
89 studies (Barton et al. 2012; Herdener et al. 2013). Finally, as stimulation is de-
90 livered immediately prior to the auditory test stimulus in the state-dependent TMS

101 paradigm, potential auditory masking due to the TMS click artefact is avoided.
102 Whilst different forms of neurostimulation has been used to modulate aspects of
103 auditory perception such as temporal discrimination (Buetti et al. 2008; Heimrath et
104 al. 2014), melody discrimination (Andoh and Zatorre 2011), phoneme categorisation
105 (Rufener et al. 2016), and tinnitus (Weisz et al. 2012), to our knowledge, TMS has
106 not previously been used to investigate AM processing.

107 We proposed three research questions. i) can AM detection ability be affected
108 by TMS? ii) do these effects show state-dependency? iii) do these effects show
109 hemispheric differences consistent with lateralised accounts of auditory processing?

110 Three pre-registered hypotheses were formulated (Partridge 2017). It was pre-
111 dicted that AM detection performance would differ between real and sham TMS con-
112 ditions. Secondly, it was predicted that TMS effects would show state-dependency;
113 i.e. performance would only be improved by TMS when the modulation rates of the
114 adaptor and test stimuli were congruent. Finally, it was predicted that effects would
115 show an interaction with hemisphere of stimulation such that left hemisphere stim-
116 ulation would have a greater effect on 40Hz AM detection performance and right
117 hemisphere stimulation would have a greater effect on 4Hz AM detection perform-
118 ance.

109 **Material and Methods**

110 **Subjects**

111 Ten subjects (4 female; $M = 23.1$, $SD = 5.14$) participated in the experiment.
112 Subjects responded to an advert and were paid or reimbursed in course credit for
113 participation except for one participant who was a member of the research team.
114 All subjects were TMS and MRI eligible, right-handed, native English speaking and
115 had self-reported normal hearing. The project was approved by the Research Gov-
116 ernance Committee, York Neuroimaging Centre, University of York and conformed
117 to the guidelines of the Declaration of Helsinki. All participants gave written in-
118 formed consent. One participant withdrew from the experiment and data from one
119 participant had to be discarded due to acoustic noise caused by building work dur-
120 ing the testing sessions, leaving a total of 8 participants. All data collection was
121 undertaken after the pre-registration document (Partridge 2017) was made publicly
122 available.

123 **Experimental Design**

124 **Audiogram**

125 Subjects underwent an air conductance pure tone audiogram to determine that
126 hearing thresholds were above eligibility requirements. Audiograms were conducted
127 using an Interacoustics AD226 audiometer (Interacoustics, Middelfart, Denmark)
128 and Telephonics TDH-39P earphones (Telephonics, NY, USA). Subjects were ex-
129 cluded from further testing if they did not meet the threshold criteria of ≤ 20 dB
130 HL at octave frequencies from 250 – 8000Hz in both ears.

131 **Psychophysical Testing**

132 A double-walled, sound-attenuated booth was used for psychophysical testing. Aud-
133 itory stimuli were presented diotically via Etymotic ER-2 headphones (Etymotic

Research Inc., IL, USA). Following the design of Viemeister (1979), a 2-alternative forced choice (2AFC) task was used to determine psychophysical thresholds for AM detection. Each stimulus consisted of three continuous 500 ms periods of broadband noise (low-pass filtered at 8 kHz). In each trial, the first or third period was randomly chosen to be sinusoidally amplitude modulated. The second (centre) 500ms period was a reference period and always consisted of unmodulated broadband noise. Participants indicated which interval they thought contained modulation by means of a key press. Participants were tested separately at AM rates of 4 and 40Hz with 20 practice trials delivered at each rate before testing began. LEDs were used to indicate the two test intervals and feedback was given after each trial. The starting phase of the modulation was drawn randomly from a uniform distribution ranging from 0 to 2π and the standard and comparison interval power were normalised to match the RMS of the centre period. Stimuli were generated at a sample rate of 44.1 kHz using Python and presented using PsychoPy (Peirce 2007) and the PyAudio module (<https://people.csail.mit.edu/hubert/pyaudio/>) through an EMU 0204 24-bit DAC (Creative Technology Ltd, Singapore). Stimuli were presented at 70 dB SPL as calibrated using an artificial ear (B&K 4153) and a sound level meter (B&K 2260). The AM depth of the comparison interval was systematically modified using an adaptive staircase procedure (Levitt 1971). Two interleaved staircases were used (1-up, 2-down; 1-up, 3-down). Before each trial, a random choice was made between the remaining staircases and this continued until each staircase had reached 14 reversals. A step size of 1 dB was used for the first 4 reversals of each staircase, which decreased to 0.5 dB for the next 4 reversals and to 0.25 dB for the final 6 reversals. Participants completed three runs (six staircases in total) at each of the 4 and 40Hz modulation rates. For 4 and 40Hz separately, an estimate of the 85% threshold from each run was calculated from the respective psychometric function (a cumulative gaussian) on a per-subject basis. The largest of the three modulation depth thresholds was discarded and the mean of the other two was used

as the threshold depth for that subject in the TMS experiment.

fMRI Acquisition and Analysis

Subjects wore earplugs underneath the sound-attenuating headphones from the fMRI-compatible auditory stimulus delivery system (MR Confon, MR Confon GmbH). fMRI data were acquired using an Interleaved Silent Steady-State fMRI sequence (Schwarzbauer et al. 2006). The sound level of the scanner noise, not accounting for attenuation provided by earplugs and ear defenders, was 81 dB SPL during the quiet period and 98 dB SPL during the acquisition period. During the acquisition periods, whole head fMRI data (GE-EPI, TR = 2 s, TE = minimum full, FA = 90°) were collected using a GE Signa HDx 3T system (General Electric, WI, USA). A 128 × 128 pixel matrix with a field of view of 25.6 cm was used, giving an in-plane resolution of 2 × 2 mm. 24 interleaved slices were collected with a slice thickness of 2mm. Slices were oriented parallel with the Sylvian fissure while ensuring bilateral coverage of Heschl’s gyrus and planum temporale.

Stimulus conditions were silence, noise, 4Hz AM noise, and 40Hz AM noise. All noise carriers were broadband (0 - 8000Hz) and the AM stimuli were fully modulated ($m = 1$). Stimuli were presented for 6 seconds followed by an acquisition period of 8s. Each stimulus was presented 6 times in each fMRI run and three runs were performed for each subject, each run lasting approximately 6 minutes. Data were analysed using Feat 5.98, part of FSL-4.1 (Smith et al. 2004), along with custom scripts which implemented filtering of the temporally non-contiguous data. Full details of this analysis procedure can be found in Hymers et al. (2015), with the exception that in this study spatial smoothing was performed using a kernel with FWHM of 2mm.

Data from the multiple fMRI runs for each subject were combined using a fixed-effects analysis. A contrast of 4Hz and 40Hz AM noise combined over unmodulated noise was performed. The results were corrected for multiple comparisons using

189 a cluster thresholding procedure ($Z > 2.3$, $p = 0.05$; Worsley 2001). TMS targets
190 were defined individually for each subject using a superficial maxima voxel in a
191 significant cluster on posterior superior temporal gyrus / planum temporale for each
192 hemisphere.

193 Sagittal whole head structural T1-weighted data (3D FSPGR, $TR = 7.8$ ms, TE
194 $=$ minimum full, $FA = 20^\circ$, Matrix 256×256 , $FOV = 29.0$ cm, 176 slices, Slice
195 thickness $= 1$ mm) were collected in the same scanning session as the fMRI data for
196 participants who did not already have a structural MRI scan available.

197 TMS

198 A 2x2x3 repeated measures design was used during the main TMS experiment. Ex-
199 perimental factors were adaptation AM rate (2 levels; 4Hz, 40Hz), test AM rate (2
200 levels; 4Hz, 40Hz) and TMS (3 levels; sham, left, right). The dependent variable was
201 accuracy on the AM detection task. Test AM rate was randomised within each ses-
202 sion, so all subjects completed six TMS sessions, one for each adaptation AM rate by
203 TMS combination. The order of sessions was approximately counterbalanced across
204 subjects using a latin square design. Each TMS session was separated by at least
205 24 hours. A Brainsight frameless stereotaxic system (Rogue Research, Montreal,
206 Canada) with chin rest and forehead support was used to monitor coil placement
207 and ensure accurate TMS delivery. A Magstim Super Rapid² (Magstim, Whitland,
208 UK) stimulator and a 80mm (external diameter of each ring) figure-of-eight coil
209 (Magstim, Whitland, UK) was used for pulse delivery. The TMS coil was oriented
210 with the handle pointing backwards, parallel with the midline. Stimulation consisted
211 of a double-pulse protocol with pulses separated by 50 ms. TMS pulse intensity was
212 set to 65% of the maximum stimulator output (maximum $= 2.6$ T) based on previous
213 state-dependent TMS studies (Cattaneo and Silvanto 2008; Cattaneo et al. 2008).
214 Before the first experimental TMS session, test pulses were delivered to ensure that
215 subjects could tolerate this TMS protocol. The left and right TMS targets were ob-

216 tained using the fMRI data as previously described. Sham TMS was performed by
217 placing the coil at the vertex and rotating by 90° to remove any physiological effect of
218 TMS but, crucially, retain peripheral factors such as the auditory artefact (Lisanby
219 et al. 2001). Stimuli were delivered during the experiment using the same Etymotic
220 ER-2 headphones and earpieces as were used during psychophysical testing.

221 A graphical outline of the TMS session can be seen in Figure 1. Every TMS
222 session began with a period of auditory adaptation during which 10 minutes of
223 broadband noise which had been fully amplitude modulated at a rate of either 4Hz
224 or 40Hz was presented depending on the condition being tested. This period was to
225 ensure participants were maximally adapted (Wojtczak and Viemeister 2005). All
226 further behavioural adaptation within the session was at the same AM rate. A block
227 of 150 trials was then performed. Each trial consisted of 6 seconds of behavioural ad-
228 aptation followed by a 2AFC task. A double-pulse TMS burst was delivered during
229 the adaptation sound, immediately prior to the 2AFC task. Each trial perceptu-
230 ally formed one continuous 7.5s auditory event. The design of the 2AFC task was
231 identical to that used during baseline psychophysical testing, aside from the fixed
232 (85% threshold) AM depth of the target interval. No feedback was given during
233 the TMS sessions. During each block the test AM rate was pseudo-randomised; 75
234 trials were modulated at a rate of 4Hz and the other 75 were modulated at a rate
235 of 40Hz. At the completion of the first block of trials, 4 minutes of fully modulated
236 AM noise (top-up adaptation) were presented at the same rate used at the start of
237 the experiment to ensure that the adaptation effect was consistent. This period also
238 allowed the participant to have a short break from responding, during which the
239 TMS coil was switched with an identical replacement to ensure the coil remained at
240 an operational temperature. A second block of 150 trials was then completed.

241 Statistical Analysis

242 Generalised linear mixed-effects models (GLMM) were fit to the TMS accuracy
243 data. This technique accounts for interdependence of the data arising from repeated
244 measurements of the same participants; it also allows adjustments for non-normal
245 distributions (Baayen et al. 2008; Dixon 2008; Jaeger 2008). A logit link function
246 was used to account for the binomial distribution of the raw data. Separate models
247 were fit to the 4Hz and 40Hz test AM rate data. Both models included fixed effects
248 of TMS condition and behavioural adaptation condition and an interaction term.
249 Participant was included as a random effect. Random intercepts and slopes for TMS
250 condition and behavioural adaptation condition were estimated for each participant.
251 The random effects structure was the maximal justified by the design (Barr et al.
252 2013). Treatment coding was used to measure the difference from the baseline
253 condition of sham TMS with 4Hz AM adaptation (the baseline condition choice is
254 arbitrary and was chosen to make other parameters easier to interpret). Finally,
255 parametric bootstrapping was conducted on the model parameters to obtain 95%
256 confidence intervals. All modelling was conducted using the *lme4* package (Bates
257 et al. 2015) in *R* software (R Core Team 2017). Parametric bootstrapping was
258 conducted using the *pbkrtest* package (Halekoh and Højsgaard 2014).

259 Results

260 Psychophysics

261 The modulation depth at which 85% accuracy was achieved was calculated indi-
262 vidually for each participant, for each AM test rate (4 and 40 Hz). The mean
263 modulation depth across participants for the 4 Hz condition was -20.7 dB and for
264 the 40 Hz condition was -21.2 dB. A paired t-test showed no significant difference
265 between thresholds for 4 Hz and 40 Hz AM detection ($t(7) = 0.888$, $p = 0.404$).

266 fMRI derivation of TMS Targets

267 Figure 2 shows targets in both hemispheres for an example participant.

268 TMS target distance measurements were recorded for TMS pulses. This is a
269 measure of the distance from the centre of the TMS coil to the fMRI-defined target.
270 Four sessions lacked these measurements due to a technical issue. A linear mixed-
271 effects model was fit to these data, with a fixed effect of TMS hemisphere and a
272 random effect of participant. Parametric bootstrapping of the model parameters was
273 conducted to obtain 95% confidence intervals. There was a negligible mean difference
274 of -0.558 mm, 95% CI [-10.025, 8.631] between left hemisphere and right hemisphere
275 conditions. There was no overall correlation between the AM task accuracy scores
276 and the target distance measurements ($r = 0.008$, $p = 0.954$).

277 TMS positioning error measurements were also recorded. This is a measure of
278 the difference between the fMRI-defined target and the estimated pulse trajectory.
279 Four sessions lacked these measurements due to a technical issue. A linear mixed-
280 effects model was fit to these data, with a fixed effect of TMS hemisphere and a
281 random effect of participant. Parametric bootstrapping of the model parameters
282 was conducted to obtain 95% confidence intervals. There was a negligible mean
283 difference of -0.031mm, 95% CI [-0.082, 0.021] between left hemisphere and right
284 hemisphere conditions. The overall mean error was 0.342mm, 95% CI [0.320, 0.364].

Sham TMS Behavioural Analysis

The effects of adaptation without TMS were assessed using the sham TMS conditions. This ensured that any noise from the TMS coil was incorporated into the baseline measure. For the 4 Hz test condition, a mean accuracy decrease of 26% was seen when participants were adapted to 4 Hz compared to when they were adapted to 40Hz. For the 40 Hz test condition, a mean accuracy decrease of 22% was seen when participants were adapted to 40 Hz compared to when they were adapted to 4 Hz AM noise. A paired t-test showed no significant difference in level of adaptation in the matched cases; i.e. 4 Hz adaptor followed by 4 Hz test versus 40 Hz adaptor followed by 40 Hz test ($t(7) = 1.222$, $p = 0.261$).

GLMM analyses

The data were divided based on test AM rate and separate generalised linear mixed effects models with logit link functions (GLMMs) were fit to the two subsets. These models assume that the log-odds of the binomial response variable varies linearly. Results are presented in logits to aid interpretation as confidence intervals are symmetrical about the point estimate and each coefficient value directly represents the effect size. Using logits also preserves the effect direction represented by the sign of the coefficients. The coefficient for the baseline condition represents the overall mean intercept and the other coefficients represent the (population-level) difference from this baseline for each condition. For consistency, the baseline condition for both models was sham TMS with adaptation to 4 Hz AM.

Whilst assessments of statistical significance using conventional metrics such as p-values are difficult to perform with GLMMs due to the unknown denominator degrees of freedom required to calculate the F-statistic, confidence intervals can be computed using parametric bootstrapping (Halekoh and Højsgaard 2014). These 95% confidence intervals can be used to approximately assess statistical significance

at the 0.05 level. If a value of 0 is not contained within the upper and lower bounds of the confidence interval, then the result is approximately statistically significant using a type-I error rate of 5%. While there are clear issues surrounding the use and interpretation of dichotomous assessments of statistical significance (McShane et al. 2017), they are conventional and informative so the (approximately) statistically significant results have been indicated by an asterisk in the results tables.

GLMM analysis of 40 Hz test rate data

Results from this model are shown in Table 1 with discussed results indicated by an asterisk. Behavioural adaptation to 40 Hz AM had a clear negative effect on the 40 Hz test rate data, as shown by the negative *40Hz Adaptation* coefficient. This result replicates previous psychophysical work on selective adaptation to AM (e.g. Wojtczak and Viemeister 2005). TMS to the left hemisphere had a net positive effect on 40 Hz AM detection over both adaptation rates, as shown by the positive *Left Hemisphere TMS* coefficient. However, these main effects are confounded by a rate by hemisphere interaction, as seen in Figure 3. The negative *Left Hemisphere TMS x 40Hz Adaptation* interaction coefficient represents the differential effect that adaptation to 40 Hz AM had compared to 4 Hz adaptation, specifically in the left hemisphere TMS condition. As the baseline condition is 4 Hz AM with sham TMS, this interaction coefficient represents the net change from sham to left TMS and 4 Hz adaptation to 40 Hz adaptation.

GLMM analysis of 4 Hz test rate data

Results from this model are shown in Table 2 with discussed results indicated by an asterisk. Accuracy on the 4 Hz AM detection task was much lower when participants were behaviourally adapted to 4 Hz AM compared to when participants were

behaviourally adapted to 40 Hz AM. This is shown by the positive *40Hz Adaptation* coefficient; the only coefficient from the 4 Hz test rate model where the 95% CI did not cross zero, as shown in Table 2. This is consistent with the aforementioned psychophysical work that showed peak adaptation for matched adaptation and test rates (Wojtczak and Viemeister 2005). The chosen baseline condition explains the difference in direction for the adaptation effect between the two models; a decrease in accuracy is shown in the 40 Hz GLMM whereas an increase in accuracy is shown in the 4 Hz GLMM. The lack of a statistically significant TMS or interaction effect suggests TMS was unable to affect AM processing in the same way as with 40 Hz processing.

348 Discussion

349 The present study was designed to investigate whether TMS to auditory areas could
350 affect AM detection performance and if so, whether the induced behavioural changes
351 showed state-dependency and/or provided support for asymmetric accounts of aud-
352 itory processing. Three specific research questions were posed.

353 The first question asked whether AM detection could be affected by TMS to
354 auditory cortex. A significant effect of left hemisphere TMS was shown compared
355 to sham TMS, but only in the 40Hz AM detection condition.

356 The second question asked whether TMS effects showed state-dependency, i.e.
357 did behavioural adaptation have an effect on the direction or degree to which TMS
358 modulated performance on the task. In the conditions with left hemisphere TMS
359 and 40Hz AM detection, state-dependent TMS effects were found, though the change
360 in behavioural performance was not in the predicted direction; a facilitation of AM
361 detection was predicted in matched adaptation conditions, however in the matched
362 40 Hz condition, TMS caused a decrease in AM detection accuracy.

363 The final question asked whether any TMS effects were consistent with asym-
364 metric models of auditory processing, with directional predictions following the AST
365 hypothesis (Poeppel 2003). Left hemisphere stimulation was predicted to preferen-
366 tially modulate 40Hz AM detection whilst right hemisphere stimulation was pre-
367 dicted to preferentially modulate 4Hz AM detection. Left hemisphere stimulation
368 was shown to affect the detection of 40Hz AM, whilst no effect of right hemisphere
369 stimulation was shown on the detection of either 4 or 40Hz AM.

370 Effect of AM rate

371 Our results show that whilst TMS to the left hemisphere affected detection of 40Hz
372 AM, neither right nor left hemisphere TMS affected detection of 4Hz AM. Before
373 considering possible explanations for this difference, some potential confounds must

374 be addressed. The number of modulation cycles within the presentation period is
375 known to affect AM detection ability (Sheft and Yost 1990). The 500ms period
376 contained 2 cycles of AM in the 4Hz test condition compared to 20 cycles in the
377 40Hz test condition. To address this possible confound, detection difficulty was
378 calibrated separately for each AM rate and for each participant.

379 Several studies have shown that BOLD signal changes are both smaller and
380 less distributed in response to higher frequency AM compared to lower frequency
381 AM (Giraud et al. 2000; Harms and Melcher 2002). Therefore, the choice of TMS
382 target locations could also affect whether, and to what degree, processing of different
383 modulation rates would be affected by TMS. Cortical TMS targets were chosen based
384 on fMRI responses to 4Hz and 40Hz AM combined, contrasted over unmodulated
385 noise to avoid biasing the targets towards areas more specialised for processing either
386 rate.

387 The observation that TMS only affected 40Hz AM detection could be due to
388 the use of a different and possibly more robust mechanism for coding lower rates
389 of modulation (such as 4Hz). Evidence from multiple modalities has converged in
390 support of such an account where low and high frequency AM is coded by different
391 mechanisms. fMRI studies have found that lower frequency AM elicits a more
392 sustained response whilst higher frequency AM produces more phasic responses at
393 onset and offset of the stimulus, possibly representing a single auditory event (Giraud
394 et al. 2000; Harms et al. 2005). Direct cortical recordings using invasive intracranial
395 electrodes have also provided strong support for a shift in coding mechanism as AM
396 rate increases (Brugge et al. 2009; Nourski et al. 2013; Nourski 2017). Non-invasive
397 electrophysiological evidence shows that the balance of phase-locked (PL) and non
398 phase-locked (NPL) activity changes as AM rate increases; PL activity dominates
399 at lower rates whilst more NPL activity is observed with increasing AM rate (Tang
400 et al. 2016). The cutoff point for this transition from mostly PL to mostly NPL
401 activity is estimated to be 50Hz (above the rates studied here), but the amount of

NPL activity does differ between 4Hz and 40Hz. Though PL activity still dominates the response to 40Hz AM, Tang et al. (2016) found a significant increase in NPL activity over that measured for 4Hz AM. It is possible that this difference in coding mechanisms might contribute to the observed results. Any mechanism which relies on coding the onset and offset of a stimulus could be more susceptible to TMS than one reliant on sustained responses. If, for example, the single cortical event coding for the onset of 40Hz AM was disrupted, this may have a significant impact, particularly at short stimulus durations in which there is little time for the system to recover. In comparison, a sustained system where PL neurons fire in synchronisation with slower modulations would likely be more robust to a single disruptive event. Further, it would be biologically useful for the system that processes low-frequency AM it to be more robust to disruption due to its importance for speech intelligibility. This explanation is challenged however, by the classic finding that with sustained periods of auditory stimulation, peak PL responses are shown for 40Hz AM; the 40Hz auditory steady-state response (Galambos et al. 1981; Ross et al. 2000). Though PL and NPL activity is evident during 40Hz processing, the role and relative importance of each mechanism is not clear. The suggestion that TMS may differentially affect disparate neuronal coding mechanisms has important implications for the design of future TMS experiments and warrants further investigation.

Hemispheric differences

Before considering explanations of the changes in behavioural performance caused by TMS to the left and right hemisphere, we can first rule out several methodological confounds. Neither the distance to the TMS target, nor the accuracy with which TMS was delivered differed significantly between the two hemispheres or between test conditions. In addition, there was no significant correlation across subjects between task accuracy scores and the distance to target, suggesting that any distance effects can be discounted.

429 Previous research using transcranial direct current stimulation (TDCS) to invest-
430 igate auditory temporal resolution using a gap detection task has shown differential
431 susceptibility of the left and right hemispheres to stimulation. A detrimental effect
432 on performance was found exclusively when anodal TDCS was applied to the left
433 hemisphere (Heimrath et al. 2014). It is interesting that the current results accord
434 with this finding as there is evidence that gap detection tasks and estimation of the
435 temporal modulation transfer function (TMTF; using the method employed in this
436 study, though the full TMTF was not estimated here) are measuring different as-
437 pects of auditory temporal acuity (Shen 2014). Disruptive TMS effects on duration
438 discrimination have been shown exclusively for the right hemisphere (Buetti et al.
439 2008). However, these studies differ not only in both the nature of the behavioural
440 task, but also the nature of the stimulus. Whilst Buetti et al. (2008) used tonal
441 stimuli, Heimrath et al. (2014) and the current study use relatively broadband noise
442 stimuli. A question of interest is therefore whether the spectral nature of the stimu-
443 lus has an influence on hemispheric lateralisation of function and how this interacts
444 with the specific behavioural task under investigation.

445 **State-dependent effects**

446 The initial prediction for this study was that TMS combined with behavioural ad-
447 aptation at a modulation rate matched to the test modulation rate would lead to
448 an improvement in AM detection accuracy. Instead, an unexpected dissociation
449 was shown between performance on the 40Hz AM detection task in the matched
450 and un-matched adaptation conditions: a behavioural facilitation was observed in
451 the unmatched condition (4 Hz adaptation) whilst a reduction in performance was
452 seen in the matched condition (40 Hz adaptation). An overarching framework that
453 accounts for both online and state-dependent effects has recently been proposed
454 (Silvanto and Cattaneo 2017). It is possible to reconcile these results within this
455 framework, however not using a purely state-dependent TMS explanation. This

suggests that modifications made to the experimental design when converting it to investigate auditory function may have affected the nature of the disruption. The majority of state-dependent TMS experiments have used visual tasks involving brief *simultaneous* presentations of multiple stimuli with TMS pulses delivered on stimulus onset (Silvanto et al. 2007; Cattaneo and Silvanto 2008; Silvanto and Muggleton 2008). To account for the necessarily more temporally extended nature of auditory stimuli, modifications were required when designing this auditory state-dependent TMS paradigm. In each trial, an auditory adaptation period immediately preceded a 2-AFC decision, with TMS delivered just prior to the onset of the 2-AFC task. In matched adaptation trials, though the stimulation is delivered whilst the participant is adapted, it is actually delivered *during* AM processing at the target rate, therefore corresponding more closely to online TMS. The suprathreshold TMS would then be expected to impair performance as the neurons tuned to the target rate have been shifted into their inhibitory range (Silvanto and Cattaneo 2017: fig.1). This key timing difference could explain the ‘virtual lesion’ style detrimental TMS effects seen in the matched 40Hz condition.

In unmatched adaptation trials, participants received TMS during processing of one rate of AM and were subsequently tested at the other rate. Within this same overarching framework, two possible explanations exist that lead to a facilitation of behavioural performance. At the point at which TMS was delivered, neural populations responsible for processing the test rate would be suppressed relative to populations responsible for processing the adaptation rate. This would lead to test rate populations being in their facilitatory range when activated by the suprathreshold TMS, leading to behavioural improvements at detecting 40Hz AM (Silvanto and Cattaneo 2017: fig. 2). Alternatively, It is also possible that the neural populations that process 40Hz AM may have been adapted by the 4Hz AM. Maximal adaptation, as measured by decrease in detection ability, occurs when adaptor and test rates are

484 identical, however there is evidence for a graded decrease in adaptation as the dif-
485 ference between the two rates increases (Houtgast 1989; Bacon and Grantham 1989;
486 Wojtczak and Viemeister 2005). Based on the estimated shape of the modulation
487 filter with centre frequency of 40Hz, it may be expected that populations involved in
488 processing 40Hz would be adapted by exposure to 4Hz AM. Further, the estimated
489 shape of modulation filters with centre frequencies of 4 and 40Hz differs such that the
490 4Hz filter is much more narrow (5Hz bandwidth), suggesting an asymmetry where
491 populations optimised for coding 4Hz would not be adapted by exposure to 40Hz
492 AM, but populations optimised for coding 40Hz may still be adapted somewhat
493 by exposure to 4Hz AM (Dau et al. 1997b). Under this assumption, the outcome
494 in the unmatched condition would follow state-dependent TMS predictions, where
495 adaptation has suppressed the activity of 40Hz populations, shifting the inhibit-
496 ory/facilitatory range of these populations such that suprathreshold TMS leads to
497 behavioural facilitation. With the current dataset, it is not possible to dissociate
498 these two mechanisms, both of which would lead to an increase in performance for
499 40Hz AM detection.

500

501 Overall, the timing of TMS delivery is central to this explanation of the observed
502 results. The importance of this parameter has been previously noted (Silvanto and
503 Pascual-Leone 2008), with differential effects shown when pulses were delivered be-
504 fore and during task performance across different studies, with and without adapt-
505 ation. In online TMS studies, no adaptation is used and suprathreshold TMS is
506 delivered during the test stimulus, causing a decrease in performance. The current
507 study therefore demonstrates that TMS can cause either disruptive or facilitatory
508 effects on 40Hz AM detection depending on which AM rate is perceived during TMS
509 delivery. Further investigating how TMS at different timepoints affects AM detec-
510 tion will help to elucidate the mechanisms of this effect and improve the utility of
511 auditory TMS as an investigative tool.

512 **Conclusions**

513 This study showed, for the first time, that low-level mechanisms involved in AM
514 detection, a key component of speech processing, can be affected using TMS. This
515 important finding demonstrates that TMS can be a useful technique for investigating
516 low-level auditory processing mechanisms and opens the door to new research in
517 this area. It was also shown that the TMS effect on AM detection shows state-
518 dependency, i.e., the underlying state of the AM detection system when TMS is
519 delivered has a differential effect on the outcome. It was further demonstrated that
520 systematically modifying this underlying state using behavioural adaptation is an
521 effective way to increase the functional resolution of TMS and alter the nature of
522 TMS effects on AM detection. The results of this study provide support for the
523 importance of the left posterior superior temporal gyrus for processing 40Hz AM.
524 It also suggests that 4Hz AM may be encoded using a different mechanism that
525 is more robust to interference from TMS. This illustrates a potential limitation of
526 the method and would benefit from further investigation. Finally, in addition to the
527 direct implications for auditory processing, methodological considerations for the use
528 and interpretation of state-dependent TMS were discussed so that important factors
529 such as subtle timing and task manipulations are accounted for in future work. This
530 study demonstrated the utility of TMS as a new and potentially valuable tool for
531 furthering understanding of low-level auditory processing in health and disease.

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Figure 1: TMS session and trial layout. Time during the session runs from top to bottom. A given session used either a 4Hz or 40Hz behavioural adaptation stimuli and one of three TMS targets (sham, left or right). Each session began with the subject listening to 10 minutes of fully modulated noise at the session adaptation rate. A block of 150 experimental trials was then performed; 75 test trials were modulated at 4Hz and the remaining 75 at 40Hz. Each trial consisted of 6s of adaptation noise (at the rate chosen for the session). Dual-pulse TMS stimulation was locked to the end of the trial adaptation stimulus. A test trial immediately followed the TMS pulses and consisted of a 2-AFC task - subjects were asked to select which of two intervals contained an AM noise. The AM depth was set based upon the initial psychophysical data for the subject. After 150 trials, subjects listened to four minutes of “top-up” adaptation noise. This was followed by a second block of 150 experimental trials of identical layout to the first block.

Figure 2: fMRI TMS target localisation data from an example participant. Overlay shows statistically significant clusters of activation ($Z > 2.3$; $p < 0.05$) in bilateral pSTG/PT in response to a contrast of 4 and 40 Hz sinusoidally amplitude modulated broadband noise conditions (combined) over unmodulated noise. TMS targets are indicated by the crosshairs. Functional data is shown here on the MNI-152 template brain - targets were transformed back into individual participant co-ordinate space. Target locations for this participant in MNI-152 co-ordinate space are: Left: $-64, -22, 8$ and Right: $60, -20, 8$

Figure 3: Difference in raw AM detection scores between sham TMS and left or right hemisphere TMS conditions are expressed here as percentage changes. Each bar represents the mean within-subject difference across all participants. Error bars represent the 95% confidence interval.

	<i>Dependent variable:</i>			
	Accuracy	95% CI		
Baseline	1.018	0.669	1.378	
Left Hemisphere TMS	0.302	0.096	0.519	*
Right Hemisphere TMS	−0.068	−0.353	0.197	
40Hz Adaptation	−1.014	−1.371	−0.663	*
Left Hemisphere TMS x 40Hz Adaptation	−0.446	−0.712	−0.202	*
Right Hemisphere TMS x 40Hz Adaptation	0.099	−0.154	0.356	

Table 1: GLMM results for the 40 Hz AM test conditions. Accuracy values and 95% CIs are in logit units. ‘Baseline’ represents the mean in the baseline condition of sham TMS with 4 Hz behavioural adaptation. All other coefficients represent the difference from this baseline, i.e. the effect size. For example, the 40Hz Adaptation co-efficient shows the effect of 40Hz behavioural adaptation compared with the baseline of 4Hz behavioural adaptation; in this case (40Hz test trials), the co-efficient shows the expected negative direction, indicating a decrease in AM detection accuracy when participants were behaviourally adapted to 40Hz. An asterisk is used to mark results discussed in the main text.

	<i>Dependent variable:</i>			
	Accuracy	95% CI		
Baseline	0.438	0.182	0.719	
Left Hemisphere TMS	0.068	−0.167	0.298	
Right Hemisphere TMS	0.205	−0.036	0.422	
40Hz Adaptation	1.437	1.195	1.679	*
Left Hemisphere TMS x 40Hz Adaptation	0.023	−0.293	0.310	
Right Hemisphere TMS x 40Hz Adaptation	−0.137	−0.434	0.147	

Table 2: GLMM results for the 4 Hz AM test conditions. Accuracy values and 95% CIs are in logit units. ‘Baseline’ represents the mean in the baseline condition of sham TMS with 4 Hz behavioural adaptation. All other coefficients represent the difference from this baseline, i.e. the effect size. For example, the 40Hz Adaptation co-efficient shows the effect of 40Hz behavioural adaptation compared with the baseline of 4Hz behavioural adaptation; in this case (4Hz test trials), the co-efficient shows the expected positive direction, indicating an increase in AM detection accuracy when participants were behaviourally adapted to 40Hz. An asterisk is used to mark results discussed in the main text.