Auditory brainstem models: K_{V1} ion-channels and depleting end-bulb synapses improve spatial encoding in reverberation

Andrew Brughera[1,2‡*], Jason Mikiel-Hunter[1‡], Mathias Dietz[3], David McAlpine[1]

[1] Department of Linguistics, and the Australian Hearing Hub, Macquarie University, Macquarie Park, New South Wales, Australia

[2] Department of Biomedical Engineering, Boston University, Boston, Massachusetts, United States of America

[3] Medizinische Physik and Cluster of Excellence "Hearing4all", Universität Oldenburg, Oldenburg, Lower Saxony, Germany

[‡] A.B. and J.M.H. contributed equally to this work.

* Corresponding author: andrew.brughera@mq.edu.au

Abstract

Listeners perceive sound-energy as originating from the direction of its source, even as the direct sound is followed only milliseconds later by reflected sound from multiple different directions. Auditory neural adaptation, before spatial information is binaurally encoded in the brainstem, is suggested as a contributing mechanism, yet the form of sufficient adaptive mechanisms remains unspecified. Though a strong preference for spatial information conveyed in early-arriving sound is observed behaviourally and neurophysiologically, investigation by simultaneously recording from binaural brainstem neurons and their monaural input neurons while controlling adaptation is yet unrealised. Therefore, here we computationally model connected neurons across the auditory brainstem, exploring two biophysical mechanisms that can account for the brainstem's emphasis of early-arriving spatial information. Matching responses in the medial superior olive (MSO), of neurons encoding interaural time differences, we demonstrate that accurate localisation in reverberant environments is enhanced by realistic pre- and post-synaptic specialisations. Short-term synaptic plasticity at the inputs from auditory nerve fibres to spherical bushy cells (SBCs) in the ventral cochlear nuclei that project bilaterally to the MSO, and K_{V1} ion-channels in the SBCs and MSO neurons, promote encoding of reliable spatial information, by suppressing responses to late-arriving sound, particularly at frequencies where reverberant sound is relatively intense in outdoor environments. Suiting weak reverberation outdoors at very low sound frequencies, weak K_{V1} activity at 200 Hz promotes accurate localisation. Applied to the lateralisation of human speech near 600 Hz in a virtual reverberant room, identical synaptic depression and strong K_{V1} activity at this higher frequency enhance correct, over spurious, localisation cues at the earliest stages of spatial processing.

Author Summary

Aurally locating a talker in a reverberant room is often challenging for hearing-impaired listeners. Sound arriving directly from the talker isn't easily distinguished from reverberant sound reflecting off walls milliseconds later. Nevertheless, normal-hearing listeners easily localise sound-sources, aurally "glimpsing" the reliable spatial information of direct sound during early, rising portions of modulated sounds, while subconsciously ignoring later-arriving, confounding information corrupted by reverberation. Understanding the successful underlying mechanisms may suggest approaches to improve auditory spatial information provided to listeners with hearing aids and cochlear implants. In the auditory brainstem, binaural neurons of the medial superior olive (MSO) preferentially respond to early-arriving spatial information. As simultaneous recordings from MSO neurons and their monaural input neurons while controlling adaptation remain unrealised, to understand the contributing mechanisms, here we identify and computationally demonstrate two mechanisms that suppress responses to late-arriving sound, ultimately emphasising early-arriving sound, and enhancing the localisation of talkers despite reverberation: synaptic depletion in the bilateral cochlear nuclei that drive the MSO, and K_{V1} ion-channels which support the encoding of spatial information in MSO neurons. Our models reflect the frequency-dependent behavioural emphasis of reliable, early-arriving auditory spatial information, demonstrating brain mechanisms that suppress unreliable spatial information by spectro-temporally opposing typical outdoor reverberation.

Introduction

Sound propagating directly from its source to a listener's ears is typically followed milliseconds later by multiple reverberant copies arriving from different directions (Fig. 1). Despite this mixture of direct and reflected sound pressure generating non-stationary spatial information in the binaural cues—the interaural time difference (ITD) and interaural intensity difference (IID)—listeners typically perceive a sound as punctate, and originating from the direction of its source. Facilitating 'cocktail party listening' – attending to a single talker against a background of many competing voices – perception of the true source location can persist even when the intensity of reflected sound matches or exceeds that of the early-arriving, direct sound. [1–3]

Figure 1. Reverberant copies of direct speech produce confounding binaural cues. (A) Anechoic speech stimulus 'church' (direct sound, without reverberation), spoken at 70 dB SPL by a female talker located +30° to the right and front of a virtual listener. Spectrogram shows speech energy <1 kHz at left ear. Gammatone filters centred at 200 Hz (light grey) and 600 Hz (dark grey) show effects of cochlear filtering on speech waveforms in the left (blue) and right (red) ears. Instantaneous ITDs (light/dark grey) (restricted to ±700us, human physiological range) were consistently near +363 μs. (**B) Reverberant speech stimulus** including direct speech plus two simulated reflections from listener's left, the first from -65° delayed by 4 ms, and the second from -130° delayed by 8 ms. Reverberant copies increased the energy at the left ear (note the generally brighter spectrogram above 400 Hz). Reverberant energy extends into the quiet pause between the vowel and final consonant (0.45-0.55 ms), generating rapidly varying instantaneous ITDs (also restricted to ±700us), along with conflicting ILD cues in the 600-Hz channel.

Neural correlates of ‘echo-suppression’ are observed in the ascending auditory pathway, from auditory nerve and brainstem, to midbrain and primary auditory cortex. The brainstem emphasises early-arriving sound at both ears, as neurons of the medial superior olive (MSO) perform binaural coincidence detection. Driven bilaterally by the left and right auditory nerve via bushy cells of the ventral cochlear nuclei, MSO neurons encode spatial information through their sensitivity to ITDs conveyed in the temporal fine structure (TFS) of low-frequency (< 1500 Hz) sounds. The resulting responses of MSO neurons tuned to ITD are strongest during rising sound-energy. Adaptation in monaural projection pathways to binaural MSO neurons is believed to contribute, yet specific mechanisms for the emphasis of early-arriving direct sound in these neural pathways remain to be identified. [4–8]

Behavioural emphasis of early-arriving ITD information is frequency dependent [9]: for amplitude-modulated 600-Hz sounds, listeners are more sensitive to ITDs conveyed during the rising-energy portion than they are to ITDs at the energy peak; this is not the case at 200 Hz, where listeners are equally sensitive to ITDs conveyed during rising and peak energy, and where, in outdoor settings, reverberant energy can be 20 dB less intense at 200 Hz than at 600 Hz [10]. For both frequencies, listeners are least sensitive to ITD during falling sound-energy, when direct sound is most likely to be corrupted by reverberation. These data suggest that spatial auditory brain mechanisms transmit reliable information, and suppress unreliable information, accounting for natural frequency-profiles in reverberant energy which decrease below 1500 Hz.

Noting the unavailability of simultaneous recordings from the MSO and cochlear nuclei with external control of adaptation, here we apply a nonlinear, computational brainstem model to explore two cooperative biophysical mechanisms for the frequency-dependent emphasis of

ITD during rising and peak sound-energy: (i) short-term synaptic plasticity (synaptic depression) at the Endbulbs of Held synapses between auditory nerve fibres and spherical bushy cells (SBCs) in the ventral cochlear nuclei [11–14]; and (ii) voltage-gated, low-threshold potassium (K_{V1}, K_{LT}) ion channels in MSO neurons [15–18] and in the SBCs [19] projecting bilaterally to the MSO. We test whether these biophysical features suppress responses to late-arriving sound, and support the emphasis of sensitivity to ITDs conveyed in early-arriving sound that is observed in single MSO neurons [4]. Then, with our nonlinear model, and a linear spiking model [20] extended to populations of MSO neurons in the left and right brain hemispheres, we explore brainstem properties consistent with the stronger weighting of ITD information conveyed during rising energy at 600 Hz—a frequency with higher reverberant energy—compared to 200 Hz, where reverberant energy is less intrusive.

Our hemispheric MSO model then probes a possible link between relative weighting of spatial information during rising energy, and correct lateralisation of natural speech in realistic acoustic environments (the “Haas effect”) [3]. We evaluate monaural synaptic depression prior to binaural interaction, in promoting correct, unambiguous judgements in the laterality of natural speech in a simulated reverberant space with direct sound and early reflections off virtual walls [4]. For the 600-Hz channel investigated, achieving unambiguous, correct lateralisation would suggest a dominance of ITD information conveyed during rising sound-energy, which facilitates correct lateralisation by emphasising ITD cues of sound arriving directly from its source, over the confounding ITD cues of its reflected copies.

Results

A nonlinear brainstem model with synaptic depression and K_{V1} activity reproduces the frequency-dependent emphasis of spatial information during rising and peak sound-energy

We first explored the extent to which synaptic depression at model SBCs in the cochlear nuclei accounts for the emphasis of ITDs during the rising energy of modulated sounds in a model MSO neuron (Fig. 2B). We did so, employing amplitude-modulated binaural beats (AMBBs) [2,4], in which binaurally presented tones of a slightly different frequency are modulated in amplitude at a rate equal to the difference in frequency across the two ears. This generates a stimulus in which each cycle of rising and falling sound-energy contains a full cycle of interaural phase disparities. AMBBs (Fig. 2A) centred at 600 Hz, with modulation rates 4 to 64 Hz, were presented to a standard model of peripheral auditory processing [21,22], which drove a nonlinear model of brainstem neurons. The model of peripheral auditory processing includes 24 adapting auditory nerve fibres: twelve each in the left and right ears, with characteristic frequency (CF) 600 Hz. (CF is the frequency at which a neuron has its lowest threshold in sound pressure level, SPL, for an action potential; CF is inherited from the frequency-tuning of the inner ear, and the resulting CFs of auditory nerve fibres that distally drive a neuron.) Each of three distinct model auditory nerve fibres projects an ipsilateral, uniformly depressing (u = 0.5) [23], excitatory synaptic input to one of the eight (four left, and four right) model SBCs. Each model SBC projects a non-depressing, excitatory synaptic input to the multi-compartment model MSO neuron. The model SBCs and MSO neuron are Hodgkin & Huxley models [24], with circuit elements that represent membrane ion-channels, including K_{V1} [25–27].

Figure 2. Amplitude-modulated binaural beats (AMBBs) [2] **and the nonlinear brainstem model: (A) AMBBs** in which AM rate is equal to binaural-beat frequency (difference between frequencies at right and left ears). Presented via headphones, interaural phase difference (IPD) cycles through 360˚ at the same rate as AM. *Start-IPD* (the IPD at zero amplitude) is a free parameter. Shown with right-carrier 616 Hz, left-carrier 584 Hz, AM 32 Hz, and *start-IPD* 270˚ (right channel trailing by 90˚), resulting in zero IPD at the midpoint of rising-amplitude. **(B) Nonlinear brainstem model** for an MSO neuron and its excitatory inputs with synaptic depression in the cochlear nuclei. AMBBs drive a model for bilateral auditory nerve fibres [21,22] projecting individually depressing synapses [23] (u = 0.5) onto model spherical bushy cells (SBCs) in the cochlear nuclei [26], which in turn project bilaterally to the model MSO neuron (best-ITD = 0). The best-ITD of a neuron is the ITD of highest spike rate, typically measured with unmodulated stimuli of equal amplitude at the two ears. The nonlinear model MSO neurons of this study have best-ITDs equal to zero. **(C) Sub-compartment** in the nonlinear brainstem model (see Methods).

Beginning without synaptic depression, a nonlinear model with very strong, non-depressing, supra-threshold synapses in the cochlear nuclei, originally developed to generate strong, sustained responses [28] consistent with strong ITD sensitivity in the MSO for unmodulated pure-tone stimuli [29], produced only slight adaptation in the spike rates of its model SBCs (Fig. 3A, top row). Without synaptic depression, the model MSO neuron responded strongly to zero ITD, its best-ITD, across the amplitude modulation (AM) cycle: most strongly at peak sound-energy, slightly less strongly during rising energy, and less strongly during falling energy (Fig. 3A, lower three rows; in a 3-way comparison of spike counts for best-ITD during rising vs. peak vs. falling energy, $p < 10^{-9}$ at each modulation frequency). The slightly larger suppression

in responses to best-ITD during falling energy is supported by adaptation in the auditory nerve model, and K_{V1}-based refractory effects in the model SBCs and MSO neuron. (AMBB stimuli had increasing IPD (positive beat direction): “best-ITD during rise” denotes start-IPD = 270°; “best-ITD at peak” denotes start-IPD = 180°; and “best-ITD during fall” denotes start-IPD = 90°.)

Figure 3. AMBB cycle histograms for nonlinear model brainstem neurons acoustically stimulated by sound frequencies centred at CF **600 Hz: (A) Without synaptic depression**, auditory nerve to SBC synapses were strongly supra-threshold. Model SBCs adapted slightly. Model MSO neuron responded to best ITD strongly at peak sound-energy, and slightly but consistently less strongly during rising and falling energy (3-way comparisons, $p < 10^{-9}$). The synchrony index—a measure of temporal alignment of spikes over the AM cycle (see Methods)—ranged from 0.133 at 4 and 64 Hz to 0.161 at 16 Hz for model SBCs, and from 0.595 (64 Hz, best-ITD at peak) to 0.794 (16 Hz, best-ITD during fall) for the model MSO neuron (Rayleigh statistic, $p < 0.001$ in all cases). **(B) With synaptic depression in the cochlear nuclei**, the auditory nerve to SBC synapses were supra-threshold at full strength. Model SBCs adapted. Model MSO neuron responded to best ITD strongly during rising energy; weakly to moderately at peak; and weakly during falling, energy (3-way comparisons, $p \leq 0.003$). Synchrony-indices to AM for model SBCs ranged from 0.0485 at 4 Hz to 0.174 at 32 Hz; for model MSO neuron, from 0.450 (64 Hz, best-ITD during fall) to 0.814 (64 Hz, best-ITD during rise) (Rayleigh statistic, $p < 0.01$ for model SBCs at 4-Hz AM, otherwise $p < 0.001$). *Definitions:* Grey silhouettes: AM envelope. Black lines: static IPD functions. Best-ITD = 0. Best-ITD during rise: *start-IPD* = 270°. Best-ITD at peak: *start-IPD* = 180°. Best-ITD during fall: *start-IPD* = 90°.

187 Next, we introduced synaptic depression in supra-threshold synapses of model SBCs,
188 producing adaption in their spike rates (Fig. 3B, top row). This adaptation followed a similar
189 time-course across modulation rates, such that at low-to-moderate rates (4 to 16 Hz) most of
190 the adaptation occurred by the peak in the AM cycle, and at moderate-to-high rates (16 to 64
191 Hz) gradual adaptation is evident across much of the AM cycle. Consistent with physiological
192 and behavioural data at 600 Hz [4,9], the model MSO neuron responded to its best-ITD
193 strongly during rising amplitude, weakly to moderately (and broadly) at peak energy, and only
194 weakly during falling energy (Fig. 3B, lower three rows; in this 3-way comparison of spike
195 counts, $p \leq 0.003$ at each modulation frequency). Adapting similarly to the model SBCs, the
196 model MSO neuron had higher spike counts for best-ITD during rising energy vs. peak energy
197 at 4- to 16-Hz modulation ($p < 0.02$), and during peak vs. falling energy at 16- to 64-Hz
198 modulation ($p < 0.0025$).

199 Thus, consistent with behavioural data at the same, 600-Hz, sound frequency, a model that
200 includes synaptic depression between the auditory nerve and cochlear nuclei that drove
201 bilateral inputs to the MSO neuron, responds preferentially to ITDs during the rising energy of
202 sounds. Without this synaptic depression, the preference for spatial cues during rising sound-
203 energy is absent, suggesting a critical role for monaural input pathways to binaural neurons in
204 emphasising spatial information that is likely to be reliable in reverberant listening conditions.

205 Sensitivity to ITDs conveyed in the temporal fine structure (TFS) of sounds is subject to highly
206 specialised biophysical constraints, constraints that are generally thought to hold for sound
207 frequencies up to 1400 Hz (higher in some non-human species), covering the range over
208 which ITDs in the TFS are discriminable. Therefore, given the emphasis to ITDs during the
209 rising energy of modulated sounds at 600 Hz—concordant with perceptual and brain-imaging

data obtained at a similar frequency [2]—we might expect a similar emphasis at the lower sound-frequency of 200 Hz. Nevertheless, despite our model implementing identical biophysical elements, we observed a very different pattern of results at 200 Hz compared to 600 Hz. These differences are reminiscent of behavioural data [9]: at 600 Hz, human ITD-sensitivity is strongest during rising energy with progressively less ITD sensitivity for peak and falling energy; but at 200 Hz, ITD sensitivity is strong for both peak and rising energy, and again weak for falling energy.

Employing the same model with monaural depressing synapses, identical to those which emphasised ITDs during the rising energy at 600 Hz, we assessed the relative emphasis of ITD cues in the modulation cycle of a 200-Hz AMBB stimulus for the modulation rates of 8 and 20 Hz employed by Hu et al. [9]. At 200 Hz, the model SBCs showed slight adaptation in spike rate across the AM cycle (Fig. 4A, top row), less adaptation than at 600 Hz. Spike counts in the model MSO neuron (Fig. 4A, lower three rows) matched the patterns of significance in human ITD-detection for AM stimuli at 200 Hz [9]: spike counts were slightly higher but not significantly for best-ITD during peak vs. rising energy, and spike counts were significantly different (higher) only for best-ITD at peak energy vs. falling energy ($p = 0.0079$ for modulation at 8 Hz; $p = 0.0014$ for modulation at 20 Hz).

Figure 4. AMBB cycle histograms for nonlinear model brainstem neurons stimulated by frequencies centred at CF **200 Hz**. Same synaptic depression and model SBCs as in Fig. 3B, adapted less at 200 Hz. **(A) Same fast model MSO neuron** as in Fig. 3B: spike counts were not significantly different for best-ITD during rising vs. peak energy, and were higher for best-ITD at peak energy vs. falling energy ($p < 0.01$). Synchrony-indices to AM for model SBCs ranged from 0.0762 at 8 Hz to 0.109 at 20 Hz; model MSO neuron from

0.433 (20 Hz, best-ITD during fall) to 0.807 (8 Hz, best-ITD during rise) (Rayleigh statistic, $p < 0.001$). **(B) Moderate-speed model MSO neuron:** spike counts were not significantly different for best-ITD during rising vs. peak energy, and were lower for best ITD during falling energy ($p < 0.005$). *Definitions:* Grey silhouettes: AM envelope. Black lines: static IPD functions. Best ITD = 0. Best-ITD during rise: *start-IPD* = 270°. Best ITD at peak: *start-IPD* = 180°. Best ITD during fall *start-IPD* = 90°. Synchrony-indices to AM for the model MSO neuron ranged from 0.825 (20 Hz, best-ITD during fall) to 0.888 (20 Hz, best-ITD during rise) (Rayleigh statistic, $p < 0.001$)

Noting recent evidence of heterogeneity in membrane speeds in the very low-frequency region of MSO [30], we applied AMBBs at 200 Hz to our nonlinear brainstem model, now modified with a moderate-speed model MSO neuron having slower dendritic and somatic membranes, derived by dividing membrane conductance values by three. The identical model SBCs again adapted less (Fig. 4B, top row) than at 600 Hz. Synaptic strength in this moderate-speed model MSO neuron was divided by two for low spike rates for best-ITD during falling energy, while retaining moderate spike rates for best-ITD during rising and peak energy (Fig. 4B, lower three rows). The moderate-speed MSO neuron then produced very few spikes at ITDs distant from best-ITD, yielding spike counts for best-ITD at peak energy that were equal to, or slightly less than, spike counts for best-ITD during rising energy. The moderate-speed model MSO neuron slightly augmented patterns of significance in human ITD-detection [9]: spike counts were not significantly different for best-ITD during rising vs. peak energy, and were significantly lower for best-ITD at falling energy (8-Hz modulation: rise vs. fall, $p = 4.08 \times 10^{-05}$; peak vs. fall, $p = 0.0049$; 20-Hz modulation: rise vs. fall, $p = 1.53 \times 10^{-09}$; peak vs. fall, $p = 1.53 \times 10^{-09}$).

255 Our nonlinear brainstem model accounts for the emphasis of rising energy in ITD encoding by
256 MSO neurons at 600 Hz, and is consistent with the shift from very strong human ITD-sensitivity
257 during rising energy at 600 Hz, to strong sensitivity during both peak and rising energy at 200
258 Hz, and with weaker sensitivity during falling energy at both frequencies. As the stimulus
259 frequency is reduced from 600 to 200 Hz, the reduction in suppression at the peak of the AM
260 cycle is likely due to decreased activation of K_{V1} channels at the lower frequency, from the
261 inherently longer quiet periods between intense input spiking [31,32].

262 *A hemispheric-difference model including synaptic depression correctly*
263 *lateralises amplitude-modulated stimuli with temporally specific ITDs*

264 To test whether synaptic depression in combination with heterogeneous neuronal properties is
265 consistent with the behavioural observations of Hu et al. [9], we employed a neural spiking
266 model of both brain hemispheres, incorporating linear model neurons in the bilateral cochlear
267 nuclei and MSOs [20], to generate a neuro-metric measure of lateralisation. Following the
268 model concept of Dietz et al. [33], two hemispheric channels ('left' and 'right') comprised
269 distinct MSO model neuron populations (50 neurons each) whose inputs from 'contralateral'
270 cochlear nucleus were delayed by 0.125 cycles of interaural phase difference (IPD, equal to
271 ITD x frequency) [34] such that they spiked preferentially for sounds arriving from contralateral
272 spatial locations (Fig. 5). The difference in spike rate between hemispheres, calculated (in 5-
273 ms epochs) as a signed d', was then used as a neuro-metric measure of lateralisation (see
274 Methods) [34,35]. A uniform synaptic depression (u = 0.55) [23] was implemented
275 independently at each synapse between an auditory nerve fibre and its target SBC of the
276 cochlear nucleus. Sinusoidally amplitude-modulated (SAM) tones, with non-zero, positive ITDs
277 positioned within the rising, peak, or falling phases of the AM cycle as per Hu et al. [9], and see

above, were presented to the linear model (Fig. 6). As in the behavioural study, the tone frequency (200 Hz or 600 Hz) and the AM rate (8 Hz or 20 Hz) were varied, as was the proportion (20% or 40%) of the AM cycle containing a non-zero ITD.

Figure 5. Overview of the hemispheric-difference model consisting of two MSO populations (red—left MSO and blue—right MSO), each containing fifty linear, single-compartment model neurons, with either fast or slow resonant properties [20]. Each MSO neuron model receives four excitatory inputs 'bilaterally' from linear, single-compartment SBC model neurons in the CN. Three independently-simulated, individually-depressing and medium-spontaneous-rate auditory nerve fibres [21] provide excitatory drive to each SBC model neuron.

Figure 6. Lateralisation by the linear, hemispheric-difference model at 200 Hz and 600 Hz, each with 8-Hz AM. (A&B) At 200 Hz, both Slow (A) and Fast (B) MSO models correctly lateralised +300 μs ITDs (top row, black) to the right, based on d'>1 in any 5ms bin (red vertical bands), most often at peak (middle column) of the AM cycle (grey silhouettes) compared to rising (left column) and falling (right column) phases (Slow MSO: Rising, 7 bins; Peak, 12 bins; Falling, 2 bins. Fast MSO: Rising, 3 bins; Peak, 4 bins; Falling, 1 bin); d' (bottom rows, black) is a difference in mean spike rates between left (top rows, red) and right (top rows, blue) MSO populations, normalised by variance. The same adapting inputs are used for both MSO neuronal speeds, therefore more correct lateralisations overall by the Slow MSO is a result of its slower integration. **At 600 Hz (C)** introducing +150 μs ITD (top row, black) produced strong onset ITD sensitivity in the Fast MSO during rising phase (left column) that decreased across the AM cycle (Fast MSO: Rising, 12 bins; Peak, 5 bins; Falling, 1 bin).

At 600 Hz, MSO neurons with fast resonant properties, i.e. akin to the nonlinear model with 100% K_{LT} (K_{V1}) conductance, demonstrated a strong sensitivity to the onset ITD, as indicated by the increased number of instances when the AM stimulus containing a (right-leading) +150 µs ITD in its rising-energy phase was correctly lateralised [d' > 1 in any bin was considered a correct lateralisation of a signal from the 'right' (Fig. 6 *pink vertical bands*)]. This ITD sensitivity decreased across the AM cycle reaching a minimum when non-zero ITDs were restricted to the falling-energy phase (Fig. 6 *bottom row*). The trend for onset dominance at 600 Hz was true for both modulation rates (8 Hz and 20 Hz) and when the proportion of the AM cycle containing non-zero ITDs was either 20% or 40% (Fig. 7 *right column*). Notably, in all three portions of the AM cycle, the number of correct lateralisations decreased as the proportion of an AM cycle containing a non-zero ITD was decreased from 40% to 20% (Fig. 7 *right column*, blue).

Figure 7. Summarising correct lateralisations of SAM stimuli by the hemispheric-difference model. Mean (±SEM) time correctly lateralised per presentation (number of correct lateralisations * bin duration / 25 presentations) by either Slow MSO neurons at 200 Hz (left column) or Fast MSO neurons at 200 Hz and 600 Hz (middle and right columns respectively), for modulation rates of 8 Hz (top row) and 20 Hz (bottom row). ITDs were inserted into either 20% (blue dotted) or 40% (black solid) of the AM cycle during Rising, Peak, or Falling energy. At 600 Hz, the Fast MSO displays dominant ITD weighting at onset that decreased significantly across AM cycle (2-way ANOVA, interaction of AM cycle phase x Percentage ITD insertion: 8-Hz AM, $F(2,48) = 8.310$, $p = 0.001$; 20-Hz AM, $F(2,48) = 50.098$, $p = 0.0001$). At 200 Hz, the Fast MSO showed equal or better ITD sensitivity at Peak compared to Rising energy (2-way ANOVA, interaction of AM cycle

phase x Percentage ITD insertion: 8-Hz AM, $F(2,48) = 7.83$, $p = 0.001$; 20-Hz AM, $F(2,48) = 36.01$, $p = 0.0001$). Slow MSO generated more correct lateralisations than Fast MSO (2-way ANOVA, interaction of AM cycle phase x Neuron Type: 8-Hz AM, $F(2,48) = 18.82$, $p = 0.0001$; 20-Hz AM, $F(2,48) = 13.12$, $p = 0.0001$) with equal or augmented ITD sensitivity at Peak for 40% non-zero ITD (Paired two-tailed T-test, Mean Peak – Rising, N = 25: 8-Hz AM, $t(24) = 2.21$, $p = 0.037$; 20-Hz AM, $t(24) = 2.21$, $p = 2.37 \times 10^{-4}$). Correct lateralisations also increased as the percentage of AM phase containing non-zero ITD was raised from 20% to 40% (3-way ANOVA, main effect of Percentage ITD insertion: Fast MSO, $F(1,24) = 418.78$, $p = 0.0001$; Slow MSO, $F(1,24) = 285.622$, $p = 0.0001$)

When an amplitude-modulated 200-Hz tone (with a right-leading, non-zero ITD of +300 μs) was presented to the fast MSO model, the onset dominance observed at 600 Hz was replaced by an increased weighting of ITD cues towards the peak of the AM cycle (Fig. 6). Indeed, the frequency of correct lateralisations at the peak of AM cycles was either equal to (8-Hz AM stimuli) or higher (20-Hz AM stimuli) than that observed at corresponding onset phases (Fig. 7 *middle column*). As at 600 Hz, reducing the proportion of the AM cycle containing a non-zero ITD from 40% to 20% also generated fewer correct lateralisations across all AM phases (Fig. 7 *middle column*, blue). Whilst the fast-resonant MSO model could reproduce behavioural trends observed by Hu et al. [9] at both carrier frequencies, it generated fewer correct lateralisations overall at 200 Hz (Fig. 7 *middle* and *right columns*). We therefore presented the same 200-Hz carrier stimulus to the linear model MSO neurons with slower, less resonant membrane properties (Fig. 6). This generated a higher number of correct lateralisations overall, while maintaining, or even augmenting, the maximum weighting of ITD at the peak AM energy in all conditions tested (Fig. 7 *left column*).

Our linear model, therefore, suggests that a slower, more integrative MSO neuron may assist lateralisation in lower-frequency channels, in particular by extending the extraction of ITD information towards peak energy in the AM cycle, where human ITD detection is best when comparing at 200 Hz across the AM cycle [9]. Additionally, our model qualitatively matched the behavioural data by demonstrating a higher propensity to lateralise stimuli of either frequency when 40% vs. 20% of the AM cycle contained a non-zero ITD.

Synaptic depression improves the hemispheric-difference model's ability to lateralise speech in artificial reverberation

If neural adaptation prior to binaural integration contributes to accurate source localisation, we would expect it to aid lateralisation of speech in a reverberant room, by emphasising ITD cues associated with direct sound over reverberation (Fig. 1 *far left*) [4]. Speech signals were presented to the neural model of lateralisation under simulated anechoic (non-reverberant) and reverberant conditions. We then observed whether the model correctly lateralised the side to which the source was located in the presence or absence of synaptic depression in SBCs of the cochlear nuclei.

In the anechoic condition (Fig. 8A), a word token ('church') was presented to the non-adapting linear model from a virtual location 1 metre away from the target and 30 degrees to the right of the midline. The speech waveform—gammatone-filtered at 600 Hz (Fig. 8A *top row*)—was more intense at the right ear (red), and led the left-ear signal (blue) by an average ITD of +363 μs (Fig. 8A *top row*, dark grey). This generated a larger response from model neurons in the 'left' MSO (Fig. 8A *middle row*) and multiple bins throughout the speech token where d' values were > 1 (Fig. 8A *pink vertical bands*), indicating that the talker was correctly lateralised to the right in the non-adapting, linear model.

Figure 8. Lateralisation of 'anechoic' and 'reverberant' speech stimuli by the hemispheric-difference model (fast MSO, 600-Hz channel) with and without synaptically adapting inputs from the auditory nerve to the cochlear nucleus: (A) Anechoic stimulus is correctly lateralised to the right (pink vertical bands) for long periods independently of non-adapting (left column) or adapting (right column) synaptic inputs. Dry speech stimulus gammatone-filtered at 600 Hz with instantaneous ITDs (top row), mean firing rates of left (middle row, red) and right (middle row, blue) MSOs and d' neuro-metric (bottom row) are displayed. **(B) Reverberant stimulus** requires adapting synaptic inputs (right column) for correct lateralisations alone (pink vertical bands). Non-adapting synaptic inputs to the cochlear nuclei produced both correct (left column, pink vertical bands) and incorrect lateralisations (left column, light blue vertical bands) due to reverberant stimulus' highly variable ITDs and confounding ILDs (top row). The inclusion of synaptic depression from the auditory nerve to the cochlear nuclei (using the same auditory nerve simulations) removes all incorrect lateralisations. Remaining correct lateralisations correspond with stimulus onsets (right column, pink vertical bands). **(C) Quantifying incorrect lateralisations with non-adapting and adapting synaptic inputs** (same auditory nerve simulations for both) over a hundred presentations of the reverberant speech stimulus. Synaptic depression produces a five-fold decrease in incorrect lateralisations ($N = 100$, $t(99) = 9.51$, $p = 1.31 \times 10^{-15}$, two-tailed paired T-test).

In the reverberant condition, the same word token was presented to the non-adapting linear model from the same angle and distance, however it was also followed by two delayed copies generated by early reflections off virtual walls added behind, and to the left of, the listener (Fig. 1B *far left*). This mixture of sound arriving direct from the source and early reflective copies led

to a more complex waveform (including a more intense signal at the ‘left ear’ (direct-to-reverberant ratio: -4dB; mean ILD: -3 dB)) whose running ITDs fluctuated between extremely large positive and negative values, culminating in an average ITD of +711 μs, a value outside the human physiological range. Although the resulting d’ output exceeded 1 in eleven epochs coinciding with waveform onsets (Fig. 8B, *left*, *pink vertical bands*), it was also briefly lower than -1 in the opposite direction during three intermediate epochs (Fig. 8B, *left*, *blue vertical bands*), indicating a potentially ambiguous left-right localisation output.

We then increased adaptation by introducing synaptic depression to the monaurally driven inputs from auditory nerve fibres to the cochlear nuclei of the linear model, and presented the same reverberant stimulus (Fig. 8B) as in the previous condition. Despite the potentially confounding ITD (and ILD) cues (Fig. 8B *top row*), adding adaptation in the monaural input pathways enhanced the performance of the binaural model MSO neurons, and generated correct lateralisations of the true source to the right: the d’ output exceeding 1 in six time bins without ever crossing below -1 (Fig. 8B *bottom row, right*). When the number of incorrect lateralisations was tallied over a hundred presentations of the reverberant stimulus (Fig. 8C), incorrect lateralisations were observed five times less frequently when synaptically depressing auditory nerve inputs were included in the linear model (mean incorrectly lateralised time for non-depressing synaptic inputs = 6.75 ± 0.50 ms/presentation vs. mean incorrectly lateralised time for depressing synaptic inputs = 1.3 ± 0.24 ms/presentation). This neuro-metric profile agrees with the psychoacoustic percept as has been previously described for similar word tokens [4], suggesting that synaptic adaptation helps to lateralise ethological sounds in reverberant environments.

Discussion

The brainstem suppresses responses to late-arriving reverberant sound in neural pathways that encode spatial cues

The ability to localise the source of a sound in reverberant environments, where reflections from acoustically opaque surfaces can degrade the accuracy of auditory spatial cues, is critical to prey and predator alike, and important for communication in human listeners. To explore the contribution of the brainstem to sound-source localisation, noting the unavailability of simultaneous recordings from the MSO and cochlear nuclei with external control of adaptation, we here apply physiologically realistic models of connected neurons across the auditory brainstem. We find that accurate localisation in reverberation is enhanced by both synaptic depression at spherical bushy cells (SBCs) in the ventral cochlear nucleus that project bilaterally to the medial superior olive (MSO, a site of primary binaural integration)—as well as by K_{V1} channels in the cochlear nuclei and the MSO that activate more strongly at relatively higher sound-frequencies. We show that these mechanisms account for the observed ability of MSO neurons to respond preferentially to ITDs conveyed during the early, rising-energy portion of low-frequency sounds near 600 Hz [4]. Reflecting the perception of normal-hearing listeners at 500 Hz [2], our models successfully glimpse the ITD cues conveyed in the temporal fine structure during the rising portion of the AM cycle, suppressing spatial information conveyed in all later portions of the AM cycle, including the portion with highest energy. Whilst relatively weak synaptic depression in the MSO may also contribute, preliminary modelling without synaptic depression in the cochlear nuclei showed that stronger synaptic depression in the MSO disrupted ITD sensitivity without sufficiently emphasising early-arriving spatial information.

Suppression by K_{V1} channels opposes typical frequency-profiles of reverberant energy in natural outdoor scenes

K_{V1} channels are known to enhance synchrony to sound in bushy cells of the anteroventral cochlear nuclei [28], and support ITD sensitivity in the MSO [15]. Our results suggest that K_{V1} channels also underlie the frequency dependence of ITD detection performance, observed behaviourally when ITDs are applied to different segments of the AM cycle [9]. Intrinsic K_{V1}-channel properties, that decrease K_{V1} activation more during the longer quiet periods that occur between periodic bursts of intense input spiking at lower stimulus frequencies [31,32], are likely contributing mechanisms for the shift from very strong human ITD-sensitivity during rising energy at 600 Hz, to strong sensitivity during both peak and rising energy at 200 Hz, with weaker sensitivity at both frequencies during falling energy when direct sound for accurate source localisation is most likely to be corrupted by reflected sound.

Natural outdoor acoustics appear to have influenced brain mechanisms that suppress responses to reverberation. In many outdoor environments, including rural forests and fields, and urban streets, reverberation-time ('T60'—the time for reverberant energy to fall by 60 decibels) decreases as sound frequency decreases below 1500 Hz [10]. As reverberation times decrease to a minimum near 200 Hz, K_{V1} activity independently decreases [31,32], yet remains highly effective in suppressing late-arriving sound at 500-600 Hz, yet suppression notably decreases by 200 Hz. To the extent that spike rates of auditory nerve fibres decrease with lower sound-frequency, synaptic depression at neurons in the cochlear nuclei may also decrease. At very low frequencies, including 200 Hz, where reverberant energy in natural, outdoor scenes is low, suppression of spatial information during peak energy is less important. However, in modern, indoor listening environments, characterised by enclosures with highly

461 reflective walls, reverberation can be high even at very low frequencies. Indoor reverberation
462 combined with weakly suppressing neurons, and with increasing perceptual thresholds for ITD
463 at sound frequencies below 500 Hz [36], may contribute to the observed low perceptual
464 weighting of very low frequencies when localising broadband sound [37]. This consistent
465 perceptual down-weighting for localisation, presumably by brain centres above the brainstem,
466 occurs even as these very low sound frequencies contain and apparently convey vital speech
467 information, including the fundamental frequency, and first formant of vowels.

468 Contrasting the relatively weak reverberation and weak suppression of late-arriving sound at
469 200 Hz, with the relatively strong suppression at 600 Hz and increasing reverberation with
470 higher sound frequency up to 1500 Hz, suggests that brainstem neurons effectively suppress
471 responses to reverberation for sound frequencies from 500 to 1200 Hz, a frequency range that
472 despite being relatively high in reverberation produces the lowest perceptual thresholds for ITD
473 discrimination in human listeners [36,38], and dominates the percept of auditory spatial cues
474 [37,39,40].

475 MSO neurons tuned to very low sound-frequencies, though remaining faster than other types
476 of neurons, nonetheless include a range of membrane time-constants [30]. By not expressing
477 more ion channels than required, the slower MSO neurons encode ITD efficiently, realising a
478 cellular energetic advantage. Consistent with the reported heterogeneity in temporal
479 properties, both moderate and fast nonlinear model MSO neurons reflected human ITD
480 sensitivity at 200 Hz [9]. Reduced, but still viable, K_{V1} activity provided ITD sensitivity at 200 Hz
481 in the nonlinear model, while combining with synaptic depression in the cochlear nuclei to
482 suppress responses during falling energy. Introducing slower membranes in linear model MSO
483 neurons boosted the hemispheric-difference model's ability to lateralise 200-Hz signals,

484 especially at their energetic peak, suggesting a functional benefit to a reduced density of K_{V1}
485 channels at lower frequencies.

486 Within the input pathways to the MSO, compared with the strong synaptic depression
487 observed *in vitro* [11–14], the contrastingly weak synaptic depression reported *in vivo* [41,42]
488 may indicate heterogeneity. In the excitatory pathway, weakly depressing synapses may
489 innervate and explain the subpopulations of spherical bushy cells with strong sustained
490 responses, both primary-like [43] and high-synchrony [28]. Inputs to the MSO driven by these
491 weakly adapting neurons would account for MSO neurons with strong sustained responses
492 [29], which may contribute to listeners' ability to locate slowly moving sources of sustained
493 sounds.

494 Whilst inhibition including GABAergic forms is linked to enhanced membrane excitability and
495 added precision in ITD encoding [17,44,45], our results suggest that synaptic depression and
496 intrinsic membrane properties, combined with excitatory binaural coincidence detection
497 mechanisms, fundamentally contribute to perceived location based on ITD. The success of our
498 simplified, purely excitatory, input model is consistent with the view that inhibition to MSO
499 neurons does not produce strongly adaptive effects, and that the glycinergic inhibition is
500 reasonably fast-acting, largely contralaterally driven and leads contralateral excitation in time—
501 with the main effect that best-ITD is shifted toward contralateral-leading ITDs by delaying the
502 net excitatory post-synaptic current generated by the contralateral ear [46,47].

503 ***Synaptic adaption enhances correct lateralisation of reverberant speech***

504 Early reflections—those following the direct signal by 50 ms or less [48]—can disrupt low-
505 frequency sound localisation in realistic auditory environments by conveying spurious ITD cues

506 in the TFS of sounds [49]. Despite this, normal-hearing listeners are highly adept at locating
507 the true source of a sound in reverberant environments including speech in reverberant
508 environments. By demonstrating that the addition of synaptic adaption to a hemispheric 2-
509 channel model emphasises ITD cues in sound onsets, our data suggest one means by which
510 complex sounds, including speech, are reliably lateralised.

511 Whilst our adapting hemispheric-difference model correctly lateralised reverberant speech, this
512 was based on its d' output surpassing a threshold value in only six of the ninety 5-ms bins
513 where a correct ITD cue was available. Nevertheless, although this neuro-metric measure may
514 not appear particularly robust, it should be remembered that only the 600-Hz frequency
515 channel was examined for the lateralisation of speech. Studies of the precedent effect—the
516 suppression of auditory information, including spatial information—for late-arriving sounds—
517 and localisation in reverberant conditions have demonstrated strong weighting of cues in the
518 500-750 Hz frequency range [37,39,40], but they also highlight the inability of subjects to
519 localise pure tones in echoic conditions, suggesting that enhanced localisation of speech in
520 reverberant conditions involves localisation cues across the low-frequency spectrum. Adding a
521 midbrain stage where neurons in the inferior colliculus (IC), for example, receive inputs from
522 MSO neurons across a wide range of CFs would further test the extent to which synaptic
523 adaptation in the cochlear nuclei improves the localisation of speech in reverberant
524 environments.

525 We note that onset-cue dominance is demonstrated extensively in the precedence effect
526 [50,51], where suppression of neural responses to a brief lagging stimulus occurs over a range
527 of delays between leading and lagging stimuli. A future localisation model combining monaural
528 synaptic depression, potentially with inhibitory echo-suppressive mechanisms, such as

529 delayed inhibition to the midbrain [52–54], and feedforward inhibition in the brainstem from
530 dorsal to ventral cochlear nucleus [55] and from ventral cochlear nucleus to MSO via the
531 trapezoid body [56–58], would provide one means of exploring whether these mechanisms act
532 cooperatively in robust onset-ITD processing in reverberant conditions. The inhibition from
533 dorsal to ventral cochlear nucleus is associated with non-monotonic rate-level functions in
534 SBCs, and not with adaptation. This inhibition has onset dynamics that are too fast to account
535 for the slower adaptive suppression of brainstem responses to late-arriving sound [4]. The
536 omission of this inhibition in our models explains why the model excitatory synapses in the
537 cochlear nuclei are slightly weaker than expected. More broadly, brainstem and midbrain
538 mechanisms may combine additively or act independently for different stimuli. At least for
539 ongoing, amplitude-modulated sounds, the emphasis early-arriving sound in ITD-encoding by
540 MSO neurons, combined with the lack an increase in this emphasis at the inferior colliculus of
541 the midbrain [4], suggests that the brainstem contributes significantly to accurate sound
542 localisation in reverberation.

543 *Early-arriving spatial cues for bilateral cochlear implant (bCI) listeners*

544 To help bCI listeners receive spatial information, bCI processors can deliver enhanced spatial
545 information that emphasises early-arriving direct sound over late-arriving reverberation. Such
546 enhanced spatial information might be added to a recently developed bilateral stimulation
547 technique that provides detectable ITDs in high-rate pulse trains by including bursts of even
548 more rapidly successive pulses [59]. High-rate pulse trains with amplitude driven by sound are
549 applied for speech intelligibility. The bursts occur at a low rate, and their contained rapid
550 succession of current pulses within each ear overcome the excessive adaptation that can
551 greatly reduce responses to ITD in bCI listeners [60,61]. Although bCI listeners are most

552 sensitive to ITD during peaks in sound-energy [9], acoustically the most accurate ITD-
553 information for source location may still occur during rising sound-energy [2]. To maximise ITD
554 sensitivity, and provide spatial information that emphasises sound-sources, bCI processors
555 can during peak energy provide pulse bursts with spatial information derived milliseconds
556 earlier from the interaural cues soon after the preceding energy minimum. Calculation of
557 interaural cues might be triggered by time since a detected energy minimum, and a
558 proportional energy increase.

559 *Conclusions*

560 Suppressive biophysical mechanisms producing adaptation in the auditory brainstem
561 contribute to sound-source localisation, by promoting reliable spatial encoding despite
562 reverberation. The frequency-dependent emphasis of auditory spatial information conveyed in
563 early-arriving sound is consistent with brain mechanisms that transmit reliable information, and
564 suppress unreliable information. As the brainstem encodes interaural time differences for
565 determining sound-source locations, its suppression of late-arriving spatial information, by
566 short-term synaptic plasticity and K_{V1} channel activity, promotes accuracy and accounts for
567 typical frequency-profiles of reverberant energy in natural outdoor scenes.

568 More generally, our modelling of ion-channels yielding realistic resting potentials and
569 membrane time constants, within neurons spectro-temporally processing salient stimuli, is
570 available to any neuroscientist. Our findings may encourage further identification of brain
571 mechanisms that encode, enhance, and apply spatial information, including in the cortex.
572 Clinically, our suggested improvement for delivery of auditory spatial cues to listeners with
573 bilateral cochlear implants is intended to inspire application of rapidly updating binaural masks
574 [62] that enhance target sound-sources while preserving spatial cues.

Methods

Nonlinear brainstem model

This computational model (Fig. 2B) incorporates an MSO neuron and its excitatory input pathways including synaptic depression in the cochlear nuclei. Amplitude-modulated binaural beats (AMBBs) at 75 dB SPL rms at peak amplitude were applied as acoustic stimuli to the Zilany et al. auditory periphery model for humans [21,22] implemented in Matlab (www.mathworks.com), including 12 left and 12 right model adapting auditory nerve fibres of medium spontaneous rate, which project to depressing synaptic inputs on model SBCs in the ventral cochlear nuclei [23,26]. Three model auditory nerve fibres drive each model SBC. Four left and four right SBCs project non-depressing, excitatory synaptic inputs to a multi-compartment model MSO neuron [36] with recent updates. These model brainstem neurons are implemented as Hodgkin & Huxley models [24] in the Python 3.7 Brian2 Neural Simulator [63].

Model SBCs with synaptic depression

Spherical busy cells (SBCs) are modelled as point neurons [26], Type II compartment, adjusted for temperature 37°C) with three independent, excitatory synapses each driven by a model auditory nerve fibre. Each model synapse is an excitatory synaptic conductance in series with an excitatory reversal potential of 0 mV. Each input spike causes a variable increment in its synapse's excitatory conductance which decays exponentially with time constant 0.2 ms. The increment (i.e., the synaptic strength) is variable due to synaptic depression. Synaptic depression at the individual synapses is modelled as in Rudnicki and Hemmert [23]: immediately after an input spike and its associated increment in excitatory

conductance, the synaptic strength is multiplied by 1 – *u,* where *u* = 0.5, comparable to measurements *in vitro* [11–13]. This synaptic depression recovers with a single-exponential function with time constant 25 ms [12].

Modelled synaptic depression contributed to realistic responses to AMBB stimuli, consistent with low synchrony to AM in the auditory nerve at high SPL [64], and reduced synchrony in primary-like neurons (including bushy cells) of the cochlear nuclei [65]. Compared with a single input, three inputs per model SBC [66] increased spike rates, further reduced synchrony to AM, and supported a realistically small number of excitatory inputs [67] to the model MSO neuron.

Model MSO neuron

The model MSO neuron has separate compartments representing the bilateral dendrites, soma, and axon of the neuron [68]. The soma is spherical and iso-potential. Best-ITD and best-IPD are zero. Parameters for each compartment (Table 1) are explained below. Certain parameters (Table 2) were adjusted for the four conditions yielding results shown in Figs. 3-4.

Table 1. Model MSO neuron parameters with membrane conductance at full value

Parameter	Dendrites (2)	Soma (spherical)	Axon
Temperature (˚C)	37	37	37
Number of sub-compartments	20	2	51
Diameter (μm)	3.5	30	2
Length (μm)	150	30	400
Resistivity, R_S (ohm x cm)	150	0 (iso-potential)	150
C_M (μF/cm^2)	1	1	1
V_{KLT} (mV)	-106	-106	-106
V_{Na} (mV)	n/a	-62.1	-62.1
V_H (mV)	-43	-43	-43
V_L (mV)	-60	-60	-65
$gmax_{KLT}$ (S/cm^2)	0.00132	0.0324	0.0595
$gmax_{Na}$ (S/cm^2)	0 (none)	0.0432	0.25
$gmax_H$ (S/cm^2)	0.00066	0.0216	0.0025
g_L (S/cm^2)	0.00005	0.00005	0.00005
V_E (mV)	0	n/a	n/a
$V_{AP\text{-}THRESHOLD}$ (mV, set)	n/a	n/a	-20
V_{REST} (mV)	-60.53	-60.52	-64.35

Table 2. Each column gives parameter values for one of the four cases explored. Adjusted parameters were CF, synaptic strength and synaptic depression of inputs to SBCs, membrane conductance in MSO soma and dendrites, and MSO synaptic strength:

Results shown in	Fig. 3A	Fig. 3B	Fig. 4A	Fig. 4B
CF (Hz)	600	600	200	200
Model SBC excitatory synaptic parameters:				
Full Synaptic Strength, Δg_E (nS)	400	83	83	83
Synaptic Time Constant, τ_E (ms)	0.2	0.2	0.2	0.2
Depression, u	0 (none)	0.5	0.5	0.5
Recovery Time Constant (ms)	n/a	25	25	25
Model MSO membrane conductance factor and excitatory synaptic parameters:				
$g_{MEMBRANE}$ Factor	1	1	1	1/3
Membrane Time Constant (ms)	0.33	0.33	0.33	1.0
Synaptic Strength, Δg_E (nS)	21	36	36	18
Synaptic Time Constant, τ_E (ms)	0.4	0.4	0.4	0.4

Eight excitatory synapses are located on the model MSO bilateral dendritic membranes, one each at 42.5, 47.5, 52.5, and 57.5% of the dendritic length. Each synapse is modelled as a variable conductance (g_E) in series with an excitatory reversal potential (V_E) of 0 mV. The synapses are non-depressing, and each is driven by a single model SBC from the same side. An input spike increments its synaptic conductance by a fixed amount, and the conductance then decays exponentially with time constant 0.4 ms. Synaptic strength (Δg_E), which is the fixed conductance-increment, was adjusted according to CF, the overall membrane conductance including g_{KLT}, and the presence or absence of synaptic depression in the cochlear nuclei.

Within the model MSO neuron, its functional electric-circuit unit the sub-compartment (Fig. 2C) connects to its neighbouring sub-compartments via series resistivity (R_S) representing the neuron's internal cytoplasm. Within each sub-compartment, the neural membrane is modelled as a transmembrane capacitance (C_M) in parallel with ion-channel populations: sodium ion (Na^+) channels, hyperpolarisation-activated cyclic nucleotide (HCN, I_h) channels for non-specific cations, and K_{LT} (K_{V1}) channels. Each ion-channel population is represented as a reversal potential (V_{Na}, V_H, V_{KLT}) in series with a conductance (g_{Na}, g_H, g_{KLT}). With the exception of a fixed leakage conductance (g_L) representing voltage-insensitive ion channels, each conductance value is equal to a maximum conductance multiplied by voltage-sensitive activation and inactivation gating variables with integer exponents [24].

Kirchhoff's current equation, applied to the model MSO neuron, states that the sum of the membrane and series currents exiting any point in the model neuron is zero:

$$0 = i_{C_M} + i_{Na} + i_{K_{LT}} + i_H + i_L + i_{S1} + i_{S2}$$

Series currents, i_{S1} and i_{S2}, are calculated by the Brian2 simulator according to the voltage differences, resistivity, and geometry of the related sub-compartments.

Capacitive membrane current (i_{C_M}) increases with membrane capacitance and the time-derivative of membrane potential *V*:

$$i_{C_M} = C_M \frac{dV}{dt}.$$

Leakage current: $i_L = g_L(V - V_L)$.

Sodium current [27]: $i_{Na} = g_{Na}(V - V_{Na})$.

Na^+ conductance: $g_{Na} = gmax_{Na} m^4(0.993h + 0.007)$.

Each voltage-sensitive ionic conductance has a constant maximum conductance value ($gmax$) (Table 1), and has voltage and time dependencies defined by a subset of the activation/inactivation variables m, h, w, z, and r, each with a rate of change governed by a first-order differential equation with a time constant divided by the Q_{10} temperature factor of $3^{(T-22)/10}$, where *T* is set equal to human body temperature, 37°C. For sodium:

$$\frac{dm}{dt} = Q_{10}(m_\infty - m)/\tau_m$$

$$\frac{dh}{dt} = Q_{10}(h_\infty - h)/\tau_h$$

For model Na^+ channels, steady-state activation (m_∞) and inactivation (h_∞), and their respective time constants (τ_m and τ_h) in milliseconds, are functions of membrane potential in millivolts, equal to those in Scott et al. [27]:

$$m_\infty = 1./(1 + \exp((V + 46.) / (-11.)))$$

$$\tau_m = ((0.141 + (-0.0826 / (1 + \exp((-20.5 - V) / 10.8)))) / 3.)$$

$$h_\infty = 1./(1 + \exp((V + 62.5) / 7.77))$$

$$\tau_h = ((4. + (-3.74 / (1 + \exp((-40.6 - V) / 5.05)))) / 3.)$$

K_{LT} current [15]:

$$i_{KLT} = g_{KLT}(V - V_{KLT}).$$

$$g_{KLT} = gmax_{KLT} w^4 z.$$

$$\frac{dw}{dt} = Q_{10}(w_\infty - w)/\tau_w$$

$$\frac{dz}{dt} = Q_{10}(z_\infty - z)/\tau_z$$

$$w_\infty = 1./(1 + \exp((V + 57.34)/(-11.7)))$$

$$\tau_w = ((21.5/((6.* \exp((V + 60.)/7.)) + (24.* \exp(-1 * (V + 60.)/50.6)))) + 0.35)$$

$$k = 0.27$$

$$z_\infty = ((1. - k)/(1 + \exp((\mathrm{V} + 67.)/6.16))) + k$$

$$\tau_z = ((170./(5.* \exp((V + 60.)/10.) + \exp((V + 70.)/8.))) + 10.7)$$

Non-inactivating HCN current [26]:

$$i_H = g_H(V - V_H).$$

$$g_H = gmax_H r\ .$$

$$\frac{dr}{dt} = Q_{10}(r_\infty - r)/\tau_r$$

$$r_\infty = 1./\,(1 + \exp((\mathrm{V} + 76.)\,/\,7.))$$

$$\tau_r = ((100000./\,(237.*\exp((\mathrm{V} + 60.)\,/\,12.) + 17.*\exp(-(\mathrm{V} + 60.)\,/\,14.))) + 25.)\,.$$

Approach for setting maximum conductance values of MSO ion-channels

By selecting equilibrium membrane potentials (V_{REST}) and equilibrium ratios of i_{Na} to i_H to i_{KLT} in each compartment (0:1:-1 in dendrites; 1:4:-5 in soma, 1:1:-2 in axon), and knowing C_M and membrane time constants, the current equation yielded a maximum conductance value for each ion-channel in each compartment that produced: K_{LT} activation in dendrites and soma; Na^+ inactivation in soma; Na^+ not inactivated in axon.

Model MSO membrane time constants

In the resulting model MSO neuron of this study, with bias current to centre the somatic membrane potential at -57.6 mV, slightly above V_{REST}, the somatic membrane impedance magnitude as a function of frequency was lowpass with a resonance at 480 Hz. Although this resonance frequency is slightly higher than typical for MSO neurons [20,69], this 480-Hz resonance frequency multiplied by 2π converts to an angular frequency of 3016 radians/s, with its reciprocal yielding a membrane time constant of 0.33 ms that is within the range of MSO neurons [70]. For AMBB stimulation centred at 200 Hz, to reflect the range of MSO membrane speeds at very low CF [30], slower somatic and dendritic membranes were also modelled by dividing the fast membrane conductances by three to yield a somatic membrane time constant of approximately 1 ms.

AMBB period histograms

For each AMBB period histogram from the nonlinear model, spikes were counted in forty non-overlapping bins, each covering 1/40 of the AM cycle. Histograms showing results from the

nonlinear model were not smoothed. Spike rates were calculated by dividing the spike count by the total time duration for each bin, across the multiple periods of eight different stimulus presentations of 0.75-second duration.

Eight starting-phases at decrements of 45° efficiently implemented IPDs

At each carrier and modulation-frequency combination, 8 acoustic stimuli, each with 1 of 8 carrier *starting-phases* (0°, -45°, -90°, …, -315°), were applied at each model ear, driving auditory nerve fibres. For computational efficiency, *start-IPD* (the IPD at zero amplitude) was achieved by pairing spike times from each *starting-phase* in one ear, with the spike times from the other ear having the appropriate difference in *starting-phase*. While maintaining the proper *start-IPD*, each AMBB period histogram pooled spikes resulting from stimuli using the 8 *starting-phases* spanning each carrier period. Thus whilst the histograms show the effects of *start-IPD*, they do not show phase-locking to fine structure of the carriers.

In this study, “best-ITD during rise” denotes *start-IPD* = 270°; “best-ITD at peak” denotes *start-IPD* = 180°; and “best-ITD during fall” denotes *start-IPD* = 90°.

Chi-squared tests for significant differences in model spike counts

For each condition and modulation frequency, a chi-squared test for one and two degrees of freedom (2-way and 3-way comparisons) compared spike counts from the nonlinear model MSO neuron stimulated with AMBBs with best-ITD occurring during rising vs. peak vs. falling amplitude. Each chi-squared test yielded a probability (p) of the null hypothesis that the differences in spike count occurred randomly.

Synchrony index and Rayleigh statistic for significant phase-locking:

For each modulation frequency and *starting-phase* combination, the synchrony index (*SI, R*) of spike times (t_i) [71] with respect to their phase θ_i within the AM cycle (with modulation frequency f_m and modulation period $T_m = 1/f_m$) was calculated:

$$\theta_i \triangleq 2\pi f_m mod(t_i, T_m)$$

$$SI = \sqrt{(\sum_{i=1}^{N} \cos\theta_i\,)^2 + (\sum_{i=1}^{N} \sin\theta_i\,)^2}$$, where N is the spike count.

The Rayleigh significance statistic ($2NR^2$) was then calculated and converted to a *p* value, the probability of the null hypothesis that the AM period-histogram of spike times resulted from a uniform distribution [72]:

p	0.10	0.05	0.025	0.01	0.001
$2NR^2$	4.605	5.991	7.378	9.210	13.816

Lateralisation model including linear-membrane models

To study how synaptic adaptation and biophysical profiles could impact lateralisation of acoustic stimuli in anechoic and reverberant conditions, we constructed a model of lateralisation whose brainstem stages (SBCs and MSO neurons) are represented by point neurons with linear biophysical properties [20]. Two stimuli were presented to the model: the first, a SAM tone with non-zero ITDs inserted at different phases of the AM cycle, as used behaviourally to determine how carrier frequency affects ITD sensitivity over the time course of an AM cycle [9]; the second, a natural speech stimulus with early reflections, has been proposed as a simple simulation of a reverberant environment where correct lateralisation is only possible if ITD cues in the onset waveform are processed preferentially [4].

SAM tones with non-zero ITDs inserted at different phases of AM cycle

This stimulus was generated according to the Hu et al. study [9] that first used it. In summary, SAM tones were created from pulse trains that had been bandpass-filtered and then amplitude-modulated. Non-stationary ITDs were added by temporally shifting individual pulses in one of either the rising, peak or falling phases of the AM cycle. For the purposes of this study, non-stationary ITDs of +300 μs and +150 μs were inserted into SAM tones of either 200-Hz or 600-Hz carrier frequency respectively. These ITD values were chosen based on individual behavioural thresholds in the Hu et al. study [9]. At each carrier frequency, four conditions were tested: two different AM frequencies (8 Hz or 20 Hz) and two different proportions of rising, peak or falling AM phases with a non-zero ITD inserted (20% or 40%). These parameters match those tested behaviourally by [9].

A natural speech stimulus with early reflections

A single monosyllabic consonant-vowel nucleus-consonant (CNC) word token, ‘church’, (spoken by an Australian-English, female voice), was selected as a stimulus (Fig. 1 and Fig. 8). To simulate its arrival from a location one metre away to the right of the midline in an anechoic environment, the word’s waveform (normalised at 70dB) was convolved with a large pinnae HRTF for +30° azimuthal location (CIPIC database, UC Davis). A reverberant space was simulated by adding to the direct (+30°) pathway two early reflections off virtual walls stood behind and to the right of the subject (Fig. 1). These reflected copies of the words arrived from -65° and -130° angles (again convolved with large-pinnae HRTFs from the CIPIC database) and were delayed by 4ms and 8ms respectively to reproduce their elongated paths [4].

Linear model circuitry

The linear model, like its nonlinear counterpart, consists of three stages: an initial auditory periphery stage (the middle/inner ear and auditory nerve fibres) and two brainstem stages (cochlear nuclei and MSO). Unlike the nonlinear model however, the linear model incorporates two parallel circuits, representing the ‘left’ and ‘right’ MSO nuclei and their inputs. The difference in output rate between these parallel circuits is utilised to calculate lateralisation of the natural stimulus. The only discernible difference between ‘left’ and ‘right’ circuits is the contralateral $\frac{1}{8}$ pi shifts in their MSO neurons’ IPD tuning curve peaks which are generated by delaying the outputs from the auditory periphery stage ipsilateral to the MSO nucleus in question. This shift is considered physiological given experimentally observed binaural tuning curves from the auditory brainstem whose optimal characteristics have been corroborated theoretically [34].

Auditory periphery stage

Peripheral processing of the acoustic stimuli in the linear model is performed using an implementation of the Zilany et al. [21] cat middle/inner ear model in Matlab. Outputs from the auditory periphery are restricted to 200-Hz/ 600-Hz for the pulse-shifted SAM tones (matching their SAM tone’s carrier frequency) and 600-Hz for lateralisation of the speech stimulus with early reflections. This latter value was chosen based on it laying in the middle of the 500-750 Hz frequency range in which TFS-ITD sensitivity is considered strongest [37]. When exploring effects, of synaptic depression at the inputs from auditory nerve to cochlear nucleus, on the lateralisation of a speech stimulus, the same auditory periphery simulations are used for both the depressing and non-depressing inputs to the cochlear nuclei.

Linear-membrane model properties

Single-compartment, linear-membrane models are used to represent both SBC and MSO neurons in the linear model. These linear-membrane models can incorporate two dynamic currents as previously described in [20]: I_w, a resonant current and/or, I_n, an amplifying current. The current balance equation for the general neural model is as follows:

$$\mathrm{c}\frac{dv}{dt} = -g_{\mathrm{M}}v - g_{\mathrm{w}}w_{\mathrm{w}} + g_{\mathrm{n}}w_{\mathrm{n}} + \mathrm{I}_{app}(t)$$

Where c is capacitance (picofarads), g_M is total membrane conductance (nanosiemens) and I_{app} is the current (picoamperes) applied to the neural model. The resonant and amplifying currents, I_w and I_n, are described by their conductances, g_W and g_n (in nanosiemens); the dynamics of their gating variables, w_w and w_n (in millivolts) are described generically by the equation:

$$\tau_{\mathrm{w}}\frac{dw_{\mathrm{w}}}{dt} = v - w_w$$

$$\tau_{\mathrm{w}}\frac{dw_{\mathrm{w}}}{dt} = v - w_w$$

Where w_x is the gating variable whose associated time constant is τ_x (milliseconds).

Two parameter sets are chosen to represent the apparent bimodality of subthreshold biophysical properties in the gerbil MSO *in vitro* [30]. These example models can be broadly characterised by their impedance profiles as either band-pass with a high resonant-frequency or band-pass with a low resonant-frequency [20]. While the band-pass model with a high-resonant frequency is exclusively chosen to represent SBCs, both model types are used to represent MSO neurons.

Synaptic properties and adaptation

As in the nonlinear model, 3 independently-simulated auditory nerve fibres provide excitatory drive to each SBC in the linear model. Excitatory unitary conductances at this synapse are modelled as alpha functions with an exponential time course of 0.2ms. Synaptic depression with a single exponential recovery is also implemented at this stage, matching the adaptation observed in the nonlinear model functionally thanks to its similar parameters (u = 0.55; τ = 25 ms).

Each MSO neuron receives 4 (independently-simulated) excitatory cochlear-nucleus inputs from “either ear” in the linear model. Alpha functions are again used to model the unitary excitatory conductances at this synapse with time courses selected relative to the resonant class of the MSO in question (i.e. band-pass with high resonant-frequency: 0.2ms; band-pass with low resonant-frequency: 0.5ms). This increase in synaptic time course is performed to reflect the slower membrane time constant associated with neurons displaying little or no resonance at all. If, as expected, MSO neurons with slower intrinsic properties still segregate inputs from either ear on either dendrite then the increased electrotonic propagation of excitatory inputs somatopetally should lead to slower excitatory potentials at their somata. Where comparisons of the two MSO resonant classes are made, the same adapting auditory nerve inputs are presented to their respective cochlear-nucleus stages, therefore reducing any potential confusion that might result from variability in the peripheral model’s output.

Spike thresholds in the linear-membrane model

Idealised thresholds for the linear-membrane model are implemented from Remme et al. [20]. A slope threshold (dv/dt) is used for all neuronal types. Threshold values for cochlear-nucleus cells are selected to produce good average firing rate without undermining the effects of

synaptic depression. Threshold values for the MSO neurons are selected to obtain maximum dynamic range of ITD tuning functions for 200/600 Hz pure tone stimuli (where dynamic range is considered the difference between the maximum and minimum ITD-modulated spike rate). A refractory period of 1 ms is implemented as in Remme et al. [20] for cochlear-nucleus neurons and MSO neurons with a high-resonant frequency whereas a longer refractory period of 2 ms is used for the MSO neurons with low-resonant frequency, reflecting longer refractory periods in neurons with lower densities of K_{LT} channels [19,26,73].

Calculating lateralisation using d' values

Lateralisation of a reverberant natural stimulus is judged in the linear model by calculating the mean spike rate difference between a population of 50 'left' and 50 'right' MSO neurons to a single stimulus presentation. d' values are calculated to quantify the degree of separation of 'left' and 'right' spike rates using the following equation:

$$d' = \frac{\mu_L - \mu_R}{\sqrt{\frac{1}{2}(\sigma_L^2 + \sigma_R^2)}}$$

Where μ_L is the mean spike rate for the 'left' population of MSO neurons in 5-ms bins; μ_R is the mean spike rate for the 'right' population of MSO neurons in 5-ms bins; σ_L is the standard deviation of the 'left' MSO population's spike rate and σ_R is the standard deviation of the 'right' population's spike rate (both calculated in 5-ms bins again).

The sign and magnitude of the d' allows judgement of whether the linear model lateralises the reverberant stimulus to the correct direction (negative d' values denote negative ITDs/left of midline; positive d' values denote positive ITDs/right of midline) and whether this lateralisation

judgment is considered significant (d’ > 1 or d’ < -1 indicated a significant lateralisation in the right and left directions respectively).

ANOVA and T-test for significant differences in lateralisation

Two-way and three-way ANOVAs are implemented to compare the duration of correct lateralisations (time correctly lateralised = bin duration x number of bins where d’ > 1) by the hemispheric model of SAM tones with non-zero ITDs in either the rising, peak or falling phases as well as the percentage of the phase including a non-zero ITD. A two-tailed T-test is also performed for 200-Hz carrier SAM tones to compare the effect of MSO neuronal type. For the speech stimulus, a paired two-tailed T-test is performed to compare the frequency of incorrect lateralisations (time incorrectly lateralised = bin duration x number of bins where d’ <-1) in the linear model with either adapting or non-adapting auditory nerve inputs.

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Author Contributions

AB and JMH contributed equally.

Conceptualisation: DM and MD

Data Curation: JMH and AB

Formal Analysis: JMH and AB

Funding Acquisition: DM

Investigation: AB and JMH

Methodology: AB (nonlinear modelling) and JMH (linear modelling)

Resources: DM, AB, and JMH

Software: AB and JMH

Supervision: DM

Visualisation: JMH and AB

Validation: AB and JMH

Writing – Original Draft Preparation: AB, JMH, and DM

Writing – Review & Editing: AB, DM, MD, and JMH

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Figures

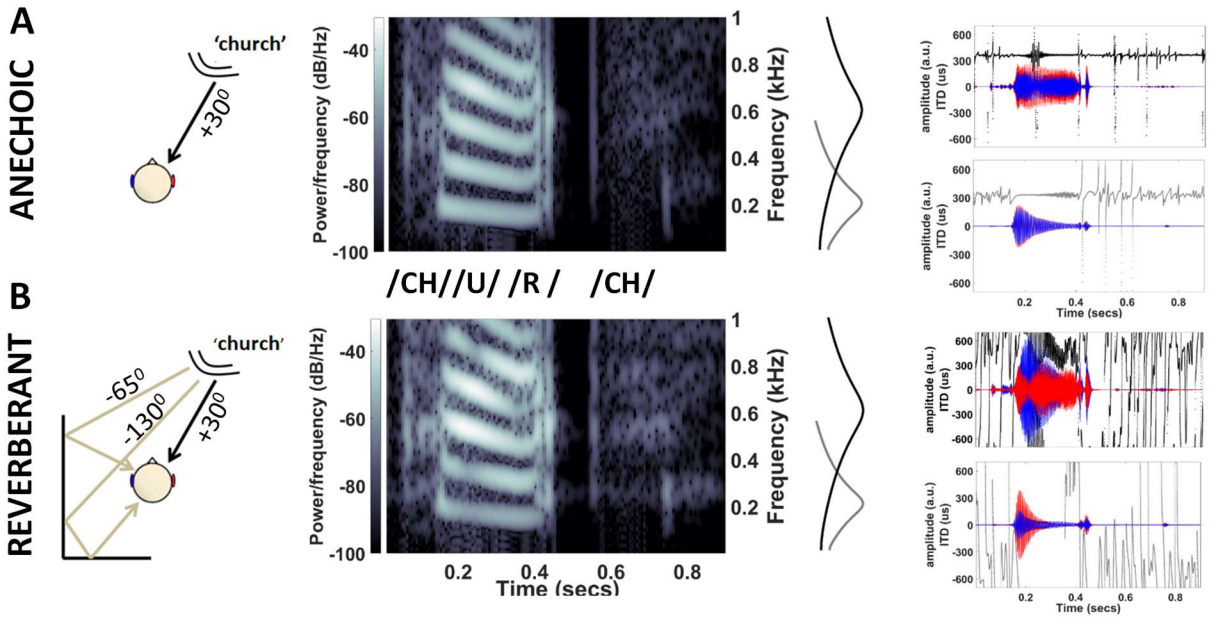
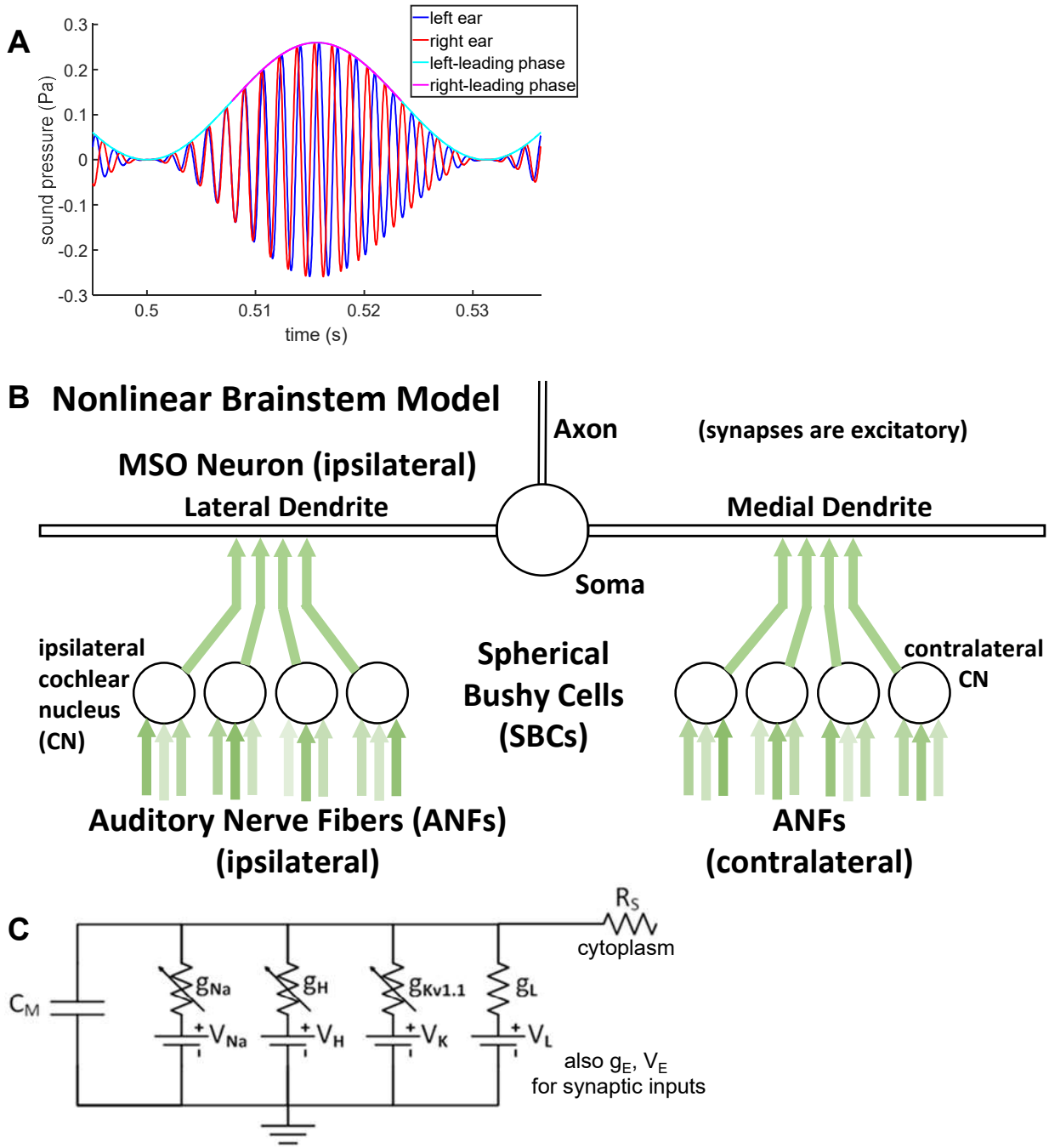


Figure 1 [in colour, online and in print]



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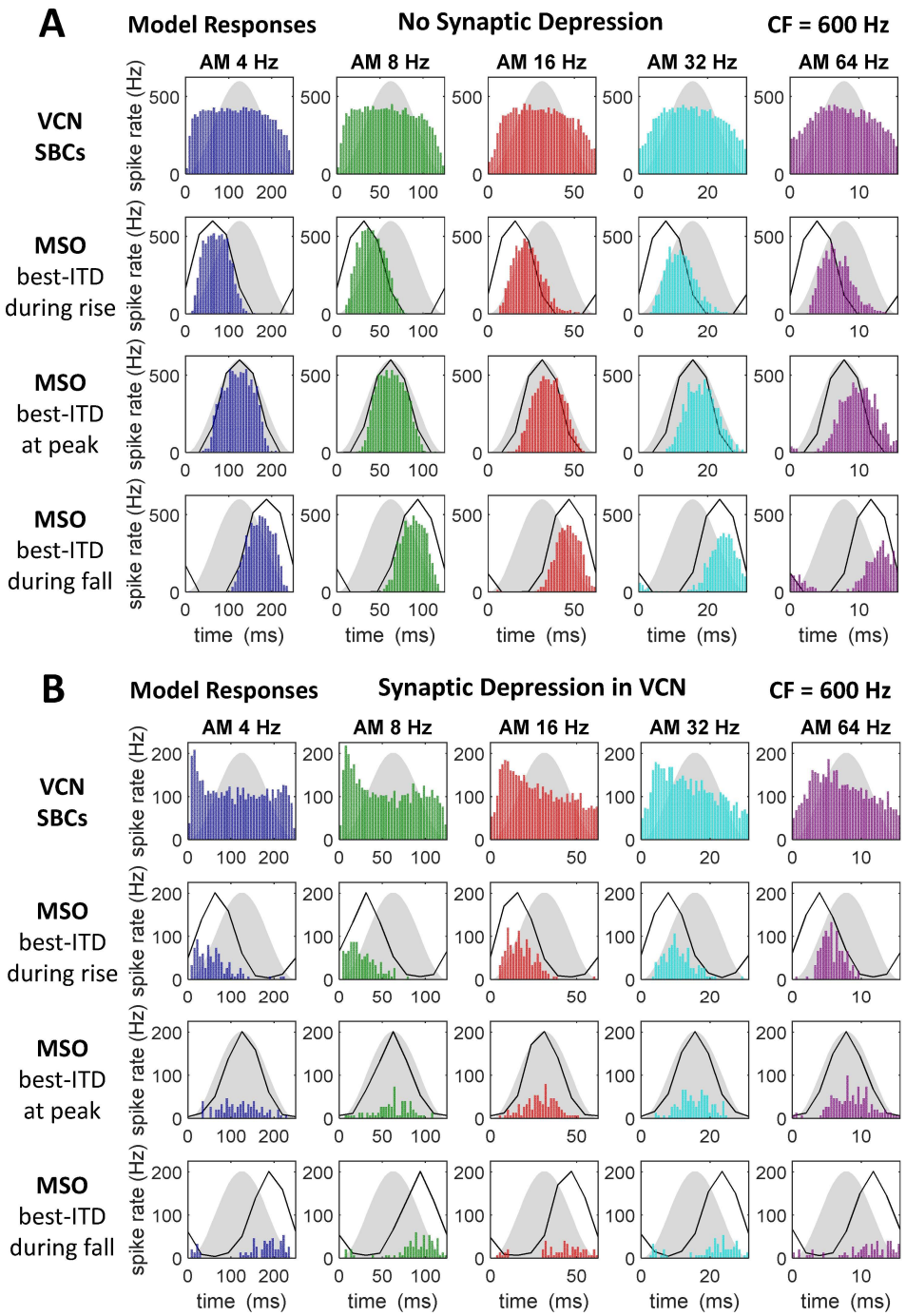

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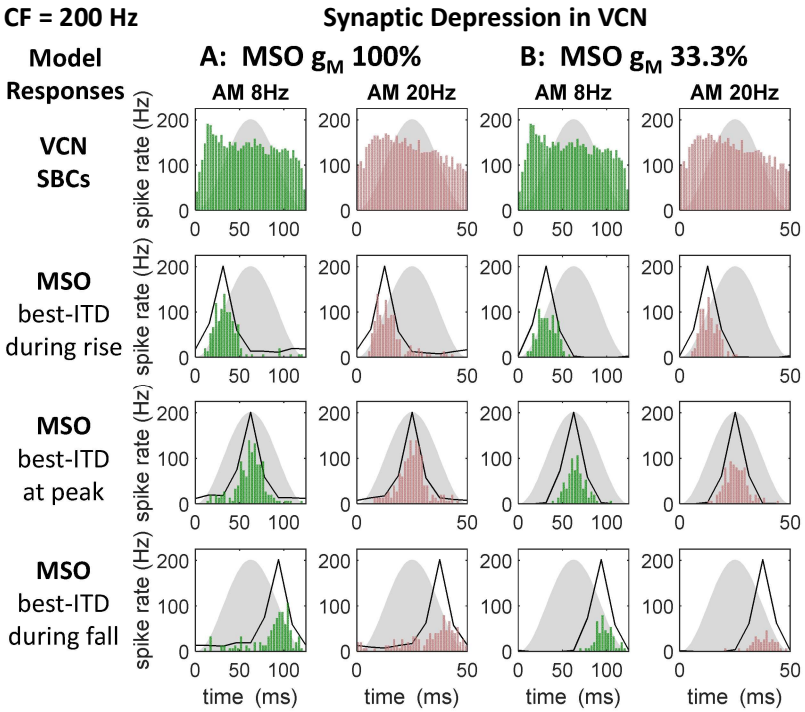

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1115 **Figure 4 [in colour, online and in print]**

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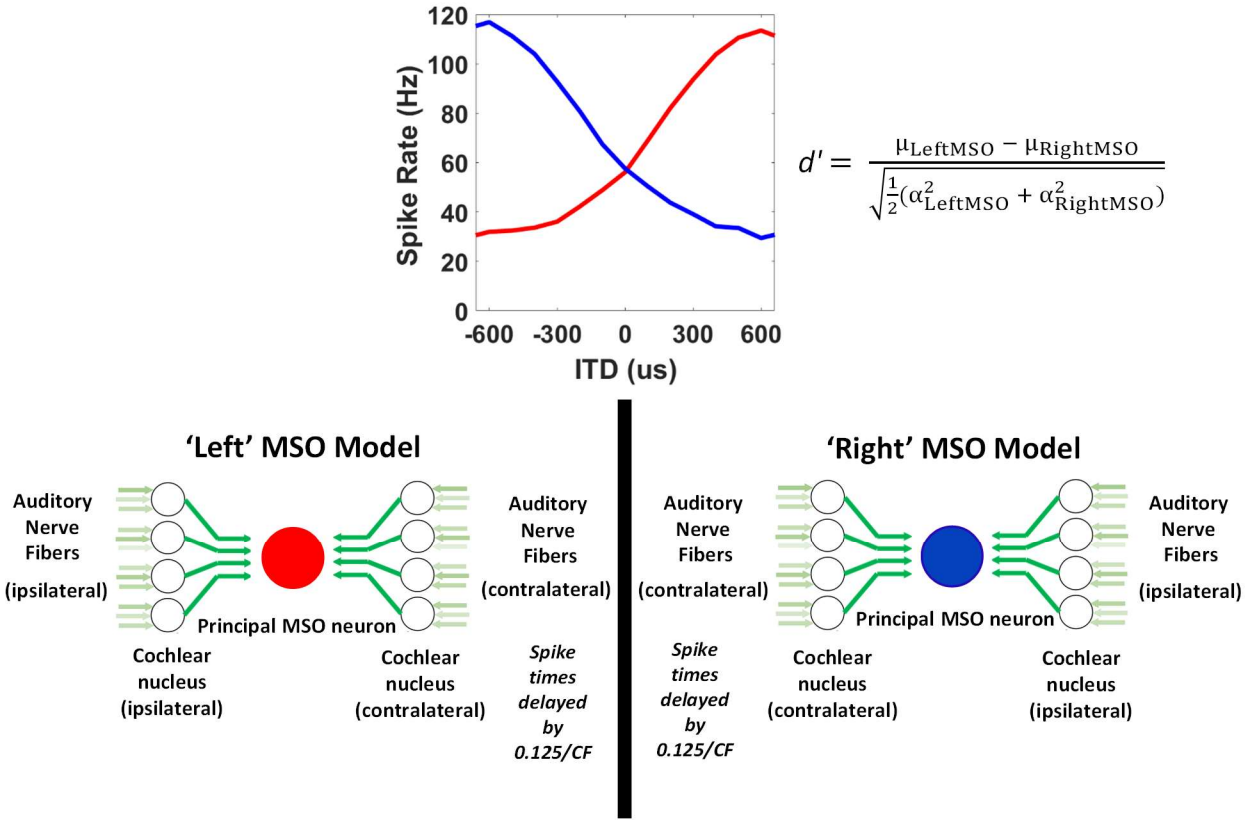

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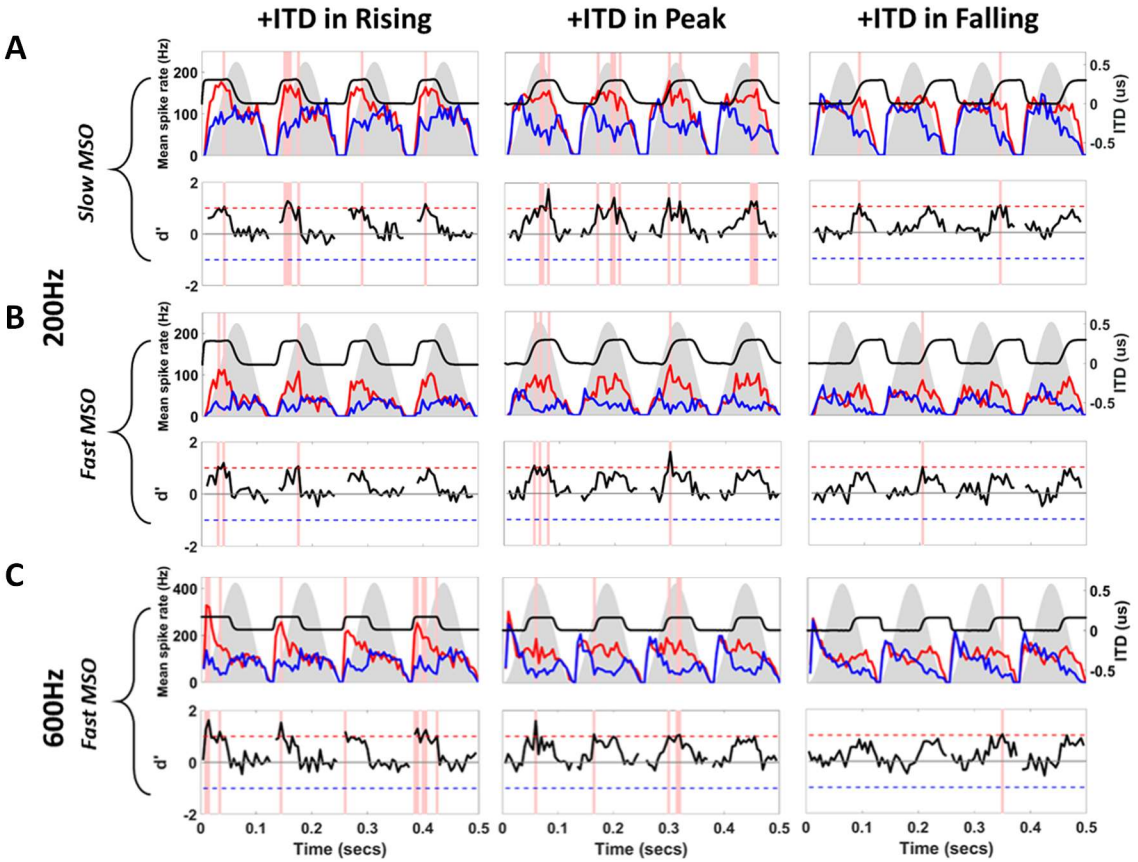

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1123 **Figure 6 [in colour, online and in print]**

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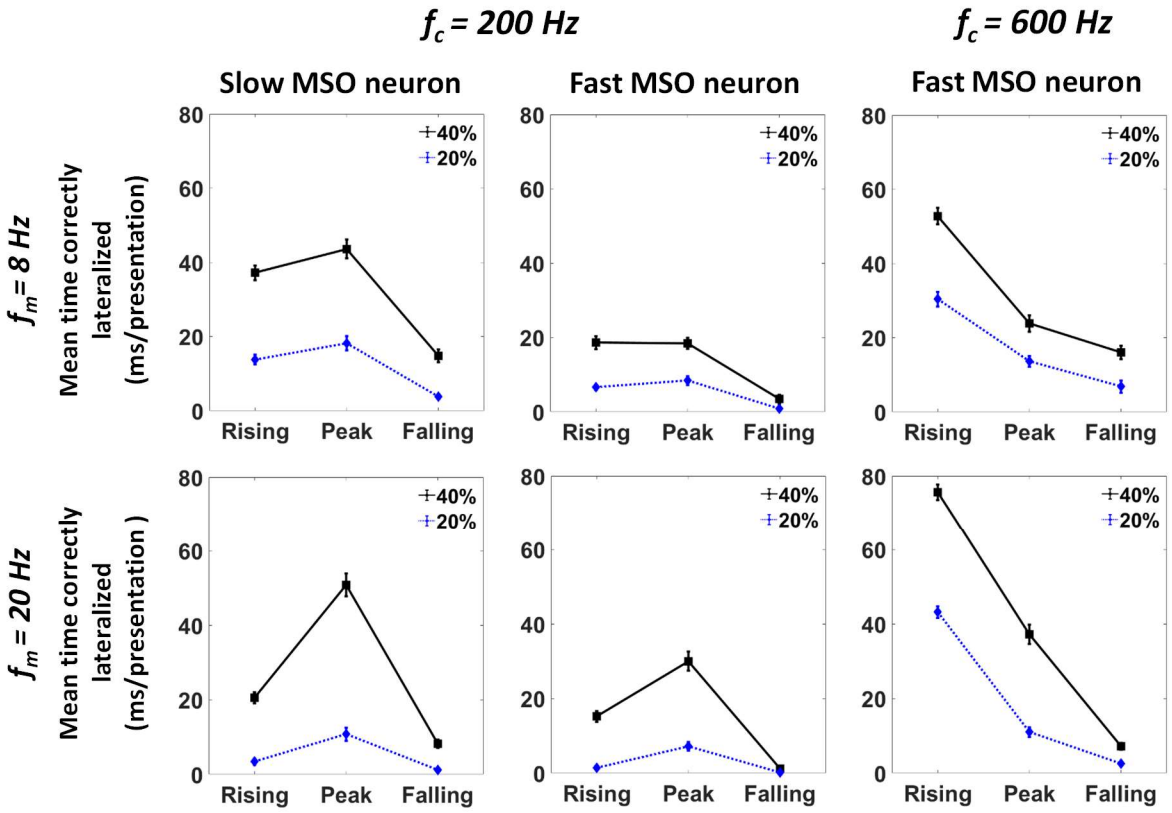

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1127 **Figure 7 [in colour, online and in print]**

1128

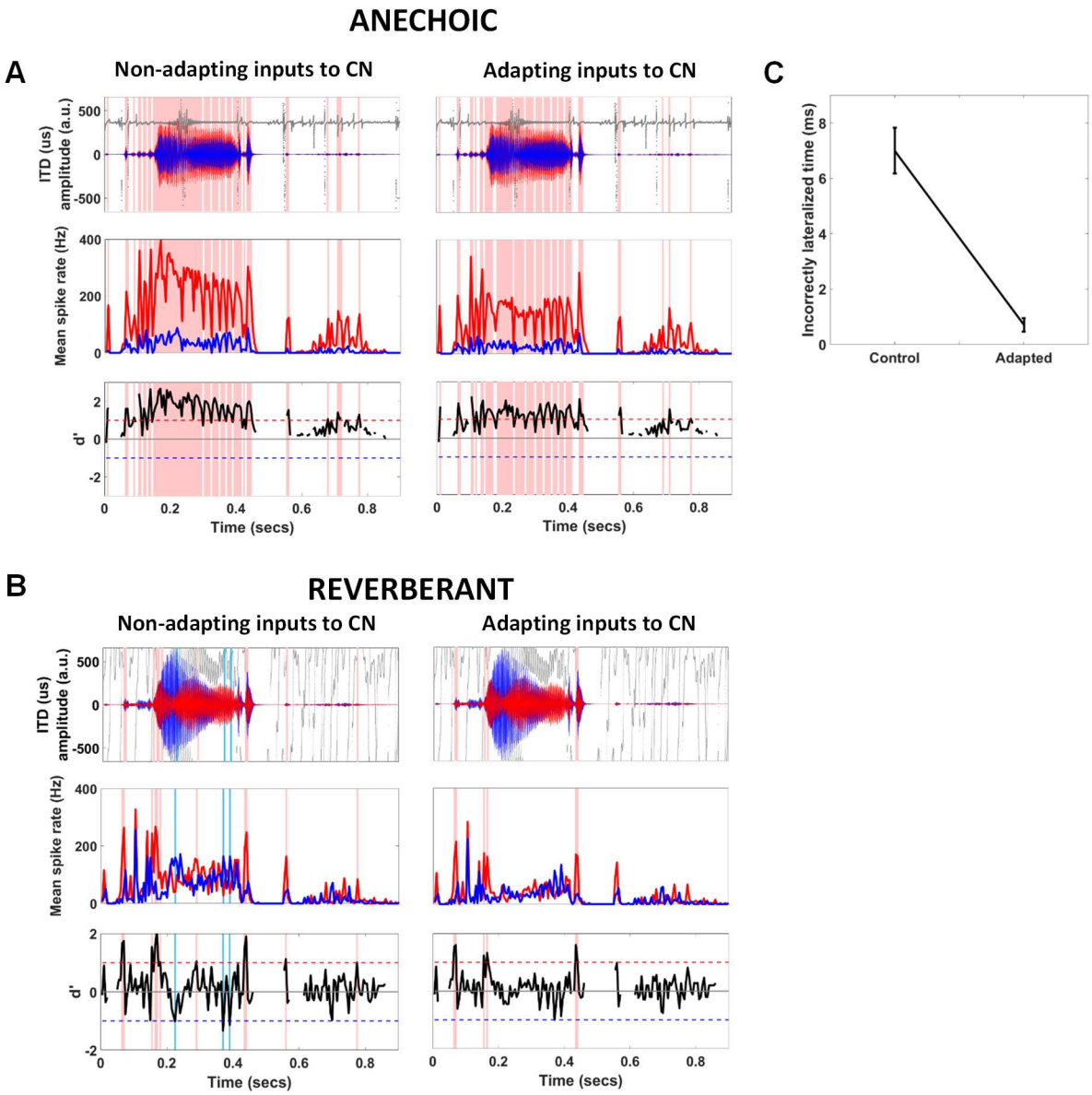

Figure 8 [in colour, online and in print]