

Top-down or bottom up: decreased stimulus salience increases responses to predictable stimuli of auditory thalamic neurons

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Key points

- Temporal imprecision leads to deficits in the comprehension of signals in cluttered acoustic environments, and the elderly are shown to use cognitive resources to disambiguate these signals.
- To mimic ageing in young rats, we delivered sound signals that are temporally degraded, which led to temporally imprecise neural codes.
- Instead of adaptation to repeated stimuli, with degraded signals, there was a relative increase in firing rates, similar to that seen in aged rats.
- We interpret this increase with repetition as a repair mechanism for strengthening the internal representations of degraded signals by the higher-order structures.

Abstract To better understand speech in challenging environments, older adults increasingly use top-down cognitive and contextual resources. The medial geniculate body (MGB) integrates ascending inputs with descending predictions to dynamically gate auditory representations based on salience and context. A previous MGB single-unit study found an increased preference for predictable sinusoidal amplitude modulated (SAM) stimuli in aged rats relative to young rats. The results suggested that the age-degraded/jittered up-stream acoustic code may engender an increased preference for predictable/repeating acoustic signals, possibly reflecting increased use of top-down resources. In the present study, we recorded from units in young-adult MGB, comparing responses to standard SAM with those evoked by less salient SAM (degraded) stimuli. We hypothesized that degrading the SAM stimulus would simulate the degraded ascending acoustic code seen in the elderly, increasing the preference for predictable stimuli. Single units were recorded from clusters of advanceable tetrodes implanted above the MGB of young-adult awake rats. Less salient SAM significantly increased the preference for predictable stimuli, especially at

Srinivasa P. Kommajosyula is a postdoctoral fellow at Southern Illinois University School of Medicine (SIU SOM) under the mentorship of Donald Caspary. His doctoral thesis on sudden death in epilepsy in audiogenic seizure models spurred his curiosity into maladaptive plasticity in networks witnessed in this model and central auditory system. His research interests include understanding the pathophysiological and compensatory changes in central auditory system with ageing and noise induced trauma. The present study highlights evidence of such changes in auditory thalamic coding of less salient stimuli that switch the preference of single unit to repeated stimuli. **Rui Cai** is a Research Instructor at SIU SOM. She obtained her PhD in East China Normal University where she studied the environmental effects on the plasticity of auditory function. She continues her work in auditory system in SIU, with an emphasis on the mechanisms of age-related hearing loss and tinnitus.



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higher modulation frequencies. Rather than adaptation, higher modulation frequencies elicited increased numbers of spikes with each successive trial/repeat of the less salient SAM. These findings are consistent with previous findings obtained in aged rats suggesting that less salient acoustic signals engage the additional use of top-down resources, as reflected by an increased preference for repeating stimuli that enhance the representation of complex environmental/communication sounds.

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Introduction

Age-related hearing loss leads to a loss of speech understanding and affects 35–50% of the 43 million individuals aged 65 years or older in the US population (Humes *et al.* 2012; Ortman *et al.* 2014). A loss of speech understanding significantly impairs quality of life, frequently leading to social withdrawal and depression (Humes *et al.* 2012; Bainbridge & Wallhagen, 2014). Peripheral changes only partially account for speech understanding deficits in elderly listeners with mild to moderate hearing loss in complex listening environments. (Alain & Woods, 1999; Dalton *et al.* 2003; Anderson *et al.* 2012; Humes *et al.* 2012; Presacco *et al.* 2016*b*). In response to peripheral hair cell and/or acoustic nerve fibre losses associated with ageing, the entire central auditory pathway shows compensatory age-related maladaptive changes (Caspary *et al.* 2008; Ouda *et al.* 2015; Caspary & Llano, 2018). Human and animal studies repeatedly show age-related declines in the temporal reliability when coding ascending acoustic representations, partly as the result of a loss of normal adult inhibitory neurotransmitter function (Fitzgibbons & Gordon-Salant, 1994; Caspary *et al.* 2008; Gordon-Salant, 2014; Godfrey *et al.* 2017; Caspary & Llano, 2018). Previous human psychophysical and electrophysiological studies have modelled ageing in auditory system by temporally jittering stimuli (Pichora-Fuller *et al.* 2007; Mamo *et al.* 2016). To compensate for these deficits with ageing, the elderly are known to use top-down resources to improve performance in auditory tasks (Ostroff *et al.* 2003; Peelle *et al.* 2010; Fakhri *et al.* 2012; Leung *et al.* 2013). In essence, when speech signals are degraded, speech understanding can be improved by engaging the cortical pathways projecting to lower-order cortical and subcortical structures that provide additional ‘meaning’/cognitive resources. These resources may provide linguistic or semantic context guiding the recognition of acoustically unclear speech (Harris *et al.* 2012; Mattys & Scharenborg, 2014; Sohoglu *et al.* 2014; Rogers & Wingfield, 2015; Peelle & Wingfield, 2016; Pichora-Fuller *et al.* 2016). Early psychophysical studies on phenome restoration posited the role of top-down resource usage that are now supported by

modern imaging techniques (Thurlow, 1957; Warren, 1970; Vaden *et al.* 2016). This function is supported by the Bayesian properties of higher cortical areas in the prediction of sensory events using concurrent cognitive resources reflected in their top-down projections, which in turn are corrected by bottom-up circuits leading to enhancement or selective diminishment of the ascending acoustic code or prediction error (Rao & Ballard, 1999; Friston, 2009; Stebbings *et al.* 2014; Parras *et al.* 2017; Kuchibhotla & Bathellier, 2018; Wang *et al.* 2019). Examples of top-down mediated processes include repetition enhancement effect for degraded signals, attended signals or speech in noise recognition (Luce & Pisoni, 1998; Eisenberg *et al.* 2002; Maunsell & Treue, 2006; Rivenez *et al.* 2006; Sheldon *et al.* 2008; Chandrasekaran *et al.* 2009; Peelle *et al.* 2010; Muller *et al.* 2013; Peelle & Wingfield, 2016; Helfer *et al.* 2018).

In the central auditory system, top-down descending corticothalamic projections to the auditory thalamus or medial geniculate body (MGB) are more extensive than ascending reciprocal thalamocortical projections. MGB can be parsed into ventral, dorsal and medial subdivisions (Morest, 1964). The ventral division is lemniscal in nature, projecting principally to layers 3/4, whereas the dorsal and medial subdivisions receive inputs from dorsal and external cortices of the inferior colliculus, tegmentum, superior colliculus and spinal cord considered to be extra-lemniscal and projecting to layers 1 and 6 of the primary auditory cortex, as well as belt areas of the auditory cortex and amygdala, amongst others (Winer *et al.* 2005; de la Mothe *et al.* 2006; Bartlett, 2013). The MGB also receives cholinergic projections that may further engage top-down resources providing cognitive and attentional resources that shape the ascending code (Rouiller & Welker, 1991; Winer *et al.* 2001; Bartlett & Smith, 2002; He, 2003; Bartlett, 2013; Malmierca *et al.* 2015; Guo *et al.* 2017; Lesicko & Llano, 2017; Sottile *et al.* 2017*a*; Sottile *et al.* 2017*b*; Schofield & Hurley, 2018). The MGB also receives tectothalamic inputs that carry ascending sensory inputs and shows stimulus-specific adaptation (SSA) to repeating stimuli, facilitating the detection of novel stimuli (Nelken, 2014; Malmierca *et al.* 2015), comprising a property considered to be of

bottom-up origin, independent of age and even enhanced by anaesthesia (Ulanovsky *et al.* 2003; von der Behrens *et al.* 2009; Richardson *et al.* 2013a; Malmierca *et al.* 2015; Nir *et al.* 2015). By contrast to afore-mentioned studies, other studies have also shown changes in MGB unit tuning properties and gain via manipulation of the auditory cortex (Orman & Humphrey, 1981; Zhang *et al.* 1997; He, 2003; Malmierca *et al.* 2015). Increased detection of acoustic signals was shown to involve corticothalamic projections that increase neural representation in the MGB (Guo *et al.* 2017). However, our current understanding of how ageing affects top-down influences at the level of the MGB is limited. A recent MGB single-unit study showed an age-related increasing preference (neuronal responses) for predictable/repeating stimuli relative to randomly presented sinusoidal amplitude modulated (SAM) stimuli. Rather than showing stimulus adaptation to repeating stimuli, MGB units from aged animals responded to repeating stimuli by increasing their discharge rates with each repeated trial, especially at higher modulation frequencies (f_m) (Cai *et al.* 2016). These changes were not observed in MGB units from anaesthetized rats, possibly reflecting the relative weakening of top-down circuits by anaesthesia (Ferrarelli *et al.* 2010; Casali *et al.* 2013; Mashour, 2014). Similar in concept to studies simulating central auditory ageing using temporal jitter, the present study hypothesized that less salient SAM stimuli will lead to a less-precise ascending upstream code, similar to that seen in the elderly, and also that this change in salience would move the single-unit preference toward predictable stimuli in young-adult MGB neurons (Fig. 1) (Pichora-Fuller *et al.* 2007; Mamo *et al.* 2016).

To test this hypothesis, single unit recordings were made from awake and anaesthetized young rats that were presented with standard, 100% depth of modulation SAM and less salient SAM stimuli (decreasing modulation depth and 'noisy' SAM stimuli). We posited that less clear acoustic information will engender the use of top-down, corticothalamic information in an effort to 'better understand' the ascending acoustic message leading to enhanced representation of predictable/repeating stimuli (Fig. 1).

Methods

Male Fischer 344 \times Brown Norway (FBN) rats, aged 4–6 months old, were obtained from the National Institute of Aging (NIA) Aging Rodent Resource Colony supplied by Charles River (Wilmington, MA, USA) and were housed individually under a reverse 12:12 h light/dark photoperiod with access to food and water available *ad libitum*. FBN rats have a long life-span and lower tumour load than other commonly used rat ageing models. They are available through rodent resources at the National Institute of Aging (nia.nih.gov/research/scientific-resources#rodent) and age-related changes in auditory structure and function have been studied extensively (Caspary *et al.* 2008; Cai *et al.* 2018; Caspary & Llano, 2018). Procedures were performed in accordance with guidelines and protocols approved by the Southern Illinois University School of Medicine Lab Animal Care and Use Committee, as well as in accordance with National Institute of Health guideline on minimizing animal usage and pain, and also conform with the regulations described by Grundy (2015).

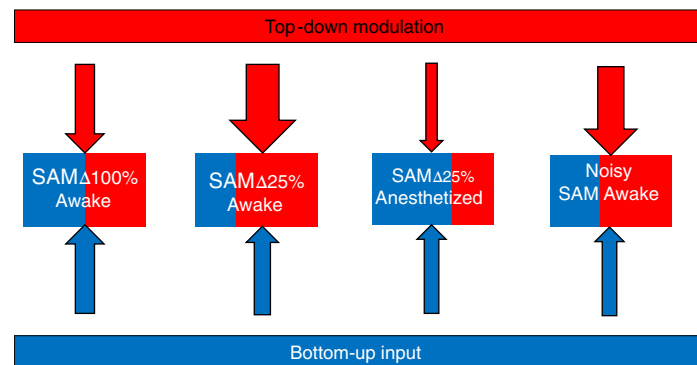


Figure 1. Schematic representation of the study hypothesis

Less salient acoustic stimuli will produce a degraded ascending acoustic code, similar to the code seen in the ageing auditory system. In the MGB, this can engage an increased use of top-down resources needed to maintain salience by enhancing responses to repeating/predictable over random stimuli. Bottom-up (blue arrows) and top-down (red arrows) MGB circuits work in concert to encode communication sounds and salient environmental information needed for survival. We hypothesize that temporally rich SAM stimuli with 100% modulation depth (SAM Δ 100%) balance the use of bottom-up and top-down resources to best code sounds in the MGB of young awake rats. We posit that decreasing the salience of SAM stimuli either by reducing the effective modulation depth (25% modulation depths: SAM Δ 25%) or by jittering the envelope of 100% modulation depth (Noisy SAM) leads to an increase in top-down mediated processes in the awake but not in anaesthetized rat MGB.

Acoustic brain stem response (ABR) recording

To ensure normal hearing thresholds, before implantation surgery, ABR tests were completed on all rats as described previously (Wang *et al.* 2009). Briefly, rats were anaesthetized with an i.m. injection of a 3:1 mixture of ketamine and xylazine at a dose of 1.4 mL kg⁻¹. Pure tones at 4, 8, 12, 16, 24, 28 and 32 kHz were presented 512 times at a rate of 20 s⁻¹ with a duration of 3 ms and rise/decay clicks of 1 ms. A recording electrode was inserted into the skin over the vertex, a reference electrode was inserted under the left mastoid and a ground wire was attached to the hind leg. ABR signal gain totalled 200,000× with filtering between 0.3 and 3 kHz. Absolute thresholds were determined based on wave I at each frequency. ABRs and single unit recording experiments were completed in a double-wall soundproof booth (Industrial Acoustic, Bronx, NY, USA).

Awake recordings

Rats recovered for 3 days after ABR testing before beginning acclimatization to the recording chamber. Starting at least 1 week prior to surgery, rats were acclimated to a modified experimental conditioning unit (Braintree Scientific, Braintree, MA, USA) with free access to water and a food reward (1/4 to 1/2 Froot Loop; Kellogg's; Battle Creek, MI, USA) until they could remain quiet/still for up to 3 h. VersaDrive4 tetrode drives (Neuralynx, Bozeman, MT, USA) were assembled and loaded with tetrodes as described previously (Richardson *et al.* 2013a; Kalappa *et al.* 2014). Each tetrode wire was gold-electroplated to an impedance between 0.5 and 2.0 MΩ and sampled at 1 kHz (nanoZ; Neuralynx). Drives were sterilized with ethylene oxide before implantation. Surgery details were similar to those described in Richardson *et al.* (2013) and Kalappa *et al.* (2014). One day prior to surgery, acetaminophen (4.5 mg mL⁻¹) was provided via drinking water and continued until day 2 after surgery to alleviate pain. Surgery was performed under anaesthesia and an i.m. injection of a ketamine/xylazine 3:1 mixture at a dose of 1.4 mL kg⁻¹ was used for induction. Rats were given sterile saline (3 mL) s.c., placed on a thermostatically controlled heating pad (Harvard Apparatus, Holliston, MA, USA) and set in a Kopf stereotaxic apparatus (Kopf Instruments, Tujunga, CA, USA) with a nose cone and chin bars. Oxygen blood saturation levels and heart rate were monitored during the surgery using PulseSense Vet (Nonin Medical, Minneapolis, MN, USA). Oxygen was administered continuously to maintain 95–100% blood saturation and isoflurane (1–2.5%) was administered as needed until surgery is completed after induction with a ketamine/xylazine mixture (VetEquip, Pleasanton, CA, USA). The level of anaesthesia was adjusted

based on the presence of pedal withdrawal or elevated heart rate.

Under sterile conditions, the skull surface was exposed and anchor screws were set in place. A craniotomy hole of 2.3 mm in diameter was drilled over the left occipitoparietal cortex, dorsal to the MGB (5.5 mm bregma and 3.5 mm of midline) and the dura was carefully removed. A ground wire was attached to a reference screw placed in the anterior right frontal bone that made contact with the dura, and the tetrode drive was slowly advanced (0.2 mm min⁻¹) to a depth of 4.5–5 mm, placing the four tetrode tips just dorsal to the MGB. Dental acrylic cement was added around the anchor screws and the drive, encapsulating the entire drive with the exception of the advancing screws and pins. The total weight of tetrode drive and dental cement was less than 10 g. Mounting the tetrode drive did not appear to alter the behaviour or demeanor of an animal, with postmortem examination indicating little damage to the surface of the brain. Following surgery, triple antibiotic ointment was applied to the edge of the headcap and wound, and an additional 2–3 mL of sterile saline was administered s.c. The animal was exposed to 100% oxygen and kept on a heating pad throughout recovery until ambulatory. The tetrode drive was coupled to an 18 pin (16 single wires, 2 ground) VersaDrive4-to-Omnetics adaptor (Neuralynx) and connected to a unity gain 18-channel headstage tethered to a preamplifier (2 × gain; 0.15 kHz high pass, 8 kHz low pass; Plexon Inc., Dallas, TX, USA). Sixteen channels of raw data were digitized using a multichannel acquisition processor (MAP) and visualized using Sort Client (Plexon Inc.). Tetrodes were advanced by turning a drive screw coupled to each tetrode and were advanced in increments of 1/4 turn (62.5 μm) with the distance recorded to aid in the localization of units (Richardson *et al.* 2013a). To avoid unit resampling, after a unit on a given tetrode was studied, the tetrode was advanced at least 125 μm. When auditory responsive units/field potentials were no longer present, tetrodes were left in position for marking.

Similar to Richardson *et al.* (2013a), spikes determined to be from single units were sorted using standard methods (amplitude threshold and principal component analysis) and saved as timestamps. Timestamps were relayed to a system running a custom program Auditory Neurophysiology Experiment Control Software (ANECS, Ken Hancock, Blue Hills Scientific, Boston, MA, USA) for stimulus generation and real-time analysis of unit responses. During the recording period, the experimenter took precautions to ensure that the animal was not asleep. Whenever there was an unexpected change in the firing rates of a single unit under investigation, data collection was paused and the booth door was opened to ensure that the animal was awake and alert. As noted above, animals were kept on a reverse day/night cycle so their active period was during the recording sessions.

When recordings were complete (1–4 weeks), rats were anaesthetized with ketamine and xylazine as described above and current pulses (5–10 μA for 5 s) were passed through the tip of each tetrode wire, producing a small lesion. Rats were cardiac perfused with PBS (0.1 M, pH 7.4) followed by 4% paraformaldehyde (Sigma-Aldrich, St Louis, MO, USA). The brain was removed, post-fixed for 24 h in 4% paraformaldehyde at room temperature and then transferred to 20% sucrose and stored at 4°C until sectioned. Frozen coronal sections (thickness 30–35 μm) were taken and the electrode tracks and sites of lesion were visible without the need for staining, and these were then used to determine the position of each recording site relative to the final location of the tetrode tip (Paxinos & Watson, 1998).

Awake recordings and attention

As described in Richardson *et al.* (2013) and Kalappa *et al.* (2014), animals were placed in a darkened acoustic chamber under gentle orienting restraint (i.e. they could turn around but were pre-trained not to do so) with only SAM stimuli to listen to. There were no other known distractors to divide their attention and so the sole activity of a rat was to attend to environmental sounds, which comprised the SAM stimuli presented from the speaker located above their heads.

Anaesthetized preparations

Rats recovered for at least 3 days following ABR testing prior to use in the anaesthesia study. Initial anaesthesia for surgery was the same as described for the awake preparation. Anaesthesia was then maintained with i.p. injections of 100% urethane (initially 1.3 mL kg^{-1} , then booster doses at one-third of the initial dose; Sigma-Aldrich) (Cai *et al.* 2014; Cai & Caspary, 2015). Rats were placed in a modified (no ear bars) stereotaxic frame in an IAC sound-attenuating booth (Industrial Acoustic Co., Inc., New York, NY, USA) with the body temperature maintained at $37 \pm 0.5^\circ\text{C}$ using a thermostatically controlled heating blanket. The skull surface and left occipito-parietal cortex, dorsal to the MGB, were exposed. A tungsten electrode was gradually advanced into MGB by piezoelectric advancer (David Kopf Instruments, Tujunga, CA, USA). The electrodes were coupled to a headstage preamplifier, MAP system and a personal computer running MAP software and Sort Client (Plexon Inc.) for real-time spike sorting.

SAM stimuli paradigms and single-unit recording procedures

Stimulus paradigms and single unit sorting/recording procedures were the same for awake and anaesthetized

preparations. Acoustic signals were generated using a 16-bit D/A converter (TDT RX6 for System III; Tucker Davis Technologies, Alachua, FL, USA) and transduced by a Fostex tweeter (model FT17H; Fostex, Tokyo, Japan) placed 30 cm above animal's head. The Fostex tweeter was calibrated off-line using a $\frac{1}{4}$ inch microphone (model 4938; Brüel & Kjær, Naerum, Denmark) placed at the approximate location of the rat's head. Calibration tables in dB sound pressure level (SPL) were used to set programmable attenuators (PA5; Tucker Davis Technologies) to achieve pure tone levels accurate within 2 dB SPL for frequencies up to 45 kHz. Response maps were used to determine the characteristic frequency (CF) of sorted single units (Cai & Caspary, 2015). Random tone-burst stimuli (duration of 50 ms, 4 ms rise/fall time, 2 Hz rate) were presented in 0.10 to 0.25 octave frequency steps (1–32 KHz) in 10 dB SPL steps (0–80 dB) to determine the response maps. Real-time single unit activity was sampled at 100 kHz using ANECS and archived for off-line analysis.

The modulation depth was decreased to 50% and 25% ($\text{SAM}_{\Delta 50\%}$ and $\text{SAM}_{\Delta 25\%}$) to create less salient versions of 100% modulated SAM. In addition, we produced a signal termed 'noisy SAM', where 100% SAM signals were jittered by adding low-pass filtered (1000 Hz) broadband noise (BBN) to the envelope of the SAM signal regardless of the carrier. The ratio of the carrier to noise rms was constant at 0, equal strength. The addition of BBN jitters the rising phase of the envelope and decreases the effective modulation depth (Fig. 2). There were no differences (<2 dB) in total energy levels for the standard and less salient SAM stimuli. SAM carrier (f_c) was set at the unit's CF or BBN. Rate modulation transfer functions (rMTFs) and temporal modulation transfer functions (tMTFs) were collected at 30–35 dB above CF or BBN threshold. SAM unit data, 30–35 dB above threshold, were collected from young-adult (aged 3–5 months) rats using either CF-tones or BBN as the carrier and choosing the SAM carrier that best drove the unit under study. The findings reported in Cai *et al.* (2018) in an FBN rat model of auditory ageing mean that age-related sensitivity changes at the apical end of the cochlea would probably have had no impact upon the previous results reported in Cai *et al.* (2016).

SAM stimuli were presented at 2 s^{-1} , with a duration of 450 ms and a 4 ms raise–fall with f_{ms} stepped between 2 and 1024 Hz. We tested whether f_{ms} sequentially/predictably stepped in descending steps/reverse order, from 1024 Hz to 2 Hz, would have effect on the results. A descending sequential f_{m} presentation order did not differ from the ascending sequential f_{m} presentation order; hence, for all reported data, stimuli were stepped from 2 Hz to 1024 Hz. Spikes were collected over a period of 500 ms, following stimulus onset with 10 or 20 stimulus repetitions at each envelope frequency. SAM stimuli were presented as two separate sets: random across trials modulation frequencies

(f_{ms}) or sequential with f_{ms} repeating (10 or 20 times) before being stepped to the next f_m in an increasing predictable order (Fig. 2). Responses to less salient SAM stimuli ($SAM_{\Delta 50\%}$ and 25% and noisy SAM) were compared with $SAM_{\Delta 100\%}$.

Statistical analysis

Responses were analysed offline. MTFs were determined using spike rate (rMTF) and temporal synchronization (tMTF) measurement at each f_m tested.

Random preference ratio (RPR) (i.e. total spikes in predictable trials/total spikes in random trials) was calculated across all f_{ms} , with a ratio of random preferring unit smaller than 0.95 and predictable preferring unit larger than 1.05. Ratios between the range of 0.95 and 1.05 were considered non-selective units. A chi-squared test was used to compare the sequence preference ratio.

A random preferring index (RPI) was calculated using the equation: $RPI = [(AUC_{RAN} - AUC_{SEQ}) / (AUC_{RAN} + AUC_{SEQ})]$, modified from the novelty response index (Lumani & Zhang, 2010; Cai *et al.* 2016) and the area under successive frequency segments of the rMTF curve (AUC) values were based on rMTF curve calculated using Prism (GraphPad Software Inc., San Diego, CA, USA). The range of RPI values varied between -1 and +1, with -1 representing a completely predictable

preferring response and with +1 representing a completely random preferring response. Repeated-measures ANOVA followed by *post hoc* Tukey correction for multiple comparisons was used to compare RPI values.

Trial-to trial response analysis to predictable SAM presentation at 256 and 512 Hz was performed by comparing the difference in trend line slopes using two-tailed analysis of covariance (ANCOVA). Phase locking ability was evaluated by standard vector strength (VS) equation:

$VS = (\frac{1}{n}) \times \sqrt{(\sum \cos \phi_i)^2 + (\sum \sin \phi_i)^2}$, where n is the total number of spikes and ϕ_i is the phase of observed spike relative to modulation frequency (Goldberg & Brown, 1969; Yin *et al.* 2011). Statistical significance was assessed using the Rayleigh statistic to account for differences in the number of driven spikes, with Rayleigh statistic values greater than 13.8 being considered statistically significant (Mardia & Jupp, 2000) (Fig. 8). To compare number of units showing phase locking ability and the quantitative vector strength data, a Wilcoxon test and a paired Student's t test were used followed by a Bonferroni correction for multiple comparisons.

Statistical analysis was performed using Prism, version 6 and SPSS, version 24 (IBM Corp., Armonk, NY, USA). All values are expressed as the mean \pm SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ were considered statistically significant.

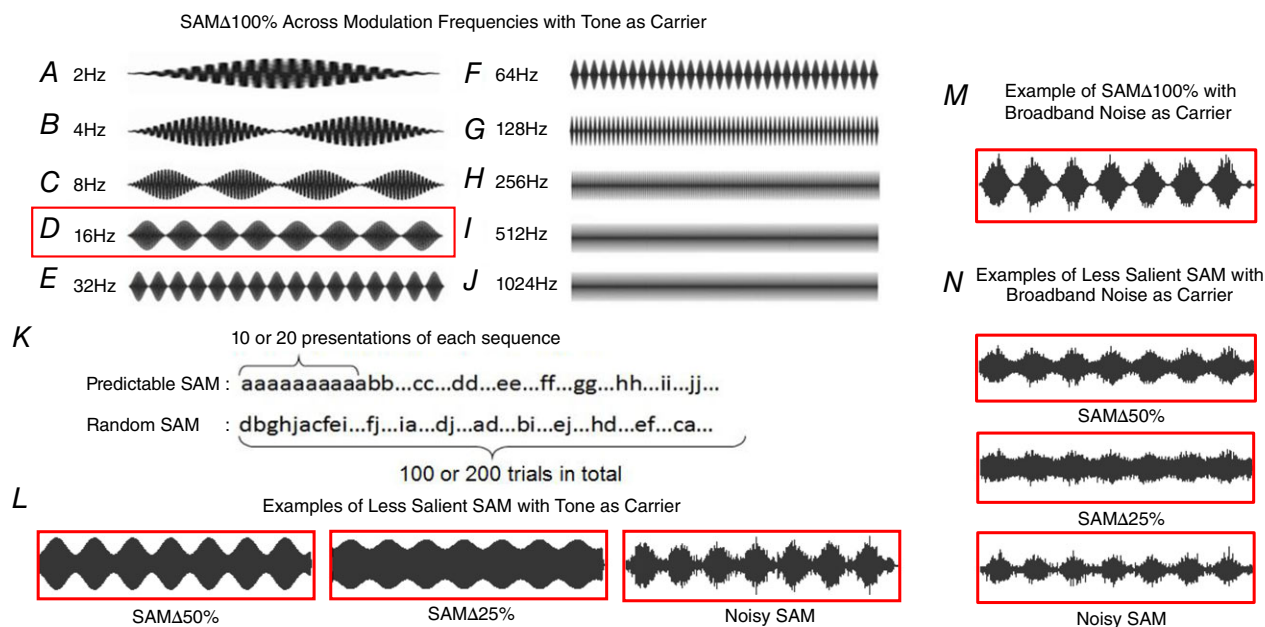


Figure 2. SAM stimuli waveforms and paradigms

A-J, SAM waveforms with tone as carrier at SAM Δ 100% in 500 ms epochs from 2 Hz to 1024 Hz modulation frequencies. K, each stimulus paradigm progressed from 2 Hz to 1024 Hz in a predictable repeated or random manner. L, exemplar waveforms of less salient SAM with tone as carrier at 16 Hz (SAM Δ 50%, SAM Δ 25% and noisy SAM). M and N, exemplar waveforms of salient and less salient SAM with BBN as carrier. Noisy SAM has jittered rising phase and decreased effective modulation depth. There were no differences (<2 dB) in total energy levels for the salient and less salient SAM stimuli regardless of carrier.

[Colour figure can be viewed at wileyonlinelibrary.com]

Results

Ninety-four carefully isolated units were recorded from the MGB of young-adult (aged 4–6 months) rats. Sixty-six units were recorded from six awake rats and 28 units from four anaesthetized rats. All units from awake and anaesthetized preparations were localized to the dorsal or ventral subdivisions of the MGB. Ninety-five percent of the units recorded were determined to be clearly discriminated single units. The remaining units were clusters of 2–3 inseparable units, with responses consistent with the single-unit findings and were included in the analyses. The number of recording sessions varied between 20 and 25 for each rat in the awake group. Between 0 and 2 units were recorded in each day's session as the electrodes were moved in small increments (62.5 microns) at the end of each day.

The tungsten electrodes used in the anaesthetized preparation (impedance 1–3 M Ω) were similar to the 0.5–2.0 M Ω impedance of VersaDrive microwires. The present study cannot rule out, with certainty, any population differences between the units sampled using different electrodes.

rMTFs and tMTFs were recorded in response to random or predictable presentation of standard (SAM Δ 100%) or less salient (SAM Δ 50%, SAM Δ 25% or noisy SAM) stimuli (Fig. 2). There were no differences in shapes of rMTFs

with 10 or 20 repetitions and so 10 repetitions were used in most subsequent recordings.

To maximize unit responses for the analyses, either a BBN or CF carrier was chosen based on which elicited the highest number of total spikes to SAM Δ 100%. Most units in this data set responded best to SAM with a BBN carrier (43 BBN and 23 CF). Units CFs and BFs ranged between 2 and 32 kHz. Similar to studies reported by Bartlett and Wang (2007, 2011) and Cai *et al.* (2014, 2015), SAM responses, based on rMTF shape across f_m , conformed to previously described band-pass, high-pass, low-pass, mixed (most common) or atypical types. BMFs ranged between 8 and 512 Hz, congruent with the rMTF profile types described above.

Preference for random or predictable stimuli with decreasing salience

We examined whether decreasing the salience of a SAM stimulus alters the MGB unit responses as reflected by an increase in the number of spikes when stimuli are presented in a random or predictable manner. An exemplar unit (Fig. 3) showed a slight preference for random presentation with SAM Δ 100%, although this same unit showed a clear preference for predictable stimuli at

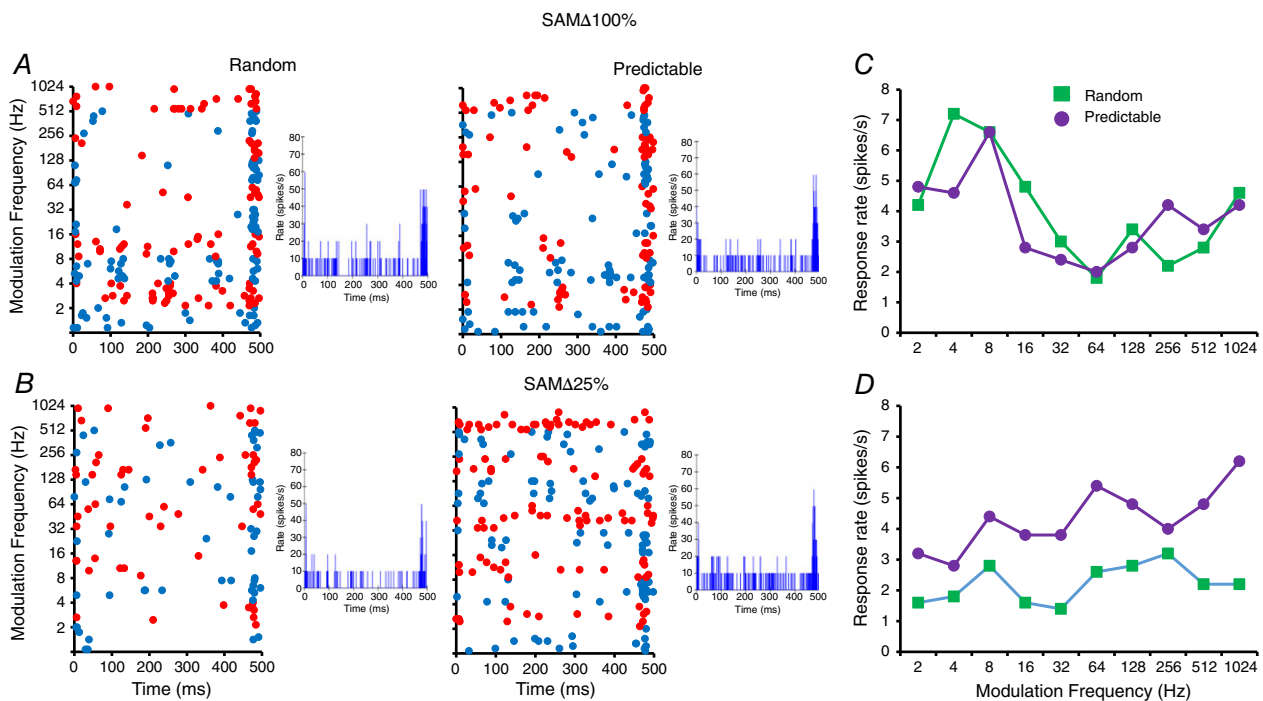


Figure 3. A representative unit from an awake young-adult rat responded differently to various stimulus paradigms

A and C, dot rasters, post-stimulus time histogram and rMTFs from this unit show similar responses to either a random or a repeating predictable sequence of SAM Δ 100%. B and D, the same MGB unit showed increased responses to a predictable repeating SAM with less salient SAM Δ 25%. Responses to predictable SAM Δ 25% increased at the highest f_{ms} .

[Colour figure can be viewed at wileyonlinelibrary.com]

SAM $\Delta_{25\%}$. Responses to random or predictable stimuli were compared when SAM salience was decreased. A difference criteria of greater than 10% change in total response (Ghitza *et al.* 2006; Cai & Caspary, 2015; Cai *et al.* 2016) was used as the qualifier to categorize the unit based on previous studies (random preference ratio = total spikes to predictable SAM/total spikes to random SAM). A qualitative comparison was made between standard SAM $\Delta_{100\%}$ and less salient SAM for the units showing random, predictable and non-selective responses. There was a significant increase in the number of units showing preference for predictable stimuli as the salience was decreased at SAM $\Delta_{50\%}$, SAM $\Delta_{25\%}$ and noisy SAM ($P < 0.05$, chi-squared test) (Fig. 4). The increase in the percentage of neurons showing predictable preference compared to SAM $\Delta_{100\%}$ was SAM $\Delta_{50\%}$, (32% vs. 9%, $P < 0.01$), SAM $\Delta_{25\%}$ (46% vs. 9%, $P < 0.0001$) and noisy SAM (33% vs. 9%, $P < 0.01$) (Fig. 4). These preference changes were not seen in MGB units recorded in anaesthetized rats (SAM $\Delta_{100\%}$ vs. SAM $\Delta_{50\%}$, SAM $\Delta_{25\%}$ and noisy SAM: 18% vs. 21%, 29% and 19%, respectively, $P > 0.05$).

rMTF differences across f_{ms} with decreasing salience (group data)

Similar to Cai *et al.* (2016), the AUC function and RPI values derived from the AUC, as described above, were used to compare responses between random and predictable stimuli across f_{ms} (Figs 5 and 6). Higher values on RPI indicate a random preference, whereas lower or negative values of RPI indicate a decreased random preference/increased predictable preference. RPI values for SAM $\Delta_{100\%}$ were greater for randomly presented stimuli, whereas stimuli with a decreasing SAM salience were found to decrease the RPI values (i.e. increasing predictable preference for SAM $\Delta_{25\%}$ and for noisy SAM). These significant salience-related changes in RPI values between SAM $\Delta_{100\%}$ vs. SAM $\Delta_{25\%}$ and noisy SAM are shown in Fig. 5 ($P < 0.001$ for SAM $\Delta_{100\%}$ vs. $\Delta_{25\%}$ and $P < 0.05$ for SAM $\Delta_{100\%}$ vs. noisy 100% depth). A similar analyses in anaesthetized rats showed no significant differences in RPI values between SAM $\Delta_{100\%}$ vs. SAM $\Delta_{50\%}$, SAM $\Delta_{25\%}$ and noisy SAM (data not shown).

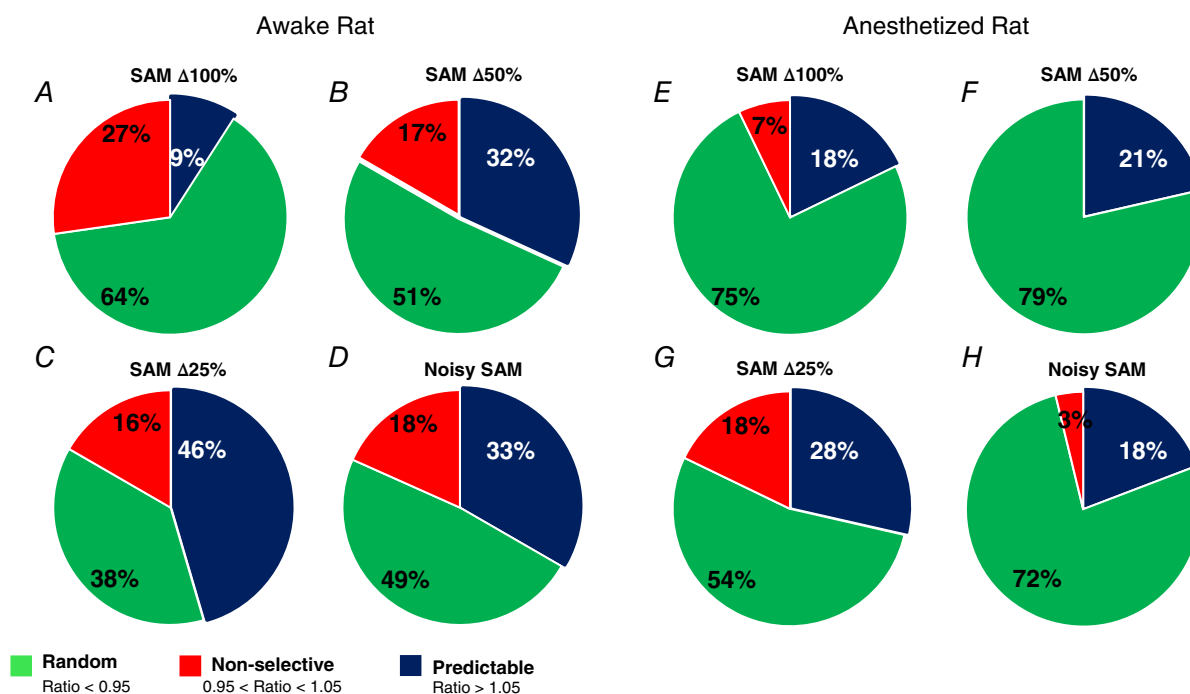


Figure 4. Response ratio comparison across all modulation frequencies between SAM stimuli sets
Percentage of MGB units showing response ratios (predictable/random) at SAM $\Delta_{100\%}$ (A) and less salient SAM stimuli sets (B–D) in awake young-adult rats. The percentage of units showing a preference for predictable SAM increased from 9% (6 of 66) at SAM $\Delta_{100\%}$ to 32% (21 of 66) SAM $\Delta_{50\%}$ and 33% percentage for noisy SAM (20 of 60). At SAM $\Delta_{25\%}$, MGB neurons from awake rats showed highest predictable-preference 46% (30 of 66). Significant differences were seen between SAM $\Delta_{100\%}$ vs. SAM $\Delta_{50\%}$, SAM $\Delta_{25\%}$ and noisy SAM (chi-squared test, $P < 0.05$). In anaesthetized rats, only non-significant differences in preference for predictable stimuli were seen between SAM $\Delta_{100\%}$ and less salient stimuli E–H, percentage of units showing preference for predictable SAM increased from 18% (5 of 28) to 21% (6 of 28) for SAM $\Delta_{50\%}$, 28% for SAM $\Delta_{25\%}$ (8 of 28) and 18% for noisy SAM (5 of 26).
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To determine whether specific random *vs.* predictable differences in firing existed across f_{ms} in awake rats, RPI values for three consecutive f_{ms} combinations were calculated as shown in Fig. 6. RPI values for units responding to $SAM\Delta_{100\%}$ were all positive, indicating a preference for random $SAM\Delta_{100\%}$ across all f_{ms} segments. By contrast, the same units showed significantly decreased RPI responses to less salient SAM, $SAM\Delta_{25\%}$ and noisy SAM for f_{ms} above 128 and 256 Hz (Fig. 6). These data show a salience-related preference shift from random toward predictable SAM stimuli, with the greatest changes for $SAM\Delta_{25\%}$ at the more challenging higher f_{ms} including 32–128 Hz, 64–256 Hz ($P < 0.05$), 128–512 Hz and 256–1024 Hz ($P < 0.01$). RPI values to noisy SAM were also significantly decreased, suggesting an increased preference for predictable stimuli at 256–1024 Hz ($P < 0.05$). Because there was an increase in firing to predictably presented less salient SAM stimuli at higher f_{ms} , we examined trial-by-trial differences between $SAM\Delta_{100\%}$ and $SAM\Delta_{25\%}$ at 256 and 512 Hz f_{ms} . Figure 7 shows trial-by-trial responses to $SAM\Delta_{100\%}$ and $SAM\Delta_{25\%}$ from a single MGB exemplar unit (A and B). Switching between repeating/predictable $SAM\Delta_{100\%}$ and $SAM\Delta_{25\%}$ (256 Hz f_{ms}) altered the unit responses from weakly adapting to increasing the discharge rate with each successive trial, as shown by the linear trend lines on the vertical histograms. Trial-by-trial responses for predictable $SAM\Delta_{100\%}$ and

$SAM\Delta_{25\%}$ were calculated and compared at 256 Hz f_{ms} for all 66 MGB units (Fig. 7C).

Similar to the exemplar, the group data at 256 Hz f_{ms} showed an increase in discharge rate across successive repetitive $SAM\Delta_{25\%}$ stimuli as opposed to no change or adaptation to successive repetitive $SAM\Delta_{100\%}$ stimuli. Slopes comparing group data trend lines between $SAM\Delta_{100\%}$ and $SAM\Delta_{25\%}$ were significantly different ($P < 0.05$). MGB units recorded from anaesthetized rat at 256 Hz f_{ms} presented $SAM\Delta_{25\%}$ showed strong adaptation in the group data ($n = 28$) with the trend line slope being significantly different from $SAM\Delta_{25\%}$ recorded from MGB units in awake rats (data not shown, $P < 0.05$). No significant changes between predictable $SAM\Delta_{100\%}$ and $SAM\Delta_{25\%}$ were observed at 512 Hz f_{ms} for all 66 neurons in awake rats. A subset of 13 single units, which showed decreases in RPI ($\Delta RPI > 0.3$) when switched from $SAM\Delta_{100\%}$ to $SAM\Delta_{25\%}$, showed a significant difference in group trend line slope ($P < 0.05$) (Fig. 7D).

tMTF differences across f_{ms} with decreasing SAM salience (group data)

The percentage of units showing temporal/envelope-locking responses across f_{ms} (2–128) during random or predictable presentation of $SAM\Delta_{100\%}$ stimuli were

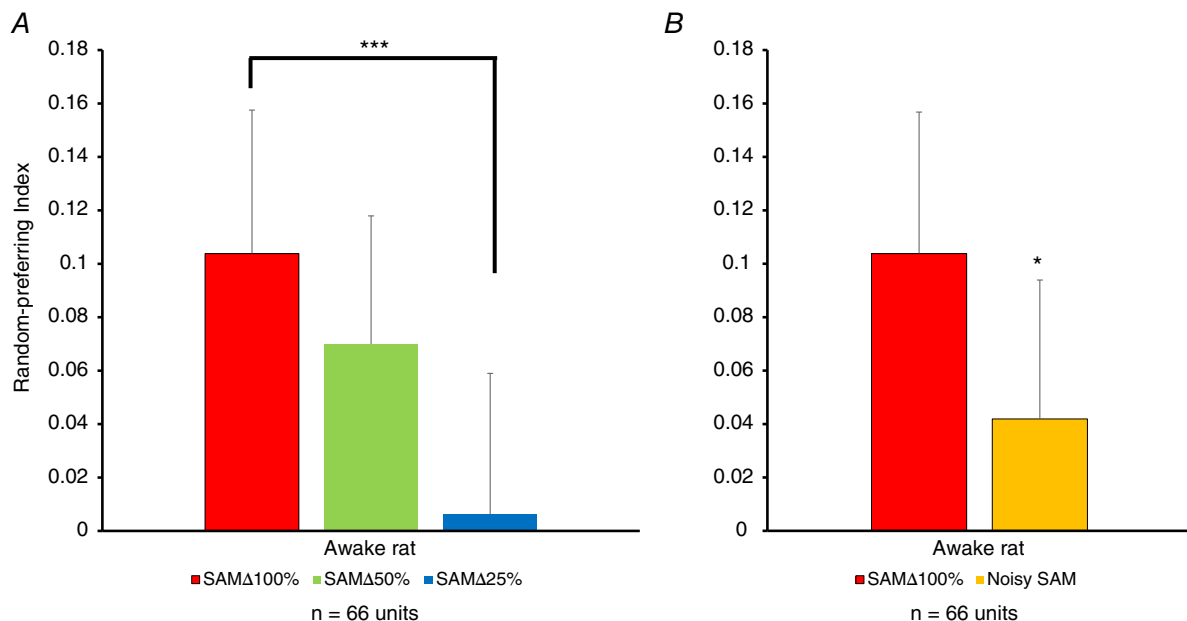


Figure 5. RPI for MGB units in awake rats across SAM stimulus sets

RPIs were calculated by finding the total AUC for random and predictable stimuli across all f_{ms} . A, consistent with findings shown in Fig. 3, the RPI recorded from awake rat MGB neurons showed a significant decrease in RPIs as SAM salience was decreased by reducing modulation depth ($SAM\Delta_{50\%}$ and $SAM\Delta_{25\%}$) B, similar to (A), jittering the stimulus (noisy SAM) showed a significant decrease in the RPI. Data are presented as the mean \pm SEM; statistical analyses were repeated-measures ANOVA followed by *post hoc* Tukey's correction using Graphpad. * $P < 0.05$; *** $P < 0.01$.

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compared with random or predictable presentation of SAM Δ _{50%}, SAM Δ _{25%} and noisy SAM (Fig. 8). A Rayleigh statistic minimum of 13.8 was used as a qualifier for the envelope-locking ability of each unit. The highest levels of locking to SAM Δ _{100%} were observed for single-unit responses near modulation frequencies centred between 8 and 16 Hz (Fig. 8). Compared to SAM Δ _{100%}, there was a significant decrease in temporal-locking ability at shallower modulation depths for both random and predictable stimuli: SAM Δ _{50%} random (at f_m 16 and 32 Hz, $P < 0.05$) and predictable stimuli presentation (at f_m 4 Hz, $P < 0.05$). SAM Δ _{25%} presented either in a random or predictable manner showed significant decreases at all f_{ms} tested ($P < 0.05$). Temporal responses to noisy SAM showed significant decreases in the percentage of units showing envelope-locking responses compared to SAM Δ _{100%} for random (at f_m 2, 4, 8, 16 and 32 Hz, $P < 0.05$) and predictable stimuli (at f_m 2, 4 and 8 Hz, $P < 0.05$). Differences between predictable and random presentation of SAM Δ _{100%}, SAM Δ _{50%}, SAM Δ _{25%} and noisy SAM stimuli were not significant. There were no significant differences in vector strength between predictable and random presentation of stimuli at different levels of salience and f_{ms} between 2 and 128 Hz (data not shown).

Discussion

In the present study, the hypothesis that age-related increases in preference coding for repeated/predictable acoustic stimuli are at least partially the result of a degraded temporal code seen in older rats and humans was tested using a degraded stimulus to simulate ageing in young animals (Tremblay *et al.* 2002; Caspary *et al.* 2008; Caspary & Llano, 2018). Consistent with our hypothesis, the presentation of less salient SAM stimuli led to a decrease in the number of neurons showing temporal/envelope locking, which mimics aged human/animal models (Caspary & Llano, 2018; Ng & Recanzone, 2018). A comparison of rate responses in single units from awake rat MGB showed a significant increase in preference for predictable stimuli and the number of spikes with each trial at a higher f_{ms} (>128 Hz) when less salient SAM stimuli were presented but not with standard SAM Δ _{100%}. This change in preference coding was not seen in units recorded from anaesthetized rat MGB. The observed relative switch from adaptive to enhanced coding for repeating/predictable, less-salient stimuli is considered to involve higher cognitive resources, which are brought into play to disambiguate the less salient acoustic message. This notion is supported by a lack of similar changes in units

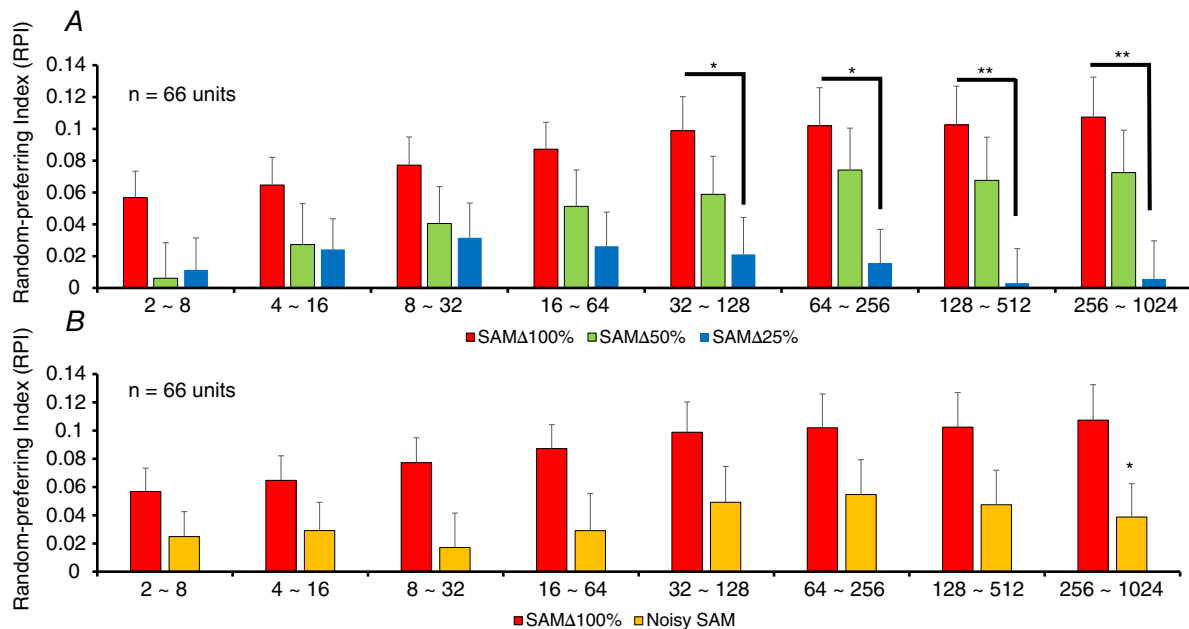


Figure 6. Comparison of RPIs across specific f_{ms} for awake rat MGB neurons in response to SAM Δ _{100%}, SAM Δ _{50%}, SAM Δ _{25%} and noisy SAM

A, RPI for MGB neurons responding to SAM Δ _{25%} showed significant decreases across higher f_{ms} of 32–128, 64–256, 128–512 and 256–1024 Hz compared to responses at SAM Δ _{100%} at the same f_{ms} . There were no significant differences between SAM Δ _{100%} and SAM Δ _{50%} at any f_{ms} . B, RPI for MGB neurons responding to noisy SAM were significantly different from SAM Δ _{100%} across f_{ms} . The significant decrease in random-preference with decreased temporal salience, when presented with SAM Δ _{25%} and noisy SAM, at higher f_{ms} is suggestive of an increase in preference for predictable stimuli at higher f_{ms} similar to previous findings in aged rats. Data are presented as the mean \pm SEM; statistical analyses were repeated-measures ANOVA with *post hoc* Tukey's correction using Graphpad. * $P < 0.05$; ** $P < 0.01$.

from anaesthetized animals in the present study, as well as by prior studies on top-down effects over bottom-up circuits and behaviour (Maunsell & Treue, 2006; Fritz *et al.* 2007; Chandrasekaran *et al.* 2009; Pelle & Wingfield, 2016; Homma *et al.* 2017; Helfer *et al.* 2018).

Effects of ageing on central auditory system and top-down processes

The present findings, obtained using temporally degraded modulated sounds in young-adult MGB units, support our hypothesis that modelled ageing using temporally degraded stimuli in young rats. These findings are consistent with studies showing an age-related increase in predictable preference or an increase in firing with repetition (de Villers-Sidani *et al.* 2010; Cai *et al.* 2016;

Cisneros-Franco *et al.* 2018). We postulated this to be the result of a temporally jittered/less salient code in aged MGB that frequently led to increases in firing with repetition. We interpret this as a mechanism for strengthening the internal representations of temporally degraded signals by engaging top-down cognitive resources. Congruent with these interpretations, previous human and animal studies also describe age-related losses in auditory temporal processing and an inability to accurately localize sound in cluttered environments (Pichora-Fuller *et al.* 2007; Dubno *et al.* 2008; Eddins & Hall, 2010; King *et al.* 2014; Harris & Dubno, 2017). Speech in noise conditions degrades speech understanding even in older individuals with healthy hearing (Pichora-Fuller *et al.* 1995). This decline in speech understanding in older individuals correlates well with a decline in temporal processing with age (Fitzgibbons & Gordon-Salant, 1994, 2011; Harris *et al.* 2012).

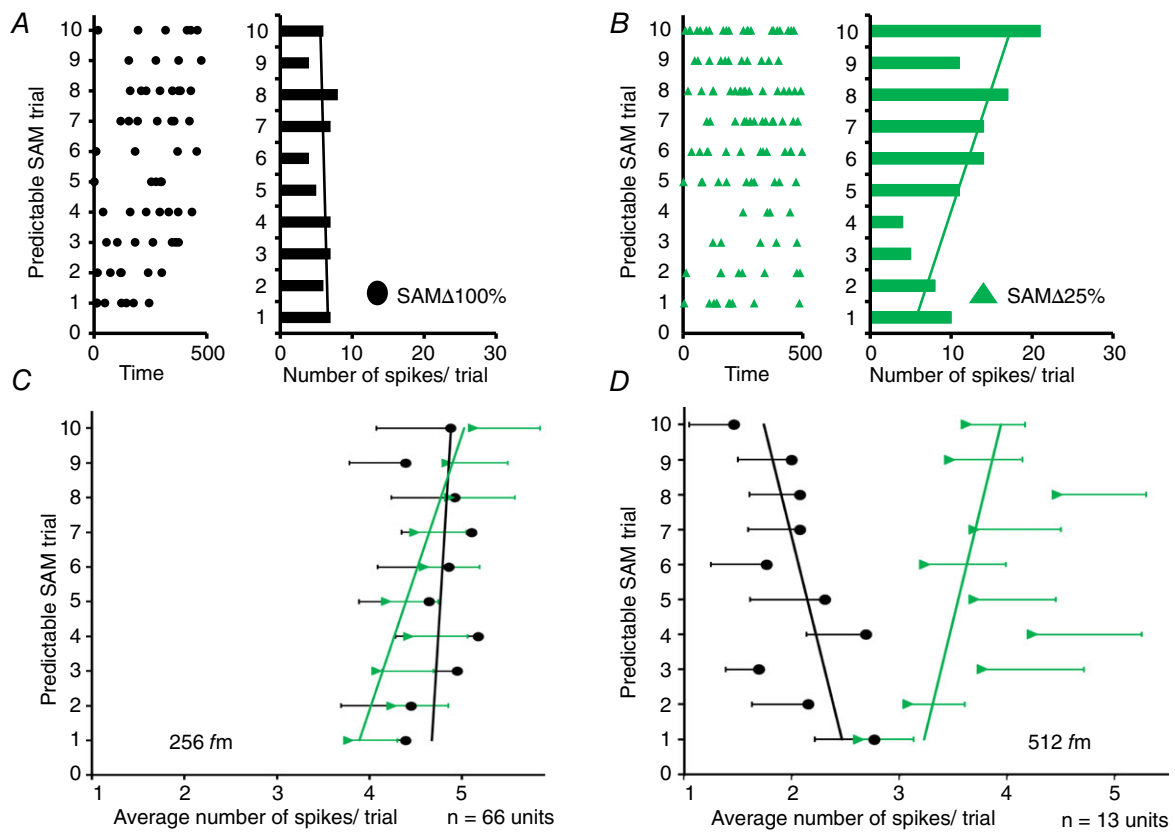


Figure 7. Trial-by-trial response analysis to predictable presentation of SAMΔ100% and SAMΔ25% at f_m 256 and 512 Hz

A, trial-by-trial measure of responses of an exemplar single-unit from the MGB of an awake rat to 10 repeating presentations of a SAMΔ100% at f_m of 256 Hz presented in predictable manner. B, responses from the same unit to 10 repeating presentations of SAMΔ25% at f_m of 256 Hz presented in a predictable manner. C, comparison of group trial-by-trial data (mean \pm SEM) of responses to predictable SAM at $f_m = 256$ Hz. The trend line slopes are significantly different for SAMΔ100% and SAMΔ25% groups when plotting average spikes to predictable presentation of 256 Hz f_m (ANCOVA, two-tailed, $P < 0.05$). D, a subset of 13 neurons (these neurons show a decrease in RPI by >0.3 when switched from SAMΔ100% to SAMΔ25%) in response to a predictable presentation of f_m at 512 Hz showed adaption with SAMΔ100% and an increase in responses with each trial of SAMΔ25% (ANCOVA, two-tailed, $P < 0.05$).

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Mechanistic insights into these deficits suggest a negative impact of ageing on the cochlea, where several studies have described some combination of sensory, neural, strial and conductive elements resulting in a decrease in the quality and intensity of sound signals reaching the central auditory system (Schuknecht & Gacek, 1993; Sergeyenko *et al.* 2013; Liberman & Kujawa, 2017; Cai *et al.* 2018). However, research conducted with normal hearing elderly humans has reported deficits in speech understanding, especially in complex acoustic environments, implicating central deficits in addition to peripheral deficits in presbycusis (Harris *et al.* 2012; Humes *et al.* 2012; Pichora-Fuller *et al.* 2017). These findings are backed by evidence obtained from human psychoacoustic studies and animal studies demonstrating disruptive age-related effects on the veracity of the ascending acoustic code in conjunction with age-related peripheral losses at the cochlea and auditory nerve fibres (Willott *et al.* 1991; Gratton *et al.* 1997; Spongr *et al.* 1997; Tang *et al.* 2014; Cai *et al.* 2018). Previous studies have also shown *de novo* age-related changes vs. deafferentation plasticity (Caspary & Llano, 2018; Occelli *et al.* 2019). Furthermore, neurochemical studies supporting the loss of speech understanding with ageing found an age-related compensatory, net down-regulation

of GABAergic and glycinergic inhibition in the cochlear nucleus, inferior colliculus, MGB and auditory cortex (Stebbins *et al.* 2014; Gao *et al.* 2015; Ouda *et al.* 2015; Godfrey *et al.* 2017; Caspary & Llano, 2018). Rodent and primate neurophysiological ageing studies highlighted an increase in discharge rates and less precise temporal-locking in central auditory structures, which are probably partly responsible for the loss of temporal processing in older humans (Pichora-Fuller & Schneider, 1992; Palombi & Caspary, 1996; Frisina, 2001; Harris *et al.* 2012; Mattys & Scharenborg, 2014; Parthasarathy *et al.* 2016; Ng & Recanzone, 2018). Modelling these less precise temporal-locked responses, as seen in aged populations, by jittering the temporal fine structure of the stimulus in young people led to decreased speech in noise recognition (Pichora-Fuller *et al.* 2007; Mamo *et al.* 2016). Similar to jitter, decreasing the depth of SAM stimuli decreases the salience of the SAM, leading to decreased perceptual ability and phase locking (Pollack & Pickett, 1963; Joris & Yin, 1992; Wingfield *et al.* 1994; Shannon *et al.* 1995; Krishna & Semple, 2000; Jorgensen & Dau, 2011; Christiansen *et al.* 2013; Srinivasan & Zahorik, 2014). Despite such temporal deficits, many older individuals can maintain speech understanding, suggesting that compensatory mechanisms are in play (Dubno *et al.* 1984; Humes *et al.* 2012; Peelle & Wingfield, 2016). This points to cognitive based resources, including attention and context-mediated enhancement of neural representations, with respect to identifying and extracting salient or difficult to identify signals in complex acoustic environments. By contrast to this compensatory strategy for enhancement, in young animals, neural representations of repeating stimuli are reduced and adapted with respect to the detection of novel stimuli (i.e. SSA) (Strange, 1989; Ohl *et al.* 1999; Ono *et al.* 2006; Davis & Johnsrude, 2007; Fritz *et al.* 2007; Shinn-Cunningham & Wang, 2008; Tremblay *et al.* 2010; Duque *et al.* 2013; Obleser, 2014; Skoe *et al.* 2014; Malmierca *et al.* 2015; Cisneros-Franco *et al.* 2018). Collectively, these studies suggest that adaptation may originate from lower structures (i.e. a bottom-up process), whereas predictions are formed by higher-order cortical structures (i.e. a top-down process) (Rao & Ballard, 1999; Anderson & Malmierca, 2013; Peelle & Wingfield, 2016; Yun Rui *et al.* 2018). However cognitive deficits are also seen with ageing (Gazzaley & Nobre, 2012). Consistent with the study by Cai *et al.* (2016), responses to SAM $\Delta_{100\%}$ showed a balance between bottom-up adaptation and descending top-down influences, reflecting a mix of random and predictable preferring neurons. In response to relatively less salient SAM $\Delta_{25\%}$, these same single units showed a clear preference for predictable signals, especially at higher f_m s (Figs 6 and 7). An absence of similar changes in anaesthetized rats is consistent with anaesthesia-related partial blockade of top-down influences, as previously

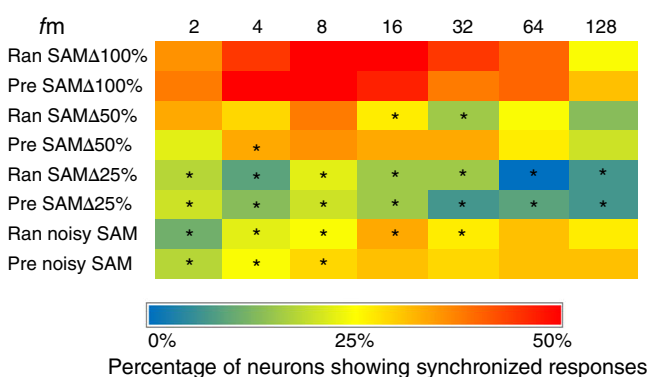


Figure 8. Percentage of neurons showing temporal-locking responses to random or predictable presentation of standard (SAM $\Delta_{100\%}$) and less salient (SAM $\Delta_{50\%}$, SAM $\Delta_{25\%}$ and noisy SAM) stimuli at lower modulation frequencies (f_m)

Each row in the heat map represents the presentation of salient or less salient stimuli either in a random or predictable manner, whereas each column represents the f_m from 2 Hz to 128 Hz. The scale below the heat map shows the colour code for the percentage of neurons (out of 66 in total) showing temporal-locking to the stimulus; hot colours (red) indicate a higher percentage of temporal-locking, whereas cool colours (blue) indicate a lower percentage of temporal-locking. Changes in the percentage of neurons showing temporal-locking when switched from standard to less salient stimuli in either random or predictable presentations are compared. There was a significant decrease in the percentage of single-units showing temporal-locking with a decrease in salience predominantly at SAM $\Delta_{25\%}$ and noisy SAM across both random and predictable presentations compared to SAM $\Delta_{100\%}$ (Wilcoxon test followed by Bonferroni correction, $P < 0.05$).

suggested by an absence of perceptual learning and cortical disconnectivity with anaesthesia (Aberg *et al.* 2009; Jordan *et al.* 2013; Mashour, 2014). These findings are in agreement with recent work showing context and experience-based predictions in humans and animals (Ostroff *et al.* 2003; Fakhri *et al.* 2012; Leung *et al.* 2013; Skoe *et al.* 2014; Sohoglu & Chait, 2016; Parras *et al.* 2017; Schwartz & David, 2018). Furthermore, repetition-induced increases in speech understanding, as well as improvements in the visual recognition of degraded objects with repetition, provide evidence in support of our interpretation of an increased response to degraded predictable stimuli (Rivenez *et al.* 2006; Muller *et al.* 2013; Helfer *et al.* 2018). Collectively, these results lend support to the hypothesis that less salient stimuli/degraded ascending acoustic code can be compensated for by an increased use of cortical cognitive (experience/contextual) and attentional resources (Bertoli *et al.* 2001; Alain *et al.* 2014; Bidelman *et al.* 2014; Presacco *et al.* 2016a; Lesicko & Llano, 2017).

Effects of ageing and top-down processes in the medial geniculate body

In the present study, less salient stimuli not only altered the preference for predictable stimuli, but also showed a decrease in envelope-locking. These results support our stimulus choice aimed at simulating temporal processing deficits observed with ageing, which are partly mediated by neurotransmitter-deficits with ageing. Age-related changes in neurotransmission impact upon the function of descending and ascending projections to the MGB, which include decreased tonic GABA currents, as well as pre- and post-synaptic changes in cholinergic receptors, and are considered to be involved in gating/modulating MGB representations (Banay-Schwartz *et al.* 1989; Richardson *et al.* 2013b; Godfrey *et al.* 2017; Sottile *et al.* 2017a; Sottile *et al.* 2017b). However, Richardson *et al.* (2013a) failed to find evidence of age-related physiological changes in MGB function using short duration pure tone SSA paradigm (Richardson *et al.* 2013a). A second ageing MGB study by Cai *et al.* (2016) used complex longer duration SAM stimuli stepped between 2 and 1024 f_m and found significant age-related changes in the response properties of MGB neurons when a random presentation was compared with a predictable/repeating presentation of stimuli. These findings are consistent with studies performed in aged rat auditory cortex showing a decrease in SSA (de Villers-Sidani *et al.* 2010; Cisneros-Franco *et al.* 2018). The use of a relatively long SAM stimulus is more complex than the short pure tones used in most SSA studies and may more closely represent animal vocalizations and human speech. These results are consistent with previous studies using more complex (frequency modulated and harmonic complex

tones) stimuli instead of pure tones, which also found an increased use of top-down resources, possibly via corticothalamic projections for sound detection. Previous MGB studies on corticothalamic stimulation have shown simulated top-down modulatory effects on responses in learning and discrimination studies in many species, including ferret, mouse, cat, gerbil, rat, guinea pig, bat and monkey (Orman & Humphrey, 1981; Zhang *et al.* 1997; Ohl *et al.* 1999; He, 2003; Ono *et al.* 2006; Rybalko *et al.* 2006; Wetzell *et al.* 2008; Guo *et al.* 2017; Homma *et al.* 2017; Barczak *et al.* 2018). Recently, Guo *et al.* (2017) examined the impact of corticothalamic stimulation on MGB discharge properties and a sound detection task. They found a gain in MGB activity that lasted for 150 ms post-stimulation, which was associated with enhanced sound detection (Guo *et al.* 2017). Few studies have investigated the effect of corticothalamic stimulation with ageing on MGB physiology (Sottile *et al.* 2017a; Sottile *et al.* 2017b). Apart from modulating MGB response properties, corticothalamic projections are implicated in the switching from temporal to rate code, possibly involving some combination of short-term NMDA/AMPA and long-term mGluR-dependent mechanisms (Lu *et al.* 2001; Bartlett & Smith, 2002; Bartlett & Wang, 2007; Wang *et al.* 2008; Rabang & Bartlett, 2011; Cai & Caspary, 2015). Although, in the present study, we found no differences in envelope-locking between random and predictable presentation of less salient stimuli, we observed increases in the rate responses with repeated presentation. Differences between dorsal vs. ventral units should be carefully addressed in the future as a result of differences in afferent projections and the physiology between MGB subdivisions (Bartlett 2013). Future studies should aim to further examine our understanding of the top-down effects on predictive coding using a direct activation/deactivation of corticothalamic neurons that addresses the role of ageing in corticothalamic modulation at the MGB.

In conclusion, the present study found that the temporal degradation of a modulated stimulus appears to simulate the temporally degraded ascending acoustic code seen in the elderly, leading to an increased preference for repeating/predictable stimuli in young animals. Furthermore, temporally degraded stimuli increase firing responses to successive repetitions of the same stimulus, as observed in previous studies, suggesting that repetition as a top-down strategy to better internalize representations (Muller *et al.* 2013; Helfer *et al.* 2018).

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Additional information

Competing interests

The authors declare that they have no competing interests.

Author contributions

SPK was responsible for data acquisition, data analyses and drafting the manuscript. SPK, RC and DMC were responsible for the interpretation of data. SPK, RC, ELB and DMC were responsible for revising the manuscript. RC and ELB were responsible for the study concept. SPK, RC, ELB and DMC were responsible for the study design. All of the experiments were conducted in the laboratory of DMC at SIU School of Medicine. All of the authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work with respect to ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and all persons designated as authors qualify for authorship, and all those who qualify for authorship, and all those who qualify for authorship are listed.

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