JNeurosci
THE JOURNAL OF NEUROSCIENCE

Research Articles | Behavioral/Cognitive

Two prediction error systems in the nonlemniscal inferior colliculus: 'spectral' and 'non-spectral'

https://doi.org/10.1523/JNEUROSCI.1420-23.2024

Received: 27 July 2023
Revised: 3 April 2024
Accepted: 10 April 2024

Two prediction error systems in the nonlemniscal inferior colliculus: 'spectral' and 'non-spectral'

Guillermo V. Carbajal[1,2], Lorena Casado-Román[1,2] & Manuel S. Malmierca[1,2,3*]

[1] Cognitive and Auditory Neuroscience Laboratory (CANELAB), Institute of Neuroscience of Castilla y León (INCYL), Salamanca, Spain
[2] Institute for Biomedical Research of Salamanca (IBSAL), Salamanca, Spain
[3] Department of Cell Biology and Pathology, Faculty of Medicine, University of Salamanca, Salamanca, Spain
* Corresponding author

ORCID

GVC: https://orcid.org/0000-0001-5266-1941

LCR: https://orcid.org/0000-0002-9583-2402

MSM: https://orcid.org/0000-0003-0168-7572

eMails

MSM: msm@usal.es, phone +34 923 294 500 ext. 5301 or ext. 6571 or ext. 5333

Abbreviated title: Two PE systems in the IC cortices

Keywords: SSA/stimulus-specific adaptation, deviance detection, repetition suppression, predictive processing, subcortical, single units, linear model.

Number of pages: 79

Number of figures (7) **and tables** (3)

Number of words for abstract (250), **introduction** (648) **and discussion** (1500)

Conflict of interest: The authors declare no competing financial interests.

Acknowledgments: This work was supported by the Spanish Ministry of Science and Innovation (MICIN) [grant number PID2019-104570RB-I00]; the Ramón Areces Foundation, Madrid, Spain [grant number CIVP20A6616]; and a MICIN PhD Fellowship held by GVC [grant number BES-2017-080030]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank Drs Edward L Bartlett and Douglas L Oliver for their insightful comments on preliminary versions of this manuscript. We thank Drs Javier Nieto-Diego, Gloria G Parras, and Catalina Valdés-Baizabal for facilitating data to increase our samples. We also thank Mr Antonio Rivas Cornejo and Ms María Torres Valles for their support with histological procedures.

Abstract

According to the predictive processing framework, perception emerges from the reciprocal exchange of predictions and prediction errors (PE) between hierarchically organized neural circuits. The nonlemniscal division of the inferior colliculus (IC) is the earliest source of auditory PE signals, but their neuronal generators, properties and functional relevance have remained mostly undefined. We recorded single-unit mismatch responses to auditory oddball stimulation at different intensities, together with activity evoked by two sequences of alternating tones to control frequency-specific effects. Our results reveal a differential treatment of the unpredictable 'many-standards' control and the predictable 'cascade' control by lemniscal and nonlemniscal IC neurons that is not present in the auditory thalamus or cortex. Furthermore, we found that frequency response areas of nonlemniscal IC neurons reflect their role in subcortical predictive processing, distinguishing 3 hierarchical levels: (1) Nonlemniscal neurons with sharply tuned receptive fields exhibit mild repetition suppression without signaling PEs, thereby constituting the input level of the local predictive processing circuitry. (2) Neurons with broadly tuned receptive fields form the main, 'spectral' PE signaling system, which provides dynamic gain compensation to near-threshold unexpected sounds. This early enhancement of saliency reliant on spectral features was not observed in the auditory thalamus or cortex. (3) Untuned neurons form an accessory, 'non-spectral' PE signaling system, which reports all surprising auditory deviances in a robust and consistent manner, resembling nonlemniscal neurons in the auditory cortex. These nonlemniscal IC neurons show unstructured and unstable receptive fields that could result from

inhibitory input controlled by corticofugal projections conveying top-down predictions.

Significant Statement

Frequency response areas of nonlemniscal neurons in the inferior colliculus correlate with certain predictive processing traits, distinguishing two prediction error systems. The 'spectral' system comprises neurons with broadly tuned receptive fields and is exclusively at play in the nonlemniscal inferior colliculus. It generates prediction errors only to low-intensity deviant sounds and is biased towards ascending changes in frequency. Hence, it provides early gain compensation to near-threshold but informative acoustic events, thereby facilitating efficient auditory discrimination under challenging conditions. The 'non-spectral' PE system reports on unexpected auditory events, uninfluenced by the acoustic spectral characteristics of deviant sounds. This accessory system comprises untuned neurons with disorganized and dynamic receptive fields, which conceivably receive top-down predictions from higher-order levels of the auditory hierarchy.

List of Abbreviations

AC: auditory cortex.

CAS: cascade control condition.

SPL: sound pressure level.

DEV: deviant condition.

FRA: frequency response area.

IC: inferior colliculus.

iMM: index of neuronal mismatch.

iPE: index of prediction error.

iRS: index of repetition suppression.

MGB: medial geniculate body.

MSC: many standards control condition.

PE: prediction error.

STD: standard condition.

U-neurons: nonlemniscal IC neurons showing U-shaped FRAs.

V-neurons: nonlemniscal IC neurons showing V-shaped FRAs.

W-neurons: nonlemniscal IC neurons showing multipeaked FRAs.

X-neurons: nonlemniscal IC neurons showing mosaic FRA

Introduction

Probability-biased processing of auditory input first appears at the inferior colliculus (IC; for review, see Malmierca et al., 2019). During an auditory oddball paradigm (Figure 1A), certain IC neurons reduce discharges to standard (STD) tones while responding vigorously to deviant (DEV) conditions (Malmierca et al., 2009). The resulting neuronal mismatch response has been interpreted as early predictive activity within the auditory pathway (for reviews, see Carbajal and Malmierca, 2018, 2020; Tabas and von Kriegstein, 2021). According to the predictive processing framework (Friston, 2003, 2009, 2010; Hohwy, 2013), high-order neural networks develop predictions to inhibit input from lower levels when it fits into the current predictive model, while lower-order levels signal back prediction errors (PE) whenever expectations are not met. Although hierarchical predictive processing was originally conceived for cortical networks (Rao and Ballard, 1999; Friston, 2005; Friston and Kiebel, 2009a; Bastos et al., 2012; Keller and Mrsic-Flogel, 2018), empirical testing in the auditory system is expanding the framework into subcortical territory, as early as the IC (Parras et al., 2017; Tabas et al., 2020; Valdés-Baizabal et al., 2020; Lesicko et al., 2022; Tabas and von Kriegstein, 2024).

The IC constitutes a crucial relay station of the ascending auditory pathway that gives rise to two parallel lines of processing (Cant and Oliver, 2018; Liu et al., 2024). The lemniscal pathway that emerges from the central nucleus presents a sharp tonotopy with minimal cortical input, whereas the nonlemniscal pathway that originates from the IC cortices shows a blurred tonotopy under heavy cortical input (Schreiner and Langner, 1997; Malmierca, 2015). In a previous study

(Parras et al., 2017), we performed extracellular recordings in both divisions of the IC (Figure 1C), medial geniculate body (MGB) of the thalamus, and auditory cortex (AC), while controlling frequency-specific adaptation induced during the oddball paradigm (Figure 1A) by means of two control sequences of alternating tones without consequent repetitions: cascade (CAS) and many-standards control (MSC; Figure 1B; Ruhnau et al., 2012). Using control-evoked activity as a benchmark, each neuronal mismatch response was dissociated in two components: (1) repetition suppression (Garrido et al., 2009a; Auksztulewicz and Friston, 2016; Grotheer and Kovács, 2016), indexed as attenuation of the STD-evoked response that could be accounted for by frequency-specific effects (Mill et al., 2011; Taaseh et al., 2011); and (2) PE, indexed as an enhancement of the DEV-evoked response due to predictive processing activity (Figure 1D). This study revealed the IC cortices as the earliest source of auditory PE signals, which amplified as they ascended through the nonlemniscal pathway into the AC in a hierarchical distribution (Parras et al., 2017). Combining this method (Figure 1) with microiontophoresis unveiled that this early flow of PE signals is modulated by dopaminergic input (Valdés-Baizabal et al., 2020). A recent study using optogenetic inactivation of the auditory corticocollicular feedback in awake mice revealed the critical role of top-down input in subcortical PE signaling (Lesicko et al., 2022). Neuroimaging data from humans also reflect predictive activity at midbrain level (Slabu et al., 2012; Cacciaglia et al., 2015; Tabas et al., 2020; Tabas and von Kriegstein, 2024). However, an in-depth analysis of neural generators and functional properties of early auditory PEs is still lacking.

The present study aims to characterize the unique traits of PE signaling in the IC, as compared to that in the MGB and AC, by correlating it with sound

intensity, direction of frequency changes, and neuronal receptive fields. Our results reveal a dual nature of predictive processing in the IC cortices that is not present in higher regions of the auditory pathway. PE signaling in nonlemniscal IC neurons with broad receptive fields is fundamentally dependent on certain spectral features, whereas untuned neurons with unstructured and dynamic receptive fields disregard acoustic aspects when reporting unexpected input. For descriptive purposes, we will refer to the distinct predictive activity of these two neural populations, respectively, as the 'spectral' and 'non-spectral' PE systems of the IC cortices.

Materials and Methods

Ethics Statement

All surgical procedures were approved by the Bioethics Committee for Animal Care of the University of Salamanca (USAL-ID-195 and USAL-ID-574) and performed in compliance with the standards of the European Convention ETS 123, the European Union Directive 2010/63/EU, and the Spanish Royal Decree 53/2013 for the use of animals in scientific research.

Surgical procedures

The surgical and recording procedures were as described elsewhere (Nieto-Diego and Malmierca, 2016; Parras et al., 2017; Valdés-Baizabal et al., 2020). Surgical anesthesia was first induced with (1) a mixture of ketamine

(100 mg/Kg) and xylazine (20 mg/Kg) injected intramuscularly and then maintained with urethane (0.8 g/Kg) injected intraperitoneally or (2) directly induced with urethane (1.5 g/kg, intraperitoneally). To ensure a stable deep anesthetic level, supplementary doses of urethane (~0.5 g/Kg) were administrated intraperitoneally when the rat recovered pedal withdrawal reflexes. Urethane was chosen over other anesthetic agents because it preserves normal neural activity better, having a modest, balanced effect on inhibitory and excitatory synapses (Maggi and Meli, 1986; Hara and Harris, 2002; Sceniak and MacIver, 2006; Duque et al., 2016).

Normal hearing of rats was verified by recording the auditory brainstem responses subcutaneously with needle electrodes. An RZ6 Multi I/O Processor (Tucker-Davis Technologies) was used to acquire the auditory brainstem response, which was processed with BioSig software (Tucker-Davis Technologies) before beginning each experiment. Stimuli used to elicit the auditory brainstem response consisted of 0.1 ms clicks at a rate of 21 clicks/s, delivered monaurally to the right ear in 10 dB steps, from 10 to 90 decibels of sound pressure level (dB SPL), in a closed system through a Beyer DT-770 earphone (0.1–45 kHz) fitted with a custom-made cone and coupled to a small tube (12 G) sealed in the ear.

Once normal hearing had been confirmed, a cannula was installed in the trachea to provide artificial ventilation to the rat with monitored expiratory CO_2, given that urethane depresses respiratory function. Likewise, to maintain body temperature at 37±1 ºC, rats were introduced a rectal thermometer and placed on a homeothermic blanket system (Cibertec). The head was stabilized in a

stereotaxic frame with a bite bar and 2 hollow specula replacing the ear bars. A sound delivery system was accommodated within the right hollow speculum. Eyes were protected with a drop of ophthalmic gel. To prevent an excess of bronchial secretions, 0.1 mg/Kg of atropine sulfate was administrated subcutaneously. To ameliorate brain edema, 0.25 mg/Kg of dexamethasone was injected intramuscularly. To prevent dehydration, 5 mL of glucosaline solution was administrated subcutaneously. The scalp was shaved, and the revealed skin was disinfected with povidone-iodine. Using a scalpel, an incision was opened along the midline to expose the skull, and the periosteum covering the parietal and the most rostral part of the occipital bones was retracted. Using a dental drill, a round craniotomy was performed in the caudal part left parietal bone, just rostral to the lambdoid suture and lateral to the sagittal suture, thereby exposing the cerebral cortex overlying the left IC. The exposed dura was removed, and the tissue beneath it was covered with 2% agar to prevent desiccation during the recording session.

Data acquisition procedures

The dataset used in this study is a compilation of extracellular single-unit recordings performed throughout a period of 7 years following the same experimental design (Figure 1). Most of the neurons from the MGB and the AC have featured in previous studies (Parras et al., 2017, 2021; Pérez-González et al., 2021). In the present study, they are combined and reanalyzed for the purpose of comparing their population trends with those of the IC, which is the focus of the present study. Regarding the IC, 125 neurons in the current dataset

have featured in two preceding studies (Parras et al., 2017; Valdés-Baizabal et al., 2020), while the remaining 190 units of the sample (60 %) were specifically recorded for this purpose. We will describe the acquisition procedures for these IC data in the following, while the methods followed for the MGB and AC data are detailed elsewhere (Parras et al., 2017).

Tungsten microelectrodes used to record the extracellular activity of IC neurons were crafted with a tip impedance of 1.5–3.5 MΩ at 1 kHz following the ensuing protocol (Merrill and Ainsworth, 1972). Experiments were performed inside a sound-insulated and electrically shielded chamber. The microelectrode was mounted on a holder over the exposed cortex, forming an angle of 20° perpendicularly rostral to the coronal plane. Using a piezoelectric micromanipulator (Sensapex), the electrode was inserted into the brain while measuring the penetration depth until strong spiking activity synchronized with the train of searching stimuli could be identified. All sound stimuli were generated using the RZ6 Multi I/O Processor (Tucker-Davis Technologies) and custom software programmed with OpenEx Suite (Tucker-Davis Technologies) and MATLAB (Mathworks). In search of evoked auditory neuronal responses from the IC, white noise bursts and sinusoidal pure tones of 75 ms duration with 5 ms rise-fall ramps were presented, varying stimuli parameters manually to prevent frequency-specific adaptation.

Once the activity of a single neuron was clearly isolated, only pure tones were used to record the experimental stimulation protocols, which ran at 4 stimuli per second. Stimuli were delivered monaurally to the ear contralateral to the left IC through a close-field speaker. We calibrated the speaker using a ¼-inch

condenser microphone (model 4136, Brüel&Kjær) and a dynamic signal analyzer (Photon+, Brüel&Kjær) to ensure a flat spectrum up to 76 ± 3 dB SPL between 0.5 and 45 kHz, and that the second and third signal harmonics were at least 40 dB lower than the fundamental at the loudest output level.

Analog signals were digitized with a RZ6 Multi I/O Processor, a RA16PA Medusa Preamplifier, and a ZC16 headstage (Tucker-Davis Technologies) at 12 kHz sampling rate and amplified 251×. Neurophysiological signals of spiking activity were band-pass filtered between 0.5 and 3 kHz using a second-order Butterworth filter. Stimulus generation, neuronal response processing, and visualization were controlled online with custom software created with the OpenEx suite (Tucker-Davis Technologies) and MATLAB. A unilateral threshold for automatic action potential detection was manually set at about 2–3 standard deviations of the background noise. Spike waveforms were displayed on the screen and overlapped on each other in a pile plot to facilitate isolation of single unit activity. The recorded action potentials were considered to belong to a single unit only when all spike waveforms were akin, clearly separable from other smaller units and the background noise, and the spike-amplitude-to-noise-ratio of the average waveform was larger than 5.

$$Signal/Noise\ Ratio = \frac{\max\left(\bar{x}(waveforms)\right) - \min(\bar{x}(waveforms))}{Std(waveforms)}$$

Experimental design

A map of response magnitude for each frequency-intensity combination was first computed, representing the receptive field of the single unit in a

frequency response area (FRA; Figures 4A and 5A). The stimulation protocol to obtain the FRA consisted of a sequence of sinusoidal pure tones ranging between 0.7–44 kHz, 75 ms of duration with 5 ms rise-fall ramps, presented at a 4 Hz rate, randomly varying frequency and intensity (3–5 repetitions of all tones).

Then, 10 frequencies separated by 0.5 octave steps at a fixed sound intensity (usually 10–20 dB above minimal response threshold) were selected so that at least 2 consecutive tones fell within the excitatory region of the FRA. These 10 tones were used to generate the control sequences (Figure 1B), and adjacent pairs within the excitatory region of the FRA were used to create oddball sequences (Figure 1A). All sequences were 400 tones in length, presented at a constant rate of 4 Hz and at a constant intensity between 10 and 70 dB SPL, in steps of 10 dB SPL.

A first complete experimental set, comprised of oddball and control sequences in both their 'ascending' and 'descending' versions (Figure 1A and B), was presented at a chosen intensity. Whenever it was possible to maintain a certain neuron isolated over a long period of time, another set would be presented at a different intensity. Usually, one intensity would be <40 dB SPL (low) and the other >40 dB SPL (high), but this depended on the receptive field of each neuron as shown by the FRA. The presentation of a set at different intensity levels did not follow any particular order. Sometimes the stability of the signal allowed to record multiple complete sets of sequences at several levels of intensity. However, such occurrence was relatively rare, since our recording protocol did not permit re-isolation attempts. When signal quality dropped below standards, the recording was interrupted, and the incomplete set discarded.

A 10% probability was used to pseudo-randomly distribute tones across control sequences within chunks of 10 stimuli, as well as to scatter DEV tones across the oddball sequence. Since only the last STD tones before a DEV were considered for analysis, this method resulted in 40 trials of DEV, STD, MSC and CAS for each given tone of interest. In the oddball paradigm, the first 10 tones were always STD, and a minimum of 3 STD preceded each DEV, which were pseudo-randomly presented with a 10% probability. Oddball sequences were labeled either 'ascending' or 'descending', depending on whether DEV had a higher or lower frequency than STD, respectively (Figure 1A). DEV and STD conditions of the oddball paradigm will be used to obtain neuronal mismatch measurements.

One limitation of the neuronal mismatch measurements obtained using the oddball paradigm is that the activity related to high-order processes of PE signaling cannot be distinguished from lower-order effects such as frequency-specific adaptation (Todorovic and de Lange, 2012; Carbajal and Malmierca, 2018). The controls allow assessing the relative contribution of both higher- and lower-order processes to the overall mismatch response (Ruhnau et al., 2012). These controls of the auditory oddball paradigm are tone sequences that must meet 3 criteria: (1) to feature the same tone of interest with the same presentation probability as that of the DEV (i.e., 10%); (2) to induce an equivalent state of refractoriness by presenting the same rate of stimulus per second (i.e., 4 Hz); and (3) to present no recurrent repetition of any individual stimulus, especially the tone of interest (Carbajal and Malmierca, 2020).

These 3 presentation criteria prevent the short-term dynamics of frequency-specific adaptation in the IC while keeping the long-term dynamics at a minimum (Zhao et al., 2011). Eliminating this minimum would be impractical due to the long-lasting effects of frequency-specific adaptation, which in the rat IC have been reported at presentation rates of up to 1 repetition per second (Pérez-González et al., 2005; Zhao et al., 2011). Consequently, even DEV-evoked responses manifest some marginal frequency-specific adaptation (Malmierca et al., 2009), and will similarly affect tones in a control sequence when presented at equal rate and probability. Note that the objective of these criteria is not to avoid inducing frequency-specific adaptation altogether during the control sequences. Their aim is to guarantee that the response to the tone of interest is subject to similar amounts of refractoriness and adaptation in DEV and control conditions, thereby allowing comparisons to reveal the influence of higher-order processes.

Hence, we can assess the portion of the mismatch response (DEV–STD) that can be attributed to frequency-specific adaptation induced during the STD train (Ulanovsky et al., 2003; Jääskeläinen et al., 2004; Mill et al., 2011). When the auditory-evoked response is similar or higher during the control than in DEV, then the mismatch response can be fully accounted for by repetition suppression, and no higher-order process of PE signaling can be deduced (i.e., DEV ≤ control; Figure 1D). Otherwise, a stronger response to DEV than to the control unveils a component of the mismatch response that can be better explained by PE signaling (i.e., DEV > control; Figure 1D).

To dissociate the relative contribution of frequency-specific effects from genuine PE signaling (Figure 1D), we generated 2 different controls for our oddball paradigms: MSC and CAS (Figure 1B). MSC presents the tone of interest embedded in a random sequence of assorted tones, where each tone shares the same 10% presentation probability as DEV in the oddball paradigm (Schröger and Wolff, 1996; Jacobsen et al., 2003). However, some authors have argued that the MSC is not fully comparable with the oddball paradigm, inasmuch as the disorganized succession of tones creates a context of uncertainty that never allows to generate high-precision predictions, whereas STD does (Ruhnau et al., 2012; Harms et al., 2014). Additionally, each tone is preceded by a different tone from trial to trial, which makes it difficult to control any possible effects of spectral processing caused by the differences in frequency steps.

CAS tries to overcome the alleged caveats of MSC by presenting tones in a regular fashion, e.g., in an increasing or a decreasing frequency succession or scale. Thus, the stimulus of interest conforms to a regularity—as opposed to DEV—, but not a regularity established by repetition—contrary to STD—, thereby restricting possible frequency-specific effects to a minimum while making CAS a more fitted control than MSC. As an additional advantage, the tone immediately preceding the tone of interest is the same in both oddball and cascade sequences, since only versions following the same direction will be compared (i.e., DEV-ascending versus CAS-ascending, DEV-descending versus CAS-descending). This allows to control for possible spectral sensitivity effects, which are responses to a rise or fall in frequency between 2 successive tones. For these reasons, CAS is usually regarded as a better control for the oddball paradigm (Ruhnau et al., 2012; Harms et al., 2014).

Histology and neuroanatomical location

At the end of each experiment, electrolytic lesions were inflicted by applying an electric current of 5 μA during 5 s through the recording electrode along the recorded tract. If still alive, animals were sacrificed by injecting a lethal dose of pentobarbital, after which they were decapitated. Brains were immediately immersed in a mixture of 4% formaldehyde in 0.1 M PB. After fixation, the neural tissue was cryoprotected in 30% sucrose and sectioned in the coronal plane at 40 μm thickness on a freezing microtome. Slices were stained with 0.1% cresyl violet to facilitate identification of cytoarchitectural boundaries. Finally, the recorded neurons were assigned to one of the main subdivisions of the IC using the standard sections from a rat brain atlas as reference (Paxinos and Watson, 2007).

The main dataset is comprised of 315 auditory neurons recorded in the IC of 51 anesthetized Long Evans rats. Additionally, 161 neurons from the MGB of 34 rats, and 181 neurons from the AC of 51 rats from our lab's database were included in this study for comparative purposes. Histological examination of the IC samples revealed that 70 neurons came from the central nucleus of the IC, the lemniscal division. The other 245 collicular neurons were in the cortical regions of the IC, the nonlemniscal division. MGB samples were comprised of 58 lemniscal (ventral division) and 103 nonlemniscal neurons (dorsal and medial divisions). The AC sample included 119 neurons from the lemniscal core (primary, anterior, and ventral fields) and 62 neurons from the nonlemniscal belt (posterior and suprarhinal fields).

Data analysis and visualization

All data analyses and data visualization were performed with MATLAB software, using the built-in functions, the Statistics and Machine Learning toolbox, and custom scripts and functions developed in our laboratory.

Code accessibility

All data and codes used in this study are available upon direct request to the corresponding author.

Baseline-corrected spike counts

Taking the 40 trials available for each tone (kHz) within each condition (DEV, STD, MSC and CAS), a peristimulus time histogram was computed to represent the action potential density over time in spikes per second from −75 to 250 ms around stimulus onset. This histogram was smoothed with a 6 ms Gaussian kernel (*ksdensity* function in MATLAB) in 1 ms steps to estimate the spike-density function over time. The baseline spontaneous firing rate was determined as the average firing rate (in spikes/s) during the 75 ms preceding stimulus onset. The excitatory response was measured as the area below the spike-density function and above the baseline spontaneous firing rate, between 0 and 180 ms after stimulus onset. In other words, the average level of spontaneous firing within the -75–0 ms time window was subtracted from the

activity recorded within the 0–180 ms time window, thereby obtaining a measurement of the evoked firing activity that is referred to as the *baseline-corrected spike count*.

After subtracting the spontaneous activity, we used a Monte Carlo method to find statistically significant responses evoked by sound within the resulting baseline-corrected spike counts. This approach consists of a probability simulation that withdraws numerical values from several random samplings. First, 1000 peristimulus time histograms were simulated using a Poisson model with a constant firing rate equal to the baseline spontaneous firing rate. With this collection of histograms, we generated a null distribution of baseline-corrected spike counts. Finally, we computed the *p* value of the original baseline-corrected spike count as $p = (g + 1)/(N + 1)$, where g is the count of null measures greater than or equal to the baseline-corrected spike count and $N = 1000$ is the size of the null sample. Hence, the Monte Carlo method allowed us to remove any unit-frequency combinations without significant firing activity evoked in response to at least one of the conditions in each experimental set (DEV, STD, or control).

Calculation of predictive processing indices

CAS and MSC were introduced to control for the repetition effects of the oddball paradigm, allowing a dissociation of frequency-specific adaptation into *PE* and repetition suppression components. To adequately compare between responses from different neurons, the spike count evoked by each tone in DEV, STD, and control was normalized as follows:

$$DEV_N = \frac{DEV}{N} \; ; \; STD_N = \frac{STD}{N} \; ; \; control_N = \frac{control}{N}$$

Where,

$$N = \sqrt{DEV^2 + STD^2 + control^2}$$

From these normalized responses, we computed the indices of *neuronal mismatch* (iMM), *repetition suppression* (iRS), and *prediction error* (iPE) as:

$$iMM = DEV_N - STD_N$$

$$iRS = control_N - STD_N$$

$$iPE = DEV_N - control_N$$

These indices range between -1 and 1. The iMM is largely equivalent to the classic Common Stimulus-Specific Adaptation Index (Ulanovsky et al., 2003; see Supplementary Figure 2 in Parras et al., 2017).

Lastly, to analyze the emergence of predictive signals around stimulus presentation, we also calculated the average iPE in 8 time windows of 20 ms width from −50 to 190 ms relative to stimulus onset.

FRA analysis and classification

We investigated whether PE signaling in the IC was influenced by the neuronal tuning bandwidth, considering the different morphologies that the FRA of IC neurons can exhibit (Figures 4A and 5A). First, the characteristic frequency (kHz) within each FRA was identified as the sound frequency that evoked a response with the lowest sound intensity. Then, the bandwidth at 30 dB SPL

above threshold was measured for each unit by calculating the difference between the base 2 logarithms of the upper and lower frequencies of the tuning curve, expressed in kHz. The most used measure to express the sharpness of frequency tuning is the Q factor. Q_n is defined as the characteristic frequency divided by the bandwidth in kHz at 'n' dB above threshold. Thus, the Q_{30} was calculated, and its correlation with the iPE was tested.

In addition, each FRA was classified according to its shape. We established 4 categories following criteria adapted from Hernández et al., (2005):

V-shaped FRAs (V; Figures 4A and 5A, first plot) must show a primary-like receptive field, similar to those observed in the auditory nerve fibers. These FRAs exhibit a very steep high frequency slope and a shallower low frequency slope. The low frequency slope might comprise two segments separated by an elbow. One of the low frequency segments has a steeper slope and extends from the tip of the FRA to about 35 dB or more above threshold. The second segment has a very shallow slope, forming the so-called low frequency tail, but it is not always present. For concision, in the text we will refer to nonlemniscal IC neurons showing V-shaped FRAs simply as 'V-neurons' or sharply tuned neurons.

Multipeaked FRAs (W; Figures 4A and 5A, second plot) had two or more excitatory regions separated by an area of little or no response. These FRAs had to meet 3 criteria: (1) the thresholds of at least two of the peaks had to differ by ≤ 30 dB; (2) separation between peaks had to be maintained for levels ≥ 20 dB above minimum thresholds; and (3), firing rate in the peaks had to be of at least ≥ 1 spike per trial. For concision, in the text we will refer to nonlemniscal IC neurons showing multipeaked FRAs simply as 'W-neurons'.

U-shaped FRAs (U; Figures 4A and 5A, third plot) responded similarly to a wide range of frequencies at its threshold level and presented relatively shallow slopes on the sides. For concision, in the text we will refer to nonlemniscal IC neurons showing U-shaped FRAs simply as ‘U-neurons’. W-neurons and U-neurons may also be collectively referred to as broadly tuned neurons.

Mosaic FRAs (X; Figures 4A and 5A, fourth plot) comprised several islands of response and/or inhibition, without revealing any consistent characteristic frequency or clear tuning. These islands of response did not form any particular or stable shape, showing dynamic changes between different mappings of the FRA. For concision, in the text we will refer to nonlemniscal IC neurons showing mosaic FRAs simply as ‘X-neurons’ or untuned neurons.

Our sample did not include some non-V-shaped FRA types featured in other IC studies, such as narrow, closed, high-tilt, and low-tilt FRAs (Hernández et al., 2005; Palmer et al., 2013). This could be due to an experimental bias introduced while choosing adequate neurons to record responses to our stimulation protocol. Narrow, closed, high-tilt, and low-tilt FRAs reflect rather small receptive fields, with little responsive space to place stimuli to generate oddball paradigms and control sequences. Hence, neurons with small receptive fields were most likely deemed unfit for recording the stimulation protocol by the experimenters.

Statistical hypothesis testing

Statistical analyses were carried out using distribution-free, nonparametric tests. These included the Friedman test for baseline-corrected spike counts and normalized responses to DEV, STD, and each control condition (CAS or MSC), as well as for the iMM, iRS, and iPE. For multiple comparison tests, *p* values were corrected for false discovery rate (FDR = 0.05) using the Benjamini-Hochberg method. A two-way analysis of variance (ANOVA) with Bonferroni-correction for multiple comparisons for factors *processing region* and *control type* was performed to directly compare between normalized responses evoked by the control sequences (CAS and MSC) within each lemniscal and nonlemniscal divisions of the IC, MGB, and AC.

To study the influence of the previous tone on the evoked responses of IC neurons during the control sequences (CAS and MSC), each trial on each sequence was extracted. For each individual trial (n), the frequency step in octaves was computed as the absolute value of the tone frequency of the trial (n) minus the tone frequency of the preceding trial (n−1), resulting in a 'frequency step' value in octaves. This frequency step could be 0.5 or 4.5 octaves during CAS, where tones are ordered regularly in increasing or decreasing frequency (Figure 2A). In the MSC, tone presentation is pseudorandom, so the frequency steps between them could be 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 or 4.5 octaves (Figure 2A). Pairs of MSC and CAS sequences using the same 10 tones presented at the same intensity to the same neuron were normalized by the largest response in either sequence. Then, trials were grouped by frequency step, control type (MSC or CAS) and either recording site (lemniscal or nonlemniscal divisions of IC, MGB or AC) or FRA category (V, W, U or X; only for nonlemniscal

IC neurons), and the normalized average response was computed for each group. A two-way ANOVA with Scheffé's procedure correction for multiple comparisons with *control type* (MSC or CAS) and *frequency step* (0.5 to 4.5 octaves in 0.5-octave steps) as factors was performed separately for each neuronal group. ANOVA results that are especially relevant to this study are at display in the comparison matrices (Figures 2 and 7), where the tone of green codifies significance level. Wherever average normalized responses were significantly different between two groups, the magnitude of such difference is expressed as a percentage.

Ten linear models were fitted using the *fitlm* function in MATLAB, with robust options. First, we replicated the 'global model' of Parras et al. (2017) regarding the hierarchical distribution of iPE (dependent variable) along the auditory pathway by introducing *region* (IC, MGB, or AC) and *pathway* (lemniscal or nonlemniscal) as predictor variables. The reference levels chosen for these factors were 'lemniscal' and 'IC', as no traces of PE signals have been observed in the central nucleus of the IC (Parras et al., 2017). Second, we expanded the original global model to account for spectral properties of the stimulation by incorporating 2 more predictors: sound *intensity* (1 to 7 B SPL in 1 B SPL steps; 1 B SPL = 0.1 dB SPL) and DEV *direction* (ascending or descending). Third, a post-hoc 'local model' using these 2 predictors (sound *intensity* and DEV *direction*) was fitted for each auditory region that yielded significant iPE values (nonlemniscal IC, nonlemniscal MGB, lemniscal AC and nonlemniscal AC), as well as for each FRA-type group of nonlemniscal IC neurons (V-shaped, multipeaked, U-shaped, and mosaic). These linear models used the values of 1 B SPL and 'descending' as reference to calculate the intercept. Finally, an

549 ANOVA was performed to identify which predictors and interactions between
550 them were significant in each of the resulting linear models: 1 global model
551 (replicating Parras et al., 2017), 1 expanded global model, 4 regional models and
552 4 FRA models.

553

554 Results

555 In the following sections, we first describe how tonal succession in CAS
556 and MSC is encoded by means of spectral processing in the lemniscal IC and
557 predictive processing in the nonlemniscal IC. Second, we present an updated
558 global model of the auditory pathway that confirms the hierarchical distribution of
559 the index of prediction error (iPE) from the nonlemniscal IC to the AC, replicating
560 Parras et al. (2017) with much larger sample sizes (IC: 82→315 units, 384%
561 increase; MGB: 58→161 units, 278% increase; AC: 70→181 units, 259%
562 increase), as well as expanding the linear model from 2 to 4 predictor variables:
563 region, pathway, intensity and DEV direction. Third, we introduce new local iPE
564 models for the nonlemniscal IC, nonlemniscal MGB, and both lemniscal and
565 nonlemniscal AC, which revealed the unique sensitivity of PE signaling in the
566 nonlemniscal IC to sound intensity and direction of frequency change. Finally, we
567 demonstrate the dependency between iPE values and the shape of the receptive
568 field or FRA in IC neurons, which defined the ‘spectral’ and ‘non-spectral’ PE
569 systems in the nonlemniscal IC.

570

Differential processing of MSC and CAS in each IC division

In agreement with previous observations in rodents (Parras et al., 2017, 2021; Casado-Román et al., 2020; Valdés-Baizabal et al., 2020; Lesicko et al., 2022) and humans (Wiens et al., 2019), the global responses elicited by CAS and MSC did not differ significantly within each of the hierarchical levels studied: IC, MGB, and AC (two-way ANOVA with Bonferroni-correction for multiple comparisons for factors *region* [$F = 250.17$, $p < 0.001$], *control* [$F = 0.5$, $p = 0.482$] and their interaction [$F = 0.99$, $p = 0.424$]). Consequently, calculations using either CAS (Table 1) or MSC (Table 2) yielded equivalent results. Hence, the models presented in the following sections use the results obtained with CAS, given its methodological advantages (see *Experimental Design* in *Materials and Methods*; Ruhnau et al., 2012; Harms et al., 2014).

MSC and CAS present different frequency steps between successive tones (Figure 2A). We analyzed how the previous tone in the control sequence could be influencing the normalized neuronal evoked response in the IC, as well as the MGB and AC (two-way ANOVA with Scheffé's procedure correction for multiple comparisons, using *control type* [MSC or CAS] and *frequency step* [from 0.5 to 4.5 octaves in 0.5-octave steps] as factors). In the following, we provide a detailed account of results regarding the IC, whereas MGB and AC results will be just succinctly outlined for comparative purposes.

Regarding the IC, the *frequency step* (lemniscal IC: $F = 307.56$, $p < 0.001$; nonlemniscal IC: $F = 107.15$, $p < 0.001$), and the *interaction* between control type and frequency step (lemniscal IC: $F = 28.51$, $p < 0.001$, nonlemniscal IC: $F =$

107.15, $p < 0.001$) had an influence on the evoked response, but not the *control type* alone.

In the lemniscal IC, frequency change from the preceding tone exerted noticeable influence, since a sizable proportion of responses to various octave separations were statistically different from each other (Figure 2B). Lemniscal IC neurons distinguished ten frequency steps more than their nonlemniscal counterparts, implying finer spectral resolution. Furthermore, equal frequency step comparisons across control sequences (0.5- and 4.5-octave steps; Figure 2A, in green) revealed that lemniscal IC neurons responded similarly to equal frequency changes presented within CAS and MSC (Figure 2B, black dotted circles).

On the other hand, contrast between frequency steps had to be larger in the nonlemniscal IC to observe a significant difference in spike counts (Figure 2C, in green), indicating more limited spectral resolution. However, nonlemniscal IC neurons responded differently to equal frequency steps depending on where they were presented, within CAS or within MSC (Figure 2C, white circles), in line with the tenets of the predictive processing framework. The 0.5-octave step yielded larger spike counts when presented in MSC than in CAS (Figure 2C, upwards black arrow). During the MSC, all frequency changes are unpredictable, including the 0.5- and 4.5-octave steps (Figure 2A, in green). In contrast, 0.5-octave steps are very predictable during the CAS, and thereby susceptible to expectation suppression (Garrido et al., 2009b; Todorovic and de Lange, 2012; Stefanics et al., 2014; Auksztulewicz and Friston, 2016; Carbajal and Malmierca, 2018; Emberson et al., 2019). Yet whenever a scale starts over during CAS, instead of the expected 0.5-octave step, it produces a 4.5-octave leap in the

opposite direction. Consequently, the first tone of each scale represents a DEV (Tervaniemi et al., 1994). The resulting PE signal could explain why nonlemniscal IC neurons fired more spikes to frequency changes of 4.5 octaves during CAS than during MSC (Figure 2C, leftwards black arrow). Thus, at the expense of finer spectral resolution, nonlemniscal IC neurons obtain early contextual sensitivity that can be accounted for by predictive processing.

Regarding the MGB, the *frequency step* (lemniscal MGB: $F = 40.32$, $p < 0.001$; nonlemniscal MGB: $F = 23.97$, $p < 0.001$), and the *interaction* between control type and frequency step (lemniscal MGB: $F = 11.87$, $p < 0.001$, nonlemniscal MGB: $F = 26.31$, $p < 0.001$) had an influence on the evoked response, but not the *control type* alone. MGB comparison matrices look mostly like that of the nonlemniscal IC, with the critical difference that MGB neurons could not distinguish between equal frequency steps presented in different sequences (similar to Figure 2C, but significance was lost for the circled comparisons pointed by arrows).

Regarding the AC, evoked responses of lemniscal AC neurons were influenced by *frequency step* ($F = 28.16$, $p < 0.001$), and the *interaction* between control type and frequency step ($F = 46.72$, $p < 0.001$), but not the *control type* alone. Similar to the MGB, the comparison matrix of the lemniscal AC looked mostly like that of the nonlemniscal IC, with the critical difference that lemniscal AC neurons could not distinguish between equal frequency steps presented in different sequences (similar to Figure 2C, but significance was lost for the circled comparisons pointed by arrows).

On the other hand, evoked responses of nonlemniscal AC neurons were influenced only by *frequency step* ($F = 12.72$, $p < 0.001$), but not the *control type* alone nor the *interaction* between control type and frequency step. In contrast with the other regions, nonlemniscal AC neurons could only distinguish between the 0.5-octave step and the 4.5-octave step of the CAS (Figure 7A).

Distribution of predictive processing indices along the auditory pathway

To find traces of predictive processing activity at neuronal level, a within-region multiple comparison Friedman test was performed between DEV, STD, and control responses, such that each pair of conditions within each auditory region was tested for a difference in medians. The corresponding indices of the IC, MGB, and AC, calculated using normalized spike counts evoked by CAS and MSC, are respectively summarized in Tables 1 and 2. These observations were fitted in a linear model with a robust regression for the iPE along the hierarchy, in an effort to replicate previous results with sample sizes tripling those of the original study (Parras et al., 2017). The model used *region* ('IC', 'MGB', 'AC') and *pathway* (Lemniscal 'Lem', Nonlemniscal 'NonLem') as categorical factors, acquiring values 1 when true and 0 when false. The reference levels chosen for these factors were 'Lem' and 'IC', as no traces of PE signals have been observed in the central nucleus of the IC (Parras et al., 2017). The resulting global model was:

$$\boldsymbol{iPE} = \mathbf{-0.059 - 0.033 * MGB + 0.249 * AC + 0.092 * NonLem}$$

$$\mathbf{+ (0.080 * MGB * NonLem + 0.017 * AC * NonLem)}$$

where the constant term (intercept = −0.059) is the reference iPE value in lemniscal IC. An ANOVA of this model revealed that the evolution of iPE along the hierarchy could be explained by the processing *region* (F = 128.50, $p < 0.001$) and the *pathway* (F = 54.94, $p < 0.001$), but not the *interaction* between both factors (in parenthesis; *cf.,* Parras et al. 2017).

Median DEV responses were stronger than STD responses all over the IC, resulting in a median iMM = 0.16 in the lemniscal IC ($p < 0.001$, Friedman test) and a median iMM = 0.44 in the nonlemniscal IC ($p < 0.001$). In the lemniscal IC, the median normalized spike count in response to both controls was 0.65, slightly stronger than the 0.59 yielded by DEV. Both DEV and control normalized responses surpassed the 0.43 normalized STD spike count. Hence, the resulting median iRS = 0.21 could account for the whole neuronal mismatch signal in the lemniscal IC ($p < 0.001$), even yielding negative iPE values (Tables 1 and 2). Conversely, in the nonlemniscal IC the median normalized DEV spike count of 0.66 surpassed the 0.64 registered for CAS, but not the 0.66 yielded by MSC. When calculated with CAS, this resulted in a significant iPE = 0.02 (Table 1), confirming the presence of significant PE signaling activity at sample level within the nonlemniscal IC ($p < 0.001$). However, this was not the case when using MSC (Table 2). In addition, the median normalized STD spike counts in the nonlemniscal IC was half of those observed in the lemniscal IC (Tables 1 and 2). The resulting median iRS = 0.42 was considerably higher among nonlemniscal neurons than in their lemniscal counterparts ($p < 0.001$).

Once previous results were replicated (Parras et al., 2017), we tested how spectral features of the stimulation affected the resulting iPE value in the whole auditory pathway. Two new predictor variables were added to the linear model: sound *intensity* and DEV *direction*. Sound *intensity* was measured in Bels (1 to 7 B SPL in 1 B SPL steps). DEV *direction* is a dichotomic variable, so the factor *ascending* acquired the numeric value of 1 when true or 0 when false, while the factor *descending* was used as reference to calculate the intercept. Hence, this expanded model used four predictors: *region* ('IC', 'MGB' or 'AC') and *pathway* (Lemniscal 'Lem' or Nonlemniscal 'NonLem'), sound *intensity* ('SPL', in Bels) and DEV *direction* (ascending 'asc' or descending 'dsc'). The reference levels chosen for these factors were 'IC', 'Lem', 1 B SPL and 'dsc'. The resulting expanded global model was:

$$\begin{aligned} \boldsymbol{iPE} = \mathbf{0.008} - \mathbf{0.293} * \boldsymbol{MGB} - \mathbf{0.049} * \boldsymbol{AC} + \mathbf{0.224} * \boldsymbol{NonLem} - \mathbf{0.015} \\ * \boldsymbol{SPL} + \mathbf{0.055} * \boldsymbol{MGB} * \boldsymbol{SPL} + \mathbf{0.067} * \boldsymbol{AC} * \boldsymbol{SPL} - \mathbf{0.032} \\ * \boldsymbol{NonLem} * \boldsymbol{SPL} + \mathbf{0.331} * \boldsymbol{MGB} * \boldsymbol{asc} + \mathbf{0.233} * \boldsymbol{AC} * \boldsymbol{asc} \\ + (0.027 * asc + 0.252 * MGB * NonLem + 0.081 * AC * NonLem \\ + 0.019 * NonLem * asc - 0.004 * asc * SPL - 0.538 * MGB \\ * NonLem * asc - 0.051 * AC * NonLem * asc - 0.022 * MGB \\ * NonLem * SPL - 0.010 * AC * NonLem * SPL - 0.070 * MGB \\ * asc * SPL - 0.054 * AC * asc * SPL + 0.005 * NonLem * asc \\ * SPL + 0.085 * MGB * NonLem * asc * SPL + 0.002 * AC \\ * NonLem * asc * SPL) \end{aligned}$$

An ANOVA revealed that iPE values throughout the auditory pathway could be explained by the processing *region* ($F = 134.90$, $p < 0.001$), *pathway*

(F = 54.19, p < 0.001), sound *intensity* (F = 37.08, p < 0.001), as well as the interaction between *region and intensity* (F = 5.81, p = 0.003), *pathway and intensity* (F = 9.10, p = 0.003), and *region and direction* (F = 3.60, p = 0.028). Neither DEV *direction* alone nor the rest of interactions between factors yielded significant effects (between parenthesis). Therefore, the expanded global model reflects the effect of spectral characteristics on auditory predictive processing, especially that of sound intensity. However, the following sections will demonstrate that those spectral influences only affected consistently the PE signaling activity of certain nonlemniscal IC neurons.

Local models of predictive processing indices for the IC, MGB, and AC

To better understand how spectral features influenced PE signals at each level of the auditory hierarchy, we fitted linear models for each index—i.e., iMM, iPE, and iRS—using *intensity* and *direction* of DEV (ascending or descending as categorical factors that acquired values 1 when true and 0 when false) as predictors for each auditory region (separately) where significant traces of predictive activity were found: the nonlemniscal divisions of IC, MGB, and AC, as well as the lemniscal fields of AC. The acoustic characteristics of oddball stimulation only affected indices in the nonlemniscal IC, but not in the rest of the auditory regions (Figure 3A).

The linear model for the iMM in the nonlemniscal IC was:

$$\boldsymbol{iMM} = \mathbf{0.698} - \mathbf{0.065} * \boldsymbol{SPL} + \mathbf{0.059} * \boldsymbol{asc} - (0.005 * SPL * asc)$$

736 The iMM reflects the oddball intensity (ANOVA, F = 204.25, $p < 0.001$) and
737 direction (F = 4.77, $p = 0.029$), but not the interaction between these factors (not
738 significant, in parenthesis).

739 The linear model for the iPE in the nonlemniscal IC was:

740 $$\boldsymbol{iPE} = \mathbf{0.228} - \mathbf{0.047} * \boldsymbol{SPL} + \mathbf{0.052} * \boldsymbol{asc} - (0.000 * SPL * asc)$$

741 Similarly, the iPE could be predicted by intensity (ANOVA, F = 75.16, $p <$
742 0.001) and direction (F = 9.52, $p = 0.002$), but not their interaction (in parenthesis),
743 whose coefficient was virtually zero.

744 In contrast with observations in the nonlemniscal IC, iPE values in the
745 nonlemniscal MGB, lemniscal AC, and nonlemniscal AC could not be accounted
746 for by any linear model reliant on intensity and direction as predictor variables
747 (note their poor fits as opposed to the nonlemniscal IC in Figure 3A). Therefore,
748 PE signaling in the nonlemniscal IC encodes deviant acoustic information,
749 whereas in higher processing levels PE signaling seems to be driven by more
750 abstract information than the intensity or direction of the auditory input.

751 The iRS remained relatively stable across different intensities and pitch
752 changes (Tables 1 and 2), and therefore, it could not be predicted by linear
753 models reliant on intensity and direction as predictors in any auditory region. In
754 contrast, the iMM and iPE observed in nonlemniscal IC neurons were larger when
755 intensities were softer, as well as in ascending oddball paradigms. As stimulation
756 intensity increased, the PE component progressively decreased (Figure 3A, first
757 plot). Also at higher intensities, a shrunk iMM equated to the iRS (Tables 1 and
758 2). Intensity and direction effects disappeared as input ascended the auditory

759 hierarchy, since no linear model of this kind could be fitted in the nonlemniscal
760 MGB or the AC (Figure 3A). Therefore, changes in the iMM of nonlemniscal IC
761 neurons due to intensity and frequency shifts were caused by how those physical
762 characteristics of the stimuli elicit PE signaling in the auditory midbrain.

763 Considering the tendency described by the linear models of the
764 nonlemniscal IC, we examined population indices dividing the samples of each
765 region into *'low intensities'* (< 40 dB SPL) and *'high intensities'* (≥ 40 dB SPL).
766 Once again, the relationship between the intensity of the stimulation and the
767 magnitude of the PE component within the evoked firing response was evident
768 only in the nonlemniscal IC neurons (Figure 3B), further confirming the
769 tendencies described by the linear models. The neuronal mismatch responses in
770 the nonlemniscal IC were significantly larger ($p < 0.001$) at low intensities (iMM =
771 0.56) than at high intensities (iMM = 0.39). As mentioned in the previous section,
772 the PE component of neuronal mismatch responses in the nonlemniscal IC was
773 rather small and only detectable with CAS (iPE = 0.02) when all the intensities
774 were included in the analysis. However, when the analysis only included the
775 nonlemniscal IC neuronal responses to low intensity stimulation, the median
776 normalized DEV spike counts tended to comfortably surpass those elicited by
777 both controls (Figure 3B, first plot, left violin), resulting in $iPE_{CAS} = 0.12$ ($p < 0.001$)
778 and $iPE_{MSC} = 0.09$ ($p = 0.001$). Conversely, at high intensities, this PE component
779 disappears completely (Figure 3B, first plot, right violin). Results of these
780 analyses using CAS and MSC are summarized in Tables 1 and 2, respectively.

781 Hence, direction of frequency and intensity manipulation only affected the
782 PE component of the mismatch response of nonlemniscal IC neurons, without

disrupting their levels of repetition suppression. This remarkable and unique population effect imply that the main function of PE signaling activity in the IC cortices is to enhance the early representation of unexpected sounds that meet certain spectral characteristics, e.g., providing dynamic gain compensation to near threshold but informative auditory input. Nevertheless, a closer inspection of different neuronal types proved that this main population effect of 'spectral' nature was not the only function of PE signaling in the IC cortices, as detailed in the following section.

PE signaling characteristics in the nonlemniscal IC depend on FRA shape

Nonlemniscal IC neurons with tuned receptive fields (V, W and U shapes), did not exhibit a significant correlation between Q_{30} factors and iPE values. However, more than 20% of nonlemniscal IC neurons in our sample showed an untuned, 'mosaic' FRA type where it was not possible to determine any Q factor, due to the lack of a clear and stable characteristic frequency in their receptive fields. The median $iPE_{CAS} = 0.21$ ($p < 0.001$) and $iPE_{MSC} = 0.15$ ($p < 0.001$) in the group of X-neurons were significantly higher ($p < 0.001$) than the median iPE values observed in the rest of nonlemniscal IC neurons, which were not significantly different from 0.

Due to this stark contrast between neural populations of the nonlemniscal IC, all previous analyses were repeated for nonlemniscal IC neurons, dividing the sample into 4 FRA categories: *V-shaped* (V), *multipeaked* (W), *U-shaped* (U) and

806 *mosaic* (X). First, we performed a within-category multiple comparison Friedman
807 test between DEV, STD, and control responses, such that each pair of conditions
808 within each FRA category was tested for a difference in medians. Samples within
809 each FRA category were then further divided into 'low intensities' (< 40 dB SPL)
810 and 'high intensities' (≥ 40 dB SPL) for additional comparisons (Figures 4C). The
811 corresponding indices calculated using both controls are summarized in Table 3.
812 The evolution of predictive processing indices values over time was also analyzed
813 for low and high intensities (Figure 5). In every condition, the iRS appears
814 immediately (Figure 5, cyan lines), whereas the iPE takes longer to emerge, if at
815 all (Figure 5, orange lines).

816 Following the general trend in the nonlemniscal IC, all FRA categories
817 showed robust repetition suppression. However, only W- and U- neurons
818 followed the population trend regarding PE signaling, with significant iPE values
819 only at low intensities. Conversely, V-neurons did not reach significant iPE values
820 in any condition, whereas X-neurons yielded robust iPE values at every level of
821 intensity. This was further confirmed by linear models that used intensity and
822 direction of DEV as predictors of iPE values for each FRA category in the
823 nonlemniscal IC, achieving good fits in the 3 tuned groups, i.e., V-, W-, and U-
824 neurons, as opposed to untuned X-neurons (Figure 4B).

825 Finally, we analyzed how the previous tone in the control sequence could
826 be influencing the normalized evoked response in nonlemniscal IC neurons
827 depending on their FRA type (two-way ANOVA with Scheffé's procedure
828 correction for multiple comparisons, using *control type* [MSC or CAS] and
829 *frequency step* [from 0.5 to 4.5 octaves in 0.5-octave steps] as factors). Again,
830 the 3 tuned groups tended to follow the same response trend, which resembled

the general trend of the nonlemniscal IC (Figure 2C). Conversely, X-neurons described a completely different pattern (Figure 7B), more akin to that of the nonlemniscal AC neurons (Figure 7A). All these data, in addition to the unstable and unstructured nature of their receptive fields, seem to set aside X-neurons from the rest of nonlemniscal IC neurons (Figure 6), suggesting higher-order capabilities. In the following, detailed results are provided for each FRA category.

Sharply tuned receptive fields: V-neurons

The linear model for V-neurons (Figure 4B, first plot) was:

$$\boldsymbol{iPE_V = 0.067 - 0.024 * SPL + 0.073 * asc} + (0.005 * SPL * asc)$$

The ANOVA of this model revealed a significant effect of intensity ($F = 5.36$, $p = 0.021$) and direction ($F = 10.75$, $p = 0.001$), but no significant interaction between factors (in parenthesis). Despite model fitness, positive iPE magnitudes in V-neurons were not significant for any sample of evoked firing responses (Table 3; Figures 4 and 5, first column; Figure 6).

Regarding frequency step discrimination, V-neuron followed the general tendency of the nonlemniscal IC population, showing evoked responses influenced by *frequency step* ($F = 103.72$, $p < 0.001$), and the *interaction* between control type and frequency step ($F = 86.76$, $p < 0.001$). Comparison matrix of V-neurons was like Figure 2C with exception of the comparison between 0.5-octave steps in MSC and CAS, which significance was lost.

Hence, V-neurons lack the high spectral resolution of their lemniscal homologues, but in exchange they manifest some contextual sensitivity. V-

neurons do not contribute to the main PE signaling effect observed at population level in the IC cortices, while being subject to stronger repetition suppression than lemniscal IC neurons (Tables 1-3). Therefore, their properties seem somewhat transitional, which hints at the possibility of V-neurons constituting the 'input level' of the predictive processing circuitry of the IC cortices (Figure 7D).

Broadly tuned receptive fields: W- and U-neurons

The linear model for W-neurons (Figure 4B, second plot) was:

$$\boldsymbol{iPE_W = 0.273 - 0.061 * SPL} + (0.016 * asc * 0.004 * SPL * asc)$$

The iPE_W was predicted only by the intensity of the oddball stimulation (ANOVA, F = 37.68, $p < 0.001$), but not for direction or the interaction between factors (both in parenthesis).

The linear model for U-neurons (Figure 4B, third plot) was:

$$\boldsymbol{iPE_U = 0.204 - 0.050 * SPL} + (0.127 * asc - 0.018 * SPL * asc)$$

The iPE_U revealed a significant effect of intensity (ANOVA, F = 39.70, $p < 0.001$), but not for direction or the interaction between factors (both between parenthesis).

In W- and U-neurons, the effect of intensity over the magnitude of the PE component within the neuronal mismatch response became evident when comparing the distribution of normalized DEV- and control-evoked spike counts (Figure 4C, second and third plots), when observing the evolution of the iPE over time (Figure 5, second and third plots), as well as when comparing the median

indices of each category at low and high intensity stimulation using both CAS and MSC (Figure 6, Table 3). Traces of PE signaling could be found at low intensity stimulation in W-neurons, but only when using CAS (iPE = 0.11; $p < 0.001$; Figure 5B, second plot). For U-neurons, a significant PE component was revealed for low intensity stimulation using both CAS and MSC (iPE = 0.11, $p = 0.003$; Figure 5B, third plot).

Regarding frequency step discrimination, U-neurons followed the general tendency of the nonlemniscal IC population (at display in Figure 3A), showing evoked responses influenced by *frequency step* ($F = 153.19$, $p < 0.001$), and the *interaction* between control type and frequency step ($F = 88.03$, $p < 0.001$). Comparison matrix of U-neurons was like Figure 2C with exception of the comparison between 0.5-octave steps in MSC and CAS, which significance was lost. In contrast, evoked responses of W-neurons were only influenced by *frequency step* ($F = 26.38$, $p < 0.001$). The comparison matrix reveals that W-neurons could only distinguish between pronouncedly different frequency steps, i.e., the 4.5-octave leap in CAS against frequency steps of 2.5 octaves or smaller.

Hence, W- and U-neurons tend to follow the general trends of the nonlemniscal IC population, with rather limited frequency-step discrimination and PE signaling heavily influenced by spectral features of auditory input. In fact, as detailed in the next section, only W- and U-neurons are responsible for the main population effect observed in the IC cortices, revealing them as the true neural substrate of a ‘spectral’ PE system (Figure 7D).

Untuned receptive fields: X-neurons

In contrast with tuned FRA categories (V, W and U), the linear model of X-neurons did not achieve a good fit, neither did they show any significant effects of intensity, direction, or their interaction (ANOVA; Figure 4B, fourth plot). The size of the PE component found in X-neurons more than doubled that of the previous categories at low intensities using both CAS and MSC (iPE = 0.23, $p < 0.001$; Figure 6). When only neuronal responses to high intensity stimulation were selected, we found that only X-neurons were able to preserve their PE component intact (iPE = 0.22, $p < 0.001$; Figure 5C), whereas the rest of FRA categories ceased issuing PE signals altogether (Figure 6).

Therefore, contrary to the general trend in the nonlemniscal IC, X-neurons yielded significantly positive iPE values across all intensities and regardless of DEV direction, more in the vein of the AC (compare fourth column of Figure 4 with the third and fourth columns of Figure 3). This differential behavior can be appreciated when comparing the distribution of normalized DEV- and control-evoked spike counts (Figure 4C), when observing the evolution of the iPE over time (Figure 5), as well as when comparing the median indices of each category at low and high intensity stimulation using both CAS and MSC (Figure 6, Table 3). This means that X-neurons do not contribute to the main effect of PE signaling observed in the nonlemniscal IC, and thereby are not part of the 'spectral' PE system.

Regarding frequency step discrimination, only the *interaction* between control type and frequency step had an influence on the evoked response of X-neurons ($F = 23.52$, $p < 0.001$). Spectral resolution of X-neurons is the poorest in

the IC cortices, only able to contrast between 0.5-octave steps and 4.5-octave leaps in the CAS (Figure 7B), in the same vein of the nonlemniscal AC (Figure 7A). This resemblance suggests again a more abstract processing of X-neurons related to higher-order processing regions of the auditory pathway.

Hence, in contrast with the main effect observed in nonlemniscal IC processing, X-neurons perform a distinct accessory function that essentially disregard spectral content to consistently report on more contextual information related to novelty or deviances within the auditory scene. X-neurons are thus the neural substrate of a 'non-spectral' PE system (Figure 7D).

Discussion

This study reveals the dual nature of predictive processing in the IC cortices, which are endowed with a main, 'spectral' PE system, and an accessory, 'non-spectral' PE system. These midbrain-level systems constitute the earliest source of PE signals in the auditory pathway, as confirmed by our expanded linear model for the hierarchical distribution of iPE values. Our results also unravel the differential processing of MSC and CAS by lemniscal and nonlemniscal IC neurons (Figure 2). Most importantly, we expand the established lemniscal-vs-nonlemniscal dichotomy by distinguishing 3 levels of hierarchical processing within the IC cortices (Figures 7D): (1) V-neurons exhibiting mild repetition suppression without signaling PEs constitute the input level of the predictive processing circuitry in the nonlemniscal IC; (2) W- and U-neurons signaling PEs that increase saliency of near-threshold unexpected sounds

946 establish the ‘spectral’ PE system; and (3) X-neurons consistently reporting all
947 surprising auditory input compose the ‘non-spectral’ PE system.

948 Sharply tuned receptive fields specialize in lower-order functions such as
949 spectral processing, but are not well suited for complex auditory integration
950 (Oliver et al., 2017). In the IC cortices, however, V-neurons discriminate less
951 frequency steps than their lemniscal homologues while manifesting some
952 contextual sensitivity. Despite not signaling PEs, V-neurons undergo stronger
953 repetition suppression than lemniscal IC neurons, although milder than other
954 nonlemniscal types (Figure 6). These transitional properties arguably make V-
955 neurons the best candidates to funnel ‘raw’ input from the central nucleus into the
956 predictive processing circuits of the IC cortices. V-shaped receptive fields are
957 inherited from lower auditory nuclei (Le Beau et al., 2001), implying that V-
958 neurons are mainly driven by bottom-up auditory input. Thus, V-neurons may
959 constitute an ‘input level’ in the nonlemniscal IC, akin to layer IV in the canonical
960 microcircuits of cortical predictive processing (Bastos et al., 2012).

961 Broadly tuned receptive fields can integrate spectral information across
962 many frequency channels (Oliver et al., 2017) and enable the main effect of
963 predictive processing in the IC cortices. W- and U-neurons increase PE signaling
964 to low-intensity sounds and ascending frequency DEVs (Figures 3 and 4).
965 Previously reported changes of neuronal mismatch responses as a function of
966 intensity and frequency in the IC (Duque et al., 2012, 2016) must be due to
967 changes in the PE component, given that repetition suppression tends to remain
968 stable across varying spectral parameters (Figures 5 and 6).

Regarding sound intensity, modeling work indicates that neurons are maximally sensitive to change for stimulus ranges where firing rates are below saturation (Abbott et al., 1997), which has been empirically confirmed in the rat IC (Duque et al., 2012). As intensity increases, W- and U-neurons exhaust their discharge capacity to signal PEs. Consequently, iPE decreases with loudness in the IC cortices (Figures 3 to 6), whereas the iRS remains unaffected (Figures 5 and 6).

Regarding ascending oddballs, enhanced responses compared to descending oddballs have also been reported in electroencephalographic data of rats (Harms et al., 2014) and humans (Peter et al., 2010). This bias might help defining figure-ground relationships in audition (Schneider et al., 2018, 2021). The difficulty of high-pitched sounds to travel long distances means that they usually carry relevant information from our nearby surroundings. Neural representation of surprising changes towards higher frequencies could be facilitated as 'figure' DEV sounds emerging from distant, 'background' STD noise.

Hence, W- and U-neurons enhance the saliency of muted unexpected sounds both indirectly, by consistently suppressing repetitive auditory input, and directly, by selectively signaling 'spectral' PEs. This neural substrate constitute the main PE system of the auditory midbrain, which provides gain to subtle but relevant spectral cues, thereby aiding auditory perception under challenging conditions—e.g., when loud background noise masks softer but informative deviant sounds, as described in the visual system (Carandini and Ferster, 1997; Hupé et al., 1998; Michel et al., 2018)—. Most interestingly, only the IC cortices provide this kind of predictive equalization reliant on spectral features (Figure 3),

993 despite MGB and AC neurons presenting multipeaked and U-shaped FRAs
994 (Polley et al., 2007; Parras et al., 2017). Therefore, the 'spectral' PE system
995 cannot be the direct product of the receptive field exclusively, but an emerging
996 property of the nonlemniscal IC circuitry. Furthermore, this agrees with the tenets
997 of predictive processing (Friston and Kiebel, 2009b), as implementing this unique
998 mechanism of dynamic gain in the IC would relieve the MGB and AC from such
999 a loading discrimination task.

1000 Finally, the lack of delimited and stable receptive fields suggests that X-
1001 neurons operate under dynamic inhibitory input (Le Beau et al., 2001) and may
1002 receive corticofugal projections (Lesicko and Geffen, 2022). Perhaps their
1003 receptive field cannot be defined in terms of frequency-intensity combinations
1004 because they are sensitive to more abstract probabilistic structures in auditory
1005 input (Tabas et al., 2020; Peng et al., 2024) or to multisensory input (Aitkin et al.,
1006 1981; Itaya and Van Hoesen, 1982; Tawil et al., 1983; Tokunaga et al., 1984;
1007 Gutfreund et al., 2002; Porter et al., 2007; Gruters and Groh, 2012; Olthof et al.,
1008 2019). Unlike in the rest of nonlemniscal IC neurons, evoked responses in X-
1009 neurons are barely influenced by sound intensity (Figures 4A and 5A). This
1010 prevents discharge saturations caused by loudness, thereby securing enough
1011 dynamic range to always afford increasing firing rates to signal PEs.
1012 Consequently, median iPE values in X-neurons more than double those of the
1013 rest of nonlemniscal IC neurons and are insensitive to intensity variations
1014 (Figures 4 to 6, fourth columns).

1015 Contrasting and complementing the 'spectral' PE system, X-neurons
1016 provide the neural substrate for a 'non-spectral' PE system, which activity bears

more resemblance with that of higher auditory regions. This similarity implies a functional connection between these neural populations through corticocollicular projections (Adams, 1980; Herbert et al., 1991; Winer et al., 2002; Malmierca and Ryugo, 2011; Schofield and Beebe, 2019), which enable an accessory PE system focused on consistently reporting unexpected auditory events while disregarding their spectral nature.

In coherence with the canonical microcircuits proposed for cortical predictive processing (Bastos et al., 2012), deep pyramidal neurons in layers V and VI generate predictions, which may be imposed on X-neurons through descending projections (Figure 7C; Games and Winer, 1988). The densest cortical input that the IC cortices receive comes from nonlemniscal AC fields (Herbert et al., 1991). Nonlemniscal AC neurons reach the highest iPE values in the auditory pathway (Parras et al., 2017, 2021) and share remarkable response similarities with X-neurons (compare fourth columns of Figures 3 and 4, and Figures 7A and B), further suggesting a functional connection between them.

Although pyramidal projections are glutamatergic (Feliciano and Potashner, 1995), electrical stimulation of the AC produces excitation and inhibition in different subpopulations of IC neurons (Mitani et al., 1983; Jen et al., 1998; Zhou and Jen, 2005; Vila et al., 2019), and AC deactivation yields disinhibition of some IC neurons (Nwabueze-Ogbo et al., 2003; Popelář et al., 2016; Blackwell et al., 2020). GABAergic neurons make up to 25% of the rat IC cortices (Merchán et al., 2005), where distribution of GABA receptors is denser than in the central nucleus (Milbrandt et al., 1996; Jamal et al., 2012; Choy Buentello et al., 2015). Moreover, previous studies demonstrated that AC

deactivation reduces neuronal mismatch responses in the IC (Anderson and Malmierca, 2013) by decreasing the PE component without disrupting repetition suppression (Lesicko et al., 2022). Hence, deep pyramidal AC neurons could impose top-down predictions on X-neurons by exciting inhibitory connections within the IC (Oliver, 2005; Beebe et al., 2016; Ito and Malmierca, 2018; Ito et al., 2018). As the predictive model receives updates through bottom-up PE signals, top-down predictions would evolve (Figure 7C), which could explain the unstable and dynamic nature of mosaic FRAs.

In conclusion, FRA analysis of nonlemniscal IC neurons evidences their complementary physiological roles and affords the distinction of two early PE systems. The 'spectral' PE system enhances saliency of near-threshold surprising sounds, while the 'non-spectral' PE system reports unexpected events in the auditory scene in a more consistent and abstract manner. Both PE systems improve overall processing efficiency in the auditory pathway by dynamically representing informative auditory events already at midbrain level, thereby sparing MGB and AC resources that can be allocated to processing more complex aspects of audition. This subcortical capacity to generate early but contextually rich neural representations of the auditory scene contravenes the traditional corticocentric understanding (Parvizi, 2009). Hierarchical predictive processing in the IC cortices may be critical to trigger attention shifts (Jane et al., 1965; Hu and Dan, 2022), set off rapid eye-head orienting movements toward sounds (Belenkov and Goreva, 1969; Thompson and Masterton, 1978; Zwiers et al., 2004; Porter et al., 2007), and assist perception and sound-guided behavior even before auditory input reaches the cortex (Ryan and Miller, 1977; Brainard and Knudsen, 1993; Metzger et al., 2006; Rinne et al., 2008; Schelinski et al.,

2022; Escera, 2023; Quass et al., 2023; Lee et al., 2024). Ultimately, our data supports claims that regard the IC as a functional analog to the primary visual cortex (Nelken et al., 2003; King and Nelken, 2009), thus furthering the notion of subcortical cognition (Janacsek et al., 2022).

CRediT Author Statement

GVC: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Data Curation, Writing–original draft, Writing–review and editing, Visualization.

LCR: Software, Validation, Formal Analysis, Investigation, Writing–review and editing, Visualization.

MSM: Conceptualization, Resources, Writing–review and editing, Supervision, Project Administration, Funding Acquisition.

REFERENCES

Abbott LF, Varela JA, Sen K, Nelson SB (1997) Synaptic Depression and Cortical Gain Control. Science (80-) 275:221–224 Available at: http://www.sciencemag.org/cgi/doi/10.1126/science.275.5297.221.

Adams JC (1980) Crossed and descending projections to the inferior colliculus. Neurosci Lett 19:1–5.

1088 Aitkin LM, Kenyon CE, Philpott P (1981) The representation of the auditory and
1089 somatosensory systems in the external nucleus of the cat inferior colliculus.
1090 J Comp Neurol 196:25–40 Available at:
1091 https://onlinelibrary.wiley.com/doi/full/10.1002/cne.901960104 [Accessed
1092 May 19, 2021].

1093 Anderson LA, Malmierca MS (2013) The effect of auditory cortex deactivation
1094 on stimulus-specific adaptation in the inferior colliculus of the rat. Eur J
1095 Neurosci 37:52–62 Available at: http://doi.wiley.com/10.1111/ejn.12018
1096 [Accessed September 12, 2017].

1097 Auksztulewicz R, Friston KJ (2016) Repetition suppression and its contextual
1098 determinants in predictive coding. Cortex 80:125–140.

1099 Bastos AM, Usrey WM, Adams RA, Mangun GR, Fries P, Friston KJ (2012)
1100 Canonical Microcircuits for Predictive Coding. Neuron 76:695–711
1101 Available at: http://linkinghub.elsevier.com/retrieve/pii/S0896627312009592
1102 [Accessed February 1, 2018].

1103 Beebe NL, Young JW, Mellott JG, Schofield BR (2016) Extracellular molecular
1104 markers and soma size of inhibitory neurons: Evidence for four subtypes of
1105 GABAergic cells in the inferior colliculus. J Neurosci 36:3988–3999
1106 Available at: https://www.jneurosci.org/content/36/14/3988 [Accessed
1107 February 17, 2024].

1108 Belenkov NY, Goreva OA (1969) Role of inferior colliculi in orienting reflex.
1109 Neurosci Transl 3:9–16 Available at:
1110 https://link.springer.com/article/10.1007/BF01124449 [Accessed February
1111 8, 2024].

1112 Blackwell JM, Lesicko A, Rao W, De Biasi M, Geffen MN (2020) Auditory cortex
1113 shapes sound responses in the inferior colliculus. Elife 9.

1114 Brainard MS, Knudsen EI (1993) Experience-dependent plasticity in the inferior
1115 colliculus: A site for visual calibration of the neural representation of
1116 auditory space in the barn owl. J Neurosci 13:4589–4608 Available at:
1117 https://www.jneurosci.org/content/13/11/4589 [Accessed February 8, 2024].

1118 Cacciaglia R, Escera C, Slabu L, Grimm S, Sanjuán A, Ventura-Campos N,
1119 Ávila C (2015) Involvement of the human midbrain and thalamus in auditory
1120 deviance detection. Neuropsychologia 68:51–58 Available at:
1121 http://dx.doi.org/10.1016/j.neuropsychologia.2015.01.001.

1122 Cant NB, Oliver DL (2018) Overview of Auditory Projection Pathways and
1123 Intrinsic Microcircuits. In: The Mammalian Auditory Pathways: Synaptic
1124 Organization and Microcircuits, pp 7–39. Springer, Cham. Available at:
1125 https://link.springer.com/chapter/10.1007/978-3-319-71798-2_2 [Accessed
1126 February 9, 2024].

1127 Carandini M, Ferster D (1997) A tonic hyperpolarization underlying contrast
1128 adaptation in cat visual cortex. Science (80-) 276:949–952 Available at:
1129 http://www.ncbi.nlm.nih.gov/pubmed/9139658 [Accessed June 2, 2018].

1130 Carbajal G V., Malmierca MS (2018) The Neuronal Basis of Predictive Coding
1131 Along the Auditory Pathway: From the Subcortical Roots to Cortical
1132 Deviance Detection. Trends Hear 22:233121651878482 Available at:
1133 http://journals.sagepub.com/doi/10.1177/2331216518784822.

1134 Carbajal G V., Malmierca MS (2020) Novelty Processing in the Auditory
1135 System: Detection, Adaptation or Expectation? In: The Senses: A

1136 Comprehensive Reference, 2nd ed. (Fritzsch B, Gothe B, eds), pp 749–
1137 776. Elsevier. Available at:
1138 https://linkinghub.elsevier.com/retrieve/pii/B9780128093245241540
1139 [Accessed May 20, 2020].

1140 Casado-Román L, Carbajal G V., Pérez-González D, Malmierca MS (2020)
1141 Prediction error signaling explains neuronal mismatch responses in the
1142 medial prefrontal cortex. PLoS Biol 18:e3001019 Available at:
1143 https://doi.org/10.1371/journal.pbio.3001019 [Accessed April 28, 2021].

1144 Choy Buentello D, Bishop DC, Oliver DL (2015) Differential distribution of GABA
1145 and glycine terminals in the inferior colliculus of rat and mouse. J Comp
1146 Neurol 523:2683–2697 Available at:
1147 http://doi.wiley.com/10.1002/cne.23810 [Accessed February 4, 2018].

1148 Duque D, Pérez-González D, Ayala YA, Palmer AR, Malmierca MS (2012)
1149 Topographic Distribution, Frequency, and Intensity Dependence of
1150 Stimulus-Specific Adaptation in the Inferior Colliculus of the Rat. J Neurosci
1151 32:17762–17774 Available at:
1152 http://www.jneurosci.org/content/32/49/17762.long [Accessed September
1153 12, 2017].

1154 Duque D, Wang X, Nieto-Diego J, Krumbholz K, Malmierca MS (2016) Neurons
1155 in the inferior colliculus of the rat show stimulus-specific adaptation for
1156 frequency, but not for intensity. Sci Rep 6:24114 Available at:
1157 http://www.ncbi.nlm.nih.gov/pubmed/27066835%5Cnhttp://www.pubmedce
1158 ntral.nih.gov/articlerender.fcgi?artid=PMC4828641.

1159 Emberson LL, Boldin AM, Robertson CE, Cannon G, Aslin RN (2019)

Expectation affects neural repetition suppression in infancy. Dev Cogn Neurosci 37:100597.

Escera C (2023) Contributions of the subcortical auditory system to predictive coding and the neural encoding of speech. Curr Opin Behav Sci 54:101324.

Feliciano M, Potashner SJ (1995) Evidence for a Glutamatergic Pathway from the Guinea Pig Auditory Cortex to the Inferior Colliculus. J Neurochem 65:1348–1357 Available at: https://onlinelibrary.wiley.com/doi/full/10.1046/j.1471-4159.1995.65031348.x [Accessed May 22, 2021].

Friston KJ (2003) Learning and inference in the brain. Neural Networks 16:1325–1352 Available at: https://www.sciencedirect.com/science/article/pii/S0893608003002454?via%3Dihub [Accessed May 2, 2019].

Friston KJ (2005) A theory of cortical responses. Philos Trans R Soc B Biol Sci 360:815–836 Available at: http://rstb.royalsocietypublishing.org/cgi/doi/10.1098/rstb.2005.1622 [Accessed October 1, 2012].

Friston KJ (2009) The free-energy principle: a rough guide to the brain? Trends Cogn Sci 13:293–301.

Friston KJ (2010) The free-energy principle: a unified brain theory? Nat Rev Neurosci 11:127–138 Available at: http://www.nature.com/articles/nrn2787 [Accessed June 4, 2019].

1183 Friston KJ, Kiebel SJ (2009a) Cortical circuits for perceptual inference. Neural
1184 Networks 22:1093–1104 Available at:
1185 https://www.sciencedirect.com/science/article/pii/S0893608009001701#b18
1186 [Accessed December 12, 2018].

1187 Friston KJ, Kiebel SJ (2009b) Predictive coding under the free-energy principle.
1188 Philos Trans R Soc B Biol Sci 364:1211–1221 Available at:
1189 http://www.ncbi.nlm.nih.gov/pubmed/19528002 [Accessed December 13,
1190 2018].

1191 Games KD, Winer JA (1988) Layer V in rat auditory cortex: Projections to the
1192 inferior colliculus and contralateral cortex. Hear Res 34:1–25.

1193 Garrido MI, Kilner JM, Kiebel SJ, Stephan KE, Baldeweg T, Friston KJ (2009a)
1194 Repetition suppression and plasticity in the human brain. Neuroimage
1195 48:269–279 Available at:
1196 https://www.sciencedirect.com/science/article/pii/S1053811909006661
1197 [Accessed February 2, 2018].

1198 Garrido MI, Kilner JM, Stephan KE, Friston KJ (2009b) The mismatch
1199 negativity: a review of underlying mechanisms. Clin Neurophysiol 120:453–
1200 463 Available at:
1201 https://www.sciencedirect.com/science/article/pii/S1388245708012686?via
1202 %3Dihub [Accessed February 4, 2012].

1203 Grotheer M, Kovács G (2016) Can predictive coding explain repetition
1204 suppression? Cortex 80:113–124 Available at:
1205 https://www.sciencedirect.com/science/article/pii/S0010945216000149?via
1206 %3Dihub#sec4 [Accessed April 27, 2018].

1207 Gruters KG, Groh JM (2012) Sounds and beyond: Multisensory and other non-
1208 auditory signals in the inferior colliculus. Front Neural Circuits 6:1–39.

1209 Gutfreund Y, Zheng W, Knudsen EI (2002) Gated visual input to the central
1210 auditory system. Science (80-) 297:1556–1559 Available at:
1211 https://www.science.org/doi/10.1126/science.1073712 [Accessed February
1212 8, 2024].

1213 Hara K, Harris RA (2002) The anesthetic mechanism of urethane: The effects
1214 on neurotransmitter-gated ion channels. Anesth Analg 94:313–318
1215 Available at: http://www.ncbi.nlm.nih.gov/pubmed/11812690 [Accessed
1216 June 3, 2018].

1217 Harms L, Fulham WR, Todd J, Budd TW, Hunter M, Meehan C, Penttonen M,
1218 Schall U, Zavitsanou K, Hodgson DM, Michie PT (2014) Mismatch
1219 negativity (MMN) in freely-moving rats with several experimental controls
1220 Malmierca MS, ed. PLoS One 9:e110892 Available at:
1221 http://dx.plos.org/10.1371/journal.pone.0110892 [Accessed February 2,
1222 2018].

1223 Herbert H, Aschoff A, Ostwald J (1991) Topography of projections from the
1224 auditory cortex to the inferior colliculus in the rat. J Comp Neurol 304:103–
1225 122 Available at:
1226 https://onlinelibrary.wiley.com/doi/full/10.1002/cne.903040108 [Accessed
1227 May 13, 2021].

1228 Hernández O, Espinosa N, Pérez-González D, Malmierca MS (2005) The
1229 inferior colliculus of the rat: A quantitative analysis of monaural frequency
1230 response areas. Neuroscience 132:203–217 Available at:

https://www.sciencedirect.com/science/article/pii/S0306452205000692?via%3Dihub [Accessed February 7, 2018].

Hohwy J (2013) The predictive mind. Oxford, England: Oxford University Press. Available at: https://books.google.es/books?hl=en&lr=&id=z7gVDAAAQBAJ&oi=fnd&pg=PP1&dq=info:q91iSdERGM8J:scholar.google.com&ots=DiAM0Xy44s&sig=rPAXCTAh2O1u2tLEwWSxb_ScB_Y&redir_esc=y#v=onepage&q&f=false [Accessed May 2, 2019].

Hu F, Dan Y (2022) An inferior-superior colliculus circuit controls auditory cue-directed visual spatial attention. Neuron 110:109-119.e3 Available at: https://doi.org/10.1016/j.neuron.2021.10.004 [Accessed February 8, 2024].

Hupé JM, James AC, Payne BR, Lomber SG, Girard P, Bullier J (1998) Cortical feedback improves discrimination between figure and background by V1, V2 and V3 neurons. Nature 394:784–787 Available at: https://www.nature.com/articles/29537 [Accessed May 19, 2021].

Itaya SK, Van Hoesen GW (1982) Retinal innervation of the inferior colliculus in rat and monkey. Brain Res 233:45–52.

Ito T, Malmierca MS (2018) Neurons, Connections, and Microcircuits of the Inferior Colliculus. In: The Mammalian Auditory Pathways (Oliver D, Cant N, Fay R, Popper A, eds), pp 127–167. Berlin: Springer, Cham. Available at: http://link.springer.com/10.1007/978-3-319-71798-2_6 [Accessed June 2, 2018].

Ito T, Ono M, Oliver DL, Ito T, Ono M, Oliver DL (2018) Neuron Types, Intrinsic Circuits, and Plasticity in the Inferior Colliculus. In: The Oxford Handbook of

the Auditory Brainstem (Kandler K, ed). Oxford University Press. Available at: http://oxfordhandbooks.com/view/10.1093/oxfordhb/9780190849061.001.0001/oxfordhb-9780190849061-e-25 [Accessed December 18, 2018].

Jääskeläinen IP, Ahveninen J, Bonmassar G, Dale AM, Ilmoniemi RJ, Levänen S, Lin F-H, May PJC, Melcher J, Stufflebeam S, Tiitinen H, Belliveau JW (2004) Human posterior auditory cortex gates novel sounds to consciousness. Proc Natl Acad Sci 101:6809–6814 Available at: http://www.pnas.org/cgi/doi/10.1073/pnas.0303760101 [Accessed June 2, 2019].

Jacobsen T, Horenkamp T, Schröger E (2003) Preattentive memory-based comparison of sound intensity. Audiol Neuro-Otology 8:338–346 Available at: http://www.ncbi.nlm.nih.gov/pubmed/14566104 [Accessed April 23, 2018].

Jamal L, Khan AN, Butt S, Patel CR, Zhang H (2012) The level and distribution of the GABABRI and GABABR2 receptor subunits in the rat's inferior colliculus. Front Neural Circuits 6:30930.

Janacsek K, Evans TM, Kiss M, Shah L, Blumenfeld H, Ullman MT (2022) Subcortical Cognition: The Fruit Below the Rind. Annu Rev Neurosci 45:361–386 Available at: https://www.annualreviews.org/doi/abs/10.1146/annurev-neuro-110920-013544 [Accessed February 11, 2024].

Jane JA, Masterton RB, Diamond IT (1965) The function of the tectum for attention to auditory stimuli in the cat. J Comp Neurol 125:165–191

Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/cne.901250203 [Accessed February 8, 2024].

Jen PHS, Chen QC, Sun XD (1998) Corticofugal regulation of auditory sensitivity in the bat inferior colliculus. J Comp Physiol - A Sensory, Neural, Behav Physiol 183:683–697 Available at: https://link.springer.com/article/10.1007/s003590050291 [Accessed February 10, 2024].

Keller GB, Mrsic-Flogel TD (2018) Predictive processing: a canonical cortical computation. Neuron 100:424–435 Available at: https://www.sciencedirect.com/science/article/abs/pii/S0896627318308572?via%3Dihub [Accessed June 4, 2019].

King AJ, Nelken I (2009) Unraveling the principles of auditory cortical processing: can we learn from the visual system? Nat Neurosci 12:698–701 Available at: http://www.nature.com/doifinder/10.1038/nn.2308.

Le Beau FEN, Malmierca MS, Rees A (2001) Iontophoresis in vivo demonstrates a key role for GABA(A) and glycinergic inhibition in shaping frequency response areas in the inferior colliculus of guinea pig. J Neurosci 21:7303–7312 Available at: http://www.ncbi.nlm.nih.gov/pubmed/11549740 [Accessed February 7, 2018].

Lee T-Y, Weissenberger Y, King AJ, Dahmen JC (2024) Midbrain encodes sound detection behavior without auditory cortex. bioRxiv:2023.06.07.544013 Available at: https://www.biorxiv.org/content/10.1101/2023.06.07.544013v2 [Accessed April 3, 2024].

Lesicko AMH, Angeloni CF, Blackwell JM, De Biasi M, Geffen MN (2022) Cortico-Fugal Regulation of Predictive Coding. Elife 11.

Lesicko AMH, Geffen MN (2022) Diverse functions of the auditory cortico-collicular pathway. Hear Res 425:108488.

Liu M, Gao Y, Xin F, Hu Y, Wang T, Xie F, Shao C, Li T, Wang N, Yuan K (2024) Parvalbumin and Somatostatin: Biomarkers for Two Parallel Tectothalamic Pathways in the Auditory Midbrain. J Neurosci 44 Available at: https://www.jneurosci.org/content/44/10/e1655232024 [Accessed March 30, 2024].

Maggi CA, Meli A (1986) Suitability of urethane anesthesia for physiopharmacological investigations in various systems. Part 1: General considerations. Experientia 42:109–114 Available at: http://www.ncbi.nlm.nih.gov/pubmed/2868911 [Accessed June 3, 2018].

Malmierca MS (2015) Chapter 29 – Auditory System. In: The Rat Nervous System (Paxinos G, ed), pp 865–946. Cambridge: Academic Press. Available at: http://www.sciencedirect.com/science/article/pii/B9780123742452000292 [Accessed April 3, 2017].

Malmierca MS, Carbajal G V., Escera C (2019) Deviance Detection and Encoding Acoustic Regularity in the Auditory Midbrain. In: The Oxford Handbook of the Auditory Brainstem (Kandler K, ed), pp 706–740. Oxford University Press. Available at: http://oxfordhandbooks.com/view/10.1093/oxfordhb/9780190849061.001.0001/oxfordhb-9780190849061-e-19 [Accessed September 19, 2019].

1327 Malmierca MS, Cristaudo S, Pérez-González D, Covey E (2009) Stimulus-
1328 Specific Adaptation in the Inferior Colliculus of the Anesthetized Rat. J
1329 Neurosci 29:5483–5493 Available at:
1330 http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.4153-08.2009.

1331 Malmierca MS, Ryugo DK (2011) Descending connections of auditory cortex to
1332 the midbrain and brain stem. In: The Auditory Cortex, 1st ed. (Winer JA,
1333 Schreiner CE, eds), pp 189–208. Boston, MA: Springer US. Available at:
1334 http://link.springer.com/10.1007/978-1-4419-0074-6_9 [Accessed
1335 September 20, 2017].

1336 Merchán MA, Aguilar LA, Lopez-Poveda EA, Malmierca MS (2005) The inferior
1337 colliculus of the rat: Quantitative immunocytochemical study of GABA and
1338 glycine. Neuroscience 136:907–925 Available at:
1339 https://www.sciencedirect.com/science/article/pii/S0306452205000564
1340 [Accessed February 4, 2018].

1341 Merrill EG, Ainsworth A (1972) Glass-coated platinum-plated tungsten
1342 microelectrodes. Med Biol Eng 10:662–672 Available at:
1343 http://link.springer.com/10.1007/BF02476084 [Accessed February 7, 2018].

1344 Metzger RR, Greene NT, Porter KK, Groh JM (2006) Effects of reward and
1345 behavioral context on neural activity in the primate inferior colliculus. J
1346 Neurosci 26:7468–7476 Available at:
1347 https://www.jneurosci.org/content/26/28/7468 [Accessed February 8, 2024].

1348 Michel MM, Chen Y, Seidemann E, Geisler WS (2018) Nonlinear Lateral
1349 Interactions in V1 Population Responses Explained by a Contrast Gain
1350 Control Model. J Neurosci 38:10069–10079.

1351 Milbrandt JC, Albin RL, Turgeon SM, Caspary DM (1996) GABAA receptor
1352 binding in the aging rat inferior colliculus. Neuroscience 73:449–458.

1353 Mill RW, Coath M, Wennekers T, Denham SL (2011) A neurocomputational
1354 model of stimulus-specific adaptation to oddball and markov sequences
1355 Sporns O, ed. PLoS Comput Biol 7:e1002117 Available at:
1356 https://dx.plos.org/10.1371/journal.pcbi.1002117 [Accessed December 12,
1357 2018].

1358 Mitani A, Shimokouchi M, Nomura S (1983) Effects of stimulation of the primary
1359 auditory cortex upon colliculogeniculate neurons in the inferior colliculus of
1360 the cat. Neurosci Lett 42:185–189.

1361 Nelken I, Fishbach A, Las L, Ulanovsky N, Farkas D (2003) Primary auditory
1362 cortex of cats: Feature detection or something else? Biol Cybern 89:397–
1363 406 Available at: https://link.springer.com/article/10.1007/s00422-003-
1364 0445-3 [Accessed February 8, 2024].

1365 Nieto-Diego J, Malmierca MS (2016) Topographic Distribution of Stimulus-
1366 Specific Adaptation across Auditory Cortical Fields in the Anesthetized Rat.
1367 PLoS Biol 14:e1002397 Available at:
1368 http://dx.doi.org/10.1371/journal.pbio.1002397.

1369 Nwabueze-Ogbo FC, Popelář J, Syka J (2003) Changes in Neuronal Activity of
1370 the Inferior Colliculus in Rat after Temporal Inactivation of the Auditory
1371 Cortex. Physiol Res 52:615–628 Available at:
1372 http://www.biomed.cas.cz/physiolres [Accessed May 22, 2021].

1373 Oliver D, Cant N, Fay R, Popper Editors A (2017) The Mammalian Auditory
1374 Pathways: synaptic organization and microcircuits. Springer. Available at:

http://www.springer.com/series/2506.

Oliver DL (2005) Neuronal organization in the inferior colliculus. In: The Inferior Colliculus, pp 69–114. Springer New York. Available at: https://link.springer.com/chapter/10.1007/0-387-27083-3_2 [Accessed May 13, 2021].

Olthof BMJ, Rees A, Gartside SE (2019) Multiple nonauditory cortical regions innervate the auditory midbrain. J Neurosci 39:8916–8928 Available at: https://www.jneurosci.org/content/39/45/8916 [Accessed April 13, 2023].

Palmer AR, Shackleton TM, Sumner CJ, Zobay O, Rees A (2013) Classification of frequency response areas in the inferior colliculus reveals continua not discrete classes. J Physiol 591:4003–4025 Available at: https://onlinelibrary.wiley.com/doi/full/10.1113/jphysiol.2013.255943 [Accessed September 27, 2022].

Parras GG, Casado-Román L, Schröger E, Malmierca MS (2021) The posterior auditory field is the chief generator of prediction error signals in the auditory cortex. Neuroimage 242:118446.

Parras GG, Nieto-Diego J, Carbajal G V., Valdés-Baizabal C, Escera C, Malmierca MS (2017) Neurons along the auditory pathway exhibit a hierarchical organization of prediction error. Nat Commun 8:2148 Available at: http://dx.doi.org/10.1038/s41467-017-02038-6.

Parvizi J (2009) Corticocentric myopia: old bias in new cognitive sciences. Trends Cogn Sci 13:354–359.

Paxinos G, Watson C (2007) The rat brain in stereotaxic coordinates.

Cambridge: Academic Press.

Peng F, Harper NS, Mishra AP, Auksztulewicz R, Schnupp JWH (2024) Dissociable Roles of the Auditory Midbrain and Cortex in Processing the Statistical Features of Natural Sound Textures. J Neurosci 44 Available at: https://www.jneurosci.org/content/44/10/e1115232023 [Accessed March 30, 2024].

Pérez-González D, Malmierca MS, Covey E (2005) Novelty detector neurons in the mammalian auditory midbrain. Eur J Neurosci 22:2879–2885 Available at: http://doi.wiley.com/10.1111/j.1460-9568.2005.04472.x [Accessed September 12, 2017].

Pérez-González D, Parras GG, Morado-Díaz CJ, Aedo-Sánchez C, Carbajal G V., Malmierca MS (2021) Deviance detection in physiologically identified cell types in the rat auditory cortex. Hear Res 399:107997.

Peter V, McArthur G, Thompson WF (2010) Effect of deviance direction and calculation method on duration and frequency mismatch negativity (MMN). Neurosci Lett 482:71–75.

Polley DB, Read HL, Storace DA, Merzenich MM (2007) Multiparametric Auditory Receptive Field Organization Across Five Cortical Fields in the Albino Rat. J Neurophysiol 97:3621–3638 Available at: http://jn.physiology.org/cgi/doi/10.1152/jn.01298.2006.

Popelář J, Šuta D, Lindovský J, Bureš Z, Pysanenko K, Chumak T, Syka J (2016) Cooling of the auditory cortex modifies neuronal activity in the inferior colliculus in rats. Hear Res 332:7–16.

Porter KK, Metzger RR, Groh JM (2007) Visual- and saccade-related signals in the primate inferior colliculus. Proc Natl Acad Sci U S A 104:17855–17860 Available at: https://www.pnas.org/doi/abs/10.1073/pnas.0706249104 [Accessed February 8, 2024].

Quass GL, Rogalla MM, Ford AN, Apostolides PF (2023) Mixed representations of sound and action in the auditory midbrain. bioRxiv Available at: /pmc/articles/PMC10541616/ [Accessed April 2, 2024].

Rao RPN, Ballard DH (1999) Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. Nat Neurosci 2:79–87 Available at: 10.1038/4580%5Cnhttp://www.nature.com/neuro/journal/v2/n1/abs/nn0199_79.html.

Rinne T, Balk MH, Koistinen S, Autti T, Alho K, Sams M (2008) Auditory selective attention modulates activation of human inferior colliculus. J Neurophysiol 100:3323–3327 Available at: https://journals.physiology.org/doi/10.1152/jn.90607.2008 [Accessed February 8, 2024].

Ruhnau P, Herrmann B, Schröger E (2012) Finding the right control: The mismatch negativity under investigation. Clin Neurophysiol 123:507–512.

Ryan A, Miller J (1977) Effects of behavioral performance on single unit firing patterns in inferior colliculus of the rhesus monkey. J Neurophysiol 40:943–956 Available at: https://journals.physiology.org/doi/10.1152/jn.1977.40.4.943 [Accessed February 8, 2024].

1445 Sceniak MP, MacIver MB (2006) Cellular Actions of Urethane on Rat Visual
1446 Cortical Neurons In Vitro. J Neurophysiol 95:3865–3874 Available at:
1447 http://www.physiology.org/doi/10.1152/jn.01196.2005 [Accessed June 3,
1448 2018].

1449 Schelinski S, Tabas A, von Kriegstein K (2022) Altered processing of
1450 communication signals in the subcortical auditory sensory pathway in
1451 autism. Hum Brain Mapp 43:1955–1972 Available at:
1452 https://onlinelibrary.wiley.com/doi/full/10.1002/hbm.25766 [Accessed
1453 February 9, 2024].

1454 Schneider F, Balezeau F, Distler C, Kikuchi Y, van Kempen J, Gieselmann A,
1455 Petkov CI, Thiele A, Griffiths TD (2021) Neuronal figure-ground responses
1456 in primate primary auditory cortex. Cell Rep 35:109242.

1457 Schneider F, Dheerendra P, Balezeau F, Ortiz-Rios M, Kikuchi Y, Petkov CI,
1458 Thiele A, Griffiths TD (2018) Auditory figure-ground analysis in rostral belt
1459 and parabelt of the macaque monkey. Sci Rep 8:1–8 Available at:
1460 https://www.nature.com/articles/s41598-018-36903-1 [Accessed February
1461 12, 2024].

1462 Schofield BR, Beebe NL (2019) Descending Auditory Pathways and Plasticity.
1463 In: The Oxford Handbook of the Auditory Brainstem, pp 610–638. Oxford
1464 University Press. Available at:
1465 https://www.oxfordhandbooks.com/view/10.1093/oxfordhb/9780190849061.
1466 001.0001/oxfordhb-9780190849061-e-17 [Accessed May 13, 2021].

1467 Schreiner CE, Langner G (1997) Laminar fine structure of frequency
1468 organization in auditory midbrain. Nature 388:383–386 Available at:

https://www.nature.com/articles/41106 [Accessed February 18, 2024].

Schröger E, Wolff C (1996) Mismatch response of the human brain to changes in sound location. Neuroreport 7:3005–3008 Available at: http://www.ncbi.nlm.nih.gov/pubmed/9116228 [Accessed February 4, 2018].

Slabu L, Grimm S, Escera C (2012) Novelty detection in the human auditory brainstem. J Neurosci 32:1447–1452.

Stefanics G, Kremláček J, Czigler I (2014) Visual mismatch negativity: a predictive coding view. Front Hum Neurosci 8:666 Available at: http://journal.frontiersin.org/article/10.3389/fnhum.2014.00666/abstract.

Taaseh N, Yaron A, Nelken I (2011) Stimulus-Specific Adaptation and Deviance Detection in the Rat Auditory Cortex Sugihara I, ed. PLoS One 6:e23369 Available at: http://dx.plos.org/10.1371/journal.pone.0023369 [Accessed October 29, 2017].

Tabas A, Mihai G, Kiebel S, Trampel R, Von Kriegstein K (2020) Abstract rules drive adaptation in the subcortical sensory pathway. Elife 9:1–19.

Tabas A, von Kriegstein K (2021) Adjudicating Between Local and Global Architectures of Predictive Processing in the Subcortical Auditory Pathway. Front Neural Circuits 15.

Tabas A, von Kriegstein K (2024) Multiple concurrent predictions inform prediction error in the human auditory pathway. J Neurosci 44:JN-RM-2219-22 Available at: https://www.jneurosci.org/content/44/1/e2219222023 [Accessed February 9, 2024].

1492 Tawil RN, Saadé NE, Bitar M, Jabbur SJ (1983) Polysensory interactions on
1493 single neurons of cat inferior colliculus. Brain Res 269:149–152.

1494 Tervaniemi M, Maury S, Näätänen R (1994) Neural representations of abstract
1495 stimulus features in the human brain as reflected by the mismatch
1496 negativity. Neuroreport 5:844–846 Available at:
1497 http://www.ncbi.nlm.nih.gov/pubmed/8018861 [Accessed February 1,
1498 2018].

1499 Thompson GC, Masterton RB (1978) Brain stem auditory pathways involved in
1500 reflexive head orientation to sound. J Neurophysiol 41:1183–1202
1501 Available at: https://journals.physiology.org/doi/10.1152/jn.1978.41.5.1183
1502 [Accessed February 8, 2024].

1503 Todorovic A, de Lange FP (2012) Repetition suppression and expectation
1504 suppression are dissociable in time in early auditory evoked fields. J
1505 Neurosci 32:13389–13395 Available at:
1506 http://www.ncbi.nlm.nih.gov/pubmed/23015429 [Accessed April 27, 2018].

1507 Tokunaga A, Sugita S, Otani K (1984) Auditory and non-auditory subcortical
1508 afferents to the inferior colliculus in the rat. J Hirnforsch 25:461–472
1509 Available at: https://europepmc.org/article/med/6481158 [Accessed May
1510 19, 2021].

1511 Ulanovsky N, Las L, Nelken I (2003) Processing of low-probability sounds by
1512 cortical neurons. Nat Neurosci 6:391–398 Available at:
1513 https://search.proquest.com/docview/230485606?pq-origsite=gscholar
1514 [Accessed September 12, 2017].

1515 Valdés-Baizabal C, Carbajal G V., Pérez-González D, Malmierca MS (2020)

Dopamine modulates subcortical responses to surprising sounds. PLoS Biol 18:e3000744 Available at: https://doi.org/10.1371/journal.pbio.3000744 [Accessed September 3, 2020].

Vila CH, Williamson RS, Hancock KE, Polley DB (2019) Optimizing optogenetic stimulation protocols in auditory corticofugal neurons based on closed-loop spike feedback. J Neural Eng 16:066023 Available at: https://iopscience.iop.org/article/10.1088/1741-2552/ab39cf [Accessed February 10, 2024].

Wiens S, Szychowska M, Eklund R, van Berlekom E (2019) Cascade and no-repetition rules are comparable controls for the auditory frequency mismatch negativity in oddball tasks. Psychophysiology 56:e13280 Available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/psyp.13280 [Accessed May 30, 2019].

Winer JA, Chernock ML, Larue DT, Cheung SW (2002) Descending projections to the inferior colliculus from the posterior thalamus and the auditory cortex in rat, cat, and monkey. Hear Res 168:181–195.

Zhao L, Liu Y, Shen L, Feng L, Hong B (2011) Stimulus-specific adaptation and its dynamics in the inferior colliculus of rat. Neuroscience 181:163–174 Available at: http://dx.doi.org/10.1016/j.neuroscience.2011.01.060.

Zhou X, Jen PHS (2005) Corticofugal modulation of directional sensitivity in the midbrain of the big brown bat, Eptesicus fuscus. Hear Res 203:201–215.

Zwiers MP, Versnel H, Van Opstal AJ (2004) Involvement of Monkey Inferior Colliculus in Spatial Hearing. J Neurosci 24:4145–4156 Available at: https://www.jneurosci.org/content/24/17/4145 [Accessed February 8, 2024].

FIGURES

Figure 1. Experimental design. **(A)** Three possible experimental conditions within an oddball paradigm for a given tone of interest f_i (colored). **(B)** Three possible control conditions set by the MSC and CAS for a given tone of interest f_i (in green). **(C)** Schematic representation of an experimental setup for in vivo extracellular recording of auditory-evoked responses in a rat brain, depicting the neuroanatomical features most relevant to this paper. **(D)** Decomposition of neuronal mismatch responses using the controls and quantification in 3 indices.

Figure 2. IC processing of control sequences. **(A)** Schematic representation of frequency step comparisons. Responses to extreme step values featuring in both MSC and CAS, i.e., 0.5-octave and 4.5-octave steps, are compared across control sequences (highlighted and framed in green). Responses to different frequency steps (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, or 4.5 octaves) within the MSC are also compared. **(B-C)** Comparison matrices showing the differences in the evoked spiking responses after different frequency steps presented within the MSC or the CAS in lemniscal and nonlemniscal divisions of the IC. The normalized mean difference between the spikes per trial in the x-axis minus those in the y-axis is noted as a percentage where statistical significances were found (ANOVA, $p < 0.05$, highlighted in green). Significant differences found in both lemniscal and nonlemniscal divisions of the IC are marked as underlined digits, all corresponding to comparisons between 4.5-octave steps in CAS with the rest of smaller steps. Two circles in each matrix mark equal step comparisons across control sequences. **(B)** The lemniscal IC better distinguished different frequency steps (note the many significant green squares) and responded similarly to equal frequency steps happening in different controls (black dotted circles). **(C)** The nonlemniscal IC did not perform this spectral processing but could instead differentiate between equal frequency steps presented in different sequences (white circles).

Figure 3. Prediction error as a function of intensity and direction of frequency change in four auditory regions that engage in predictive processing. **(A)** Linear models fitted for the iPE (calculated with CAS or MSC) using dB SPL and direction of frequency change (ascending or descending) as predictors. Error bars denote mean and standard error of the mean for each intensity level and direction. The only models that achieved a statistically significant adjustment were in the nonlemniscal IC (first plot), revealing a clear tendency to show higher iPE values at lower intensities. **(B)** Violin plots comparing the spike counts evoked by DEV (in red) and CAS (in green) at low intensities (< 40 dB SPL, left violin) and high intensities (≥ 40 dB SPL, right violin).

Figure 4. Prediction error as a function of intensity and direction of frequency change in four types of FRA. **(A)** Categories of FRA shapes recorded in the nonlemniscal IC. **(B)** Linear models fitted for the iPE using dB SPL and direction (ascending or descending) as predictors. Error bars denote mean and standard error of the mean for each SPL and direction. The only models that did not achieve a statistically significant adjustment were those of the neurons that exhibited mosaic FRAs (fourth plot). Note that these neurons tended to show high iPE values, regardless of the intensity or direction of frequency change. **(C)** Violin plots comparing the spike counts evoked by DEV (in red) and CAS (in green) at low intensities (< 40 dB SPL, left violin) and high intensities (≥ 40 dB SPL, right violin). Note how the category of mosaic FRAs (fourth plot) completely deviates from the rest.

Figure 5. Time course of iPE (in orange) and iRS (in cyan) for each FRA type. **(A)** Categories of FRA shapes recorded in the nonlemniscal IC. **(B)** Time course of the iPE and iRS (mean ± standard error of the mean) when the intensity of stimulation was low (< 40 dB SPL). Black asterisks mark a significant value ($p < 0.05$, Wilcoxon signed-rank test, FDR-corrected for 8 comparisons) for the corresponding time window of 20 ms. Note that all but sharply tuned neurons (V, first plot) showed significant traces of PE signaling at low intensity stimulation. **(C)** Time course of the average iPE and iRS when the stimulation intensity was high (≥ 40 dB SPL). Note that whereas the iRS prevails largely unchanged across all categories, only the untuned neurons showing mosaic FRAs preserved their iPE values at high intensity stimulation (fourth plot).

Figure 6. Summary of results. **(A)** Median iPE (orange) and iRS (cyan) of each FRA category recorded in the nonlemniscal IC, represented with respect to the baseline set by CAS (green horizontal bar), at low and high intensity stimulation (left and right plots, respectively). Thereby, iPE is upwards-positive while iRS is downwards-positive (see Figure 1B). Striped regions in the bars mark negative iPE values. Asterisks denote statistical significance of the indices against zero: *n.s.*, nonsignificant, *****$p < 0.05$, ******$p < 0.01$, *******$p < 0.001$. **(B)** Median iPE and iRS of each FRA category represented with respect to the baseline set by MSC (green horizontal bar).

Figure 7. Early emergence of predictive processing in the auditory system. **(A-B)** Comparison matrices for, respectively, the nonlemniscal AC and the group of X-neurons in the nonlemniscal IC, setting X-neurons apart from the rest of nonlemniscal IC neurons (cf. Figure 2C) and implying a functional connection between both neural substrates. **(C)** Schematics of connectivity between the IC, MGB and AC. Descending projections targeting the nonlemniscal pathway extend the hierarchical exchange of predictions and prediction errors to earlier stages of auditory processing, presumably improving its overall efficiency. **(D)** Diagram summarizing our proposed classification of neuronal and functional elements in the intrinsic circuitry of the IC. 'Raw' spectral information from the central nucleus flows into the predictive processing circuitry of the IC cortices via V-neurons, which constitute the first filter of redundant input. Once at the

beginning of the nonlemniscal pathway, unexpected input will be consistently reported to higher-order processing levels by the ‘non-spectral’ PE system constituted by X-neurons with untuned receptive fields. When a deviant sound is close to the hearing threshold or is moving to a higher pitch, unexpected input additionally benefit from dynamic gain compensation provided by the ‘spectral’ PE system formed by W- and U-neurons with broad receptive fields.

TABLES

Table 1. Median normalized spike counts and indices calculated using CAS in each auditory region and at different intensities of stimulation. Significant iPE values are highlighted in bold (Friedman test).

	IC		MGB		AC	
ALL INTENSITIES	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**
Units	70	204	41	52	97	49
Tones	616	1711	183	364	586	407
DEV	0.589	0.661	0.591	0.684	0.745	0.795
STD	0.432	0.225	0.241	0.162	0.159	0.175
CAS	0.647	0.640	0.672	0.627	0.570	0.495
iMM	0.156	0.436	0.350	0.522	0.586	0.620
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*
iPE	**-0.058**	**0.021**	-0.081	**0.057**	**0.175**	**0.301**
p value	*0.008*	*0.007*	*0.271*	*0.006*	*0.000*	*0.000*
iRS	0.214	0.415	0.431	0.465	0.412	0.319
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*
LOW INTENSITIES (< 40 dB SPL)	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**
Units	33	79	7	14	33	11
Tones	161	468	20	61	168	65
DEV	0.624	0.716	0.533	0.688	0.724	0.790
STD	0.455	0.160	0.173	0.147	0.144	0.257

CAS	0.609	0.596	0.743	0.669	0.604	0.435
iMM	0.169	0.556	0.359	0.541	0.580	0.533
p value	*0.000*	*0.000*	*0.003*	*0.000*	*0.000*	*0.000*
iPE	0.014	**0.120**	-0.211	0.019	0.120	**0.355**
p value	*0.094*	*0.000*	*0.426*	*0.464*	*0.113*	*0.000*
iRS	0.154	0.436	0.570	0.522	0.461	0.178
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.007*
HIGH INTENSITIES (≥ 40 dB SPL)	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**
Units	63	171	36	46	74	46
Tones	455	1243	163	303	418	342
DEV	0.581	0.643	0.600	0.682	0.750	0.799
STD	0.428	0.252	0.273	0.164	0.166	0.163
CAS	0.654	0.656	0.660	0.612	0.553	0.519
iMM	0.153	0.391	0.327	0.518	0.583	0.636
p value	0.000	0.000	0.000	0.000	0.000	0.000
iPE	**-0.074**	-0.014	-0.060	**0.070**	**0.197**	**0.280**
p value	0.000	0.507	0.375	0.008	0.000	0.000
iRS	0.227	0.405	0.387	0.448	0.386	0.356
p value	0.000	0.000	0.000	0.000	0.000	0.000

1649

Table 2. Median normalized spike counts and indices calculated using MSC in each auditory region and at different intensities of stimulation. Significant iPE values are highlighted in bold (Friedman test).

	IC		MGB		AC	
ALL INTENSITIES	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**
Units	70	235	53	96	103	57
Tones	614	1912	214	569	635	465
DEV	0.586	0.659	0.615	0.669	0.714	0.770
STD	0.424	0.191	0.302	0.189	0.164	0.177
MSC	0.646	0.657	0.659	0.634	0.627	0.541
iMM	0.162	0.468	0.313	0.480	0.550	0.592
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*
iPE	**-0.060**	0.002	-0.044	0.035	**0.087**	**0.229**
p value	*0.000*	*0.686*	*0.371*	*0.467*	*0.005*	*0.000*
iRS	0.222	0.465	0.357	0.445	0.463	0.364
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*
LOW INTENSITIES (< 40 dB SPL)	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**
Units	32	98	6	42	39	16
Tones	160	531	18	114	195	97
DEV	0.611	0.707	0.724	0.679	0.726	0.708
STD	0.440	0.151	0.193	0.193	0.161	0.236
MSC	0.591	0.620	0.625	0.607	0.599	0.615
iMM	0.171	0.556	0.531	0.486	0.565	0.472

p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*
iPE	0.020	**0.087**	0.099	0.072	**0.127**	0.094
p value	*0.218*	*0.001*	*0.617*	*0.162*	*0.027*	*0.085*
iRS	0.151	0.468	0.432	0.414	0.438	0.379
p value	*0.000*	*0.000*	*0.003*	*0.000*	*0.000*	*0.000*
HIGH INTENSITIES (≥ 40 dB SPL)	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**	**Lem.**	**Nonlem.**
Units	63	196	49	91	80	51
Tones	454	1381	196	455	440	368
DEV	0.159	0.642	0.593	0.659	0.712	0.791
STD	-0.080	0.221	0.318	0.186	0.165	0.172
MSC	0.238	0.666	0.661	0.640	0.635	0.514
iMM	0.238	0.420	0.275	0.473	0.547	0.619
p value	0.000	0.000	0.000	0.000	0.000	0.000
iPE	**-0.080**	**-0.025**	-0.068	0.019	0.076	**0.277**
p value	0.000	0.014	0.277	0.908	0.059	0.000
iRS	0.318	0.445	0.342	0.454	0.470	0.342
p value	0.000	0.000	0.000	0.000	0.000	0.000

1653

Table 3. Median indices calculated using both controls for each FRA category recorded in the nonlemniscal IC. Significant iPE values are highlighted in bold (Friedman test).

	CAS				MSC			
ALL INTENSITIES	**V**	**W**	**U**	**X**	**V**	**W**	**U**	**X**
Units	54	44	62	44	61	50	76	48
Tones	375	535	484	317	406	578	587	341
iMM	0.225	0.467	0.501	0.532	0.231	0.481	0.543	0.501
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*
iPE	-0.019	-0.014	-0.010	**0.214**	**-0.052**	-0.012	-0.010	**0.146**
p value	*0.660*	*0.571*	*0.676*	*0.000*	*0.012*	*0.133*	*0.189*	*0.000*
iRS	0.244	0.480	0.511	0.318	0.283	0.492	0.553	0.355
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*
LOW INTENSITIES (< 40 dB SPL)	**V**	**W**	**U**	**X**	**V**	**W**	**U**	**X**
Units	20	20	24	15	24	23	33	18
Tones	87	151	119	111	96	163	147	125
iMM	0.225	0.467	0.501	0.532	0.346	0.583	0.648	0.545
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*
iPE	0.039	**0.107**	**0.114**	**0.230**	-0.006	0.063	**0.098**	**0.166**
p value	*0.110*	*0.000*	*0.003*	*0.000*	*0.427*	*0.256*	*0.017*	*0.000*
iRS	0.300	0.485	0.530	0.282	0.352	0.520	0.551	0.379
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*

HIGH INTENSITIES (≥ 40 dB SPL)	V	W	U	X	V	W	U	X
Units	46	39	52	34	52	45	63	36
Tones	288	384	365	206	310	415	440	216
iMM	0.202	0.404	0.455	0.539	0.210	0.444	0.504	0.482
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*
iPE	-0.032	**-0.051**	**-0.048**	**0.218**	**-0.063**	**-0.034**	**-0.042**	**0.132**
p value	*0.707*	*0.006*	*0.028*	*0.000*	*0.015*	*0.013*	*0.004*	*0.000*
iRS	0.233	0.454	0.502	0.321	0.273	0.478	0.546	0.350
p value	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*	*0.000*

1657