Neuroscience

Beyond Auditory Relay: Dissecting the Inferior Colliculus's Role in Sensory Prediction, Cognitive Decision-Making, and Reward Prediction

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Abstract

The Inferior Colliculus (IC) has traditionally been regarded as an important relay in the auditory pathway, primarily involved in relaying auditory information from the brainstem to the thalamus. However, this study uncovers the multifaceted role of the IC in bridging auditory processing, sensory prediction, and reward prediction. Through extracellular recordings in monkeys engaged in a sound duration-based novelty detection task, we observed a "climbing effect" in neuronal firing rates, indicative of an enhanced response over sound sequences linked to sensory prediction rather than reward anticipation. Further exploration revealed a direct correlation between IC neuronal activity and behavioral choices, suggesting its involvement in decision-making processes. Additionally, our findings demonstrate reward prediction errors within the IC, highlighting its complex integration in auditory and reward processing. This research challenges conventional views of the IC, showcasing its integral role in cognitive and sensory processing and emphasizing its importance in integrated brain functions.

eLife assessment

This study presents a **valuable** finding on the role of the Inferior Colliculus in sensory prediction, cognitive decision-making, and reward prediction. The evidence supporting the claims of the authors is **solid**. The work will be of interest to neurobiologists working on auditory processing.

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Introduction

The brain's architecture is a complex hierarchy, where functions become increasingly sophisticated from lower to higher levels. The cerebral cortex, for instance, is pivotal for higher-order cognitive functions such as decision-making, motivation, attention, learning, memory, problem-solving, and conceptual thinking (Kremkow and Alonso, 2018; Miterko et al., 2018). Conversely, subcortical sensory systems are traditionally viewed as mere conduits for sensory information (Sherman, 2016), despite suggestions of thalamic structures playing roles in advanced perceptual tasks (Jones, 2012; Sherman, 2005). Yet, the involvement of sensory neurons below the thalamo-cortical level in cognitive behaviors remains an underexplored domain. Within the auditory hierarchy, spanning seven stages from the cochlea to the auditory cortex (AC) (Pickles, 2015), the inferior colliculus (IC) emerges as a crucial intermediary, instrumental in processing spatial representations (Cohen and Knudsen, 1999; Ono and Ito, 2015) and novelty detection (Malmierca et al., 2009; Perez-Gonzalez et al., 2005). Utilizing the oddball paradigm, researchers have identified stimulus-specific adaptation (SSA) within the inferior colliculus (IC) (Ayala et al., 2016; Duque and Malmierca, 2015; Malmierca et al., 2009; Valdés-Baizabal et al., 2021; Valdés-Baizabal et al., 2017), where neurons decrease their response to frequently occurring sounds while maintaining robust reactions to deviant ones. This phenomenon, indicative of predictive coding, underscores the IC's relevance with sensory prediction. Exploration along the auditory pathway suggests SSA's origination from the IC (Carbajal and Malmierca, 2018; Khouri and Nelken, 2015; Song et al., 2023). Intriguingly, the dynamic interplay between sensory prediction and sensory encoding, particularly within lower sensory systems charged with the faithful representation of external stimuli, remains an underexplored yet captivating area of inquiry.

Traditionally viewed as a key player in auditory processing, the inferior colliculus (IC) is situated in the auditory midbrain and serves as a vital conduit, channeling inputs from the brainstem's auditory nuclei towards the thalamocortical auditory pathway. Intriguingly, the IC is endowed with dopamine receptors and exhibits nerve terminals positive for tyrosine hydroxylase, signifying a channel for dopaminergic inputs originating from the subparafascicular thalamic nucleus (Harris et al., 2021; Nevue et al., 2015; Nevue et al., 2016). This positions the IC as a crucial intersection where auditory processing and reward mechanisms converge. Recent research underscores the significant influence of dopamine on modulating auditory responses within the IC (Gittelman et al., 2013; Hoyt et al., 2019). This modulation suggests a complex interplay wherein dopamine has the potential to either suppress or enhance neural activity in the IC, depending on various factors (Gittelman et al., 2013; Hoyt et al., 2019). This amalgamation of sensory and reward coding within the IC paves new paths for research, urging a deeper inquiry into how this midbrain entity integrates auditory and reward information to mold behavioral processes, thereby challenging the traditional auditory-centric view of the IC and opening avenues for understanding its multifaceted role in cognitive and sensory modulation.

In this research, we embarked on a novelty detection task centered around sound duration with trained monkeys, performing extracellular recordings in the IC. Our observations unveiled a 'climbing effect'—a progressive increase in firing rate after sound onset, not attributable to reward but seemingly linked to sensory experience such as sensory prediction. Moreover, we identified signals of reward prediction error and decision-making. These findings propose that the IC's role in auditory processing extends into the realm of complex perceptual and cognitive tasks, challenging previous assumptions about its functionality.

Results

Response dynamics of IC neurons in duration novelty detection

Neurons within IC (**Supplementary Fig.1**) are distinguished by their ability to sustain firing, illustrating a consistent encoding of sound duration through tonic firing throughout the entire auditory length in one example neuron (**Fig. 1A**). An analysis of 104 neurons (53 from Monkey B and 51 from Monkey J) demonstrated that these neurons maintained sustained firing responses to sounds of varying durations—100, 500, and 1000 ms (**Fig. 1B**). This sustained firing behavior suggests the IC's role in processing temporal aspects of auditory perception, highlighting its potential involvement in functions related to duration perception.

Despite traditionally being viewed as a lower-level nucleus within the auditory pathway in comparison to the auditory cortex, and rarely explored from a perceptual standpoint, this study breaks new ground by examining the involvement of IC neurons in duration perception. Monkeys were trained to perform a novelty detection task focusing on duration. **Figures 1C** and **1D** outline the behavioral task, presenting repetitive sounds in blocks with oddball stimuli. Each block consisted of 3 to 6 repeated white-noise bursts of 300-ms duration at 600-ms interstimulus intervals, concluding with either a standard sound (control condition) or a deviant sound (**Fig. 1D**). Monkeys were required to press a button within 600 ms after the offset of the deviant stimulus to receive a water reward. Correct rejections occurred when the monkey refrained from pressing the button within 600 ms following a standard sound in control trials, where the deviant duration equaled the standard duration. The task difficulty was modulated by setting deviant durations at five levels: 300 (control), 357, 425, 506, and 600 ms (**Fig. 1D**), with the pressing ratio approaching zero in the control condition and increasing with the deviant duration, reaching 1 at the 600 ms deviant duration in one example session (**Fig. 1E**).

The initial analysis focused on the deviant response during correct trials, revealing that an example IC neuron exhibited continuous firing throughout the sound presentation (**Fig. 2A**). Following the peak response in the initial 0-60 ms window, the neuron's firing rate began to increase approximately 100 ms after the sound's onset, continuing until the sound's conclusion. This phenomenon, illustrated by aligning the responses to the sound's offset (**Fig. 2B**), indicated a proportional increase in firing rate with longer sound durations, suggesting a duration-dependent "climbing effect." To quantitatively assess this dynamic, the neuronal firing rate was examined across different sound durations within two distinct temporal windows: the "onset window" (0-60 ms post-sound onset) and the "late window" (−100-0 ms relative to sound offset). Notably, the firing rate of the example neuron in the late window escalated with increasing duration ($p = 6.51e-23$, ANOVA with post hoc test; red in **Fig. 2C**), while remaining constant in the onset window ($p = 0.69$, ANOVA with post-hoc test; black in **Fig. 2C**), contrasting sharply with the non-behavior condition (**Supplementary Fig. 1**) which showed no climbing effect.

To assess if the "climbing effect" was contingent on behavioral context, we compared responses across behavior and non-behavior conditions. Sound durations were analyzed at three levels (100, 500, and 1000 ms for the non-behavior condition as shown in **Fig. 1A, B**) and five levels (300, 357, 425, 506, and 600 ms for the behavior condition, illustrated in **Fig. 1C, D**). In the same neuronal population (n=99), the firing rate increased after the peak onset response for the behavior situation (red line of **Supplementary Fig. 2A**), while the firing rate stayed constant for the non-behavior condition from 100 ms to the end of the sound (blue line of **Supplementary Fig. 2A**). The "Response Dynamic Index" (RDI) was introduced to quantify the climbing effect, calculated as the normalized difference between responses in the late window (−100-0 ms relative to the sound's offset) and the after-peak window (100-200 ms relative to the sound's onset). This comparative analysis indicated a significantly higher RDI in the behavior condition ($p = 4.40e-19$,

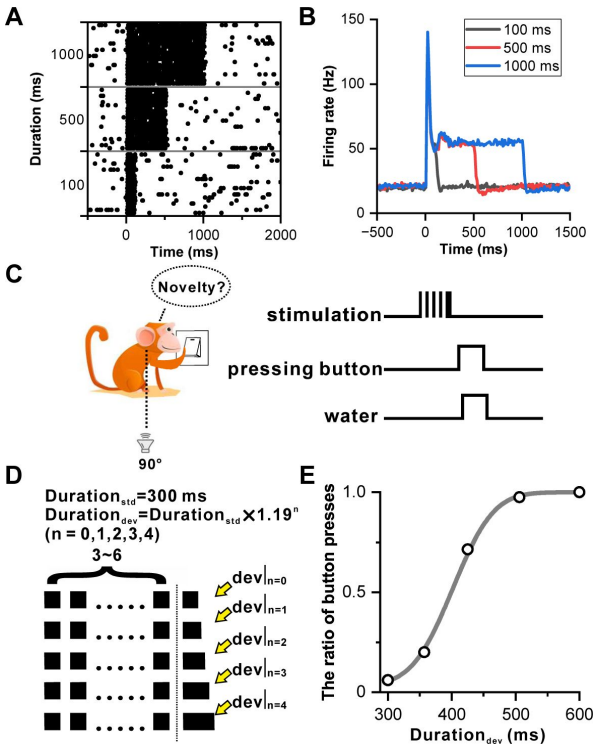

Figure 1

Sustained Firing in IC and Novelty Detection Paradigm Based on Sound Duration.

(A) Raster plots of a representative neuron depicting the response profile to white noise stimuli with varying durations (100 ms, 500 ms, and 1000 ms). **(B)** PSTHs of neuronal population responses (n=104) to the stimuli described in **A** (black, 100-ms white noise; red, 500-ms white noise; blue, 1000-ms white noise). **(C)** Schematic display of novelty detection behavior. A button is positioned in front of the monkey, and a loudspeaker is placed contralateral to the recording site at the height of the monkey's ear. Within each experimental block, a series of repeated 300-ms white noise bursts (WNB) serves as the standard stimulus, accompanied by a rare-duration WNB serving as the deviant stimulus. Following the presentation of the deviant stimulus, the primate is required to press the designated button within a 600-ms timeframe to obtain a water reward. **(D)** Oddball stimulation paradigm employed in all experimental blocks. While the duration of the standard sound remains constant at 300 ms, the duration of the novel sound deviates from the standard sound across five distinct levels. This deviation is determined by the formula: $Duration_{deviant} = Duration_{standard} \times \lambda^{n}$ (where n=0,1,2,3,4; λ = 1.19). Furthermore, the number of standard stimuli within each block is randomly selected from a range of 3 to 6. Upon completion of the deviant sound, the primate is required to press the designated button within a 600-ms window to receive the reward. In the absence of a deviant sound (control condition), the reward is granted if the primate refrains from pressing the button within 600 ms after the onset of the final sound. **(E)** Cumulative Gaussian fits of psychophysical data in one example session. The duration of the deviant sound is plotted along the abscissa, while the ratio of button presses is plotted along the ordinate.

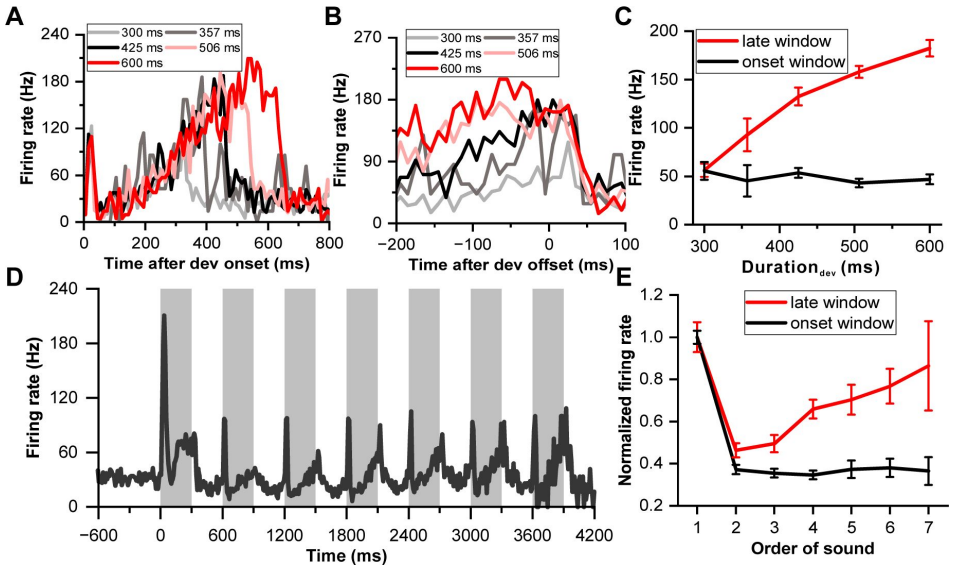

Figure 2

Neuronal climbing effect in novelty detection behavior.

(A) Peri-stimulus time histograms (PSTHs) depicting example neuronal responses to different deviant sounds aligned to deviant onset (light gray, 300-ms deviant sound; gray, 357-ms deviant sound; black, 425-ms deviant sound; pink, 506-ms deviant sound; red, 600-ms deviant sound). **(B)** The same neuronal responses as in **A**, but this time aligned to the offset of the deviant stimulus. The PSTHs represent the neural activity before the offset of each deviant sound. The color scheme remains consistent with **A** to indicate the different deviant durations. **(C)** Firing rate to deviant stimuli in two windows: the late window ([-100 0] ms relative to offset time) and the onset window ([0 60] ms relative to onset time) (red, late window; black, onset window). **(D)** PSTH showing neuronal responses to standard sounds (1-7) from the neuron described in **A**. **(E)** Normalized firing rate of the neuron described in **A** to standard sounds in two temporal windows (late window: [-100 0] ms relative to offset time; onset window: [0 60] ms relative to onset time) plotted as a function of the order of the sounds (red, late window; black, onset window).

paired t-test, **Supplementary Fig. 2B**), indicating the climbing effect's reliance on behavioral context. Additionally, RDIs across various deviant sounds showed strong correlations ($p < 0.001$, Pearson Correlation Analysis, **Supplementary Fig. 3**) and similar values across differing deviants (**Supplementary Fig. 3**). Detailed insights into the tonotopic distribution of the climbing effect within the IC are provided in **Supplementary Fig. 4**.

Exploration into whether the climbing effect manifested in responses to preceding standard stimuli showed that the same example neuron exhibited the climbing effect post-peak response to standard stimuli, which intensified as successive standard sounds progressed from the second to the seventh stimulation (**Fig. 2D**). The firing rate markedly decreased from the first to the second sound in both the late window ($p = 3.33e-11$, paired t-test, red in **Fig. 2E**) and onset window ($p = 2.02e-40$, paired t-test, black in **Fig. 2E**). The rate then increased in the late window ($p = 3.05e-5$, ANOVA with post hoc test: second versus fourth, $p = 0.0398$; fourth versus seventh, $p = 1.00$; red in **Fig. 2E**) but remained consistent in the onset window ($p = 0.963$, ANOVA with post hoc test, black in **Fig. 2E**) from the second to the seventh sound. Interestingly, no climbing effect was noted in the late window for the first stimulus, and the effect amplified with each subsequent standard presentation.

To monitor the dynamic of the climbing effect across repetitive sound presentations, we analyzed responses to the 300 ms sound across the entire oddball block in population. We normalized the firing rate relative to the response to the first stimulus in the block, considering both the onset and late windows (**Fig. 3A**), to account for variability across the neuronal population. In the onset window, responses remained relatively stable from the second to the seventh sound (black line, **Fig. 3A**). Conversely, in the late window, responses ascended from the second to the fourth stimulus (ANOVA with post-hoc test: second versus fourth, $p = 8.29e-4$, red line, **Fig. 3A**) and maintained a stable level from the fourth to the seventh stimulus ($p = 0.653$, ANOVA with post hoc test, red line, **Fig. 3A**). This pattern was mirrored in the peri-stimulus time histograms (PSTHs), which consolidated responses from the second to the seventh stimulus in one scale (left ordinate in **Fig.3B**) and the first stimulus in another scale (right ordinate in **Fig.3B**) for comparative purposes. Onset responses to the second through seventh stimuli completely overlapped, but responses in the late window diverged. The response profile remained flat in the late window for the first stimulus (black in **Fig.3B**), indicating a minimal climbing effect. Remarkably, starting from the second stimulus, the climbing effect began to manifest and progressively intensified, with a notable increase observed from the second to the fourth stimulus. This effect appeared to stabilize and overlap in responses from the fourth to the seventh sound (**Fig. 3B**), illustrating the nuanced modulation of neuronal firing rates across successive sound presentations within the oddball sequence.

Reward effect on neuronal responses of IC neurons

The accumulation of the climbing effect alongside repetitive sound presentations suggests a potential linkage to reward prediction, mirroring an increase in the probability of receiving a reward as the sound sequence extends. A specialized experimental setup was utilized to determine if the anticipation of a reward drives the climbing effect. In this setup, a sequence of 1000-ms white noise bursts was played across 150 trials (**Fig. 4A**), segmented into an initial 50-trial phase without reward (early no-reward block), a subsequent 50-trial phase with a water reward dispensed 500 ms after the sound offset (reward block), and a concluding 50-trial phase without reward (late no-reward block). An exemplary IC neuron exhibited sustained firing throughout the 1000-ms sound across all trials (**Fig. 4B**), with a spike cluster coinciding with the reward delivery, indicating a reward-responsive behavior within the IC neuron (**Fig. 4B**). The PSTHs for these conditions revealed nearly identical responses during the sound period ($p = 0.098$, ANOVA with post hoc test, **Fig. 4C**), suggesting the absence of a climbing effect following the peak response.

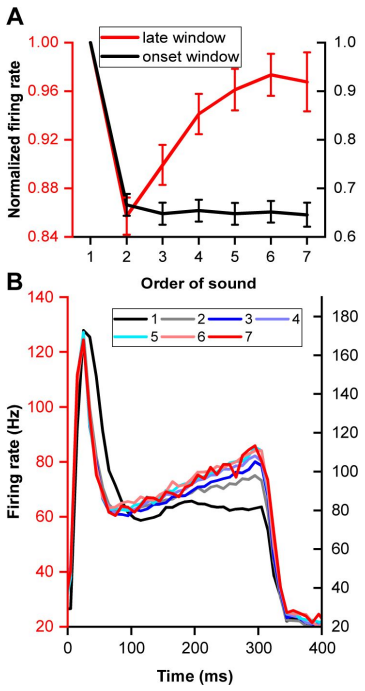

Figure 3

Relationship between neuronal climbing effect and order of sounds.

(A) Average normalized responses to standard sounds in the onset window and offset window (red, late window; black, onset window. n=99). The left axis represents the scale for responses in the late window, and the right axis represents the scale for responses in the onset window. **(B)** PSTHs depicting the responses of the neuronal population to the 300-ms sounds, ranging from the first to the sixth order in the block (black, first; gray, second; blue, third; light blue, fourth; cyan, fifth; pink, sixth; red, seventh). The left axis represents the response scale for sounds from the second to the seventh, and the right axis represents the response scale for the first sound.

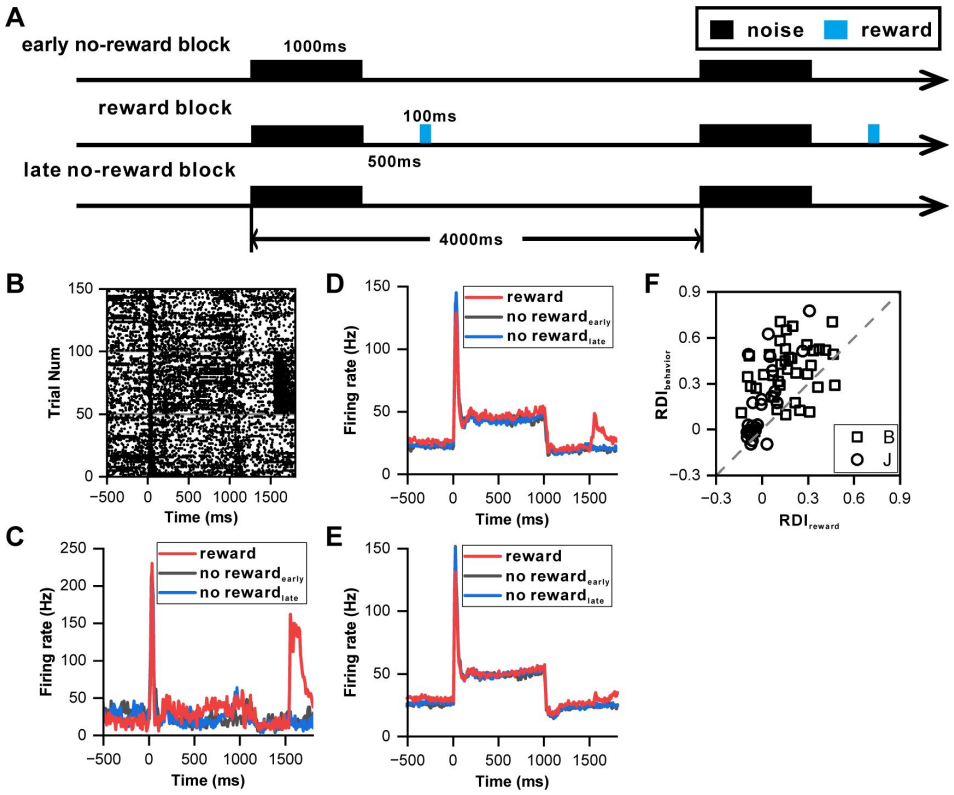

Figure 4

Influence of reward on inferior colliculus neurons.

(A) Schematic representation of the reward protocol. The protocol involves the presentation of a 1000-ms white noise stimulus at 60 dB SPL, repeated 150 times with a 4-second interstimulus interval. The experimental design comprises three blocks: an initial 'early no-reward' block consisting of 50 trials without reward, a 'reward' block of 50 trials with water reward administered 500 ms after sound offset, and a final 'late no-reward' block of 50 trials without reward. **(B)** Raster plots of a representative neuron depicting the response patterns during the reward protocol. **(C)** PSTHs of the neuron in **B** representing the neuronal responses during the reward block, early no-reward block, and late no-reward block (red, reward block; black, early no-reward block; blue, late no-reward block). **(D)** PSTHs of the neuronal population exhibiting significant reward responses (n=24) representing the neuronal responses during the reward block, early no-reward block, and late no-reward block (red, reward block; black, early no-reward block; blue, late no-reward block). **(E)** Equivalent responses as in **D** but from neurons with nonsignificant reward responses (n=35). **(F)** Scatterplots of RDI in reward block versus RDI in behavior protocol (square, monkey B; circle, monkey J; n=63).

Out of fifty-nine IC neurons tested using this protocol, twenty-four demonstrated significant reward responses ($p < 0.05$, paired t-test, **Fig. 4D**), while thirty-five showed no significant reward response (**Fig. 4E**). Across both neuron types, PSTHs following the onset peak response maintained a consistently flat profile (**Fig. 4D, E**). However, the RDI during the reward condition, calculated from the normalized difference between responses in the late window and the after-peak window, indicated a behavior-dependent climbing effect, with most values lying above the unitary line ($p = 9.75e-11$, paired t-test, **Fig. 4F**). Furthermore, an additional set of twenty-two neurons was analyzed using 500-ms sounds within the reward protocol to ensure consistency in sound duration. This analysis showed that the PSTH firing rate increased in the behavioral condition but remained flat in the reward condition following the peak response (100-500 ms) (**Supplementary Fig. 5A**). The majority of these neurons' RDIs exceeded the unitary line in pairwise comparisons ($p = 3.02e-5$, paired t-test, **Supplementary Fig. 5B**), reinforcing the notion that the climbing effect is contingent upon the behavioral context rather than the reward.

Reward prediction error in IC neuronal response

Notably, the reward response of the showcased neuron in **Fig. 4B** was more pronounced at the start of the reward block. To explore this, we compared the first 15 trials to the last 15 trials within the reward block (**Fig. 5A**), revealing that the reward response (0-200 ms relative to the reward onset) was significantly stronger during the initial trials ($p = 1.50e-2$, ANOVA, **Fig. 5A**). Twenty-eight neurons exhibiting significant reward responses were compiled; auditory responses were consistent across initial and final trials ($p = 0.534$, ANOVA, **Fig. 5B**), yet the reward responses in the initial trials were markedly higher ($p = 7.00e-3$, ANOVA, **Fig. 5B**). A comparison on an individual neuronal basis showed most points below the unity line ($p = 3.20e-3$, paired t-test, **Fig. 5C**), indicating a variance in reward responsiveness.

For another example neuron without a reward response (**Fig. 5D**), auditory and reward responses between the first and last trials were indistinguishable for both phases ($p = 0.378$ for auditory response, ANOVA, **Fig. 5D**; $p = 0.637$ for reward response period, ANOVA, **Fig. 5D**). A collection of thirty-five neurons without reward responses exhibited similar firing rates for both auditory and reward response periods across trials ($p = 0.506$ for auditory response, ANOVA, **Fig. 5E**; $p = 0.585$ for reward response period, ANOVA, **Fig. 5E**), with the majority of pairwise comparisons aligning closely with the unity line ($p = 0.62$, paired t-test, **Fig. 5F**).

The heightened responses during the initial trials of the reward block suggest the presence of a reward prediction error, marked by an unexpected reward at the start, which gradually becomes predictable towards the block's end. This phenomenon was further investigated by examining the responses in the duration novelty detection task. In the control condition, where the reward was unpredictable, a distinct response was observed, contrasting with the predictable reward scenario in the deviant condition. In **Fig. 6**, two example IC neurons responded to the deviant sounds and subsequent rewards, each exhibiting a climbing effect post-peak response. The firing rate of these neurons returned to baseline post-sound for all durations, with a noticeable cluster of neuronal responses following the control condition sound presentation, absent in all four deviant conditions (top row of **Fig. 6**). When responses were aligned to reward delivery (the bottom row of **Fig. 6**), notable reward responses were only observed in the control condition ($p < 0.001$, ANOVA), underscoring the auditory IC neurons' capability to encode reward prediction errors.

Decision related signal of IC neurons in duration novelty detection

We have shown the neuronal dynamic of IC neurons in the duration novelty detection task for correct trails. Next, we will explore whether the IC, a lower-level nucleus of the auditory pathway, plays a role in decision making of a duration-related task. During a session where a monkey excelled in performing the task (**Fig. 7A**), trials were categorized based on the monkey's decisions—whether to press a button or not. Particularly in instances involving two specific

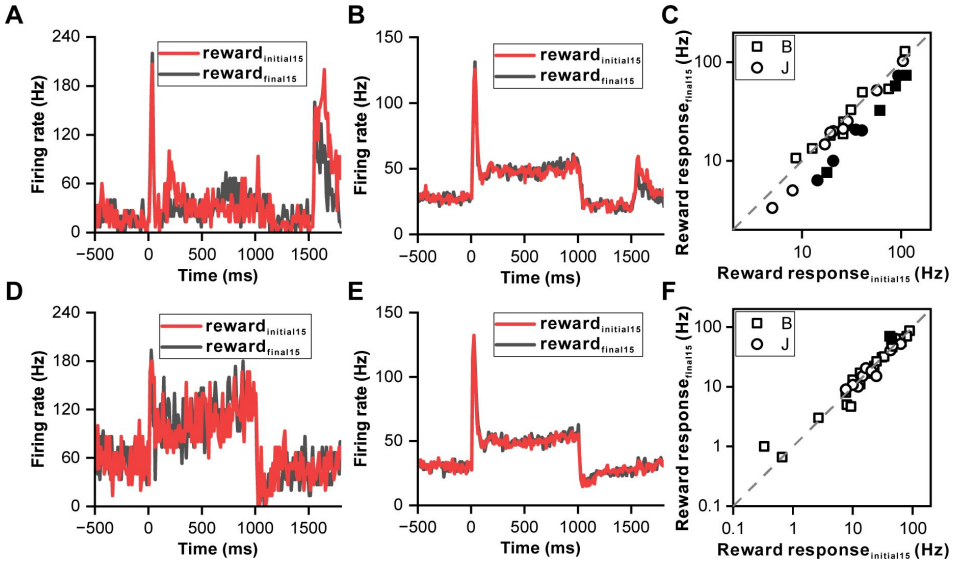

Figure 5

Reward prediction error in inferior colliculus neurons.

(A) PSTHs of the representative neuron in **Figure 6B** depicting its response profiles during the initial 15 reward trials (red) and the final 15 reward trials (black). **(B)** PSTHs of the neuronal population with significant reward responses (n=28) demonstrating the firing activity of these neurons during the initial 15 reward trials (red) and the final 15 reward trials (black). **(C)** Scatterplots of reward responses in initial 15 reward trials versus final 15 reward trials from neurons in **B**. The data points are color-coded, with solid circles representing neurons that exhibit a significant difference in reward responses between the initial and final reward trials. Conversely, open circles represent neurons wherein the difference in reward responses between the two trial sets is nonsignificant. The square and circle symbols correspond to monkey B and monkey J, respectively. **(D)** PSTHs of a neuron with nonsignificant reward responses demonstrating the response patterns of the neuron, similar to those presented in **A**. **(E-F)** Equivalent PSTHs and scatterplots as in **B-C** but from neurons with nonsignificant reward responses (n=35).

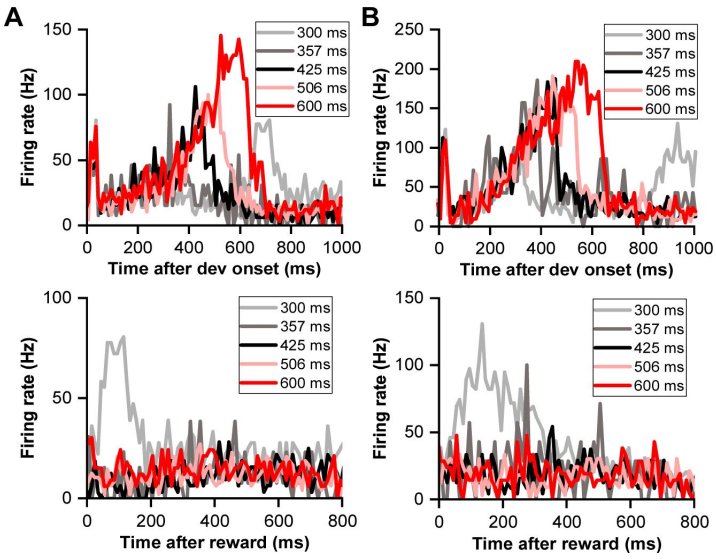

Figure 6

Reward prediction error in novelty detection behavior.

(A) PSTHs illustrating neuronal responses aligned to deviant onset (top) and reward time (bottom). **(B)** PSTHs demonstrating neuronal responses aligned to deviant onset (top) and reward time (bottom) in another neuron.

deviant durations (357 ms and 425 ms), where the likelihood of pressing the button hovered around 50%, a sufficient number of trials were available to assess the correlation between neuronal activities and the monkey's decisions. This focus aims to delve deeper into how neuronal responses might inform or influence behavioral outcomes in these scenarios.

Analysis did not show the deviant response being influenced by the sequence of preceding standard sounds (**Supplementary Fig. 6**), leading to an aggregation of conditions for evaluation. In an illustrative neuron responding to the 357-ms deviant sound, the activation was markedly stronger when the monkey identified the sound as deviant and opted to press the button (indicated by the red color in **Fig. 7B**), in stark contrast to when the monkey did not perceive the sound as deviant, thus choosing not to press the button (illustrated in black color of **Fig. 7B**). Aligning this observation with the moment of button press further accentuated the response disparity ($p = 1.32e-8$, ANOVA, right panel in **Fig. 7B**).

To quantitatively assess the decision related signal, an analysis incorporating Receiver Operating Characteristic (ROC) was conducted (**Fig. 7C**), revealing a pronounced difference in firing rates aligned with the act of pressing the button ($p = 2.58e-6$, ANOVA, **Fig. 7C**). The area under the ROC curve (AUC), signifying detection probability, stood at 0.86 ($p < 0.001$, permutation test), indicating a high likelihood that an ideal observer could discern between the two choices based solely on the neuronal firing rate.

Across 69 recorded sessions showcasing reliable behavioral outcomes (**Fig. 7D**), population-level PSTHs highlighted a tendency for heightened responses during trials where the button was pressed ($p = 3.08e-4$, ANOVA, left panel of **Fig. 7E**), with a notable difference preceding the button press ($p = 7.93e-7$, ANOVA, right panel of **Fig. 7E**). The average detection probability across these sessions was 0.56, surpassing the chance level of 0.5 ($p = 2.57e-4$, t-test, **Fig. 7F**), with fifteen out of sixty-nine neurons showing significant detection probabilities. Specifically for the 425-ms sound trials, eight out of sixty-eight neurons displayed a significant detection probability, with an average value of 0.54, also above the chance level ($p = 4.30e-2$, t-test, **Supplementary Fig. 7**).

Discussion

The study unveils novel insights into the inferior colliculus's (IC) role in auditory processing, highlighting its involvement beyond traditional sensory encoding. Neurons within the IC exhibit a sustained firing pattern, indicating a robust processing of sound duration, which is crucial for temporal perception (**Fig. 1**). A behavior-dependent "climbing effect" in neuronal firing rate suggests that IC's response to auditory stimuli is modulated by the context of the behavior, with a significant increase in response as the sound sequence progresses, implying a link to sensory experience (**Fig. 2**, 3). This effect was further supported by experiments that distinguished between behavior and reward conditions, showing that the climbing effect is contingent upon the behavioral context rather than mere reward anticipation (**Fig. 4**, 5). Additionally, IC neurons encoded reward prediction errors, demonstrating a nuanced capability to adjust responses based on reward predictability (**Fig. 6**). Lastly, evidence of decision signals in IC neurons correlated with the monkey's decisions in a duration novelty detection task, indicating a direct involvement in decision-making processes related to auditory perception (**Fig. 7**). Overall, our results strongly suggest that the inferior colliculus is actively engaged in sensory experience, decision making and reward prediction, shedding light on its intricate functions in these processes.

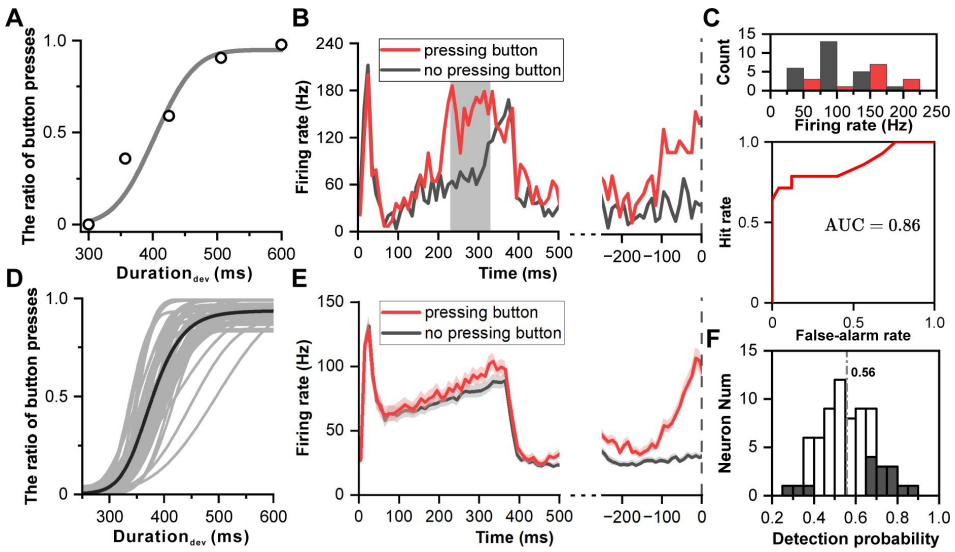

Figure 7

Neuronal responses of decision making in novelty detection behavior.

(A) Cumulative Gaussian fits of psychophysical data in the example recording session. The duration of the deviant sound is plotted along the abscissa, while the ratio of button presses is plotted along the ordinate. **(B)** PSTHs showing example neuronal responses to deviant sound with 357-ms duration (red, pressing button after deviant sound; black, no pressing button after deviant sound). The left side of the subfigure shows the PSTHs aligned to the onset of the deviant sound, while the right side shows the PSTHs aligned to the time of button presses. **(C)** Top: Distribution of neuronal responses to 357-ms deviant sound categorized based on the behavioral choice made by the subject (red, pressing the button; black, no pressing the button). Bottom, receiver operating characteristic (ROC) analysis of comparison between two distributions. **(D)** Cumulative Gaussian fits to psychophysical data in population (n=69). **(E)** PSTHs showing neuronal responses to deviant sound with 357 ms duration in population (red, pressing button after deviant sound; black, no pressing button after deviant sound; left, aligned to deviant onset; right, aligned to time of pressing button). **(F)** Distribution of detection probability: This panel displays the distribution of detection probability (DP), with significant DP indicated by black bars.

Sensory experience and response dynamics in IC

The IC neurons showed a rising firing rate after the onset peak (**Fig. 2A-D**). The climbing effect was strongly modulated by perception (**Supplementary Fig.2**), echoing results from previous research (Metzger et al., 2006). This change was not due to reward, as shown by an experiment controlling for reward effects (**Fig. 4**). Reward only caused minor changes in the response profile (**Fig. 4D**). Therefore, the climbing effect reflects perception rather than reward. Another intriguing aspect of the profile change is its modulation along successive sound presentations in the oddball paradigm. The rising profile becomes steeper from the first to the fourth stimulation and then remains relatively stable from the fourth to the seventh stimulation (**Fig. 3B**). This modulation by preceding sensory experiences challenges the traditional view of the IC as merely a relay station, suggesting a more complex role in auditory processing influenced by both ascending and descending neural pathways. The IC's extensive descending network of connections, including those from the auditory cortex (Adams, 1980; Andersen et al., 1980; Bajo and Moore, 2005; Coleman and Clerici, 1987; Diamond et al., 1969; FitzPatrick and Imig, 1978; Winer et al., 2002), thalamic nuclei (Adams, 1980; Kuwabara and Zook, 2000; Winer et al., 2002), and limbic system areas (Adams, 1980; Coleman and Clerici, 1987; Larue et al., 2005; Marsh et al., 2002), underscores its integration within broader sensory and cognitive processes, potentially underpinning the observed climbing effect.

The accumulation of the climbing effect across successive sound presentations appears to be intrinsically linked to the structure of oddball stimulation. Within the oddball paradigm, both sensory and reward predictions intensify alongside the recurrence of standard sounds, suggesting that the strength of these predictions could significantly influence neuronal responses. Our experimentation with rewards has effectively dismissed the role of reward prediction (**Figs. 4** and **5**), highlighting the potential significance of sensory prediction in molding the climbing effect. Historically, oddball stimuli have been a focal point for investigating novelty detection within the auditory cortex (Carbajal and Malmierca, 2018; Malmierca et al., 2015; Rui et al., 2018; Zhai et al., 2019), though many studies lacked incorporation of a relevant behavioral task (Khouri and Nelken, 2015; Song et al., 2023). Sensory prediction was indirectly assessed by contrasting predictive and non-predictive stimuli in control experiments, hence not addressing sensory prediction in a direct, real-time manner (Carbajal and Malmierca, 2018; Fishman and Steinschneider, 2012; Parras et al., 2017). The progression of the climbing effect with successive sound presentations could potentially offer a direct and real-time perspective on the impact of sensory prediction. Notably, while the onset response remained consistent from the second through the seventh sound, significant dynamic changes in the late response window suggest a prolonged period is required for sensory prediction to exert its influence. Nonetheless, a comprehensive understanding of this dynamic change necessitates further detailed exploration.

Decision related signal in IC

Having established how behavioral modulation affects responses in IC, we now delve into the relationship between IC responses and behavioral choices in a trial-by-trial analysis within a duration novelty detection task. This approach provides insight into the potential role of sensory neurons in perceptual tasks by comparing neural responses and perceptual decisions concurrently in the same subject. While numerous studies have explored this dynamic for cortical neurons (Tsunada et al., 2016), the contribution of subcortical neurons to decision-making processes remains less understood. To our knowledge, this study offers the direct correlation between IC neuron activity and perceptual choice, observed in real-time during experiments with animals (**Fig. 1**). These correlations are crucial for understanding the mechanisms by which population encoding and decoding influence and direct behavior. Focusing on the novelty detection task—a ubiquitous aspect of sensory systems and an ongoing phenomenon in daily life—we employed an

oddball paradigm with randomized presentations of standard sound numbers (**Fig. 1**) to simulate natural occurrences of novel stimuli. This approach allowed us to closely examine both the behavioral responses of monkeys and the corresponding neuronal correlates in the IC.

When neural responses were grouped based on behavioral choices, the PSTHs diverged (**Fig. 7B**), indicating a strong correlation between neural firing variations and choice variations. Notably, within the overall population, the two PSTHs, sorted by the monkeys' choices, diverged before the end of the sound, converged after its end, and diverged once more prior to the movement decision (**Fig. 7E**). This pattern during the sensory encoding phase underscores a potential critical role for IC in managing duration-sensitive behaviors. Traditionally, decision signals are thought to be predominantly driven by top-down inputs, as evidenced by previous studies (Cumming and Nienborg, 2016; Nienborg et al., 2012; Nienborg and Cumming, 2009). While the decision-related signal in the IC may derive from these top-down mechanisms, our findings also entertain the possibility that variations in IC neuronal activity could directly modulate higher brain areas, influencing behavioral outcomes. In either scenario, our findings clearly demonstrate the IC's significant involvement in cognitive processing, extending well beyond its traditional role as a mere auditory relay station.

Furthermore, neuronal responses to sound duration typically become more transient throughout the auditory pathway with neurons in the thalamus and cortex primarily showing onset responses (Anderson and Linden, 2011; deCharms and Merzenich, 1996; DeWeese et al., 2003; He, 2001; Metzger et al., 2006; Nevue et al., 2015; Rauschecker et al., 1995; Xia et al., 2000; Yasui et al., 1991; Zhai et al., 2019). However, exceptions exist, as sustained neurons have been identified in the medial geniculate body (MGB) (Allon et al., 1981; Bartlett and Wang, 2011) and the auditory cortex (AC) (Lu et al., 2001; Malone et al., 2002; Rauschecker et al., 1995; Wang et al., 2005). In stark contrast, the majority of Inferior Colliculus (IC) neurons exhibit sustained responses to prolonged sounds across various species, including frogs (Ratnam and Feng, 1998), bats (Luo et al., 2008), and rodents (Pérez-González et al., 2006; Xia et al., 2000; Yin et al., 2008). Our examination of IC neurons in macaque monkeys revealed a similar sustained firing pattern in response to long-duration sounds (**Fig. 1A-B**), aligning with observations across diverse species. This evolutionary conservation of sustained response characteristics in the IC suggests its capacity to encode sound duration. However, the implications of this capability for behavior have remained uncertain. The present study offers direct evidence highlighting the significant role of the IC in decision-making processes related to duration perception (**Fig.7**).

Reward effect and reward prediction error in IC

In addition to the role in sensory processing, another important finding in our study is the existence of a reward effect and a reward prediction error in the IC. The connection between the IC and the reward system is not very clear, but some studies have suggested that dopamine may play a role in modulating auditory processing in the inferior colliculus (Gittelman et al., 2013; Hoyt et al., 2019; Nevue et al., 2015). Dopamine is a neurotransmitter that is involved in the reward system and other functions (Hoyt et al., 2019). Dopamine may have heterogeneous effects on the responses of many neurons in the IC, such as suppressing or enhancing neural activity, depending on various factors (Hoyt et al., 2019; Nevue et al., 2015). However, the exact mechanisms and functions of dopamine modulation in the inferior colliculus are still not fully understood. In this study, we first noticed that some auditory neurons responded to the reward (**Fig. 4B, D**), but the reward modulation effect on auditory responses is slim in the awake monkey (**Fig. 4B-E**).

Like the response of the dopaminergic neurons in the reward system (Hollerman and Schultz, 1998), the reward response of IC neurons displays prediction error signals, which were uncovered in two experiments. Firstly, during the experiment in which sound was followed by reward, the reward responses were significantly stronger in the initial 15 trials than in the final 15

trials (**Fig. 5A-C**), as the reward is a surprise at the beginning while becoming a routine at the end. Secondly, during the novelty detection task, as the number of standard sounds was randomly chosen and the monkeys were not informed about the end of the stimulation in the control trials, the reward in such trials was not expected, but then a strong response was detected (**Fig. 6**). By contrast, during the deviant trials, the monkey pressed the button, expected a reward, and no reward response was detected (**Fig. 6**). Collectively, these findings affirm the presence of reward prediction error signals in the IC, underscoring its sophisticated engagement in reward-related auditory processing dynamics.

Methods

Subjects and Apparatus

Experiments were conducted in a sound-proof room. Acoustic stimuli were digitally generated using a computer-controlled Auditory Workstation (Tucker-Davis Technologies, TDT, Alachua, FL) and delivered via a loudspeaker (LS50, KEF, UK). The sound pressure was calibrated with a ¼"condenser microphone (Brüel & Kjær 4954, Nærum, Denmark) and a PHOTON/RT analyzer (Brüel & Kjær). All stimuli were presented contralateral to the recording site.

Data were collected from two male rhesus monkeys (M. mulatta), which were chronically implanted with a plastic head-restraint ring and a recording grid, as described in detail in previous publications (Gong et al., 2024; Yu et al., 2012; Yu et al., 2015). All procedures were approved by the Animal Care and Use Committee of Zhejiang University and were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

We recorded extracellular neural activity using epoxy-coated tungsten microelectrodes (FHC, 2–4 MΩ). Electrodes were inserted into the inferior colliculus based on MRI structure (SF. 1a) through 26-gauge transdural guide tubes and were advanced by a remote-controlled microdrive (FHC). Raw neural activity was amplified and filtered (300 Hz to 3000 Hz). The spike train of the neuron was analyzed off-line. Single units were identified based on waveform shape, latency, and amplitude. Only well-isolated neurons were included in the analyses.

Auditory Stimulation

Tones (100 ms; 5-ms rise-fall time) with multiple combinations of frequencies and intensities were presented to determine the frequency response areas (FRAs). Tones were presented randomly with 5 repetitions at each frequency (0.5–48 kHz in 26 logarithmic steps) and intensity (0–70 dB SPL in 10 dB steps) and interstimulus intervals of 300 ms. We used the FRAs to determine the CF.

To assess the ability of sustained firing in the IC, we presented white noise bursts with three kinds of duration (100 ms, 500 ms, 1000 ms) at 2-s interstimulus intervals. The three sound durations were randomly presented at 60 dB SPL, each for 20 trials.

To explore the reward effect on the neuronal firing of IC neurons, 1000-ms white noise was presented 150 times at 60 dB SPL at 4-s interstimulus interval (**Fig. 5A**). The initial 50 trials consisted of no reward (early no-reward block), the middle 50 trials consisted of a reward of water 500 ms after the offset of each sound (reward block); and the final 50 trials again consisted of no reward (late no-reward block). (At the beginning of the experiment, we presented stimuli only 100 times, consisting of early no-reward block and reward block and collected 4 IC neurons.)

Behavioral Protocol

Animals were trained to perform a novelty detection task in two steps: 1) train the monkeys to press the button after the sound; 2) train the monkeys to press the button only after the deviant sound is presented. At both steps, the monkeys received a water reward when they made the correct response.

During the recording session, the sound was presented in blocks (**Fig. 1A-B**). In each block, 3 to 6 repeated white noise bursts (standard sound) were presented at 600-ms interstimulus interval, and the last stimulus was either the same sound (the control condition) or a deviant sound (**Fig. 1A-B**). The monkey needed to press the button immediately within 600 ms after the offset of the deviant stimulus to get the reward of a drop of water. The task reaction time setting precluded the possibility that the monkey made the decision just because it was the last stimulus in the block; in the control condition, the monkey did not need to press the button within 600 ms after the onset of the last stimulus to get the reward. The number of standard stimuli was randomly selected from 3 to 6 to avoid that the monkey made the decision based on counting the number of sounds and avoided that the monkey guessed when the deviant would be presented, so that the monkey had to press the button based on the detection of the current deviant stimulus. In each recording session, the standard duration was kept the same (300 ms), but the deviant duration was systematically changed to control the difficulty of the task according to the following formula: $\text{Duration}_{\text{deviant}} = \text{Duration}_{\text{standard}} * \lambda^{n}$ (n=0,1,2,3,4) (λ=1.19), where $\text{Duration}_{\text{deviant}}$ and $\text{Duration}_{\text{standard}}$ were deviant and standard duration, respectively. Thus, in each session, 5 conditions were presented. Each condition was usually presented 30-40 times. During the recording, all sounds were presented at 60 dB SPL with 5 ms rise-fall time in the profile.

We assessed the behavior of the monkey according to two criteria: 1) the monkey made the correct rejection. In the control condition, the ratio of pressing a button had to be less than 0.1; 2) The monkey made the correct hit. In the most differential condition, the ratio of pressing the button had to be greater than 0.85. Only the behavior meeting these two criteria was kept for further analysis.

Data analysis

To characterize the climbing effect, we defined a factor termed the response dynamic index (RDI). RDI is calculated according to the following formula:

$$RDI = \frac{Fir_{offset}^{[-100\ 0]} - Fir_{onset}^{[100\ 200]}}{Fir_{offset}^{[-100\ 0]} + Fir_{onset}^{[100\ 200]}}$$

$Fir_{offset}^{[-100\ 0]}$ and $Fir_{onset}^{[100\ 200]}$ were the neuronal firing rates within the late window (−100-0 ms relative to the offset of the sound) and the after-peak window (100-200 ms relative to the onset of the sound), respectively.

To define a reward-responsive neuron, we compared the response within 100 ms after the reward and the response within 200 ms before the reward was offered in the reward blocks (paired t-test). A neuron was considered reward-responsive only if the difference reached significance ($p < 0.05$).

Behavioral performance was quantified by plotting the proportion of “pressing button” choices as a function of duration difference between the deviant and standard sounds in ratio. Psychometric data were fit with a Gaussian integral function:

$$p(r) = \frac{1}{b\sqrt{2\pi}} \int_{0}^{r} e^{-\frac{(x-a)^2}{2b^2}} dx$$

In this expression, p is the proportion of pressing button choices, r is the ratio between deviant and standard duration.

Author contributions

Conceptualization, X.Y.; Methodology, X.Y., X.D., and H.X.; Investigation and Data Curation, X.D., H.X., P.S., Y.Z., H.Y., X.B., Q.H., H.T., Z.T., P.C. and X.Z.; Writing – Original Draft, X.Y. and X.D. and J.P.R.; Writing – Review & Editing, X.D., H.X. and J.P.R.; Funding Acquisition, X.Y. and Y.Z.; Resources, X.Y.; Software, X.D., H.X., P.S., Y.Z., H.Y., X.B., Q.H., H.T., Z.T., P.C. and X.Z.; Validation and Visualization, X.D. and H.X.; Supervision, X.Y.

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Declaration of interests

The authors declare no competing interests.

Figure Legends

Figure S1

Neurons in the inferior colliculus with sustained response.

(A) 7T MRI with recording electrode: High-resolution 7T MRI scans displaying the recording electrode in place within the brains of two monkeys (left, monkey J; right, monkey B).
(B) Localization of recording sites on fMRI image. The red dots overlaid on the fMRI image indicate the locations of the recording sites within the inferior colliculus. The fMRI image was acquired at a plane positioned 1 mm posterior to the ear bar zero (EBZ). The red dots represent the projection of the recording sites onto this specific plane.

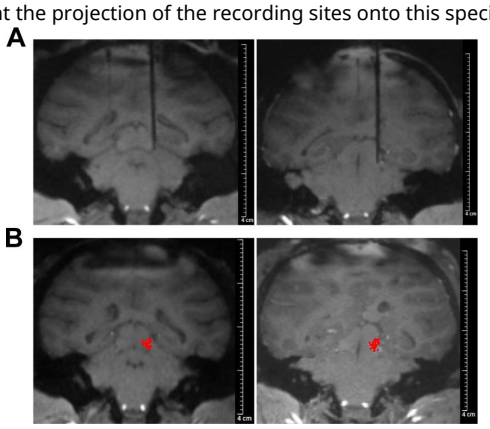


Figure S2

Comparison of neuronal responses between behavior protocol and non-behavior protocol.

(A) PSTHs comparing neuronal responses in non-behavior and behavior protocols (red: responses to 506-ms deviant sound in behavior protocol; blue: responses to 500-ms sound in non-behavior protocol; n=99). The colored area indicates the error band (standard error). **(B)** Scatterplots of RDI in non-behavior protocol versus behavior protocol (square, monkey B; circle, monkey J). Each data point represents the RDI value of an individual neuron, allowing for a comparison between the two protocols.

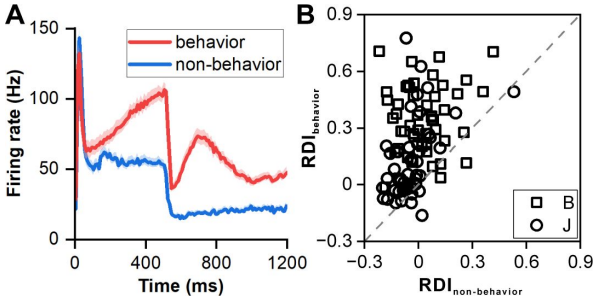


Figure S3

Response dynamic index (RDI) of different deviant sounds.

(A) Scatterplots of RDI for 506-ms deviant sound versus RDI for 357-ms deviant sound (n=99). **(B)** Scatterplots of RDI for 506-ms deviant sound versus RDI for 425-ms deviant sound. **(C)** Scatterplots of RDI for 506-ms deviant sound versus RDI for 600-ms deviant sound.

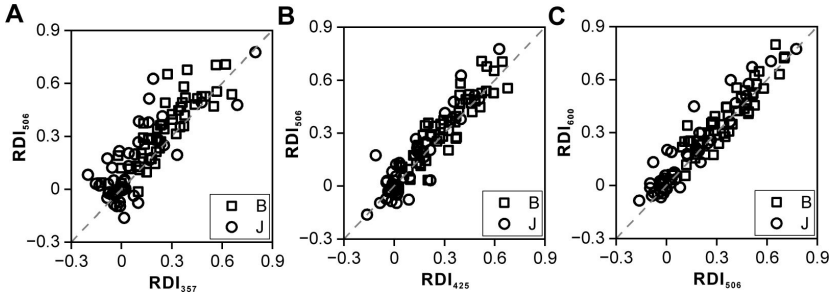


Figure S4

Three-dimensional representation of recorded neurons based on response dynamic index (RDI).

(A) Three-dimensional representation of the recorded neurons obtained from monkey B relative to EBZ. Each neuron is assigned a distinct color based on its RDI. **(B)** Three-dimensional representation of the recorded neurons obtained from monkey J relative to EBZ. Each neuron is color-coded according to its RDI.

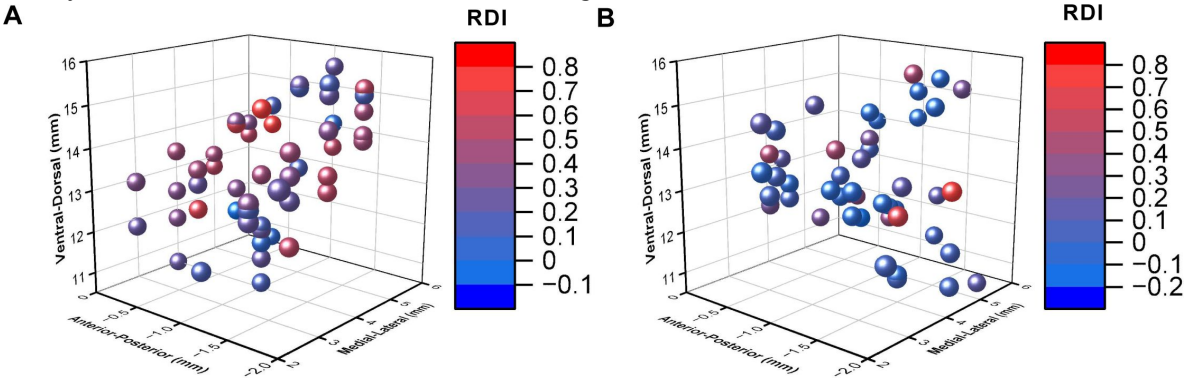


Figure S5

Influence of reward on neuronal responses.

(A) PSTHs showing neuronal population responses (n=22) in reward protocol with 500-ms sound (blue) and behavior protocol (red). **(B)** Scatterplots of RDI in reward block with 500-ms sound versus RDI in behavior protocol (square, monkey B; circle, monkey J).

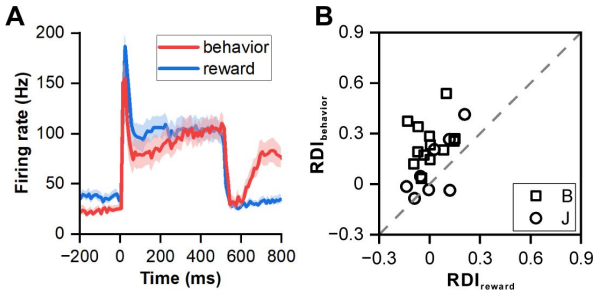
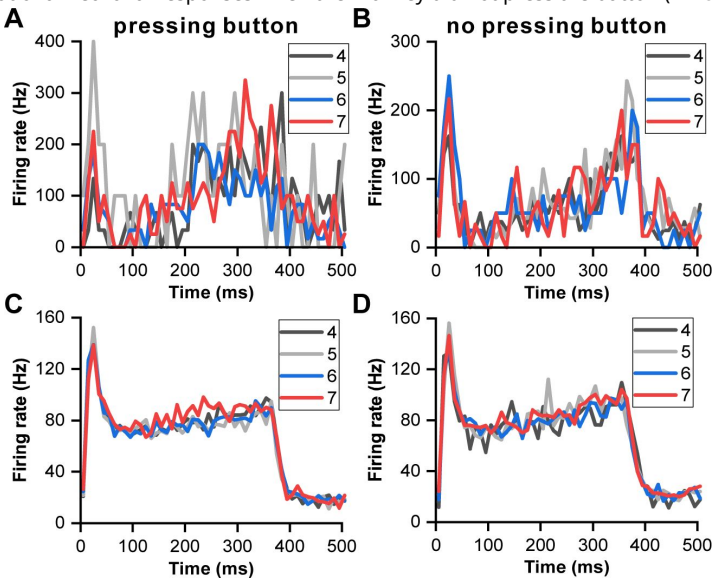


Figure S6

Influence of sound numbers on neuronal responses to 357-ms deviant sound.

(A) PSTHs illustrating the neuronal responses to 357-ms deviant sounds with different orders in the block when the monkey pressed the button. The PSTHs are color-coded, with grey representing the fourth order, light gray representing the fifth order, blue representing the sixth order, and red representing the seventh order. These responses are obtained from the neuron depicted in Figure 8B. **(B)** PSTHs illustrating the neuronal responses to 357-ms deviant sounds with different orders in the block when the monkey didn't press the button. **(C)** Populational neuronal responses when the monkey pressed the button (n=49). **(D)** Populational neuronal responses when the monkey did not press the button (n=49).



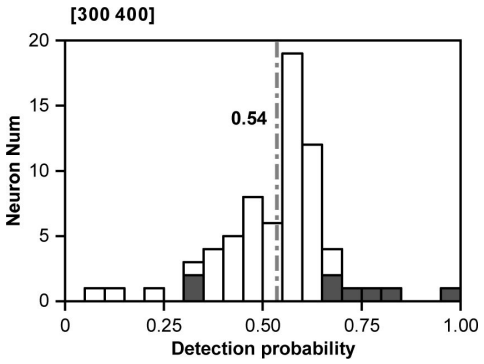


Figure S7

Distribution of detection probability (DP) for 425-ms deviant sounds.

Within the distribution, significant DP values are indicated by the presence of black bars.

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Editors

Reviewing Editor
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Reviewer #1 (Public review):

Summary:

This work made a lot of efforts to explore the multifaceted roles of the inferior colliculus (IC) in auditory processing, extending beyond traditional sensory encoding. The authors recorded neuronal activitity from the IC at single unit level when monkeys were passively exposed or actively engaged in behavioral task. They concluded that 1） IC neurons showed sustained firing patterns related to sound duration, indicating their roles in temporal perception, 2) IC neuronal firing rates increased as sound sequences progress, reflecting modulation by behavioral context rather than reward anticipation, 3) IC neurons encode reward prediction error and their capability of adjusting responses based on reward predictability, 4) IC neural activity correlates with decision-making. In summary, this study tried to provide a new perspective on IC functions by exploring its roles in sensory prediction and reward processing, which are not traditionally associated with this structure.

Strengths:

The major strength of this work is that the authors performed electrophysiological recordings from the IC of behaving monkeys. Compared with the auditory cortex and thalamus, the IC in monkeys has not been adequately explored.

Weaknesses:

(1) The authors cited several papers focusing on dopaminergic inputs in the IC to suggest the involvement of this brain region in cognitive functions. However, all those cited work were done in rodents. Whether monkey's IC shares similar inputs is not clear.
(2) The authors confused the two terms, novelty and deviation. According to their behavioral paradigm, deviation rather than novelty should be used in the paper because all the stimuli have been presented to the monkeys during training. Therefore, there is actually no novel stimuli but only deviant stimuli. This reflects that the author has misunderstood the basic concept.
(3) Most of the conclusions were made based on correlational analysis or speculation without providing causal evidences.
(4) Results are presented in a very "straightforward" manner with too many detailed descriptions of phenomena but lack of summary and information synthesis. For example, the first section of Results is very long but did not convey clear information.
(5) The logic between different sections of Results is not clear.
(6) In the Discussion, there is excessive repetition of results, and further comparison with and discussion of potentially related work are very insufficient. For example, Metzger, R.R., et al. (J Neurosc, 2006) have shown similar firing patterns of IC neurons and correlated their findings with reward.

https://doi.org/10.7554/eLife.101142.1.sa3

Reviewer #2 (Public review):

Summary:

The inferior colliculus (IC) has been explored for its possible functions in behavioral tasks and has been suggested to play more important roles rather than simple sensory transmission. The authors revealed the climbing effect of neurons in IC during decision-making tasks, and tried to explore the reward effect in this condition.

Strengths:

Complex cognitive behaviors can be regarded as simple ideals of generating output based on information input, which depends on all kinds of input from sensory systems. The auditory system has hierarchic structures no less complex than those areas in charge of complex functions. Meanwhile, IC receives projections from higher areas, such as auditory cortex, which implies IC is involved in complex behaviors. Experiments in behavioral monkeys are always time-consuming works with hardship, and this will offer more approximate knowledge of how the human brain works.

Weaknesses:

These findings are more about correlation but not causality of IC function in behaviors. And I have a few major concerns.

Comparing neurons' spike activities in different tests, a 'climbing effect' was found in the oddball paradigm. The effect is clearly related to training and learning process, but it still requires more exploration to rule out a few explanations. First, repeated white noise bursts with fixed inter-stimulus-interval of 0.6 seconds was presented, so that monkeys might remember the sounds by rhymes, which is some sort of learned auditory response. It is interesting to know monkeys' responses and neurons' activities if the inter-stimuli-interval is variable. Second, the task only asked monkeys to press one button and the reward ratio (the ratio of correct response trials) was around 78% (based on the number from Line 302). so that, in the sessions with reward, monkeys had highly expected reward chances, does this expectation cause the climbing effect?

"Reward effect" on IC neurons' responses were showed in Fig. 4. Is this auditory response caused by physical reward action or not? In reward sessions, IC neurons have obvious response related to the onset of water reward. The electromagnetic valve is often used in water-rewarding system and will give out a loud click sound every time when the reward is triggered. IC neurons' responses may be simply caused by the click sound if the electromagnetic valve is used. It is important to find a way to rule out this simple possibility.

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Reviewer #3 (Public review):

Summary:

The authors aimed to investigate the multifaceted roles of the Inferior Colliculus (IC) in auditory and cognitive processes in monkeys. Through extracellular recordings during a sound duration-based novelty detection task, the authors observed a "climbing effect" in neuronal firing rates, suggesting an enhanced response during sensory prediction. Observations of reward prediction errors within the IC further highlight its complex integration in both auditory and reward processing. Additionally, the study indicated IC neuronal activities could be involved in decision-making processes.

Strengths:

This study has the potential to significantly impact the field by challenging the traditional view of the IC as merely an auditory relay station and proposing a more integrative role in cognitive processing. The results provide valuable insights into the complex roles of the IC, particularly in sensory and cognitive integration, and could inspire further research into the cognitive functions of the IC.

Weaknesses:

Major Comments:

(1) Structural Clarity and Logic Flow:
The manuscript investigates three intriguing functions of IC neurons: sensory prediction, reward prediction, and cognitive decision-making, each of which is a compelling topic. However, the logical flow of the manuscript is not clearly presented and needs to be well recognized. For instance, Figure 3 should be merged into Figure 2 to present population responses to the order of sounds, thereby focusing on sensory prediction. Given the current arrangement of results and figures, the title could be more aptly phrased as "Beyond Auditory Relay: Dissecting the Inferior Colliculus's Role in Sensory Prediction, Reward Prediction, and Cognitive Decision-Making."

(2) Clarification of Data Analysis:
Key information regarding data analysis is dispersed throughout the results section, which can lead to confusion. Providing a more detailed and cohesive explanation of the experimental design would significantly enhance the interpretation of the findings. For instance, including a detailed timeline and reward information for the behavioral paradigms shown in Figures 1C and D would offer crucial context for the study. More importantly, clearly presenting the analysis temporal windows and providing comprehensive statistical analysis details would greatly improve reader comprehension.

(3) Reward Prediction Analysis:
The conclusion regarding the IC's role in reward prediction is underdeveloped. While the manuscript presents evidence that IC neurons can encode reward prediction, this is only demonstrated with two example neurons in Figure 6. A more comprehensive analysis of the relationship between IC neuronal activity and reward prediction is necessary. Providing population-level data would significantly strengthen the findings concerning the IC's complex functionalities. Additionally, the discussion of reward prediction in lines 437-445, which describes IC neuron responses in control experiments, does not sufficiently demonstrate that IC neurons can encode reward expectations. It would be valuable to include the responses of IC neurons during trials with incorrect key presses or no key presses to better illustrate this point.

https://doi.org/10.7554/eLife.101142.1.sa1

Author response:

> ***Public Reviews:***
>
> ***Reviewer #1 (Public review):***
>
> *Summary:*
>
> *This work made a lot of efforts to explore the multifaceted roles of the inferior colliculus (IC) in auditory processing, extending beyond traditional sensory encoding. The authors recorded neuronal activitity from the IC at single unit level when monkeys were passively exposed or actively engaged in behavioral task. They concluded that 1）IC neurons showed sustained firing patterns related to sound duration, indicating their roles in temporal perception, 2) IC neuronal firing rates increased as sound sequences progress, reflecting modulation by behavioral context rather than reward anticipation, 3) IC neurons encode reward prediction error and their capability of adjusting responses based on reward predictability, 4) IC neural activity correlates with decision-making. In summary, this study tried to provide a new perspective on IC functions by exploring its roles in sensory prediction and reward processing, which are not traditionally associated with this structure.*

> *Strengths:*
>
> *The major strength of this work is that the authors performed electrophysiological recordings from the IC of behaving monkeys. Compared with the auditory cortex and thalamus, the IC in monkeys has not been adequately explored.*

We appreciate the reviewer's acknowledgment of the efforts and strengths of our study. Indeed, our goal was to provide a comprehensive exploration of the multifaceted roles of the inferior colliculus (IC) in auditory processing and beyond, particularly in sensory prediction and reward processing. The use of electrophysiological recordings in behaving monkeys was central to our approach, as we sought to uncover the underexplored aspects of IC function in these complex cognitive domains. We are pleased that the reviewer recognizes the value of investigating the IC, a structure that has not been adequately explored in primates compared to other auditory regions like the cortex and thalamus. This feedback reinforces our belief that our work contributes significantly to advancing the understanding of the IC's roles in cognitive processing.

We look forward to addressing any further points the reviewers may have and refining our manuscript accordingly. Thank you for your constructive feedback and for recognizing the strengths of our research approach.

> *Weaknesses:*
>
> *(1) The authors cited several papers focusing on dopaminergic inputs in the IC to suggest the involvement of this brain region in cognitive functions. However, all those cited work were done in rodents. Whether monkey's IC shares similar inputs is not clear.*

We appreciate the reviewer's insightful comment on the limitations of extrapolating findings from rodent models to monkeys, particularly concerning dopaminergic inputs to the Inferior Colliculus (IC). While it is true that most studies on dopaminergic inputs to the IC have been conducted in rodents, to our knowledge, no studies have been conducted specifically in primates. To address the reviewer's concern, we have added a statement in both the introduction and discussion sections of our manuscript:

- Introduction: " However, these studies were conducted in rodents, and the existence and role of dopaminergic inputs in the primate IC remain underexplored."

- Discussion: " However, the exact mechanisms and functions of dopamine modulation in the inferior colliculus are still not fully understood, particularly in primates. "

> *(2) The authors confused the two terms, novelty and deviation. According to their behavioral paradigm, deviation rather than novelty should be used in the paper because all the stimuli have been presented to the monkeys during training. Therefore, there is actually no novel stimuli but only deviant stimuli. This reflects that the author has misunderstood the basic concept.*

We appreciate the reviewer's clarification regarding the distinction between "novelty" and "deviation" in the context of our behavioral paradigm. We agree that, given the nature of our experimental design where all stimuli were familiar to the monkeys during training, the term "deviation" more accurately describes the stimuli used in our study rather than "novelty."

To address this, we have revised the manuscript to replace the term "novelty" with "deviation" wherever applicable. This change has been made to ensure accurate terminology is used throughout the paper, thereby eliminating any potential misunderstanding of the concepts involved in our study.

We thank the reviewer for pointing out this important distinction, which has improved the clarity and precision of our manuscript.

> *(3) Most of the conclusions were made based on correlational analysis or speculation without providing causal evidences.*

We appreciate the reviewer's concern regarding the reliance on correlational analyses in our study. Indeed, we acknowledge that the conclusions drawn primarily reflect correlations between neuronal activity and behavioral outcomes, rather than direct causal evidence. This limitation is inherent to many electrophysiological studies, particularly those conducted in behaving primates, where direct manipulation of specific neural circuits to establish causality is often challenging.

This limitation becomes even more complex when considering the IC's role as a key lower-level relay station in the auditory pathway. Manipulating IC activity could potentially affect auditory responses in downstream pathways, which, in turn, may influence sensory prediction and decision-making processes. Moreover, we hypothesize that the sensory prediction and reward signals observed in the IC may not have direct causal effects but may instead be driven by top-down projections from higher cognitive regions. However, it is important to emphasize that our study provides novel evidence that the IC may exhibit multiple facets of cognitive signaling, which could inspire future research into the underlying mechanisms and broader functional implications of these signals.

To address this, we have taken the following steps in our revised manuscript:

(1) Clarified the Scope of Conclusions: We have revised the language in the Results and Discussion sections to explicitly state that our findings represent correlational relationships rather than causal mechanisms. For example, we now refer to the associations observed between IC activity and behavioral outcomes as "correlational" and have refrained from making definitive causal claims without supporting experimental evidence.

(2) Proposed Future Directions: In the Discussion section, we have included suggestions for future studies to directly test the causality of the observed relationships. We acknowledge the need for further investigation to substantiate the causal links between IC activity and cognitive functions such as sensory prediction, decision-making, and reward processing.

We believe these revisions provide a more balanced interpretation of our findings while emphasizing the importance of future research to build on our results and establish causal relationships. Thank you for raising this critical point, which has led to a more rigorous and transparent presentation of our study.

> *(4) Results are presented in a very "straightforward" manner with too many detailed descriptions of phenomena but lack of summary and information synthesis. For example, the first section of Results is very long but did not convey clear information.*

We appreciate the reviewer's feedback regarding the presentation of our results. We understand that the detailed descriptions of phenomena may have made it difficult to discern the key findings and overarching themes in the study. We recognize the importance of balancing detailed reporting with clear summaries and synthesis to effectively communicate our findings.

To address this concern, we have made the following revisions to the manuscript:

(1) Condensed and Synthesized Key Findings: We have streamlined the presentation of the Results section by condensing overly detailed descriptions and focusing on the most critical

aspects of the data. Key findings are now summarized at the end of each subsection to ensure that the main points are clearly conveyed.

(2) Enhanced Section Summaries: We have added summary statements at the end of each major results section to synthesize the findings and highlight their significance. This should help guide the reader through the narrative and emphasize the key takeaways from each part of the study.

(3) Improved Flow and Clarity: We have revised the structure and organization of the Results section to improve the flow of information. By rearranging certain paragraphs and refining the language, we aim to present the results in a more cohesive and coherent manner.

We believe these changes will make the Results section more accessible and informative, allowing readers to more easily grasp the significance of our findings. Thank you for your valuable suggestion, which has significantly improved the clarity and impact of our manuscript.

> *(5) The logic between different sections of Results is not clear.*

We appreciate the reviewer's observation regarding the lack of clear logical connections between different sections of the Results. We acknowledge that a coherent flow is essential for effectively communicating the progression of findings and their implications.

To address this concern, we have made the following revisions:

(1) Enhanced Transitions Between Sections: We have introduced clearer transitional statements between sections of the Results. These transitions explicitly state how each new section builds upon or relates to the previous findings, creating a more cohesive narrative.

(2) Integration of Findings: In several places within the Results, we have added brief synthesis paragraphs that integrate findings across sections. These integrative summaries help to tie together the different aspects of our study, demonstrating how they collectively contribute to our understanding of the Inferior Colliculus's (IC) role in sensory prediction, decision-making, and reward processing.

(3) Clarified Rationale: At the beginning of each major section, we have clarified the rationale behind why certain experiments were conducted, connecting them more clearly to the overarching goals of the study. This should help the reader understand the purpose of each set of results in the context of the broader research objectives.

We believe these changes improve the overall coherence and readability of the Results section, allowing readers to better follow the logical progression of our study. We are grateful for this constructive feedback and believe it has significantly enhanced the manuscript.

> *(6) In the Discussion, there is excessive repetition of results, and further comparison with and discussion of potentially related work are very insufficient. For example, Metzger, R.R., et al. (J Neurosc, 2006) have shown similar firing patterns of IC neurons and correlated their findings with reward.*

We appreciate the reviewer's insightful critique regarding the excessive repetition in the Discussion and the lack of sufficient comparison with related work. We acknowledge that a well-balanced Discussion should not only interpret findings but also place them in the context of existing literature to highlight the novelty and significance of the study.

To address these concerns, we have made the following revisions:

(1) Reduction of Repetition: We have carefully revised the Discussion to minimize redundant repetition of the Results. Instead of restating the findings, we now focus more on their implications, limitations, and how they advance the current understanding of the Inferior Colliculus (IC) and its broader cognitive roles.

(2) Incorporation of Related Work: We have expanded the Discussion to include a more comprehensive comparison with existing literature, specifically highlighting studies that have reported similar findings. For example, we now discuss the work by Metzger et al. (2006), which demonstrated similar firing patterns of IC neurons and correlated these with reward-related processes. This comparison helps contextualize our results and emphasizes the novel contributions our study makes to the field.

We believe these revisions have significantly improved the quality of the Discussion by reducing unnecessary repetition and providing a more thorough engagement with the relevant literature. We are grateful for the reviewer's valuable feedback, which has helped us refine and strengthen the manuscript.

> ***Reviewer #2 (Public review):***
>
> *Summary:*
>
> *The inferior colliculus (IC) has been explored for its possible functions in behavioral tasks and has been suggested to play more important roles rather than simple sensory transmission. The authors revealed the climbing effect of neurons in IC during decision-making tasks, and tried to explore the reward effect in this condition.*
>
> *Strengths:*
>
> *Complex cognitive behaviors can be regarded as simple ideals of generating output based on information input, which depends on all kinds of input from sensory systems. The auditory system has hierarchic structures no less complex than those areas in charge of complex functions. Meanwhile, IC receives projections from higher areas, such as auditory cortex, which implies IC is involved in complex behaviors. Experiments in behavioral monkeys are always time-consuming works with hardship, and this will offer more approximate knowledge of how the human brain works.*

We greatly appreciate the reviewer's positive summary of our work and recognition of the effort involved in conducting experiments on behaving monkeys. We agree with the reviewer that the inferior colliculus (IC) plays a significant role beyond mere sensory transmission, particularly in integrating sensory inputs with higher cognitive functions. Our study aims to shed light on these complex functions by revealing the climbing effect of IC neurons during decision-making tasks and exploring how reward influences this dynamic.

We are encouraged that the reviewer acknowledges the importance of investigating the IC's role within the broader framework of complex cognitive behaviors and appreciates the hierarchical nature of the auditory system. The reviewer's comments reinforce the value of our research in contributing to a more nuanced understanding of how the IC might contribute to sensory-cognitive integration.

We thank the reviewer for highlighting the significance of using behavioral monkey models to approximate human brain function. We are hopeful that our findings will serve as a stepping stone for further research exploring the multifaceted roles of the IC in cognition and behavior.

We will now proceed to address the specific concerns and suggestions provided by the reviewer in the following sections.

> *Weaknesses:*
>
> *These findings are more about correlation but not causality of IC function in behaviors. And I have a few major concerns.*

We appreciate the reviewer's concern regarding the reliance on correlational analyses in our study. We acknowledge the importance of distinguishing between correlation and causality. As detailed in our response to Question 3 from Reviewer #1, we recognize the limitations of relying on correlational data and the challenges of establishing direct causal links in electrophysiological studies involving behaving primates.

We have taken steps to clarify this distinction throughout our manuscript. Specifically, we have revised the Results and Discussion sections to ensure that the findings are presented as correlational, not causal, and we have proposed future studies utilizing more direct manipulation techniques to assess causality. We hope these revisions adequately address your concerns.

> *Comparing neurons' spike activities in different tests, a 'climbing effect' was found in the oddball paradigm. The effect is clearly related to training and learning process, but it still requires more exploration to rule out a few explanations. First, repeated white noise bursts with fixed inter-stimulus-interval of 0.6 seconds was presented, so that monkeys might remember the sounds by rhymes, which is some sort of learned auditory response. It is interesting to know monkeys' responses and neurons' activities if the inter-stimuli-interval is variable. Second, the task only asked monkeys to press one button and the reward ratio (the ratio of correct response trials) was around 78% (based on the number from Line 302). so that, in the sessions with reward, monkeys had highly expected reward chances, does this expectation cause the climbing effect?*

We thank the reviewer for raising these insightful points regarding the 'climbing effect' observed in the oddball paradigm and its potential relationship with training, learning processes, and reward expectation. Below, we address each of the reviewer's specific concerns:

(1) Inter-Stimulus Interval (ISI) and Rhythmic Auditory Response:

The reviewer suggests that the fixed inter-stimulus interval (ISI) of 0.6 seconds might lead to a rhythmic auditory response, where monkeys could anticipate the sounds. We appreciate this perspective. However, we believe that rhythm is unlikely to play a significant role in the 'climbing effect' for the following reason: The 'climbing effect' starts from the second sound in the block (Fig.2D and Fig.3B), before any rhythm or pattern could be fully established, as a rhythm generally requires at least three repetitions to form. Unfortunately, we did not explore variable ISIs in the current study, so we cannot directly address this concern with the data at hand.

(2) Reward Expectation and Climbing Effect:

The reviewer raises an important concern about whether the 'climbing effect' could be influenced by the monkeys' high reward expectation, especially given the high reward ratio (~78%) in the sessions. While it is plausible that reward expectation could contribute to the observed increase in neuronal firing rates, we believe the results from our reward experiment (Fig. 4) suggest otherwise. In this experiment, even though reward expectation was likely formed due to the consistent pairing of sounds with rewards (100%), we did not observe a climbing effect in the auditory response. The presence of reward prediction error (Fig. 4D) further suggests that while the monkeys may form reward expectations, these expectations do not directly drive the climbing effect.

To clarify this point, we have added sentences in the revised manuscript to explicitly discuss the relationship between reward expectation and the climbing effect, emphasizing that our findings indicate the climbing effect is not primarily due to reward expectation.

We believe these revisions provide a clearer understanding of the factors contributing to the climbing effect and address the reviewer's concerns effectively. Thank you for these valuable suggestions.

> *"Reward effect" on IC neurons' responses were showed in Fig. 4. Is this auditory response caused by physical reward action or not? In reward sessions, IC neurons have obvious response related to the onset of water reward. The electromagnetic valve is often used in water-rewarding system and will give out a loud click sound every time when the reward is triggered. IC neurons' responses may be simply caused by the click sound if the electromagnetic valve is used. It is important to find a way to rule out this simple possibility.*

We appreciate the reviewer's concern regarding the potential confounding factor introduced by the electromagnetic valve's click sound during water reward delivery, which could be misinterpreted as an auditory response rather than a response to the reward itself. Anticipating this possibility, we took measures to eliminate it by placing the electromagnetic valve outside the soundproof room where the neuronal recordings were performed.

To address your concern more explicitly, we have added sentences in the Methods section of the revised manuscript detailing this setup, ensuring that readers are aware of the steps we took to eliminate this potential confound. By doing so, we believe that the observed reward-related neural activity in the IC is attributable to the reward processing itself rather than an auditory response to the valve click. We appreciate you bringing this important aspect to our attention, and we hope our clarification strengthens the interpretation of our findings.

> ***Reviewer #3 (Public review):***
>
> *Summary:*
>
> *The authors aimed to investigate the multifaceted roles of the Inferior Colliculus (IC) in auditory and cognitive processes in monkeys. Through extracellular recordings during a sound duration-based novelty detection task, the authors observed a "climbing effect" in neuronal firing rates, suggesting an enhanced response during sensory prediction. Observations of reward prediction errors within the IC further highlight its complex integration in both auditory and reward processing. Additionally, the study indicated IC neuronal activities could be involved in decision-making processes.*
>
> *Strengths:*
>
> *This study has the potential to significantly impact the field by challenging the traditional view of the IC as merely an auditory relay station and proposing a more integrative role in cognitive processing. The results provide valuable insights into the complex roles of the IC, particularly in sensory and cognitive integration, and could inspire further research into the cognitive functions of the IC.*

We appreciate the reviewer's positive summary of our work and recognition of its potential impact on the field. We are pleased that the reviewer acknowledges the significance of our findings in challenging the traditional view of the Inferior Colliculus (IC) as merely an auditory relay station and in proposing its integrative role in cognitive processing.

Our study indeed aims to provide new insights into the multifaceted roles of the IC, particularly in the context of sensory and cognitive integration. We believe that this research

could pave the way for future studies that further explore the cognitive functions of the IC and its involvement in complex behavioral processes.

We are encouraged by the reviewer's positive assessment and are committed to continuing to refine our work in response to the constructive feedback provided. We hope that our findings will contribute to advancing the understanding of the IC's role in the broader context of neuroscience.

We will now proceed to address the specific concerns and suggestions provided by the reviewer in the following sections.

> *Weaknesses:*
>
> *Major Comments:*
>
> *(1) Structural Clarity and Logic Flow:*
>
> *The manuscript investigates three intriguing functions of IC neurons: sensory prediction, reward prediction, and cognitive decision-making, each of which is a compelling topic. However, the logical flow of the manuscript is not clearly presented and needs to be well recognized. For instance, Figure 3 should be merged into Figure 2 to present population responses to the order of sounds, thereby focusing on sensory prediction. Given the current arrangement of results and figures, the title could be more aptly phrased as "Beyond Auditory Relay: Dissecting the Inferior Colliculus's Role in Sensory Prediction, Reward Prediction, and Cognitive Decision-Making."*

We appreciate the reviewer's detailed feedback on the structural clarity and logical flow of the manuscript. We understand the importance of presenting our findings in a clear and cohesive manner, especially when addressing multiple complex topics such as sensory prediction, reward prediction, and cognitive decision-making.

To address the reviewer's concerns, we have made the following revisions:

(1) Reorganization of Figures and Results:

We agree with the suggestion to merge Figure 3 into Figure 2. By doing so, we can present the population responses to the order of sounds more effectively, thereby streamlining the focus on sensory prediction. This will allow readers to more easily follow the progression of the results related to this key function of the IC.

We have reorganized the Results section to ensure a smoother transition between the different aspects of IC function that we are investigating. The new structure will better guide the reader through the narrative, aligning with the themes of sensory prediction, reward prediction, and cognitive decision-making.

(2) Revised Title:

In line with the reviewer's suggestion, we have revised the title to "Beyond Auditory Relay: Dissecting the Inferior Colliculus's Role in Sensory Prediction, Reward Prediction, and Cognitive Decision-Making." We believe this title more accurately reflects the scope and focus of our study, as it highlights the three core functions of the IC that we are investigating.

(3) Improved Logic Flow:

We have added introductory statements at the beginning of each section within the Results to clarify the rationale behind the experiments and the logical connections between them. This should help to improve the overall flow of the manuscript and make the progression of our findings more intuitive for readers.

We believe these changes significantly enhance the clarity and logical structure of the manuscript, making it easier for readers to understand the sequence and importance of our findings. Thank you for your valuable suggestion, which has led to a more coherent and focused presentation of our work.

> *(2) Clarification of Data Analysis:*
>
> *Key information regarding data analysis is dispersed throughout the results section, which can lead to confusion. Providing a more detailed and cohesive explanation of the experimental design would significantly enhance the interpretation of the findings. For instance, including a detailed timeline and reward information for the behavioral paradigms shown in Figures 1C and D would offer crucial context for the study. More importantly, clearly presenting the analysis temporal windows and providing comprehensive statistical analysis details would greatly improve reader comprehension.*

We appreciate the reviewer's insightful comment regarding the need for clearer and more cohesive explanations of the data analysis and experimental design. We recognize that a well-structured presentation of this information is essential for the reader to fully understand and interpret our findings. To address this, we have made the following revisions:

(1) Detailed Explanation of Experimental Design:

We have included a more detailed explanation of the experimental design, particularly for the behavioral paradigms shown in Figures 1C and 1D. This includes a comprehensive timeline of the experiments, along with explicit information about the reward structure and timing. By providing this context upfront, we aim to give readers a clearer understanding of the conditions under which the neuronal recordings were obtained.

(2) Cohesive Presentation of Data Analysis:

Key information regarding data analysis, which was previously dispersed throughout the Results section, has been consolidated and moved to a dedicated subsection within the Methods. This subsection now provides a step-by-step description of the analysis process, including the temporal windows used for examining neuronal activity, as well as the specific statistical methods employed.

We have also ensured that the temporal windows used for different analyses (e.g., onset window, late window, etc.) are clearly defined and consistently referenced throughout the manuscript. This will help readers track the use of these windows across different figures and analyses.

(3) Enhanced Statistical Analysis Details:

We have expanded the description of the statistical analyses performed in the study, including the rationale behind the choice of tests, the criteria for significance, and any corrections for multiple comparisons. These details are now presented in a clear and accessible format within the Methods section, with relevant information also highlighted in the Result section or the figure legends to facilitate understanding.

We believe these changes will significantly improve the clarity and comprehensibility of the manuscript, allowing readers to better follow the experimental design, data analysis, and the conclusions drawn from our findings. Thank you for this valuable feedback, which has helped us to enhance the rigor and transparency of our presentation.

> *(3) Reward Prediction Analysis:*

> *The conclusion regarding the IC's role in reward prediction is underdeveloped. While the manuscript presents evidence that IC neurons can encode reward prediction, this is only demonstrated with two example neurons in Figure 6. A more comprehensive analysis of the relationship between IC neuronal activity and reward prediction is necessary. Providing population-level data would significantly strengthen the findings concerning the IC's complex functionalities. Additionally, the discussion of reward prediction in lines 437-445, which describes IC neuron responses in control experiments, does not sufficiently demonstrate that IC neurons can encode reward expectations. It would be valuable to include the responses of IC neurons during trials with incorrect key presses or no key presses to better illustrate this point.*

We deeply appreciate the detailed feedback provided regarding the conclusions on the inferior colliculus (IC)'s role in reward prediction within our manuscript. We acknowledge the importance of a robust and comprehensive presentation of our findings, particularly when discussing complex neural functionalities.

In response to the reviewers' concerns, we have made the following revisions to strengthen our manuscript:

(1) Inclusion of Population-Level Data for IC Neurons:

In the revised manuscript, we have included population-level results for IC neurons in a supplementary figure. Initially, we focused on two example neurons that did not exhibit motor-related responses to key presses to isolate reward-related signals. However, most IC neurons exhibit motor responses during key presses (as indicated in Fig.7), which can complicate distinguishing between reward-related activity and motor responses. This complexity is why we initially presented neurons without motor responses. To clarify this point, we have added sentences in the Results section to explain the rationale behind our selection of neurons and to address the potential overlap between motor and reward responses in the IC.

(2) Addition of Data on Key Press Errors and No-Response Trials:

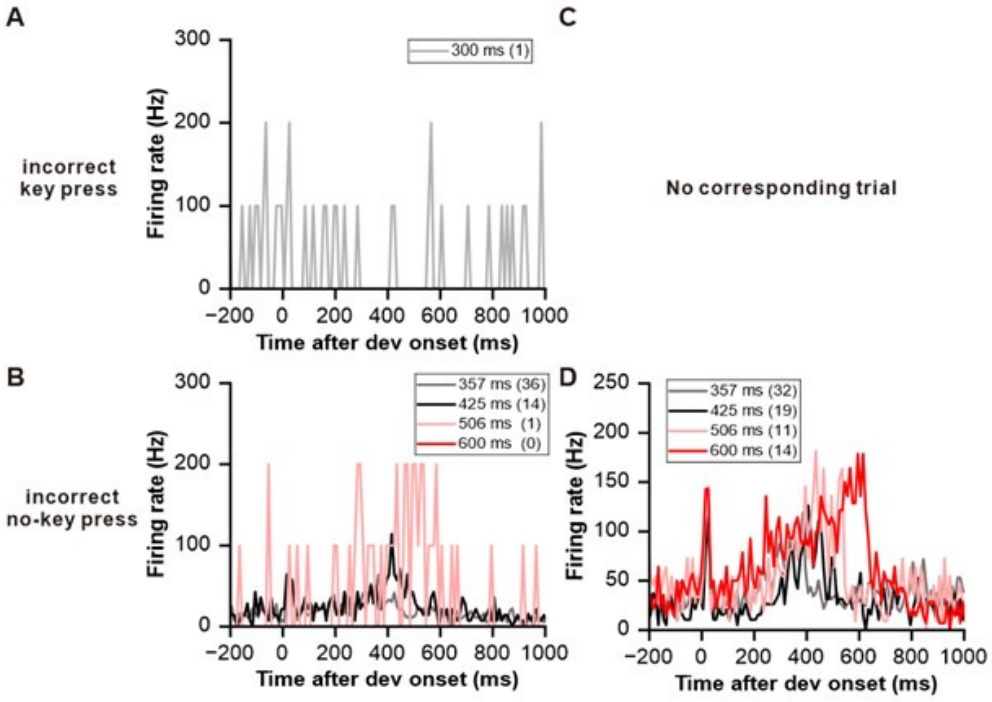
In response to the reviewer's suggestion, we have demonstrated Peri-Stimulus Time Histograms (PSTHs) for two example neurons during error trials as below, including incorrect key presses and no-response trials. Given that the monkeys performed the task with high accuracy, the number of error trials is relatively small, especially for the control condition (as shown in the top row of the figure). While we remain cautious in drawing definitive conclusions from this limited trials, we observed that no clear reward signals were detected during the corresponding window (typically centered around 150 ms after the end of the sound). It is important to note that the experiment was initially designed to explore decision-making signals in the IC, rather than focusing specifically on reward processing. However, the data in Fig. 6 demonstrated intriguing signals of reward prediction error, which is why we believe it is important to present them.

When combined with the results from our reward experiment (Fig. 5), we believe these findings provide compelling evidence of reward prediction errors being processed by IC neurons. Additionally, we observed that the reward prediction error in the IC appears to be signed, meaning that IC neurons showed robust responses to unexpected rewards but not to unexpected no-reward scenarios. However, the sign of the reward prediction error should be explored in greater depth with specifically designed experiments in future studies.

Author response image 1.

(A) PSTH of the neuron from Figure 6a during a key press trial under control condition. The number in the parentheses in the legend represents the number of trials for control

condition. (B) PSTHs of the neuron from Figure 6a during non-key press trials under experimental conditions. The numbers in the parentheses in the legend represent the number of trials for experimental conditions. (C-D) Equivalent PSTHs as in A-B but from the neuron in Figure 6b.



We are grateful for the reviewer's insightful suggestions, which have allowed us to improve the depth and rigor of our analysis. We believe these revisions significantly enhance our manuscript's conclusions regarding the complex functionalities of IC.

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