

Novelty detector neurons in the mammalian auditory midbrain

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Abstract

Novel stimuli in all sensory modalities are highly effective in attracting and focusing attention. Stimulus-specific adaptation (SSA) and brain activity evoked by novel stimuli have been studied using population measures such as imaging and event-related potentials, but there have been few studies at the single-neuron level. In this study we compare SSA across different populations of neurons in the inferior colliculus (IC) of the rat and show that a subclass of neurons with rapid and pronounced SSA respond selectively to novel sounds. These neurons, located in the dorsal and external cortex of the IC, fail to respond to multiple repetitions of a sound but briefly recover their excitability when some stimulus parameter is changed. The finding of neurons that respond selectively to novel stimuli in the mammalian auditory midbrain suggests that they may contribute to a rapid subcortical pathway for directing attention and / or orienting responses to novel sounds.

Introduction

An important function of the auditory system is to differentiate behaviourally uninteresting patterns of sound, which are often repetitive, from novel sounds that may require attention or action. Neurons in all parts of the inferior colliculus (IC) are known to show decreased responsiveness to trains of identical stimuli (Palombi & Caspary, 1996; Nuding et al., 1999), especially when these are presented at high repetition rates. However, to date there have been no systematic attempts to characterize the relation between the observed response decrement to repetitions of identical stimuli and the IC neurons' responses to novel stimuli. This study focuses on neurons in the dorsal and external cortical areas of the rat IC that showed a rapid and pronounced decrement in responsiveness to trains of identical stimuli, i.e. stimulus-specific adaptation (SSA) even at low repetition rates, but briefly recovered their responsiveness whenever some stimulus parameter was changed. As a consequence, these neurons responded selectively to novel stimuli. Their properties are consistent with the range of stimulation paradigms that produce mismatch negativity (MMN), an event-related potential associated with unexpected stimuli in humans and animals (Näätänen, 1995).

Materials and methods

Surgical procedures

Experiments were performed on 21 adult male rats with body weights between 200 and 365 g. Surgical anaesthesia was induced and maintained with urethane (1.5 g/kg, i.p.), with supplementary doses (0.5 g/kg, i.p.) given as needed. Urethane was chosen as an anaesthetic because its effects on multiple aspects of neural activity including inhibition and spontaneous firing are known to be less than those of barbiturate anaesthetics (e.g. Hara & Harris, 2002; Neuert et al., 2004). The trachea was cannulated, and atropine sulphate (0.05 mg/kg, s.c.) was administered to reduce bronchial secretions. Body temperature was maintained at $38\text{ C} \pm 1\text{ C}$. Details of surgical preparation were as described elsewhere (Malmierca et al., 2003, 2005; Hernández et al., 2005). The animal was placed in a stereotaxic frame in which the ear bars were replaced by hollow specula that accommodated a sound delivery system. All experiments were carried out with the

approval of, and using methods conforming to the standards of, the University of Salamanca Animal Care Committee.

Acoustic stimuli and electrophysiological recording

A craniotomy was performed to expose the cerebral cortex and the cerebellum overlying the IC. A tungsten electrode (Merrill & Ainsworth, 1972) was lowered through the cortex and used to record extracellular single unit responses in the IC. Neuron location in the IC was based on stereotaxic coordinates, physiological criteria of tonotopicity and response reliability (Palombi & Caspary, 1996; Rees et al., 1997; Nuding et al., 1999; Syka et al., 2000; Malmierca et al., 2003, 2005) as well as histological verification using electrolytic lesions (5–10 mA for 5–10 s) to mark the sites where novelty responses were recorded as well as sites to be used for reconstruction of electrode tracks (Rees et al., 1997; Syka et al., 2000; Malmierca et al., 2003).

Stimuli were delivered through a sealed acoustic system (Rees et al., 1997; Malmierca et al., 2003, 2005) using two electrostatic loudspeakers (TDT–EC1) driven by two TDT–ED1 modules. Pure tone bursts, noise bursts, and frequency and amplitude modulated stimuli were generated and delivered to one or both ears under computer control using the TDT System 2 (Tucker-Davis Technologies, Alachua, FL, USA) hardware and custom software (Faure et al., 2003). Typically, tones were 75 ms duration and 5 ms rise /fall time, at the neuron's characteristic frequency (CF), with selected parameters varied one at a time during testing. The electrode was advanced using a Burleigh microdrive. Action potentials were recorded with a BIOAMP amplifier (TDT), the 10 \times output of which was further amplified and bandpass-filtered (TDT PC1; f_c , 500 Hz and 3 kHz) before passing through a spike discriminator (TDT SD1). Spike times were logged on a computer by feeding the output of the spike discriminator into an event timer (TDT ET1) synchronized to a timing generator (TDT TG6). Stimulus generation and on-line data visualization were controlled with custom software. Spike times were displayed as dot rasters ordered by the acoustic parameter varied during testing. Peristimulus rastergrams were produced with Igor Pro software (WaveMetrics, Inc.). Search stimuli were pure tones, noise bursts, and sinusoidally amplitude-modulated (SAM) or frequency-modulated (SFM) signals.

To the extent possible, the approximate frequency tuning of the cell was audiovisually determined at the stimulus duration that evoked the strongest spiking. The minimum threshold and CF of the cell were obtained by an automated procedure with 10–25 stimulus repetitions at each frequency and intensity step. The frequency response area was plotted using EXCEL and SIGMAPLOT software.

Stimuli were presented in three different modes. In ‘random’ presentation mode, values of the variable parameter were randomized across trials. In ‘non-interleaved’ or ‘block’ mode, a block of 10–25 identical stimuli was presented, after which the parameter value was changed, and another block of trials was presented, with this procedure being repeated at each step from the start value to the end value of the variable parameter. In ‘sequential’ mode, a single stimulus was presented at each parameter value, stepwise from the start value to the end value, with the sequence repeated until the desired number of repetitions was obtained. Frequency was usually varied in 10 logarithmic steps spanning the estimated frequency response area of the neuron, at 10 or 20 dB above its estimated threshold. Amplitude was usually varied in 5 or 10 dB steps, at the estimated CF. In block or sequential mode the usual sequence was from a lower attenuation (i.e. higher amplitude) to a higher attenuation (lower amplitude). Duration was usually varied in ten linear steps from 2 ms to 200 ms for a tone at CF, 10 or 20 dB above threshold. The modulation rate of SAM and SFM stimuli was varied in ten logarithmic steps from 20 to 2000 Hz. To quantify a neuron’s tendency to respond to novel stimuli, for each set of stimulus conditions we calculated a ‘novelty response index’ (NRI) using the following formula: $NRI = \frac{P_1 - P_{2...n}}{P_{max}}$

Where P_1 is the probability of a response to the first presentation of a stimulus, $P_{2...n}$ is the probability of a response to subsequent presentations of the same stimulus, and P_{max} is the larger of the two values. Using this formula, the novelty response index would be +1 if the neuron responded only on the first trial and no other, it would be -1 if it did not respond on the first trial, but responded on others, and 0 if the probability of responding was equal on the first trial and subsequent trials.

Histological verification of recording sites

At the end of each experiment the animal was given a lethal dose of sodium pentobarbital and perfused transcardially with phosphate buffered saline (0.5% NaNO₃ in PBS) followed by fixative (a mixture of 1% paraformaldehyde and 1% glutaraldehyde in rat Ringer's solution). Sagittal or transverse sections (50 μ m) were cut on a freezing microtome. Every other section was stained with 0.1% thionin blue to facilitate identification of cytoarchitectural boundaries.

Results

We recorded from 409 single neurons throughout the IC while presenting multiple repetitions of a sound (see Materials and methods for details). Stimulus-specific adaptation (SSA) was defined as a response decrement of 50% or more over the course of ten identical stimulus presentations.

A small subpopulation of neurons exhibited a high degree of SSA at relatively slow repetition rates, but briefly and reliably recovered their responsiveness whenever some stimulus parameter was changed. As a consequence, these neurons responded selectively to novel stimuli. Figure 1A shows an example of such a neuron. In this case, blocks of 100 repetitions of a given frequency were presented in ascending order starting with a block of trials at 7.0 kHz and ending with a block at 30.5 kHz. This cell could be driven at frequencies spanning a large part of the rat's auditory range, but only for a few presentations at any given frequency. Thus, instead of being selective for a specific frequency range, the neuron was selective for any frequency that had not recently been presented. The time between the last stimulus of one block and the first stimulus of the next block was the same as the time between stimuli within a block, so the transition from one block to the next was comparable to the 'oddball' paradigm that has been used in other experiments (e.g. Ulanovsky et al., 2003). For comparison, Fig. 1B shows data from a neuron that did not show SSA to multiple stimulus presentations at a constant frequency, nor enhanced responses to novel frequencies.

Although many neurons in the IC, including those in the central nucleus, exhibited some degree of SSA in response to a repeated stimulus, the majority required repetition rates higher than 4/s to elicit it. A small subpopulation of neurons showed SSA at all of

the repetition rates tested, down to 0.5/s, and responded in a highly selective manner to novel stimuli. Neurons that showed SSA at a repetition rate of 4/s or less, with a return to the original level of response for one or more trials when a stimulus parameter was changed were classified as ‘novelty’ units. Figure 2 shows an example of a novelty neuron’s response at three different repetition rates. At each repetition rate, blocks of 25 identical stimuli were presented in ascending order of frequency (24.5 kHz to 30.2 kHz). The repetition rate was then changed from high (4/s) to low (1/s). At a rate of 4/s, habituation was such that the neuron responded only to the first stimulus presentation of the entire sequence. At slower repetition rates (2/s and 1/s), the probability of response to the first presentation of a novel frequency was 100%, but the probability of a response to subsequent presentations was still extremely low, less than 10%. It is interesting to note that the response latency of this neuron and the one illustrated in Fig. 1A was always shorter in response to the first trial of a block than it was to any of the subsequent trials in that block to which the neuron responded.

Using the above criteria, 25 units showed novelty selectivity. Three of these units were not histologically localized, but of the remaining 22, 19 were located in the external cortex of the IC and three in the dorsal cortex of the IC (Malmierca et al., 1993; Table 1). None of these units was located in the central nucleus of the IC. The percentage of novelty units was approximately 6% of all IC units recorded, and 16.5% of those histologically localized outside the central nucleus. In cases where we recorded multiunit activity in the vicinity of novelty units, it typically exhibited rapid SSA and novelty responses similar to those of single units, suggesting that novelty units are located in clusters. Although the experiments were performed in anaesthetized animals, it seems unlikely that the high degree of habituation and novelty responses were due to the anaesthesia as similar novelty responses have been observed in the IC of awake bats during the course of other studies (Casseday & Covey, 1996; E. Covey, unpublished observations).

Figure 3 illustrates the relation between SSA and repetition rate for the cells that we classified as novelty units compared to the population of IC units as a whole. The novelty response index, calculated as described in the Materials and methods, is a measure of the neuron’s probability of a response to the first presentation of a specific set of parameter

values compared to responses to all other trials under that same set of parameter values. The novelty response indices of most IC neurons (left column) are distributed around zero at all repetition rates, while those of neurons classified as novelty units are skewed toward positive values at all repetition rates.

Note that at the fastest rates ($> 5/s$), some IC units not classified as novelty units had indices of +1. This suggests that some units in the central nucleus of the IC show SSA at high repetition rates, and that their responses, like those of the novelty units, can be restored by changing a stimulus parameter.

The novelty unit in Fig. 1A, like other similar units from which we recorded, had virtually no spontaneous activity, so its firing reliably signalled the occurrence of a change in the stimulus. The fact that novelty units typically could be driven across a broad range of stimulus parameter values suggests that they receive highly convergent input. Parameters that, when changed, temporarily restored responses of novelty units included frequency (in 87% of cases where this parameter was varied), intensity (71%), duration (31%), the modulation rate of an SAM stimulus (70%) or the modulation rate of an SFM stimulus (67%). SSA and restoration of response by a change in the stimulus occurred even though the repetitive and novel stimuli were separated by identical interstimulus intervals, indicating that habituation was stimulus-specific and not due solely to intrinsic properties of the neuron that set its recovery time after firing.

To rule out the possibility that novelty responses were driven by a specific direction of change in stimulus energy, a subset of eight neurons were tested with both increasing and decreasing series of values of attenuation and/or duration in sequential and block modes. There was no systematic correlation between magnitude of novelty response index and direction of change in either of these presentation modes.

All of the novelty units from which we recorded were transient responders. This is consistent with the finding that a large proportion of units in the dorsal peripheral regions of the mouse IC have transient onset responses (Reetz & Ehret, 1999). Novelty units were distributed throughout the entire audible frequency range of the rat (Heffner et al., 1994), and had thresholds similar to those of the other IC neurons from which we recorded.

Because novelty units typically showed a complete cessation of firing after one or a few presentations of any given stimulus, it was often difficult to determine their frequency response areas and other conventional forms of tuning to auditory stimulus parameters. One would expect neurons that exhibit SSA to respond better to randomized stimuli than to blocks of identical stimuli, so we tested both novelty neurons and those that did not show SSA using randomized stimuli, blocks of identical stimuli, and sequential variation of a stimulus parameter from a beginning value to an ending value, with the sequence repeated ten times. Figure 4A and B compare response as a function of sound amplitude, collected under the three different stimulus presentation paradigms for a novelty neuron and one that did not exhibit SSA. For the neuron that did not show SSA, the three curves are superimposed. The novelty unit only responded to a few presentations at any given amplitude, so its responses to identical stimuli presented in blocks were greatly reduced compared to the random condition. When stimuli were presented in sequential mode, the response to the beginning value equalled that for random stimulation, because it always represented a large change relative to the ending value. However, responses to other values were reduced compared to the random condition. This general pattern was seen in all novelty units tested. For novelty neurons, the highest spike counts were always obtained in random presentation mode and the lowest in block mode. Spike counts evoked by sequential presentation varied from neuron to neuron, but were generally higher than those obtained in block mode. This pattern of response to different modes of stimulus presentation was similar regardless of what parameter was varied.

Figure 4C compares the frequency response areas of a novelty neuron and one that did not show SSA, measured using the three stimulus presentation modes. Again, the response of the novelty unit was greatly reduced in block mode compared to random or sequential mode, but the response of the non-habituating neuron was similar in all three modes.

Figure 5 shows population data on the neurons' novelty response index in the three presentation modes. The values for the general population of IC neurons (left column) were distributed around zero for all three modes, while those of novelty units (right

column) were clearly skewed towards positive values even in sequential and random presentation modes.

This finding suggests that novelty units were sensitive not only to changes in simple parameters such as frequency or amplitude, but also to changes in more complex sound patterns. Figure 6A and B compares the responses of a novelty unit and one that did not show SSA (non-habituating) to a sinusoidally amplitude-modulated (SAM) stimulus at different modulation rates. The responses of the non-habituating neuron were very similar in all three presentation modes. The novelty neuron responded to SAM at its best modulation rate on nearly every trial in random mode, but in block mode it only responded on the first trial of a block. In sequential mode, responses were also poor, indicating that the progressive changes in modulation rate in this mode were not as effective in driving the cell's response as were the unpredictable changes in random mode.

Even when presented with stimuli that contained repetitive patterns of change such as sinusoidal amplitude modulation (SAM), novelty units responded at the beginning of the stimulus, but never showed ongoing phase locking. The finding that novelty neurons did not phaselock to SAM is consistent with the idea that the rate of modulation within a stimulus was sufficiently high to cause suppression of responses after the first few modulation cycles, and that the highly predictable pattern of change within each stimulus was not sufficient to reverse the habituation. The fact that these transiently responding neurons were often tuned to a specific modulation frequency can be explained if we assume that they experience interacting patterns of excitation and inhibition elicited by the first two cycles of the stimulus, with facilitation at some periods and inhibition at others (Covey et al., 1996; Casseday et al., 1997). Novelty units thus appear to habituate to a complex stimulus pattern, indicating that changes of amplitude alone are not sufficient to drive them, if the changes follow a rapid and predictable sequence. Rather, what is needed is a change from an 'expected' pattern of change to an 'unexpected' one. Such a response suggests that neurons in the dorsal and external cortex of the IC possess relatively complex computational capacities compared to neurons at lower levels, and implies a sort of 'primitive intelligence' (Näätänen et al., 2001).

Discussion

In order for a novelty response to occur, the nervous system must register and retain information about the history of stimulation. The duration of sensory (echoic) memory in monkeys and humans has been estimated to be in the order of a few seconds (Javitt et al., 1994; Näätänen & Escera, 2000). Our observation that novelty units show SSA in response to repetitive stimuli presented at interstimulus intervals of one to two seconds is consistent with this time scale. The fact that they are relatively unresponsive to stimuli at repetition rates greater than 4 or 5 / s suggests that they may also play a role in segmentation of a stream of sound, signalling the onset of a new event.

Novelty neurons were confined to the lateral, dorsomedial and rostral portions of the IC (Irvine, 1992; Malmierca, 2003), a region that in the rat receives dense innervation from auditory cortex (Herbert et al., 1991; Saldaña et al., 1996). This pattern of connectivity raises the possibility that descending projections from cortical neurons specialized to respond to novel stimuli (Ulanovsky et al., 2003) contribute to the responses of novelty units in the IC. If the cortical input were excitatory, one might expect the response latencies of IC novelty units to be longer than those of nonhabituating units because they could not respond until they received the excitatory input from the cortex. Although the distribution of latencies for novelty units was shifted to slightly longer values than for non-habituating neurons (Fig. 7), there is no statistically significant difference between the mean latencies of the two populations (18.2 ± 8.2 ms for novelty units, and 20.2 ± 10.3 ms (SD) for other units, $P \approx 0.879$). This suggests that descending excitatory input is either not the principal mechanism for novelty responses or that it would have to come from cortical neurons with relatively short latencies. The fact that the cortical MMN peaks have latencies of 85 ms or more further suggests that IC novelty responses precede those in the cortex (Näätänen et al., 2005). However, if descending cortical input were acting in an inhibitory manner, suppression of responses to stimulus repetitions through direct or indirect inhibitory effects of cortical input would not necessarily affect the IC neurons' response latencies. Thus, it remains to be determined whether novelty responses are shaped by descending cortical projections, feedback loops within the IC,

Recordings of evoked potentials in humans reveal differential responses to an oddball stimulus embedded among repetitive trials of identical stimuli. The MMN (Näätänen et al., 1978) has been extensively studied in relation to novelty detection (Tiitinen et al., 1994), sensory memory (Näätänen & Escera, 2000) and various pathological conditions (Javitt et al., 1994; Näätänen & Escera, 2000). Although the MMN has most commonly been localized to the auditory cortex (Pincze et al., 2001), it persists in sleep and under anaesthesia (Atienza et al., 2001), suggesting that it is preattentive in origin. The fact that we observed SSA and novelty responses in anaesthetized animals is consistent with the idea that novelty responses are preattentive in origin. A few studies have reported MMN in the thalamus or midbrain of mammals (Kraus et al., 1994; King et al., 1995). Novelty responses similar to those we report here have also been described in the midbrain of frogs (Bibikov, 1977; Bibikov & Soroka, 1979), but to our knowledge, this is the first report of such selectivity in individual neurons of the mammalian auditory midbrain. These findings suggest that novelty detection by midbrain neurons is a feature shared by many vertebrate species, and that the MMN is one manifestation of a widespread and fundamental sensory phenomenon that operates at both cortical and subcortical levels.

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Abbreviations

CF, characteristic frequency; IC, inferior colliculus; MMN, mismatch negativity; SAM, sinusoidally amplitude-modulated; SFM, sinusoidally frequencymodulated; SSA, stimulus-specific adaptation.

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Figures

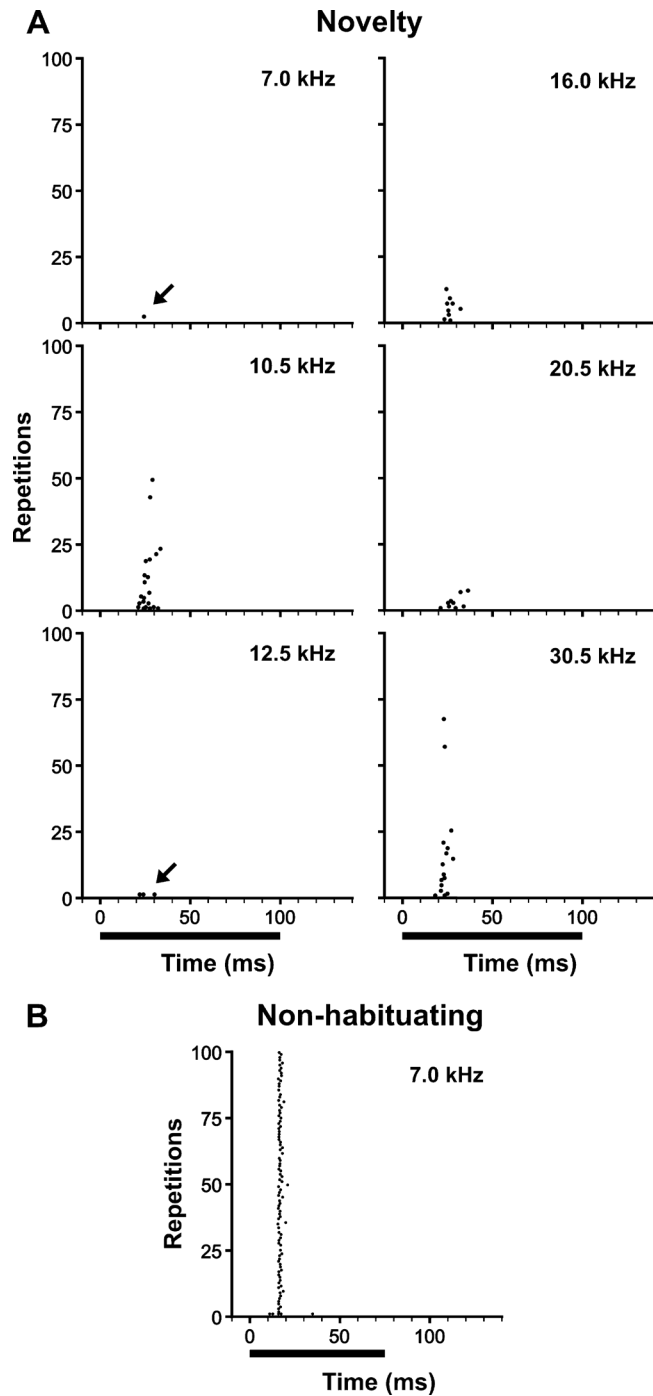


Fig. 1. Stimulus specific adaptation (SSA) and selective responses to novel stimuli.
(A) Dot raster plots show responses of a novelty neuron to six blocks of 100 identical

trials at a repetition rate of 4/s. The stimulus frequency for a block is indicated in the upper right corner of each plot. In this case, blocks were presented in ascending order starting with a block of 100 trials at 7.0 kHz and ending with a block at 30.5 kHz. The interval between blocks was the same as the interval between trials within a block. This neuron responded to tones of virtually any frequency audible to the rat as long as it had not been presented in the recent past. Arrows indicate spikes fired in response to the first presentation within a block. (B) Dot rasters showing responses for an IC neuron that did not show SSA. This neuron responded only to tones within a well-defined frequency response area and its response did not diminish over 100 trials. Bars beneath the abscissa represent stimulus duration. The repetition rate was 4/s.

All stimuli were 20 or 25 dB above threshold.

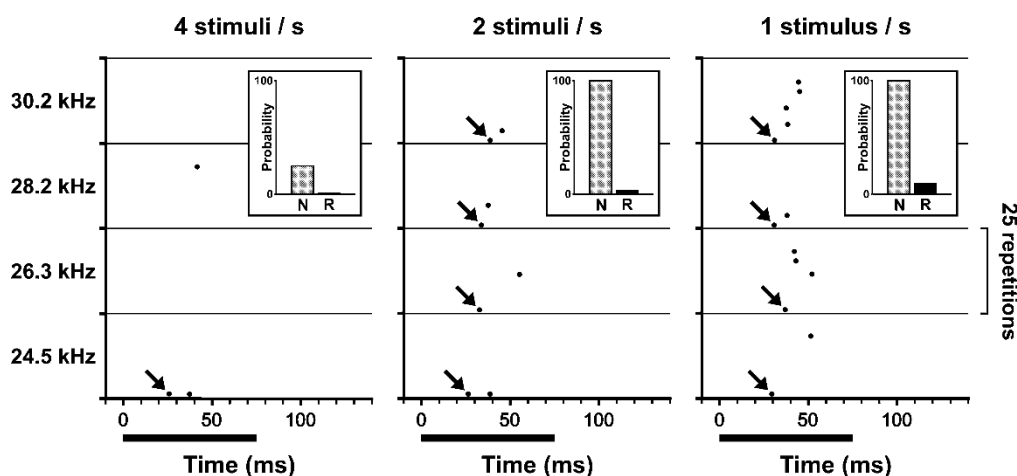


Fig. 2. Responses of a novelty neuron at three different stimulus repetition rates. The dot rasters show responses to four different frequencies, presented in blocks of 25 identical stimuli each. At each repetition rate, blocks were presented in ascending order of frequency (24.5 kHz to 30.2 kHz). Repetition rate was changed from high (4/s) to low (1/s). Arrows indicate spikes fired in response to the first presentation of each frequency block. The interval between the last presentation of one block and the first presentation of the new block was the same as that between presentations within a block. Thus, the first presentation of a new frequency represents a novel, or ‘oddball’ stimulus. The insets represent the probability of a response occurring on the first trial at a given frequency (N, grey bars) vs. subsequent presentations of that frequency (R, black bars).

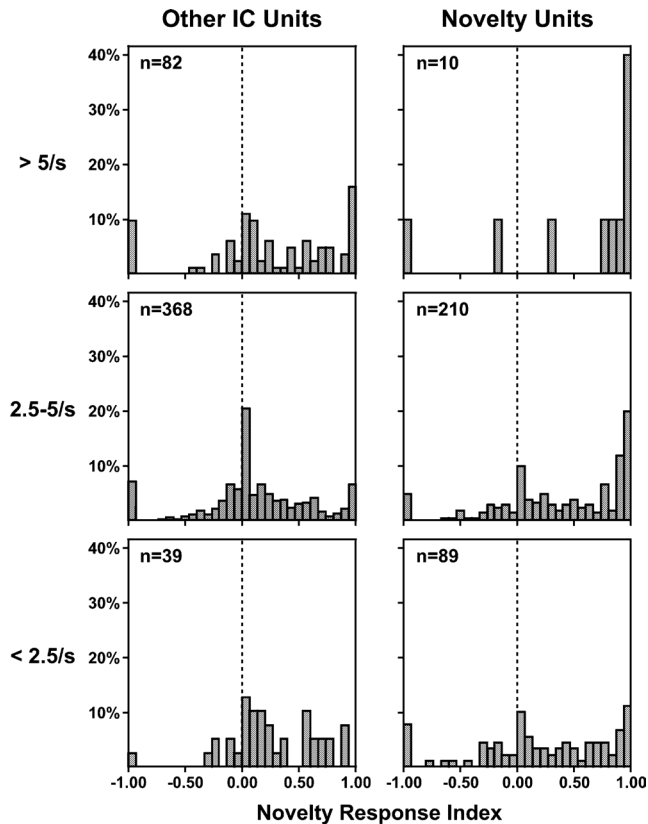


Fig. 3. Distribution of novelty response indices for three different repetition rate ranges, with frequency as the variable parameter. The novelty response index was calculated for each block of trials under a given set of conditions, so n represents number of blocks for which data were obtained across all novelty units (right column) and all other IC units (left column). Heights of bars are normalized as percentage total. Significant differences were found between novelty units and other units at repetition rate $>5/s$ ($P \approx 0.021$), and repetition rate $2.5-5/s$ ($P < 0.001$). Statistically significant differences were also found for ‘other IC units’ between repetition rates $>5/s$ and $2.5-5/s$ ($P \approx 0.013$) and repetition rates of $2.5-5/s$ and $<2.5/s$ ($P \approx 0.049$). For novelty units there was also a significant difference between repetition rates $>5/s$ and $<2.5/s$ ($P \approx 0.049$) and repetition rates of $2.5-5/s$ and $<2.5/s$ ($P \approx 0.027$).

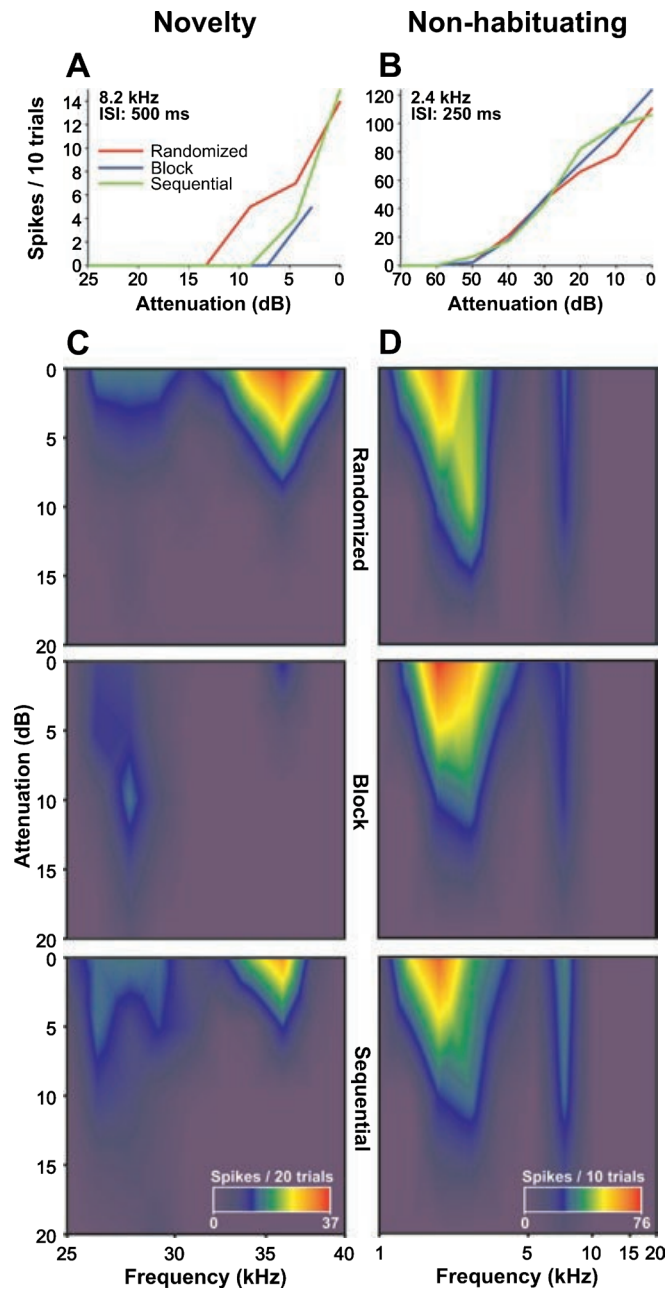


Fig. 4. Effect of stimulus presentation mode on rate-level functions and frequency response areas. Rate-level functions of a novelty neuron (A) and an IC neuron that did not exhibit SSA (non-habituating) (B) measured using three different stimulus presentation paradigms. In both plots, red lines indicate randomized stimulus presentation; green lines indicate sequential presentation; blue lines indicate block presentation. (C) Frequency response area of a novelty neuron measured using three different stimulus presentation paradigms. (D) Frequency response area of an IC neuron

that did not exhibit SSA (nonhabituating) measured using the same three stimulus presentation paradigms.

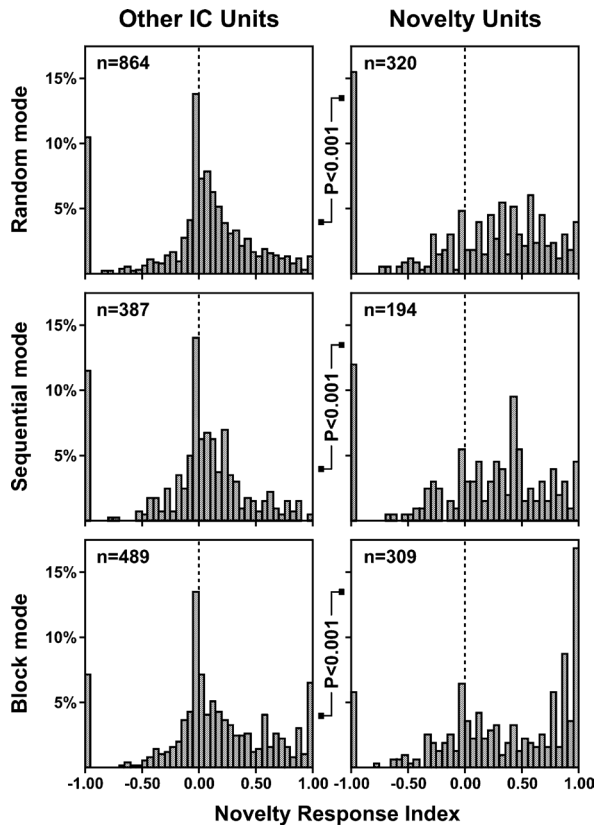


Fig. 5. Distribution of novelty response index values for all novelty units (right column) and all other IC units (left column) in three different stimulus presentation modes. The novelty response index was calculated for each block of trials under a given set of conditions, so n represents number of blocks for which data were obtained. The greatest skew toward positive values was for novelty units in block presentation mode, but there was a statistically significant difference ($P < 0.001$) between novelty neurons and other IC neurons in all three presentation modes.

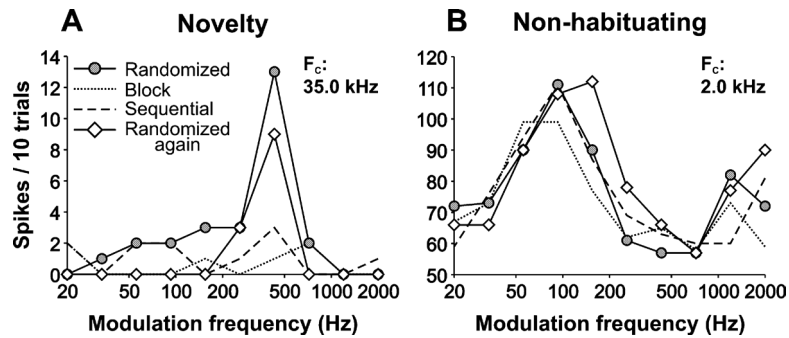


Fig. 6. Effect of stimulus presentation mode on response to sinusoidal amplitude modulations (SAM). Responses of a novelty unit (A) and a non-habituating unit in the IC (B) to SAM stimuli presented using three different stimulus paradigms. Plots show spike counts as a function of modulation frequency for randomized, sequential and block presentation as well as the randomized paradigm repeated again to control for effects of long-term stimulation history. All modulations were at a depth of 100%; the carrier frequency was the neuron's CF. All stimuli had a peak amplitude of 20 dB above threshold and a duration of 100 ms. F_c , carrier frequency.

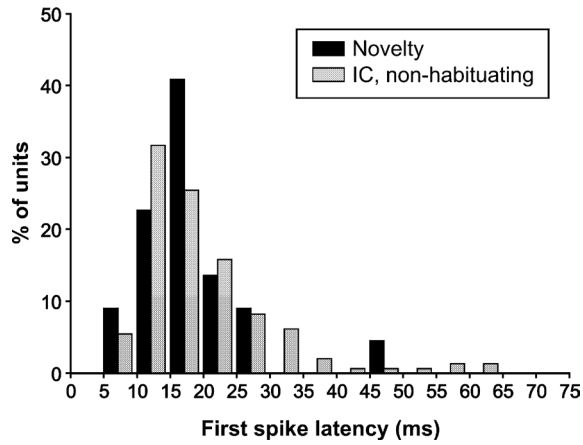


Fig. 7. Latency distribution for novelty units and other IC units. Normalized distribution of average first spike latencies for novelty neurons (black bars) and other IC neurons (grey bars).

intrinsic properties of IC neurons, or some combination of these and/or other factors.

Tables

Table 1. Distribution of different classes of neurons in the central nucleus, dorsal cortex and external cortex of the inferior colliculus (IC)

	Non-novelty neurons		Novelty neurons	
	(n)	(%)	(n)	(%)
Central IC	95	100	0	0
Dorsal IC	25	89.3	3	10.7
External IC	86	81.9	19	18.1
Total	206	90.4	22	9.6

The number of neurons in this data set is less than the total sample because it includes only those that were at sites containing marks for histological localization.