Temporal Representation of the Delay of Iterated Rippled Noise in the Dorsal Cochlear Nucleus

Veronika Neuert, Jesko L. Verhey, and Ian M. Winter

1Centre for the Neural Basis of Hearing, The Physiological Laboratory, Cambridge, United Kingdom; and 2AG Neurosensorik, Carl von Ossietzky Universität, Oldenburg, Germany

Submitted 29 July 2004; accepted in final form 16 December 2004

Neuert, Veronika, Jesko L. Verhey, and Ian M. Winter. Temporal representation of the delay of iterated rippled noise in the dorsal cochlear nucleus. J Neurophysiol 93: 2766–2776, 2005; doi:10.1152/jn.00774.2004. It has been suggested that the dorsal cochlear nucleus (DCN) is involved in the temporal representation of both envelope periodicity and pitch. This hypothesis is tested using iterated rippled noise (IRN), which is generated by a cascade of delay and add [IRN(+)] or delay and subtract [IRN(−)] operations. The autocorrelation functions (ACFs) of the waveform and the envelope of IRN(+) have a first peak at the delay, which corresponds to the perceived pitch of the IRN. With the same delay, the pitch of IRN(−) is generally an octave lower than for IRN(+). This is reflected in a first peak at twice the delay in the ACF of the waveform for IRN(−). In contrast, for identical delays, the ACF of the envelope for both IRN(+) and IRN(−) is the same. Thus the use of IRN allows the distinction between envelope- or fine-structure sensitivity. Recordings were made from 135 single units (BFs <5 kHz) in the DCN of the anesthetized guinea pig using IRN with delays ranging from 1 to 32 ms. In our sample 42% were sensitive to the periodicity of IRN(+) and were tuned to a particular delay in their first-order interspike interval histograms (ISIHs). This tuning was highly correlated with their response to white noise. Most units with best frequencies (BFs) <500 Hz show a different all-order ISIH for IRN(+) and IRN(−), which corresponds to the perceived pitch difference, whereas units with higher BFs show a similar response to IRN(+) and IRN(−). The results indicate that low-frequency units (BF <500 Hz) in the DCN may be involved in the representation of the waveform fine structure, although units with BFs >500 Hz are able to encode only the envelope periodicity of broadband IRN in their temporal discharge characteristics.

INTRODUCTION

The dorsal cochlear nucleus (DCN) is one of the main targets of auditory nerve fibers and the principal cells of the DCN provide a direct input, by the dorsal acoustic stria, to the contralateral inferior colliculus (IC), bypassing the superior olivary complex (Adams 1979; Adams and Warr 1976; Davis 2002; Oliver 1984; Oliver et al. 1997, 1999; Osen 1972; Rhode et al. 1983; Ryugo and Willard 1985). The DCN also receives descending input from a multitude of higher auditory structures. However, the role of the DCN in signal processing is still not entirely understood. It has been implicated in sound localization (Young and Davis 2002) but, because of the limited phase-locking ability of single units in the DCN, it has traditionally been assumed that the DCN is a structure with little sensitivity in the temporal domain (Goldberg and Brownell 1973; Lavine 1971; Rhode et al. 1983; van Gisbergen et al. 1975a,b). More recently it has been shown that some DCN units are capable of precise phase-locking to the envelope of amplitude-modulated (AM) sounds. Such units have been implicated in the processing of temporal information and the encoding of periodicity pitch (Frisina et al. 1994; Kim et al. 1990; Langner 1983, 1988, 1992). This observation gains particular importance with the ability to implant electrodes on the surface of the DCN in patients with a severely damaged auditory nerve (e.g., Coletti et al. 2000; Edgerton et al. 1982; Eisenberg et al. 1987; Lejeune 1997; Marangos et al. 2000). Because temporal features of a sound are vital for all forms of communication, it is important, in ensuring appropriate stimulation with the implants, to know how this information is represented in the DCN.

To test the ability of the DCN to represent the periodicity of complex sounds we have recorded the responses of single units to iterated rippled noise (IRN), a quasi-periodic stimulus that elicits a clear pitch. IRN is produced by repeatedly delaying a random noise by a delay (d) and adding it back to [IRN(+)], or subtracting it from [IRN(−)], the original. The first stage produces rippled noise and the following stages iterate the process. The delay-and-add process introduces temporal regularity into the fine structure of the noise as well as a “ripple” into the long-term power spectrum of the wave (e.g., Yost 1996a; Yost et al. 1996). Examples of IRN(+) and IRN(−) are shown in Fig. 1. The peaks in the amplitude spectrum (2nd row) are at multiples of 1/d for IRN(+) and at 1/(2d) and its odd-integer multiples for IRN(−). The peaks get sharper with increasing number of iterations, n, accompanied by an increase in pitch strength (Patterson et al. 1993, 1996; Yost 1996a,b; Yost et al. 1993). For IRN(+) the perceived pitch is always equal to the reciprocal of the delay and for the IRN(−) stimulus used in this study (with 16 iterations) the perceived pitch is equal to 1/(2d). The autocorrelation function of IRN(+) has peaks at the delay and its integer multiples (Fig. 1, 3rd row). The autocorrelation function of IRN(−) has negative peaks corresponding to the delay and odd-integer multiples of the delay, and positive peaks at even-integer multiples of the delay. In contrast to the differences between the autocorrelation functions of the stimulus waveform, the autocorrelation functions of the envelope are virtually identical for IRN(+) and IRN(−) (Fig. 1, 4th row). Thus for IRN(−), the pitch is determined by the fine structure and not the envelope of the waveform. This property, together with the ability to easily
manipulate the pitch and pitch strength, have made IRN the stimulus of choice for recent studies on pitch. Griffiths et al. (2001), for example, used IRN and fMRI to show that activity in the cochlear nucleus, IC, medial geniculate body, and auditory cortex increased with temporal regularity. In addition, it was shown that areas of the temporal lobe distinct from the primary auditory cortex are involved in the processing of melodies created with IRN (Griffiths et al. 1998, 2001; Patterson et al. 2002).

Previous studies have demonstrated that the predominant interval in an autocorrelogram analysis of populations of auditory nerve fibers provides a robust representation of the pitch for a wide variety of complex sounds, although notable exceptions exist (Cariani and Delgutte 1996a,b). This finding has been extended to the use of IRN in both the auditory nerve and ventral cochlear nucleus (VCN) (Shofner 1991, 1999; ten Kate and van Bekkum 1988; Wiegrebe and Winter 2001a; Winter et al. 2001), where it was shown that the delay of rippled noise produced with a positive and negative gain. Units with low BFs seemed to show a stronger temporal response to rippled noise than units with higher BFs. Shofner (1991) observed the strongest synchrony to the rippled-noise delay for phase-locked units with BFs <1.5 kHz. The upper BF limit for units encoding the delay was typically around 3 to 3.5 kHz.

Using infinitely iterated rippled noise (IIRN), Shofner (1999) confirmed his earlier findings, showing that the majority of phase-locking primary-like (PL) units had peaks in their neural autocorrelograms at integer multiples of the delay when the gain was 1 but nulls flanked by a pair of positive peaks at d and odd-integer multiples of d when the gain was −1. Chopper units on the other hand mostly showed peaks at multiples of the delay irrespective of the gain. Because IIRN with positive and negative gain has the same envelope autocorrelogram function, Shofner (1999) concluded that some PL units encode the waveform fine structure of the stimulus, whereas chopper and non-phase-locked PL units encode features of the stimulus envelope. In a study on the VCN of the guinea pig, Winter et al. (2001) showed that the delay of IIRN(+) is not only represented as peaks in the all-order ISIHs, but the units were also tuned to certain IRN periodicities as estimated by their first-order ISIHs. Winter et al. (2001) showed that the peak in the band-pass interval enhancement plot of onset chopper (OC) and sustained chopper (CS) units was correlated with the peak in the first-order ISIHs in response to white noise. The aim of this study was to extend the findings of Shofner (1999) and Winter et al. (2001) in the VCN by studying the responses of units in the DCN to IRN(+) and IRN(−). The latter stimulus gives insight into whether units in the DCN are able to respond to the fine structure of the waveform of IRN in their temporal responses, and not simply to its envelope. This would demonstrate a possible involvement in pitch processing for DCN units. It was found that 57 out of 135 DCN units responded to the IRN periodicity and were tuned to a certain delay and the majority of units with BF <500 Hz (13 out of 18) responded differently to IRN(+) and IRN(−), indicating a sensitivity to waveform fine structure.

**METHODS**

**Physiology**

Experiments were performed on 23 pigmented guinea pigs (*Cavia porcellus*), weighing between 345 and 550 g. The animals were anesthetized with urethane [1.5 g/kg, intraperitoneally (ip)]. Hypnorn was administered as supplementary analgesia (1 mg/kg, intramuscularly). Anesthesia and analgesia were maintained at a depth sufficient to abolish the pedal withdrawal reflex (front paw). Additional doses of Hypnorn (1 ml/kg) or urethan (1 ml) were administered on indication. Incisions were preinfiltrated with the local anesthetic Lignocaine (subcutaneously). Core temperature was monitored with a rectal probe and maintained at 37°C using a thermostatically controlled heating blanket (Harvard Apparatus). The trachea was cannulated and on signs of suppressed respiration, the animal was ventilated artificially with a pump (Bioscience UK). Surgical preparation and recordings.
took place in a sound-attenuated chamber (Industrial Acoustics). The animal was placed in a stereotaxic frame, which had ear bars coupled to hollow speculae designed for the guinea pig ear. A mid sagittal scalp incision was made and the peristium and the muscles attached to the temporal and occipital bones were removed. The bone overlaying the left bulla was fenestrated and a silver-coated wire was inserted into the bulla to contact the round window of the cochlea for monitoring compound action potentials (CAPs). The hole was resealed with Vaseline. The CAP threshold was determined at selected frequencies at intervals during the experiments. If the thresholds had deteriorated by more than 10 dB and were nonrecoverable (such as by removing fluid from the bulla) the experiment was terminated.

A craniotomy was performed exposing the left cerebellum. The overlying dura was removed and the exposed brain surface was covered with 1.5% agar in saline to prevent desiccation. At the end of each experiment, 2 electric lesions (10 μA for 10 s) were made to mark the position of either the last electrode track or a position nearby. The animal was overdosed with sodium pentobarbitone (ip) and perfused with vascular flush (0.9% NaCl) followed by fixative (1% glutaraldehyde, 3% formaldehyde solution). For reconstruction of the sections and stained with cresyl violet.

The experiments performed in this study have been carried out under the terms and conditions of the project license issued by the United Kingdom Home Office to the third author.

Recordings

Single units in the DCN were recorded extracellularly with glass-coated tungsten microelectrodes (Merrill and Ainsworth 1972). Electrodes were advanced in the sagittal plane by a hydraulic microdrive (650 W; David Kopf Instruments, Tujunga, CA) through the cerebellum at a 45° angle. Single units were isolated using broadband noise and sinusoidal tones as search stimuli. All stimuli were digitally synthesized in real time with a PC equipped with a Digi 9636 PCI card that was connected optically to an AD/DA converter (ADI-8 DS, RME Audio, Mittweida, Germany). The AD/DA converter was used for D/A conversion of the stimuli as well as for A/D conversion of the amplified (>1,000) neural activity. The sample rate was 96 kHz. The AD/DA converter was driven using ASIO (Audio Streaming Input Output) and SDK (Software Developer Kit) from Steinberg (Lloyd 2002).

After D/A conversion, the stimuli were equalized (phonic graphic equalizer, model EQ 3600; Apple Sound) to compensate for the speaker and coupler frequency response and fed into a power amplifier (Rotel RB971) and a custom-built programmable end attenuator (0–75 dB in 5-dB steps) before being presented over a speaker (Radio Shack 30–1777 tweeter assembled by Mike Ravicz, MIT, Cambridge, MA) mounted in the coupler designed for the ear of a guinea pig. The stimuli were acoustically monitored using a condenser microphone (Ban dK 4134) attached to a calibrated 1-mm-diameter probe tube that was inserted into the speculum close to the eardrum. Neural spikes were discriminated in software, stored as spike times on a PC and analyzed off-line.

Unit classification

On isolation of a unit, its BF and excitatory threshold were determined using audiovisual criteria. Spontaneous activity was measured over a 10-s period. Only units with BF <5 kHz were included in this study.

Single units were classified based on their peristimulus time histograms (PSTH), the interspike interval (ISI) distribution, and the coefficient of variation (CV) of the discharge regularity. The latter was calculated by averaging the ratios of the mean ISI (μ) and its SD (σ) between 12 and 20 ms after onset, as defined by Young et al. (1988). The onset was determined visually with a cursor. PSTHs were generated from spike times collected in response to 250 sweeps of a 50-ms tone at the unit’s BF at 20 and 50 dB suprathreshold. Rise–fall time of the tones was 1 ms (cos2 gate) and the starting phase was randomized. The tone bursts were repeated with a period of 250 ms. The onset rate was determined by summing up all the spikes that occurred in a 1-ms window centered at the bin containing the maximum number of spikes within the first 2 ms of the response. The steady-state rate was determined by averaging the activity over 10 ms starting at 30 ms after the onset (Winter and Palmer 1995).

PSTHs were classified as pause-build, chopper, on-sustained, sustained, phase-locking, and unusual. A pause-build PSTH was defined as an onset response followed by a reduction of more than 20% in discharge rate relative to the steady-state rate for more than 7 ms and a subsequent build-up in firing rate at 20 or 50 dB suprathreshold. Units with a build-up response lacking the onset component also fell into the pause-build category. Chopper units showed regular peaks in their PSTH and had a CV value of <0.35. The distinguishing feature of on-sustained units was an onset rate of >400 spikes/s and an onset-to-steady-state discharge rate ratio >3.5. PSTHs that lacked a prominent onset response but showed sustained firing with a steady-state rate of >50 spikes/s were classified as sustained and units that showed phase-locking, manifested by several peaks in the first-order interval distribution, at multiples of the stimulus periods. Units that did not fall into any of the above described categories were termed unusual.

Units were also classified based on their response map, taking into account the rate-level functions to tones and noise and their spontaneous discharge rate. Response maps were created from the responses to 50-ms tones (repetition period 200 ms). The frequency of the tone bursts was varied in 0.1-octave steps from ≥1 octave below BF to ≥1 octave above BF. The sound level varied from ≥5 dB below threshold to ≤40–80 dB above threshold in 5-dB steps. To reveal inhibitory areas for units that had low spontaneous activity, additional response maps were collected in the presence of a simultaneously gated tone at BF, usually 10 dB above threshold.

Rate-level functions (RLFs) were constructed from the responses to 50-ms BF tones or broadband noise (repetition period 200 ms, 10 repetitions) varying randomly in sound level from below threshold to ≤40 dB above threshold in 2-dB steps.

The response map classification was based on Stabler et al. (1996). If the unit did not show any signs of inhibition it was classified as a type I unit. The maximum response to noise of a type II unit was one third or less of the unit’s maximum response to BF tones. In addition type II units had no spontaneous activity. Units were classified as type III if they had a V-shaped excitatory response area with inhibitory side bands and gave an excitatory response to noise, the maximum of which exceeded one third of the maximum response to a BF tone. For units without spontaneous activity it is not possible to distinguish inhibitory sidebands from a response map generated using a single tone. These units are therefore commonly classified as a separate category, type I/III. In the current study a response map in the presence of a low-level excitatory tone burst, usually positioned at 10 dB above BF threshold was routinely measured. This low-level tone burst evoked a small amount of neural activity that acted as a surrogate spontaneous discharge rate. This technique allowed the determination of the presence of suppressive sidebands. Thus there was normally no ambiguity between type I and type III. A unit that was driven by a low-level BF tone but was completely inhibited at higher levels (response below spontaneous rate or zero) and gave an excitatory response to noise was classified as type IV. These units had large inhibitory areas. Units with response properties intermediate between the type III and type IV response have been classified as type IV-1 units. The initial peak in the RLF of a type IV-1 unit was followed by a decrease in discharge rate resulting in a reduction of >25% at 50 dB above threshold but not reaching spontaneous rate (Stabler et al. 1996).
Complex stimuli

IRN was generated by adding a delayed version of the noise to itself. For the iteration, the output of one delay and add stage served as the input to the next stage (Yost 1996a,b; Yost et al. 1996). The number of iterations was always 16 and the gain was either 1 [IRN(t)] or minus 1 [IRN(t)]. The reciprocal of the delay was varied in half-octave steps from 31 to 1,000 Hz (delays 1–32 ms). The stimuli had a duration of 500 ms and were presented with a period of 1 s. The rise–fall time was 10 ms (cos^2 gate) and the stimuli were low-pass filtered with a cutoff frequency of 10 kHz. Responses were also collected from 500-ms, low-pass filtered (cutoff at 10 kHz) white noise (WN) and presented at the same level as the complex stimuli. Each stimulus condition was presented in random order with 25 repetitions. The repetition period was 1 s. IRN was refreshed on each presentation. If a unit was lost before 15 repetitions were presented, the data were discarded. Before presenting the IRN stimuli a rate-level function was recorded using 500-ms white noise stimuli varying in sound level in 5-dB steps. The IRN stimulus was then played at a sound level that had evoked a near-maximum discharge rate in response to the white noise. This resulted in a mean sound level of 78 dB SPL (±12 dB) or, with respect to the units’ thresholds, a mean level of 39 dB SL (±9 dB).

To enable a comparison of the responses of DCN units to those in the VCN as reported by Winter et al. (2001), “interval enhancement” values were calculated. The interval enhancement is defined as the proportion of intervals that remained after the proportion of intervals (with a duration equal to the IRN delay) in the response to WN was subtracted from the proportion of those intervals in the response to the IRN delay. Interval enhancement was calculated only if the unit showed significant peaks in its first-order interval statistics for at least 3 delays in comparison with its response to white noise with the same sound level. A peak was significant if there were more first-order ISIs in response to IRN than to the white noise stimulus at the IRN delay (one-tailed Student’s t-test, \( P < 0.05 \)). The interval enhancement values were plotted as a function of the delay and fitted with a gamma function on a logarithmic delay axis (see Fig. 6, top panel). Following Wiegrebe and Winter (2001a), the position of the peak of the fitted function was termed the best delay. The best delay was compared with the peak of the first-order ISIH in response to WN. This was obtained by calculating the average number of first-order ISIs in response to the WN in half-octave windows centered at the delays (thus obtaining the same number of points as present in the interval enhancement plot). These points were then also fitted with a gamma function (see Fig. 6, bottom panel). A goodness of fit was calculated as the sum of the absolute differences between the gamma-fit and average number of first-order ISIs at each delay value divided by the maximum value of the gamma-fit to the averaged WN first-order ISIH. If this goodness-of-fit measure exceeded 1.3, the unit was not included in the best delay analysis.

For comparison of the responses to IRN(+) with the responses to IRN(−) the single units were classified into waveform and envelope responders based on the autocorrelations of the neural spike trains (i.e., the all-order ISIs). All-order ISIs were also used in Shofner (1991, 1999) for the classification into waveform and envelope responders. Units that had significant peaks (one-tailed Student’s t-test, \( P < 0.01 \)) at the same delay(s) in the responses to IRN(+) and IRN(−) were classified as envelope responders; to qualify as a waveform responder, the unit had to show a peak at a particular delay in response to IRN(+) but not IRN(−) and have a peak at the position of twice the delay in response to IRN(−) with the same delay.

**RESULTS**

Responses to IRN(+) were collected from 135 single units with BF <5 kHz. For 46 of these units responses were also collected to IRN(−). Units were classified according to their PSTHs in response to pure tones at BF as well as according to their response maps. Examples of the different PSTH unit types are shown in the 1st column of Fig. 2. From top to bottom the insets show a pause-build (PB), a chopper (C), an on-sustained (OS), a sustained (S), a phase-locking (PHL), and an unusual (UN) unit. The different response map types (types I, II, III, IV-t, IV) are shown from left to right at the top of Fig. 2. Response maps were collected for only 73% of the units in the current sample. The remaining units together with 4 units that were classified as unusual in the response map classification are shown in the column “Not Classified.” The numbers in brackets in the last column and the bottom row of Fig. 2 give the distribution of the different PSTH and response map types, respectively. The majority of units had a pause-build PSTH. In the response map classification, type III units occurred most often followed by type IV-t units. The units were assumed to be located in the DCN for the following reasons: 1) all units were located in the appropriate position along the tonotopic axis of the DCN (i.e., before the abrupt change from low to high best frequencies that indicates the DCN/PVCN border), 2) reconstruction of the electrode tracks showed that all tracks coursed their way through the DCN, and 3) all units had either a pause-build PSTH pattern and/or a type II or type IV response map or were located in the same track and immediate vicinity of a pause-build or type II or type IV unit.

![FIG. 2](http://jn.physiology.org/)

**FIG. 2.** Number of units for which gave a significant temporal response to IRN(+) as a function of peristimulus time histogram (PSTH) (rows) and response map type (columns). Total number of units for each category is given in brackets. C, chopper; PB, pause-build; OS, on-sustained; S, sustained; PHL, phase-locking; UN, unusual; T I–T IV, response map types I to IV. For 26% of the units no response map was collected; these are shown in the column “not classified” together with 4 units with an unusual response map. In the type I category 5 units with a type I/III response map (2 PB, 2 PHL, 1 OS) are included. Overall 42% of dorsal cochlear nucleus (DCN) units gave a temporal response to IRN(+).
Single-unit responses to IRN(+)

According to the statistical criteria described in the METHODS, the quasi-periodicity of IRN was reflected in the temporal response characteristics of 57 of the 135 units tested (42%), spanning the entire BF range tested (166 Hz – 4.8 kHz). Figure 2 shows the number of units in each response map/PSTH combination that responded to the temporal regularity of the IRN stimuli. PHL, OS, and type I units most often responded to the temporal regularity, whereas sustained and type II units were largely insensitive to the quasi-periodicity of IRN.

The first-order and all-order ISIIs of the responses of a low-frequency PB unit to IRN [best frequency (BF) = 170 Hz]. Left column: first-order ISIIs. Right column: all-order ISIIs. Shown in gray are the responses to an equal-energy white noise (WN) stimulus. This unit phase-locked to pure tones at BF and had a type III response map. Only a selection of the measured IRN delays (\(d\)) is shown. Dashed lines indicate the position of the delay and twice the delay in the histogram. A significant enhancement in the response to IRN compared with WN is denoted with a filled circle. There are significant peaks in the first-order ISIIs for the delays 4, 5.7, and 8 ms and in the all-order ISIIs there are peaks up to the longest delay shown. Inset, top left: PSTH in response to a BF tone at 50 dB suprathreshold. Unit 1062001.

FIG. 3. First- and all-order interspike interval histograms (ISIHs) of the responses of a low-frequency PB unit to IRN [best frequency (BF) = 170 Hz]. Left column: first-order ISIIs. Right column: all-order ISIIs. Shown in gray are the responses to an equal-energy white noise (WN) stimulus. This unit phase-locked to pure tones at BF and had a type III response map. Only a selection of the measured IRN delays (\(d\)) is shown. Dashed lines indicate the position of the delay and twice the delay in the histogram. A significant enhancement in the response to IRN compared with WN is denoted with a filled circle. There are significant peaks in the first-order ISIIs for the delays 4, 5.7, and 8 ms and in the all-order ISIIs there are peaks up to the longest delay shown. Inset, top left: PSTH in response to a BF tone at 50 dB suprathreshold. Unit 1062001.

Over a third of units with a BF > 500 Hz (39%) did not show a significant temporal response. Many of these units

enhancement of the responses to certain delays of the IRN stimuli. The inset at the top left of the figure shows the PSTH of the unit’s responses to 250 repetitions of a BF tone, 50 dB above threshold. The unit had a BF of 170 Hz and was classified as a Pauser. In the first-order ISIIs there are significant peaks; that is, the number of intervals corresponding to the delay of the IRN was significantly greater than the number of intervals with the same duration in the WN response (\(P < 0.05\)), at the delays between 4 and 8 ms (as indicated by the filled circles). In the all-order ISIIs all delays > 2 ms show a significant peak (\(P < 0.01\)). This result—a low-pass response in the all-order interval statistics but a band-pass response in the first-order interval statistics—has also been observed in the VCN (Wiegrebe and Winter 2001a; Winter et al. 2001). Note that the highest peak in the first-order, as well as the all-order ISIIs, is close to the peak in the first-order ISIIs in response to WN around 4 ms. An example of a low-frequency unit that did not reflect the quasi-periodicity of the IRN stimuli in its responses is shown in Fig. 4 (same format as in Fig. 3). This PB unit with a BF of 253 Hz gave a generally weaker response to the stimuli and did not show any significant enhancement in the responses to any of the IRN delays compared with the WN response. Over a third of units with a BF < 500 Hz (39%) did not show a significant temporal response. Many of these units

FIG. 4. First- and all-order interval histograms (AOIHs) of the responses of a low-frequency unit to IRN [best frequency (BF) = 253 Hz] that did not respond to the temporal regularity of the IRN. Same format as in Fig. 3. This unit was classified as PB according to its PSTH and as type IV in the response map classification. Note that the response is much weaker than that in the previous example (compare scale of the ordinates). PSTH at the top left was in response to pure tones at 20 dB above the unit’s threshold. Unit 1089002.
(9/12) responded only weakly to the stimuli (i.e., <30 spikes/stimulus). For units with higher BF the proportion of units not sensitive to the IRN periodicity was even higher but a quarter of the units did give a temporal response. Figure 5 shows an example of a unit with a BF of 3.9 kHz and an on-sustained PSTH. In contrast to the units shown before, this unit responded with equal strength to all stimuli. The delays from 2 to 8 ms were reflected by significant peaks in the first-order and all-order ISIHs, whereas the longer delays (16–32 ms) were reflected only in the all-order ISIHs.

**Comparison of the responses to IRN(+) and white noise**

It has been shown for PB and CS units in the DCN/PVCN that there is a close relationship between the intrinsic oscillation of a unit and its best modulation frequency (Kim et al. 1990). Winter et al. (2001, 2003) also showed a correlation between the peak in the first-order ISIH in response to WN and the peak in the periodicity tuning seen in the first-order ISIHs in response to IRN. The examples shown in Figs. 3 and 5 suggest that such a correlation may also exist in the DCN. Figure 6 shows results of the fitting procedure to the interval-enhancement plot and the WN first-order ISIH of the unit shown in Fig. 3. The top panel shows interval enhancement as a function of delay (the peak of this function is the best delay) and the bottom panel shows the average number of first-order ISIs in response to the WN in half-octave windows centered at the delays (the peak of this function is known as the WN peak). The curves show the fitted gamma functions; for this unit the position of the best delay and the WN peak is the same, 4.4 ms. The best delays of DCN units are distributed between 2.1 and 11.5 ms, corresponding to a frequency range of 87 to 476 Hz. The mean values of the WN peak and the best delay are 6.5 ± 2.3 and 6.5 ± 2.5 ms, respectively (calculated from a total of 53 units that were included in the best delay analysis; see METHODS). For all unit types the correlation between WN peak and best delay was 0.9. There were no significant differences between different PSTH or response map types (one-way ANOVA).

No significant differences were found in the amount of interval enhancement at the best delay for the different response map types (one-way ANOVA). Using the PSTH classification, interval enhancement was significantly greater for PHL than for PB units (one-way ANOVA, *P* < 0.01). However, in a frequency-matched comparison (i.e., units from the PB group with BFs >0.7 kHz were excluded) there was no significant difference between low-frequency PB units and PHL units. The magnitude of the temporal response appears more related to unit BF than unit type.
Comparison between responses to IRN(+) and IRN(−)

For 46 units (26 PB, 10 PHL, 7 OC, and 3 C) responses were collected to IRN(+) and IRN(−) at the same sound level. An example of the response of a PB unit with a BF of 409 Hz is shown in Fig. 8. The 2 circles in each panel indicate whether the peak at the delay (left circle) and at twice the delay (right circle) were significant (filled circle; Student’s t-test, \( P < 0.01 \)) or nonsignificant (open circle). The response to delays are shown that classified the unit as a waveform responder: the unit showed a significant peak \( P < 0.01 \) at the delay in the all-order ISIH for IRN(+) (2nd column) and no peak at the delay but a significant peak at twice the delay in the all-order ISIHs for IRN(−) (4th column). Note that this unit would also be classified as a waveform responder if the decision had been based on the first-order ISIHs (1st and 3rd columns) because for 4 and 8 ms the same pattern of peaks as that of the all-order ISIHs is obtained. An example of a response of a PB unit with a higher BF (1.1 kHz) is shown in Fig. 9. The unit shows very similar first-order and all-order ISIHs for IRN(+) and IRN(−) with significant peaks at the delays in the all-order ISIHs for both IRN(+) and IRN(−). Thus the unit is classified as an envelope responder. The unit would also be classified as an envelope responder if the first-order ISIHs (1st and 3rd columns) had been used for the classification.

Thirteen of the 46 units tested with IRN(+) and IRN(−) were classified as waveform responders and 17 as envelope responders. Six of the 13 waveform responders were classified as PHL and one as OS. The remaining 6 units had a PB PSTH pattern. All but one of the PB units also showed a phase-locked response to pure tones. However, not all of the 18 units (10 PHL, 8 PB) that showed a phase-locked response to pure tones were classified as waveform responders: 3 were classified as envelope responders and 4 showed an inconsistent response. The BF of all waveform responders was <500 Hz.

Envelope responders mostly had either a PB (8 units) or an OS PSTH (6 units). In general, their BF was >500 Hz. Only 2 units with lower BFs (394 and 494 Hz) were classified as envelope responders. The different response map types were represented in the different response classes to similar degrees. If instead of the all-order ISIs the first-order ISIs had been used for the classification, 10 units would be classified as waveform responders and 10 would be classified as envelope responders. The rest would fall into neither of the 2 categories. Units classified as a waveform or envelope responders based on the

![DCN unit sensitive to the waveform fine structure. First-order and all-order ISIHs of the responses of a PB unit to IRN(+) (left) and IRN(−) (right). Shown in gray are the responses to an equal-energy WN stimulus. Dashed lines indicate the position of the delay and twice the delay in the histogram. Two circles denote whether the peaks at the delay and/or at twice the delay (left and right circles, respectively) were significant (fied circles; one-tailed Student’s t-test, \( P < 0.01 \)) or nonsignificant (open circles). Peaks in the ISIHs in response to the delay of IRN(+) are replaced by troughs and 2 peaks to either side of the delay in response to IRN(−). Peak at twice the delay (second dotted line) in the responses to IRN(−) on the other hand is enhanced. BF of this unit was 409 Hz and it phase-locked to pure tones at BF. Unit 1042011.](https://jn.physiology.org/doi/10.1152/jn.01042011)
first-order ISI always fell in the same category on the basis of the all-order ISIs.

**Discussion**

Of our sample of DCN units (BF <5 kHz) 42% preserved the quasi-periodicity of IRN(+) for some delays in their first-order and all-order ISIs. Although the all-order ISIHs were generally low-pass in the frequency domain, the first-order ISIHs conveyed the IRN(+) delay in a band-pass fashion with a preferance for a certain delay. This preferred delay was highly correlated with the peak in the first-order ISIH of the response to WN. A subset of units were also tested with IRN(−). It was found that units with BFs <500 Hz could encode the difference in the waveform fine structure between IRN(+) and IRN(−). These results support recent findings that some DCN units are sensitive to the temporal structure of sounds. However, the results also show that, although many units in the DCN are sensitive to the quasi-periodicity of IRN, only units tuned to very low frequencies are potentially involved in the encoding of the temporal fine structure and thus pitch of broadband IRN.

**Does the temporal response depend on unit type?**

With the exception of unusual units and type II units, all PSTH and response map categories could reflect the IRN periodicity in their temporal responses. Phase-locking units were the most likely PSTH group to show a temporal response; furthermore, units sensitive to the waveform fine structure nearly always phase-locked to pure tones at BF. There was no apparent difference in the responses depending on whether the phase-locking unit had a pause in its pure-tone PSTH. In addition, units with an onset response such as OS units were more likely to show a temporal response than units that lacked an onset response (e.g., as sustained units; Fig. 2). Both phase-locking and a well-defined onset response are signs that the unit is able to elicit precisely timed spikes; thus it is not surprising that those units were more prone to reflect the IRN periodicity in their responses. Most units that gave a temporal response to IRN had a type III or type I response map but again response map type was not a clear indicator as to how the unit would respond; some type I units and type III units did not respond significantly to the IRN periodicity. The results presented in this study suggest that the unit’s ability to respond to the temporal regularity of IRN depends on its ability to fire precisely timed spikes, which favors certain unit types, but that one cannot predict the responses to IRN stimulus based on the PSTH or response map type of the unit. If the unit did give a temporal response to the IRN stimuli its BF has been shown to be the strongest indicator as to the magnitude of the temporal response and whether it would respond to the waveform fine structure or the envelope irrespective of unit type.

**Effect of anesthesia**

In barbiturate-anesthetized cats the amount of inhibition in the DCN has been reported to be greatly reduced in comparison to awake preparations (Evans and Nelson 1973; Gdowski and Voigt 1997; Young and Brownell 1976). In the current study many units showed signs of inhibitory influence and the proportions of the different response map types recorded in the anesthetized guinea pig were very similar to those found in the decerebrate gerbil, including several units with a type V (purely inhibitory) response area. Furthermore 64% of the units of the current sample had spontaneous rates above 2.5 spikes/s and 80% of those units had spontaneous rate above 15 spikes/s. In the gerbil under barbiturate anesthesia only 12.5% of the units showed spontaneous rate above 2.5 spikes/s (Gdowski and Voigt 1997). In addition, the proportion of units with nonmonotonic rate-level functions was much higher (56%) than what was reported by Stabler et al. (1996; 36% of 413 units) who used neurolept anesthesia. Thus our results suggest that anesthesia has not had a profound influence on the responses of single units.

**Comparison of the best delays between VCN and DCN units**

The finding that most units represented particular delays only in their first-order ISIs but responded to a range of delays extending to longer values in their all-order ISIs agrees with the study of Winter et al. (2001). Winter et al. (2001) also showed a strong correlation between the peak of the WN first-order ISIH and the best delay in response to IRN for sustained chopper (CS) and onset chopper units (OC) and that these unit types had a range of best delays of 3.75–13 ms (OC) and 2.25–10.8 ms (CS). Primary-like (PL) units encoded the difference in the waveform fine structure or the envelope irrespective of unit type.
0.72 and 0.81, respectively). In addition, the best delays of DCN units are very evenly spread over a wide range of frequencies. However, the range of IRN delays encoded in the first-order ISIH of PB units does not extend to values as low as those for some of the PL and transient chopper units of the VCN. The results agree with the finding that synchronization to AM stimuli of DCN units is also restricted to lower frequencies than those in the VCN (e.g., Kim et al. 1990; Rhode and Greenberg 1994).

Kim et al. (1990) showed that there was a close relationship between the intrinsic oscillation of a unit and its best modulation frequency. Winter et al. (2003) suggested that the response to WN could be a measure of the intrinsic oscillation of a unit and conclude that the findings in the VCN support the observation of Kim et al. (1990). The same can be concluded from the current study. The range of best modulation frequencies and corresponding intrinsic oscillations of PB units in the study by Kim et al. (1990) was approximately 100–400 Hz. This is very similar to the range of best delays (87–476 Hz) and WN peaks (93–357 Hz) found for PB units in the current study.

Winter et al. (2001) also looked at the relationship between the peak in the WN first-order ISIH and the unit’s BF. They report that the greatest range of peaks was found for OC units with BFs between 5 and 10 kHz. In the present study no recordings have been made from units in this BF region; however, the range of WN peaks found for DCN units with BFs between 0.1 and 5 kHz is as great as what has been observed in the VCN. The VCN data included only units with BFs >600 Hz, whereas many units in the present study had lower BFs. It is possible that the higher correlation of WN peak and best delay observed in the present study is attributable to the presence of many low-frequency units, which were particularly sensitive to the temporal regularity of IRN.

The comparison of the results from the VCN and DCN leads to the conclusion that PB units in the DCN seem just as well suited to encode the delay of IRN(+) in their first-order ISIs for a wide range of frequencies as are CS and OC units in the VCN. Note that non-PB units in the DCN also showed a very strong correlation between WN peak and best periodicity and encoded delays over a similarly wide range.

Fine structure or envelope encoders?

A crucial test for a unit that is a possible candidate for pitch processing is whether it is sensitive to the waveform fine structure of the stimulus or only responds to the envelope of the waveform. Only the waveform fine structure contains unambiguous information about the pitch, as has been shown for IRN produced with a positive and negative gain, which has a different pitch but shares the same waveform envelope. This question was not addressed by Winter et al. (2001) but Shofner (1999) showed that many phase-locking PL units in the VCN could encode the difference of IRN(+) and IRN(−). These units had peaks in their neural autocorrelograms at integer multiples of the delay when the gain was 1 but nulls flanked by a pair of positive peaks at the delay and odd-integer multiples of the delay when the gain was −1. A similar result was obtained in the present study for DCN units with BFs <500 Hz. These units responded with a peak at the delay in their first-order and all-order ISIHs to IRN(+) but this peak was replaced by a trough, often flanked by 2 peaks on either side, in response to IRN(−). The units also showed a peak at twice the delay, especially in the all-order ISIH. With the exception of one PB and one OS unit, all waveform responders phase-locked to pure tones at BF. Units with higher BF either showed little sensitivity to the IRN periodicity or responded with peaks in their ISIHs at the delay of IRN(+) as well as IRN(−), and were thus classified as envelope responders. However, some of those envelope responders could nonetheless be involved in pitch processing. It has been shown that even for IRN(−) with 16 iterations the pitch does not always correspond to 1/(2d) (Wiegrebé and Winter 2001b). For high-pass–filtered IRN stimuli, with cutoff frequencies between 625 Hz and 5 kHz and delays of 8 ms or longer, human listeners did not hear the octave shift when comparing IRN(+) and IRN(−). If the BF and best delay of a unit are taken as indicators as to which IRN “harmonic” the unit is tuned, one would not expect to see different responses to IRN(+) and IRN(−) for units with best delays of ≈8 ms. Thus 9 of the 17 units we identified as envelope responders would not be expected to respond to the differences between IRN(+) and IRN(−).

The finding that mainly phase-locking units could distinguish between IRN(+) and IRN(−) agrees with the studies of Shofner (1991, 1999) in the VCN. However, the ability to distinguish between IRN(+) and IRN(−) seems to be restricted to units with lower BFs than what has been reported in the VCN. Shofner (1999) does not explicitly state the upper BF limit for VCN units that represented the difference of IRN(+) and IRN(−) in their temporal response, but he states that mainly phase-locking PL units encoded the difference. Shofner (1991) grouped units with BFs ranging from 0.16 to 3.1 kHz together to a “phase-locked” group, and showed that the units in the group gave different responses to rippled noises with a positive and negative gain. Shofner (1999) shows an example of a primary-like unit (BF = 0.85 kHz) that responded clearly to the differences in IRN(+) and IRN(−). This is a higher BF than that of any of the waveform responders in the DCN. Thus although many units in the DCN respond to the periodicity of IRN, only units tuned to low frequencies are able to encode the temporal fine structure. However, it is possible that high BF units may respond to the fine structure of low-pass–filtered IRN stimuli at high sound levels.

In conclusion many pause-build units and other unit types (mainly phase-locking and on-sustained units) in the DCN are able to represent the periodicity of IRN(±) in their first-order interspike intervals. A subset of DCN units, with BFs <500 Hz, were sensitive to the temporal fine structure of the waveform; however, it is clear that units in other regions of the cochlear nucleus may be more suited to encode temporal fine structure to higher frequencies. Shofner (1991, 1999) demonstrated that units classified as primary-like in the anteroventral cochlear nucleus are capable of encoding temporal fine structure with BFs at least as high as 1.6 kHz. The role of chopper units in representing the delay of IRN is less certain. Chopper units with relatively high BFs are unable to distinguish between IRN(+) and IRN(−) in their temporal discharges, although some chopper units are able to show strong interval enhancement to the delay of IRN(+) when the delay overlaps with the
chopping frequency of the unit. For some units this enhancement is level independent (Wiegrebé and Winter 2001a; Winter et al. 2001). Computational models have also supported the role of chopper units in the encoding of periodicity pitch (Wiegrebé and Meddis 2004). Taken together, these studies suggest that for units with low BF’s, there are multiple parallel ascending pathways that could provide a temporal representation of the delay of iterated rippled noise, based on interspike intervals, to higher levels of the auditory system.

ACKNOWLEDGMENTS

We thank two anonymous reviewers and L. Wiegrebé for many helpful comments in the preparation of this manuscript.

GRANTS

This work was supported by the Wellcome Trust.

REFERENCES


