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The Volley theory and the Spherical Cell puzzle

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Abstract

Temporal coding in the auditory nerve is strikingly transformed in the cochlear nucleus. In contrast to fibers in the auditory nerve, some neurons in the cochlear nucleus can show “picket fence” phase-locking to low-frequency pure tones: they fire a precisely timed action potential at every cycle of the stimulus. Such synchronization enhancement and entrainment is particularly prominent in neurons with the spherical and globular morphology, described by Osen (1969). These neurons receive large axosomatic terminals from the auditory nerve - the endbulbs and modified endbulbs of Held - and project to binaural comparator nuclei in the superior olivary complex. The most popular model to account for picket fence phase-locking is monaural coincidence detection. This mechanism is plausible for globular neurons, which receive a large number of inputs. We draw attention to the existence of enhanced phase-locking and entrainment in spherical neurons, which receive too few endbulb inputs from the auditory nerve to make a coincidence detection of endbulb firings a plausible mechanism of synchronization enhancement.

Keywords

temporal coding; binaural; synchronization; amplitude modulation; cochlear nucleus; jitter

Biological taxonomy is always fraught with splitting vs. lumping difficulties. Kirsten Osen’s morphological parcellation of the cochlear nucleus (CN)(Osen, 1969) was a landmark achievement because it hit exactly the right level along the splitter-lumper dimension. Her parcellation proved to dovetail very well with the physiological parcellation of response categories based on responses to short tone bursts (Kiang et al., 1965a, Pfeiffer, 1966). Other studies lent further credence to Osen’s scheme in terms of projections patterns (Warr, 1982) and intrinsic electrical properties (Oertel, 1999). Osen’s insightful observations have thus served as an organizational principle which enabled the remarkable progress in the understanding of this nucleus in the 1970s and 1980s.

The study of the CN highlights one of the most interesting features of the auditory system: its morphological and physiological specializations to process temporal information in the acoustic waveform. We focus here on temporal processing and two neuron types, called the spherical and globular cells by Osen, and point out an unsolved puzzle.

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The volley theory

100 years ago, Lord Rayleigh (Strutt, 1907) showed a relationship between the perceptual localization of sound and the interaural phase of tones at the two ears. Even earlier, Thompson (Thompson, 1877) had described the sensitivity of humans to ongoing interaural phase differences for low-frequency tones. These observations established unequivocally that temporal information at the two ears is accessed by the CNS and that it is used in spatial perception. These early pioneers thereby provided strong support for the “telephone” theory, as opposed to the “resonance” theory: theories which can be traced back to Helmholtz and Rutherford and which today are referred to as temporal and place coding.

Besides the binaural psychophysical observations, there was also physiological evidence for the telephone theory (see Davis, 1984 for an interesting personal historical account). Early recordings of gross evoked potentials showed responses that phase-locked to the stimulus waveform up to several kHz (Wever and Bray, 1930a). Investigators puzzled over this for two reasons. First, it was known from single cell recording in other systems that neurons display refractory behavior and are limited in their firing rates to a few hundred spikes per second (microelectrode recordings from single auditory neurons only became available much later: Galambos and Davis, 1943, Tasaki, 1954). How could auditory neurons have temporal information above frequencies corresponding to “normal” firing rates? Second, how could neurons be phase-locked and at the same time carry intensity information in their discharge rate? The latter was seen as a requirement based on observations in other sensory systems (Adrian, 1928). The volley theory (Wever and Bray, 1930b) solved these difficulties and argued that the resonance and telephone theories were not mutually exclusive. Wever and Bray reasoned that single fibers can be synchronized to the stimulus waveform even if they do not fire at every stimulus cycle, and that the combined output of a *group* of fibers can carry the temporal waveform in a volley of spikes. In their words, “The situation is something like beating a tattoo with the two hands working alternately, and establishing a total frequency double that of either hand.” (Wever and Bray, 1930b). Here we illustrate that the temporal code which is distributed over different fibers at the level of the auditory nerve (AN) is transformed at successive synaptic levels to a more robust code at the single cell level.

Single unit phase-locking and its enhancement

Computer-aided AN recordings (Kiang et al., 1965b, Rose et al., 1967, Johnson, 1980) systematically demonstrated phase-locking at frequencies far higher than maximal firing rates sustained by AN fibers, which are ~ 300 Hz. As hypothesized by Wever and Bray, AN fibers skip cycles, even at very low frequencies, and the upper limit of phase-locking is thus not imposed by refractoriness (even though this statement is still encountered, e.g. Shepherd, 1994). The most popular metric used to quantify phase-locking is the vector strength (VS, Goldberg and Brown, 1969). Spikes randomly distributed with respect to phase result in a VS near 0, while spikes occurring at a fixed phase yield values near 1 (Fig. 1). With this measure, phase-locking in the AN shows a low-pass characteristic with an upper limit of ~ 4-5 kHz in the cat (Johnson, 1980, Joris et al., 1994a) and somewhat lower in rodents (Palmer and Russell, 1986, Paolini et al., 2001, Taberner and Liberman, 2005). The exact limiting step(s) at the level of the cochlea are not known, but a number of candidate processes such as hair cell membrane capacitance have been proposed (Palmer and Russell, 1986, Weiss and Rose, 1988).

Phase-locking changes in quality in the ascending auditory system. Generally, there is a decrease in the upper frequency limit at successive synaptic levels. More surprisingly, central auditory neurons often show an enhancement of phase-locking relative to the AN. There are two aspects to this phenomenon. First, discharges are restricted to a narrower range of phase angles, reflected in higher VS values (Fig. 1). For example, when studied at their characteristic

frequency (frequency of lowest threshold, CF), some neurons of the ventral CN (VCN) show higher VS values than AN fibers. This happens for frequencies below approximately 1 kHz (Joris et al., 1994a). Equally striking is the observation that neurons may lack enhanced phase-locking at their CF but may instead show enhancement for frequencies in their low-frequency tail (see below) (Rhode and Smith, 1986; Joris et al., 1994b) (Rhode, this issue 2008).

A second aspect of enhanced phase-locking, which has received less attention, is entrainment. In response to short tone bursts, some neurons can discharge a spike at every cycle up to frequencies of ~ 700 Hz (Godfrey et al., 1975; Rhode and Smith, 1986; Rhode and Kettner, 1987; Joris et al., 1994a). Both components, high VS and entrainment, likely contribute to the strongly phase-locked gross potentials measured in the CNS (Boudreau, 1965). The combination of enhanced phase-locking and entrainment means that these neurons can be described as “volley-detectors”: they seem to collect phase-locked spikes from a group of AN inputs to produce a precise pulse train at the stimulus frequency (Fig. 2D).

Fig. 1 illustrates phase-locking for an AN fiber and a VCN neuron, tuned to the same frequency of 670 Hz (panel A). Panels B and C show dot rasters in response to 50 short tones at this frequency. There is a vertical alignment of dots in both cases, but clearly this alignment is better in panel C. The red dots indicate spike times which are identical, within a 50 μ s window, across responses to at least 2 stimulus presentations (of the 50 shown): for the black dots there is no matching spike time in any of the other spike trains. The VCN neuron (panel C) tends to fire a spike on every cycle over a narrow phase-range of the sinusoidal stimulus waveform, resulting in a preponderance of spike times that are coincident across stimulus repetitions. The AN neuron is more stochastic in its firing, often skipping one, two, or more cycles, and the spikes are less well aligned across repetitions. The cycle histograms (Fig. 1D,E) show the instantaneous discharge rate directly as a function of stimulus phase. A flat distribution would indicate an absence of phase-locking at the frequency of the histogram. There is phase-locking in both fibers, but there is more dispersion in the AN response. The same distributions are also shown in polar format, from which an averaged vector can be calculated. The magnitude of this vector, normalized for the overall discharge rate, is the VS and is much higher for the VCN fiber (0.93) than for the AN fiber (0.64). Despite a stimulus frequency that is high relative to “routine” neuronal firing rates, this VCN neuron also showed entrainment. This is illustrated by the dominance of inter-spike intervals equal to the stimulus period (Fig. 1G), while the AN fiber shows a multimodal distribution (Fig. 1F) indicating frequent skipping of stimulus cycles.

So far, we have only discussed phase-locking to the fine-structure of pure tones i.e. to the fluctuations of instantaneous pressure in these waveforms. Sounds also have a temporal envelope, which is perceptually important, and auditory neurons phase-lock to these envelopes (reviewed by Joris et al., 2004). Again such phase-locking can be enhanced in CN neurons relative to the AN, and there are phenomenological parallels between the enhancement of phase-locking to fine-structure and to envelopes. For example, the enhancement of envelope phase-locking does not extend to modulation frequencies as high as in the AN.

Fig. 3 illustrates enhanced phase-locking to both fine-structure and envelope for a neuron recorded in the superior olivary complex (SOC), which contains output fibers from the VCN and their postsynaptic targets, organized into several different nuclei. Panel A shows the frequency threshold tuning curve. The other two panels in the left column show VS (Fig. 3B) and average firing rate (Fig. 3C) for pure tones, presented at many different sound levels (dB SPL is indicated with color code on the ordinate of panel A). Although this neuron does not phase-lock to pure tones at its CF (2460 Hz, indicated with a vertical line), it shows enhanced synchronization for frequencies in the low-frequency “tail” of the tuning curve (Fig. 3B). An example of a period histogram to a tone in the low frequency tail (at 400 Hz) is shown in the top panels (histogram “X”), which has a high VS of 0.95. Moreover the neuron also entrains

almost perfectly to low-frequency stimuli, if the stimulus level is sufficiently above threshold. Indeed, at 80 dB the firing rate (Fig. 3C) is close to equality (dashed line in panel C) with the stimulus frequency up to about 500 Hz, and this entrainment is present for the entire (1 second) duration of the stimulus. Thus a 300 Hz tone evokes 300 spikes/s, a 400 Hz tone evokes 400 spikes/s, etc. In stark contrast, the response to CF tones is quite low. The other panels (D-G) show responses to amplitude modulated tones, which are discussed below.

Enhanced phase-locking to fine-structure is not only present for pure tones, but also for non-periodic stimuli. This is somewhat less straightforward to quantify than phase-locking to pure tones or other periodic stimuli. A coincidence or autocorrelation analysis (Joris, 2003, Joris et al., 2006) shows that, compared to AN responses (Louage et al., 2004), many VCN neurons show temporally “enhanced” properties not only to tones but also to broadband noise, again both in terms of entrainment and reduced jitter (Louage et al., 2005). Henceforth, we will use the term “high-sync” as a general term to indicate enhanced phase-locking to fine-structure.

One important issue is whether enhanced phase-locking is functionally relevant. “Enhanced” implies something positive, but high-sync responses actually represent the stimulus waveform in a rather distorted way. For example, the waveform of low-frequency sine waves is more faithfully tracked by the probability of discharge of AN fibers than by “high-sync” fibers. One can question whether a highly regular pulse train at the stimulus period is a better temporal representation than the more stochastic representation at the level of the AN. Our viewpoint is similar to that of Davis, in his proposition of separate auditory systems (Davis, 1984) which has been echoed by many workers. For binaural tasks that involve a comparison of the timing of events at the two ears, the high-sync representation seems advantageous. An ideal observer analyses shows indeed better binaural discrimination thresholds when based on phase-locked VCN fibers projecting to binaural nuclei, than when based on AN responses (Louage et al., 2006). For other perceptual attributes that may be based on temporal coding (e.g. pitch, Cariani and Delgutte, 1996a) it is less clear whether the high-sync representation of VCN neurons is also an enhanced (in the sense of superior) representation. Although it has been little studied, CN fibers with high-sync responses seem to have smaller dynamic ranges than AN fibers (Joris et al., 1994a, Fig. 1), so that they are probably not good encoders of sound intensity, at least not in terms of their average rates. The conflicting demands of the encoding of frequency, time, and intensity were already discussed in the first half of the previous century (Davis, 1984). At present, the dominant view is that such multiple demands are the *raison d'être* for the morphological and physiological diversity in the CN (Kiang et al., 1973, Irvine, 1986, Rhode and Smith, 1986, Cant and Benson, 2003, Young and Oertel, 2004).

Relationship to morphological cell types in CN

Before discussing the relationship of high-sync responses to the CN cell types described by Osen, we focus on two of the cell types described by her which are of particular interest to us: the spherical and globular cells (Osen, 1969). Our focus has two reasons. As mentioned, the use of temporal information by the CNS is clearly established physiologically and psychophysically for binaural hearing. The basic circuits involved in the time comparisons are known, and spherical and globular neurons are an essential component of these circuits. Although there are still several open questions and controversial issues on even the most basic features of these circuits (Joris and Yin, 2007), there is no disagreement that temporal comparison of the sound waveforms at the two ears requires phase-locking. For no other human perceptual ability is this established as well. A second reason to focus on spherical and globular cells is an intriguing puzzle regarding the mechanisms underlying synchronization enhancement, as will become clear below.

These neurons have a restricted distribution in the anteroventral CN (AVCN), in the spherical cell area and globular cell area. The correspondence of Osen's scheme to the other main CN parcellation scheme (Brawer et al., 1974) has been discussed elsewhere (Cant and Morest, 1984, Irvine, 1986). We will use the nomenclature of Cant and Morest, which fuses the two schemes (Cant and Morest, 1984): spherical bushy cells (SBCs) and globular bushy cells (GBCs).

As summarized by Cant (Cant, 1991), there is a SBC pathway and a GBC pathway, which provide direct excitatory and indirect inhibitory input, respectively, to binaural nuclei in the SOC. Most of the information available on these pathways is based on degeneration studies (e.g. Warr, 1966, 1969, Osen, 1970, Warr, 1982) or studies using axonal transport of neural tracers either injected grossly (e.g. Tolbert et al., 1982, Shneiderman and Henkel, 1985, Cant and Casseday, 1986) or into single cells or axons (Sento and Ryugo, 1989, Spirou et al., 1990, Ryugo and Sento, 1991, Smith et al., 1991, Smith et al., 1993).

In the cat the SBC population in the rostral-most AVCN has CFs that span the low and medium frequency range. Their cell bodies are larger than their counterparts in the caudal region of this nucleus, where the CFs span the entire frequency range (Osen, 1969). The consensus from the studies mentioned above is that large SBCs send projections to the appropriate frequency regions of the medial superior olive (MSO) bilaterally and the lateral superior olive (LSO) ipsilaterally where they form excitatory terminations on the dendrites of principal cells. Other SOC projections from this population include both ipsilateral and contralateral periolivary nuclei and perhaps the contralateral ventral nucleus of the lateral lemniscus (VNLL) as well. Projections of the small spherical cells in more caudal areas of the AVCN are less well documented but it appears that they have the ipsilateral LSO as their main target and may not project across the midline.

The more oval shaped cell bodies of the GBCs with their somewhat less dense, more highly spread out dendritic arbors are located in the more caudal reaches of the AVCN in and around the nerve root area (Harrison and Warr, 1962, Osen, 1969)(Rhode this issue, 2008). Their primary termination sites appear to be on cells in brainstem nuclei that provide inhibitory inputs to other regions. These include the large calyx of Held terminals onto glycinergic cells of the contralateral medial nucleus of the trapezoid body (MNTB) that provide inhibitory inputs to LSO and MSO cells (Glendenning et al., 1985, Kuwabara et al., 1991, Banks and Smith, 1992, Cant and Hyson, 1992, Smith et al., 1998, Chirila et al., 2007) (Kopp-Scheinpflug et al., 2008, this issue), terminals onto neurons of the ipsilateral lateral nucleus of the TB that provide inhibitory inputs to MSO cells (e.g. Cant and Hyson, 1992, Spirou and Berrebi, 1997, Spirou et al., 1998); and a contralateral projection to superior paraolivary nucleus or dorsomedial periolivary nucleus that sends a GABAergic projection to the inferior colliculus (e.g. Kuwabara et al., 1991, Smith et al., 1991, Kulesza and Berrebi, 2000). Other projections to the VNLL and the ipsilateral LSO (in certain species) have been reported (Friauf and Ostwald, 1988, Kuwabara et al., 1991, Smith et al., 1991).

Which neurons show enhanced phase-locking relative to the AN? The phenomenon is surprisingly common, especially at "tail frequencies". One major exception is the dorsal CN where phase-locking to fine-structure is very limited (Goldberg and Brownell, 1973, Rhode and Smith, 1986). Perhaps one of the earliest high-sync examples in the literature is in a study of the MSO, in which the response to a 375 Hz tone shows a unimodal interval histogram (Moushegian et al., 1967). Scattered examples are present in many CN recordings from the cat, and show that high-sync responses can be generated by several of the main cell types described by Osen (1969): SBCs, GBCs, octopus cells, and multipolar cells (Lavine, 1971, Godfrey et al., 1975, Rhode and Smith, 1986, Rhode and Kettner, 1987, Carney, 1990, Joris et al., 1994a, Joris et al., 1994b)(Rhode, this issue 2008), as well as by neurons of the MNTB,

MSO, and LSO (Yin and Chan, 1990, Finlayson and Caspary, 1991, Joris and Yin, 1995, Smith et al., 1998, Tollin and Yin, 2005). The phenomenon has also been encountered in the CN and MNTB of macaque monkeys (Joris and van der Heijden, 2004). It seems less prominent in rodents: an extensive study in the rat (Paolini et al., 2001) found enhanced synchronization in the AVCN and MNTB, though not to the same degree as in the cat. Enhancement and entrainment appear to be present in the rat LSO as well (Caspary and Finlayson, 1991) and was observed in a non-bushy neuron in gerbil (Feng et al., 1994, Ostapoff et al., 1994). Enhanced synchronization was not seen in SBCs of the guinea pig (Winter and Palmer, 1990). In birds, the phenomenon has been described in the chick (Fukui et al., 2006), but in the owl there is only minor enhancement in nucleus magnocellularis relative to the AN (Koppl, 1997). It should be pointed out that even in the cat there are several extensive studies that show little difference between the highest VS values found in the VCN vs. the AN (Bourk, 1976, Blackburn and Sachs, 1989), while the difference is rather striking in axonal recordings from SBC and GBC fibers in the trapezoid body (TB) (Joris et al., 1994a, Joris et al., 1994b, Louage et al., 2005). Possible explanations for these discrepancies have been offered elsewhere (Joris et al., 1994a): we return to this issue in the final section.

Mechanisms of synchronization enhancement

There have been a surprisingly large number of modeling studies on the phenomenon of enhanced synchronization and entrainment. The most common model is one in which coincidence of a number of excitatory inputs on neurons with a short membrane time constant (Oertel, 1983) is required before a postsynaptic spike is generated (Joris et al., 1994a, Rothman and Young, 1996). The degree of enhancement in such models is a complex interplay of the number of inputs, their amplitudes, their temporal and spatial distribution, and several postsynaptic factors (Rothman et al., 1993, Rothman and Young, 1996, Kuhlmann et al., 2002, Reed et al., 2002, Rothman and Manis, 2003, Ito and Akagi, 2005, Maki and Akagi, 2005, Xu-Friedman and Regehr, 2005b, a). Increasing the number of subthreshold inputs increases the VS values (Rothman et al., 1993, Joris et al., 1994a, Rothman and Young, 1996, Ito and Akagi, 2005, Xu-Friedman and Regehr, 2005b, a). A coincidence scheme is plausible for enhanced synchronization in GBCs because these cells have a large number of AN inputs (Spirou et al., 2005) which are presumably subthreshold (Smith and Rhode, 1987, Paolini et al., 1997) (Rhode this issue 2008), as well as limited temporal summation due to their fast membrane time constant (Wu and Oertel, 1984, Manis and Marx, 1991). Similar ideas apply to other cell types in the CN which have enhanced temporal properties relative to the AN and which receive many small subthreshold AN inputs (Winter and Palmer, 1995, Jiang et al., 1996, Cai et al., 1997, Levy and Kipke, 1998, Cai et al., 2000, Oertel et al., 2000, Kalluri and Delgutte, 2003b, a). It has been particularly challenging to model the combination of enhanced synchronization and other physiologically observed properties (entrainment, spontaneous rate, shape of poststimulus time histograms at higher frequencies, etc.) while at the same time maintaining realistic physiological and anatomical parameters. While coincidence detection is a common ingredient in most GBC models, its exact biological implementation is not entirely clear yet (Rothman and Young, 1996, Spirou et al., 2005).

The presence of high-sync responses in GBCs is functionally important in several ways. GBCs provide, via the MNTB, highly phase-locked inhibition to the LSO (Smith et al., 1991, Smith et al., 1998), and low-frequency LSO neurons are indeed sensitive to interaural time differences (ITDs) of low-frequency sounds (Finlayson and Caspary, 1991, Joris and Yin, 1995, Tollin and Yin, 2005). Second, this inhibition is also supplied to the MSO (Spangler et al., 1985, Adams and Mugnaini, 1990, Smith, 1995, Smith et al., 1998), and there is evidence that it influences ITD-processing in this nucleus (Grothe and Sanes, 1994, Brand et al., 2002). The MNTB is predominantly a high-frequency nucleus (Guinan et al., 1972, Tsuchitani, 1977). Because GBCs also phase-lock to the stimulus envelope (Rhode and Greenberg, 1994, Joris

and Yin, 1998), they provide, again via the MTNB, inhibition which is phase-locked to envelopes, so that the LSO is sensitive to ITDs of the envelope of high-frequency sounds (Joris and Yin, 1995, Batra et al., 1997). Sound envelopes carry important information not only regarding sound position in space but also regarding sound identity: study of responses to stimulus envelopes is thus interesting not only from a binaural but even more from a monaural viewpoint. Furthermore, such responses also bear on the proposed mechanisms of coincidence detection. Before turning to enhanced synchronization in SBCs, we pause to examine similarities in enhanced phase-locking to fine-structure and envelope.

GBCs with CFs just above the range of phase-locking are an interesting test case of coincidence detection (Joris et al., 1994b). In principle, coincidences among the spike trains of inputs to CN neurons, at the millisecond time scale of interest here, can be affected by 1) intrinsic correlations in firing between AN fibers, e.g. of fibers innervating the same inner hair cell, 2) phase-locking to the fine-structure of the sound, 3) phase-locking to the envelope of the sound or the local cochlear vibration pattern. As far as known, source 1 (Fig. 2A) is not present and is not further considered here, though admittedly absence of evidence here does not constitute evidence of absence (Johnson and Kiang, 1976, Kiang, 1990)(Young and Sachs, this issue 2008). Sources 2 and 3 are stimulus-induced (Fig. 2D) and can thus be manipulated by the experimenter. Source 2 is not present for pure tones above the range of pure-tone phase-locking, i.e. a few kHz in mammals (Fig. 2C). Source 3 is not present for unmodulated pure tones or at high rates of amplitude modulation, if we only consider the ongoing part of the response and ignore effects of onset and offset of the stimulus.

For GBC neurons with a CF above a few kHz, pure tones above the phase-locking limit generate AN input spike trains that are random relative to each other. In fact, such tones are the only stimulus for which spike trains evoked in the AN inputs to the GBC neuron are mutually random. If the GBC neuron is a coincidence detector, its firing rate should increase by increasing the correlation among the inputs to the neuron. A first way to achieve this is to increase the stimulus level. In response to a high-frequency tone, chance occurrences of coincidences across inputs elicit output spikes in the GBC neuron (Fig. 2C). An increase in sound level generates an increased firing rate in the AN fibers, and thus also an increased firing rate in the GBC because the number of chance coincidences increases. A second way to increase the correlation among the inputs is to lower the tone frequency to the range of phase-locking (Fig. 2D). Indeed, lowering the tone to frequencies in the “tail” of the tuning curve that generate phase-locking, causes an increase in firing rate of GBC neurons accompanied by exquisite phase-locking and entrainment (Joris et al., 1994b). This behavior can be modeled with a coincidence operation (Rothman and Young, 1996). Note that lowering the stimulus frequency causes these increased firing rates in the GBC neurons even though their AN inputs, which are presumably tuned to the same CF, show decreased firing rates under these circumstances. A third way to increase the correlation among the inputs is amplitude modulation of a tone (Fig. 2D), even when the spectral components of the stimulus are outside the range of phase-locking to fine-structure. Within certain limits (Joris and Yin, 1992) amplitude modulation causes temporal alignment of spikes across AN fibers, and should therefore increase the number of coincidences driving the postsynaptic GBC neuron.

Fig. 3 shows responses of a neuron recorded ventrally in the SOC with a CF of 2.4 kHz (see legend regarding the identity of this neuron). The response rate to pure tones at its CF (2.4 kHz, panel C) is moderate, from a spontaneous rate of 4 spikes/s to a maximum of 125 spikes/s to short tone bursts and even lower to the 1 s tones shown in Fig. 3C (35 spikes/s). As already discussed, lowering the frequency of a pure tone causes a dramatic increase in firing rate, with high synchronization and entrainment. The panels of the middle and right column show very similar behavior to amplitude modulation. For example, when a 2.4 kHz carrier tone is modulated at 410 Hz, its spectral components are in a range (see circle and bar “Z” in panel

A) where pure-tone phase-locking and high firing rates are absent for tones presented individually. The amplitude modulation causes a tremendous increase in firing rate with high synchronization (panel F) and entrainment (panel G). Similar behavior is observed for a carrier frequency of 1.5 kHz (middle column). This is in sharp contrast to the responses of AN fibers, which show little change in firing rate with variations in modulation frequency or modulation depth (Joris and Yin, 1992). The similarity in firing rates of the responses to pure tones and to amplitude modulation, over the common range of frequencies (100 – 1000 Hz), is particularly striking.

These responses illustrate how the temporal spike patterns in the AN can be transformed at the earliest stages of the central auditory system into a rate code. Stimuli with different spectrum but the same periodicity can give rise to firing rates equaling this periodicity. It will be interesting to examine how invariant such responses are for spectrum, using stimuli that are more amenable to parametric manipulation (Cariani and Delgutte, 1996a, b, Wiegrebe and Winter, 2001).

The puzzle of enhanced synchronization in spherical bushy cells

SBCs are the most numerous projection neurons of the CN (Osen, 1970) and provide the excitatory input to MSO neurons. Sensitivity to ITDs in MSO neurons is the premier example of temporal sensitivity in the mammalian central nervous system, and it is therefore important to understand the temporal behavior of SBC neurons. While monaural coincidence detection may be an adequate model for enhanced synchronization and entrainment in globular bushy neurons and other CN neurons with many AN inputs, it is problematic for SBCs. First, we review the evidence that SBCs show enhanced phase-locking.

Out of 7 intra-axonally labeled low-frequency TB fibers with high-sync behavior, two appeared to be axons of SBCs; the other 5 were axons of GBCs (Joris et al., 1994a). The physiology for one labeled spherical bushy neuron is shown in Fig. 1, the anatomy and physiology of the other labeled neuron is shown in Fig. 5 of Smith et al. (1993). The cell body was not recovered in those two cases but the morphological class was inferred based on the main projection targets (MSO for SBCs; MNTB for GBCs). While the morphological classification of these two neurons is thus indirect, the observation that the direct projection from the CN to MSO is purely derived from SBCs (Cant and Casseday, 1986) leaves little room for doubt. Similarly, the presence of a labeled calyx of Held in the MNTB in the other 5 high-sync neurons shows that these axons were from GBCs. Thus, even though the number of labeled high-sync neurons is very small, the data strongly suggest that both spherical and globular bushy neurons display this behavior.

There are other, more indirect, indications that both groups of neurons show enhanced synchronization. Recordings in the TB of the cat show a paucity of responses with VS values in the range of the AN (Joris et al., 1994a, Louage et al., 2005), suggesting that the bulk of low-frequency inputs to the binaural nuclei is synchronized more strongly than the AN. Also, some of the high-sync TB fibers have high spontaneous rates. For CFs in the phase-locking range, low and high spontaneous rates are rather strongly associated with GBCs and SBCs, respectively (Spirou et al., 1990, Joris et al., 1994a), again suggesting that both GBCs and SBCs contribute high-sync responses. However, there are also reasons to doubt that these TB recordings give the full picture. Extensive AVCN recordings by Rose and colleagues did not reveal high-sync neurons (there is brief mention of the phenomenon in Rose et al., 1974, but no supporting data are shown). Likewise, several population studies of the VCN reported no or few high-sync neurons (Bourk, 1976, Blackburn and Sachs, 1989, Winter and Palmer, 1990). Possible reasons for this discrepancy between studies of the AVCN and studies of its output tract have been given earlier (Joris et al., 1994a). The most straightforward explanation

is recording bias: strongly phase-locked field potentials in the AVCN hamper spike isolation with traditional metal electrodes, while this is not a problem for axonal recordings with micropipettes in the TB. Field potentials are also absent when using high-impedance micropipettes in the AVCN, and such recordings indeed reveal high-sync GBC neurons (Rhode, this issue 2008). On the other hand, there is a clear bias towards recording from thicker axons in the TB and the axons of SBCs are thinner in diameter than those of GBCs. Possibly a combination of these factors explains why high-sync phase-locking has been much less reported in units from the AVCN than from its output tract. Taken together, the available data show that both kinds of bushy cells can show enhanced synchronization but the prevalence of this behavior is unclear. It is interesting to note that at higher CFs there is a clear difference between SBCs and GBCs: only the latter show enhanced synchronization when stimulated in their low-frequency tail (Joris et al., 1994b). Diversity in phase-locking behavior in SBCs, and the respective roles of pre- and postsynaptic factors (Sento and Ryugo, 1989, Cant, 1991, Cao et al., 2007), are interesting topics in themselves.

Neurons in the spherical cell area have only between 1-4 inputs. This number is derived from morphological observations after bulk tracer injections in the AN (Ryugo and Sento, 1991); from quantitative comparison of AN endbulbs and SBC counts (Melcher, 1993); and from EM observations (Nicol and Walmsley, 2002). At least for the cat, 4 inputs seems already on the high side and the modal number of endbulb inputs is probably 2 (Ryugo and Sento, 1991).

In summary, the available evidence suggests that SBCs with a small number of large inputs show the high-sync phenomenon. Can enhanced synchronization and entrainment be obtained with few, suprathreshold inputs? In a dynamic clamp study of bushy cells in slices of the mouse AVCN (Xu-Friedman and Regehr, 2005b, a), the effect was studied of the number of simulated active inputs as well as the shape of their temporal input distribution (Gaussian or alpha) on the jitter and reliability of the postsynaptic response. Again, jitter became smaller with an increasing number of inputs. Interestingly, for alpha-distributed inputs jitter reduction was achieved with even a small number of suprathreshold inputs. This occurs through a “first-come-only-served” kind of mechanism: the first arriving suprathreshold input triggers the postsynaptic neuron. Similar reductions in jitter are present in the simulations of Rothman and colleagues (Rothman and Young, 1996, Rothman and Manis, 2003) but require a large number of inputs (≥ 10), which is not realistic for SBCs. Examination of real AN spike trains shows that patterns as observed in the SBC of Fig. 1 can not be obtained from a combination of few suprathreshold inputs. This is illustrated by a simple simulation (Louage, van der Heijden, Joris, unpublished) on actual AN responses. Two or 3 spike trains from a single AN fiber were combined into a single new spike train (mimicking convergence on a SBC neuron), and a sliding window was then applied to impose refractoriness. When this is repeated for random combinations of spike trains from the same AN fiber (e.g. combinations of 3 spike trains drawn from the 50 spike trains shown in Fig. 1B), the resulting simulated SBC output shows no or at best a modest increase in VS. In fact, it seems unlikely that spike trains as in Fig. 1C can be obtained by any combination of 2 or 3 spike trains from Fig. 1B: there simply are not enough input spikes to generate both higher VS and entrainment.

Again, it is important to point out that it has not been shown directly that SBCs with few inputs display high-sync behavior. A direct demonstration would require an anatomical reconstruction of the number of AN inputs on a SBC neuron with known high-sync physiology. Ideally, such an SBC neuron should be anatomically labeled in its entirety (both cell body and dendrites and all axonal branches) and its inputs should be determined with electron microscopy (Nicol and Walmsley, 2002, Satzler et al., 2002, Hoffpauir et al., 2007). New tracing, reconstruction, and recording methodologies (Helmchen and Denk, 2005, Briggman and Denk, 2006, Hoffpauir et al., 2007, Wickersham et al., 2007) offer hope that such feats will be within reach. If indeed

SBCs with few inputs display high-sync behavior, a rethinking of synaptic and cellular mechanisms of coincidence detection will be in order.

Perhaps the most plausible scenario for high-sync responses in SBCs is mentioned in the discussion of Rothman and Young (1996). These authors performed simulations where a mixture of few (even a single) suprathreshold AN input(s) in combination with a large number (19-49) of subthreshold inputs produce enhanced phase-locking. Bouton terminals and even axodendritic synapses from endbulbs of AN fibers on SBCs have been described (Cant and Morest, 1979, Liberman, 1991, Ryugo and Sento, 1991) and could be the substrate providing the subthreshold inputs. Cross-correlational analysis between AN fibers and high-frequency SBCs are in line with this proposal (Young and Sachs, this issue 2008).

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Abbreviations

- AN**
auditory nerve
- AVCN**

	anteroventral cochlear nucleus
CF	characteristic frequency
CN	cochlear nucleus
DMPO	
GBC	globular bushy cell
ITD	interaural time difference
LSO	lateral superior olive
LNTB	lateral nucleus of the trapezoid body
MNTB	medial nucleus of the trapezoid body
MSO	medial superior olive
SBC	spherical bushy cell
SOC	superior olivary complex
TB	trapezoid body
VCN	ventral cochlear nucleus
VNLL	ventral nucleus of the lateral lemniscus
VS	vector strength

Fig. 1.

Phase-locking and its enhancement. A: frequency threshold tuning curves for a fiber recorded in the auditory nerve (AN: with lowest thresholds) and one in the trapezoid body (TB). The TB fiber is one of 2 labeled high-sync spherical bushy cells (SBC) in Smith et al. (1993). The solid circle indicates CF and threshold for the AN fiber and the stimulus level and frequency for the responses in panels B, D, F. The empty circle indicates CF and threshold for the SBC and the stimulus level and frequency for its responses in the lower row of panels. B,C: dot rasters of responses to 50 repetitions to short (25 ms) tones at the CF (670 Hz). Red dots indicate coincidences across the 50 spike trains within a 50 μ s window, i.e. if a pair of spikes differs 50 μ s or less in spiketime, both spike occurrences are colored red. Conversely, a black mark

means that there is no other spike within 50 μ s in any of the other spiketrains. D,E: period or cycle histograms of responses to 100 repetitions as in B,C. The data are also shown in polar form. The magnitude (VS) is 0.64 for the AN fiber and 0.93 for the SBC (average phase is 0.64 and 0.84 cycles, respectively). The total number of spikes in these histograms is 667 (AN fiber) and 1775 (SBC). The period histograms are on the same scale, but not the polar plots, where the outer circle indicates instantaneous rates of 1000 and 6000 spikes/sec. F,G: inter-spike intervals of the response over the same 10-25 ms window. The dots under the abscissa indicate integer multiples of the stimulus period. To remove onset effects, the period (D,E) and inter spike interval (F,G) histograms are for a 10-25 ms response window; the number of bins is always 100 and the scales of the axes are identical for AN and SBC responses. The average spike rate was 233 spikes/s (AN) and 474 spikes/s (SBC). Spontaneous rate was 90 spikes/s (AN) and 175 spikes/s (SBC). The maximal entrainment index (Joris et al., 1994a) was 0.34 (AN) and 0.91 (SBC).

Fig. 2.

Factors that potentially affect the number of coincident spikes. Depicted are 3 AN fibers converging on a CN neuron that acts as a coincidence detector. The arrangement in A and B, where these afferents also innervate a single inner hair cell, is hypothetical. For ease of presentation, action potentials (red if coincident) are depicted on axons as if these were timelines. A: intrinsic coincidences reflect a structural feature (e.g. collaterals from the same fiber, innervation of the same hair cell) rather than coincidences arising from coupling to the stimulus. B: in the absence of intrinsic coincidences, chance coincidences are still possible. C: in response to a high-frequency tone, there is no coupling of spikes to the fine-structure of the stimulus and the probability of coincidences in the afferents is small. D: in response to low-frequency tones or amplitude-modulated (AM) tones which cause coupling of the spikes to the stimulus, a higher number of coincidences is obtained, leading to a high rate of output spikes that are strongly phase-locked to the stimulus.

Fig. 3.

Example of enhanced phase-locking to pure tones and to the envelope of amplitude-modulated tones. A: threshold tuning curve (2 runs). B,C: responses to pure tones, 1 second in duration, over a range of frequencies and SPLs. D-G: responses to amplitude-modulated tones, 600 ms in duration, over a range of frequencies and SPLs. The bottom row shows average firing rates (C,E,G). The middle row (B,D,F) shows strength of phase-locking. The cycle histograms for 3 data points, indicated with the arrows in panels B-G, are shown in top panels X,Y,Z. The stimulus frequencies and levels are also indicated in panel A. The dashed line in the bottom panels indicates equality between response rate in spikes/s and stimulus frequency (in Hz). The abscissa scale is the same for all main panels. The small panels (top right, X-Z) show period

histograms for a pure tone of 400 Hz (60 dB) and for amplitude modulation with envelope frequency $f_m = 410$ Hz and carrier $f_c = 1.5$ kHz (panel Y) or 2.4 kHz (panel X) at 50 dB. The topmost histogram shows the post-stimulus time histogram to a 25 ms, 60 dB tone at the CF of 2.4 kHz.

There is uncertainty regarding the identity of this neuron. Spikes were monopolar and were recorded ipsilateral to the driving ear at a depth of 3.6 mm in the TB/SOC with a 4 M Ω tungsten electrode (Thomas recording, Giessen, Germany) which has the ability to record from axons. The location was just dorsolateral of the MSO at a position agreeing with the tonotopic map of this nucleus (Guinan et al., 1972). Although the physiological responses are monaural and “GBC-like” in several respects, the response to short tone bursts had an onset latency of 4.7 ms and notch duration of 2 ms, which are rather high for a 2.4 kHz GBC neuron; the responses to envelope modulation differ from a previous sample of GBC neurons (Joris and Yin, 1998); and the recording was remarkably stable for many hours. Possibly the responses were derived from an SOC neuron receiving GBC input (e.g. from the lateral nucleus of the trapezoid body, Cant and Hyson, 1992). Whether GBC or SOC neuron, the reasoning regarding the mechanisms of the increase in firing rate for pure tones and amplitude modulation remains the same, but possibly the responses reflect two stages of coincidence detection (one operating in the CN on AN fibers, one operating in the SOC on GBC fibers).