compared to the cerebellum were estimated using a simplified reference region model.12,13 The model derives BP from the ratio of the volumes of distribution of the ligand in the striatum relative to the cerebellum. BP is a composite function of parameters, as follows:

\[ BP = \frac{f_1 \cdot B_{\text{max}}}{K_{\text{D,free}}} \cdot \frac{1 + \sum F_i}{1 + \sum K_{i}} \]

where \( K_{\text{D,free}} \) is the total concentration of specific binding sites, \( K_{\text{D,free}} \) is the equilibrium dissociation constant of the ligand, \( f_1 \) is the ‘free fraction’ of unbound ligand in the tissue, and \( F_i \) and \( K_{i} \) are the concentrations and equilibrium dissociation constants, respectively, of \( i \) competing endogenous ligands. Changes in BP are attributed to changes in \( F_i \) for endogenous dopamine. Striatal ROIs were outlined on an add-image of summed time frames, using an edge-fitting algorithm set at a fixed threshold (40%) of the image maximum. The ventral (comprising the ventral half of the putamen) and dorsal (comprising the dorsal half of the putamen and the body of the caudate nucleus) striata were operationally defined. The cerebellum was defined by cluster analysis16. BP and R1 values were calculated for the striatal ROIs using the TACs for \([^{11}C]\)RAC binding up to 50 min after injection.17 Differences in \([^{11}C]\)RAC binding at baseline and during the task were tested with repeated-measure ANOVA, with three within-subject factors (task versus baseline, left versus right hemisphere and dorsal versus ventral striatum). Spearman rank correlation coefficients were calculated for the relationship between changes in \([^{11}C]\)RAC-BP and performance level during the game for each ROI.

SPM analysis. Parametric images of \([^{11}C]\)RAC-BP18 were analysed using SPM96 (ref. 21). The \([^{11}C]\)RAC-R images were used to define the stereotactic transformation parameters for the \([^{11}C]\)RAC-BP images. Contrasts of the condition effects at each voxel of the \([^{11}C]\)RAC-BP images were assessed using the t-value, with the highest performance level entered as a covariate of interest, giving a statistical image for each contrast.

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The role of dendrites in auditory coincidence detection

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Coincidence-detector neurons in the auditory brainstem of mammals and birds use interaural time differences to localize sounds1–2. Each neuron receives many narrow-band inputs from both ears and compares the time of arrival of the inputs with an accuracy of 10–100 μs (refs 3–6). Neurons that receive low-frequency auditory inputs (up to about 2 kHz) have bipolar dendrites, and each dendrite receives inputs from only one ear2. Using a simple model that mimics the essence of the known electrophysiology and geometry of these cells, we show here that dendrites improve the coincidence-detection properties of the cells. The biophysical mechanism for this improvement is based on the nonlinear summation of excitatory inputs in each of the dendrites and the use of each dendrite as a current sink for inputs to the other dendrite. This is a rare case in which the contribution of dendrites to the known computation of a neuron may be understood. Our results show that, in these neurons, the cell morphology and the spatial distribution of the inputs enrich the computational power of these neurons beyond that expected from ‘point neurons’ (model neurons lacking dendrites).

Over the past 40 years it has become widely accepted that dendrites play a major role in neuronal computation7. Despite intensive efforts to decipher this role8–10, however, the contribution of the dendrites to the function of the single neuron remains elusive. Nevertheless, the existence of different dendritic geometries and their plausible effect on computation have been used as evidence for dendritic computation11,12. As analysis of dendritic computation is most powerful when the role of the neuron is understood, we used brainstem auditory coincidence detectors to demonstrate the computational advantages of having synaptic inputs on the dendrites rather than on the cell body.

Coincidence detectors of the auditory brainstem are binaural neurons that respond maximally when they receive simultaneous inputs from the two ears. This condition is met when delay line inputs from each ear exactly compensate for a delay introduced by the computational power of these neurons beyond that expected from 'point neurons' (model neurons lacking dendrites).

Received 23 September 1997; accepted 20 March 1998.


Acknowledgements. M.K. was supported by a grant from the Theodore and Vada Stanley Foundation Research Program; R.N.G., V.J.C., D.B. and P.M.G. were supported by the Medical Research Council, and A.D.L. was supported by a fellowship from the British Brain and Spine Foundation. We thank P. Dayan and I. Farde for discussions and comments on the manuscript, and K. Friston, A. Holmes and J. Ashburner for statistical advice and help with the SPM analysis.

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two ears)\(^1\)–\(^4\). These coincidence-detecting neurons are particularly suitable for an analysis of dendritic function. First, they have stereotyped bipolar dendrites (Fig. 1a)\(^7\),\(^8\). Second, the inputs from each ear are segregated on the dendrites, with inputs from the ipsilateral ear terminating on the dorsal dendrites and inputs from the contralateral ear on the ventral dendrites\(^7\),\(^8\). Third, the length of the dendrites increases with decreasing best frequency of the sound stimulus in the chick\(^7\)–\(^18\) (Fig. 1a), suggesting a computational role for the dendrites. Fourth, the electrophysiological properties of these neurons have been well characterized\(^19\),\(^20\). As is appropriate for timing devices, these coincidence detectors do not respond to slowly varying inputs and fire one or few spikes in response to a step current injection (Fig. 1c).

We used data from the neurons of the ITD circuit to construct a minimal biophysical model that mimicked the essential properties of the coincidence detectors (Fig. 1b, c; see Methods)\(^4\),\(^19\)–\(^22\). This model, like earlier models\(^23\)–\(^26\), detected coincidences when inputs from both ears arrived directly at its soma (Fig. 1d). In the present model, however, we were able to investigate the contribution of dendrites. We modelled two simple dendrites as unbranched cables (electronic length, 0.2\(\lambda\)), on the basis of measured dendritic lengths and the biophysical properties of the coincidence detectors (see Methods)\(^7\),\(^20\). The model cell received 12 inputs, 6 from each ear. In some cases, all 12 inputs were located on the soma, and in other cases, all 6 inputs from the left ear were located on one dendrite, 0.1\(\lambda\) from the soma, and all 6 from the right ear on the other dendrite (Fig. 2a). The inputs were phase-locked (Fig. 2b; see Methods).

When a sound moves around the head, there is a phase shift between the two ears, and the response of the coincidence detector varies in cyclic fashion between best ITD (maximum) and worst ITD (minimum; Fig. 1d and 2c). Any mechanism that increases the maximum and at same time decreases the minimum of these ITD plots improves the detection of sound localization. Indeed, in model ITD plots, the contrast between the maximal and minimal spike rates was greater when the inputs from each ear were segregated and located on the dendrites (Fig. 2c). This improvement in coincidence detection produced by locating the inputs on the dendrites was robust\(^6\). We showed this by changing the single (unitary) synaptic conductance (USC) as a parameter for several different input configurations, as maximal and minimal spike rates also depended upon USC amplitude (Fig. 2d). For each configuration, maximum and minimum spike rates increased with increasing synaptic conductance. Best coincidence detection (Fig. 2d, dotted line) was achieved when the inputs were segregated on the dendrites, and when the dendrites were thin (see Methods).

This improvement in ITD coding is based on local computation at the dendrites. In general, synaptic inputs sum nonlinearly,
because the driving force for excitatory synaptic currents decreases with depolarization. Hence, the net synaptic current from several inputs arriving simultaneously at nearby sites on the same dendrite is smaller than the current generated if these inputs arrive at different dendrites. Figure 3a illustrates how the segregation helps to improve coincidence detection. Thus, the conductance threshold, or minimum synaptic conductance needed to trigger a somatic action potential, is higher when the synaptic events are on the same dendrite, compared with when they are split between the bipolar dendrites. In the bipolar model, when the inputs are segregated and the phase shift is 0°, inputs arrive simultaneously at both dendrites and it is comparably easy to generate an action potential. When the phase shift is 180°, at every half cycle inputs arrive on only one dendrite and the conductance threshold is large. In the point neuron, however, the conductance threshold does not vary when the phase shifts are 0° and 180°. Thus, the difference between the firing rates in the 0° and the 180° phase shift cases is larger for the bipolar neuron with segregated inputs than for the point neuron.

Action-potential thresholds depended on whether the inputs were on the cell body or the dendrites (Fig. 3b). We used the concept of conductance threshold to explain the difference between segregated and non-segregated inputs. For each model configuration, points above the curve represent combinations of supra-threshold synaptic inputs from left (g_L) and right (g_R) ears. When binaural inputs arrive at the same location, action potentials fire when g_L + g_R is larger than a fixed conductance threshold (Fig. 3b, straight dashed line). Conductance-threshold plots are not linear when the inputs from each ear are segregated on different dendrites. We used the biophysical model to calculate these thresholds and show that the conductance threshold (g_L + g_R) for equally distributed inputs (g_L = g_R, points I and II in Fig. 3b) is smaller than the threshold (g_Th) for inputs arriving from only one side (g_L = 0 or g_R = 0; points III and IV). Thus, the model cell was most likely to fire action potentials when stimulated by coincident inputs from each ear.

As dendritic length varied with best frequency in the chicken, we also investigated the effects of stimulus frequency and dendritic length on coincidence detection. The performance of the model (Fig. 2d) deteriorated with inputs of higher frequencies (Fig. 3c; the curves for higher frequencies were to the left of those of lower frequencies, reflecting poorer coincidence detection). Furthermore, at higher frequencies the contrast between the maximum and minimum spike rates did not change much when the inputs were on the dendrites. The main reason for the reduction in dendritic advantage at higher stimulus frequencies was input jitter. At higher frequencies, jitter resulted in an overlap in time between inputs from both ears, even when there was a 180° phase shift between them. The effect of this overlap on the conductance threshold was comparably large when the inputs were on the dendrites; even a small ‘erroneous’ input from one ear significantly lowered the conductance threshold for the inputs from the other ear (compare, for example, points III and V in Fig. 3b). As a result, at high frequencies the firing rate in the 180° mode could be even larger than in the somatic model, making the dendrites a burden instead of an advantage. This prediction of a negligible dendritic length required to detect higher frequencies conforms to the observation of short dendrites on high-frequency-coincidence detectors in chickens.

From this analysis, we understood that in the presence of jitter,
severe nonlinear summation is a disadvantage. With long dendrites, larger voltages were required at the dendritic site to trigger a spike at the soma, as the opposite dendrite served as a current sink and the voltage gradient from the dendritic site to the soma was steeper. As a result, the summation of inputs at the dendritic site was more nonlinear than for shorter dendrites, and could worsen the coincidence detection at high stimulus frequencies. For example, when \( f_{\text{stim}} = 500 \text{ Hz} \), the best coincidence detection occurred when the dendrites were about 0.4 \( \lambda \) each, whereas optimal dendritic lengths were shorter for higher frequencies.

A simple bipolar integrate-and-fire model that retained the biophysical model’s essential features improved our understanding of how the nonlinear summation on bipolar dendrites enhances coincidence detection and why the optimal dendritic length was shorter for higher frequencies. Suppose that, within a given stimulus cycle, left-ear afferents evoked a net synaptic input conductance \( g_\text{L} \) and right-ear afferents evoked \( g_\text{R} \). In response, the neuron fired with probability \( P(g_\text{L}, g_\text{R}) \). If the afferent inputs arrived at a single site and if the noise-free neuron had a sharp fixed threshold, then \( P = 1 \) if \( g_\text{L} + g_\text{R} \geq g_{\text{th}} \) and \( P = 0 \) otherwise, where \( g_{\text{th}} \) is the conductance threshold at this input site. When the inputs were segregated on the bipolar dendrites, the nonlinear integration of inputs seen in the biophysical model could be mimicked by using the condition \( g_{\text{L}} + g_{\text{R}} \geq g_{\text{th},b} \), where \( \alpha \leq 1 \) depended on the nonlinear integration at the dendrites (Fig. 3b).

Assuming \( n \) afferents from each ear, and independence between synaptic events in different stimulus cycles and in different input trains, the probability, \( b_{in} \), that \( i \) synaptic events were delivered by one ear’s afferents in a stimulus cycle could be approximated using a binomial distribution. We calculated the probability for postsynaptic firing in a stimulus cycle when there is no phase shift between the left and right inputs \( (P_0) \) and when the binaural phase shift is \( 180^\circ \) \( (P_{180}) \); these probabilities depend on \( g_{\text{syn}} \), the USC (see Methods). The cell’s mean firing rate is \( P_{0,\text{stim}} \) for the 0° phase shift case and \( P_{180,\text{stim}} \) for the 180° case. This simple analytical model yields results in qualitative agreement with those from our minimal biophysical model (Fig. 4a). It embodies the combined essential effects due to randomness in the number of the synaptic events per cycle and the nonlinear integration caused by the spatial distribution of the afferents.

The role of jitter was demonstrated in the integrate-and-fire model by a simple modification. We assumed that in the 180° phase shift case, a fraction, \( \beta \), of the input conductance from one ear might shift in the integration of the inputs from the other ear (see Methods). Analysis of the input trains of the biophysical model showed that \( \beta \) is comparably small for \( f_{\text{stim}} \approx 500 \text{ Hz} \), whereas it can approach 0.4 when \( f_{\text{stim}} = 1,000 \text{ Hz} \). In this modified model, coincidence detection was worse at higher frequencies, and the dendritic advantage was diminished (Fig. 4b). Without considering jitter \( (\beta \approx 0 \text{ for all frequencies}) \), putting inputs on dendrites \( (\alpha < 1) \) was advantageous even at high frequencies. Using the modified model it was easy to demonstrate that when \( \beta \) was non-zero, there was an optimal \( \alpha \) for best coincidence detection (Fig. 4c). As longer dendrites have smaller values of \( \alpha \), there is an optimal dendritic length for each frequency, and this optimal length decreases with higher frequencies. These predictions match the changes in dendritic length observed in the chicken coincidence detectors (Fig. 1a).

We have shown how dendrites improve coincidence detection in the cells of the auditory brainstem, using basic biophysical mechanisms to explain their computational role. One mechanism is the segregation of the inputs on the dendrites, allowing nonlinear integration between the inputs from left and right ears. The second mechanism is a modulation of the nonlinearity of the integration by using the dendrites as current sinks for each other. The computational module isolated in the auditory coincidence detectors might be used in other neurons with branched dendritic trees, perhaps as part of a more complex computation. For example, in cortical neurons, the segregation of inputs on the two main branches of the pyramidal-cell apical tree might use a similar computational module, with the same biophysical mechanism as the brainstem auditory cells. The segregation of inputs on the many basal dendrites might also be involved in such a mechanism. The investigation of other cells with known functions could yield a set of plausible ‘computational building blocks’ that might help to decipher the dendritic code in more complex cells with unknown functions.

**Methods**

**Point-neuron model.** Data from nucleus magnocellularis and nucleus laminaris cells were used to construct the model, which mimicked the properties of coincidence detectors, including phase-locking to about 1.5 kHz to 2.2 kHz. The fast potassium currents \( (\tau < 1 \text{ ms}) \) that repolarize the cell were modeled, whereas slow potassium currents \( (\tau > 10 \text{ ms}) \) were substituted by a steady-state conductance. The model equations were Morris–Lecar type:

\[
\frac{dV}{dt} = \left( -\frac{1}{C_m}g_{\text{Na}}m(V)V - V_s + g_{\text{K}}(V - V_K) + g_{\text{L}}w(V - V_c) + g_{\nu}(V - V_L) \right) - \frac{1}{C_m}w(V - \nu(V))w(V) + I \]

\[
dw/dt = \delta\left(w(V) - w(V_{\text{th}})\right) \]

where \( C_m = 0.0147 \text{ nF}, g_{\text{Na}} = 33 \text{ nS}, V_s = 20 \text{ mV}, V_{\text{th}} = 0 \text{ mV}, g_{\text{K}} = 237 \text{ nS}, V_K = -70 \text{ mV}, g_{\text{L}} = 7 \text{ nS}, V_c = -62.5 \text{ mV}, w_{\text{th}}(V) = 1[1 + \exp(V - V_c)/V_c], \nu(V) = 1[1 + \exp(V - V_L)/V_L], \quad \tau_w(V) = 1/k(w(V) - w(V_{\text{th}})).

**Figure 4** Bipolar integrate-and-fire model. a. Contrast enhancement in the integrate-and-fire model demonstrated with parametric plots for different input configurations (as in the biophysical model; Fig. 2d). We assumed 12 input lines, 6 from each side; \( f_{\text{stim}} = 600 \text{ Hz} \) and \( f_{\text{syn}} = 350 \text{ Hz} \). b. The effect of jitter on coincidence detection for various frequencies is demonstrated in the modified integrate-and-fire model. \( \beta = 0 \) for 600 Hz, 0.15 for 750 Hz, and 0.3 for 1000 Hz. The dendritic \( (\alpha = 0.5) \) case for 750 Hz with \( \beta = 0 \) is also shown. c. The effect of \( \alpha \) on coincidence detection in the modified integrate-and-fire model. \( f_{\text{stim}} = 750 \text{ Hz}, \beta = 0.15 \). The optimal coincidence-detection properties are found here for \( \alpha = 0.6 \). For \( \alpha = 0.2 \), coincidence detection is worse than for \( \alpha = 1 \), reflecting the loss of dendritic advantage.
V, V_e), and, in mV, V_1 = -42.5, V_2 = -1, V_3 = -43.0, V_4 = -4, V_5 = -60.0, and V_6 = 64. Simulation results were obtained by numerical integration of differential equations over 10 s.

**Bipolar-neuron model.** See Fig. 2a. The soma was the same as in the point-neuron model (20 μm diameter, R_soma = 135 MΩ); the dendritic diameter was either 4 μm (thick dendrites) or 2 μm (thin dendrites), with axial resistivity R_a = 200 Ω cm and membrane resistance R_m = 1,700 Ω cm². For a dendrite of diameter 4 μm, λ = 290 μm, whereas for a dendrite of diameter 2 μm, λ = 200 μm. Parameters were based on recordings from chicken coincidence detectors. Dendrites were modelled by 0.05-λ-connected compartments and had either active membrane (identical to the point neuron) or passive membrane (voltage-dependent conductances fixed to their resting values). Because synaptic inputs arrived at the cell in every cycle, it was insufficient to use a simple threshold function to recognize action potentials in the somatic response. We therefore added a long axon with a higher density of voltage-dependent conductances. We counted only action potentials that propagated.

**Synaptic input model.** See Fig. 2b. For every input train, at every stimulus cycle, the probability of an input arriving was defined as f_{pre}/f_{max} where f_{pre} was the stimulus frequency and f_{max} was the average spike rate of the input train. f_{pre} = 350 Hz for all stimulus frequencies. The stimulus cycles were regulated as independent events. To account for the jitter in the phase-locking of the inputs to the stimulus, measured by vector strength (VS)¹, we shifted each input in time from the beginning of the cycle by a random variable t_{shift} ~ N(0, σ) where σ = 1,000 μm, or 2 ln(VS)/2μm). For VS ≥ 0.2, this resulted in input trains with the required VS. Except in Fig. 1d, we used VS = 0.7. In Fig. 1d, VS = 0.8. Synaptic inputs were rectangular conductance changes, 0.4 ms wide.

**Bipolar integrate-and-fire model.** The probability that the coincidence-detector neuron would fire in a given stimulus cycle was assumed to be

\[ P(x_s, y_s) = \frac{1}{1 + \exp\left(-x_s - y_s\right)} \]

where \( x_s \) and \( y_s \) were the total synaptic input conductance during this cycle from the left and right ears, respectively. We used \( k = 0.05 \) and \( \tau_s = 1 \) (the positive parameter \( k \) determines the steepness of the sigmoid threshold function). With a sigmoid \( P(x_s, y_s) \) (rather than the condition \( x_s + y_s > g_s \), which is equivalent to the sigmoids function when \( k \) approaches 0), we approximately accounted for the effects of small intrinsic noise, jitter in a composite input, and a graded threshold for the spike-generating mechanism. The probability \( b_{pre} \) (see text) was calculated by

\[ b_{pre} = \int_{y_{min}}^{y_{max}} \int_{x_{min}}^{x_{max}} \frac{f_{pre}}{f_{max}} f_{pre} f_{max} \exp(-S) \, dx \, dy \]

where input combinations are summed with index \( i \) for the left side and index \( j \) for the right. On the other hand, if the binaural phase shift was 180°, the probability to fire during one cycle (that is, the probability that inputs from the left or the right ear will cause firing) was approximated by

\[ P_{ins} = 2 \sum_{i} b_{pre} P(g_{syn}, 0) \]

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