

# Instructed learning in the auditory localization pathway of the barn owl

Eric I. Knudsen

Department of Neurobiology, Stanford University School of Medicine, Stanford, California 94305, USA (e-mail: [eknudsen@stanford.edu](mailto:eknudsen@stanford.edu))

A bird sings and you turn to look at it — a process so automatic it seems simple. But is it? Our ability to localize the source of a sound relies on complex neural computations that translate auditory localization cues into representations of space. In barn owls, the visual system is important in teaching the auditory system how to translate cues. This example of instructed plasticity is highly quantifiable and demonstrates mechanisms and principles of learning that may be used widely throughout the central nervous system.

Our sense of auditory space derives from the associations we have formed between specific auditory cues and locations in the world that produce them. The dominant auditory localization cues are the relative timing and level of the sound at both ears. The central auditory system analyses these and other cues and associates particular values of these cues with locations in space. Although many animals can localize sounds soon after birth<sup>1,2</sup>, the exact relationships between cue values and locations in space are shaped and modified by experience<sup>3-5</sup>.

Because experience can alter sound localization, and because the pathways that mediate sound localization have been identified to a large extent, the auditory localization pathway has become a model system for studying mechanisms by which the nervous system learns from experience<sup>5-7</sup>. The most extensively studied species in this regard is the barn owl (*Tyto alba*), a nocturnal predator with a highly evolved capacity for sound localization which rivals that of humans<sup>8,9</sup>.

In barn owls, the pathways that process sound localization cues have been elaborated extensively, the tuning of neurons to localization cues is sharp, and the representation of auditory cue values in the brain is systematic<sup>10</sup>. These properties have enabled sensitive, quantitative assessment of experience-dependent plasticity in this species. Experimental manipulation of the owl's sensory experience has revealed functional, anatomical and pharmacological changes in the central auditory system that accompany behavioural learning. The results show an inherent advantage of innate neuronal connections over connections that are acquired with learning, a decline in learning with age, and an increased capacity for learning in adults that have had appropriate experience as juveniles. This review summarizes these findings and the mechanisms and principles that have been illuminated by them.

## Experience shapes auditory orienting behaviour

Sound localization cues result from the interaction of the head and ears with the incoming sound stimulus<sup>9,11</sup>. These

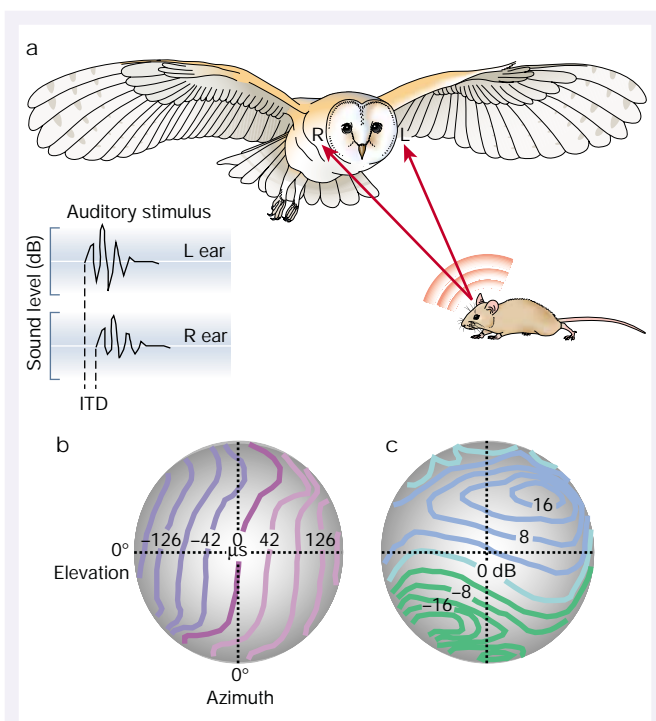


cues consist of interaural timing differences (ITDs), interaural level differences (ILDs) and the amplitude spectrum of the sound at each ear. ITD results from a difference in the distance that sound must travel to reach the near versus the far ear (Fig. 1a) and is the primary cue for the horizontal (azimuthal) location of a sound source (Fig. 1b). ILD and amplitude spectrum result from the frequency-dependent directional

properties of the head and ears. ILD, like ITD, varies with the azimuth of a stimulus, except in nocturnal owls such as the barn owl (Fig. 1c) for which ILD varies also with the elevation of a stimulus, owing to an asymmetry of the external ears. Amplitude spectrum has a complicated relationship with the horizontal and vertical locations of a sound source and contributes to localization in both azimuth and elevation.

To localize sound, the central nervous system (CNS) must measure the values of these cues and then associate particular cue values with the location in space that produces them. This task is complicated by the variation in the correspondence of cue values with locations in space across sound frequencies and across individuals, owing to differences in the size and shape of the head and ears. In addition, the neural representation of acoustic cues can change over the lifetime of an animal as a result of hearing loss and the development and ageing of the nervous system<sup>12</sup>.

It is not surprising, therefore, that the auditory system calibrates its interpretation of localization cues based on experience<sup>3-6</sup>. Adaptive adjustment of sound localization by barn owls has been demonstrated by subjecting owls to a variety of sensory manipulations and measuring the effects of those manipulations on the accuracy of auditory orienting behaviour, which is extremely precise in barn owls<sup>8</sup>. One class of manipulations has involved altering the correspondence of auditory cue values with locations in space by plugging one ear<sup>13,14</sup>. Initially, monaurally occluded owls, like monaurally occluded humans, mislocalize sounds towards the side of the open ear. But after many weeks of experience with an earplug, young owls recover accurate orienting responses despite the presence of the

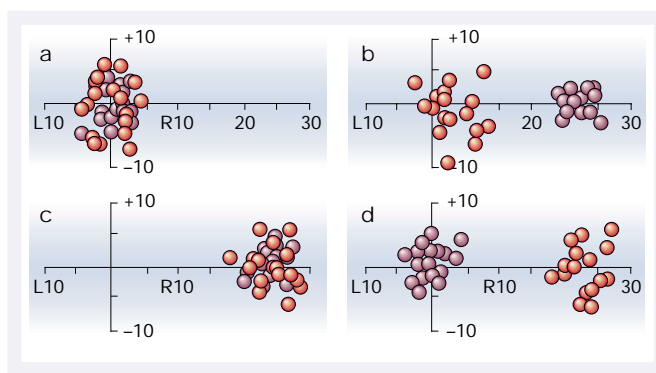


**Figure 1** The relationship between auditory cue values and locations in space for a barn owl. **a**, Sound waves generated by movements of a mouse are received by the owl's left and right ears. The sound waveform in the right ear (inset) is delayed and attenuated relative to that in the left ear. **b**, **c**, Correspondence of interaural timing difference (ITD, **b**) and interaural level difference (ILD, **c**) values with locations in space for 6-kHz sound. The globes represent space around the head relative to the line of sight (the eyes of a barn owl are nearly stationary). Contour lines indicate locations that produce equivalent values of each cue. For ITD values, purple indicates left ear leading and pink indicates right ear leading, while for ILD values, green indicates left ear greater and blue indicates right ear greater. The spatial patterns of ITD and ILD change with sound frequency. The strong dependence on elevation of the ILD cue results from a vertical asymmetry of the barn owl's ears. For animals with symmetrical ears, and for barn owls at frequencies below 4 kHz, the spatial patterns for ILD are approximately symmetrical about the mid-sagittal plane, as they are for ITD. Data are from ref. 23 and are based on probe-tube measurements from the external ear canals with sounds presented in a free field.

earplug. When the earplug is removed, the owls initially make orienting errors in the opposite direction, but these errors disappear gradually with normal experience. Thus, certain manipulations of hearing cause owls to learn new associations between auditory cue values and locations in space.

A second class of sensory manipulations has involved leaving auditory cues normal, but changing the locations in the visual field to which cue values correspond by exposing owls to a visual field that is displaced by prismatic spectacles<sup>15</sup>. Because owls cannot move their eyes by more than a few degrees, those wearing prisms must learn new associations between cue values and locations in the visual field in order to bring their auditory and visual worlds into mutual alignment. This is what young owls do. Over a period of many weeks, they adjust their auditory orienting responses according to the optical displacement imposed by the prisms (Fig. 2). This learning is adaptive because it causes these owls to orient to sounds so that they see the source of the sound through the prisms.

Prism experience also causes changes in other visually guided behaviours. Just as humans adjust reaching and throwing movements when wearing prisms<sup>16</sup>, owls adjust flight and strike behaviours<sup>17</sup>. Visuomotor adjustment occurs more rapidly than auditory-visual realignment and does not decline with age. Although the plasticity that underlies visuomotor adjustment is



**Figure 2** Plasticity of auditory orienting behaviour of a juvenile owl, resulting from prism experience. **a**, Before prisms; **b**, day 1 with visual field displaced 23° to the right by prismatic spectacles; **c**, day 42 with 23° prisms; **d**, prisms removed. Data points indicate final head orientation to auditory (red) or visual (purple) stimuli, presented in the dark, as measured with a search coil. Stimulus position was varied randomly. Responses are plotted relative to the true location of the stimulus source. Data are from ref. 72.

distinct<sup>18</sup>, the behavioural changes that result from these adjustments could help in driving auditory-visual realignment.

## Neural correlates of learning

### The auditory localization pathway

Neural correlates of behavioural learning are apparent in the auditory localization pathway (Fig. 3). The processing of auditory localization cues in the brainstem has been studied in a variety of species, and intensively in the barn owl. In all species, ITDs and ILDs are processed in parallel pathways and, because ITD and ILD depend on frequency, these cues are measured in frequency-specific channels<sup>10,19,20</sup>. Neurons that encode these frequency-specific cue values are organized according to their frequency tuning ('tonotopically') in the nuclei up to and including the level of the primary auditory field in the forebrain<sup>21,22</sup>.

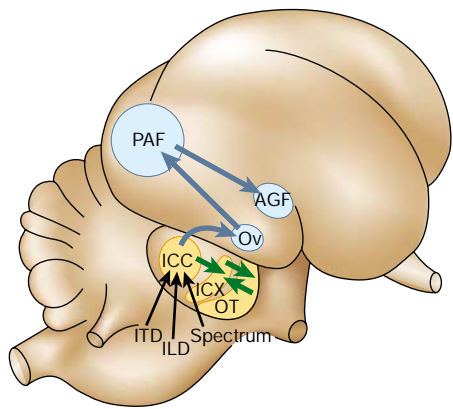
The information contained in a single, frequency-specific channel is spatially ambiguous (for example, a given value of ILD at 6 kHz can correspond to sounds from many different locations; Fig. 1c). Therefore, to transform the information about cues into an explicit representation of space, the auditory system integrates information across frequencies and across cues<sup>23</sup>, a process that occurs in parallel in the midbrain and forebrain (Fig. 3).

In the midbrain localization pathway, cue information from the tonotopically organized central nucleus of the inferior colliculus (ICC) is combined across frequency channels in the external nucleus of the inferior colliculus (ICX)<sup>20,24</sup> to create a map of space. This is conveyed to the optic tectum (also called the superior colliculus in mammals), where it contributes to auditory orienting behaviour<sup>25-27</sup>. In the forebrain localization pathway, cue information is combined across frequency channels beyond the level of the primary auditory field to create clustered representations of space<sup>20,28,29</sup>. Here, neighbouring neurons are tuned to similar locations or localization cue values, but no global topography exists across a structure. The auditory spatial information in the forebrain pathway contributes to a wide variety of higher-order functions such as working memory, planning complex motor responses and executive control of orienting behaviour<sup>27,30-32</sup>.

### Functional plasticity

Consistent with their effects on auditory orienting behaviour, auditory and visual manipulations cause adaptive changes in the tuning of forebrain and midbrain neurons to sound localization cues. In the forebrain pathway, where space is encoded in a clustered representation, plasticity is usually observed as changes in the distribution of cue values to which neurons are tuned across a large population of





**Figure 3** Midbrain and forebrain pathways that mediate auditory orienting responses. This cartoon represents a lateral view of a barn owl's brain. Coloured surfaces represent anatomical structures in the midbrain (yellow) and forebrain (blue). Arrows indicate the flow of information; for clarity, not all connections are shown. ITD, ILD and sound spectrum are processed in parallel in brainstem pathways that project to the central nucleus of the inferior colliculus (ICC) in the midbrain. Spatial information in the ICC is conveyed both to the forebrain, via the thalamic nucleus ovoidalis (Ov), and to the external nucleus of the inferior colliculus (ICX). AGF, archistriatal gaze fields; OT, optic tectum; PAF, primary auditory field.

sampled neurons<sup>33,34</sup>. In contrast, in the midbrain pathway, because space is encoded as a map, the assay for plasticity is much more precise<sup>35</sup>. Here, plasticity can be quantified for each neuron as the difference between observed tuning and the tuning predicted by the physical location of the neuron in the nucleus. In the optic tectum, neurons respond to both visual and auditory stimuli and the determination of a neuron's location in the tectum is made accurately from the location of the neuron's visual receptive field, which does not change with experience<sup>36</sup>. Largely because of the predictive power afforded by mapped representations, studies of the midbrain pathway have provided all that we know about the cellular mechanisms underlying adaptive plasticity in the auditory localization pathway.

**Site of plasticity**

Before we can explore the mechanisms that underlie behavioural learning, we must determine where in the CNS the cellular changes take place. This has been accomplished in the midbrain localization pathway.

In this pathway, the ICX has been shown to be a site of large-scale adaptive plasticity. In young owls that have experienced either

sustained abnormal hearing or prismatic displacement of the visual field, the tuning of neurons in the ICX and optic tectum to sound localization cues is altered adaptively<sup>36,37</sup> (Fig. 4). For example, when a young owl experiences a sustained horizontal displacement of the visual field, neurons in the ICX and optic tectum soon begin responding to values of ITD that correspond to a shift in their auditory receptive fields by the amount of the visual field displacement<sup>38</sup> (Fig. 4). Gradually, these 'learned responses' become strong, and responses to the normal ITD range, termed 'normal responses', disappear over a period of weeks.

In contrast, the tuning of neurons to the same auditory localization cues remains unchanged in the ICC of prism-reared owls. Thus, in the ICX, where representations of localization cue values are transformed into a map of space, these representations are shaped powerfully by experience.

Associated with the functional changes that take place in the ICX, there is a corresponding change in the anatomy of the axonal projection from the ICC to the ICX<sup>39,40</sup>. The ICC–ICX projection in normal owls is topographic. In prism-reared owls that have acquired shifted maps of ITD in the ICX, the ICC–ICX projection is broader than normal with bouton-laden axons located both in the normal projection zone and in an abnormal zone where they could support the newly learned ITD tuning (Fig. 5a). The density of the abnormally located axons and boutons exceeds that observed in juvenile owls (Fig. 5b). Therefore, prism experience must induce the formation of learned circuitry in the ICX at least in part through axonal sprouting and synaptogenesis. Interestingly, normal circuitry also persists, showing that alternative learned and normal circuits can coexist in this network.

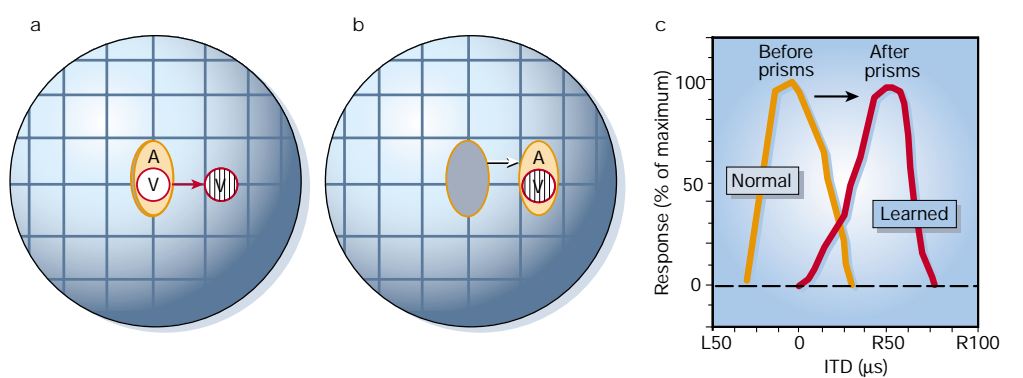
**Mechanisms of learning**

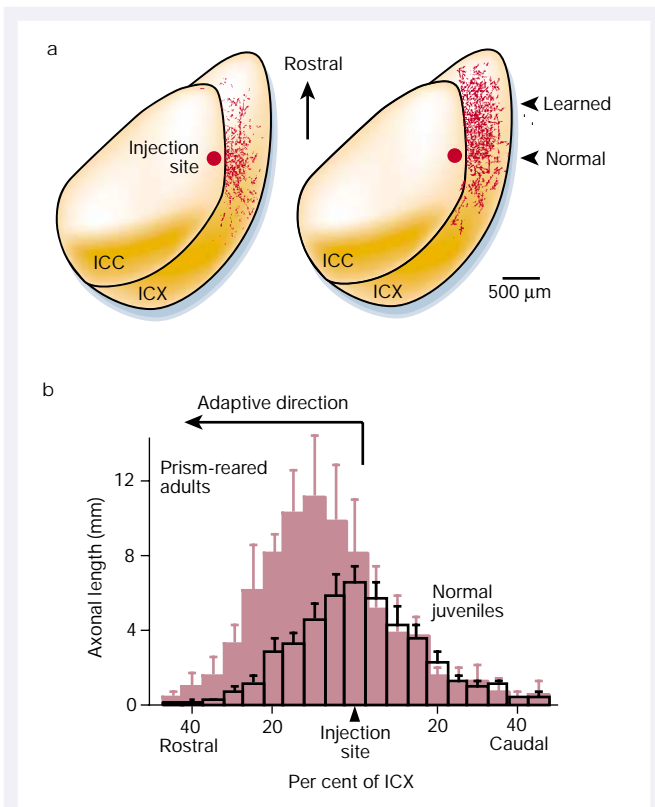
Given that the ICX is a site where experience-dependent changes take place, what mechanisms, besides the anatomical remodelling discussed above, are involved in the functional plasticity?

**NMDA receptors**

Neuropharmacological studies have revealed that particular kinds of neurotransmitter receptors contribute critically to the learning process. A special class of glutamate receptor, the *N*-methyl-D-aspartate (NMDA) receptor, is crucial in the expression of newly learned responses. Normal auditory responses in the ICX are driven by glutamatergic synapses, with more than 50% of the synaptic currents provided by NMDA receptors<sup>41</sup> (Fig. 6a). After the first few weeks of prism experience, many ICX neurons express both normal and learned responses. At this stage, when a selective blocker of NMDA receptors (D,L-2-amino-5-phosphonovaleric acid or AP5) is applied focally in the ICX, normal responses decrease by about 50% (as

**Figure 4** Plasticity of auditory tuning in the optic tectum of a juvenile barn owl resulting from prism experience. Most neurons in the optic tectum respond to both auditory and visual stimuli and have auditory and visual receptive fields that are mutually aligned in space. **a**, An example of the effect of 23° prisms on the location of a neuron's visual receptive field (encircled V). The globe represents space relative to the owl's line of sight. The auditory receptive field (A) is orange. **b**, After the owl has experienced prisms for 8 weeks, the auditory receptive field has shifted to align with the prismatically displaced visual receptive field. **c**, Plasticity of ITD tuning. ITD tuning of 2 units, both with visual receptive fields located at 0° azimuth with the prisms removed (as shown in **a**), measured before (normal) and after (learned) 8 weeks of prism experience. L, left ear leading; R, right ear leading.





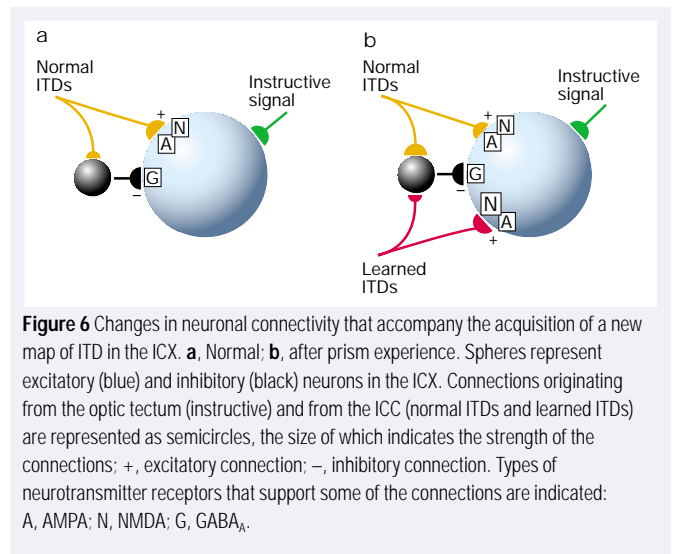
**Figure 5** Plasticity of the anatomical projection from the ICC to the ICX, resulting from prism experience. **a**, Digital image drawings of labelled axons in horizontal sections through the ICX after focal injections of a tracer (biocytin) in the ICC. Data from a normal juvenile are shown on the left, whereas the right image shows data from a prism-reared owl with a rostrally shifted map of ITD in the ICX. **b**, Composite spatial distributions of labelled axons for normal juveniles ( $n = 7$ ; open black bars) and prism-reared adults with shifted maps of ITD ( $n = 4$ ; purple bars). Data are from ref. 40.

expected), but learned responses are greatly suppressed and, in some cases, eliminated<sup>38</sup>. In contrast, when a selective blocker of AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (6-cyano-7-nitroquinoxaline-2,3-dione or CNQX) is applied at the same site, normal responses tend to be suppressed more than learned responses. Thus, in addition to their well-known role in inducing long-term synaptic potentiation in the hippocampus and cerebral cortex, NMDA-receptor currents in the ICX contribute differentially to the functional expression of newly learned responses; this differential contribution disappears over time.

These results indicate that synapses mediating newly learned responses in the ICX have a higher NMDA/AMPA current ratio than synapses mediating normal responses (Fig. 6b). When combined with the anatomical data presented earlier (Fig. 5), these results lead to the intriguing hypothesis that learned responses depend, at least in part, on the formation of new synapses and that these new synapses initially are dominated by NMDA-receptor currents<sup>42</sup>. If true, then as a result of the dependence of NMDA receptors on coincident depolarization and ligand binding for activation<sup>43</sup>, these synapses would have the advantage that they would transmit information to the postsynaptic neuron only when it was depolarized, perhaps by an instructive signal (see below). Otherwise, the synapses would remain ineffective and so would not disrupt the established pattern of information processing.

#### GABA<sub>A</sub> receptors

Another kind of neurotransmitter receptor, the  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) receptor, also contributes importantly to functional



**Figure 6** Changes in neuronal connectivity that accompany the acquisition of a new map of ITD in the ICX. **a**, Normal; **b**, after prism experience. Spheres represent excitatory (blue) and inhibitory (black) neurons in the ICX. Connections originating from the optic tectum (instructive) and from the ICC (normal ITDs and learned ITDs) are represented as semicircles, the size of which indicates the strength of the connections; +, excitatory connection; -, inhibitory connection. Types of neurotransmitter receptors that support some of the connections are indicated: A, AMPA; N, NMDA; G, GABA<sub>A</sub>.

plasticity. GABA<sub>A</sub>-receptor currents inhibit neurons in the ICX<sup>44</sup>. Early in the learning process, strong lateral inhibition mediated by GABA<sub>A</sub> receptors suppresses responses to adaptive, newly functional inputs. Blocking GABA<sub>A</sub> receptors at this stage causes tuning curves to shift further in the adaptive direction, revealing the full extent of the excitatory plasticity that has occurred<sup>45</sup>. Initially, therefore, GABAergic inhibition masks and, perhaps, opposes excitatory plasticity, thereby preserving the established functional properties of the network.

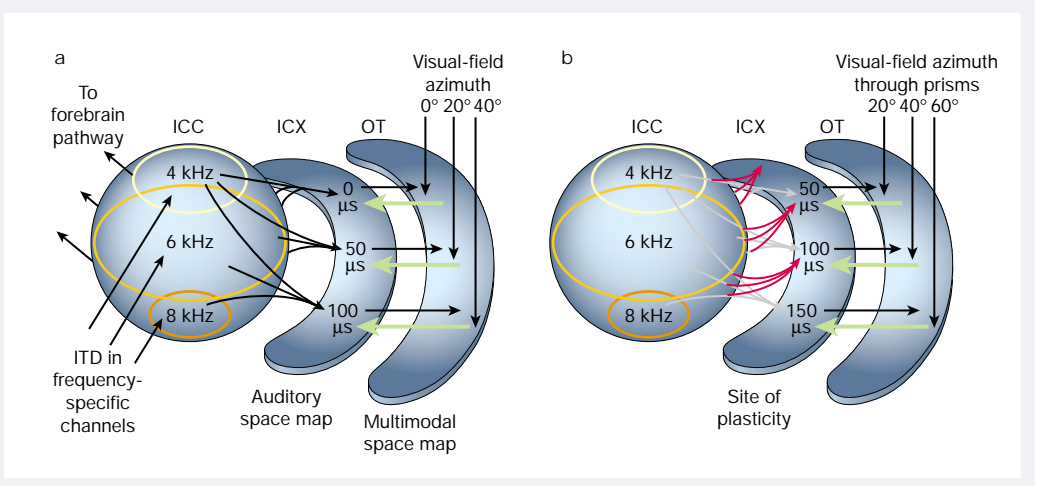
By the end of the learning process, however, GABA<sub>A</sub> receptors have a new role<sup>46</sup>. In an ICX that is expressing a fully shifted map of ITD, in which normal responses have been eliminated, focal application of a GABA<sub>A</sub>-receptor blocker causes the immediate appearance of normal responses. Thus, in a shifted ITD map, synapses that support normal responses remain active and coexist with synapses that support learned responses (consistent with the anatomy discussed above), but responses to the normal synapses are differentially inhibited by GABAergic inhibition (Fig. 6b; orange connection to black, inhibitory neuron). In this case, GABAergic inhibition eliminates normal responses so that tuning curves shift fully, enabling the selective expression of the learned ITD map. Clearly, changes in the pattern of inhibition, as well as changes in the pattern of excitation, contribute critically to this adaptive plasticity.

#### The instructive signal

Much of the plasticity that has been observed in the CNS has been induced using paradigms that involve injury to the nervous system, deprivation or excessive use<sup>47,48</sup>. In these examples, the relative strength of activation across inputs is changed dramatically and the plasticity can be accounted for entirely by competitive, self-organizational forces. But the same is not true for the adaptive adjustment of the auditory space map<sup>49</sup>. In this case, the auditory system is instructed to change its representations of cue values, guided by information provided by a teaching signal. But where does this signal come from and how does it work?

The prism experiments show that the dominant instructive signal in the ICX is provided by the visual system (although other instructive influences exist<sup>50</sup>). The dominance of visual input in this pathway makes sense, in that the primary function of the pathway is to orient gaze towards auditory targets<sup>26,27</sup>. A visually based signal that calibrates the representation of auditory cues in the ICX could be either a topographic template of the visual field or a foveation-dependent visual signal indicating whether or not auditory orienting responses are accurate<sup>49</sup>. A topographic template signal could instruct changes in the auditory space map by reinforcing auditory synapses that contribute to activity patterns that match those evoked by the visually based template signal and weakening auditory synapses that do not. Alternatively, a

**Figure 7** The effect of prism experience on information flow in the midbrain auditory localization pathway. **a**, The pathway in a normal owl; and **b**, in a prism-reared adult with a shifted map of ITD<sup>40</sup>. ITD is measured and mapped in frequency-specific channels in the brainstem. This information ascends to the ICC, and converges across frequency channels in the projection from the ICC to the ICX, where a map of space is created. The map is conveyed to the optic tectum (OT), where it merges with a visual map of space. Green arrows represent the instructive pathway from the OT to the ICX<sup>53</sup>.



foveation-based instructive signal could guide changes in the auditory space map by strengthening auditory synapses that contribute to orienting movements that cause the stimulus source to fall in the centre of gaze and weakening synapses that do not<sup>51</sup>.

A recent experiment has distinguished between these possibilities by exposing owls to different optical conditions at the centre of gaze and in the periphery<sup>52</sup>. A template-based instructive signal predicts different adaptive adjustments in each region of the auditory space map, according to the optical conditions that exist in each region of the visual field. In contrast, a foveation-based instructive signal predicts similar adjustments across the entire space map according to the optical conditions that exist at the centre of gaze. The result of this experiment is that different portions of the auditory space map adjust differently depending on the local visual conditions. Thus, the dominant instructive signal that shapes the auditory space map is a topographic template of visual space.

The source of an instructive signal to the ICX originates from the optic tectum (Figs 6, 7; green connections). Anatomical studies have shown a point-to-point projection from neurons largely in the intermediate layers of the optic tectum back to the ICX<sup>53</sup>. This projection forms even before owls hatch<sup>54</sup>. The projecting neurons have dendrites that extend into the superficial tectal layers, which receive direct input from the retina, and others that extend into the deep tectal layers, which receive feedforward auditory input from the ICX and visual input from the forebrain. A small lesion placed in the tectum eliminates adaptive plasticity in the corresponding portion of the auditory space map in the ICX, while the rest of the auditory map continues to shift adaptively in response to experience<sup>55</sup>. Similar effects have been observed in ferrets<sup>56</sup>: removal of the superficial layers of the superior colliculus disrupts the development of a normal auditory space map, as assessed in the deep layers of the superior colliculus. The site of plasticity, however, has not been determined in mammals.

The data show that, in barn owls, the optic tectum provides the ICX with a topographic signal that instructs the representation of auditory cue values in the space map (Fig. 7). Because precise, topographic visual activity is strong in the tectal layers where the feedback projection originates<sup>35</sup>, the tectal signal to the ICX may simply be a retinotopic visual template. But despite numerous attempts, no evidence of a visual instructive signal has been recorded in the ICX of passive, restrained owls, which suggests that the instructive signal might be gated in some fashion, perhaps by attention.

These findings suggest that activity from the visual system is sent into the auditory system as an instructive input to guide the transformation of auditory cue values into a topographic map of space. The same signal is presumably responsible for, and indeed normally used for, adaptive auditory adjustments in response to changes in hearing<sup>6,57,58</sup>. This visual instructive signal shapes a common repre-

sentation of space for the auditory and visual systems from information that is initially encoded in very different coordinate frames.

A wide variety of transformations in the CNS could be shaped by an analogous strategy. For example, commands for complicated movements are encoded in retinocentric or other sensory frames of reference in some areas of the brain<sup>59–62</sup>. By studying how the visual system exerts its influence on the auditory space map, we may learn some of the mechanisms by which the nervous system instructs such complex transformations.

### Principles of learning

Learning is a balance of innate and experiential influences

The capacity of a network to learn from experience is limited by innate factors that establish and refine initial patterns of connectivity<sup>63</sup>. Innate patterns of connectivity can contain remarkable specificity, imparting a high degree of functionality that reflects many generations of selection<sup>64</sup>.

The influence of innate patterns of connectivity is apparent in the plasticity of auditory orienting behaviour. For example, owls can alter this behaviour dramatically in response to abnormal sensory conditions only when they are young. In contrast, owls raised with abnormal sensory experience can learn normal orienting behaviour at any age once normal sensory conditions are established<sup>15</sup>.

Innate patterns of connectivity are suggested also by the essentially normal maps of ITD that form in owls that are blind from birth or that have been raised with prisms from the day of eye opening<sup>15,65</sup>. In prism-reared owls, the normal map of ITD that forms initially is subsequently altered by prism experience.

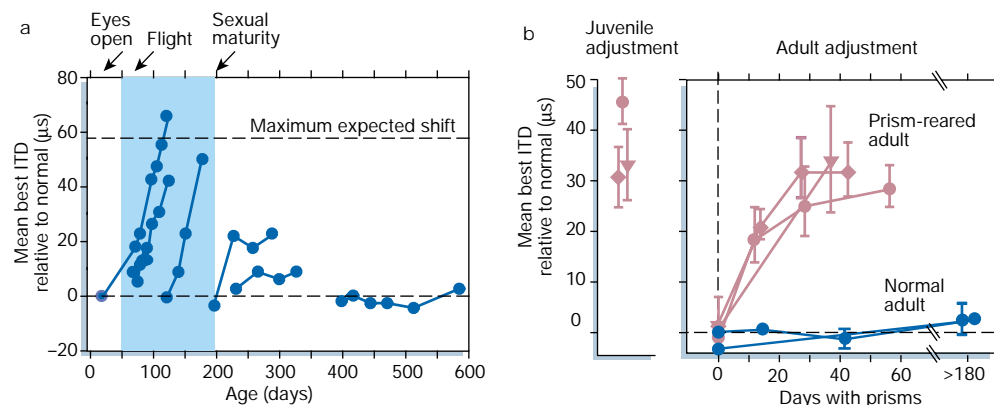
A preference for normal patterns of connections is apparent also in the anatomy and physiology of the ICC–ICX projection. As mentioned previously, in the ICX of prism-reared owls that are expressing shifted maps of ITD, the normal anatomical projection persists along with the learned projection (Fig. 5), even in owls that have never experienced normal correspondences between ITDs and visual locations<sup>39,40</sup>. Thus, synapses that support normal responses do not require experiential validation in order to become established. Moreover, in shifted maps, the synapses supporting normal responses remain active, but action potentials triggered by them are suppressed by inhibition (Fig. 6b). The converse is not true: in an ICX that has previously expressed a shifted map, blocking inhibition does not cause an immediate re-expression of previously learned responses<sup>46</sup>. Apparently, the strength of learned connections can be reduced to zero through experience, whereas the strength of normal connections cannot. In both respects, synapses that support normal responses seem to be privileged.

### Young is better than old

As is true for many behaviours and circuits in the brain, the capacity to change auditory orienting behaviour and the functional



**Figure 8** Effect of age and prior experience on ITD map plasticity, as induced by prism experience. **a**, The sensitive period for visual calibration of the ITD map in the optic tectum. These data are from six owls that had 23° prisms mounted over the eyes at different ages. The data points indicate the mean shift of ITD tuning measured for a population of sites. The shaded zone indicates the sensitive period, during which large-scale changes in the ITD map take place under these conditions. Data are from ref. 15. **b**, A trace of juvenile learning persists in adult owls.



Plasticity of the ITD map, induced initially in three juvenile owls (left) by experience with 23° prisms, was re-expressed when these owls were exposed to the same sensory conditions as adults (right, purple symbols). The blue symbols indicate the plasticity of the ITD map in two normally raised owls. All adult owls were over 1 year old when tested. Data are from ref. 67.

properties of neurons in the localization pathway decreases with age<sup>15,57</sup>. Large-scale adaptive changes in orienting behaviour and in the map of ITD in response to abnormal sensory experience occur in juvenile owls, but not in adult owls under the same conditions (Fig. 8a). A strong age dependence in the plasticity of the auditory space map has also been documented in the superior colliculus of ferrets and guinea pigs<sup>6,66</sup>.

In barn owls, learning that occurs during the juvenile sensitive period increases the capacity for plasticity in adulthood<sup>67</sup>. An ICX that has acquired an alternative map of ITD during the sensitive period is capable of re-acquiring that map in adulthood, if the same sensory conditions are imposed on the owl (Fig. 8b). The ICX cannot, however, acquire an abnormal map in the adult that has not been learned previously during the juvenile period<sup>67</sup>. Thus, the act of learning an ITD map during the sensitive period leaves a trace in this pathway that endures into adulthood, even though it is not expressed. The plasticity observed in adults reflects the range of learning that occurred during the juvenile period along with innate predispositions. Analogous, long-lasting effects of learning during the sensitive period on adult performance have been reported for song learning in song birds<sup>68</sup>, imprinting in birds and mammals<sup>69,70</sup>, and language learning in humans<sup>71</sup>. Current research is attempting to identify the nature of this persistent learning trace in the owl's auditory localization pathway.

### Future directions

Auditory orienting behaviour is a highly quantifiable behaviour that can be shaped powerfully by experience. The pathways in the CNS that contribute to this behaviour are highly conserved across species and are largely identified. In barn owls, the tuning of neurons in these pathways for sound localization cues is unusually sharp and, in the midbrain pathway, the representation of cue values is mapped. Analyses of cellular mechanisms that underlie experience-driven, adaptive changes in orienting behaviour have shown adaptive changes in the nervous system's representation of auditory localization cues, in its anatomical circuitry, and in the contributions of various neurotransmitter-receptor currents to postsynaptic responses. All of these changes are guided by the action of a visually based instructive signal. The results have documented the effects of innate and experiential influences on plasticity, changes in the capacity for plasticity as animals mature, and the enduring effects that early learning can have on adult plasticity.

Future research will delve deeper into the mechanisms of instructed learning in this and in other systems. The cellular and molecular events that underlie learning are known only in rough outline, and

virtually nothing is known about the nature of instructive signals, how they guide plasticity and how they themselves are regulated. The instructive roles played by neuromodulatory systems, such as the cholinergic, noradrenergic and dopaminergic systems that are activated during attention, arousal and learning, are unknown. Also unknown are the factors responsible for the decline in learning capacity with age and the identity of the trace that is left in the adult brain by juvenile learning. From such knowledge, we may discover how to drive learning faster and farther, particularly in adult animals. Finally, research in other species and in other systems will determine the degree to which the mechanisms and principles of learning that have been shown to operate in the auditory localization pathway of barn owls apply generally in the CNS. □

- Field, J., Muir, D., Pilon, R., Sinclair, M. & Dodwell, P. Infants' orientation to lateral sounds from birth to three months. *Child Dev.* **51**, 295–298 (1980).
- Ashmead, D. H., Clifton, R. K. & Reese, E. P. Development of auditory localization in dogs: single source and precedence effect sounds. *Dev. Psychobiol.* **19**, 91–103 (1986).
- Hofman, P. M., Van Riswick, J. G. A. & Van Opstal, A. J. Relearning sound localization with new ears. *Nature Neurosci.* **1**, 417–421 (1998).
- King, A. J., Schnupp, J. W. & Doubell, T. P. The shape of ears to come: dynamic coding of auditory space. *Trends Cogn. Sci.* **5**, 261–270 (2001).
- Knudsen, E. I. Mechanisms of experience-dependent plasticity in the auditory localization pathway of the barn owl. *J. Comp. Physiol.* **185**, 305–321 (1999).
- King, A. J. A map of auditory space in the mammalian brain: neural computation and development. *Exp. Physiol.* **78**, 559–590 (1993).
- Shinn-Cunningham, B. Adapting to remapped auditory localization cues: a decision-theory model. *Percept. Psychophys.* **62**, 33–47 (2000).
- Knudsen, E. I., Blasdel, G. G. & Konishi, M. Sound localization by the barn owl measured with the search coil technique. *J. Comp. Physiol.* **133**, 1–11 (1979).
- Middlebrooks, J. C. & Green, D. M. Sound localization by human listeners. *Annu. Rev. Psychol.* **42**, 135–159 (1991).
- Konishi, M., Takahashi, T. T., Wagner, H., Sullivan, W. E. & Carr, C. E. in *Auditory Function* (eds Edelman, G. M., Gall, W. E. & Cowan, W. M.) 721–745 (Wiley, New York, 1988).
- Blauert, J. *Spatial Hearing: The Psychophysics of Human Sound Localization* (MIT Press, Cambridge, MA, 1997).
- Carr, C. E. & Boudreau, R. E. Development of the time coding pathways in the auditory brainstem of the barn owl. *J. Comp. Neurol.* **373**, 467–483 (1996).
- Knudsen, E. I., Esterly, S. D. & Knudsen, P. F. Monaural occlusion alters sound localization during a sensitive period in the barn owl. *J. Neurosci.* **4**, 1001–1011 (1984).
- Knudsen, E. I., Knudsen, P. F. & Esterly, S. D. A critical period for the recovery of sound localization accuracy following monaural occlusion in the barn owl. *J. Neurosci.* **4**, 1012–1020 (1984).
- Brainard, M. S. & Knudsen, E. I. Sensitive periods for visual calibration of the auditory space map in the barn owl optic tectum. *J. Neurosci.* **18**, 3929–3942 (1998).
- Lackner, J. R. in *Intersensory Perception and Sensory Integration* (eds Walk, R. D. & Pisk, H. L.) 143–173 (Plenum, New York, 1981).
- Knudsen, E. I. & Knudsen, P. F. Visuomotor adaptation to displacing prisms by adult and baby barn owls. *J. Neurosci.* **9**, 3297–3305 (1989).
- Baizer, J. S., Kralj-hans, I. & Glickstein, M. Cerebellar lesions and prism adaptation in macaque monkeys. *J. Neurophysiol.* **81**, 1960–1965 (1999).
- Irvine, D. R. F. in *The Mammalian Auditory Pathway: Neurophysiology* (eds Popper, A. N. & Fay, R. R.) 153–231 (Springer, New York, 1992).
- Cohen, Y. E. & Knudsen, E. I. Maps versus clusters: different representations of auditory space in the midbrain and forebrain. *Trends Neurosci.* **22**, 128–135 (1999).

21. Clarey, J. C., Barone, P. & Imig, T. J. in *The Mammalian Auditory Pathway: Neurophysiology* (eds Popper, A. N. & Fay, R. R.) 232–334 (Springer, New York, 1992).
22. Cohen, Y. E. & Knudsen, E. I. Representation of binaural spatial cues in Field L of the barn owl forebrain. *J. Neurophysiol.* **79**, 879–890 (1998).
23. Brainard, M. D., Knudsen, E. I. & Esterly, S. D. Neural derivation of sound source location: resolution of spatial ambiguity in binaural cues. *J. Acoust. Soc. Am.* **91**, 1015–1027 (1992).
24. Wagner, H., Takahashi, T. & Konishi, M. Representation of interaural time difference in the central nucleus of the barn owl's inferior colliculus. *J. Neurosci.* **7**, 3105–3116 (1987).
25. Stein, B. E. & Meredith, M. A. *The Merging of the Senses* (MIT Press, Cambridge, MA, 1993).
26. Wagner, H. Sound-localization deficits induced by lesions in the barn owl's auditory space map. *J. Neurosci.* **13**, 371–386 (1993).
27. Knudsen, E. I., Knudsen, P. F. & Masino, T. Parallel pathways mediating both sound localization and gaze control in the forebrain and midbrain of the barn owl. *J. Neurosci.* **13**, 2837–2852 (1993).
28. Schreiner, C. E. Order and disorder in auditory cortical maps. *Curr. Opin. Neurobiol.* **5**, 489–496 (1995).
29. Recanzone, G. H. Spatial processing in the auditory cortex of the macaque monkey. *Proc. Natl Acad. Sci. USA* **97**, 11829–11835 (2000).
30. Rauschecker, J. P. & Tian, B. Mechanisms and streams for processing of “what” and “where” in auditory cortex. *Proc. Natl Acad. Sci. USA* **97**, 11800–11806 (2000).
31. Heffner, H. & Heffner, R. S. Effect of bilateral auditory cortex lesions on sound localization in Japanese macaques. *J. Neurophysiol.* **64**, 915–931 (1990).
32. Knudsen, E. I. & Knudsen, P. F. Disruption of auditory spatial working memory by inactivation of the forebrain archistriatum in barn owls. *Nature* **383**, 428–431 (1996).
33. Miller, G. L. & Knudsen, E. I. Early visual experience shapes the representation of auditory space in the forebrain gaze fields of the barn owl. *J. Neurosci.* **19**, 2326–2336 (1999).
34. Miller, G. L. & Knudsen, E. I. Early auditory experience induces frequency-specific, adaptive plasticity in the forebrain gaze fields of the barn owl. *J. Neurophysiol.* **85**, 2184–2194 (2001).
35. Knudsen, E. I. Auditory and visual maps of space in the optic tectum of the owl. *J. Neurosci.* **2**, 1177–1194 (1982).
36. Brainard, M. S. & Knudsen, E. I. Experience-dependent plasticity in the inferior colliculus: a site for visual calibration of the neural representation of auditory space in the barn owl. *J. Neurosci.* **13**, 4589–4608 (1993).
37. Mogdans, J. & Knudsen, E. I. Early monaural occlusion alters the neural map of interaural level difference in the inferior colliculus of the barn owl. *Brain Res.* **619**, 29–38 (1993).
38. Feldman, D. E. & Knudsen, E. I. Pharmacological specialization of learned auditory responses in the inferior colliculus of the barn owl. *J. Neurosci.* **18**, 3073–3087 (1998).
39. Feldman, D. E. & Knudsen, E. I. An anatomical basis for visual calibration of the auditory space map in the barn owl's midbrain. *J. Neurosci.* **17**, 6820–6837 (1997).
40. DeBello, W. M., Feldman, D. E. & Knudsen, E. I. Adaptive axonal remodeling in the midbrain auditory space map. *J. Neurosci.* **21**, 3161–3174 (2001).
41. Feldman, D. E. & Knudsen, E. I. NMDA and non-NMDA glutamate receptors in auditory transmission in the barn owl inferior colliculus. *J. Neurosci.* **14**, 5939–5958 (1994).
42. Feldman, D. E. & Knudsen, E. I. Experience-dependent plasticity and the maturation of glutamergic synapses. *Neuron* **20**, 1067–1071 (1998).
43. Cotman, C. W., Monaghan, D. T. & Ganong, A. H. Excitatory amino acid neurotransmission: NMDA receptors and Hebb-type synaptic plasticity. *Annu. Rev. Neurosci.* **11**, 61–80 (1988).
44. Fujita, I. & Konishi, M. The role of GABAergic inhibition in processing of interaural time difference in the owl's auditory system. *J. Neurosci.* **11**, 722–729 (1991).
45. Zheng, W. & Knudsen, E. I. GABAergic inhibition antagonizes adaptive adjustment of the owl's auditory space map during the initial phase of plasticity. *J. Neurosci.* **21**, 4356–4365 (2001).
46. Zheng, G. L. & Knudsen, E. I. Functional selection of adaptive auditory space map by GABA-mediated inhibition. *Science* **284**, 962–965 (1999).
47. Kaas, J. H. Plasticity of sensory and motor maps in adult mammals. *Annu. Rev. Neurosci.* **14**, 137–167 (1991).
48. Gilbert, C. D., Sigman, M. & Crist, R. E. The neural basis of perceptual learning. *Neuron* **31**, 681–697 (2001).
49. Knudsen, E. I. Supervised learning in the brain. *J. Neurosci.* **14**, 3985–3997 (1994).
50. Knudsen, E. I. & Mogdans, J. Vision-independent adjustment of unit tuning to sound localization cues in response to monaural occlusion in developing owl tectum. *J. Neurosci.* **12**, 3485–3493 (1992).
51. Rucci, M., Ttoni, G. & Edelman, G. M. Registration of neural maps through value-dependent learning: modeling the alignment of auditory and visual maps in the barn owl's optic tectum. *J. Neurosci.* **17**, 334–352 (1997).
52. Hyde, P. S. & Knudsen, E. I. A topographic instructive signal guides the adjustment of the auditory space map in the optic tectum. *J. Neurosci.* **21**, 8586–8593 (2001).
53. Hyde, P. S. & Knudsen, E. I. Topographic projection from the optic tectum to the auditory space map in the inferior colliculus of the barn owl. *J. Comp. Neurol.* **421**, 146–160 (2000).
54. Luksch, H., Gauger, B. & Wagner, H. A candidate pathway for a visual instructional signal to the barn owl's auditory system. *J. Neurosci.* **20**, RC70 (2000).
55. Hyde, P. S. & Knudsen, E. I. The optic tectum controls visually guided adaptive plasticity in the owl's auditory space map. *Nature* **415**, 73–76 (2002).
56. King, A. J., Schnupp, J. W. & Thompson, I. D. Signals from the superficial layers of the superior colliculus enable the development of the auditory space map in the deeper layers. *J. Neurosci.* **18**, 9394–9408 (1998).
57. Knudsen, E. I. Experience alters spatial tuning of auditory units in the optic tectum during a sensitive period in the barn owl. *J. Neurosci.* **5**, 3094–3109 (1985).
58. Gold, J. I. & Knudsen, E. I. A site of auditory experience-dependent plasticity in the neural representation of auditory space in the barn owl's inferior colliculus. *J. Neurosci.* **20**, 3469–3486 (2000).
59. Batista, A. P., Buneo, C. A., Snyder, L. H. & Anderson, R. A. Reach plans in eye-centered coordinates. *Science* **285**, 257–260 (1999).
60. Cohen, Y. E. & Andersen, R. A. Reaches to sounds encoded in an eye-centered reference frame. *Neuron* **27**, 647–652 (2000).
61. Troyer, T. W. & Doupe, A. J. An associational model of birdsong sensorimotor learning I. Efference copy and the learning of song syllables. *J. Neurophysiol.* **84**, 1204–1223 (2000).
62. Klier, E. M., Wang, H. & Crawford, J. D. The superior colliculus encodes gaze commands in retinal coordinates. *Nature Neurosci.* **4**, 627–632 (2001).
63. Katz, L. C. & Shatz, C. J. Synaptic activity and the construction of cortical circuits. *Science* **274**, 1133–1138 (1996).
64. Tinbergen, N. *The Study of Instinct* (Oxford Univ. Press, New York, 1976).
65. Knudsen, E. I., Esterly, S. D. & du Lac, S. Stretched and upside-down maps of auditory space in the optic tectum of blind-reared owls: acoustic basis and behavioral correlates. *J. Neurosci.* **11**, 1727–1747 (1991).
66. Withington-Wray, D. J., Binns, K. E. & Keating, M. J. A four-day period of bimodality auditory and visual experience is sufficient to permit normal emergence of the map of auditory space in the guinea pig superior colliculus. *Neurosci. Lett.* **116**, 280–286 (1990).
67. Knudsen, E. I. Capacity for plasticity in the adult owl auditory system expanded by juvenile experience. *Science* **279**, 1531–1533 (1998).
68. Konishi, M. Birdsong: from behavior to neuron. *Annu. Rev. Neurosci.* **8**, 125–170 (1985).
69. Hess, E. H. *Imprinting: Early Experience and the Developmental Psychobiology of Attachment* (Van Nostrand Reinhold, New York, 1973).
70. Scott, J. P. Critical periods in behavioral development. *Science* **138**, 949–958 (1962).
71. Newport, E. L., Bavelier, D. & Neville, H. J. in *Language, Brain and Cognitive Development: Essays in Honor of Jacques Mehler* (ed. Doupoux, E.) 481–502 (MIT Press, Cambridge, MA, 2001).
72. Knudsen, E. I. & Knudsen, P. F. Sensitive and critical periods for visual calibration of sound localization by barn owls. *J. Neurosci.* **63**, 131–149 (1990).

#### Acknowledgements

I thank P. Knudsen for technical support and B. Linkenhoker and Y. Gutfreund for helpful comments on the manuscript. This work was supported by grants from the National Institutes of Health, the March of Dimes and the McKnight Foundation.