Figure 2. Birds in the zone.

Black-capped chickadee (left) and Carolina chickadee (right). Painting copyright David Sibley, reproduced with permission.

perhaps only at certain regions of the genome. Some parts of the genome may move with the zone and others get left behind, but the extent to which this happens does depend on the fitness of hybrids. The black-capped/Carolina chickadee zone apparently results in hybrids of very low fitness and introgression of genes from one side of the zone should be rare. Other studies based on small molecular datasets have found some evidence for introgression [14,15], which may be ancient. However, alternatives, such as shared ancestral polymorphism, have been hard to rule out.

Limited, or no, introgression may be contrasted with the findings from other moving zones, in which the species involved are younger and gene exchange more frequent. Rohwer *et al.* [16] found that the hybrid zone in Washington State between southern hermit warblers and northern Townsend's warblers was likely to be moving south. This was inferred from the presence of hermit warbler mitochondrial DNA in Alaskan Townsend's warblers, 2,000 km to the north of the present zone. Dominance of Townsend's males is implicated in zone movement, and the discordance between plumage and mtDNA could be explained if male plumage and associated dominance traits moved south but the females disperse more or less at random. Hybrid zones between recently separated groups such as these are calling out for genomic analyses along the lines pioneered by Taylor *et al.* [7]: climate change not only affects range limits, but also the potential for hybridization and introgression during a protracted speciation process.

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Hearing Damage and Deafness: A Role for the Circadian Clock

Severe noise can cause permanent hearing damage. A recent study now shows that the capacity to recover from noise damage varies with time of day, driven by circadian clock control of a nerve growth factor (BDNF) in the inner ear.

Andrew S.I. Loudon

We are all familiar with the effects of loud noise on our hearing. These include 'ringing in the ear' and temporary deafness, but for severe noise trauma, these effects can be permanent. The cause of these problems resides in the spiral cochlea of the inner ear, specifically involving damage to the delicate hairs of the inner ear, which are tuned to specific frequencies, and also importantly the dendrites of the auditory nerve.

The circadian clock is known to be regulated by environmental stimuli, of

which the best studied are the effects of light, mediated in mammals by the retina [1]. In contrast, remarkably little is known of how auditory stimuli are perceived across the circadian cycle, although earlier studies in rats have shown important effects of the circadian cycle in response to acoustic startle [2]. As reported in this issue of *Current* Biology, Meltser *et al.* [3] explored this further by testing reactions of mice using the well-established acoustic startle response (ASR), in which mice are exposed to a loud noise. This revealed that mice exposed to acoustic startle during the day had faster response times and higher magnitude responses than those tested in the night phase. This is important as mice are nocturnal, and thus their startle responses are inversely correlated with activity. The authors next showed that severe noise trauma induced temporary damage to the auditory dendrites, manifested as synaptic swelling. However, when they tested two weeks later, the ABR (auditory brainstem response) of mice exposed to loud sounds at night revealed permanent damage, while the day-tested group recovered. Thus, the severity of damage depends on the time of day that mice were exposed to damaging sound levels.

Subsequent studies revealed that the cochlea contains a self-sustained circadian clock, which continues to tick in culture, as assessed by studying oscillations of the bioluminescent luciferase circadian reporter PER2–LUC [4]. Remarkably, cochlea from night-stimulated mice even revealed marked long-term suppression of amplitude for this and several other clock genes when cultured over several days in the laboratory. The brain-derived neurotrophic factor (BDNF) is known to be involved in repair of the auditory nerve following (noise) damage or nerve cell loss [5,6], so the authors tested whether BDNF was involved. In the day-time, mRNA levels of BDNF rose over 30-fold, but following stimulation at night there was no response. This strongly suggests that BDNF activation is gated by a circadian clock within the cochlea, only allowing activation of this gene at certain specific phases of the circadian cycle (Figure 1). BDNF acts on the tropomyosin kinase type B receptor (TrkB) [7], on which the drug 7,8-dihydroxyflavone (DHF) also acts.

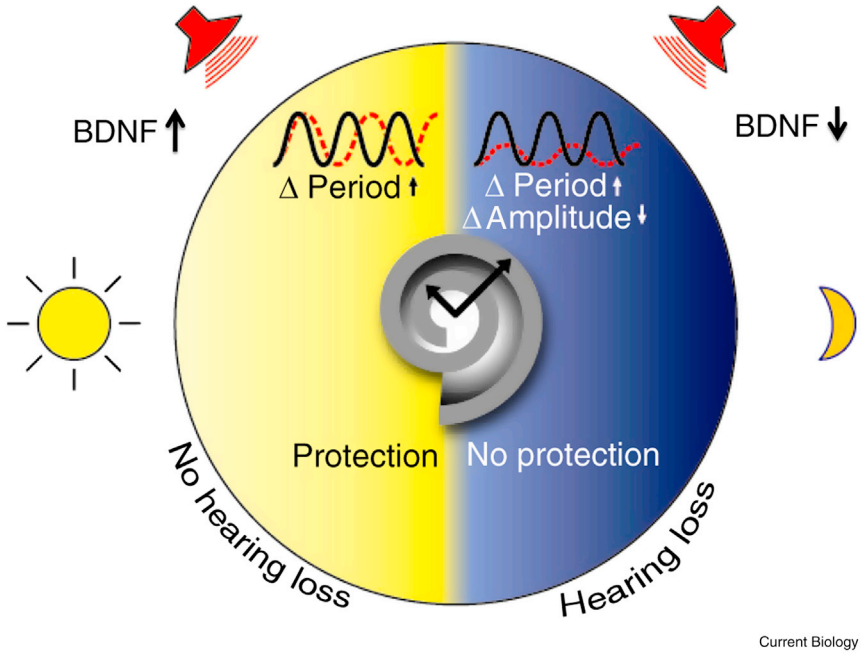

Figure 1. Noise damage and circadian repair mechanisms in the cochlea.

Severe noise causes damage to the neuronal synapses within the inner hair cells of the cochlea, regulated by a cochlea circadian clock, with greatest sensitivity to damage occurring in the nocturnal phases. This is also reflected in long-term suppression of circadian clock genes following nocturnal exposure to damaging noise levels. Recovery of synaptic function is mediated by the brain-derived neurotrophic factor (BDNF), but BDNF is only induced in response to severe noise during the day, and is thus regulated by a cochlear clock. Treatment with the drug DHF can mimic BDNF by acting on the BDNF receptor, and can substitute for the loss of a normal nocturnal BDNF response, and thus protect the cochlea from damaging effects of severe noise at night.

DHF strongly increased the amplitude of expression of PER2–LUC in cultured cochlea, and this effect was largely blocked by another drug (ANA12) which antagonizes the system.

Excitotoxicity induced by noise causes swelling of the dendrites of the auditory neuron, but these can recover through re-growth to restore hearing. BDNF thus emerges as a possible candidate linking the core clockwork of the cochlea to recovery of the nervous system following noise damage at different circadian phases. To test this, mice were treated with DHF prior to noise over-exposure and the ABR was then measured. During the day, DHF had no protective effect, and here the authors reasoned that endogenous BDNF levels were sufficient and capable to engage the TrkB receptor. In contrast, DHF protected night-stimulated mice from noise trauma, when assessed two weeks later. In these studies, the primary impact of severe noise seemed to be on the delicate hair cells of the cochlea. Within the cochlea, there is a specialized type of neuronal synapse — the synaptic ribbon — found in the inner hair cell, that promotes rapid neurotransmitter release and signal transduction. This feature allows for rapid and precise, as well as sustained, neurotransmissions, which are critical for the complex sensory systems such as vision and hearing. These ribbons are permanently lost following severe noise trauma at night, but remarkably, pre-treatment with DHF protected synaptic ribbons from loss. Collectively, this nails down BDNF as a strong candidate acting on the TrkB receptor to mediate time-of-day differences in the severity of noise-induced trauma.

There are a number of intriguing issues raised by this study. There are several other Trk receptors and also neurotrophins known to be involved in the control of auditory neurite growth [8]. It appears, however, that these important circadian effects are mediated primarily by BDNF and the TrkB receptor. BDNF and TrkB are known to be under circadian control [9] and BDNF is also known to be involved

in re-modelling of other parts of the nervous system, including the memory centres of the brain in the hippocampus [10]. Here, it interacts with stress hormones secreted from the adrenal gland (cortisol in man; corticosterone in mice), mediated by the nuclear hormone glucocorticoid receptor, GR [11]. GR is known to be an important regulator of BDNF, and is thought to be the key link between early life stress effects on brain function and dendritic development, many of which can persist throughout life. We are only just starting to appreciate how nuclear hormone signaling systems couple to the circadian clockwork, and recent studies now point to a direct interaction between proteins encoded by so-called core clock genes (PERIOD, CRYPTOCHROME, REVERB) and hormone signaling pathways [12]. For instance, there is now evidence that rhythmic action of glucocorticoids may depend on oscillations of CRYPTOCHROME, which forms a physical partnership with the GR to repress its action at specific phases of the cycle [13]. So, although the authors did not explore this, one important question is whether auditory responses, and long-term effects on nerve damage, might be mediated by stress hormones, which themselves are tightly clock-controlled. Adrenal glucocorticoids will likely also be strongly activated by strong noise stimulation, but if they are key players, then the rhythmic interaction of the GR with the core clockwork of the cochlea may be involved.

Finally, there is an obvious and important practical implication for human health. Noise levels at work are controlled by a complex legal framework, which defines tolerable levels, and requires the wearing of protective hearing devices. To what extent has such legislation accounted for possible circadian effects in man, and would it not now be important to assess whether shift-workers are especially vulnerable? In addition, many people voluntarily expose themselves to excessive noise in discos and night-clubs, and anecdotal evidence suggests that this appears to be an exclusively nocturnal activity in our species. It is now important to test whether we show similar phasic effects to mice — with increased vulnerability at night. One intriguing prediction is that we might be better able to cope with noise in the night-time, since in man the daily rhythm of adrenal stress hormones rises in the day, and falls at night — the opposite to that seen in nocturnal mice.

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Music Biology: All This Useful Beauty

Some healthy people fail to derive pleasure from music despite otherwise preserved perceptual and reward responses. Such 'musical anhedonia' implies the existence of music-specific brain reward mechanisms, which could provide a substrate for music to acquire biological value.

Camilla N. Clark, Laura E. Downey, and Jason D. Warren

Few problems in biology are as tantalising as the problem of music. Music is universal in human societies, apparently ancient and apt to generate powerful emotional responses [1]. These are all properties that a biologically salient stimulus ought to have; however, these abstract sounds serve no obvious biological purpose and, unlike language, have no straightforward messaging function. This apparent paradox has long polarised neurobiologists and philosophers alike: in one account, music had a specific role in human evolution, probably linked to emotional social signalling [2]; in the other, it is a mere neural confection, a spandrel of language [3].

One important line of evidence in support of a biological role for music is the existence of specific neural mechanisms that process it: if evolution fashioned music-specific brain systems, it is reasonable to conclude that music (or proto-music) filled some evolutionary role for our species and to ask what that role might have been. Evidence for such music-specific brain systems has mainly been adduced in patients with focal brain damage who show dissociated patterns of performance when processing music versus other kinds of complex sounds [4]. Such cases, while informative,