we still do not understand exactly how the population-wide co-ordination of this switch is achieved [15,16]. If malaria parasites really can detect kin and respond to their presence, their means of within-host communication are much more sophisticated than hitherto realised, and exploring the underlying mechanisms could prove hugely enlightening.

The experimental demonstration that gametocyte sex ratio influences ookinete production *in vitro* is an important milestone, and suggests that studies assessing the determinants of transmission success in malaria should take account of gametocyte sex ratio in addition to other factors such as gametocyte density and maturity. Reece *et al.*'s [4] contribution to the body of work showing that gametocyte sex ratio is a flexible fitness-determining trait that can be adjusted in response to a variety of factors also re-emphasizes the importance of bearing in mind such crafty parasite tricks when designing interventions like anti-malarial drugs and transmission-blocking strategies.

In conclusion, this recent work [4], apart from providing strong and novel support for sex allocation theory demonstrates yet another way in which this medically important parasite displays a form of sophisticated and responsive behaviour. That the responses hinge on the apparent ability of the parasites to discriminate kin is exciting, and suggests a form of social behaviour in these organisms that might not be generally expected. It also raises question of how studies of, and interventions against, this deadly parasite should take account of its flexible adaptive behaviour.

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Synaesthesia: The Sounds of Moving Patterns

A newly reported form of synaesthesia in which seeing visual motion induces auditory experiences challenges traditional ideas about the neural mechanisms of synaesthesia and may shed light on how the brain integrates information from sound and vision.

Edward M. Hubbard

In synaesthesia, sensory and cognitive experiences lead to additional, unusual experiences, such as seeing colours when looking at letters or numbers [1] or when listening to speech [2], or even tasting flavours in the mouth in response to musical intervals [3]. Although synaesthesia was first brought to the attention of the scientific community over 100 years ago, the neural mechanisms that lead to these experiences are still debated. In this issue of *Current Biology*, Saenz and Koch [4] report a previously unknown form of synaesthesia — 'hearing-motion' synaesthesia, in which seeing moving or flickering visual patterns leads to specific auditory experiences. This form of synaesthesia raises numerous questions about the neural basis of synaesthesia, and promises to shed light on fundamental questions about how the brain integrates information from multiple sensory modalities.

In order to demonstrate the reality of these synaesthetic experiences, Saenz and Koch [4] asked subjects to identify whether two successively presented auditory (beeps) or visual (flashes) sequences were the same or different. Consistent with previous studies, the authors showed that non-synaesthetic control participants were more accurate with auditory sequences than with visual sequences. For each of four hearing-motion synaesthetes, however, performance was no worse for visual sequences than for auditory sequences, consistent with their reports of hearing sounds in response to the visual flashes. This perceptual advantage provides an objective demonstration of the reality of the synaesthetes' reports.

This form of synaesthesia is a challenge for traditional accounts of the neural basis of such experiences, which suggest that synaesthesia arises either from cross-activation between adjacent cortical regions [1] or reduced inhibition of feedback from multisensory areas [5]. Although many visual areas respond strongly to simple flashes and motion, none of these lie

directly adjacent to early auditory areas, contrary to the cross-activation account. Such interactions may, however, be directly mediated by still undiscovered long-range connections between primary visual and auditory cortices similar to those that have been previously demonstrated between primary auditory and visual cortices [6]. Indeed, recent physiological studies have shown that visual stimuli can modulate neural firing rates in primary auditory cortex within about 80 ms of stimulus onset, suggesting fairly direct connections between early visual areas and primary auditory areas [7].

Conversely, numerous brain areas are known to be involved in audio-visual integration, including regions of the parietal cortex and the superior temporal sulcus (for a recent review, see [8]). A recent functional magnetic resonance imaging (fMRI) study [9] has demonstrated increased activity in the superior temporal sulcus to simultaneous audio-visual stimuli compared with non-simultaneous audio-visual stimuli, and shown that multisensory interactions in the superior temporal sulcus drive increased activation of sensory specific visual and auditory areas. This suggests that hearing-motion synaesthesia could arise through increased activation of these same feedback pathways. But this does not explain why these synaesthetic experiences are specific to flashes and motion, as the superior temporal sulcus is also involved in integration of face and voice information [10] and other learned audio-visual pairings, such as between tools and the sounds they make [11]. Clearly, a full understanding of the neural mechanisms of hearing-motion synaesthesia will require substantial progress in understanding the mechanisms of audio-visual integration.

But the interest of this phenomenon is not limited to its implications for models of synaesthesia. Rather, it is hoped that the study of synaesthesia will lead to better understanding of how the brain processes information from multiple sensory modalities [12]. For example, both synaesthetes and non-synaesthetes map higher pitched sounds to brighter lights, suggesting that such mappings arise from mechanisms that are common to everyone [13]. Because the experiences reported by synaesthetes are often exaggerated forms of the same multi-sensory interactions that are present in non-synaesthetes, synaesthesia may serve as a useful 'model system' to explore multisensory interactions, in much the same way that the study of barn owls has served as a useful model system for understanding auditory localization.

Interestingly, hearing-motion synaesthesia, in which visual motion elicits sound percepts, is the converse of a recently described illusion in which two auditory beeps cause a single flash to appear as two flashes [14]. Such illusions are thought to arise because of the greater temporal precision of the auditory system compared with that of the visual system — "modality appropriateness" [15] — and may be mediated by the long-range connections between primary auditory and visual cortices mentioned above [6,16]. Consistent with the modality appropriateness hypothesis, effortful recoding of visual information into an auditory format [17] can increase performance on a task similar to that used by Saenz and Koch [4]. Given that hearing-motion synaesthesia occurs automatically and involuntarily, as do other forms of synaesthesia, it may be a useful model system for exploring audio-visual influences in the temporal domain.

As this is the first report of this form of synaesthesia, there are many open questions which will have to be explored. As discussed above, the neural mechanisms of this form of synaesthesia remain to be explored, but other aspects of this initial report will also require further investigation. For example, Saenz and Koch [4] note that during the experimental session, the synaesthetic sound percepts became more similar to the sound of the beeps used in the auditory sequences. Is this change due to some fundamental difference between hearing-motion synaesthesia and other forms of synaesthesia, or is this similar to rapid acquisition of additional grapheme-colour correspondences reported by some synaesthetes [18]? Similarly, what role do mechanisms of audio-visual plasticity play [19,20] in the genesis of this form of synaesthesia? Clearly there are many open questions to still be investigated, but these explorations will further our understanding not only of synaesthesia, but also the mechanisms by which the brain integrates information from multiple sensory modalities more generally.

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Neurodegeneration: RNA Turns Number One Suspect in Polyglutamine Diseases

Polyglutamine expansion diseases are triggered by the accumulation of toxic proteins. A new study reports that RNA molecules containing long CAG repeats can also be toxic to neurons and may play a significant role in pathogenesis.

Serge Birman

Trinucleotide expansion diseases are known to be of two varieties — those caused by toxic activity of a mutant protein and those triggered by aberrant RNA molecules containing long repeats in untranslated regions (UTRs) [1]. Inherited neurodegenerative disorders, such as Huntington's and Kennedy's diseases, and several forms of spinocerebellar ataxia (SCA) are caused by the expansion of a CAG repeat in translated exons, leading to expression of mutant proteins containing abnormally long polyglutamine domains. Until recently, it was believed that accumulation of the mutant protein was solely responsible for the pathogenesis [2]. In a recent paper [3], Bonini and colleagues describe that RNA toxicity is involved in polyglutamine expansion diseases, thus potentially unifying pathogenic mechanisms generated by non-coding and coding trinucleotide repeats.

The initial finding of these authors that suggested a role of RNA in pathogenesis was the identification of Muscleblind, an RNA-binding protein and a splicing factor [4], as a modifier of the eye phenotype in a *Drosophila* model of Machado-Joseph disease or SCA3 [5]. The protein product of the mutant ataxin-3 gene, which has been implicated in SCA3, contains an expanded polyglutamine tract encoded by around 70 CAG repeats in its carboxy-terminal domain [6,7]. Co-expression of *Drosophila* Muscleblind (the MblA isoform) or human homologue MBNL1 in the *Drosophila* eye markedly accelerated the depigmentation and photoreceptor degeneration that is triggered by pathogenic segments of mutant ataxin-3 [3]. Muscleblind also enhanced eye defects induced by a segment of the Huntington's disease protein but not those mediated by the tau protein, which lacks a polyglutamine domain. Co-expression of Muscleblind also accelerated the death of flies expressing the pathogenic SCA3 protein in all neurons. Conversely, the lifespan of these flies was significantly prolonged in a genetic background heterozygous for a null *muscleblind* allele.

In contrast to the previous results, an altered form of MBNL1 that cannot bind well to RNA did not significantly enhance the eye phenotype triggered by mutant ataxin-3 [3]. The Muscleblind protein is known to bind to CUG or CCUG repeat RNAs, which are the toxic agents of myotonic dystrophy type 1 and 2, respectively. The pathogenic mechanism in these diseases involves the sequestration of Muscleblind and other splicing factors by the mutant RNA in nuclear foci, thus disturbing the normal patterns of splicing in various cell types [4,8,9]. Formation of double-stranded hairpin structures is required for the association of the CUG repeat RNA with Muscleblind. But MBNL1 was also shown to bind CAG repeat RNA, which forms a similar stable double-stranded structure, both *in vitro* and in cultured cells [10,11] (Figure 1). Interestingly, in living flies, overexpression of Muscleblind increased the level of CAG repeat RNA as well as polyglutamine peptides [3], suggesting that this protein increases deleterious phenotypes by stabilizing the pathogenic agent, whether it be RNA or protein.

To determine the exact nature of the toxic agent in their model, Bonini and colleagues [3] engineered a mutant ataxin-3 segment in which the continuous CAG repeat was replaced by an interrupted CAACAG repeat. Both repeats were expected to be translated into the same polyglutamine tract. In spite of similar levels of expressed protein, the eye phenotypes observed with each construct were strikingly different, being much alleviated with the interrupted repeat. Similarly, the lifespan of flies expressing the mutant ataxin-3 in all neurons at the same level was prolonged, but not completely rescued, when the CAG repeat was replaced by the CAACAG repeat. Interestingly, protein inclusions were found at similar abundance in both types of transgenic flies, indicating that intensity of the deleterious phenotypes does not correlate with the number of inclusions. The interrupted CAACAG repeat RNA is not expected to form stable double-stranded hairpin structures. Accordingly, co-expression of Muscleblind only slightly enhanced the eye phenotype observed with the interrupted construct and did not increase the level of this particular RNA.

Therefore, part of the toxicity in SCA3 could be due to the CAG repeat RNA. To determine whether RNA can be toxic in the absence of mutant protein, the authors expressed untranslated expanded CAG repeats inserted in the 3′-UTR of the DsRed gene, an ectopic fluorescent marker. Targeted expression of untranslated CAG repeat RNA in neurons induced progressive locomotor deficits, a reduction in lifespan and brain degeneration in adult flies. Expression in the eye did not modify the external morphology of this organ but resulted in degeneration of the internal retina. Therefore, untranslated CAG repeat RNA appears