100 YEARS AGO

The present position of the Röntgen rays in military surgery was described by Major J. Battersby in a paper read before the Röntgen Society on Tuesday. … After the battle at Omdurman 121 British wounded were conveyed to the surgical hospital at Abadieh. Of that number there were 21 cases in which the bullet could not be found, or its absence proved by ordinary methods. In 20 out of these 21 cases an accurate diagnosis was arrived at with the help of the rays, the odd case, who was suffering from a severe bullet wound in the lung, being too ill for examination at the time. … In many cases the X-rays prevented much suffering to the patient, which would have been caused by probing, the use of the finger, or enlarging the wound in the ordinary search for the bullets, as the skiagraph at once indicated the exact position of the bullet. … With regard to apparatus, the most serious difficulty at present is the best method of generating the primary electrical current for charging the storage batteries. … In the Sudan a small dynamo, driven by means of a tandem bicycle, answered admirably, and was readily transported by rail and river to Abadieh; but as at present constructed, it is unsuitable for mule, camel, or human transport.

From *Nature* 12 January 1899.

50 YEARS AGO

Some months ago, Dr. P. Tate gave a review of white-eyed mutants of Diptera. In his paper Tate stated that in *Calliphora erythrocephala* the male never manifests the white-eyed character. Some years ago a white-eyed mutant of *Calliphora erythrocephala* appeared in our mass cultures, and in this case both white-eyed females and males occurred. We reared the mutant and obtained a mass culture of it. At that time, however, we were busy with other work, and so we did not investigate the mutant as to the mode of inheritance. Unfortunately, after some time the culture was allowed to die out. It is evident that the mutation found in our culture differs from that of Tate, his mutation being sex-limited, which was not the case with ours. It is interesting to note that the same visible character may be due to different gene mutations.

From *Nature* 15 January 1949.

atomic-scale surrounding of an atom. Because cryogenic detectors can be built from many different materials, they may become a tool to study the internal structure of many solids in table-top experiments, without the use of large synchrotron light sources and expensive X-ray monochromators. □

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Neurobiology

Modulation minimizes masking

Brian C. J. Moore

The ability to distinguish auditory signals from background noises is important for many organisms to detect — and avoid becoming — prey. This ability was probably also significant during evolution, and on page 154 of this issue Nelken *et al.*[1] suggest how the auditory system may have evolved to exploit the properties of natural sounds.

Laboratory studies of auditory masking have traditionally used background sounds (maskers) such as white noise, which contains a range of different frequencies. Such noise fluctuates randomly in intensity, and these fluctuations are independent in different frequency regions. For example, if white noise is passed through two band-pass filters, one centred at 500 Hz and the other at 2,000 Hz, the output of the two filters will show independent, random fluctuations in intensity. More recently, 'comodulated' maskers have been used, in which the fluctuations in intensity are correlated in different frequency regions. These can be created by amplitude modulating a white noise with a low-frequency noise. The low-frequency modulator causes the amplitude of the noise to fluctuate slowly in an irregular way, and the pattern of fluctuation is the same in all frequency regions.

Humans are often much better at detecting signals in comodulated maskers than in white noise, an effect called 'comodulation masking release' (CMR)[2–4]. However, the extent to which CMR occurs outside the laboratory is unclear. Now, Nelken *et al.*[1] describe a new way to analyse naturally occurring sounds, and show that many such sounds are comodulated. They also show that the responses of neurons in the cat auditory cortex to a tone signal in noise are greater for comodulated than for unmodulated noise. These findings lead the authors to suggest that the auditory system may have evolved to exploit comodulation in natural situations.

Many properties of auditory masking can be understood in terms of the responses of the basilar membrane within the inner ear (Fig. 1). Each point on this membrane behaves like a filter that responds to a limited range of frequencies. One end is tuned to high frequencies, the other to low frequencies, with a continuous gradation inbetween. These filters are often called 'auditory filters'. Almost 60 years ago, Fletcher[5] proposed that, when trying to detect a sinusoidal tone (such as the sound of a tuning fork) in background noise, listeners use the output of a single auditory filter tuned to the frequency of the tone. That filter passes the tone at full intensity, but rejects most of the background noise. Although this theory can account for many aspects of masking[6], in the mid-1980s Hall *et al.*[2] showed that, when comodulated maskers were used, the results could be explained only if listeners compared the outputs of auditory filters tuned to different frequencies.

Figure 2 compares the masking produced by white noise (filtered to contain a limited range of frequencies around the signal frequency) with that produced by comodulated noise filtered in a similar way. The threshold for detecting the signal is plotted as a function of the range of frequencies in the noise (the bandwidth). As the bandwidth is increased, the total intensity of the masker increases. For

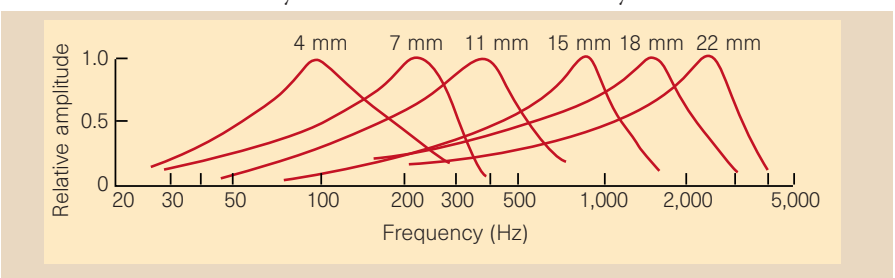

Figure 1 **Frequency responses at six different points along the basilar membrane in the inner ear[8]. The membrane is about 35 mm long, and the position of each point is indicated, measured relative to the end that responds best to low frequencies.**

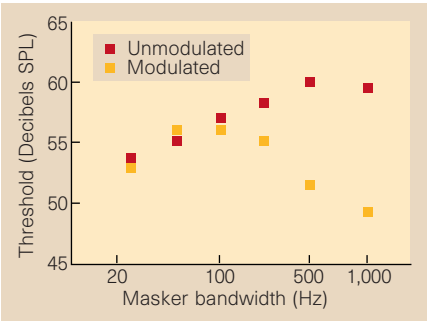

Figure 2 **Thresholds for detecting a 1,000-Hz tone as a function of the bandwidth of a noise masker[2]. One masker is unmodulated (random) noise; the other is comodulated noise. For the unmodulated noise, the masked threshold at first increases as the masker bandwidth is increased . This is because more noise passes through the auditory filter centred at the signal frequency. Beyond a certain bandwidth the threshold no longer increases because the added noise falls outside the pass band of the auditory filter centred at the signal frequency. For the comodulated noise, however, the threshold decreases as the bandwidth is increased beyond 100 Hz. SPL, sound pressure level.**

unmodulated noise, the masked threshold at first increases with the masker bandwidth, but beyond a certain bandwidth the threshold no longer increases. For the comodulated noise, however, the threshold *decreases* as the bandwidth is increased beyond 100 Hz — in other words, adding more noise to the masker makes the signal easier to hear! Presumably, once the noise bandwidth is large enough, listeners can compare the output of the auditory filter centred at the signal frequency with the outputs of filters tuned away from that frequency. When only the comodulated masker is present, the outputs of all filters fluctuate in a similar way over time. But when the signal is present, the common pattern of fluctuation is disrupted, indicating that the signal is there.

Nelken *et al.*[1] first analysed natural sounds such as animal vocalizations. Each sound was decomposed into a noise-like carrier signal and an envelope representing the amplitude modulation of that signal. (The envelope is like a smooth curve, joining the amplitude peaks of the sound.) To check that this was an appropriate way to analyse the sounds, the authors re-synthesized them from the carrier and the envelope. Where the result was similar to the original, the sounds were described as 'separable'. Mixtures of vocalizations and non-animal sounds were usually separable, whereas the calls of single animals were often non-separable. Nelken *et al.* also developed a 'fluctuation index' by which they quantified the extent to which temporal fluctuations in different frequency bands were correlated over time. About 29% of the sounds showed significant comodulation, and the authors attributed this to two factors: first, animals can synchronize their calls to form clusters; and second, local turbulence in the atmosphere can affect the propagation of sounds.

The authors then studied neurons in the primary auditory cortex of the cat, and found that the responses were locked to the temporal envelope of modulated noises. Envelope locking often increased with bandwidth. Adding a tone to these sounds disrupted the pattern of envelope locking, providing a cue for detection of the tone. As with humans (Fig. 2), the reduction increased as the bandwidth of the modulated background increased. So could this be the neuronal mechanism that underlies CMR? That remains to be seen. Experiments with humans indicate that CMR involves selectively listening for the signal during the temporal 'dips' in the masker envelope[3,7]. Also, for human listeners, CMR increases as the masker bandwidth increases over a large range of bandwidths (Fig. 2), whereas the envelope-locking observed by Nelken *et al.* varied with bandwidth only for the narrower bandwidths. Nonetheless, Nelken and colleagues' results certainly represent progress in the search for the neural mechanisms of CMR. □

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Signal transduction

An anchor for activation

Peter ten Dijke and Carl-Henrik Heldin

A critical mechanism for regulating the speed and specificity of signal transduction is to restrict the subcellular localization of the signalling components[1,2]. Anchor proteins, tethered to specific subcellular structures through protein–protein or protein–lipid interactions, can then serve as a platform to bring them together. Members of the transforming growth factor (TGF)-β family, for example, transmit their signals from the plasma membrane to the nucleus through combinations of serine/threonine kinase receptors and their downstream effectors, known as Smads[3].

A report by Tsukazaki *et al.*[4] in *Cell* now shows how the first intracellular step in the TGF-β/Smad pathway occurs. The authors have identified an anchor protein called SARA (Smad anchor for receptor activation), which recruits Smad2 and Smad3 to the TGF-β receptor. Moreover, SARA mutants that interfere with the subcellular localization of Smad2 potently inhibit TGF-β responses, demonstrating the importance of SARA in the TGF-β signalling pathway (Fig. 1, overleaf).

Smads are pivotal to intracellular signalling by members of the TGF-β family. Smad2 and Smad3 are receptor-regulated Smads that interact with, and become phosphorylated by, activated type-I receptor kinases. The phosphorylated Smad then binds Smad4, and this heteromeric complex is translocated to the nucleus where it controls the transcription of target genes.

Tsukazaki and colleagues[4] identified SARA by probing a bacterial expression library with Smad2's conserved carboxy-terminal domain. They found that SARA contains a FYVE domain, a motif that has been identified in 30 other proteins from yeast to mammals[5,6], including the mammalian early endosomal antigen (EEA)-1 and hepatocyte growth-factor-regulated tyrosine kinase substrate (Hrs). Hrs, in fact, also seems to be implicated in signalling downstream of serine/threonine kinase receptors (K. Sugamura *et al.*, personal communication). Moreover, the FYVE domain of EEA1 binds the membrane phospholipid phosphatidylinositol-3-phosphate (PtdIns(3)P)[5,6], suggesting that FYVE domains may be able to anchor proteins at the inner leaflet of the cell. The FYVE domain could act in a similar way to the pleckstrin homology domain which, in several other signal-transduction molecules, recognizes specific polyphosphoinositides[7].

Tsukazaki *et al.* show that the subcellular localization of SARA is controlled through interactions mediated by the FYVE domain, probably via membrane-associated PtdIns(3)P. Immunofluorescence confocal microscopy revealed that, whereas SARA is normally present in a punctuate pattern, SARA mutants that lack the FYVE domain are diffusely localized throughout the cell. But although SARA determines the cellular distribution of Smad2, Smad2 has no effect on SARA localization. So, SARA, which is absent from the nucleus, may help to keep non-activated Smad2 in the cytoplasm. Interestingly, SARA and TGF-β type-II receptors localize to common subcellular domains[8]. Importantly, SARA mutants that are mislocalized, but retain their ability to bind Smad2, fail to direct Smad2 to its appropriate subcellular location and strongly inhibit TGF-β-induced transcriptional responses[4].

The assembly of a heteromeric complex