

- virus-induced type I interferon. *Nat. Immunol.* 4, 1009–1015.
13. Diebold, S.S., Montoya, M., Unger, H., Alexopoulou, L., Roy, P., Haswell, L.E., Al-Shamkhani, A., Flavell, R., Borrow, P., and Reis e Sousa, C. (2003). Viral infection switches non-plasmacytoid dendritic cells into high interferon producers. *Nature* 424, 324–328.
 14. Leitner, W.W., Hwang, L.N., deVeer, M.J., Zhou, A., Silverman, R.H., Williams, B.R., Dubensky, T.W., Ying, H., and Restifo, N.P. (2003). Alphavirus-based DNA vaccine breaks immunological tolerance by activating innate antiviral pathways. *Nat. Med.* 9, 33–39.
 15. Williams, B.R., and Sen, G.C. (2003). Immunology. A viral on/off switch for interferon. *Science* 300, 1100–1101.
 16. Jacobs, B.L., and Langland, J.O. (1996). When two strands are better than one: the mediators and modulators of the cellular responses to double-stranded RNA. *Virology* 219, 339–349.
 17. Yang, Y., Huang, C.T., Huang, X., and Pardoll, D.M. (2004). Persistent Toll-like receptor signals are required for reversal of regulatory T cell-mediated CD8 tolerance. *Nat. Immunol.* 5, 508–515.
 18. Lang, K.S., Recher, M., Junt, T., Navarini, A.A., Harris, N.L., Freigang, S., Odermatt, B., Conrad, C., Ittner, L.M., Bauer, S., et al. (2005). Toll-like receptor engagement converts T-cell autoreactivity into overt autoimmune disease. *Nat. Med.* 11, 138–145.
 19. Fujii, S., Liu, K., Smith, C., Bonito, A.J., and Steinman, R.M. (2004). The linkage of innate to adaptive immunity via maturing dendritic cells *in vivo* requires CD40 ligation in addition to antigen presentation and CD80/86 costimulation. *J. Exp. Med.* 199, 1607–1618.
 20. Silk, J.D., Hermans, I.F., Gileadi, U., Chong, T.W., Shepherd, D., Salio, M., Mathew, B., Schmidt, R.R., Lunt, S.J., Williams, K.J., et al. (2004). Utilizing the adjuvant properties of CD1d-dependent NK T cells in T cell-mediated immunotherapy. *J. Clin. Invest.* 114, 1800–1811.

Tumour Immunology Unit, Cancer Research UK, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DS, UK.
1E-mail: mariolina.salio@molecular-medicine.oxford.ac.uk
2E-mail: vincenzo.cerundolo@molecular-medicine.oxford.ac.uk.

DOI: 10.1016/j.cub.2005.04.025

Multisensory Integration: Strategies for Synchronization

Recent studies have shown that our ability to match the timing of inputs from objects that can be both seen and heard is highly adaptable and takes into account target depth and the relatively slow speed of sound.

Andrew J. King

The ability of animals to detect individual events in the external world using more than one sense has a considerable impact on perception and behaviour. Combining information across the senses about a common source can improve the localization and discrimination of objects and speeds up reactions to them [1]. But this relies on the binding together of appropriate multisensory signals — those originating from the object in question as opposed to other, unrelated stimuli. Temporal synchrony is a particularly powerful binding cue, and the results of several recent studies have revealed that humans are able to maintain accurate judgments of when visual and auditory cues occur simultaneously, despite variations in the relative time it takes for the signals to arrive.

A number of neural and non-neural factors influence how long it takes for the visual and auditory signals arising simultaneously from a common source to reach multisensory neurons in the brain. Sound travels much more slowly

than light and therefore arrives later. On the other hand, the process of sound transduction by the hair cells of the inner ear is many times faster than phototransduction in the retina [2]. This gives rise to a difference in the response latency of auditory and visual neurons of around 40–50 milliseconds, which is further increased by the longer neural transmission times in the visual system (Figure 1).

A range of temporal disparities exists within which humans are unable to tell that auditory and

visual signals are asynchronous [3,4]. In keeping, however, with the inter-sensory difference in neural processing time, the stimuli are generally judged to be simultaneous when the sound is delayed relative to the light [5,6]. The required delay can, of course, occur naturally because of the difference in their velocities. Moreover, by introducing a delay that offsets the difference in response latency, it has been shown that auditory and visual signals arriving together at multisensory neurons, such as those in the superior colliculus, often interact to produce enhanced responses [7,8].

However, neither the relative time of arrival nor the neural transmission times within the central nervous system are fixed. For example, response latencies of nerve cells vary to some extent with factors such as stimulus

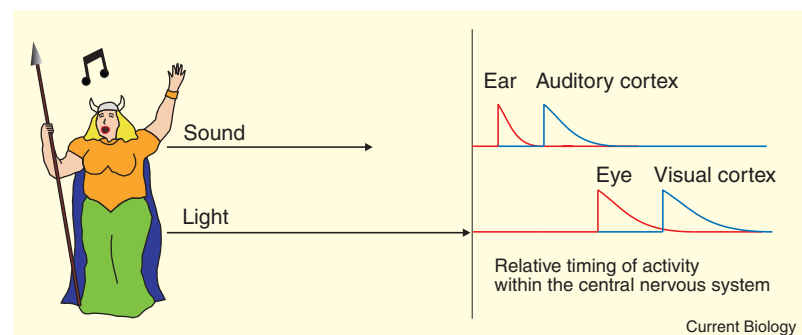


Figure 1. The timing of visual and auditory events in the brain.

Because of the relatively slow speed of sound, auditory stimuli reach the observer slightly later than visual stimuli, by an amount that varies with source distance. But auditory transduction in the ear is faster than visual transduction in the eye. Moreover, because of the greater distances involved, the neural transmission time from the sense organs to the cerebral cortex is longer in the visual system.

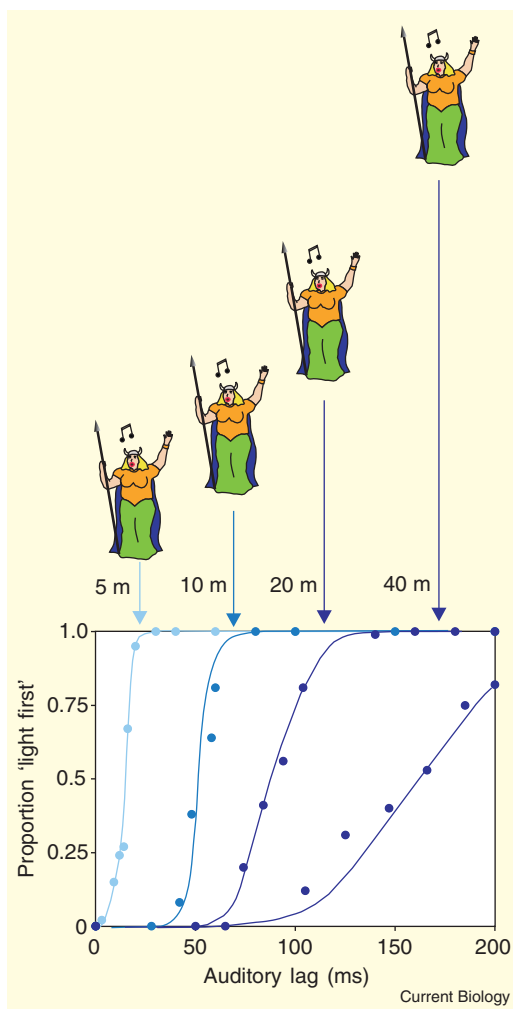


Figure 2. Judgments of visual–auditory simultaneity scale with auditory depth and therefore compensate for the variable sound travel time from the source to the subject.

Psychometric functions are shown for one observer at each of four auditory distances. These plot the proportion of trials in which the visual stimulus was judged to have occurred before the auditory stimulus, as a function of the delay or lag of the auditory stimulus. As the distance of the source increases, progressively larger delays between the arrival of the light and the sound are needed for the signals to be judged as simultaneous, as defined by the half-height of the psychometric functions. (Based on [14].)

intensity and contrast and, in the case of visual stimuli, with the region of the retina that is stimulated [9]. More importantly, because of its relatively slow velocity, the time taken for sound to arrive at the ears scales with distance, whereas light reaches the photoreceptors effectively instantaneously at all distances. Consequently, the inter-stimulus delay needed to cancel the difference in neural processing time is provided only over a relatively narrow range of target distances, implying a limit on our ability to use temporal synchrony to bind multisensory signals.

Compensating for Target Distance

One way round this would be for the temporal window within which auditory and visual signals are perceived as being simultaneous to vary depending on the distance of the multisensory event from the

observer. Several attempts have now been made to investigate this issue [9–14]. Although the findings of these studies are mixed, there is growing evidence that the brain incorporates information about target depth and sound velocity when judging that different modality signals are temporally aligned.

The inter-stimulus interval at which auditory and visual stimuli are perceived as simultaneous can be estimated by presenting pairs of sounds and lights with variable delays between them and measuring the interval at which the subject can no longer tell which one came first. This is then repeated at different real or simulated target distances. In the absence of any compensation for sound velocity, we would expect to find that as target distance is increased, a progressive delay of the light relative to the sound is required for the signals to be

perceived as temporally coincident. In fact, the opposite result has been reported in studies in which the distance of the visual stimulus [12], auditory stimulus [14] or both [9,10] have been varied.

In the most recent of these studies, Alais and Carlile [14] simulated distant sounds by mixing brief noise bursts with an impulse response function that had previously been measured in the Sydney Opera House. The stimulus comprised an initial component, representing the sound energy that reaches the subject's ears directly from the source, plus a long reverberant tail due to multiple reflections from the auditorium walls. The ratio of the direct-to-reverberant energy — the major cue for auditory distance perception [15,16] — was varied by reducing the amplitude of the direct component of the signal while leaving the reverberant tail unchanged.

As with other studies in which stimulus distance was varied [9,12], Alais and Carlile [14] found that as the simulated source distance was increased, the auditory stimulus had to be delayed by an amount corresponding to the additional sound travel time in order for it to be aligned with the visual stimulus (Figure 2). This equates to the stimuli being perceived as simultaneous at the point when they are actually produced by the multisensory source. Interestingly, loudness cues alone were insufficient to induce this shift in the visual–auditory interval corresponding to subjective simultaneity. This — and the greater distances involved — would explain why the flashes and bangs of a firework rarely appear to be synchronized.

Recalibrating Perceptual Estimates of Simultaneity

Further insights into how multisensory synchronization is maintained have come from studies in which subjects have been exposed for a few minutes to auditory and visual stimuli separated by a fixed time lag [17,18]. This resulted in a shift in the interval at which the sound and

light were adjudged to occur simultaneously in the direction of the time lag experienced during the exposure period. In other words, humans can recalibrate their percept of visual-auditory temporal synchrony, apparently in much the same way they adapt to cross-modal spatial conflicts [5,19].

The results of all of these studies indicate that a dynamic neural mechanism exists for matching the auditory and visual signals arising from a multisensory event. It could be argued that this is rarely needed for coordinating the lip movements and speech sounds of a person within normal conversational range. Nevertheless, when they do occur, changes in physical transmission time and neural processing time appear to be accommodated by shifting the window of integration on the basis of experience or when reliable depth cues are present. This in turn implies flexibility in the capacity of neurons to register the relative timing of multisensory signals and therefore highlights a potentially useful way of probing the adaptive capabilities of the brain.

References

1. Calvert, G.A., Spence, C., and Stein, B.E., eds. (2004). *The Handbook of Multisensory Processes*. (Cambridge, MA: MIT Press.)
2. Fain, G.L. (2003). *Sensory Transduction*. (Sunderland, MA: Sinauer Associates.)
3. Dixon, N.F., and Spitz, L. (1980). The detection of auditory visual desynchrony. *Perception* 9, 719–721.
4. Munhall, K.G., Gribble, P., Sacco, L., and Ward, M. (1996). Temporal constraints on the McGurk effect. *Percept. Psychophys.* 58, 351–362.
5. Slutsky, D.A., and Recanzone, G.H. (2001). Temporal and spatial dependency of the ventriloquism effect. *Neuroreport* 12, 7–10.
6. Lewald, J., and Guski, R. (2003). Cross-modal perceptual integration of spatially and temporally disparate auditory and visual stimuli. *Brain Res. Cogn. Brain Res.* 16, 468–478.
7. King, A.J., and Palmer, A.R. (1985). Integration of visual and auditory information in bimodal neurones in the guinea-pig superior colliculus. *Exp. Brain Res.* 60, 492–500.
8. Meredith, M.A., Nemitz, J.W., and Stein, B.E. (1987). Determinants of multisensory integration in superior colliculus neurons. I. Temporal factors. *J. Neurosci.* 7, 3215–3229.
9. Kopinska, A., and Harris, L.R. (2004). Simultaneity constancy. *Perception* 33, 1049–1060.
10. Engel, G.R., and Dougherty, W.G. (1971). Visual-auditory distance constancy. *Nature* 234, 308.
11. Stone, J.V., Hunkin, N.M., Porrill, J., Wood, R., Keeler, V., Beanland, M., Port, M., and Porter, N.R. (2001). When is now? Perception of simultaneity. *Proc. R. Soc. Lond. B. Biol. Sci.* 268, 31–38.
12. Sugita, Y., and Suzuki, Y. (2003). Implicit estimation of sound-arrival time. *Nature* 427, 911.
13. Lewald, J., and Guski, R. (2004). Auditory-visual temporal integration as a function of distance: no compensation for sound-transmission time in human perception. *Neurosci. Lett.* 357, 119–122.
14. Alais, D., and Carlile, S. (2005). Synchronizing to real events: subjective audiovisual alignment scales with perceived auditory depth and speed of sound. *Proc. Natl. Acad. Sci. USA* 102, 2244–2247.
15. Bronkhorst, A.W., and Houtgast, T. (1999). Auditory distance perception in rooms. *Nature* 397, 517–520.
16. Moore, D.R., and King, A.J. (1999). Auditory perception: The near and far of sound localization. *Curr. Biol.* 9, R361–R363.
17. Fujisaki, W., Shimojo, S., Kashino, M., and Nishida, S. (2004). Recalibration of audiovisual simultaneity. *Nat. Neurosci.* 7, 773–778.
18. Vroomen, J., Keetels, M., de Gelder, B., and Bertelson, P. (2004). Recalibration of temporal order perception by exposure to audio-visual asynchrony. *Brain Res Cogn Brain Res* 22, 32–35.
19. Vroomen, J., and de Gelder, B. (2004). Perceptual effects of cross-modal stimulation: Ventriloquism and the freezing phenomenon. In *The Handbook of Multisensory Processes*. G.A. Calvert, C. Spence, and B.E. Stein, eds. (Cambridge, MA: MIT Press), pp. 141–150.

University Laboratory of Physiology,
Parks Road, Oxford OX1 3PT, UK.

DOI: 10.1016/j.cub.2005.04.022

Sensorimotor Integration: Locating Locomotion in Neural Circuits

Neural components of the circuits that transform sensory cues into changes in motor activities are largely unknown. Several recent studies have now functionally mapped the sensorimotor circuits responsible for locomotion behaviors under defined environmental conditions in the nematode *Caenorhabditis elegans*.

Aravinthan D.T. Samuel¹ and Piali Sengupta²

Animals are able to navigate diverse and complex environments by transforming sensory cues into patterns of locomotion. The autonomous navigation capabilities of robots are crude in comparison to the highly evolved sensorimotor strategies of living organisms. Bacteria are able to swim up or down chemical gradients using a biased random walk determined by a biochemical system occupying just 1 femtoliter [1]. The

nematode is able purposefully to navigate the mechanical, chemical and thermal heterogeneities in its soil habitat using strategies wired into a neural circuit with only 302 neurons [2]. Our technology is far from matching these remarkable feats of sensorimotor integration. Nevertheless, studying the underlying mechanisms might uncover the solutions that have evolved to address these complex navigational problems, perhaps improving our own design efforts.

Mapping an entire sensorimotor circuit in an animal requires knowledge of the underlying

anatomical connectivities of the nervous system, and the ability to manipulate the functions of the component neurons and to define and quantify the behavioral outputs. The nematode *Caenorhabditis elegans* meets all these requirements with the additional benefits of physiology and powerful genetics. But having a ‘wiring diagram’ — an anatomical description of the connectivities of all neurons — is not enough. Neurons are highly interconnected: practically every neuron has multiple synaptic inputs and outputs, an intricate Gordian knot of synaptic connectivity [2]. Only a few previous studies [3–5] have attempted to ascribe functions to these connections. In three studies [6–8] of the sensorimotor correlates of worm locomotion, we are beginning to see the knot unravel.

Worm locomotion lends itself to quantitative description as it can