channel affinity at night and decreases it during the day. Interestingly, inhibition of Erk phosphorylation also inhibits rhythmic changes in CamKII, while inhibition of CamKII phosphorylation does not affect changes in p-Erk. Based on this finding, the authors suggest that Erk is upstream of CamKII in a signaling pathway from the clock (see figure).

The simplest and most plausible interpretation is that the cultured photoreceptors are cell autonomous oscillators driving changes in Erk and CamKII to control physiology at the level of the cGMP-gated channel. A potential caveat is that the measured changes were from mixed cell cultures. Although the cultures were enriched in photoreceptors, the factors driving circadian changes in Erk and CamKII are not known and could involve intercellular signals. Within the intact retina, the diffusible modulators melatonin and dopamine, driven at least in part by circadian oscillators, play such a role, and dopamine receptors that modulate cAMP levels are found on photoreceptors (Cahill and Besharse, 1993, 1995). Molecular definition of the mechanisms that couple the "clock" to changes in Erk and CamKII phosphorylation would clarify this issue.

Like most significant contributions, that of Ko, Ko, and Dryer may prove most important in raising new questions. For example, how does Erk and CamKII activity control channel gating? Previous work has shown that the cGMP-gated channel of rods can be modified by phosphorylation (Molokanova et al., 1997) and by Ca^{2+}/calmodulin binding (Hsu and Molday, 1993). However, in the absence of direct analysis of channel phosphorylation by Erk and CamKII, it remains possible that the effects are indirect.

Likewise, the molecular mechanism coupling the clock to rhythmic changes in Erk and CamKII activity is not directly addressed. Circadian clocks often control rhythmicity through transcriptional regulation of downstream genes, and this can occur through a mechanism similar to that of CLOCK/BMAL regulated transcription of oscillating clock genes . However, Erk protein abundance does not vary during the day; it is p-Erk that is rhythmically controlled. Thus, one must look upstream of MEK1, the enzyme responsible for activating Erk, or to the phosphatases necessary for Erk dephosphorylation. It is also likely that cross-talk between Erk and other signaling pathways is involved. For example, dopamine-induced decreases in cAMP at night are known to mediate phase shifts in the core photoreceptor oscillator (Hasegawa and Cahill, 1999), and the cAMP pathway can lead to increased activation of Erk in some system.

Recent reports relating Erk activation to circadian phase shifting suggests a more general role for p-Erk in clock cells. For example, a rhythm in p-Erk similar to that reported by Ko et al. has also been seen in chick pinealocytes. Here light acutely reduces p-Erk at night, and inhibition of Erk phosphorylation appears to phase shift the clock (Sanada et al., 2000). p-Erk has also been implicated in circadian phase shifting in the mammalian suprachiasmatic nucleus (Obrietan et al., 1998). Interestingly, cross-talk with a cAMP signaling system involved in phase shifting (Ginty et al., 1993) may be of significance in the mammalian systems.

The studies on phase shifting differ from that of Ko et al. in that p-Erk is proposed to be in an "input" pathway to the clock. Although based on different systems that could use p-Erk signaling in different ways, these data raise the interesting question of whether p-Erk plays a role both as an "output" and an "input" of the clock. Recent modeling of circadian clocks suggests that rhythmic clock outputs can feedback onto the core oscillator to increase its overall stability (Roenneberg and Merrow, 2000). What is needed now is to determine whether p-Erk plays a role in both phase shifting and in output pathways in the same cellular clock system.

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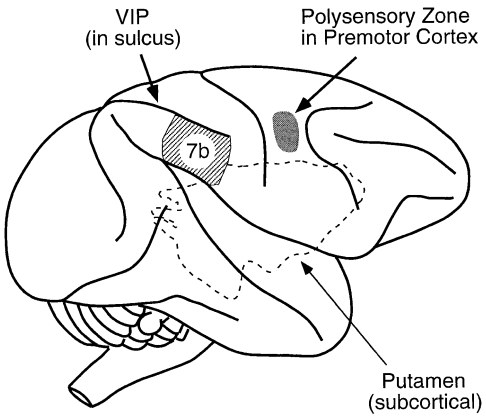
A System of Multimodal Areas in the Primate Brain

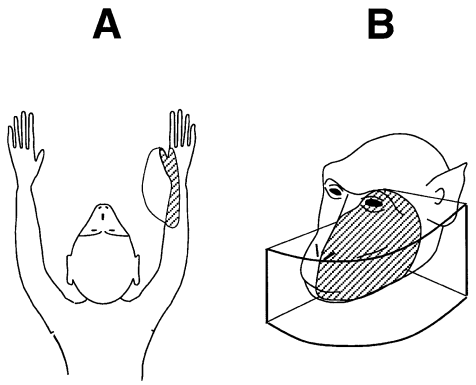
The primate cerebral cortex has traditionally been divided into separate territories for vision, touch, audition and movement. These functions are known to overlap in many parts of cortex, but until recently the regions of overlap were not well studied. In this issue of *Neuron*, Bremmer et al. (2000) report a major advance in understanding at least one set of areas in the human brain in which the senses are integrated. This finding joins a growing set of work in monkeys and humans on the integration of the senses with each other and with the control of movement.

Vision, touch, and audition converge in many areas of the monkey brain, including the deep layers of the



Side View of a Macaque Monkey Brain Showing the Location of Four Interconnected Multimodal Areas

VIP: ventral intraparietal area.



Two Examples of Bimodal, Visual-Tactile Neurons from Premotor Cortex

In both cases, the tactile receptive field (stippled) matched the location of the visual receptive field (outlined).

superior colliculus, the superior temporal polysensory area, the putamen, the intraparietal sulcus, and parts of premotor cortex (Graziano and Gross, 1996). Multimodal responses can also be induced in a variety of brain areas with appropriate training. Tell a person to imagine a picture of a cat, and visual cortex becomes active; in this case, an entrained auditory signal activates a part of cortex that is usually only visual (Goldenberg et al., 1989). Train a monkey to associate a felt object or a sound with a picture, and visual cortical areas respond to these nonvisual stimuli (Heanny et al., 1988; Colombo and Gross, 1994). In other words, perhaps as a function of mental imagery, the neurons can respond to a range of sensory stimuli.

Among this catalog of multimodal brain areas, one interconnected set of areas stands out for its distinctive response properties. These areas are shown in the first figure in a side view of the monkey brain. Neurons in these areas respond to the sight, sound, and feel of objects moving in the space near the body, usually within reaching distance (Graziano and Gross, 1998). These responses do not depend on training the monkey on a task and are robust even in anesthetized monkeys. Most of these multimodal neurons are directionally selective. They may respond, for example, to a tactile stimulus swept across the skin in one direction, but not in the opposite direction. The same neurons will usually have a matching directional preference for visual stimuli moving in the space near the tactile receptive field. Some neurons prefer visual stimuli moving toward or away from the body.

These multimodal response have been studied most thoroughly in monkey premotor cortex (Rizzolatti et al., 1981; Graziano et al., 1997). Though sensory responses can be found throughout all of premotor cortex, especially in trained monkeys, this particular type of multimodal response to nearby objects is found only in a few clusters usually just posterior to the bend in the arcuate sulcus. The second figure shows the response properties of two bimodal, visual-tactile neurons studied in premotor cortex. In each case, the neuron responded when the monkey saw or felt an object near a particular part of the body. Other neurons in premotor cortex are trimodal, responding to tactile, visual, and auditory stimuli. Remarkably, these trimodal neurons are able to distinguish the distance to the sound source; they respond best to nearby sounds regardless of the intensity of the stimulus (Graziano et al., 1999).

Almost identical neuronal responses encoding the space near the body have been described in the putamen and also in areas 7b and VIP in the parietal lobe (Colby et al., 1993; Graziano and Gross, 1996). These brain areas are all monosynaptically interconnected and therefore appear to form a single integrated system. However, even though the sensory properties of these neurons have been extensively characterized, their function is still unknown. One hypothesis is that they detect and localize threatening objects near the body and help to organize a defensive reaction.

Does the human brain also contain a set of areas that processes the sight, sound, and feel of objects moving in the space near the body? Bremmer et al. (2000) presented visual, tactile, and auditory stimuli to human subjects in an MRI scanner. These three types of stimulation were presented on separate trials. The tactile stimulus was a stream of air blowing across the face. The visual stimulus was a display of moving dots on a screen. The auditory stimulus, presented through headphones, gave the illusion of a sound source travelling in front of the subject's face from one side to the other. As expected, the moving visual stimulus, when compared to a control stimulus that was stationary, activated areas in the occipital, temporal, and parietal lobes that are known to be visually responsive. The tactile stimulus, when compared to a resting control condition, activated primary and secondary somatosensory areas. The auditory stimulus, when compared to a resting control condition, activated primary and secondary auditory areas. Thus, the traditional, separate territories for vision, touch, and audition were engaged.

In addition to these expected activations in the primary and secondary sensory areas, other presumably higher-order brain areas were also activated. Several brain areas in particular appeared to be multimodal. They became active whether visual, tactile, or auditory stimuli were presented. One of these multimodal areas

was located in the intraparietal sulcus, closely matching the location of the multimodal area VIP in the monkey brain as shown in the first figure. A second area was in a restricted part of premotor cortex, closely matching the multimodal region of monkey premotor cortex. A third area was in the upper bank of the lateral fissure. The correspondence to the monkey brain is less clear in this case. Part of monkey area 7b extends into the upper bank of the lateral fissure and therefore perhaps corresponds to this region of activation in the human brain. There are, however, other areas in the monkey lateral fissure that may also be multimodal but that are almost totally unstudied (Robinson and Burton, 1980). Clearly more monkey single-neuron experiments are now needed to explore this relatively unknown territory.

In summary, Bremmer et al. (2000) show that the human brain contains a system of multimodal areas similar to those in the monkey brain. The function of these areas is not yet clear. As in the case of the monkey, perhaps they play a role in detecting nearby threatening objects and coordinating a defensive reaction.

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