

tation experiments showed that this was indeed the case.

In a final series of experiments, Huang et al. demonstrated that CAK β /Pyk2-evoked increases in synaptic responses occlude LTP and are NMDA receptor and Ca²⁺ dependent. Infusion of CAK β /Pyk2 into CA1 neurons caused an \sim 3-fold increase in AMPA receptor EPSP slope, and no further long-term increase was evoked by subsequent tetanic stimulation. Importantly, infusion of CAK β /Pyk2 into neurons in which NMDA receptors were blocked with MK-801 did not show an increase in EPSP slope. These results show that CAK β /Pyk2 does not modulate AMPA receptors directly and that NMDA receptor activation is required for the CAK β /Pyk2 evoked increase in AMPA-mediated synaptic responses. Inclusion of the calcium chelator BAPTA (10 mM) prevented the CAK β /Pyk2-mediated increase in AMPA receptor EPSPs. The CAK β /Pyk2-mediated increase in NMDA receptor EPSCs in slices and the NMDA receptor component of mMPSCs in cultures were not blocked by increased calcium buffering.

The results are impressive, but there are some interesting aspects and implications of the work that are yet to be determined. For example, these authors have reported previously that Src-induced potentiation of AMPA receptors is Ca²⁺ dependent, whereas Src-induced potentiation of NMDA receptors is Ca²⁺ independent (Lu et al., 1998). These data suggest that the Ca²⁺-sensitive step occurs after tyrosine phosphorylation of NMDA receptors but prior to enhancement of AMPA receptor function. As summarized above, increased calcium buffering prevents CAK β /Pyk2-evoked potentiation of AMPA EPSPs but not CAK β /Pyk2-evoked increases in NMDA receptor function. However, in their Discussion, the authors suggest that activation of CAK β /Pyk2 is likely to be by Ca²⁺ and/or PKC; indeed, the Ca²⁺ sensitivity of CAK β /Pyk2 is well documented (Girault et al., 1999). It is therefore unclear what signal leads to CAK β /Pyk2 activation following tetanic stimulation. One possibility could be a Ca²⁺-independent isoform of PKC.

Another aspect of particular interest is the possible contribution of G $\alpha_{q/11}$ -coupled G protein-coupled receptors (e.g., group 1 mGluRs). It has been shown that the G $\alpha_{q/11}$ -coupled muscarinic and lysophosphatidic (LPA) receptors activate Src via PKC to enhance NMDA receptor currents (Lu et al., 1999). Separately, it has been reported that activation of group 1 mGluRs can also potentiate NMDA responses (Fitzjohn et al., 1996). These observations open the intriguing question of whether the CAK β /Pyk2-Src pathway is involved in the cross-talk between mGluRs and NMDA receptors and how this relates to LTP induction.

A related question is what is the role of the Src family kinase Fyn in this system? Deletion of the gene encoding Fyn alters FAK phosphorylation and impairs LTP (Grant et al., 1992). Infusion of Fyn potentiates NMDA receptor-mediated currents, and it has been shown to interact with the NR2A subunit via the scaffold protein PSD95 (Tezuka et al., 1999), although it was not detected in the NMDA receptor multiprotein complex by Grant and coworkers (Husi et al., 2000).

The work reported by Huang and coworkers represents a further step toward our understanding of the complex interplay between proteins during the induction

of LTP. The realization of the importance of the tyrosine kinases in this phenomenon and continued focus on the roles they play, and the mechanisms by which they are activated, will continue to shed new light on the molecular processes underlying synaptic potentiation.

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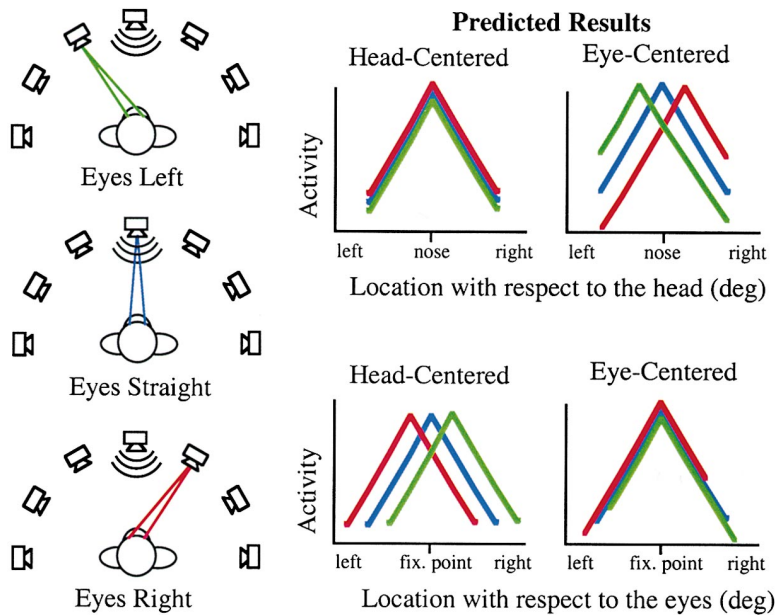
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Hearing and Looking

Many objects in the real world have multiple sensory attributes—for example, an object may both reflect light and emit sound. This leads to the percept that both the sound and the light originate from the same object, even though the neural processing of spatial information by the visual and auditory system is very different. In the visual system, space is encoded at the level of the retina based on the position of the activated photoreceptors. Thus, visual space must initially be represented in an eye-centered reference frame. In the auditory system, spatial information must be computed based on differences in intensity and timing of the stimulus at the two ears and on spectral cues resulting from reflections of the stimulus by the torso, head, and pinnae. Thus, since the ears are fixed to the head, auditory spatial information should be represented in a head-centered reference frame. At some point in the nervous system, these two



the neuron would have the greatest response to the right of the fixation point when the monkey is looking toward the left, and the reverse when the monkey is looking toward the right. If the neuron responded in an eye-centered reference frame, the opposite would be true. Groh et al. (2001) found something between these two.

reference frames must somehow align in order to create the unified percept of a single object.

A central question is what reference frame(s) the nervous system uses to encode the spatial attributes of single- and multimodal stimuli and how these reference frames could be used to generate unified percepts. Several studies have investigated how the position of an auditory stimulus relative to the head and to the eyes modulates neuronal responses in multimodal regions of the brain (see Andersen, 1997). For example, in the parietal lobe (Stricanne et al., 1996) and the superior colliculus (Jay and Sparks, 1987), the responses of neurons to auditory stimuli are modulated by the eye position, so most of these neurons do not represent space in a purely head-centered reference frame. What has not been carefully examined is how early in the processing pathway that the reference frame of auditory neurons can be modulated.

The results from experiments tackling this issue are reported by Groh et al. (2001) in this issue of *Neuron*. They measured the responses of single neurons to noise stimuli in the inferior colliculus while monkeys were either looking to the left, to the right, or straight ahead (see figure, left column). The inferior colliculus has traditionally been considered a “relay” nucleus, in which inputs from the auditory brainstem converge and are then relayed to the thalamus. One would therefore expect these neurons to encode acoustic space in a head-centered reference frame (see figure, middle column), and not an eye-centered reference frame (see figure, right column). Groh et al. (2001) found that approximately one-third of the neurons encountered showed neither a head-centered nor an eye-centered reference frame, but something in between.

This result indicates that the visual system can influ-

Head-Centered versus Eye-Centered Reference Frames

The left column shows a schematic of the types of trials used in the experiments by Groh et al. (2001). In this example, the speaker located directly in front of the monkey emits a noise stimulus, but the monkey may be fixating on a visual target to the left (top, green lines), directly ahead (middle, blue lines), or to the right (bottom, red lines). For each cell, all auditory locations were tested with the monkey fixating each of these three different targets. The plots in the right two columns show the expected results depending on whether the neuron’s reference frame is head-centered (left) or eye-centered (right). Each colored line represents the neural response when the monkey is fixating at one of the three locations and is plotted as a function of the auditory stimulus location relative to the orientation of the head (top two plots); the same data are replotted centered on the fixation point (bottom two plots). For a head-centered reference frame, the three colored lines should be superimposed when plotted with respect to the head. When plotted with respect to the fixation point, in this example,

ence auditory spatial processing at a very early level and raises several interesting questions. How is the eye position information incorporated in the responses of inferior collicular neurons? How does eye position influence the spatial processing of other auditory areas such as the thalamus and cortex? Is it the strategy of the nervous system to encode spatial information across all sensory modalities in a similar reference frame as soon as possible? Investigating these questions should provide key insights into general mechanisms of sensory representations and perception.

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