atory postsynaptic currents, indicating that compensatory rearrangement of connections had preserved synaptic function.

Unsurprisingly, given the actin binding and PIP_2-modulating functions of the effector domain, the changes in spine morphology produced by transfecting MARCKS phosphorylation mutants were accompanied by reorganization of the actin cytoskeleton. The effects were opposite for pseudophosphorylated MARCKS, which enhanced the clustering of actin at the tips of spines, and the nonphosphorylatable mutant, which instead induced dispersal of actin clusters away from the spine tip. These differences were also reflected in their effects on actin filament dynamics, which produce rapid changes in the shapes of spine heads (Dunaevsky et al., 1999; Fischer et al., 1998). This motile activity was significantly reduced in cells expressing pseudophosphorylated MARCKS, whereas the nonphosphorylatable mutant had no detectable effect. Actin-dependent spine motility is downregulated by glutamate receptor activation (Fischer et al., 2000; Korkotian and Segal, 2001; Richards et al., 2004), suggesting that MARCKS phosphorylation may represent one of the pathways involved in receptor-dependent regulation of spine plasticity.

What, then, are the signaling events involved in these effects of MARCKS phosphorylation? To answer this question Calabrese and Halpain examined the effects of treating cultured cells with a phorbol ester, which activates neuronal PKC, and found the same loss of spines and shrinkage of those remaining that they had earlier produced by transfecting cells with pseudophosphorylated MARCKS. Significantly, transfecting cells with the nonphophorylatable form of MARCKS could antagonize these effects of phorbol ester. Altogether these observations are consistent with a scheme in which activity-induced phosphorylation of MARCKS by PKC inhibits its interaction with cell membrane, unmasking PIP_2 clusters associated with lipid rafts, which then signal to the actin cytoskeleton to alter spine motility and morphology. This interpretation is supported by experiments in which direct manipulation of lipid rafts was shown to strongly affect the maintenance of spine morphology (Hering et al., 2003). However, phosphorylation of the effector domain also influences binding to calcium/calmodulin, suggesting that MARCKS has additional effects on neuronal function beyond those addressed by these experiments.

Ultimately, these experiments should help untangle some of the complexities of MARCKS function and its relationship to PKC-dependent plasticity mechanisms. This should not only further our understanding of the cellular mechanisms involved in learning and memory but may also shed some light on evidence for abnormal MARCKS expression in patients with bipolar disorders and suicide victims (McNamara et al., 2005).

Andrew Matus
Friedrich Miescher Institute
Maulbeerstrasse 66
4058 Basel
Switzerland

Selected Reading

Calabrese, B., and Halpain, S. (2005). Neuron *48*, this issue, 77–90.

Dunaevsky, A., Tashiro, A., Majewska, A., Mason, C., and Yuste, R. (1999). Proc. Natl. Acad. Sci. USA *96*, 13438–13443.

Fischer, M., Kaech, S., Knutti, D., and Matus, A. (1998). Neuron *20*, 847–854.

Fischer, M., Kaech, S., Wagner, U., Brinkhaus, H., and Matus, A. (2000). Nat. Neurosci. *3*, 887–894.

Hering, H., Lin, C.C., and Sheng, M. (2003). J. Neurosci. *23*, 3262–3271.

Holtmaat, A.J., Trachtenberg, J.T., Wilbrecht, L., Shepherd, G.M., Zhang, X., Knott, G.W., and Svoboda, K. (2005). Neuron *45*, 279–291.

Janmey, P.A., and Lindberg, U. (2004). Nat. Rev. Mol. Cell Biol. *5*, 658–666.

Korkotian, E., and Segal, M. (2001). Neuron *30*, 751–758.

Laux, T., Fukami, K., Thelen, M., Golub, T., Frey, D., and Caroni, P. (2000). J. Cell Biol. *149*, 1455–1472.

McNamara, R.K., Hussain, R.J., Simon, E.J., Stumpo, D.J., Blackshear, P.J., Abel, T., and Lenox, R.H. (2005). Hippocampus *15*, 675–683.

Richards, D.A., De Paola, V., Caroni, P., Gahwiler, B.H., and McKinney, R.A. (2004). J. Physiol. *558*, 503–512.

Sheu, F.S., McCabe, B.J., Horn, G., and Routtenberg, A. (1993). Proc. Natl. Acad. Sci. USA *90*, 2705–2709.

DOI 10.1016/j.neuron.2005.09.013

Neural Gallops across Auditory Streams

We continually rely on our ability to segregate the myriad sounds in our environment—phones ringing, people talking—into separate "auditory streams," each originating from a different source. In this issue of *Neuron*, Micheyl et al. provide the most direct evidence to date linking single-unit spiking responses from auditory cortex to the perception of distinct auditory streams.

Imagine that you are in a noisy auditorium at the Society for Neuroscience meeting — part of a crowd listening to a poster presentation. You are dimly aware of a woman's voice behind you. Suddenly, you hear your name. Your attention shifts and you recognize the voice: your NIH program officer! And she is saying . . . . Well, what she is saying is beyond the scope of this preview; but we often find ourselves in situations such as this that require us to pick out one conversation among many in a crowd. This is sometimes called the "source separation problem" or the "cocktail party problem." The source separation problem is not limited to humans; a monkey similarly must be able to detect the cry of a dominant member of a troop amidst the cacophony of the jungle. Stream segregation is such a difficult problem that, except under special circumstances, no known computer algorithm works well in real-world scenarios in which many concurrent streams are present (Bell and Sejnowski, 1995; Zibulevsky and Pearlmutter, 2001). Happily, both we humans and mon-

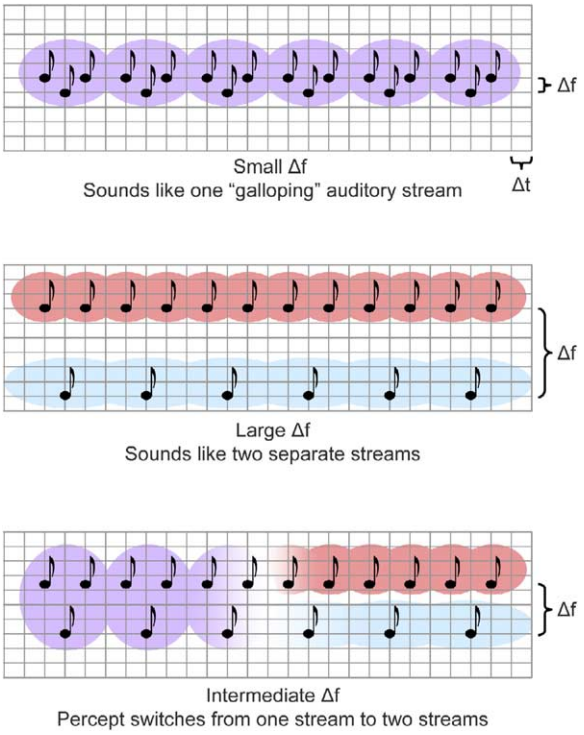

Figure 1. Auditory Streaming Can Be Affected by Low-Level Stimulus Parameters

The difference in acoustic frequency between two alternating tones partly determines whether they are perceived as one "galloping" auditory stream, two separate streams, or a single stream that can switch to two streams after an interval.

keys have evolved powerful strategies to solve this task, despite its computational difficulty.

Why might we hope to find a neural correlate of stream segregation? The focus of research on sensory cortex is often how the low-level properties of sensory stimuli, such as pitch or modulation rate, are represented. Of course, part of what the auditory processing hierarchy must do is to represent some of these simple properties. However, the cortex must do more than that; it must transform the raw sensory representations into forms that are useful for behavior. Auditory streams can be thought of as the relevant "objects" to be segmented and identified during "auditory scene analysis" (Bregman, 1990). It is therefore reasonable to suppose that the cortex organizes the auditory world into distinct streams—corresponding to people, animals, or objects in the world—that have biological relevance to the listener. However, little is known about how stream segregation is actually accomplished in the brain.

Fortunately, one need not consider the full problem of source separation in a complex auditory environment in order to discover interesting aspects of stream segregation. One example from a relatively simple class of stimuli that has long played a role in the study of stream segregation (Bregman, 1990) is depicted in Figure 1. It consists of an ongoing series of triplets of alternating pure tones—a high-frequency tone and a low-frequency tone—separated by silent gaps. If the frequency difference (Δf) between the high- and low-frequency notes is small (Figure 1, top), then neighboring tones tend to bind together perceptually, resulting in a single auditory stream that sounds like a galloping horse (purple stream), with each triplet of notes playing the role of hoofbeats. Conversely, if Δf is large (Figure 1, middle), the high- and low-frequency tones no longer bind to each other, and subjects tend to report hearing two separate streams, each consisting of a constant series of beeps (pink and blue streams).

At intermediate values of Δf, something surprising happens: after a few seconds of listening, the initial percept of a single, galloping auditory stream switches to the combined percept of two distinct streams (Figure 1, bottom). This is a compelling phenomenon; although the acoustic stimulus is unchanging throughout its presentation, one's psychological experience is qualitatively different after the perceived switch than it was at the beginning of the listening trial.

As a first step toward uncovering the cortical mechanisms underlying stream segregation, physiologists have sought neural correlates of the perceived streams. Fishman and colleagues (Fishman et al., 2001, 2004) have shown that multiunit spiking responses to tone sequences in the primary auditory cortex of awake monkeys follow the pattern that one might expect on the basis of published psychophysical data from human subjects. Those authors reasoned that if each auditory stream were represented by a distinct group of simultaneously active cortical neurons, then activity recorded in one location should be high in response to those tones that participated in the corresponding auditory stream and suppressed following the other tones. Indeed, this was in fact observed, providing solid evidence for the existence of neural correlates of stream segregation in primary auditory cortex. However, detailed comparison between the neural responses and the published psychophysical results was hampered by the fact that the two data sets were obtained in different laboratories under slightly different stimulus conditions.

Micheyl and colleagues (Micheyl et al., 2005) took this experimental paradigm a step further. They conducted both psychophysical experiments in humans and single-unit extracellular recordings in the primary auditory cortex of awake monkeys using identical stimuli, like those depicted in Figure 1. To facilitate the quantitative comparison between the cortical responses and human psychophysical data, they devised a simple model that predicted whether human listeners would report one or two auditory streams on the basis of the relative activity of monkey cortical neurons responding to tones participating in each of the possible streams shown in Figure 1. Specifically, if a neuron's firing rate exceeded a threshold (fit to data) in response to every tone in the series of presented tones, then that neuron was assumed to represent the full stimulus as a single stream, which, in turn, predicted that the stimulus would also be *perceived* as a single stream (i.e., as the galloping percept depicted in the top panel of Figure 1) by the monkey. However, because of the difficulties in querying the monkey's percept, human observers' percepts were used as a surrogate. Conversely, if the neuron's firing rate exceeded threshold only in response to

the high-frequency tones, then the model predicted that two concurrent streams (the pink and blue streams, middle panel of Figure 1) would be perceived; presumably a separate group of neurons, representing the second stream, responded only to the low tones in this case. The threshold was optimized to minimize errors made by the model.

Micheyl et al. (2005) repeated this experiment for several values of Δf and two different tone repetition rates (Δt) and found good quantitative agreement for a wide range of stimulus parameter values. It was particularly impressive that the model could accurately predict the average time course of the perceptual switching from one to two streams that is experienced by human listeners, under almost the full range of parameter values tested. By focusing on the slow buildup of stream segregation over time (Figure 1, bottom panel), they were able to track changes in perception and neural response under unchanging stimulus conditions. This ensured that the perceptual and physiological nonstationarity that they measured reflected the neural dynamics of auditory streaming in the absence of any confounds resulting from variations in the acoustic stimulus.

A major strength of this work is that Micheyl and colleagues used the same stimulus for physiological and psychophysical testing. The next step will be to collect behavioral and neural responses simultaneously in a single subject, an approach that has been invaluable in studies of vision (Parker and Newsome, 1998) and of other sensory modalities (Romo and Salinas, 2003).

It has been known since the earliest single-unit recordings (Hubel et al., 1959; Hocherman et al., 1976; Fritz et al., 2003) that neurons in auditory cortex can be profoundly modulated by behavioral context and attentional demands. It is therefore perhaps surprising that, in spite of this early evidence, only in the last decade has the focus returned to the characteristics of auditory cortex neurons in the awake animal (deCharms et al., 1998; Barbour and Wang, 2003; Fritz et al., 2003). Studies such as the one by Micheyl and colleagues that combine psychophysics and electrophysiology promise to elucidate the neural mechanisms underlying both our conscious experience of the auditory world and our impressive ability to extract useful auditory streams from a sea of distracters.

Michael R. DeWeese and Anthony M. Zador
Cold Spring Harbor Laboratory
Cold Spring Harbor, New York 11724

Selected Reading

Barbour, D.L., and Wang, X. (2003). J. Neurosci. *23*, 7194–7206.

Bell, A.J., and Sejnowski, T.J. (1995). Neural Comput. *7*, 1129–1159.

Bregman, A.S. (1990). Auditory Scene Analysis: The Perceptual Organization of Sound (Cambridge, MA: The MIT Press).

deCharms, R.C., Blake, D.T., and Merzenich, M.M. (1998). Science *280*, 1439–1443.

Fishman, Y.I., Reser, D.H., Arezzo, J.C., and Steinschneider, M. (2001). Hear. Res. *151*, 167–187.

Fishman, Y.I., Arezzo, J.C., and Steinschneider, M. (2004). J. Acoust. Soc. Am. *116*, 1656–1670.

Fritz, J., Shamma, S., Elhilali, M., and Klein, D. (2003). Nat. Neurosci. *6*, 1216–1223.

Hocherman, S., Benson, D.A., Goldstein, M.H., Heffner, H.E., and Hienz, R.D. (1976). Brain Res. *117*, 51–68.

Hubel, D.H., Henson, C.O., Rupert, A., and Galambos, R. (1959). Science *129*, 1279–1280.

Micheyl, C., Tian, B., Carlyon, R.P., and Rauschecker, J.P. (2005). Neuron *48*, this issue, 139–148.

Parker, A.J., and Newsome, W.T. (1998). Annu. Rev. Neurosci. *21*, 227–277.

Romo, R., and Salinas, E. (2003). Nat. Rev. Neurosci. *4*, 203–218.

Zibulevsky, M., and Pearlmutter, B.A. (2001). Neural Comput. *13*, 863–882.

DOI 10.1016/j.neuron.2005.09.010