resides on the external (noncytosolic) surface (Mao and Obeid, 2008). This implies that the newly produced sphingosine must translocate across the plasma membrane and across the cytosol to reach synaptobrevin (Figure 1, top row). Alternatively, the ceramidase may reside in the synaptic vesicle lumen (Figure 1, bottom row). This is less likely because no ceramidases were found in a quantitative analysis of synaptic vesicle constituents (Takamori et al., 2006). In addition, the positively charged sphingosine would need a facilitator to leave the luminal leaflet of the vesicle membrane (as argued above). Such facilitators have been described, for instance the Niemann-Pick type C NPC1 protein (Lloyd-Evans et al., 2008), but this protein was also not found in synaptic vesicles (Takamori et al., 2006). Finally, not only the production of sphingosine, but also of its precursor, ceramide, may be regulated locally at the active zone (not depicted). This could assist the secretion promoting effects of sphingosine by activating a phosphatase activity as Sit4/CAPP and dephosphorylation of relevant proteins at the target membrane. This proposed mechanism is analogous to the way diacylglycerol promotes the activity of a specific class of molecules (C1-domain-containing proteins), although in the case of sphingosine, the interaction between protein and lipid has not been precisely defined yet.

Many labs would probably give their annual budget for the methodology that would allow them to directly observe what is going on in the microdomains at the active zone, where synaptic vesicles, the proteins of the fusion machinery, Ca^{2+} channels, and lipid domains all reside together and where everything important with regard to secretion seems to happen. Unfortunately, methods are still lacking to observe the proteins generating the force to merge the lipid bilayers, to monitor local lipid production, and to witness the rearrangements in lipid domains, protein complexes, and their reciprocal interactions. Until that time, we have to rely on indirect evidence. One crucial direction will be to localize ceramidases, phospholipases, and DAG-lipases to define their site of action, their potential activity dependence, and to find specific and acute ways to interfere with their activity.

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Inhibitory Plasticity in Auditory Cortex

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Arguably the most important property of neuronal circuits in general, and of cortical circuits in particular, is plasticity—the ability to change in response to past experience. While many studies of plasticity emphasize changes in excitatory transmission, in this issue of *Neuron*, Galindo-Leon et al. demonstrate the important role that increased inhibition may play in shaping cortical responses to behaviorally relevant stimuli.

The cerebral cortex is plastic. The strength of the connections between neurons can change at multiple timescales, from seconds to years, and this ability is crucial for adapting animals (including humans) to their changing environment. Plasticity is strongest during early development: critical periods open and close at very young ages, determining the largescale structure of sensory cortices (Hensch, 2005). However, the cortex remains plastic even in adulthood.

Studies of plasticity in adult auditory cortex have a long history. Weinberger (reviewed in Weinberger, 2004) used

classical conditioning paradigms, in which a tone was followed by an aversive stimulus, to show that within a few tens of minutes neurons in auditory cortex shifted their frequency tuning, increasing the responses to the conditioned stimulus. These studies have since been extended in numerous directions (Suga and Ma, 2003). Acetylcholine (ACh) and other neuromodulators have been shown to be crucial for evoking plasticity in auditory cortex (Edeline, 1999). In fact, simply coupling ACh release with sound stimulation is enough to evoke massive reorganization of the adult cortex (Kilgard, 2003). Plastic changes can be evoked by exposure to rich soundscapes for a few weeks. Depending on the details of the experiment, such exposure may enhance (Engineer et al., 2004) or depress (Norena et al., 2006) cortical responses to sounds. Plastic changes may be much faster as well. Thus, sensory responses to irrelevant stimuli are depressed while responses to important stimuli may increase within seconds of the initial exposure (Fritz et al., 2003; Ulanovsky et al., 2003). At the other extreme, intriguing results suggest that auditory cortex of musicians is larger than that of nonmusicians (Schneider et al., 2002): it is tempting to hypothesize that the use of auditory cortex by musicians increases its size, although cause and effect cannot be dissociated in this case.

Overall, the emerging picture is of a tight correlation between the external world of sounds and its behavioral meaning on the one hand, and the resulting internal representations on the other hand, at all possible timescales: the reflection of the macrocosmos in the microcosmos. This large amount of plasticity may be crucial for the success of animals in varying environments: consider that both cats and squirrels are highly successful in big cities, although they obviously evolved in very different ecological niches.

Plasticity in auditory cortex has been mostly associated with an increase in the responses of neurons to the behaviorally relevant sound (or decreases in the responses to irrelevant sounds, as in Fritz et al., 2005). The common model for explaining these results includes a conjunction of two signals. The first signal is the sensory signal itself. The second is a signal from outside the auditory system that indicates the behavioral importance of the stimulus; this signal is often assumed to be an increase in ACh, although other neuromodulators evoke plasticity in auditory cortex as well (Edeline, 1999). The increase in ACh level, coupled with the specific stimulus that is presented, for example a pure tone, presumably increases the efficacy of the excitatory synapses that were activated while the stimulus was on. A recent study using intracellular recordings (Froemke et al., 2007) documented this process from the point of view of a single neuron, showing different stages of the plastic process.

Functionally, the increased response to the relevant stimulus, while keeping the responses to other stimuli the same or smaller, makes the representation of the relevant stimulus more salient—it is easy for a "downstream station" (whatever that means) to detect activity resulting from the presentation of the relevant stimulus. This effect can be restated as an improvement in signal-to-noise ratio—the signal here consists of the population responses to the relevant stimulus, while the noise would be the population responses to nonrelevant stimuli. Since the excitatory responses to the relevant stimuli are larger, the signal is larger, while the noise would remain the same or even decrease.

There may be however other ways in which it is possible to make the responses to relevant stimuli more salient. In this issue of *Neuron*, Galindo-Leon et al. (2009) demonstrate a novel aspect of plasticity in auditory cortex: an increased inhibition of the responses away from the representation of the relevant stimulus. Like an increase in the excitatory responses to a relevant stimulus, such inhibition would also increase the salience of the representation of the relevant stimulus, but in a slightly different sense.

The study of Galindo-Leon et al. is different from many previous ones in a number of ways. First, it uses the mouse as the experimental model. The mouse has many advantages as an experimental animal, not the least being the possible future use of molecular biology and genetics as tools for understanding cortical function. Mice communicate vocally, and their communication calls have a simple "syntax" (Holy and Guo, 2005). Yet the mouse also has disadvantages as an experimental model—for example, mice don't hear much below 1 kHz, and much of their vocal communications is done at ultrasonic frequencies (above 20 kHz, the upper frequency limit of human hearing). In contrast, humans hear frequencies as low as 20 Hz, and a substantial amount of the sounds that are of interest to humans contain energy below 1 kHz. Since there are some fine, but important, differences between the way in which mammals process low- and high-frequency sounds, experimental questions studied in the mouse model must be selected well.

A second aspect in which this study is different from many previous ones is the use of a different and arguably more "natural" paradigm of cortical plasticity: the changes in the responses to pup calls in mothers relative to virgin females. This paradigm, first introduced by Liu (the senior author on the Galindo-Leon et al. paper) and Schreiner (Liu and Schreiner, 2007), is based on two foundations. The first is the demonstration of the behavioral relevance of this specific class of pup calls (the ultrasonic isolation calls; Ehret, 2005). These calls are emitted by pups lost outside the nest, and evoke a stereotypic behavior in mothers: they approach the source of the sound, retrieve the pup and bring it back to the nest. The second foundation of this paradigm is a deep statistical analysis of the structure of these calls, which made it possible to select a set of variants of the isolation call that cover the natural variability in its structure (Liu et al., 2003). Such characterization is of extreme importance in the study of natural sound ensembles. Without a good coverage of the acoustical variability of isolation calls, it is difficult to generalize the results of electrophysiological experiments to the whole class. Building on these foundations, Liu and Schreiner (2007) have already demonstrated significant differences in the representation of isolation calls in mothers relative to virgin female mice. The responses in mothers were stronger, more tightly locked to the stimuli, and as a result carried more information about the calls.

The third aspect in which the current study is different from previous ones is novel and crucial: Galindo-Leon et al. conducted their electrophysiological recordings in awake mice. They observed in both mothers and virgins a significant population of "call-suppressed" neurons,

neurons that are suppressed by any of the versions of the isolation calls used in this study (and therefore, since these calls cover well the possible variants of isolation calls, these neurons are presumably inhibited by any isolation call). Such neurons were much less common in anesthetized mice.

The major new observation of Galindo-Leon et al. is that the population of call-suppressed neurons is more strongly suppressed in mothers than in virgins. The stronger suppression was evident both in the responses of single neurons and in the local field potentials (LFPs) recorded from the electrodes that had the call-suppressed neurons. Most importantly, the increase in the suppression was largest in recording locations whose preferred frequency was away from the typical frequencies of the isolation calls.

What are the functional consequences of this finding? The mouse auditory cortex is to a large extent organized by frequency. Neurons have best frequencies, although neurons in auditory cortex often respond to a wide range of frequencies around their best frequency. Furthermore, their responses to complex, natural sounds (and the isolation calls are certainly more complex than pure tones) are not necessarily predicted simply from the responses to pure tones. Nevertheless, neuronal best frequency is an important characterization of auditory neurons: there is a map of best frequencies, which corresponds to the tendency of neurons with similar best frequencies to cluster together. Neurons whose best frequencies correspond to the frequency content of the calls are preferentially located in a specific subregion of auditory cortex where neurons of very high best frequencies reside. Similarly, neurons whose best frequencies are much lower would cluster mostly in a different subregion of auditory cortex. The result of Galindo-Leon et al. suggests that when presenting isolation calls, the contrast in the activity between these two subregions of auditory cortex is substantially enhanced in mothers relative to virgins.

This result can also be interpreted as an increase in signal-to-noise ratio of the representation of relevant stimuli, although the signal and the noise have to be interpreted differently than in previous studies of auditory cortex plasticity. The signal here is the neuronal activity evoked at the locations in the frequency map that are selective to the frequency range of the isolation calls, while the noise would be the neuronal activity in other parts of the frequency map. Rather than increasing the overall activity level in response to the relevant stimuli (in fact, the average response to isolation calls over all auditory cortex may even decrease in mothers), such an enhancement may make the representation of these sounds spatially more distinct than that of other, behaviorally less relevant sounds. The sharpening of the spatial pattern of responses evoked by behaviorally relevant sounds is a novel concept, which would certainly influence future studies of cortical plasticity.

The paper of Galindo-Leon et al. opens many questions for future research. For example, it doesn't deal at all with the mechanisms of plasticity. Pregnancy and birth cause myriad physiological changes in mothers. Which of these trigger plasticity in auditory cortex? Based on previous evidence, a plausible model would include changes in the levels of neuromodulators in auditory cortex, allowing plasticity to occur. But which neuromodulators? At what stage do they change? And how do they interact with sensory stimuli to evoke plasticity?

A second important question brought into sharp relief by the paper is the theoretical issue of the correct rules to govern plasticity in inhibitory synapses. Most studies of plasticity at the cellular level have to do with the plasticity of excitatory synapses. These mostly follow versions of Hebb's rule: coactivation causes increased synaptic efficacy, with modern refinements such as spike-time-dependent plasticity (Gutig et al., 2003), which specifies also the relative timing of spikes in the presynaptic and postsynaptic neurons. While these rules are understood well, rules governing plasticity in inhibitory synapses are understood substantially less well. The experimental demonstration of inhibitory plasticity in an interesting context may spur theoretical studies of such rules.

The paper of Galindo-Leon et al. is an excellent example of the multidisciplinary approach to neuroscience, using behavior, sensory ecology, and electrophysiology in a powerful combination. It increases our understanding of the importance of plastic changes in inhibitory transmission, and opens new avenues for future research.

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