melanoma cells could be reversibly converted into pigmented melanoma cells, although the conversion toward the pigmented state is favored. Thus, invasive melanoma cells are in a metastable state allowing them to migrate or become stationary according to the local environment. TGFβ signaling was directly controlling the pigmented status of melanoma cells by regulating Brn2 expression. However, both the pigmented and the non-pigmented populations exhibit similar clonogenicity *in vitro* and *in vivo*, and therefore the undifferentiated state may not be enriched with tumor-initiating cells.

These two new studies from Sahai and colleagues [6,15] provide new clues for unraveling the mechanisms driving metastasis in heterogeneous primary tumors. The findings further emphasize that distinct populations of solitary cells can transiently acquire the ability to migrate and the invasive machinery necessary to disseminate through blood vessels. Intriguingly, lymph node metastasis, hypothesized here to occur by collective cell migration, is well known to be independent of dissemination via blood vessels and is the preferred mode of dissemination for some tumors, such as head and neck carcinoma. In breast cancers that exhibit these two types of invasion, the lymph node and bone marrow status are independent prognostic indicators. Micrometastatic carcinomas in bone marrow are better indicators of tumor recurrence than micrometastasis in sentinel lymph nodes, suggesting that EMT is a critical mechanism for blood-borne metastasis in breast and other types of carcinoma. Of note, this mechanism operates at early stages of carcinoma formation [16–18]. These findings prompt the need to develop more appropriate models to assess individual cell motility, since the current *in vitro* models that examine migration using poorly cross-linked 3D matrices and transplantation into the fat pad of mice may not fully mimic the highly reticulated stroma in human tumors [19]. Additional studies in human carcinoma are also essential in order to validate the role of collective cell migration in tumor dissemination.

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Auditory Cortex: Representation through Sparsification?

The recent discovery of combination-sensitive neurons in the primary auditory cortex of awake marmosets may reconcile previous, apparently contradictory, findings that cortical neurons produce strong, sustained responses, but also represent stimuli sparsely.

Ben D.B. Willmore and Andrew J. King

Recent advances in neural recording techniques have led to a debate over the most fundamental principles of representation in the primary auditory cortex (A1). As researchers increasingly study A1 in awake animals in preference to their long-established anesthetized preparations, conflicting claims have been made about the responsiveness of the neurons found there and their selectivity for particular sound features. A recent study [1] may help to reach a consensus on this matter, by showing that some A1 neurons respond vigorously to certain complex stimuli, even when responses to the elements of those stimuli are weak or nonexistent. This suggests that nonlinear mechanisms in auditory cortex can result in highly selective, 'sparse' responses, but that these responses can still be strong for ecologically relevant stimuli.

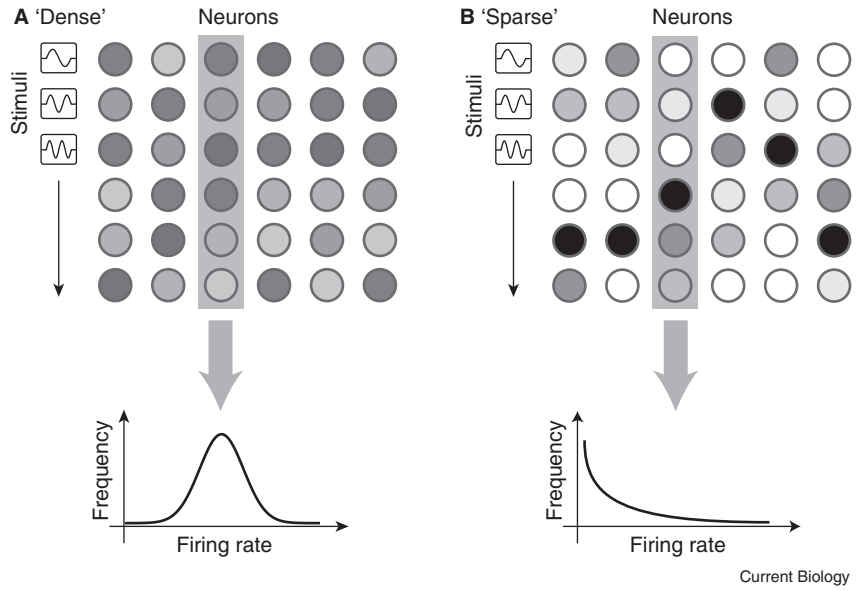

Figure 1. Sparse coding.

(A) Neural codes are often assumed to be dense. In a dense code, a large proportion of neurons produce action potentials in response to every stimulus, and so activity (indicated by gray shading) is approximately evenly spread throughout the neural population. (B) In contrast, in a sparse code, a small, changing subset of neurons produces strong responses to each stimulus (black shading), whereas the rest of the population is quiescent or weakly active (white and pale shading). The resulting exponential response distribution of firing rate and the statistical independence between neurons reduce the redundancy of the neural code, while maximizing the information content of each action potential.

Responses in Auditory Cortex of Awake Animals: Sustained or Sparse?

It is often stated that neural responses in the cortex of awake, behaving animals are qualitatively different from those recorded under anesthesia. In anesthetized mammals, the responses of A1 neurons are generally dominated by a transient increase in firing rate that may not persist beyond the first few tens of milliseconds after a sound has begun. Such transient activity is consistent with responses observed in other sensory systems, but there is real doubt about the importance of these responses for neural coding. If the response stops shortly after the beginning of the sound, it is unclear how ongoing features of a sustained sound can be represented.

Some studies have shown that this is actually an oversimplification, as significant stimulus-related information can be found well after the end of the sound in the activity of A1 neurons recorded in anesthetized animals [2,3]. Nevertheless, there is no doubt that sustained responses are more common in the awake animals than under anesthesia [4]. More intriguingly, Wang *et al.* [5] reported that such responses occur for particular sounds, and that different subsets of neurons produce sustained responses in response to different sounds. This suggests that acoustic stimuli are represented by prolonged increases in firing in varying subsets of neurons, questioning the significance of transient responses in the rest of the neural population.

However, these experiments used conventional extracellular recording methods. As Olshausen and Field [6] have argued, there is a potentially serious bias problem with this type of recording. Extracellular recording measures only action potentials or spiking activity. Thus, if a neuron produces no action potentials, it will not be detected. Even neurons that produce action potentials only occasionally will tend to be missed. This means that extracellular recordings will be biased towards those neurons that produce strong responses, and are therefore likely to overestimate the activity of the population.

To assess more accurately how different sounds are represented by the population of neurons in auditory cortex, Hromádka *et al.* [7] sequentially sampled the activity of A1 neurons in awake rats using cell-attached recordings. With the cell-attached technique, it is possible to know that the recording pipette is in contact with a neuron, even if the neuron does not produce any action potentials. This method therefore avoids the bias inherent in extracellular recording. Hromádka *et al.* [7] found that only a handful — less than 5% — of the neurons sampled produced well-driven responses to simple or naturalistic stimuli, while the majority of neurons failed to respond at all to any of these sounds.

Other studies have shown that, as well as being relatively rare events, individual action potentials can carry significant amounts of information. This has been demonstrated in mouse barrel cortex, for example, where optical activation of a small number of action potentials in a sparse subset of neurons can alter an animal's behavior [8]. Thus, it would seem that perceptual decisions might be made on the basis of modest changes in firing rate by cortical neurons.

Theory of Sparse Coding

These two lines of evidence regarding the nature of the cortical representation appear to be in conflict. On the one hand, we have a view in which only sustained volleys of action potentials, generated by specific stimuli, matter. On the other, individual action potentials are thought to be significant and capable of determining an animal's behavior.

To reconcile these two points of view, it is helpful to take a theoretical perspective. The notion of 'sparse coding' [9,10] stems from the viewpoint that action potentials should be relatively rare events. Such rarity is likely to be metabolically efficient — action potential production is a major part of cortical energy consumption [11] — and may produce redundancy-reducing neural codes that are particularly well-suited to natural sensory signals [12].

The visual cortex is believed to represent natural visual input using a sparse code [9,13], in which only a small proportion of neurons are active at any given time. Consequently, small subsets of the population participate in the representation of each stimulus, as shown in Figure 1. A sparse code is the opposite of a dense code, where a large proportion of neurons are active at all times, each contributing a small

amount to the representation of each stimulus. Chechik *et al.* [14] have shown that redundancy is lower in A1 than in the thalamus; this is consistent with the idea that the auditory representation is sparser in the cortex than in subcortical structures.

Sparse coding provides a clear theoretical account of the infrequent responses observed by Hromádka *et al.* [7]. But further investigation of the idea of sparse coding suggests that the strong responses observed in marmoset auditory cortex by Sadagopan and Wang [1] are also what should be expected from a sparse code. As shown in Figure 1, redundancy reduction and the maximization of information transmitted by each spike require neurons to have sparse, exponential response distributions — each neuron should produce disproportionately strong responses to a small proportion of stimuli. This is precisely the pattern of activity observed by Sadagopan and Wang [1].

Nonlinear Combination Sensitivity

The most important aspect of the study by Sadagopan and Wang [1] is that they present evidence which begins to reveal how the sparse responses in auditory cortex might arise. They show that many A1 neurons are sensitive to precise temporal and spectral combinations of tone pips, even though those neurons do not respond to the individual tone pips when presented alone. This suggests that A1 neurons are performing a highly nonlinear processing of sound; a standard linear model predicts that the neurons would respond weakly to each of the components of any complex sound that elicited a strong response.

Going back to the pioneering studies of Nobuo Suga and colleagues [15] in echolocating bats, combination sensitivity has long been known to be a property of neurons at higher levels of the auditory system. This is reminiscent of the conjunction-sensitive responses of neurons in area V4 of visual cortex. For example, Pasupathy and Connor [16] showed that V4 neurons are sensitive to both the elements and the position of visual boundary stimuli. This suggests that similar mechanisms of conjunction sensitivity operate in visual and auditory cortex, and also implies, as recently argued [17], that A1 might be more similar to higher visual areas than to primary visual cortex.

In both of these sensory systems, such highly nonlinear combination sensitivity presents a significant challenge to standard techniques for investigating neural responses to complex stimuli. Methods for characterizing such responses frequently assume (or test) a linear model relating the responses to the presented stimulus [18]. The linear model is powerful and tractable, and even when its assumptions are not precisely met, it can provide a reasonable description of neural processing [19]. As a result, the linear model continues to be the basis of many studies of sensory processing. Sadagopan and Wang [1] demonstrate a fundamental failure of the linear model: responses to combinations cannot be predicted from responses to the elements of those combinations. If, as seems highly probable, nonlinear combination sensitivity is an important mechanism in higher cortex, then understanding neurons in such areas will require the development of new classes of nonlinear models.

Another consequence of showing that A1 neurons can be highly selective for complex sounds is that this paves the way for investigating how these stimulus preferences are organized within the cortex. This is a controversial topic, but A1 clearly lacks the highly ordered organization that characterizes the primary cortical fields in other sensory modalities [17]. Indeed, one previous study [14] has demonstrated that neighboring A1 neurons can have quite different stimulus preferences. However, Sadagopan and Wang [1] note that nonlinear combination sensitivity is most prevalent in the superficial regions of the cortex, which is consistent with other recent evidence for laminar differences in the response properties of A1 neurons [20]. A more detailed investigation into the cortical location of these nonlinear interactions should help to reveal how this sparse representation of complex sounds arises, and provide further insights into the functional circuitry of A1.

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