atonigral neurons[6]. Kelz and colleagues[1] tested the hypothesis that ΔFosB could mediate some of the persistent neural and behavioral changes accompanying chronic drug exposure. By expressing *ΔfosB* under the control of a tetracycline-regulated promoter, the authors were able to investigate the effects of this protein without the multifarious homeostatic adaptations produced in nucleus accumbens and other striatal neurons by repeated administration of cocaine. In behavioral tests, *ΔfosB*-expressing animals found cocaine more rewarding than did appropriate control mice. The transgenics also had greater sensitivity to the locomotor stimulant effects of cocaine, without demonstrating differences in sensitization. Because ΔFosB is a transcription factor (**Fig. 1**), Kelz and colleagues[1] have correlated the expression of ΔFosB with increased expression of a potential target, the GluR2 subunit of AMPA receptors. A likely role for GluR2 in the ΔFosB-induced enhancement of the rewarding properties of cocaine was demonstrated by separately expressing GluR2 by virally mediated gene transfer[1].

The results of these studies are surprising and interesting because ΔFosB was initially thought to represent a homeostatic response to cocaine. Indeed one might have predicted opposite results based on the *fosB* knockout mouse[7], which also exhibits increased sensitivity to the rewarding and locomotor stimulant effects of cocaine. The approach taken by Kelz and colleagues overcomes some of the limitations of analyzing a knockout mouse that lacks FosB and ΔFosB throughout development. The mouse described by Kelz and colleagues could serve as a model of enhanced vulnerability for cocaine use, and at the same time suggests that cocaine, acting via ΔFosB, might increase its own rewarding properties without inducing locomotor sensitization. Investigation of the physiological effects of increased GluR2 expression and identification of other alterations in gene expression in the ΔFosB-expressing line should provide useful insights into regulation of brain reward circuits. It will also be interesting to see what happens when this line of mice receives chronic cocaine; it is possible that effects of extra ΔFosB expression, either on homeostasis or on associative learning, will emerge.

In addiction research to date, there have been major efforts to investigate homeostatic adaptations to excess neurotransmitter stimulation[4]. This has led to the search for molecular species that undergo long-lived up- or downregulation in response to repeated drug administration. Indeed, the isoforms of *ΔfosB* that were studied by Kelz and colleagues[1] were initially interesting precisely because of their prolonged upregulation by cocaine[6]. Although homeostatic changes are clearly significant, the long-term relapse risk that characterizes addiction is undoubtedly related to associative learning mechanisms[8]. Mechanistically, it is clear that short-term molecular events that produce long-term changes in synaptic structure[9] are likely to be critical actors and deserve at least as much attention as the search for long-lived molecular species. It will be interesting to determine the impact of ΔFosB on the induction of molecular changes that might be involved in synaptic plasticity. This paper also whets our intellectual appetites for additional lines of mice expressing additional drug-inducible genes with steadily improving spatial and temporal control.

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I see a face—a happy face

Mike W. Oram and Barry J. Richmond

Information analysis shows that face-selective neurons in inferior temporal cortex encode different stimulus attributes early and late in their response to the same image.

Much of our understanding of sensory processing comes from studies on the primate visual system. Many different visual cortical areas have been described, each containing neurons that fire selectively in response to particular stimulus attributes—such as color, orientation or motion—or to specific stimuli such as faces. The activity of these neurons carries information about whether or not their preferred stimulus is present, and it has generally been assumed that this evoked activity bears a constant relationship to the stimulus throughout the response period. For instance, if a neuron in the inferior temporal cortex fires in response to a face, it has been assumed that this activity continues to signal the same information at the beginning, middle and end of the response period. In a recent issue of *Nature*, however, Sugase and colleagues[1] present findings that challenge this view. By using information theory to analyze the neuronal responses to faces and other stimuli, they show that the information carried by the responses changes over time, from a more global to a more specific level of stimulus discrimination.

The authors recorded the responses of single neurons in the inferior temporal cortex while the monkeys viewed pictures of colored shapes, human faces or monkey faces. The faces were from different individuals, and the face of any individual could show different expressions (happy, surprised, angry and so on). This allowed the authors to examine the degree to which a neuron was signaling information at different levels of discrimination: face versus non-face, monkey versus human, individual identities and different facial expressions. The initial phase of the response contained information only at the more 'global' levels (face versus non-face and human versus monkey) and did not signal either identity or facial expression. A few tens of milliseconds later, however, information about these global levels decreased (although not to zero), and new information about identity and facial expression appeared. Because no behavioral response was required, the changing neuronal responses seem to be driven only by the stimulus itself. These

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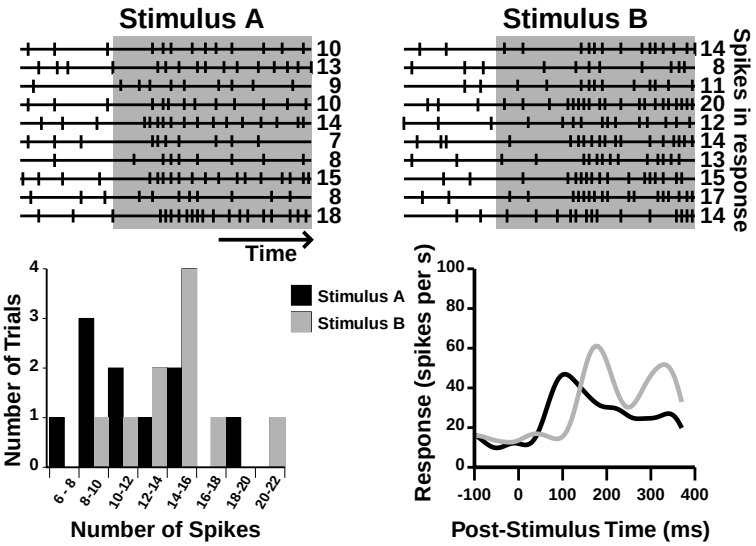

Fig. 1. Spike count, response latency and the waveform of responses could all convey information. The stimuli (A or B) were presented one at a time during the period indicated by the shaded areas. Each horizontal row represents the duration of a neural response to a single stimulus presentation, with the tick marks indicating the time at which a spike occurred. The stimuli can be distinguished from each other using the number of spikes (lower left), the response latency and the waveform (lower right). See text for further details.

findings provide neurophysiological support for a top-down mechanism for visual processing and thus have profound implications for computational and theoretical models of brain function.

The idea that individual sensory neurons can carry information about different stimulus attributes is not new. To understand the significance of the new findings, it is helpful to consider some of the previous studies examining the information content of neural responses. One study of inferior temporal cortex found that the time course of the neuronal response contains additional information that is not measurable from the spike count alone[2] (see **Fig. 1**). Two stimuli (labeled A and B) are presented repeatedly, and each presentation evokes a certain number of spikes. On average, stimulus B produces more spikes than stimulus A, so the spike count provides some information about stimulus identity. This discrimination is imperfect, because intertrial variability leads to a considerable overlap between the distributions of spike counts for the two stimuli. When the time course of the response is considered, however, two further sources of information emerge. The response latency (the time before the spike count rises above background) is shorter for stimulus A than for stimulus B, and the waveform of the response is also different, with a single peak for stimulus A versus two peaks for stimulus B. Thus, three different measures of neuronal activity each provide the same type of information (A versus B), but the total quantity of information is greater when all three measures are combined.

Different aspects of the neuronal response can also signal information about more than one attribute of the stimulus[3,4]. For example, the response latency of neurons in the primary visual cortex is related to the contrast of the stimulus but is independent of its orientation. Conversely, the overall spike count depends strongly on stimulus orientation but is independent of contrast[3].

Another coding strategy is to use a single response measure, such as the spike count, to convey information about combinations of stimulus attributes. For example, some neurons in the inferior temporal cortex are selective for both color and shape and require specific combinations in order to show their maximal firing response[5]. Similarly, cells in the superior temporal sulcus are responsive to images of moving bodies and are selective for specific combinations of body shape and direction of motion[6]. In these examples, information about the different stimulus attributes is encoded simultaneously and can be explained by simple feedforward processing[6,7]. Such a mechanism seems unlikely to explain the findings of Sugase and colleagues, where new information appears at a later stage in the neuronal response.

At first sight, the findings of Sugase and colleagues might seem more akin to the phenomenon of behavioral modulation, in which top-down information about behavioral significance of a stimulus causes the response to evolve over time. One example of this occurs in temporal and frontal cortex, where neurons that fire in response to a particular visual stimulus also show enhanced firing when that visual stimulus is held in memory[8]. The changes in activity due to the behavioral significance attributed to the stimulus appear after the initial phase of the resonse[9] with a delay compa-

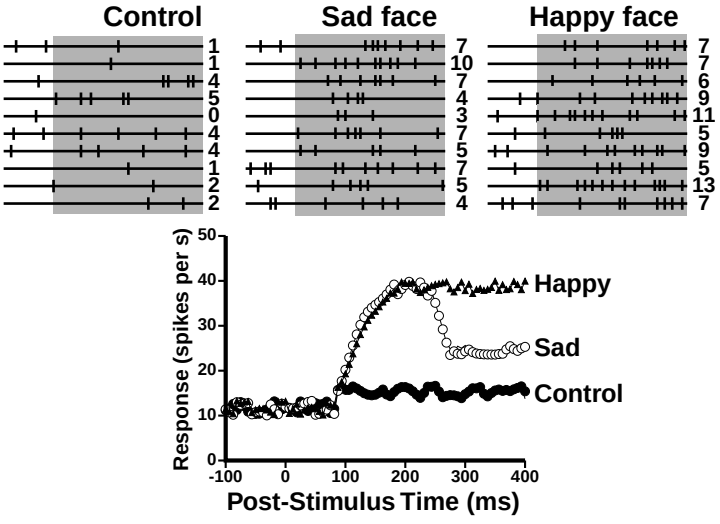

Fig. 2. Schematic illustrating how different information is conveyed at different times in neurons of inferior temporal cortex. The initial phases of the responses discriminate between faces and control objects, whereas the later stages of the same responses also allow discrimination between expressions. See Sugase *et al.*[1] for details.

rable to that seen by Sugase and colleagues[1]. However, the activity described by Sugase and colleagues seems difficult to attribute to behavioral influences, because the animals were not required to make any behavioral response but merely viewed the stimuli passively.

The above examples illustrate several coding strategies: multiple response measures encoding the same stimulus, multiple response measures encoding multiple stimulus attributes, a single response measure encoding combinations of attributes, or a single response encoding a stimulus and its behavioral significance. In contrast to all of these examples, Sugase and colleagues have shown that a single response measure can evolve over time to encode new information, in the absence of any external cues.

How might this increase in information content come about? Computational models of visual processing often make use of feedback and lateral inhibition to enhance weak or noisy signals[10,11]. These models receive some experimental support from recordings in primary visual cortex[12–14], but they can only work in cases where the information for the feedback or inhibitory signals is already present in the responses. It seems unlikely that local feedback or lateral inhibition could explain the results of Sugase and colleagues, because they found very few neurons that contained any detectable information about face identity or expression during the early phase of the response. Instead, this information must be introduced via top-down inputs from other brain areas. Top-down processes are typically used by modelers to allow sensory processing to be modulated by information not present in the initial responses, such as behavioral significance or semantic knowledge. However, they can also be used in models involving reciprocal interactions between different sensory areas, in which signals from one area are conveyed to another area where new information from another source is added. The resultant signal containing the new information, which might reflect other sensory processes, memory or behavioral significance, can then be sent back to modulate activity in the earlier area. In the present example, computations in the inferior temporal cortex would establish the presence of a face, and this information would be passed to other areas that would extract information about identity and facial expression. As the authors discuss, the inferior temporal cortex has many connections to and from cortical and subcortical areas that are implicated in social and emotional processing. The delay of some 50 ms between the signal that a face was present and the appearance of information about identity or expression is also consistent with the idea that the initial signal from the temporal cortex passes to other regions that process it further and then relay the resulting signals back to the temporal cortex.

As with any innovative and exciting study, the findings of Sugase and colleagues raise more questions than they answer. Where does the 'new' information about identity and expression come from? Does the total amount of information encoded by the inferior temporal neurons increase over time, or does the new information replace the old? Assuming that the new information is introduced from elsewhere in the brain, how does it affect the processing that occurs within the inferior temporal cortex itself? Ultimately, it will be important to understand the relationship between this neural activity and behavior. For instance, does the discriminatory behavior of these neurons match the ability of the monkey to make behavioral discriminations? Can the monkey's behavior be altered by disrupting this top-down processing, for instance using selective lesions or microstimulation? If it turns out that the changes in information content over time have functional significance, then our understanding of how brain areas process information, both locally and in combination with other areas, will have been substantially advanced.

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Switching the hippocampus off and on

Memory consists of interdependent but dissociable processes, such as encoding, storage, consolidation and retrieval. Lesion studies have shown that the hippocampus is necessary for declarative memory, but pinning down its exact contribution to these individual stages has proved tricky. Because brain lesions are permanent, they cannot unambiguously dissociate the stages of memory.

Richard Morris and his colleagues (University of Edinburgh Medical School) have now developed a technique that could overcome this problem. On page 898, they report reversible, temporary inactivation of the hippocampus with LY326325, a selective water soluble antagonist of AMPA/kainate glutamate receptors. The authors infused the dorsal hippocampus (inclusive of areas CA1-CA3 and the dentate gyrus) of rats with this drug during training and/or retention on a version of the water maze test. The authors verified physiologically that they could selectively 'switch off' the dorsal hippocampus for varying periods and then switch it on again and have it work normally afterward. This technique revealed that the hippocampus is critical for both encoding and retrieval of spatial memory. This approach represents a potentially powerful way to test whether the functional integrity of various brain areas is necessary for specific memory processes.

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