features can be simultaneously recorded for each analyte-binding event. For example, the current amplitude, voltage-dependence and typical kinetics can, together, produce a distinctive signature for each of several analytes, even though the sensor binding selectivity is minimal. Furthermore, use of an adapter together with an information-rich single-channel recording method may avoid the contradictory requirements of high selectivity (to achieve specificity) but rapid reversibility (to achieve speed in a changing environment). Because fresh adapters can be continuously flushed into the device, even an adapter (or carrier) that binds tightly to the analyte can maintain the system’s speed if the adapter association with the channel exhibits rapid reversibility.

Although it will obviously be of great interest to identify the atomic-level changes that account for changes in ionic current flow upon adapter and analyte binding, there remain many questions about the ultimate capabilities of single-channel pores in atomic-scale investigations of individual molecules. What are the fundamental physical processes that limit the sensitivity and speed with which single-molecule measurements can be made? Can electronic currents be used to replace ionic currents? Can robust membrane–pore systems be engineered using advanced materials science and nanolithography techniques, perhaps in conjunction with the methods of biological or chemical engineering? Can sensitive electronic circuitry and photonic sensing capabilities ultimately be integrated directly into a membrane–pore system, as they have for other chemical sensors11? These questions may not be answerable today. But, in the twenty-first century, exciting new nanoscale tools and molecular machines will surely emerge at this interface of biology, chemistry and physics.

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Neurobiology

Attraction is relative not absolute

Masataka Watanabe

Suppose you like wine very much, and are faced with the choice of ordinary table wine or Beaujolais Nouveau — the latter is probably very attractive. But if presented with Beaujolais Nouveau and a superior wine, such as Romanée-Conti, the attraction of the Beaujolais Nouveau may subside. A similar phenomenon called ‘reinforcement contrast effect’ seems to occur in animal-learning studies, and Tremblay and Schultz7 now show (page 704 of this issue) that a region of the brain called the orbitofrontal cortex may be actively involved in this process.

Fifty years ago, in an experiment by Zeaman6, rats were trained to run to a goal, for which they received a large reward. They were then shifted suddenly to a small reward. A second group of rats was trained the other way round; that is, they were first given a small reward and then shifted to a larger one. The animals that were shifted from a small to a larger reward immediately ran faster than would have been expected if the large reward were used alone. Conversely, those rats shifted from a large to a small reward ran more slowly than would have been expected with the small reward alone. The results indicated that the relative — but not absolute — magnitude of reward determines the attraction, as assessed by the eagerness of the rats to run to the goal.

Where in the brain is the attraction of a reward evaluated? To find out, Tremblay and Schultz7 trained monkeys in a modified delayed-response task (Fig. 1). When the monkey pressed a lever at the bottom of an experimental panel, a picture ‘cue’ was presented briefly on either the right or left side of the panel. Then there was a delay, after which the animal had to press the lever (right or left) above which the picture had been presented. This meant that, to obtain a reward, the monkey had to retain a memory of where the picture (although not what picture) was presented. Within a block of several tens of trials, the same two pictures were used continuously, and each picture always predicted one kind of reward.

Tremblay and Schultz found that whereas neurons in the lateral part of the prefrontal cortex showed changes in activity during the delay period, according to the position or identity of the picture, neurons in the orbitofrontal cortex were not sensitive to these factors. The orbitofrontal cortex — so called because it is located above the orbit, or eye socket — occupies the ventral surface of the prefrontal cortex (Fig. 2, overleaf). Humans and monkeys with damage to the orbitofrontal cortex often show impaired motivational and emotional behaviour9, such as altered reward preferences. Consistent with this, the authors found that many orbitofrontal neurons were sensitive to the different rewards. They observed such responses when the picture cue was presented, during the expectation of reward, or after the monkey had received the reward.

Figure 1 shows the activity of such an orbitofrontal neuron. The neuron is more active when the monkey sees a square, which predicts a morsel of apple, than when it is presented with a triangle, which predicts a piece of lettuce (Fig. 1a). But in the next trial block, when a square predicts apple and a plus sign a piece of banana, the same neuron shows higher activity to the cue for banana, because monkeys prefer bananas to apples, and apples to lettuce (Fig. 1b). The attraction of the apple now seems to subside, and the neural activity to the square cue is reduced. In fact, it is similar to the activity for the triangle cue, which predicted the lettuce reward in the previous trial block. So, the activity of orbitofrontal neurons reflects the relative, but not absolute, attraction of the reward.

Once a monkey has had enough of the reward, the orbitofrontal neurons stop responding to the reward and to the cues that predict it10. This process is specific to the nature of the reward, indicating that activity of the orbitofrontal neurons is determined by how much the monkey wants the reward10. The work of Tremblay

Figure 1 Activity of an imaginary orbitofrontal neuron reflecting relative reward preference. To gain a reward, the monkey must remember where (right or left side) the cue is presented. a, A triangle predicts a lettuce reward, and a square predicts an apple. The monkey prefers apple to lettuce, so activity of the neuron is greater when the animal sees the square. b, This time, a square predicts an apple and a plus sign predicts a banana. Because the monkey prefers banana to apple, activity of the neuron is greatest with the plus sign, and much lower than in the previous test with the square. (Figure illustrated by Chiharu Tomita.)
Aged the ozone layer for decades to come. The modifying the Earth's stratosphere, has diminished several times in the 1990s, and has led to substantial, and legally, under the Protocol; in large part this is because HCFCs are due to be phased out by 2030, and some parts of the refrigeration and air-conditioning industry have hesitated to invest in short-term HCFC technologies. Likewise, HCFCs have not replaced CFCs in aerosols or foam plastics, where hydrocarbons or 'not-in-kind' substitutes have filled these niches. Yet HCFC use — and therefore emissions and atmospheric concentrations — are predicted to increase substantially, and legally, under the Protocol over the next decade as HCFCs continue to be used as CFC substitutes in refrigeration (Fig. 1b).

Another emerging player is halon-1211 (CBrClF2), a fire-fighting chemical used increasingly in developing countries such as China and Korea, which now account for over 95% of global production of halons.

Under the Protocol, emissions of halon-1211 were thought to have peaked in the late 1980s (ref. 4), but atmospheric observations indicate near constant2,5 or possibly growing6 emissions (Fig. 1c and d). Using inventories based on atmospheric observations, emissions in the late 1990s are 50–60% higher than those predicted from global production data7. Presumably global production has been underestimated, or emissions from the bank are larger than assumed (or both). Studies by Montzka et al.8 and a group involving one of us9 conclude that, in the near term (as opposed to CFC-12 in the long term), halon-1211 emissions pose the largest threat to ozone recovery.

Prompt and continuing progress towards ozone recovery requires that emissions of halocarbons must be reduced faster than is apparent from current observations of the atmosphere. The United Nations Environmental Programme is facilitating such an accelerated phasing out of halon use in China, with production of halon-1211 scheduled to end by 2006, four years ahead of the Protocol7. In addition, the technology exists to recycle or destroy the bank of CFC refrigerants that would otherwise vent to the atmosphere when refrigeration systems are scrapped. The uses of HCFCs could be restricted to refrigeration, where their identity and recycling is again possible, and emphasis could be placed on use of very short-lived gases such as HCFC-123 (CHCl2CF3) that pose a minor risk to the ozone layer8. All in all, it is possible that ozone depletion can be halted in the next decade. But it will require a level of global stewardship that still poses a substantial challenge to all parties to the Montreal Protocol.

and Schultz1 adds a new dimension to characterization of the orbitofrontal neuronal activity — the relative attraction of the incentive.

It is important to place these results into the broader context of the part played by the prefrontal cortex in cognition. Studies of the prefrontal cortex have focused on the lateral prefrontal cortex in relation to working memory5,6. Current debates centre on whether dorsal and ventral parts of the lateral prefrontal cortex are functionally segregated according to what information is retained in working memory, or how that information is kept there6. But the orbitofrontal cortex — which occupies quite a large proportion of the prefrontal cortex — is not essential for working memory. If this area of the brain is damaged, working-memory tasks are not impaired. Moreover, clinical and noninvasive studies indicate that the orbitofrontal cortex is important for estimating the pleasantness or value of objects, emotional reactions3,7 and motivational operations such as expectation of reward8,9. The lateral prefrontal cortex, which is considered to be more involved in cognitive operations, is also implicated in reward expectancy9,10. It is clear, then, that theories to describe the functions of the primate prefrontal cortex will have to include the motivational parameters that underlie much of our behaviour10.

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Uncertain road to ozone recovery

Paul J. Fraser and Michael J. Prather

The manufacture and emission of chlorofluorocarbons (CFCs), our inadvertent global experiment in modifying the Earth’s stratosphere, has damaged the ozone layer for decades to come. The Montreal Protocol, which was agreed in 1987 and revised several times in the 1990s, and has the aim of reducing global emissions of ozone-depleting chemicals, has gone a significant way to solving the ‘ozone problem’1. However, as described by Montzka and colleagues on page 690 of this issue2, the road to ozone recovery remains uncertain.

The authors report the good news that, by 1997, the lower-atmospheric burden of ozone-depleting halogen compounds (chloro- and bromocarbons) had declined by 3% from its 1993–94 peak; and they provide a reminder that this decline is almost entirely due to the rapid atmospheric removal of the solvent methyl chloroform (CH3CCl3), global emissions of which are now virtually zero. But concentrations of other halocarbons — carbon tetrachloride (CCl4) and CFC-11 (C2ClF), for instance — are falling more slowly, and those of others such as CFC-12 (CCl2F2) are still rising. If the decline in emissions of these other halocarbon species does not gather pace, the overall fall in halogen concentrations in the atmosphere will stall sometime during the next decade.

What are the barriers to ozone recovery? Montzka et al.1 have identified several, namely, emissions of refrigerant CFCs, of HCFCs (hydrochlorofluorocarbons) as interim CFC replacements, and of halons (bromocarbons) as fire-fighting chemicals. In the developed world, a large ‘bank’ of CFC-12 in old refrigeration and vehicle air-conditioning systems continues to leak slowly into the atmosphere. Although new CFC production declined by a factor of 4–5 from 1986 to 1995 in accord with the Montreal Protocol, the developing world (China, India, Mexico) has increased production by 2–3 fold (largely of CFC-12), so that in 1995 it accounted for 45% of global CFC production3. This figure is presumably even larger now. The combined effect of these emissions is continuing growth of CFC-12 in the atmosphere (Fig. 1a, overleaf), and this is the biggest single long-term threat to ozone recovery.

Fortunately, HCFC emissions to date have been only 50% of those permitted under the Protocol; in large part this is because HCFCs are due to be phased out by 2030, and some parts of the refrigeration and air-conditioning industry have hesitated to invest in short-term HCFC technologies. Likewise, HCFCs have not replaced CFCs in aerosols or foam plastics, where hydrocarbons or ‘not-in-kind’ substitutes have filled these niches. Yet HCFC use — and therefore emissions and atmospheric concentrations — are predicted to increase substantially, and legally, under the Protocol over the next decade as HCFCs continue to be used as CFC substitutes in refrigeration (Fig. 1b).

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Figure 2 Lateral and ventral views of the orbitofrontal cortex of the monkey. Tremblay and Schultz1 show that this region of the brain is involved in assessing the relative — but not the absolute — attraction of a reward.

Lateral prefrontal cortex

Orbitofrontal cortex

Ventral view

Lateral view