SENSORY CODING

Brain waves deciphered

John P. Miller

THE expression 'brain waves' has been adopted into our colloquial vocabulary, and conjures up a sense of mystery in matters related to mind and brain. And rightly so — although waves of electrical activity in recordings from mammalian brains were first seen more than 120 years ago[1], the physiological significance of these oscillations remains a matter of conjecture. On page 162 of this issue, Wehr and Laurent[2] take us a step closer towards understanding the functional relevance of brain waves. Specifically, they show how a considerable amount of information about sensory stimuli is encoded by the sequences of oscillatory activity within groups of nerve cells.

What we commonly refer to as brain waves are electrical oscillations that emerge from coordinated electrical activity across large groups of neurons[3]. Such oscillatory activity is a general property of neural systems in many animal species, ranging from snails[4] to humans[5]. In most areas of the human brain, recordings from single cells show little or no overt evidence of oscillatory activity. But when an electroencephalogram is taken by placing a button-sized probe on a person's scalp, oscillations at several characteristic frequencies are clearly visible. They arise from a synchronized rhythmic electrical activity across large groups of neurons.

To illustrate, consider a group of a thousand nerve cells in an olfactory centre of the brain, all of which are responsive to the same olfactory stimulus — say, the smell of a rose. Assume that the presentation of this odour elicits a uniformly spaced sequence of approximately 40 action potentials over a period of one second in each of those cells. What would the combined activity of all of the cells look like when recorded with a large-scale electrode? If the cells were not synchronized with one another, then the 40,000 action potentials that they generated would be distributed fairly uniformly within the one-second response interval. In this case, the combined activity would form a 'flat', featureless signal at a scalp electrode. However, if all of those cells fired their action potentials in near-synchrony, the 40,000 action potentials would be organized into 40 groups of 1,000 events during the one-second interval. Summation of this pattern would result in wave-like oscillations at 40 Hz.

This stimulus-evoked oscillatory synchronization is reasonably well understood in many cases, yet we still do not know the significance of these oscillations within the context of brain function. Do any details of the synchronized oscillations encode significant information, or are the oscillations merely epiphenomena of the complex mass-activity of nervous systems? If the oscillations are involved in encoding information, what is that information, and what is the nature of the 'neural code' through which the information is represented?

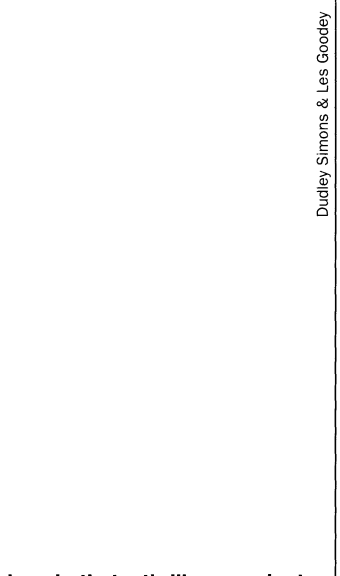
These are precisely the types of questions being addressed by Laurent and colleagues. By studying olfactory coding in the antennal lobe system in the locust brain, they previously found that, when a locust is presented with certain odours, oscillatory waves of activity are generated in the antennal lobe at frequencies of about 20 Hz (refs 6, 7). These oscillatory patterns are strikingly similar to the waves of activity that are generated at the equivalent processing stage in mammalian olfactory systems[3]. By recording the activity in both single neurons and whole neural networks, they were able to show that each odour leads to the synchronous activation of a specific ensemble of neurons within the antennal lobe. Each 'assembly' comprises about 100 of the roughly 800-strong class of cells known as the projection neurons.

Laurent and colleagues went on to predict that different odours could be encoded by the subset of these neurons that is involved in the electrical activity elicited by the odour. Each individual projection neuron could belong to many different assemblies and participate in the coding for many different odours. This corresponds to a 'spatial combinatorial code', whereby each odour elicits the activation of a different spatial pattern of 100 neurons within the 800-cell array. The unique assembly of cells that are stimulated by a particular odour could be identified by their synchronous firing, so the observed oscillations are a direct correlate of this functional 'tag'.

Wehr and Laurent[2] have now extended the hypothesized combinatorial encoding scheme to the temporal domain. They show that the set of neurons that is activated during the presentation of any particular odour changes in a reliable, stimulus-specific manner. Although around 100 projection neurons are activated during the presentation of any odour, only a small subset of these is maximally active during any single cycle of the oscillations. In other words, each 100-cell assembly is made up of several sub-assemblies, each of which has a different time course for its contribution to the overall response pattern. So whereas one cell might fire with high probability during the

PALAEONTOLOGY

Fossil fortune cookie



Dudley Simons & Les Goodey

***CATHAYMYRUS diadexus*, pictured here (and described by Shu *et al.* on page 157 of this issue) is a fortune cookie. Of the more than 10,000 fossils known from the 535-million-year-old Chengjiang fauna of China, *Cathaymyrus* is represented by just one. The trivial name *diadexus* comes from the Greek for a harbinger of good fortune, in the explicit hope that more specimens turn up.**

***Cathaymyrus* joins select company — the scarce and contentious fossils that convene around the base of the family tree of the chordates. This taxonomic rank includes all vertebrates and, for instance, the tunicates of tide pools and the lancelets (or amphioxus) of inshore waters. *Cathaymyrus* looks most like a lancelet, as does the better-known *Pikaia gracilens* from the celebrated Burgess Shales fauna of Canada, which is about ten million years younger than the Chengjiang fauna.**

Debate springs eternal over the affinities of other forms, for example *Yunnanozoon*, also from the Chengjiang fauna. And the picture is muddied further by other strange fossils. Most (but not all) agree that the bizarre echinoderm-like fossils called calcichordates probably are not chordates; on the other hand, many (but not all) now concede that the phosphatic tooth-like conodonts belonged to fully vertebrate chordates.

The diversity of chordates in the past was probably much greater than the Recent fauna gives us cause to believe. This is why fossils claimed to have chordate affinity will always seem unusual, and generate controversy. If only the fossil record were a little better: one hopes that the invocation of *Cathaymyrus diadexus* has the desired effects. Henry Gee

first three cycles, another might fire only during the second to the fifth cycles, and so on. Each odour would elicit the activation of a different sequence of spatial patterns of about 100 projection neuron cells. This spatio-temporal combinatorial coding scheme is likely to be much more efficient than a spatial coding scheme, because each set of sub-assemblies could be activated in different temporal sequences to indicate different odours. But here again, oscillations are direct correlates of the functional tags for specific odours.

In a related study[8], MacLeod and Laurent investigated the physiological mechanisms that underlie inter-cell synchronization. They were able to abolish the synchronization in the odour-coding assemblies without affecting the temporal response properties of the individual cells. This was done by blocking inhibitory synapses onto the projection neurons by another class of neurons within the olfactory network. These results support theoretical models that have been proposed for several other systems — including the mammalian olfactory cortex[9] — which depend on inhibitory interactions to achieve oscillatory synchronization.

Determination of the neural coding schemes that are at work in nervous systems is an important goal. Not only is the nature of neural coding of great interest, but a knowledge of the coding schemes will be necessary for the development of theories about cortical function and neural computation. Through their work on the locust olfactory system, Wehr and Laurent have taken us closer to achieving this aim. □

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HIV

One on one meets two

Simon Wain-Hobson

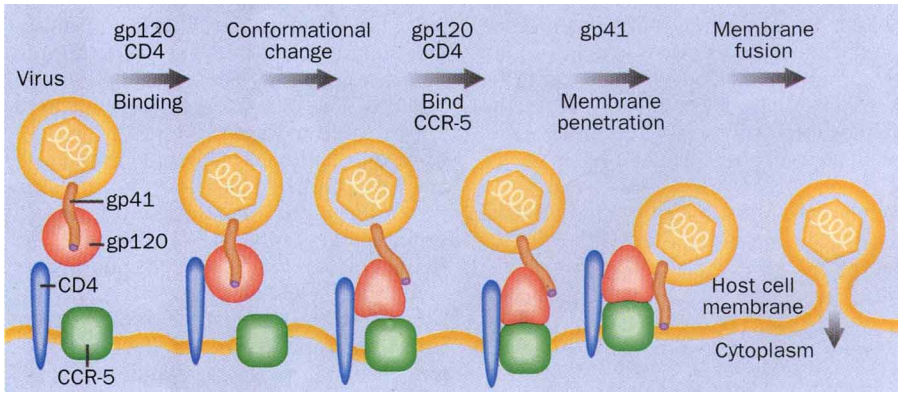
VIRUSES identify their target cells by recognizing protein or carbohydrate molecules on the cell surface. Once the virus has docked, subsequent manoeuvres allow it to enter the cell and nucleic-acid replication ensues. More than ten years ago, the CD4 molecule was found to be the receptor for human immunodeficiency virus[1,2]. But it was quickly shown that CD4 was not enough, and the hunt began for the second receptor. Despite the use of some awesome firepower to track down the missing receptor, it was only earlier this year that it was identified as a transmembrane, G-protein-associated molecule called CXCR-4 (ref. 3). Since then, the field has moved quickly — there is now known to be another HIV co-receptor, termed CCR-5, which is related to CXCR-4. Most HIV isolates use CCR-5 as the second receptor[4,5], and two papers by Wu *et al.*[6] and Trkola *et al.*[7] on pages 179 and 184 of this issue now provide a possible mechanism by which the CCR-5 receptor could mediate the entry of HIV into the host cell.

HIV encodes a glycoprotein precursor called gp160 that is cleaved by cellular enzymes into gp120 and gp41, which are surface and transmembrane proteins, respectively: gp120 is non-covalently attached to gp41, which is anchored in the viral lipid bilayer (see figure). High-affinity binding of gp120 to the first HIV receptor, CD4, causes conformational changes in gp120. These can be detected by the occlusion of some epitopes for monoclonal antibodies. The results of Wu *et al.* and Trkola *et al.* indicate that these conformational changes lead to the creation of a new recognition site on gp120 for CCR-5, to which it binds with nanomolar affinity. The two groups used a simple biochemical approach to show this previously unsuspected interaction. CCR-5 acts as a receptor for a class of molecules known as β-chemokines; for example, macrophage inflammatory protein (MIP)-1α and -1β and RANTES (regulation-upon-activation normal T expressed and secreted). By using radioactively labelled MIP-1β, both groups were able to show that the binding of MIP-1β to CCR-5 could be blocked by the gp120/CD4 complex.

It will come as no surprise to HIV aficionados that the V3 loop of gp120, something akin to a molecular Achilles heel, is involved in these interactions. Not only is the V3 loop the target of neutralizing antibody, but it is also involved in dictating the use of CCR-5 or CXCR-4. The part played by V3 was elegantly shown by using gp120 derivatives in which V3 had been deleted — and there was no longer an interaction between gp120 and CCR-5.

Wu *et al.* and Trkola *et al.* also found that many of the monoclonal antibodies that can neutralize HIV in a simple culture assay[8] blocked the binding of gp120/CD4 to CCR-5. This is a satisfying finding given the difficulties of working with gp120, which is a large, heavily glycosylated, polymorphic molecule that has defied many attempts to crystallize it. Moreover, neutralizing antibodies often block viral infection by smothering the regions that are involved in receptor binding. By using two receptor molecules, one might have thought that HIV had made life difficult for itself, allowing the immune system to strike twice. But compared with many other viruses, anti-HIV neutralizing-antibody titres are low, indicating that HIV has found a robust solution to coping with the wrath of the immune system.

Yet there is still something missing. Studies of many enveloped viruses indicate that the hydrophobic amino terminus of the transmembrane protein (that is, gp41 in HIV) must somehow interact with the membrane of the host cell. This situation has been well characterized in influenza virus: the receptor-binding envelope protein is called haemagglutinin, and it is analogous to HIV gp160. In the same way as gp160 is cleaved into gp120 and gp41, haemagglutinin is cleaved into HA1 and HA2. The crystal structure of haemagglutinin shows that the amino terminus is



HIV-encoded gp120 recognizes the host-encoded CD4 receptor. This interaction leads to a conformational change in gp120, allowing it to bind to a second receptor, CCR-5, as shown by Wu *et al.*[6] and Trkola *et al.*[7] At some point to be defined, the amino terminus of gp41 is uncovered, allowing penetration of the host cell membrane and fusion of the viral and host cell membranes. Stripped of its lipid protection, the capsid complex moves into the cytoplasm, and reverse transcription is initiated depending on the availability of nucleoside triphosphates.