Rolling back the frontiers in the brain

A global scientific programme using a sweeping range of techniques to tackle some of the most daunting problems in biology ought to be impossible. But it works.

IN one of the first talks at the conference on "Information Storage, Transfer and Retrieval" organized by the Human Frontier Science Program (HFSP) in Hakone, Japan, on 5–8 April, Lubert Stryer (Stanford Medical School) told of a conversation in 1969 with Henri Peyre, then professor of French at Yale. Unimpressed by Stryer's account of how he intended to determine the molecular basis of vertebrate vision, Peyre remarked that the truly interesting question was the molecular basis of remorse.

That goal is not yet within reach, but as a statement of the HFSP's bold ambitions, it could hardly be bettered. The programme's review committee aims to select the best proposals for studies of the human brain from Japan, Europe and North America, using techniques ranging from molecular biology to computer modelling. By no means all of the work described at this meeting was supported by the HFSP, but enough of it was to suggest the HFSP is in good shape.

Not all of the work described concerned the nervous system. The helices formed by linear polybipyridines (Jean-Marie Lehn, Université Louis Pasteur, Strasbourg, and Collège de France, Paris), the unexpected interdependence of elements in the c-*fos* promoter (Tom Curran, Roche Institute of Molecular Biology, New Jersey), and the tumour-suppressor activity of the interferon-induced transcription factor IRF1 (Tadatsugu Taniguchi, Osaka University) clearly have implications for all cells.

But, in general, the neural theme was dominant. Discussion of neural lineage commitment focused on *Drosophila* bristle-formation; both the transcription factor JκRBP (Tasuku Honjo, Kyoto University) and the signal-receptor pair *Delta* and *Notch* (Patricia Simpson, Institut de Chimie Biologique, Strasbourg) are important. Two molecules directing axonal targeting were also featured (Corey Goodman, HHMI, University of California, Berkeley, and Friedrich Bonhoeffer, Max Planck Institut, Tübingen); although the first, at least, appears to be a homophilic cell-adhesion protein, like the second it can also repel non-expressing neurons.

Nor was neuronal signalling neglected. Jean-Pierre Changeux (Institut Pasteur, Paris) described mutations in the amino acids lining the pore of the nicotinic acetylcholine receptor that convert it into an anion channel. Signal termination, too, was scrutinized (Stryer); excited photorhodopsin in vertebrate rods stays active until falling intracellular calcium levels detach two calcium ions bound by the protein recoverin, freeing recoverin from the membrane by inducing retraction of its phospholipid anchor.

Such phenomena can directly affect animal behaviour. Conditioning of the startle response in fish depends on a new-found plasticity in gap junctions and inhibitory synapses, while some inhibitory neurons become active only on conditioning (Henri Korn, Institut Pasteur, Paris). Just as striking is the modulation of GABA transmission in the accessory olfactory bulb by type 2 metabotropic glutamate receptors (Shigetada Nakanishi, Kyoto University); the resulting olfactory memories appear necessary, *inter alia*, for sexual fidelity in female rats.

But the molecular basis of most processing is less clear. Habit formation and visual recall are mediated by anatomically and pharmacologically distinct systems in monkeys (Mortimer Mishkin, NIMH, Bethesda), but study of the synapses involved lies ahead. Markus Raichle's studies of human habit formation using ^{15}O positron emission tomography suggest a related distinction (University of Washington, St Louis).

A different specialization is evident in the prefrontal cortex (Patricia Goldman-Rakic, Yale University School of Medicine, and Michael Petrides, Montreal Neurological Institute): the position, features and list order of visual objects are all handled by separate regions. Even more remarkably, a nearby region on the left side of this area appears to mediate discrimination of events closely spaced in time (Paula Tallal, Rutgers University). Ninety per cent of dyslexic patients lack this ability, and cannot distinguish syllables differing only in their first 40 milliseconds, but the problem affects other senses as well. The lateralization of speech, rather than being uniquely human, may therefore represent an adaptation of previously existing neuronal circuitry, an idea supported by the recent demonstration that rats share the 'right-ear advantage' previously thought to be confined to humans.

But fine temporal discrimination is involved in other phenomena as well. The inositol triphosphate and ryanodine receptors may in fact act as 'coincidence detectors', releasing calcium only when triggered both by cytoplasmic calcium and their respective second messengers (Michael Berridge, University of Cambridge). And the synchronized waves of activity that sweep the ganglion cells of each ferret retina before they receive visual input are vital if each eye is to be correctly connected to separate layers in the lateral geniculate nucleus (Carla Schatz, University of California, Berkeley).

The features of a single object may even be grouped by synchronizing the firing of all neurons involved, allowing overlapping percepts to be rapidly distinguished (Wolf Singer, Max Planck Institute for Brain Research, Frankfurt). Multielectrode recordings of amblyopic strabismic monkeys show that cortical neurons driven by the disadvantaged eye indeed encode object features normally but fire asynchronously in response to stimuli the monkey cannot see.

Elsewhere, however, information is stored differently. Neurons in the inferior temporal cortex of monkeys trained to associate paired abstract designs show highly selective responses to pair members (Yasushi Miyashita, University of Tokyo). Similarly, simultaneous recording of as many as 148 neurons in the hippocampus of an active rat shows that most cells monitored respond selectively to particular locations (Bruce McNaughton, University of Arizona, Tucson). An intriguing aspect of this technical *tour de force* is that cells whose firing was correlated during exploration were again co-activated during slow-wave sleep, suggesting that the hippocampus 'downloads' memories to the cortex while it is 'off-line'.

But it is in modelling brain function on the basis of such information that the HFSP's breadth is most clearly beneficial. McNaughton's data, for instance, have been used to build a model of hippocampal function in which a partial cue can elicit information stored in the cortex to reinstate the memory (Edmund Rolls, University of Oxford). Even more impressive are cases in which the model not only correctly predicts neuronal responses to a given stimulus, but can be shown to improve robot arm performance (Mitsuo Kawato, ATR Human Information Processing Research Laboratories, Kyoto) or to respond in a life-like way to complex visual illusions (Terrence Sejnowski, Salk Institute, San Diego).

Despite such spectacular advances, it will be a long time before the stupendous complexity of most neural systems is understood. But there can surely be few things more interesting to mankind than our brains, and, the HFSP has clearly hit on a winning formula for their study. It is therefore particularly sad that more countries have not emulated Japan's example and given the programme the financial support it deserves. Other member nations should be overcome by remorse, whether they understand its molecular nature or not, and reach for their cheque books.

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