that have been considered, the 'flashing ratchet' has attracted particular attention because of its likely relevance to biology[7]. In this ratchet, a noise-driven particle — which might be attached to a vesicle carrying a macromolecule — diffuses within a periodic potential (a cyclic variation of the particle's potential energy with position). This potential can typically take one of two forms — it can either be flat, with no variation at all, or it can have a series of ratchet-shaped teeth. The system flashes back and forth between these two configurations. As a result — depending on the shape of the teeth and the characteristics of the noise — the particle will diffuse preferentially either to the right or to the left; given noise of appropriate intensity, there will be a net current. Remarkably, there is still a net current of particles, albeit a smaller one, even if the potential is tilted so that the particles have to run uphill. Yet if the flashing ceases, the system stops working. Current will not flow uphill for either of the two configurations taken alone.

Surprising though it may seem, there appears to be a close relationship between flashing ratchets and certain mathematical games. Juan Parrondo (Universidad Complutense de Madrid, Spain) has devised two simple games whose behaviour was shown by Derek Abbott (University of Adelaide and organizer of *UPoN'99*) and colleagues to model closely that of a flashing ratchet. Either game played on its own results in loss for the player. But if play alternates randomly between the two games the result is a win — that is, two losing strategies can result in a win. The games are amenable to rigorous mathematical analysis, and promise to pave the way to a detailed understanding of ratchet phenomena. Such models could have a bearing on population genetics and evolutionary biology, as well as on game theory in economics.

In surveying stochastic resonance, Sergey Bezrukov (National Institutes of Health, Bethesda, Maryland) admitted ruefully that early perceptions now seem inadequate. In particular, the once standard definition[8] of stochastic resonance as an effect confined to bistable systems that can exist in two different states (including systems with thresholds) is not very useful because the phenomenon occurs much more widely. In fact, the only general definition of stochastic resonance that remains tenable is that the effect arises whenever a nonlinear system has a large, strongly noise-dependent susceptibility[9] (a quantity that relates the periodic response of the system to the weak periodic force that gives rise to it).

What do stochastic resonance, Brownian ratchets and, indeed, most other fluctuational phenomena have in common? It has slowly been realized that a unifying feature in many cases is reliance on 'special' fluctuations that occur infrequently. For example, a system will usually wait for a long time below a potential barrier for a fluctuation of exactly the right shape and strength to carry it over. These large, rare fluctuations are of fundamental importance in understanding the behaviour of noise-driven systems. They are starting to be understood, even in the dauntingly complex, non-equilibrium cases found in practical situations.

Advances have recently been made in experimenting on large, rare fluctuations. Riccardo Mannella (University of Pisa, Italy) described experiments that have confirmed the validity of the so-called logarithmic susceptibility, a new physical quantity[10] for describing large fluctuations in periodically driven non-equilibrium systems. These results are immensely encouraging because, if large fluctuations can be properly understood, it may then be possible to control their destructive power (for example, in the spontaneous failure of lasers) and, perhaps, to exploit them (such as when minimizing the energy requirements for desired transitions). Noise is starting to look altogether friendlier and more useful than it did in earlier times. ■

Peter V. E. McClintock is in the Department of Physics, University of Lancaster, Lancaster LA1 4YB, UK.
e-mail: p.v.e.mcclintock@lancaster.ac.uk

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Neurobiology

Young receptors make smart mice

T. V. P. Bliss

Animals can learn because of changes in the brain which allow new information to be acquired, stored and later recalled. But what are these changes and where do they occur? At the cellular level, changes probably occur at synapses — the junctions between nerve cells. This idea is formalized in the Hebb rule, which states that a synapse between cell A and cell B will be strengthened if the two cells are active at the same time[1]. Neuroscientists can explore the properties and behavioural implications of the Hebb synapse by studying an experimental model of synaptic plasticity known as long-term potentiation (LTP)[2]. Synapses that show LTP are found in several parts of the brain, notably in the hippocampus (a cortical structure which, in humans, is required for the formation of autobiographical memories). Does LTP, then, supply the synaptic underpinning of memory? A report by Tang *et al.*[3] on page 63 of this issue provides new evidence in support of this hypothesis, showing that LTP is considerably enhanced in transgenic mice with improved learning performance.

Long-term potentiation is induced by brief, repeated stimulation of defined neural pathways in the hippocampus. The resulting increased efficacy of synaptic transmission

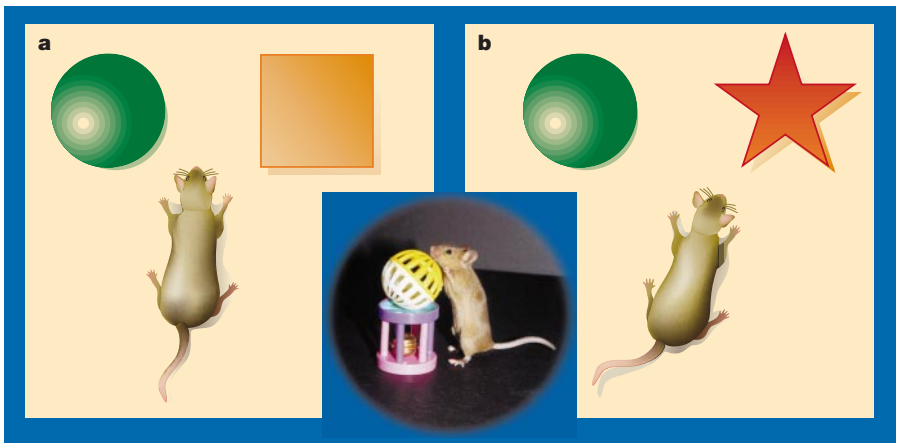

Figure 1 **Object-recognition task.** a, **In an initial training session the mouse explores two objects in a box, devoting roughly equal time to each.** b, **When the mouse is then re-exposed to one of these objects, together with a new object, it spends more time exploring the new object. Tang *et al.*[3] find that this bias is enhanced in transgenic mice (inset) overexpressing the NR2B subunit of the NMDA receptor, indicating improved recognition memory.**

can last for hours (in slices cut from the hippocampus) or several days (*in vivo*). If drugs are used to block the induction of LTP, rats have trouble finding their way around a maze, suggesting that LTP is necessary for spatial learning[4]. And using transgenic mice, researchers can explore what happens to LTP and learning when specific proteins are overexpressed or deleted. When genes involved in regulating synaptic transmission are deleted, most of the mice can no longer sustain normal LTP. This impairment is usually accompanied by a defect in spatial learning.

To appreciate what Tang *et al.*[3] have done, it is necessary to understand certain properties of a membrane protein called the NMDA (*N*-methyl-D-aspartate) receptor. This receptor binds to the excitatory neurotransmitter glutamate and controls the initiation of LTP in most hippocampal pathways. The receptor forms a channel that does not open unless two conditions are satisfied simultaneously — glutamate must bind to the receptor, and the membrane in which the receptor is embedded must be strongly depolarized. Once the channel opens a flux of calcium ions enters the cell, triggering the induction of LTP.

The NMDA receptor is made up of an NR1 subunit (Box 1), which is obligatory for channel function, and a selection of developmentally and regionally regulated NR2 subunits (A to D). The functional properties of the receptor depend on its subunit composition. For example, the glutamate-evoked current (which is important in determining the amount of Ca^{2+} that enters the cell) has a longer duration in receptors containing NR2B subunits than in those containing NR2A subunits. The proportion of NR2B subunits is higher in young animals than in adults[5], and this may account for the greater degree of LTP seen in young animals[6]. With this in mind, Tang *et al.* engineered a transgenic mouse that overexpresses the NR2B subunit in the adult brain. They then asked three questions. First, would the mutant show an increase in NMDA-receptor-mediated current? Second, would it, as an adult, show the enhanced level of LTP normally seen in young animals? And finally, would this make a smarter mouse? The answer to all three questions seems to be yes.

The authors successfully expressed the transgene in two different mouse lines, with similar physiological and behavioural effects in both. Glutamate-evoked NMDA-receptor-mediated currents were larger and of a longer duration in cultured neurons from transgenic than from normal animals. (Presumably, although direct evidence is not offered, this was also the case in the hippocampal slices in which LTP was monitored.) Tang *et al.* also found that LTP was greatly enhanced in the two transgenic lines, with a flat initial time course reminiscent of LTP in young rather than adult animals.

The consequences of overexpressing the NR2B subunit on learning and memory — or, at least, on those kinds of learning that depend on the hippocampus in rodents — seem unequivocal. The transgenic mice showed improved learning scores compared with normal mice in three different tests of their ability to acquire and retain information. In one of these tests, fear conditioning, a tone is paired with a mild foot-shock in a particular box. The mouse will freeze, indicating memory of the shock, when it is replaced in the box some time later. This 'context specificity' is thought to depend on the hippocampus.

The authors found that associative learning was enhanced in the transgenic mice. Furthermore, when the animals were repeatedly given the tone alone or repeatedly returned to the box in which they had been trained, without being given further shocks, the conditioned response was extinguished more rapidly in the transgenic animals than in normal mice. Tang *et al.* regard this as further evidence for improved learning — an interpretation that requires extinction of the response to be seen as active relearning, rather than a passive forgetting of the previously learned association. In two other tasks (object recognition, shown in Fig. 1, and the water maze, in which animals have to locate a submerged platform in a pool of opaque water), the transgenic animals again scored more highly than normal mice.

Although this is not the first report of a transgenic animal showing both enhanced LTP and improved learning[7], Tang and colleagues' work is striking for two reasons. First, there is the clear link between manipulation of a specific gene (overexpression of the NR2B subunit) and the physiological consequence (enhanced Ca^{2+} flux, leading to greater LTP). The second reason is the variety of tasks examined, which adds strength to the authors' conclusion that they have indeed made a smarter animal.

An improvement in LTP has been reported in other transgenic mice. When the genes encoding postsynaptic density-95 (PSD-95; a cytoplasmic protein that binds the NMDA receptor)[8] and GluR2 (a subunit of the AMPA subtype of glutamate receptor)[9] were deleted, both showed enhanced LTP. Yet their performance in the water maze was impaired. Compare this with Tang and colleagues' mice, which showed an improved performance in the water maze. The PSD-95 knockout mice were also defective in another form of activity-dependent synaptic plasticity, long-term depression (LTD). By contrast, LTD appeared normal in Tang and colleagues' mice. This may explain the different responses in the water maze — bidirectional changes in synaptic efficacy are thought to be important for efficient storage in neural nets[10].

Several genetically targeted mice have been described in which a reduction in LTP has not been matched by diminished performance in hippocampal-dependent learning (see, for example, ref. 11). Against this background, where changes in LTP correlate with changes in learning in some transgenic animals but not in others, it is not surprising that a consensus on the role of synaptic plasticity in learning has been hard to achieve[12]. But the impressive data obtained by Tang *et al.* will bolster the majority view that synap-

Box 1: The NMDA receptor and schizophrenia

In the work discussed in the main article here, Tang *et al.*[3] show that mice in which the NR2B subunit of the NMDA receptor is overexpressed display a striking increase in synaptic plasticity and learning ability. But what about mutations of the essential NR1 subunit? Mice with targeted ablation of this subunit lack functional NMDA receptors and are not viable. However, newly developed mutants, genetically engineered to express about 5% of the normal number of NR1 subunits, live to maturity. And, according to a report by Mohn *et al.*[13] in the latest issue of *Cell*, these mice may provide the best rodent model of schizophrenia so far.

Mohn and colleagues find that reduced expression of the NR1 subunit (and, hence, the NMDA receptor) leads to increased motor activity and rapid repetitive behaviour (stereotypy), as well as reduced social and sexual interactions. These 'symptoms' are all characteristics of pharmacologically induced models of schizophrenia.

The finding that a reduced number of NMDA receptors leads to schizophrenic types of behaviour should help to distinguish between two rival theories as to the causes of the disease. The first, the 'dopamine hypothesis', derives from the observation that antipsychotic drugs share a common action in blocking receptors for the neurotransmitter dopamine. This theory attributes the behavioural and cognitive abnormalities of schizophrenia to increased levels of dopamine. The second theory, the 'glutamate-dysfunction hypothesis', evolved from the observation that phencyclidine, an antagonist of the NMDA receptor, produces symptoms that mimic schizophrenia in people and mice. According to this hypothesis, the disease is caused by a disturbance in the balance between the reciprocal actions of glutamate and dopamine on subcortical structures[14]. So the results of Mohn *et al.* support the glutamate-dysfunction hypothesis. **T. V. P. B.**

tic plasticity is an essential component of the neural processes underlying learning and memory in the vertebrate brain. ■

T. V. P. Bliss is in the Division of Neurophysiology, National Institute for Medical Research, Mill Hill, London NW7 1AA, UK.
e-mail: tbliss@nimr.mrc.ac.uk

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Dark matter

Lumpy haloes spin faster

James Binney

More than 90% of the mass of the Universe is thought to be made up of dark matter. The density of this mysterious matter has been most precisely measured in the outer reaches of disk-shaped spiral galaxies, where very little light is emitted by stars. It is generally accepted that galaxies are surrounded by dark matter 'haloes' in which the visible galaxy is embedded, so helping to explain the rapid rotation of stars and gas far from the galactic centre. How much dark matter coexists with stars near the centre of galaxies is less certain, but numerical studies of the dynamics of bar-shaped galaxies have been used to impose an upper limit on the central dark-matter density[1].

Tremaine and Ostriker[2] now suggest in *Monthly Notices of the Royal Astronomical Society* that, because of an unexpectedly strong interaction with the galactic disk, dark haloes may have a rapidly spinning central bulge, similar to the stellar cores of galaxies. If this is true, it will come as a relief to advocates of the 'cold dark matter' (CDM) picture of the Universe, which predicts that many disk galaxies should be dominated by dark matter even at their centres.

For galaxies to shine, some of their mass must be luminous baryons, rather than dark matter. According to the CDM model, during galaxy formation this baryonic matter loses energy through radiation and therefore collapses into a compact, rapidly spinning disk near the centre of a much larger and barely rotating dark-matter halo. Rapidly spinning, self-gravitating bodies are prone to becoming rotating bars, and most disk galaxies have bars at their centres. More than ten years ago, Weinberg[3] pointed out that a rapidly spinning bar embedded in a slowly rotating dark halo would transfer angular momentum to the halo through dynamical friction. In this way the rotation of the halo would be accelerated, but the bar would be slowed down. So, if the density of dark matter is high at the centre of galaxies, bars should rotate slowly. But observations show that most bars are still rapidly rotating, suggesting that dark matter is unimportant in the centres of galaxies. Although Weinberg's arguments were mostly analytical, they were later confirmed by numerical simulations[1].

Tremaine and Ostriker[2] weaken this line of reasoning by arguing that a disk as well as a bar may be able to cause the halo to spin faster, in which case the bar will not be severely slowed by the halo. Non-axisymmetric features of the disk, such as the spiral structure, are not massive enough to transfer significant angular momentum to the halo. But Tremaine and Ostriker suggest that the disk and halo may be effectively coupled by inhomogeneities in the halo, which gravitationally concentrate the orbits of stars and gas in the disk. This creates regions of higher disk density, which in turn gravitationally pull the halo irregularities around in the sense of the disk's rotation.

Are the interiors of dark haloes sufficiently lumpy for effective coupling of the disk and halo as proposed by Tremaine and Ostriker? Until recently the standard picture of a dark halo was a smooth object with a radial density gradient that decreased from the outside inwards. As numerical simulations of halo formation grew more detailed, it became apparent that, in the CDM picture at least, haloes must be full of high-density blobs and strings[4]. This is because structure formation is a 'bottom-up' process, starting with the formation of very low-mass haloes, many of which merge to form middle-size haloes, and so on. When small haloes merge to form a more massive halo, the outer layers of the haloes are quickly stripped off by tidal forces, whereas the cores stay intact for much longer. In addition, as a stripped core falls through a more massive halo, it loses a ribbon of particles — a 'tidal streamer' — that moves on essentially the same orbit as the parent halo. Tremaine and Ostriker estimate the number of tidal streamers and intact halo cores that are needed to ensure sufficient transfer of angular momentum between disk and halo.

100 YEARS AGO

On removing some virgin cork from the wall of a conservatory a short time ago, I was much struck with the way in which a small black female spider clung to her two egg-bags, despite the fact that the piece of cork to which she was clinging had been thrown roughly to the ground. … Knowing how fully alive to danger the spider race is in general, I thought that this remarkable instance of devotion to maternal promptings on the part of a naturally sensitive creature ought not to be disregarded. I accordingly removed the mother very carefully, and placed her on some rockwork, where I noticed she seemed to be very uneasy, moving restlessly about as if searching for something. I then took the egg-bags and placed them beside her. As I expected, she seemingly failed to recognise them, or at least manifested a repugnance to them, and ran away for a little distance. Subsequently, however, she returned, and proceeded to examine the bags with scrupulous care by means of her palpi; and evidently satisfied with this scrutiny that they were really her own cherished property, she commenced to spin a web about them to secure them in their place.
From *Nature* 31 August 1899.

50 YEARS AGO

There is an old Egyptian saying that whoever has once drunk of the waters of the Nile will want to go back and drink them again. I do not know if that has ever been said of the waters of the Tyne, but it is certainly true that the British Association always welcomes an invitation to Newcastle. … We came first in 1838 when England was mainly an agricultural country. The 111 years that have elapsed have seen profound changes in our national life, particularly the prodigious advancement of national science and of its daughter technology. Among the many resulting achievements has been a great increase in the certainty and the length of life. The world population has risen more rapidly than ever before; it is now estimated by the Food and Agriculture Organisation at about 2,300 millions, and the increase at about 20 millions a year — an average addition of two every three seconds, day and night, year after year, and the two may become three or more as science advances, social services improve, and bodies such as the World Health Organisation become fully operative. Can they all be fed?
From *Nature* 3 September 1949.