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EDITORIAL

Seeing the evidence: learning from images in neuroscience

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SUMMARY

The cover of this issue heralds a series of articles in which a visual image derived from cell biology or neuroscience is used to promote understanding of the biological mechanisms fundamental to psychiatry. 'Images in neuroscience' are intended to demonstrate the structures and mechanisms of the basic building blocks of brain function, including ionotropic and metabotropic receptors, second messenger systems, specialised ion channels, transmitter pathways, transporters, neuroglial function, and the complex mechanisms within cells that are being revealed, as new genetic associations for mental illness are discovered.

DECLARATION OF INTEREST

None.

The idea that a visual image can convey a complex biological meaning is most iconically seen in the double helix of DNA proposed by Watson & Crick in 1953. Crick's wife, the artist Odile Crick, drew the image for their *Nature* article. The strength of that image is that as well as providing a chemical structure accounting for the known pairing of nucleotide bases, it also revealed a mechanism for genetic replication and suggested a mechanism, later elaborated by Crick, for signalling the assembly of proteins (Watson 1968).

In addition to the double helix, other discoveries of the early 1950s were crucial in helping us to understand the brain. In 1950, chlorpromazine was synthesised by Paul Charpentier in the laboratories of Rhône-Poulenc, as part of the development of antihistamines; it was tested in patients in 1951 and became available for prescription as the first antipsychotic in 1952 (Shorter 1997). Alan Hodgkin & Andrew Huxley proposed mechanisms of neuronal excitability and conduction, implying the existence of membrane channels for specific ions regulated by voltage changes across the membrane (Hodgkin 1952). Paul Fatt & Bernard Katz elucidated the quantal mechanism of synaptic transmission, implying vesicular storage and release of acetylcholine (Fatt 1952). In 1957, Julius Axelrod discovered that noradrenaline released into a synapse is taken back into the presynaptic nerve ending by a reuptake mechanism, thus identifying one of the 'transporters' that provide a basis for understanding antidepressants (Whitby 1961). The roles of γ-aminobutyric acid (GABA) and glutamate (Hayashi 1952; Curtis 1960) as transmitters were also established.

Thus, by the end of the 1950s, there were strong theoretical models of voltage-sensitive ion channels, of chemical transmission across synapses by acetylcholine, and of reuptake transporters and membrane 'receptors' that obeyed laws of activation and competitive antagonism, similar to those for enzymes that were known to be protein structures. Antipsychotics and antidepressants had become available, and GABA, glutamate and noradrenaline were also recognised as transmitters.

What were then abstract models have been elucidated and given form by the techniques of cell biology, pharmacology and molecular genetics. The theoretical 'models' now have a physical reality that can be visualised either directly or graphically. Dopamine and serotonin have also been established as important neurotransmitters.

Long-term potentiation and the cellular basis of memory

When Eric Kandel received the Nobel Prize in 2000, it acknowledged decades of work on the biological basis of memory formation. The image on the front cover of this issue of *Advances* and reproduce in black and white in Fig. 1 summarises some of his achievements, a model for the cellular basis of declarative or explicit memory, underlying the phenomenon of long-term potentiation (LTP) in the hippocampus.

In his book *In Search of Memory,* Kandel (2006) recalls the lifetime experiences that stimulated his curiosity into why some exciting events are vividly remembered and why some distressing events can never be forgotten. He describes his childhood in pre-war Vienna, his education as a Jewish émigré in the USA, his training in medicine and psychiatry (predominantly psychoanalytical) and his discoveries through a series of extraordinary collaborations with leading neuroscientists.

His search was guided by the principle elaborated by Donald Hebb (1949) that when neurons

repeatedly discharge together, the connections between them become more extensive, providing a basis for memory. His early work on the giant sea snail *Aplysia* provided a model for the associative form of implicit memory (Kandel 1965), corresponding in humans to fear conditioning involving the amygdala, and operant conditioning involving the striatum and cerebellum.

Transmitting memory into shape

As a result of studies of patients with bilateral removal of the medial temporal lobes, it was known that the hippocampus is important in processing information for storage as declarative or explicit memory (Scoville 1957). In 1973, Bliss & Lomo described the phenomenon of long-term potentiation in the hippocampus, whereby intense repetitive stimulation of axons synapsing onto pyramidal neurons in the hippocampus causes an increase in the response of those pyramidal cells to subsequent stimulation. Long-term potentiation is the most enduring change in neuronal function known in neuroscience and may provide a cellular basis for the formation of declarative memory.

Figure 1 illustrates a crucial aspect of this model, a change in synaptic strength when the cell detects the coincidence of two separate inputs. The CA1 region of the hippocampus brings together multisensory information for memory formation, for example memory about places. The CA1 cells of the hippocampus receive an input from the excitatory transmitter glutamate released by collateral fibres of the CA3 pyramidal neurons. For long-term potentiation to occur, two types of glutamate receptor are involved. The α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor is a gated sodium channel whose activation by glutamate allows sodium entry, depolarising the adjacent cell membrane. *N*-methyl-D-aspartic acid (NMDA)-type glutamate receptors are normally insensitive to glutamate because they are blocked by a magnesium ion. However, depolarisation of the membrane displaces the magnesium ion, and the NMDA-type receptor can then be activated by glutamate. In this sense, the NMDA receptor detects the coincidence of recent depolarisation and the presence of glutamate.

N-methyl-D-asparatic acid receptors are also gated ion channels, but are more complex than AMPA receptors and permit the passage of both sodium and calcium ions. Calcium ions entering the cell act as second messengers, activating various intracellular processes: these processes bring about changes in the function and structure of the synapse, leading by several mechanisms to long-term potentiation.

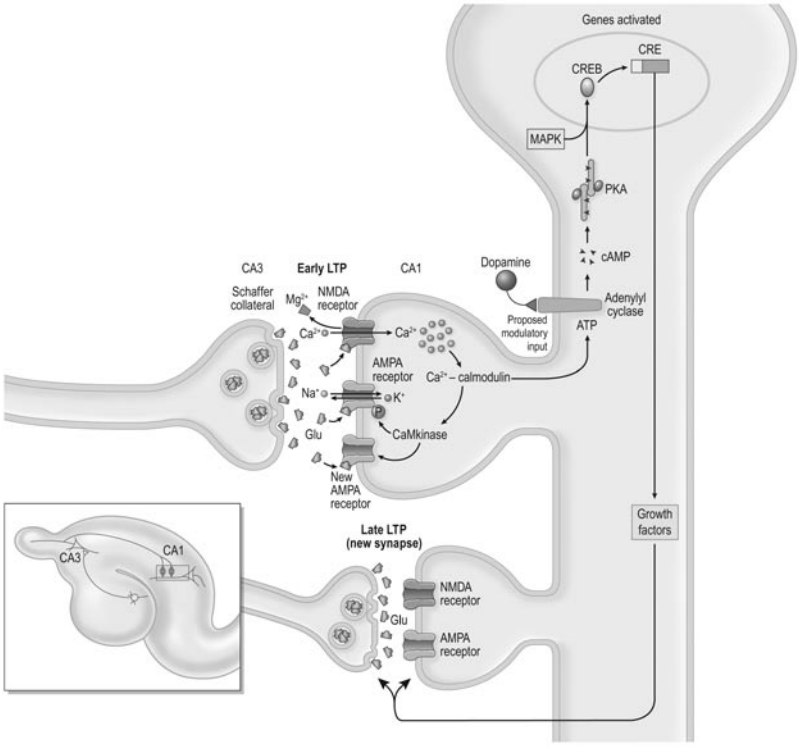

FIG 1 Kandel's model for the cellular and molecular basis of declarative memory formation in the hippocampus (see Kandel 2000). Artist: Philip Wilson.

The main pathway illustrated leads to the formation of new AMPA receptors. Binding calcium with calmodulin to activate calcium–calmodulin-dependent protein kinase (CaMK), which phosphorylates preformed AMPA receptors, causes other AMPA receptors to become located in the membrane (Malenka 1999; Miles 2005) and others to be synthesised.

The early phase of long-term potentiation involves enhanced sensitivity of receptors to glutamate as well as enhanced release of the transmitter. Nitric oxide may act as a signal to the presynaptic nerve ending to release more transmitters. Postsynaptically, local receptors are trafficked to the membrane. In the later phase of long-term potentiation, signals translate to the nucleus of the cell and lead to protein synthesis and to structural changes, i.e. the formation of new synapses. This involves the stimulation by calcium ions of adenylate cyclase, forming cyclic adenosine monophosphate (cAMP), which activates cAMP-dependent protein kinase A (PKA) and, together with mitogen-activated protein kinase (MAPK), leads to the production of cAMP-response element-binding protein (CREB), which acts within the nucleus to trigger genes, leading to the production of growth factors.

In its simplest form, the coincidence that is detected is that of recent depolarisation (by

glutamate released from one presynaptic pathway) with glutamate release onto NMDA receptors from another presynaptic neuron. However, the model also permits the detection of other coincident inputs. For example, the adenylate cyclase can also be activated by other transmitters such as serotonin in *Aplysia* and by dopamine in the mammalian brain, and Kandel suggests that in this role dopamine signals the salience of the initial input.

Our understanding of long-term potentiation and the molecular basis of memory is still developing. Si *et al* (2003) identified a protein cytoplasmic polyadenylation element-binding protein (CPEB) that enables the signal from the nucleus to activate local protein synthesis; CPEB has some structural similarities and self-replicating properties in common with prions. Kovacs *et al* (2007) identified a molecule called transducer of regulated CREB activity 1 (TORC1) that senses the coincidence of cAMP and calcium ions in neurons, and leads to the synthesis of factors enhancing synaptic transmission. Cao *et al* (2008) used pharmacological inhibition to turn off CaMK in a mouse genetically engineered to overexpress this molecule, and were able to selectively remove specific memories.

Generalisability and clinical implications

The phenomenon of long-term potentiation has been found in other brain areas besides the hippocampus, and may have wide clinical implications.

Understanding the mechanisms of long-term potentiation offers hope of developing interventions to treat disorders of memory and learning, including phobias, obsessive–compulsive disorder and post-traumatic stress disorder (Morrison 2002). The role of dopamine in long-term potentiation is relevant to symptom formation (e.g. delusions) in psychosis. The cellular mechanisms involved in long-term potentiation have also been implicated in hypotheses about the pathophysiology of depression (see Zaman 2001). The role of CPEB may caste light on the pathogenesis of prion diseases.

Conclusions

Evolution was a controversial idea as an explanation for the variety of species, and became a serious contender only after Darwin (1859) had proposed natural selection as the mechanism by which it might occur. In this sense, the mechanism becomes a part of the evidence. When the mechanism can be captured as an image, the evidence is even more compelling. Understanding the cellular mechanisms by which the brain operates will empower the psychiatrist of the future. We hope that the images that will appear in *Advances* in the 'Images in neuroscience' series will facilitate that understanding.

Eric Kandel is only the second trained psychiatrist to win a Nobel Prize in physiology or medicine; the first and the only practising clinician was Julius Wagner-Jauregg in 1927 for fever therapy in general paresis (Howes 2009). It is fitting that Kandel's work on memory formation should provide the opening image for this series.

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From *My Sister and Myself*

Selected by Femi Oyebode

IN OTHER WORDS

It is a curious business certainly. Here are three doctors, three strangers to me and to Nancy [his sister], Drs Brodie, Glover and Walker, and I run to them for help in a matter which covers, includes and exposes the whole of our family life. In a few letters, half an hour's or an hour's conversation, I have to convey to them somehow our characters and history and personal relationships – everything that constitutes our half century of life and beyond. They make up a sort of tribunal to which I have to take my own and the family guilt, the family failure, and they are expected, on what I care or choose to tell them, not only to withdraw my sister from her self-imposed psychosis, but rearrange our shabby and unsuccessful personal relations, in such a way that we shall not destroy ourselves or each other again. What I am saying to these doctors, in effect, is 'Comfort me in my guilt. I have mismanaged my domestic affairs so badly that my sister preferred death to my care, in which she no longer believes. Can you somehow pull her out of it, so that I shall not feel responsible, for the rest of my days? Can you, without knowing any of us, or anything really about any of us, create an atmosphere in which we can all live?' No wonder Dr Brodie seems to me not to understand or give due importance to the dreadful subtleties which seem to me involved. Yet I expect him somehow to launder this half-century-old dirty washing.

J. R. Ackerley (1896–1967) was literary editor of *The Listener* from 1935 to 1959. This extract is from *My Sister and Myself: The Diaries of J. R. Ackerley*, covering the years 1948–1957. This volume, edited and introduced by F. King, was published by Hutchinson in 1982. Reproduced with kind permission of the publisher.

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