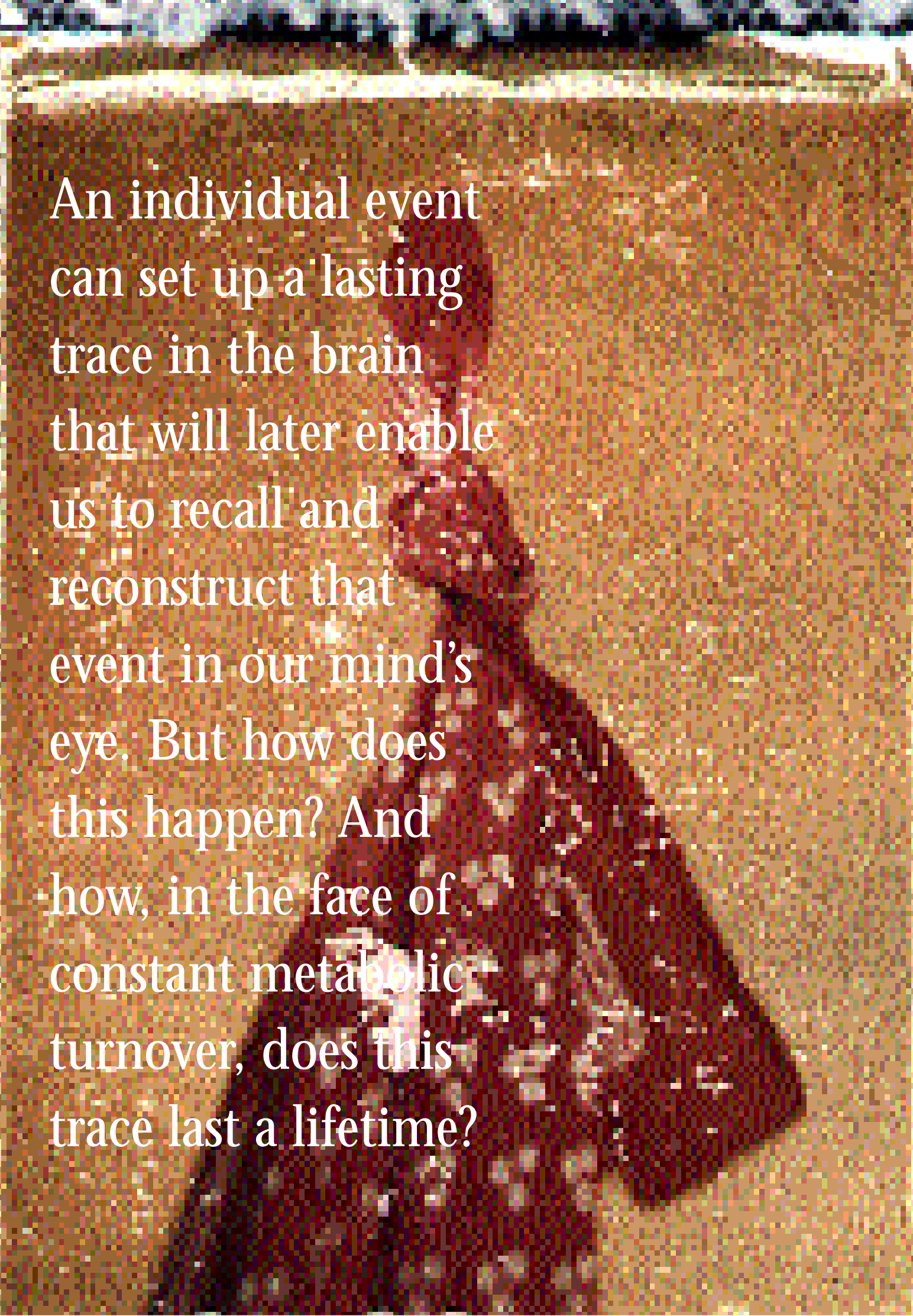


# THE M E

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THANKS FOR  
THE MEMORY  
How the brain  
remembers



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# aide-mémoire

We rely on memory more than we may realise - not just to remember events in the past, or the future, but also to help us perform everyday tasks. But how do our brains remember?

Professors Richard Morris and Rick Lathe are tackling this complex question.

**O**N 6 JUNE 1994 men now long past their youth returned to the beaches of Northern France where, 50 years before to the day, they had played their part in the liberation of Western Europe. D-Day was a day in their lives they would never forget. And so important is recollecting the events of that day, whether in thinking of fallen comrades or in talking to old friends, that these old soldiers came back from all over the world to commemorate the occasion. Memory, and the expression of it, is central to our lives.

Remembering specific events is the type of memory we usually associate with the word as it is used colloquially, whether in recalling the minutiae of day-to-day life or our part in more significant events such as a war. This type of memory reflects our ability to recreate in the mind's eye a set of events that happened at a specific place and a specific time. Psychologists refer to it as 'episodic' or autobiographical memory. Such memories last a long time, albeit somewhat unreliably, and their possession and their communication to others helps us to define our own individuality.

The scientific study of memory has, however, revealed that it comes in multiple forms. We possess a distinct short-term memory system - which can very accurately hold onto small amounts of information for a brief period.

We use it to remember speech long enough to interpret the flow of conversation, for doing mental arithmetic, and for remembering where we put down that spanner a moment ago when we set about repairing something.

Within the domain of long-term

memory, formal distinctions have been made between our ability to remember events (episodic memory), to acquire and use general knowledge (sometimes called semantic memory), and to learn motor and cognitive skills whose execution can, in many cases, be outside the domain of consciousness (often called procedural memory).

These distinctions between types of memory go beyond the descriptive, for they reflect fundamentally different ways in which the mind represents and stores information. Research by experimental psychologists has refined these distinctions and illuminated the varied processes by which they work.

**W**E AND our colleagues in Edinburgh are presently involved in studies focusing on the neural mechanisms of memory. Such research is central to attempts to understand how the brain works physically. Not only would such an understanding be of fundamental interest in its own right, but it could point to new techniques (including new drugs) with which to improve memory in old age or in people who have sustained neurological illnesses that limit their capacity to recollect.

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approach the problem. Clinical evidence is an important starting point. Over the past century, the formal study of people who have sustained brain injuries has given valuable insights into the areas of the brain that might be critical. It turns out that damage in distinct brain regions can cause selective disturbances of the different forms of memory mentioned earlier.

Episodic memory is particularly affected by damage to structures in the middle of the brain including the hippocampus, parts of the thalamus and various regions connecting these two. Semantic memory and the learning of motor skills are affected by damage elsewhere. These observations have been supplemented by experiments with laboratory rats under much more controlled conditions, and by discoveries made using new brain scanning techniques such as positron emission tomography (PET) and functional magnetic resonance imaging.

If a car doesn't work, and you discover that the fault lies in the carburettor, it certainly helps you to get closer to solving the problem. But an analogy between neuroanatomical localisation and car maintenance, while helpful, is potentially misleading in one important respect. For the brain scientist's task is that of reverse engineering. We know the brain is made up of anatomically distinct bits, but we still don't know, in detail, what the various bits do, nor how they do what they do. Our task is not so much to fix the brain as to find out what it consists of. It is as if, to continue the analogy, not only do we not know where the carburettor is located, nor what it looks like, we don't even know whether there is a carburettor.



Memory, and the expression of it, is central to our lives.

However, while understanding the brain mechanisms of memory certainly involves discovering how the psychological distinctions between different forms of memory map onto the underlying anatomical systems - clearly it involves a lot more. We also need to learn how these systems interact physiologically, how information is represented in the nervous system as patterns of neural activity, and how these in turn cause biochemical changes that give rise to the lasting structural alterations of the nervous system that actually store information.

**A**N IDEA that neuroscientists are presently very excited about is what they refer to as "neural plasticity". Jargon aside, this concept refers to the wide range of ways in which cells in the brain can change during development in response to variations in diet, circulating hormones, or patterns of brain activity.

It used to be held that the adult brain, unlike other parts of the body (such as our skin), was relatively unadaptable. It's true that it doesn't readily generate new cells and, once damaged (as in a stroke), is unable to replace damaged cells with new

ones (at least on its own). But it turns out that the normal adult brain is capable of responding appropriately to many kinds of natural stimuli - and the phenomenon of memory is one obvious example of brain plasticity in action.

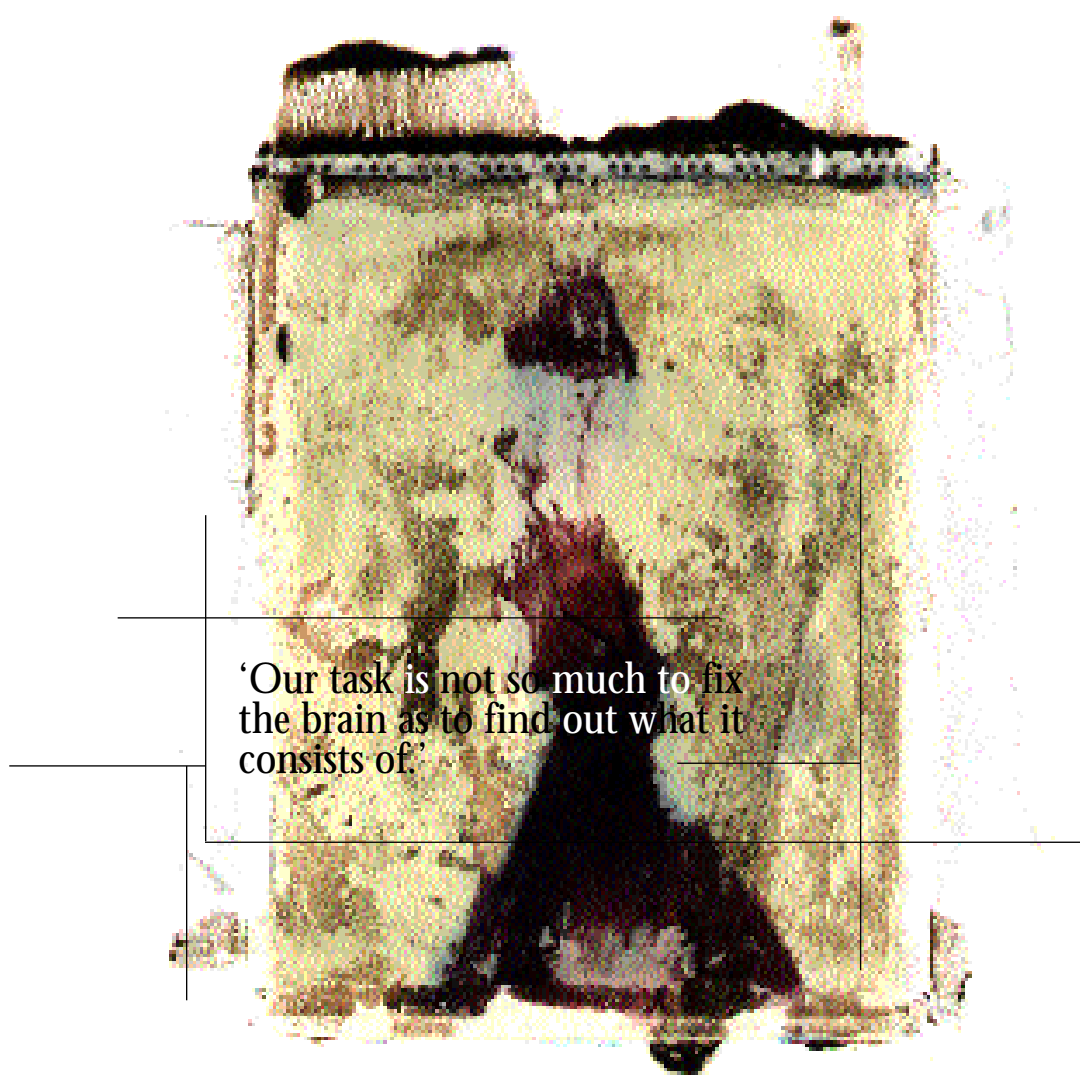
Episodic memory is the simplest illustration of this truism. An individual event, like a day in June 50 years ago, can set up a lasting trace in the brain that will later enable us to recall and reconstruct that event in our mind's eye. But how does this happen? And how, in the face of constant metabolic turnover, does this trace last a lifetime?

One line of thought holds that neurons have a mechanism at their synaptic junctions for registering the conjunction between two neural events (synapses are the points of contact between neurons - where the fibres from one cell release chemical messengers such as glutamate that then activate the next cell). Activity in the nerve fibre arriving at the synapse is detected, by a special glutamate receptor in synapses, as coinciding with activity occurring in the cell to which it is connected. Once registered, biochemical mechanisms then cause that synapse to be strengthened

and, from that moment onwards, communication between the respective neurons is much more effective.

Thus, if activity in one group of nerve fibres represented, say, a particular melody, and activity in the cells to which they were connected represented the time or place where one was located, it would be possible to make an association between these two things so that hearing that melody again reminded one ever after of that time and place. Such a neural mechanism for associating events had long been postulated, and work in Edinburgh by David Willshaw (now at the Centre for Cognitive Science) and Christopher Longuet-Higgins established some years ago how it could enable multiple associative memories to be overlaid in a distributed manner.

We, and many others, are exploring this type of synaptic plasticity with a view to understanding its functional significance. In our laboratories at the Centre for Neuroscience, we use novel drugs to increase or decrease plasticity at hippocampal synapses, and have been testing whether they alter learning or memory. To date, our results seem encouraging. Rats trained to swim in a large pool of opaque



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water with a view to finding a hidden platform show impairments in learning what to do - and remembering it later - when given drugs that block synaptic plasticity. Steven Martin and Robert Steele of the Department of Pharmacology have, for example, recently found that animals can remember spatial information for a short time in the presence of one of these drugs, but cannot remember it for much longer than about an hour. The exact nature of the learning impairment still eludes us, but we feel we have a handle on a fundamental mechanism in the brain. Understanding it better may point the way towards drugs that could improve memory.

Even the exotic pharmacological agents of the research laboratory, many a far cry from what you can get at the pharmacist, do not always have the selectivity one

would like. Drugs acting at synapses that use glutamate are reasonably selective, but new developments in molecular neurobiology have shown that there are several types of glutamate synapse. They come in many different varieties, each with different properties, and they vary a great deal in their distribution on individual neurones as a function of age and location. In addition, the administration of drugs cannot always be relied upon to give the kind of selectivity to specific parts of the brain that the research scientist would like.

**A**CCORDINGLY, WE are exploring a radically different approach. Using the sophisticated techniques now available at the Centre for Genome Research, Bill Skarnes has engineered a number of mice in which he has tagged genes that are selectively expressed in the brain. One of these mice - called kin - appears to have a disruption of a gene that is expressed only in the hippocampus. Together with Muriel Steel, a postdoctoral fellow at the CGR, we are attempting to exploit this neuronal specificity by creating a situation in which neural plasticity is altered in the hippocampus but nowhere else.

If this plasticity is the substrate of episodic memory, as we suppose on the basis of our pharmacological studies, such animals should be completely normal except in this one respect. We hope soon to be able to test this. A forgetful mouse might be a small start on the trail towards understanding the daily problems of a patient with amnesia or Alzheimer's disease.

In peacetime, the battle moves to a different front. The new discipline of neuroscience, one of Edinburgh's strengths in teaching and research, is giving us exciting insights into the workings of mind and brain. Coupled with the armament of novel molecular engineering techniques, we have a realistic prospect of pushing back the frontiers of our knowledge in a way that could have significant practical implications.

*The authors are, respectively, members of the Department of Pharmacology and the Centre for Genome Research; both are members of the University of Edinburgh's Centre for Neuroscience. Their research is supported by grants from the Medical Research Council, the Biotechnology and Biological Sciences Research Council and the Human Frontiers Science Programme.*