

## Headlines

### Volume 91

#### **Learning, Memory and Language**

A major breakthrough in understanding how the brain accomplishes learning and memory began with the study of a person known by his initials, H.M. As a child, H.M. developed severe and intractable epilepsy, and an experimental surgical treatment involving removal of the medial regions of his temporal lobes greatly alleviated the seizures. However, the surgery left H.M. with severe amnesia. He can remember recent events for only a few minutes and is unable to form explicit memories of new experiences. Talk with him awhile, and then leave the room. When you return, he has no recollection of ever having seen you. Despite his inability to remember new information, H.M. remembers his childhood very well. From these observations, researchers concluded that the parts of H.M.'s medial temporal lobe that were removed, including the hippocampus and parahippocampal region, play critical roles in converting memories of experiences from short-term memories to long-term, permanent memories. The fact that H.M. retains some memories for events that occurred long before his surgery indicates that the medial temporal region is not the site of permanent storage but instead plays a role in the organization and permanent storage of memories elsewhere in the brain.

The medial temporal region is richly connected to widespread areas of the cerebral cortex, including the regions responsible for thinking and language. Whereas the medial temporal region is important for forming, organizing, consolidating, and retrieving memory, cortical areas are important for the long-term storage of knowledge about facts and events and for how this knowledge is used in everyday situations. Our ability to learn and consciously remember everyday facts and events is called declarative memory. Studies using functional brain imaging have identified a large network of areas in the cerebral cortex that work together to support declarative memory. These cortical areas play a distinct role in complex aspects of perception, movement, emotion, and cognition.

When we have new experiences, information initially enters working memory, a transient form of declarative memory. Working memory depends on the prefrontal cortex as well as other cerebral cortical areas. Studies on animals have shown that neurons in the prefrontal cortex maintain relevant information during working memory and can combine different kinds of sensory information when required. In humans, the prefrontal cortex is highly activated when people maintain and manipulate memories. Distinct areas within the prefrontal cortex support executive functions, such as selection, rehearsal, and monitoring of information being retrieved from long-term memory. To serve these functions, the prefrontal cortex also interacts with a large network of posterior cortical areas that encode, maintain, and retrieve specific types of information, such as visual images, sounds, and words, as well as where important events occurred and much more.

Semantic memory is a form of declarative knowledge that includes general facts and data. Although scientists are just beginning to understand the nature and organization of cortical areas involved in semantic memory, it appears that different cortical networks are specialized for processing particular kinds of information, such as faces, houses, tools, actions, language, and many other categories of knowledge. Studies using functional imaging of normal humans have revealed zones within a large cortical expanse that selectively process different categories of information, such as animals, faces, or words.



Our memories of specific personal experiences that happened at a particular place and time are called episodic memories. It is generally believed that the medial temporal lobe areas serve a critical role in the initial processing and storage of these memories. Studies have shown that different parts of the parahippocampal region play distinct roles in processing “what,” “where,” and “when” information about specific events. The hippocampus links these elements of an episodic memory. The linkages are then integrated back into the various cortical areas that represent the details of each type of information. The fact that H.M. and other people with amnesia show deficits in some types of memories and not others indicates that the brain has multiple memory systems supported by distinct brain regions.

Nondeclarative knowledge, the knowledge of how to do something, is expressed in skilled behaviour and learned habits and requires processing by the basal ganglia and cerebellum. The cerebellum is specifically involved in motor tasks that are time-dependent. The amygdala appears to play an important role in emotional aspects of memory attaching emotional significance to otherwise neutral stimuli and events. The expression of emotional memories involves the hypothalamus and sympathetic nervous system, which support emotional reactions and feelings. Thus, the brain appears to process different kinds of information in separate ways.

How exactly are memories stored in brain cells? After years of study, much evidence supports the idea that memory involves a persistent change in synapses, the connections between neurons. In animal studies, researchers found that this occurs in the short term through biochemical events that affect the strength of the relevant synapses. Turning on certain genes may lead to modifications within neurons that change the strength and number of synapses, stabilizing new memories. Researchers studying the sea slug *Aplysia californica*, for example, can correlate specific chemical and structural changes in relevant cells with several simple forms of memory that the animal shows. Another important model for the study of memory is the phenomenon of long-term potentiation (LTP), a long-lasting increase in the strength of a synaptic response following stimulation. LTP occurs prominently in the hippocampus, as well as in the cerebral cortex and other brain areas involved in various forms of memory.

LTP occurs through changes in the strength of synapses at contacts involving N-methyl-d-aspartate (NMDA) receptors. Subsequently, a series of molecular reactions plays a vital role in stabilizing the changes in synaptic function that occur in LTP. These molecular events begin with the entry of calcium ions into the synapse, which activates the cyclic adenosine monophosphate (cAMP) molecule. This molecule activates several kinds of enzymes, some of which increase the number of synaptic receptors, making the synapse more sensitive to neurotransmitters. In addition, cAMP activates another molecule, called cAMP-response element binding protein (CREB). CREB operates within the nucleus of the neuron to activate a series of genes, many of which direct protein synthesis. Among the proteins produced are neurotrophins, which activate growth of the synapse and increase the neuron’s responsiveness to stimulation.

Many studies have shown that the molecular cascade leading to protein synthesis is not essential to initial learning or to maintaining short-term memory; however, this cascade is essential for long-term memory. In addition, studies using genetically modified mice have shown that alterations in specific genes for NMDA receptors or CREB can dramatically affect the capacity for LTP in particular brain areas, and the same studies have shown that these molecules are critical to memory.

The many kinds of studies of human and animal memory have led scientists to conclude that no single brain centre stores memory. It most likely is stored in distributed collections of cortical processing systems that are also involved in the perception, processing, and analysis of the material

being learned. In short, each part of the brain most likely contributes differently to permanent memory storage.

## Language

One of the most prominent human abilities is language, a complex system involving many components, including sensory motor functions and memory systems. Although the neural basis of language is not fully understood, scientists have learned a great deal about this function of the brain from studies of patients who have lost speech and language abilities owing to stroke, and from brain imaging studies of normal people.

It has long been known that damage to different regions within the left hemisphere produce different kinds of language disorders, or aphasias. Damage to the left frontal lobe can produce nonfluent aphasias, such as Broca's aphasia, a syndrome in which speech production abilities are impaired. Speech output is slow and halting, requires effort, and often lacks complexity in word or sentence structure. By comparison, comprehension of heard speech is spared, although structurally complex sentences may be poorly understood.

Damage to the left temporal lobe can produce fluent aphasia, such as Wernicke's aphasia, in which comprehension of heard speech is impaired. Speech output, although of normal fluency and speed, is often riddled with errors in sound and word selection and tends to be unintelligible gibberish. Damage to the superior temporal lobes in both hemispheres can produce word deafness, a profound inability to comprehend auditory speech on any level. Whereas Wernicke's aphasics can often comprehend bits and pieces of a spoken utterance and can comprehend isolated words, patients with word deafness are functionally deaf for speech, lacking the ability to comprehend even single words, despite being able to hear sound and even identify the emotional quality of speech or the gender of the speaker. Research on aphasia has led to several conclusions regarding the neural basis of language. Researchers once believed that all aspects of language ability were governed only by the left hemisphere. Recognition of speech sounds and words, however, involves both left and right temporal lobes. In contrast, speech production is a strongly left-dominant function that relies on frontal lobe areas but also involves posterior brain regions in the left temporal lobe. These appear to be important for accessing appropriate words and speech sounds.

Recently, functional imaging methods have identified new structures involved in language. For example, systems involved in accessing the meaning of words appear to be located (in part) in the middle and inferior portions of the temporal lobe. In addition, the anterior temporal lobe is under intense investigation as a site that may participate in some aspect of sentence-level comprehension. Recent work has also identified a sensory-motor circuit for speech in the left posterior temporal lobe, which is thought to translate between speech recognition and speech production systems. This circuit is involved in speech development and is thought to support verbal short-term memory.

Although the understanding of how language is implemented in the brain is far from complete, there are now several techniques that may be used to gain important insights into this critical aspect of brain function.

*This article is an extract from Brain Facts, A Primer on the Brain and Nervous System, published by the Society for Neuroscience*

## Every six seconds, someone somewhere will die from a stroke

In launching World Stroke Day the World Stroke Organization (WSO) called for urgent action in the global fight against stroke by launching its “One in Six” campaign. The theme was identified to mirror today’s reality that one in six people worldwide will have a stroke in their lifetime. Every six seconds, someone somewhere will die from a stroke. With the fight against stroke at a crossroads, WSO members in 92 countries around the world have united to put forth a simple life-saving message on World Stroke Day: Do not take chances. One in six people is at risk for stroke – it could be you.

The campaign is asking people to commit to six stroke challenges:

The six stroke challenges:

- Know your personal risk factors: high blood pressure, diabetes, and high blood cholesterol.
- Be physically active and exercise regularly.
- Avoid obesity by keeping to a healthy diet.
- Limit alcohol consumption.
- Avoid cigarette smoke. If you smoke, seek help to stop now.
- Learn to recognize the warning signs of a stroke and how to take action.

The WSO will be introducing initiatives to stem the rise in stroke cases, especially in resource-challenged countries where two-thirds of all individuals that have suffered from a stroke now live and where health systems are already challenged to the limit.

“We must act now or it will be too late” says Sweden’s Professor Bo Norrving, WSO president, and Finnish Professor Markku Kaste, World Stroke Day founding campaign chair. “Think of six people you care about... one of them will have a stroke” they added. “But this can be prevented. Complacency and inaction will only contribute to escalating the disease burden.”

15 million people have a stroke each year.

According to the World Health Organization, stroke is the second leading cause of death for people above the age of 60, and the fifth leading cause in people aged 15 to 59. Stroke also attacks children, including newborns. Each year, nearly six million people die from stroke, 2000 of them in New Zealand. In fact, stroke is responsible for more deaths annually than those attributed to AIDS, tuberculosis and malaria put together. Stroke is also the leading cause of long-term disability irrespective of age, gender, ethnicity or country. On average, 17 New Zealanders have a stroke every day, over 6000 a year.

Three-time Tour de France champion and stroke survivor Alberto Contador notes “Stroke can attack anytime and at any age. The good news is that stroke can be beaten. Not only can it be prevented, but people who have experienced a stroke can regain their quality of life with the appropriate long-term care and support. I am an example.”

Prof Kaste has appointed Alberto Contador at the first World Stroke Day Goodwill Ambassador. Contador was 21 when he fell during the 2004 Tour of Asturias race and went into convulsions. He was diagnosed with a congenital vascular disorder, which can cause hemorrhagic stroke, and returned to road cycling eight months later. Prof Kaste says Contador's journey to become a cycling great after this serious illness is "truly an inspiration."

## Dr Barry Snow – 14 years on the Scientific Advisory Committee



Neurological Foundation Scientific Advisory Committee Chairman Dr Barry Snow is standing down after 14 years of outstanding service.

Dr Snow became a member of the Neurological Foundation Scientific Advisory Committee in 1996 and then chairman in 1999. Under his leadership, the SAC has been responsible for awarding nearly \$14 million in New Zealand-centred neurological research and education grants.

Dr Snow was educated at Auckland Medical School and spent his first house surgeon year at Rotorua Hospital. After his FRACP examinations in 1983, he pursued geriatric training before changing to neurology at Auckland Hospital. In 1987 he was awarded a Chapman Fellowship for advanced training and research. From 1988 to 1995 he taught at the University of British Columbia Medical School in Vancouver. There he was engaged in research into movement disorders, particularly Parkinson's disease; he has published over 100 papers in this field. He returned to New Zealand in 1995 to join the Department of Neurology at Auckland Hospital, and set up the Auckland Movement Disorders Clinic. Dr Snow was Clinical Director of Neurology from 1999 until 2010, and was recently appointed Medical Director, Adult Health Services at the Auckland District Health Board.

Dr Snow is now a member of the Neurological Foundation Council, and this appointment and his contribution to the Scientific Advisory Committee were marked at the Foundation's 6 December 2010 Annual General Meeting.

Dr John Reynolds has been elected Chairman of the Scientific Advisory Committee. Dr Reynolds is a Senior Lecturer in Neuroscience and Medicine at the University of Otago and has been a member of the SAC for six years. He is a former Chapman Fellow of the Neurological Foundation of New Zealand. Dr Reynolds is the Deputy Director of the University's Brain Health Research Centre, and a recipient of one of ten inaugural Rutherford Discovery Fellowships; this award will allow Dr Reynolds to undertake applied research into stroke and epilepsy.

## A revamped neurosurgical service for the south

The Governance Board will be responsible for building one South Island neurosurgery service which will eventually have seven to eight neurosurgeons, with at least three in Dunedin. It will be chaired by Professor Andrew Kaye, the James Stewart Professor of Surgery and Head of Department of Surgery at the University of Melbourne and the Director of Neurosurgery at the Royal Melbourne Hospital.

The service's Dunedin node will have a heavy emphasis on academic neurosurgery, which involves both research and teaching and builds on the University of Otago's internationally acclaimed neurosciences departments. The University will appoint and support a Professor of Neurosurgery and a Senior Lecturer in Neurosurgery to be based in Dunedin. Christchurch will maintain at least four neurosurgeons with the opportunity to grow and develop as the service expands.

Mr Bridgman said the Panel's process, deliberations and report were of the highest quality. "I have been briefed by the full Panel and I strongly support their recommendations," Mr Bridgman said. "They have proposed a solution which changes the paradigm for neurosurgery in the South Island," he said. "I have spoken to the current Chairs of the South Island DHBs and I have asked them to assist me, the Governance Board and the National Health Board to make this new service work for the benefit of the people they represent and serve." He said he was satisfied from the Panel's report that consolidating neurosurgery on Christchurch was not the best solution either clinically or financially. "The Panel is clear that the impact on patient outcomes combined with the developments in neurosurgery and the ageing population, mean consolidating in Christchurch is not the right decision," he said. "Nor is the idea of retaining two neurosurgeons in Dunedin – that is not a sustainable service." Mr Bridgman said the Panel's recommendation to establish academic neurosurgery in Dunedin and to work with orthopaedic surgeons in the region to extend the amount of neurosurgeon involvement in spinal surgery, fundamentally changed the nature of the service.

### Recommendations

The South Island Neurosurgery Expert Panel's recommendations are that:

1. The South Island Neurosurgery Service is established as a regional, distributed service with nodes in Christchurch and Dunedin.
2. An independent Governance Board is established and given the delegated authority and support to lead the business and clinical development of the Service for the benefit of all South Islanders. This authority extends to all appointments and re-appointments of neurosurgeons and key clinical staff to the Christchurch and Dunedin nodes.
3. The Governance Board be chaired by Professor Andrew Kaye with the following additional membership.
  - an independent neurosurgeon
  - the Chair of Southern DHB
  - the Chair of Canterbury DHB
  - an expert consumer advisor
  - one of the Chairs of Nelson Marlborough DHB, South Canterbury DHB and West Coast DHB, on an annual rotational basis
  - a senior University of Otago nominee
  - a South Island Iwi nominee



4. The Governance Board have an initial term of three years, with review after two years
5. The Governance Board be responsible to the National Health Board, through its National Director
6. The Governance Board be supported by a clinical director and a manager, both employed by the National Health Board, which will also provide administrative support to the Board
7. The Governance Board publish a six-monthly report. The report to be publically available
8. The South Island Neurosurgery Service develops an academic neurosurgical component in Dunedin, supported by the University of Otago and comprising, as a minimum, an appointment at Professorial level, an appointment at Senior Lecturer level, and appropriate infrastructural support
9. Urgent attention be given to building the Dunedin node, in association with the University of Otago
10. The South Island Neurosurgery Service is built to include seven, then eight neurosurgeons, with a minimum of three neurosurgeons in Dunedin. The numbers refer to people and not full time equivalent measures. Careful consideration be given to the prudent and integrated development of subspecialisation
11. Employment arrangements to be with the resident DHBs, as outlined in Section 6.1 of this document
12. The Service must ensure equitable patient access to neurosurgery by managing the available South Island-wide capacity. The Governance Board needs to develop a South Island-wide service delivery plan, the key elements of which are a single point of entry, contracted volumes for first specialist assessments inpatient case-mix, access to diagnostics such as MRI and interventional neuro-radiology. Other key factors are the availability of intensive care, high dependency unit and neuro-rehabilitation beds
13. The service establish neurosurgical outreach services throughout the South Island as outlined in Section 5.3 of this document
14. The Governance Board be charged with developing a population based funding model to ensure equitable access
15. The Governance Board, in conjunction with Health Workforce New Zealand and the Royal Australasian College of Surgeons, develop a strategic neurosurgical workforce plan for the South Island Neurosurgery Service. This plan to include the development of an integrated Royal Australasian College of Surgeons SET programme in neurosurgery for the South Island Service
16. The Governance Board, in conjunction with the Medical Council of New Zealand and the Royal Australasian College of Surgeons, review the current processes for the assessment of international medical graduates for registration in the vocational scope of practice of neurosurgery and ensure they are robust, timely and practical

**In support of the above recommendations, the Panel also recommends that:**

- a. A data set be developed to monitor the clinical, administrative and financial success of the service and to support sound strategic planning
- b. Patient recovery and related patient transport services be reviewed across the South Island
- c. Closer co-ordination is developed between the two South Island rehabilitation services
- d. The requirements of neurosurgery are linked into the current review of South Island information technology systems
- e. A review of this process occurs in order to capture the generic lessons for the wider New Zealand health sector

**Professor Andrew Kaye**

Professor Kaye graduated from the University of Melbourne in 1973, and subsequently trained in Neurosurgery at The Royal Melbourne Hospital and The Royal Children's Hospital in Melbourne. He undertook further neurosurgery training in Oxford, London and at The Cleveland Clinic. On returning to Australia in 1983 he was appointed Neurosurgeon at The Royal Melbourne Hospital, and commenced research into neuro-oncology at the Ludwig Institute for Cancer Research. He was appointed Professor of Neurosurgery at The University of Melbourne in 1992, and the James Stewart Professor of Surgery and Head of the Department of Surgery at The University of Melbourne, Royal Melbourne Hospital in 1997.

He is the Head of the Department of Neurosurgery at the Royal Melbourne Hospital. For the past ten years he has been the Chairman of the Board of Examiners for final year Medicine at the Faculty of Medicine, Dentistry and Health Sciences at The University of Melbourne. His main clinical and research interest involves neuro-oncology and cerebrovascular disease. In 1992 he was awarded the John Mitchell Crouch Fellowship by the Royal Australasian College of Surgeons, and in 1997 was appointed the Sir Arthur Sims Commonwealth Travelling Professor. In 2003 the American Association of Neurological Surgeons honoured him with the Ronald Bittner Award for contributions to the treatment of brain tumours and in 2006 the Paul Bucy Award for his contribution to neurosurgery education. In 2004 he presented the Sir John Eccles Lecture at the Australian Neuroscience Society. In 2010 he was awarded the Medal of Honour from the World Federation of Neurosurgical Societies for ..."outstanding contribution to neurosurgery." He was awarded the Commonwealth of Australia Centenary Medal in 2003 and Order of Australia in 2004.

## **Grant for Alzheimer's research: Astrocyte calcium signalling, neurotoxicity and amyloid beta**

A $\beta$  is the main component of amyloid plaques\* which are present in the brains of Alzheimer's patients. The protein is thought to cause behavioural and cognitive impairment due to the damage and death of neurons in the critical memory and navigational part of the brain called the hippocampus. Both amyloid plaques and neurofibrillary tangles\*\* are clearly visible by microscopy in the brains of those afflicted by Alzheimer's disease, and the plaques feature as dense deposits of A $\beta$  and cellular material outside and around neurons.

The neurotoxicity of A $\beta$  was first reported in 1990, and it is now widely accepted that the accumulation of A $\beta$  deposits in the brain is the main driving force for the pathogenesis of the disease. This philosophy has become known as the amyloid hypothesis, although there are several hypotheses surrounding neuronal alteration and death in Alzheimer's disease. Because of the lack of evidence surrounding the nature of A $\beta$  effects on neuronal functions, the amyloid hypothesis, which is predominantly focused on neurons, is still controversial. Very recent accumulating evidence in numerous studies however demonstrates that A $\beta$  can play a major role in the progression towards neuronal cell death in Alzheimer's disease, and variants of the amyloid hypothesis have become the dominant focus of research. Central to most Alzheimer's research is the motivation to discover the stages within the pathogenesis of the disease that, if inhibited, could slow down – or prevent – the disease, and this is a key factor in Bai's study.

Bai has long had an avid interest in amyloid and the mechanisms of cell death in age-related diseases, originally sparked by his 1995-1999 PhD focus on Type 2 diabetes. Like Alzheimer's and other neurodegenerative diseases, Type 2 diabetes is distinguished by the death of cells that generate chemical signal molecules to control the biological activities of the body, and amyloid accumulation is often present inside or surrounding the expired cells.

To further explore the neuronal death process specifically in Alzheimer's disease, Bai's research is investigating the role of astrocyte calcium regulation in A $\beta$ -mediated neuron cell death using in vitro tissue culture models of rat brain hippocampus. Regulated amounts of calcium are necessary for normal neuronal function (calcium ions are involved in brain cell communication, and this is known as calcium signaling), but too much calcium can kill a neuron. The amyloid hypothesis assumes that A $\beta$  plays a role in allowing an influx of unlimited amounts of calcium into neurons, and Bai's study will focus on the specific role that the calcium regulators play in astrocytes which functionally support the neurons in many ways. Effectively, these calcium modulators could be the biochemical pathway through which altered neuronal structure and function occurs.

Astrocytes are the star-like house-keeping glial cells in the brain. Bai says astrocytes have been mostly ignored over the last 20 years as they were considered a mere support cell to the much more famous neurons, but recent research has shown that astrocytes are also directly involved in the critical regulation of signaling between neurons. In a recent previous study published in the journal *Neurotoxicity* in January 2010, Bai and Professor Janusz Lipski, Head of Molecular Neurophysiology at the University of Auckland, focused on stroke-related neuronal cell death, and reported that oxidative stress-related cell death can be specific to astrocytes, but not in neurons, indicating that astrocytes may be implicated in neuronal cell death. Bai's current study hypothesises that the A $\beta$ -induced calcium signaling and oxidative stress in astrocytes contributes to subsequent neuronal cell death.

Bai says that if his study shows that astrocytes are implicated in neuronal cell death, the next stage is to try to understand how modulating calcium signaling in these cells could alter neuron survival after exposure to A $\beta$ . Control of the calcium activities and therefore the signaling may pave the path for therapeutic interventions in the management of Alzheimer's disease. Bai says that the therapy options would include the development of an inhibitor that could specifically act on astrocyte calcium signals to prevent the neurons from A $\beta$  attack.

Because of the complex nature of Alzheimer's disease, prevention is a long and complex research road with modest progress to date so many scientists, like Bai, are focusing on the potential of providing important insights to be used in the formulation of treatments. Bai says "My great hope is that my research will lead to a positive discovery that can translate to treatment to slow down or even halt the progress of the Alzheimer's disease."

Bai says "This is my first independent grant and it means so much. I am so proud, and am very appreciative to Sir Graeme Douglas and the Neurological Foundation. I am absolutely passionate about this research."

### **Amyloid plaques**

\*Amyloid plaques are one of the two brain abnormalities that define Alzheimer's disease (AD). The other hallmark is neurofibrillary tangles. Technically, an individual may display all the behavioural and cognitive symptoms of AD, but if the brain does not contain the hallmark plaques and tangles, there is no diagnosis of AD. The appearance of amyloid plaques in the brain can precede the behavioural symptoms by years.

Amyloid plaques are sticky build-up which accumulates outside nerve cells, or neurons. Amyloid is a protein that is normally found throughout the body. For reasons as yet unknown, in AD, the protein divides improperly, creating a form called beta amyloid which is toxic to neurons in the brain. No one really knows why beta amyloid is formed or why it causes cell death. However beta amyloid does its work, the result is that neurons begin to die. Plaques begin to form that consist of these degenerating neurons and clumps of the amyloid protein itself. The body cannot break these clumps down and dispose of them, so they accumulate in the brain.

The apoE4 gene, a genetic abnormality which has been implicated in AD, may be involved in the production of amyloid plaques. The gene may produce a protein that latches on to the toxic beta amyloid and makes it impossible for the body to dissolve. As a result, the beta amyloid accumulates as plaques in the brain. Molecules called free radicals may also play a role. Normally, free radicals play important roles in the body, such as helping the immune system fight off disease. However, too many free radicals can start to upset the delicate balance within a neuron. Nerve cells producing beta amyloid seem also to produce more free radicals. It may be the case that free radicals thus boost beta amyloid production.

*Amyloid plaque data reproduced with permission from Catherine E. Myers.*

Myers, Catherine E. (2006) "Amyloid Plaques," retrieved from <http://www.memorylossonline.com/glossary/amyloidplaques.html>