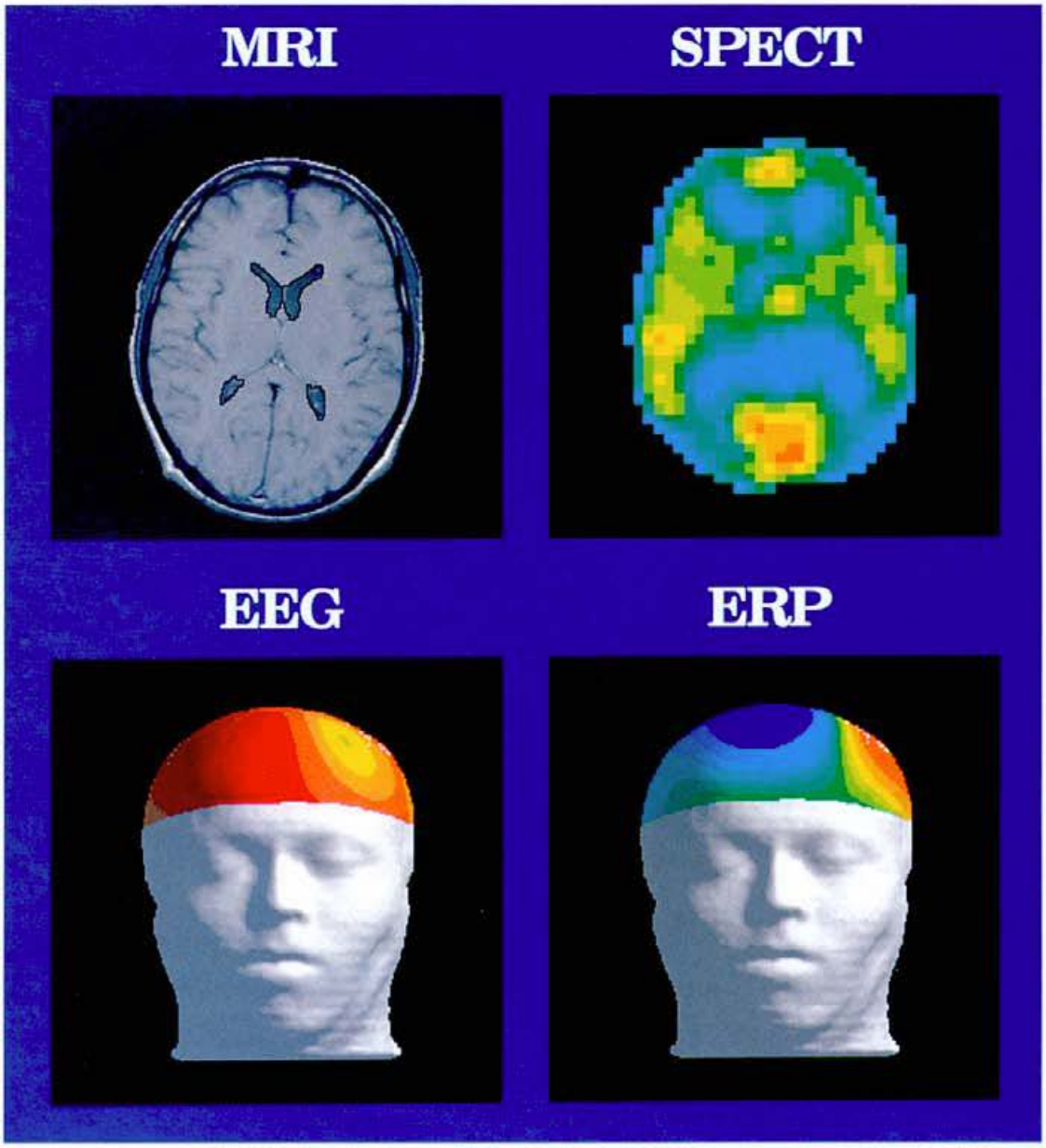



Magnetic Resonance Imaging (MRI) and Single-Photon Emission Computed Tomography (SPECT) images of the human brain provide information on anatomy and chemical activity. Electro-encephalography (EEG) and Event-Related Potential (ERP) measurements show aspects of electrical activity.

# Getting to know the brain

## New imaging techniques should increase understanding of changes in the brain associated with neurological and psychiatric disorders

Forty weeks after its conception, a baby is ready to be born. The check and double-check process that began almost as soon as the fertilised egg first divided has ensured that all the foetus's systems are functioning, and that it is capable of surviving in the world outside the uterus. The effortful miracle of childbirth is about to occur.

If recent suggestions by American researchers are correct, that miracle is initiated by the baby itself, who 'decides' when to be born... and who conveys that message to the mother through signals originating in the paraventricular nucleus, a tiny structure in the hypothalamus at the base of the brain.

Experiments on sheep by Peter Nathanielsz and Thomas MacDonald, of Cornell University, U.S.A., indicate that birth is triggered when the paraventricular nucleus stimulates the pituitary gland to release hormones. These in turn stimulate the adrenal gland to release another hormone, which 'migrates' out of the foetus and into the placenta. There the adrenal hormone cortisol converts progesterone into oestrogen — which stimulates contractions in the mother's uterus.

Descartes, it seems, may have been more right than he imagined: a baby thinks, and therefore it is.

The discovery has significance not so much for what it has contributed to our understanding of the complexities of birth — although that is a significant accomplishment in itself — but because it adds to the sense of wonder we feel when confronted by the baffling complexities of the human brain. Despite a century or more of intensive research, the 'thinking cauliflower' that provides us with the curiosity, and the ability, to examine the cauliflower itself is less well

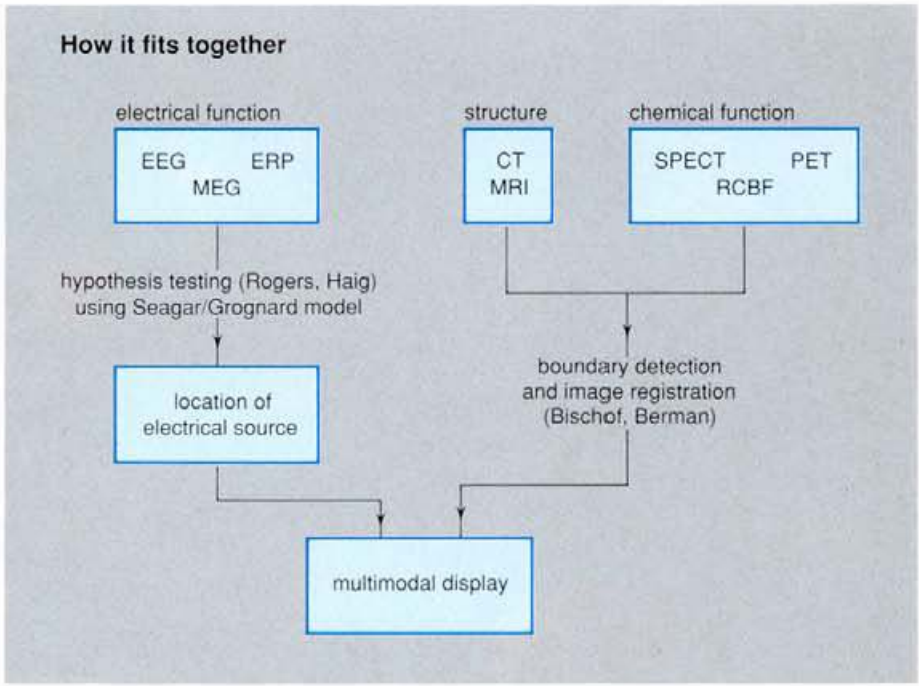
known than the depths of Earth's oceans.

Most of what we know about how the brain works comes from the study of single nerves in the brains of animals, particularly the ubiquitous laboratory rat. Over the past two decades, however, scientists have developed an impressive battery of techniques to investigate the mysteries of the living, working human brain. Ways to measure brain structure include CAT or CT (X-ray computerised tomography) and MRI (magnetic resonance imaging), while techniques ranging from EEG (electro-encephalography) and MEG (magneto-encephalography, which employs SQUIDs, or super-conducting quantum interference devices), to ERP (evoked response potential), RCBF (regional cerebral blood flow), SPECT (single-photon emission computerised tomography) and PET (positron emission tomography) assess brain function (see the box on page 29).

Nevertheless, we still know frustratingly little about how brain function is related to detailed structure. For example, neuroscientists once thought the only function of the cerebellum was to control balance and co-ordination; they have recently found that it also stores our memories of rote movements, such as the fingering of musical instruments. We have also learned that physical abnormalities in early childhood or damage to, say, the speech area on the left side of the brain do not necessarily mean the child will be unable to talk: the plasticity of brain function is such that another part of the brain can 'take over' control of speech. We cannot blithely assign functions to particular brain regions in the way phrenologists once 'mapped' human character on the skull; instead, every aspect of brain function has to be thought of as occurring in a number of interconnected neural networks.

A major problem is that the methods used to investigate brain structure or function tend to do just that: look at structure or function. There is little crossover between techniques, making it extremely difficult to locate the structures that perform identified functions (notwithstanding the additional difficulties outlined above). Electrical and nuclear-medicine methods measure activity, not anatomy; imaging techniques such as CT or MRI scans provide superbly detailed pictures of brain anatomy, but little insight into how the brain works.

Also, different ways of measuring brain function vary widely in their time scales. While electrical (EEG, ERP and MEG) systems measure events in milliseconds — in 'real time', or the time frame in which brain function actually occurs — radio-isotope techniques such as PET and SPECT (which measure chemical activity) need several minutes in which to build up a portrait of events within the brain.




**The diagram outlines the roles of the various researchers, and technologies, in the project. The work in the left branch defines the location in the brain where electrical activity is occurring, allowing readings to be superimposed on anatomical images in the multimodal display. Work in the right branch registers three-dimensional images of structure and chemical function so that they also can be incorporated.**

In 1989, researchers from the CSIRO Divisions of Radiophysics, Mathematics and Statistics and Information Technology, and from the Australia Telescope National Facility and the Cognitive Neuroscience Unit at Westmead Hospital in western Sydney, began a demonstration project designed to address those limitations and to extend our knowledge of the brain. This project builds on a decade of work by the Westmead neuroscience unit in measuring and imaging complementary aspects of human brain function and structure.

Their research has implications not only for 'pure' science (the United States scientific community has nominated the 1990s as the Decade of The Brain) but also for medicine — in particular, for the investigation and treatment of mental illnesses, such as schizophrenia and depression, and brain malfunctions such as those that cause epilepsy and similar disorders.

The major aim of the collaborative project — led and co-ordinated by Division of Radiophysics researcher Dr Robert Gill — has been to bring together structural and functional measurements of the brain in a 'multimodal' display combining data from a variety of sources in a computer workstation. The researchers sought to add to our knowledge of how the brain works (and what happens in dysfunctional situations... in other words, when the brain doesn't work) by employing new ways of combining human expertise and machine efficiency. The idea was to make it possible to collate and combine data on both structure and function in a portrait of the living, working brain that is far more comprehensive and detailed than any based on one or two measurements.

One branch of the project involved improving the presentation of structural information. Ms Leanne Bischof of the Division of Mathematics and Statistics first had to 'crack' the computer codes behind different kinds of displays so that software that enabled, say, CT data to be compared in a meaningful way with, say, MRI data could be developed. Next, she and colleague Dr Mark Berman had to develop a solution — applicable to the whole range of imaging techniques involved

## The many techniques, and acronyms

### COMPUTERISED TOMOGRAPHY (CT)

This technique relies on the fact that X-rays passing through the brain lose energy in proportion to the density of the tissue through which they travel — cortex, cerebellum, ventricles and so on. The CT scanner works by rotating around the subject's head, 'photographing' the brain as a series of slices; differences in brain density are reconstructed into a two-dimensional image with an accuracy of a millimetre.

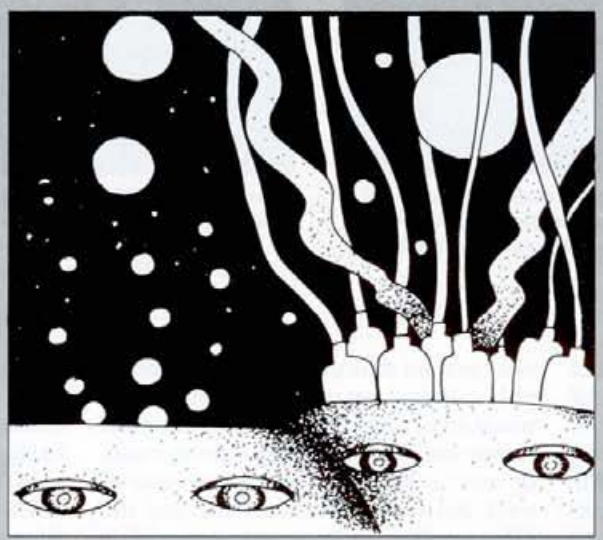
Scans are relatively demanding, requiring the subject to remain motionless for several minutes, and CT images differentiate only poorly between grey and white matter, with the resolution of some structures blurred by the skull.

### MAGNETIC RESONANCE IMAGING (MRI)

When a subject's head is placed within a static magnetic field generated by a powerful super-conducting magnet, naturally occurring elements in the brain — for example, hydrogen, which makes up almost two-thirds of the atoms in the brain — act like bar magnets, aligning themselves within the field. A brief pulse of radio frequency waves is then passed through coils positioned around the head, causing the hydrogen atoms to resonate in the short-wave radio frequency range.

An MRI scanner detects the time the hydrogen atoms take to re-align themselves into the static field and translates this information into a two-dimensional image that provides remarkably detailed information about brain structure (with far higher resolution of grey versus white matter than a CT scan).

The MRI scanner can look at the brain in three planes: coronal (from the front to the back of the head), axial (from the top to the bottom) and sagittal (from side to side), providing an effectively three-dimensional view at intervals of millimetres — and providing researchers and clinicians with a marvellously detailed portrait of brain structure.



### ELECTRO-ENCEPHALOGRAPHY (EEG)

This 'old faithful' of brain function measurements is non-invasive, employing electrodes on the scalp to provide a rough indication of general electrical activity. The technique measures electrical activity occurring inside the brain, on the outside of the head; researchers must interpret a muffled, distorted signal that might have passed through up to 1·5 kg of brain (itself composed of tissue of varying densities as well as fluid-filled ventricles) then the deadening insulation of the skull and a centimetre or more of scalp before it reaches the electrodes.

'De-blurring' and modelling techniques are helping researchers understand the nature and distribution of EEG activity.

### EVENT-RELATED POTENTIALS (ERP)

These are transient electrical potentials elicited in response to separate, reproducible events, whether sensory, motor or cognitive (from a pin-prick to recognising particular visual patterns or singing *Row, Row, Row Your Boat* aloud, raising your left index finger every time you come to a word of four letters). The ERPs, which are averages of a large number of EEGs, become stronger when the same stimulus is presented many times. Researchers use them to attempt to identify networks of neurons that underlie a function of interest.

### MAGNETO-ENCEPHALOGRAPHY (MEG)

Because the electrical activity measured by EEGs becomes 'smeared' by the different electrical resistances of the structures through which it must pass *en route* to scalp electrodes, researchers make use of the fact that a magnetic field surrounds these electrical currents... and that magnetic fields are 'transparent' to biological tissue.

Magnetic fields can therefore be measured close to their source, and with little distortion, using a SQUID (superconducting quantum interference device) that enables researchers to detect electrical activity in the brain with high sensitivity. However, SQUID technology has not yet been developed into a brain-imaging system. Dr Graeme Sloggett's superconducting sensors and technology project within the Division of Radiophysics has developed thin-film technology to measure magnetic fields from the brain, leading to an effective way of screening out periodic electronic 'noise' from MEG measurements.

An exciting possibility for the future is research into superconducting SQUIDs that operate at liquid nitrogen temperatures rather than the much lower liquid helium temperatures previously required.

### REGIONAL CEREBRAL BLOOD FLOW (RCBF)

This is measured indirectly, using *gamma*-emitting substances such as xenon-133, a chemically inert gas that is inhaled by the subject or injected intravenously. The gas saturates the brain and, over the ensuing 10 to 12 minutes, is cleared from there at a rate proportional to blood flow correlated with brain metabolism. This technique measures activity in the cortex — the outer part of the brain — and, though it has a useful spatial resolution of about 1 cm, its temporal resolution is in minutes.

### SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)

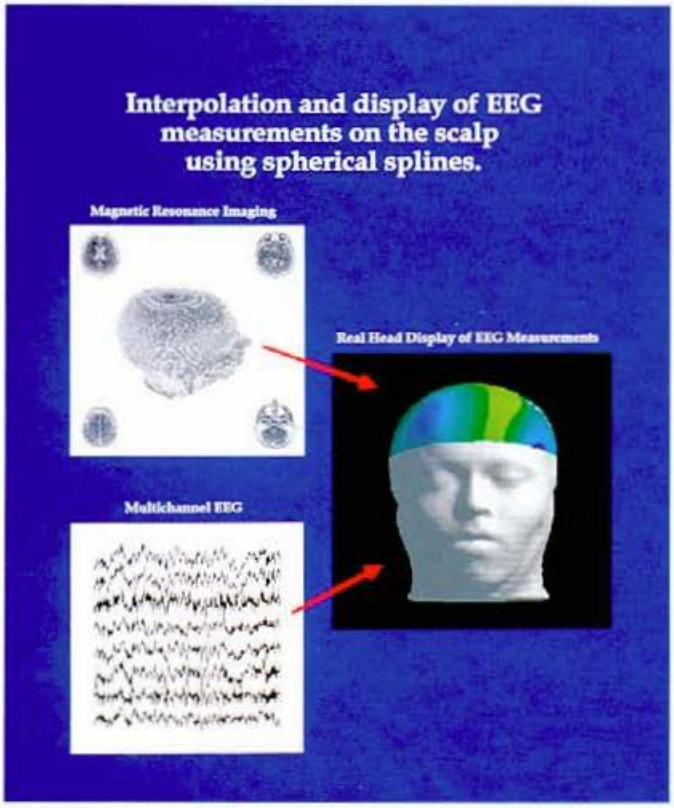
This technique employs radioisotopes of elements, such as iodine, technetium and thallium, that are not normally metabolised in the brain. They can be injected and used to map the activity of particular neurons, since they become trapped in or on neurons within minutes. The activity of these neurons can then be mapped to present a three-dimensional picture of cortical and subcortical activity.

Offering moderate spatial resolution (plus or minus 6 mm), SPECT is considerably cheaper than positron emission tomography. There are 180 SPECT machines in Australia, each worth some $400 000, as compared with two $10-million PET machines.

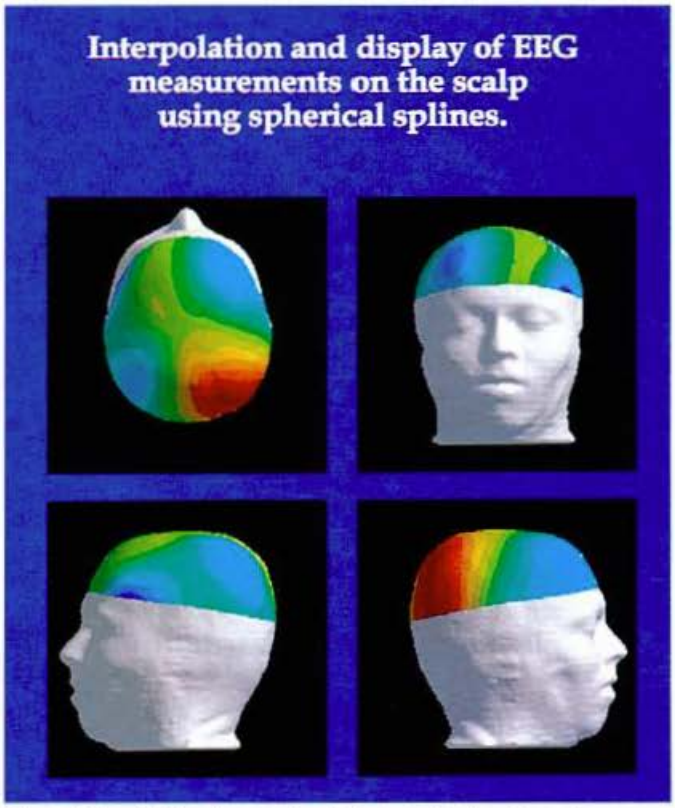
### POSITRON EMISSION TOMOGRAPHY (PET)

This employs positron-emitting isotopes with short half-lives (from 2 to 110 minutes) that attach to naturally occurring substances (neurotransmitters, glucose, water, amino acids and so on) without altering the biological fate of those substances. Positrons collide with electrons in the brain, leading to the creation of a pair of *gamma* rays that are given off in opposite directions. The points at which these rays are emitted can then be measured with a ring of *gamma* detectors outside the head, to construct images that reflect the cortical and subcortical distribution of brain metabolism and chemistry.

All three nuclear medicine technologies offer good spatial resolution but poor temporal resolution.




MRI 'slices' are stacked to create a mathematical model of an individual's head. Information from multi-channel EEG recordings is then displayed (using false colours) on a three-dimensional image of the same head.




The multimodal imaging work-station can display the voltage distribution of electrical activity in the brain from virtually any angle.

in the multimodal program — to a perennial problem in multimodal imaging: image registration.

The heart of this problem is that images such as those of brain function can't easily be compared with images of structure. As mentioned, MRI scans provide sharp images of brain structure; CT scans provide poorer resolution of brain tissue but show the skull clearly; EEG and MEG scans show electrical activity, but relate it only poorly to structure... and so on.

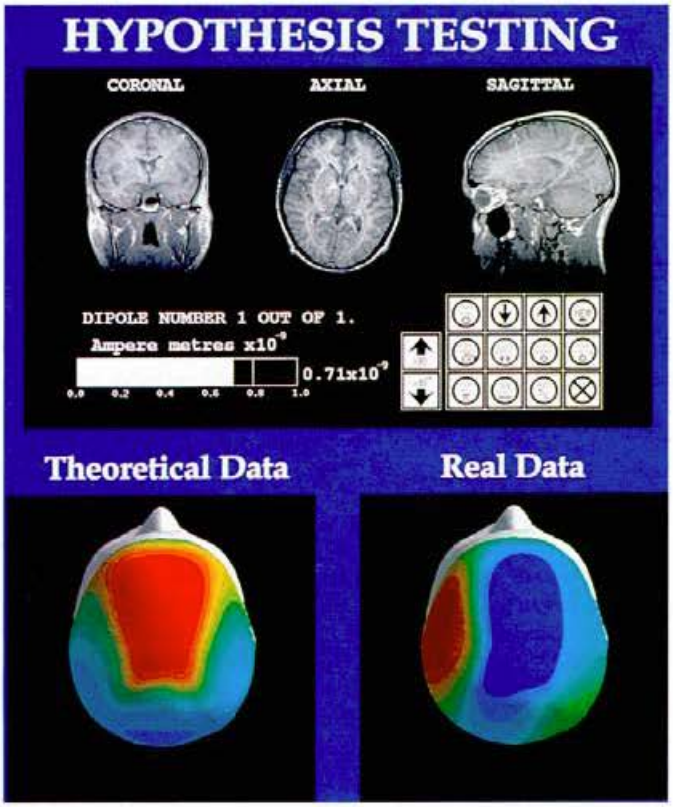
What Ms Bischof and Dr Berman had to find was a way of plotting recognisable, stable anatomical markers — for example, the inner and outer surfaces of the skull, scalp or particular brain tissues that showed up well in a variety of images — then find a way of superimposing images so that they could build up a picture that accurately registered the geography of brain, skull and scalp. The picture thus constructed would, they hoped, mean that one kind of measurement could be compared with others.

In the past, the only way to achieve those targets was literally to clamp a frame, containing small amounts of materials that show up in a variety of images (and that thus allow each image to be aligned correctly with others) on to a subject's head. The frame prevented movement of the measuring devices and, in most cases, of the subject's head as well, but was so cumbersome and unpleasant that scientists were unwilling to use it. Ms Bischof and Dr Berman succeeded in identifying natural markers in the brain and skull, thus making a rigid frame unnecessary. They then applied a computing sequence, called head and hat modelling, to find the best fit between pictures provided by, say, a CT scan and a SPECT scan... in other words, to line up, or register, the images.

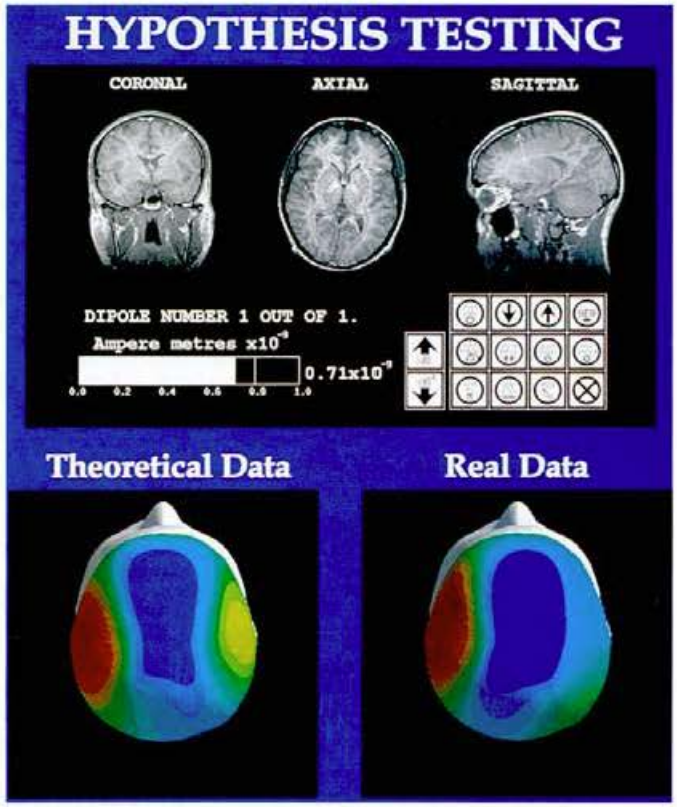
Reconstructing brain function (shown by EEG, PET or SPECT measurements) involves remote sensing in that signals must pass through several different kinds of tissue before they reach a recording device, such as scalp electrodes. To analyse those signals, researchers have to account for how the various tissue types within the brain — as well as the skull and the scalp — influence the signals that are recorded.

Unfortunately, they have not been able to simply back-track along the path of a signal to find its origin; they do not yet have the mathematics to calculate the precise source of the signal using recording equipment on the outside of the head. (Nevertheless, the research team has achieved notable success in addressing this apparently insoluble problem, by employing the 'information fusion' approach described a bit later.)

As part of the Division of Radiophysics' initial involvement with Westmead Hospital, Dr Andrew Seagar and Dr Rene Grognard designed a mathematical model that allows researchers to look at how brain function is expressed on the outside of the head, and to track how electrical or magnetic activity signals within the brain are related to measurements on the scalp. (Oddly enough, the model actually addresses the 'wrong' question, since it asks, 'if I can detect an electrical source at a specific point in the brain, what will I measure with EEG or ERP recordings?' The ultimate aim of the project was, in fact, to reverse that question, so that it became: 'if I have these EEG/ERP measurements, where is the underlying electrical source located?')




The researcher generates a hypothesis to explain ERP activity — in this case, the pattern produced by an auditory stimulus — and indicates the possible location and orientation of the activity (white arrows) on MRI images. The hypothesised ERP voltage distribution (left) can then be compared with the measured distribution (right).




The information fusion approach allows a hypothesis to be 'adjusted' to a useful match between the calculated voltage distribution and the measured distribution.

Dr Seagar and Dr Grognard began with a basic three-dimensional model that consists of two nested spheres representing the brain and the skull. As the human head and brain are so complicated in a geometric sense, this model was far from a reasonable portrait — not only because it reduced bulbous, ovoid shapes to spheres but also because it ignored the fact that white matter, ventricles, grey matter, skull and scalp individually and severally affect measurements. The researchers' next — albeit mathematically extremely complex — step was to combine their expertise in electrical engineering and mathematics to develop a model that consists of five nested spheres (each of which expresses, mathematically, the unique electrical conductivity of the brain, skull or scalp element that it represents). Applying this, they can test hypotheses about the sources of electrical activity confident that the model is a reasonable approximation of reality.

Dr Seagar, Dr Grognard and Mr Young Choi are now extending the technique by replacing spheres with representations of the actual surfaces of objects such as the ventricles, the inner surface of the skull and so on; they are using MRI images to develop mathematical descriptions of three-dimensional surfaces from two-dimensional images.

Finding ways of collecting, displaying and registering images was only the first part of this ambitious project. The second major element involved information fusion, applying a procedure devised by Mr Glynn Rogers originally for use in geophysics. The procedure, which employs the judgment and imagination of human experts to 'fuse' information from a number of sources into a single conceptual entity, makes use of one of the basic tenets of the scientific method: the principle of inductive inference.

Put simply, inductive inference is the process scientists use to construct their ideas about how the world works. Having observed a series of events (say, the Sun rising in the east many times), a researcher extrapolates from observation to theory, postulating a relationship between them ('if the Sun rises in the east n+1 times, then it will always rise in the east'). The process of extrapolation doesn't end there, however: by comparing the explanation with reality — in other words, with further observation and experiments — the researcher can refine the explanation to provide a more complete and accurate account of what is happening. Ultimately, this not only provides an insight into the world, but also enables the researcher to extend what he or she has learned from particular instances into general principles.

The software developed by Mr Rogers's team enables the computer to enhance the link between the formal scientific method and human expertise — the 'educated intuition' that is an essential part of a researcher's intellectual competence — allowing researchers and clinicians to examine images of, say, ERP measurements and then to construct and test a hypothesis to determine what lies behind those measurements.

For example, they could examine an ERP image showing electrical activity in the brain, then use a computer workstation to postulate likely sources for specific aspects of that activity. The computer calculates the voltage distribution that would be measured for

nominated sources (using the Seagar/Grognard model, which allows for the effects of electrical conduction in the brain, ventricles, skull and scalp), then displays an image corresponding to the researcher's hypothesis.

The computer can provide information on how closely the hypothesis approaches reality by comparing the two sets of data and, more importantly, it can also 'improve' that hypothesis by modifying it just enough so that it fits the measured data. If this process can be performed quickly enough, by using high-performance computers, a 'dialogue' can be established between the human expert and the computer, using images as a language. However, Mr Rogers warns that substantial further development is needed to refine the process, and to explore approaches to displaying and analysing the resulting images.

Mr Albert Haig, a member of his group, has begun this exploration by taking a 'stack' of properly registered MRI images, applying the methods of mathematically representing surfaces developed by Dr Seagar and Dr Grognard to identify and describe the surface of the head and then creating a third image by 'wrapping' the ERP voltage image on to the result. The combination means researchers and clinicians can now display a rendition of the image as it is actually 'reflected' on the subject's head — an important part of the visualisation component of information fusion.

This information fusion procedure has wide potential application, and would provide an invaluable teaching aid enabling science students to hone their skills on screen, helping to develop their scientific intuition. In the more immediate context of brain imaging, it provides a means not only of testing different hypotheses but also of examining the way in which, for example, one record of brain function compares with another, or with a record of brain structure.

The multimodal brain imaging team is applying the fusion approach to the extremely difficult task of relating structural and functional changes in the brain to a variety of diseases and disorders. Dr Evian Gordon, a brain researcher at the University of Sydney and head of the Cognitive Neuroscience Unit at Westmead Hospital, regards multimodal imaging as an inevitable part of future neuroscience work.

He believes it has the potential to integrate what he describes as the 'complementary windows' available into brain function, and predicts that it will also open new windows into the way the brain processes information. It will also be used to identify and profile changes in brain structure and function involved in neurological and psychiatric disorders and, more importantly, provide an objective appraisal of how medication affects brain function.

Dr Gordon has recently returned from establishing collaborative contact with key researchers in the current United States–Canadian 'brain-mapping' project, and believes this kind of co-operation will identify research niches for Australian expertise: analysing brain function in terms of 'real-time'-related electrical activity is a weak link in data fusion efforts worldwide, and the expertise in signal processing developed by the Division of Radiophysics has already shown considerable potential in this field.

In addition to its contribution to brain research and multimodal imaging, the information fusion approach developed by the team will ultimately provide the designers of future generations of computers with intellectual tools to help them create human–computer interaction software and image-processing systems that will incorporate the visual scanning strategies, processing speed, parallel processing abilities and pattern-recognition potential of the human brain.

*Carson Creagh*

**More about the topic**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