BRAIN CONNECTIONS

Ideas that a map of brain function could be clinically useful fell out of fashion many years ago, but new imaging technology is resurrecting them, as **Geoff Watts** reports

A scanning technology still in its infancy may eventually offer a more complete understanding of brain disorders from autism to schizophrenia. If it does, at least part of the credit should go not only to the researchers now developing it but to some of the great neuroanatomists of the 19th century.

The history of science is an endless saga of competing ideas in which new insights emerge, develop, and flourish—or, as often as not, get replaced by something better. It is unusual for an idea to fade and then, decades later, be resurrected. But this is more or less what's happened to the ideas of Meynert, Wernicke, and other European anatomists of their era. The obstacle to earlier development was that it took another century to invent the scanning technology required to test them.

Among the handful of today's researchers eager to deploy this new technology is Marco Catani of the Centre for Neuroimaging at London's Institute of Psychiatry. Looking back at the work of his predecessors, he finds himself impressed. Through dissection and observation of postmortem material they came up with the idea that many of the functions of the brain are localised. More than that, they began to fashion a crude wiring diagram. "It was a revolutionary idea," Dr Catani says, "to go from anatomy to function."

Early links

Some of the earliest detail came from Theodore Meynert, a Viennese professor of psychiatry who died in 1892. Although simple brain functions may be localised in one part of the cortex, higher functions, he insisted, are the product of interactions between different areas of the brain: interactions that require connecting pathways of nervous tissue—association tracts—running through the white matter which underlies the grey.

If this is true, failures of these links—disconnections—will affect the normal workings of the brain. This disconnection concept was seized on and promoted by one of Meynert's students, Karl Wernicke. "He was the person to come up with the first example of a disconnection syndrome," says Dr Catani. "He called it conduction aphasia." Patients with this condition can understand spoken and written words, write, and talk fluently; but they skip or repeat words when speaking, or substitute one for another. Although aware of their mistakes, they find it difficult to correct them. Wernicke attributed this to a disconnection between the areas of the brain responsible for speech production and comprehension. Disconnections between other areas produced other conditions such as agnosia and apraxia.

Interest in this "associationist" view waned in the first half of the 20th century. "There wasn't sufficient anatomical knowledge to come up with connectionist models for all the different functions," says Dr Catani. "And people then started saying that to know about clinical-anatomical correlations wasn't helpful in understanding how the brain works." The field languished until the mid-1960s, when the celebrated American neurologist Norman Geschwind arranged to retranslate some of the 19th century work. Reading it, he realised that useful observations and insights had been abandoned. In two long papers published in 1965 in the journal *Brain* he resurrected the associationist school of thought, added his own ideas, and offered a new and more elaborate theory of brain function.[1 2]

Visual evidence

Geschwind did experiments on monkeys. But like the 19th century anatomists he too ran up against the limits of what could be achieved without some non-invasive way of investigating living brains. The breakthrough in the study of soft tissue, including the brain, was the advent of magnetic resonance imaging (MRI). But although MRI is good at showing the grey matter, the brain's white matter—home to the bundles of myelinated axons connecting the higher centres in the grey matter to each other—do not show up so well. The remedy lay in a variant of the technique with the daunting title "diffusion tensor MRI."[3]

Brains are not all anatomically identical; certain areas including those for language are more complex than once thought

Catani explains this using an analogy. Suppose, he says, you're suspended above a motorway and want to know in which direction it's been built. But it's night and you can't see the road itself. What do you do? One solution would be to point a camera at it, and open the shutter on a long exposure. The resulting picture will be scored with red and white streaks: the lights of the traffic. Their orientation reveals the direction of the road. Diffusion tensor MRI does something similar. Its equivalents to moving cars are diffusing water molecules. The equipment can detect the direction they're moving in. And since water molecules are more likely to diffuse parallel to the membranes of nerve cells than to cross them, the alignment of the axons in white matter can be inferred. The computer can compile three dimensional images of these tracts of connecting nerve tissue.

This approach to tractography, as it's known, is still in its relative infancy and not yet perfect, says Chris Frith of the Wellcome Trust Centre for Neuroimaging. "The technique of measuring the direction of the fibres is fine. The more problematic part is to build up a picture of exactly what the fibres connect to when they reach the cortex." Although some wrinkles remain to be ironed out, Professor Frith has no doubt that, as resolution improves, so will the value of the technique.

Not surprisingly, this and other work carried out over the past few decades has showed Geschwind's conception—never mind that of his predecessors—to be less than complete. The current view no longer attributes all loss of higher function to simple disconnection. Dr Catani talks of "topological" dysfunctions,[4] in which the failure lies within a part of the cortex and could be caused by too much activity as well a loss of it. He describes dysfunctions of the pathways as "hodological" from the Greek word *hodos*, a road or path. Some conditions feature failures of both types.

Clinical potential

Many of the disconnection disorders reported by the early anatomists were relatively rare. So too are others since recognised, from prosopagnosia to colour anomia. But does

contemporary thinking about connection failures also relate to more common disorders? Dr Catani thinks it does. In stroke, for example. Brains are not all anatomically identical; certain areas including those for language are more complex than once thought. "Knowing this helps us to a better understanding of stroke," says Dr Catani. "We've learnt that connections between the language areas are more developed on the left than on the right side of the brain. In a normal population, 60% of people are extremely left lateralised; another 20% are bilateral but still with more on the left; the rest are bilateral and symmetrical." There's also a sex difference. Among women the distribution across the three groups is more or less equal, whereas 85% of men are extremely lateralised.

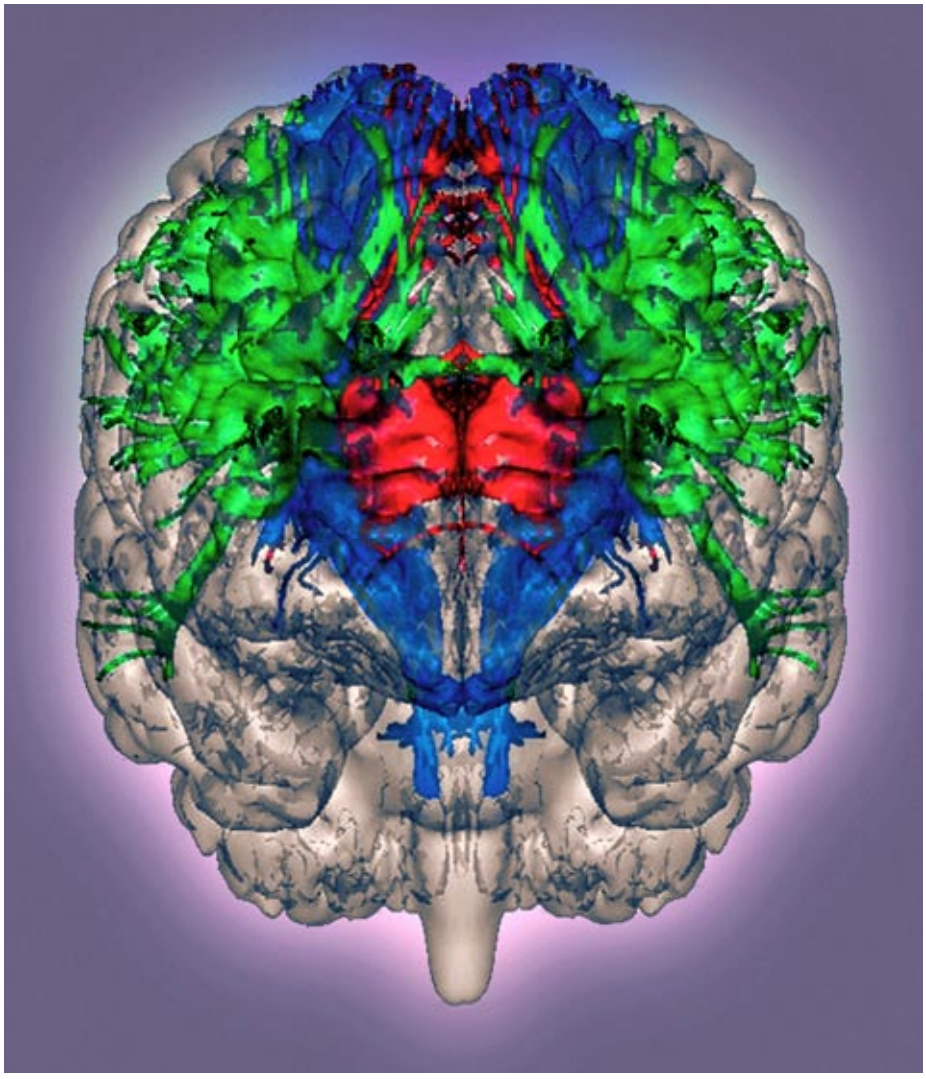
"This begins to explain why two people who've had apparently similar strokes on the same side of the brain may have different degrees of language impairment. Women tend to recover better following a stroke. Maybe it's because more of them are more bilateralised."

Moving to autism, it's possible not only to plot association tracts but also to measure the integrity of their fibres.[5] This shows defects in the neural circuitry that may underpin what is already believed to be one of the roots of autism: a failure of the feedback system by which we learn what forms of behaviour are or are not appropriate.

Although it's still early days, Dr Catani thinks the technology has the potential to illuminate the mechanisms of other brain disorders—not least in conditions where there is no evidence of gross lesions. This could open up new therapeutic strategies. If the nerve tract at fault in autism relies on a specific neurotransmitter you might develop a drug to modulate it. The same approach might be applied to auditory hallucinations in schizophrenia, possibly a result of hyperactivity in the language pathways of the brain. Experiments with transcutaneous nerve stimulation are already underway, and in some patients there is preliminary evidence of benefit using drugs.

What of stroke? "If you could predict in six months' time who will or will not do well, you could focus therapy on those with a better chance of recovery, and look for other ways of dealing with those unlikely to benefit."

Dr Catani is taking part in a collaborative study of dementia in which the aim is to map specific symptoms to specific nerve tracts. Depending on which tracts are damaged, it may be language or memory or movement that is most affected. "If we can see how the progression of the disease correlates with anatomical changes, we may do better at predicting its course."



ZEPHYR/SPL

Frontal coloured 3D diffusion tensor imaging scan of a healthy brain showing bundles of white matter nerve fibres

Although tractography using diffusion tensor MRI is still principally a research tool, Dr Catani sees no reason why it shouldn't eventually find a place in routine practice. With the right software, he says, existing machines can perform scans of this kind. "But interpreting the images requires extra anatomical knowledge. Because white matter connections don't show up with classic MRI, staff aren't currently trained to identify association tracts."

One of the next developments, still largely unexplored, will be to use diffusion tensor MRI in conjunction with functional MRI, the technique that allowed investigators to study blood flow in the brain and infer which regions are active and under what circumstances. "If you use functional MRI to identify an area that's particularly active," says Frith, "you can then use diffusion tensor MRI to see what it's connected to."

The old anatomists could only infer the function of a tract of nervous tissue. With scanning technology researchers are increasingly able to see what's going on as it happens. Only connect.

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Competing interests: None declared.

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Cite this as: *BMJ* 2009;338:b1317