PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Reverse engineering the human brain

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Phil. Trans. R. Soc. Lond. A 2000 **358**, 497-511
doi: 10.1098/rsta.2000.0543

THE ROYAL SOCIETY

Reverse engineering the human brain

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Advances in the physical sciences often foster advances in the biological sciences. In this paper I deal with just one of those many contributions and describe a trail that leads from Faraday's discovery of electromagnetic induction to a technique called transcranial magnetic stimulation (TMS), which can be used to temporarily prevent the brain from carrying out some of its normal functions. The 'lead time' between Faraday (1831) and TMS (1985) was over 150 years, clearly longer than any Department of Trade and Industry would like. The path shows how scientific disciplines can interact, and, in the case of TMS at least, how the scientific concepts were always ahead of the technology. Having shown how much the use of the technique owes to other strands of investigation, I outline some of the advances in understanding brain function made by using TMS, and, in particular, the improvement it makes upon electrical stimulation and studies of the effects of brain damage. Finally, I make three predictions about the contribution that the technique will make to further discoveries in the 21st century.

Keywords: magnetic brain stimulation (TMS); virtual patients; neuropsychology; reversible legions

Reverse engineering (definition from the on-line dictionary of computing): 'The process of analysing an existing system to identify its components and their interrelationships and create representations of the system in another form or at a higher level of abstraction'.

1. Electromagnetism and the brain

In a letter to Oersted in 1850, Michael Faraday remarked that, concerning scientific discoveries, 'we have little idea at present of the importance they may have ten or twenty years hence' (see Cantor 1991). It is a view with which no research scientist will disagree, but even Faraday may have been surprised at the lifespan and biography of one his most widely known discoveries. In 1831 Faraday demonstrated that a moving magnetic field could induce an electric current in a nearby circuit (Faraday 1832), a discovery he believed would 'probably have great influence in some of the most important effects of electric currents'. At the time of this discovery it was already known from Luigi Galvani's (1737–1798) experiments, showing that electrical currents could produce muscle contractions, that nervous tissue had *something* to do with electricity; and, in 1838, Matteucci (1811–1868) had introduced the term 'muscle current' to describe the activity of muscle tissue previously referred to as 'animal electricity'. Ten years later, Du Bois-Reymond (1818–1896) demonstrated a

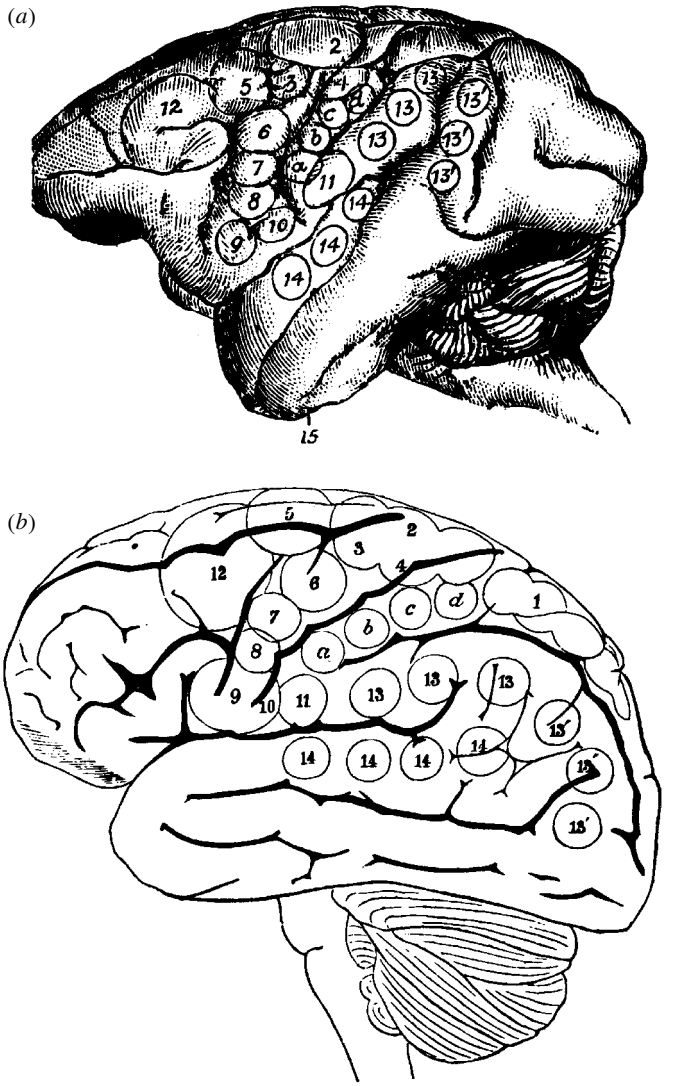

Figure 1. (*a*) Ferrier (1876) mapped the different functions of the macaque brain by direct stimulation of the cortex and (*b*) transposed the functions to the human visual cortex.

direct relationship between electric current and nerve-cell activity. Even so, it took until 1939 and the work of Hodgkin & Huxley to show that nerve cells generate action potentials and that brain activity *depends* upon electrical activity: the brain, then, is a machine that runs on electricity.

2. The first wave of stimulation studies

These discoveries ushered in what can be thought of as the first wave of stimulation studies as a means of reverse engineering brain function. Physiologists began

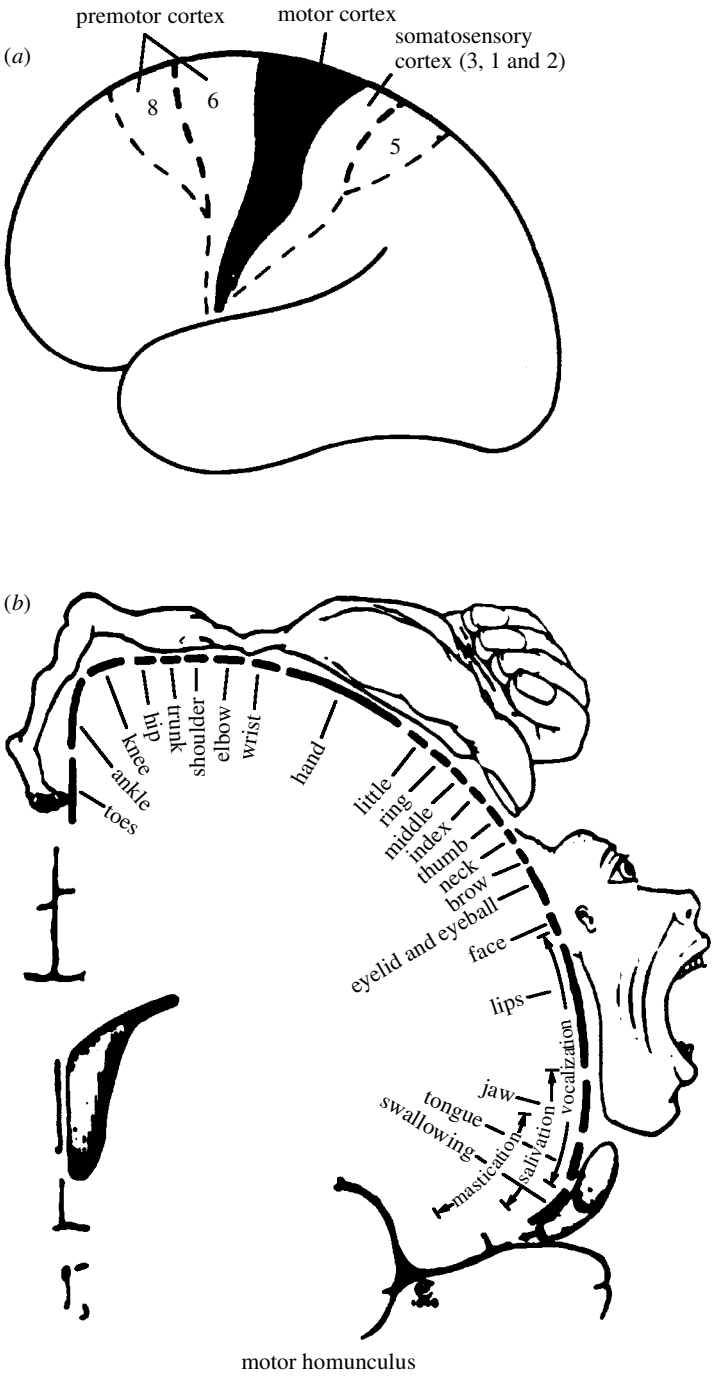

Figure 2. The motor homunculus produced by Penfield & Rasmussen (1950) from direct stimulation studies. Note that the body is distorted and those areas that produce fine motor actions and manipulations (the hand and the mouth) are disproportionately represented. This map is a slice taken through the region at F on figure 7.

to apply electrical stimulation to the cerebral cortex, and, in doing so, were able to produce movements in muscles on the contralateral side of the body. Working on dogs and monkeys, Ferrier (1875, 1876) used magnetically induced currents to produce a map of cortical function (figure 1), and the technique of direct stimulation to map function was later extended to human subjects. Penfield and his colleagues (see Penfield & Rasmussen 1950) applied electrical stimulation to the cortex of patients undergoing neurosurgery and were able to delineate the way in which body movements were represented in the brain (figure 2). They also confirmed the location of speech reception and production areas, identified a third speech-related area, and stimulated areas that produced specifically tactile or visual sensations. One patient, identified as case J.V., experienced seeing familiar people and familiar scenes when stimulated in the temporal lobe.

There were several limitations to these methods of investigating brain function. The invasive nature of the experiments meant that they could only be carried out in patients who were awaiting surgery, and, of course, this restricts the kinds of experiments one can do. Another important limit was the specificity of the movements or perceptions produced. The motor cortex is required for fine and important skills such as typing, threading needles and giving complex hand signals to other road users, but Penfield's stimulation elicited actions that were 'not more complicated than those a newborn infant is able to perform' (Penfield & Rasmussen 1950, p. 47). Finally, some brain regions, for example the parietal and frontal cortices, which Penfield & Rasmussen (1950) referred to as 'elaboration areas', did not respond to electrical stimulation because the brain does not only produce perceptual and motor outputs but also transforms them: it would be difficult to imagine how stimulation would elicit awareness of a transformation. For example, at some stage in reading, your brain is able to encode printed letters as sounds but stimulation never caused a subject to report anything like this. Penfield & Rasmussen (1950) were aware of this and concluded that in these cases stimulation 'sheds no light upon the function of an area unless the patient is making use of that area at the moment' (Penfield & Rasmussen 1950, p. 234). What is needed then is some way of reverse engineering the brain *in action*.

3. Reverse engineering with broken brains

Another wave of reverse engineering, neuropsychology, began soon after the first and got into full flight with the report by Pierre Paul Broca (1824–1888) that damage to a part of the lower-left frontal lobe rendered patients unable to produce speech. The approach taken in neuropsychology is to investigate the abilities of patients who have suffered brain damage and from the pattern of their deficits to infer something about the function of that region or about the general organization of the system under investigation (Shallice 1988). The study of patients with focal brain damage (neuropsychology) formed perhaps the most important source of knowledge about the organization and function of the brain for the next half-century, and the kinds of dissociations demonstrated were both informative and intellectually seductive. For example, one patient, L.M., has been reported to be severely impaired in the perception of movement but less so in the perception of shapes and textures and not at all in the perception of colours (Zihl *et al*. 1983), while another (Zeki 1993) perceived the world totally devoid of colour without suffering any marked reductions in move-

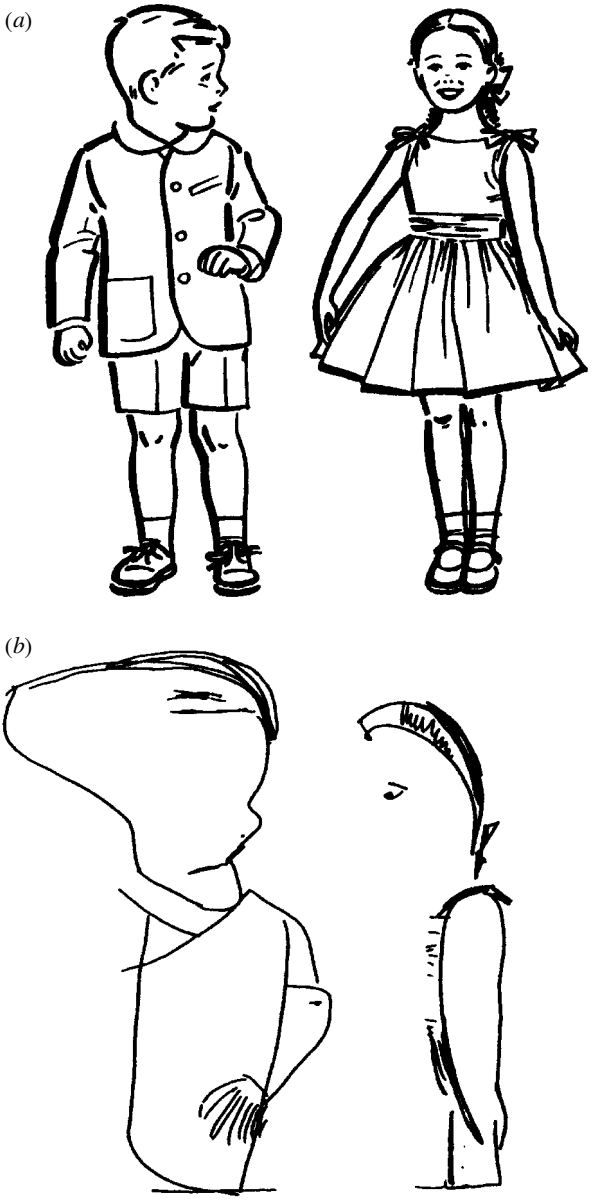

Figure 3. Visual neglect. The bottom two parts of the figure (*b*) are a patient's recreations of the top two (*a*). The patient misses out the left-hand side of each body. Similar effects have been obtained with magnetic stimulation.

ment and form perception. Other such functional dissociations abound: patient D.F. has very poor visual perception of orientation but can, nevertheless, *use* information about orientation in order to grasp objects or put objects through differently oriented holes (Goodale & Milner 1992). Other specific and curious deficits include the loss of awareness of half of the body or of objects (figure 3), or an inability to name

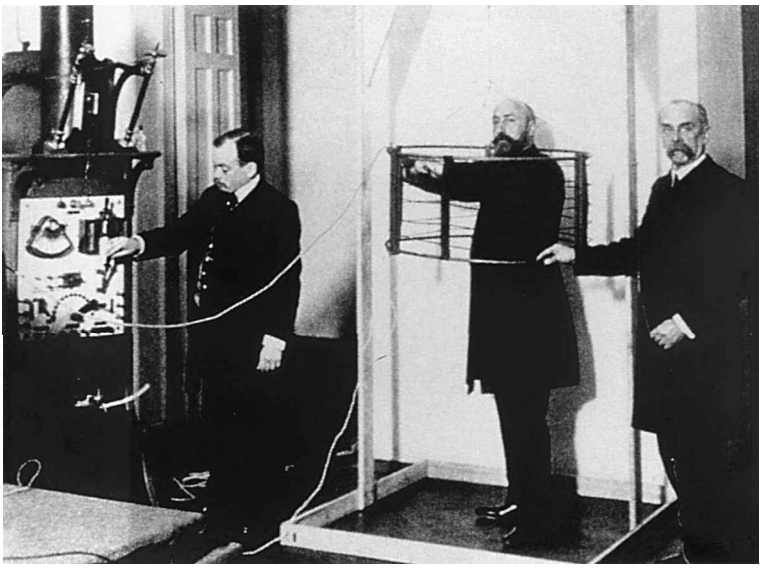

Figure 4. d'Arsonval and colleagues showing the apparatus used to induce visual phosphenes. This photograph was taken in 1911.

an object presented to the right-hand side of the brain when it is disconnected from the left-hand side (Gazzaniga 1995). All of these examples suggest that the brain is organized according to the relative functional specializations of its different regions (Zeki 1993).

In many respects, the classic findings of neuropsychology have formed the bedrock of much of what we know about how we see, hear, speak, move and even feel. Nonetheless, neuropsychology has not always influenced theories about how the intact brain carries out tasks (Shallice 1988). This is partly because nature is a poor surgeon: accidental brain damage is usually spatially diffuse, interrupts several functions, is irreversible, and the time of its occurrence cannot be predicted. Another problem with the lesion method in general, even when specific areas can be removed from animals, is that it does not possess any degree of temporal resolution. This is critical when one considers the nature of psychological models of brain function. Our models always contain stages of processing that are part parallel and part serial. In other words, to understand brain processes means understanding them in time as well as in space. Knowledge of precisely *when* the brain carries out specific functions is not an add-on intellectual luxury, and there are several accounts that demonstrate that the relative timing of brain activity across different brain regions may be fundamental to any accurate description of how the brain performs many complex tasks (see, for example, Singer & Gray 1995; Bressler *et al*. 1993; Bartels & Zeki 1998; Hupe *et al*. 1998).

The electrical stimulation method could not address the role of association or elaboration areas and the lesion method is hampered by the lack of temporal resolution. What is needed for another wave of reverse engineering, then, is the ability to stimulate the brain while it is doing something, or to be able to reversibly disrupt its functioning to give the lesion method a temporal dimension. The story of how we are able to achieve both of these takes us back to Faraday.

4. Back to the future

Recall that Faraday discovered electromagnetic induction, and we know that the brain is a conductor of electricity. It follows that exposing the brain to a changing magnetic field will result in an induced electrical field and, therefore, neural activity. This was soon appreciated, and, as the 19th century drew to its close, d'Arsonval (1896) reported the first production of visual percepts (spots or flashes of light called phosphenes) induced by magnetic stimulation (figure 4). The subject also reported feelings of vertigo, and, under some conditions, muscle contractions as well.

One might have thought that d'Arsonval's discovery would be sufficient to generate further studies of brain function by magnetic stimulation, but the technical solutions to this had to wait for the best part of the last century until Barker *et al.* (1985; see also Barker *et al.* (1989)) successfully stimulated the motor cortex (see figure 2 and region F in figure 7) and produced movements of the hands without causing the subjects any discomfort. The magnetic pulse was generated by current (up to 8 kA) flowing through a small coil held above the subject's head. The current was discharged over a period of 1 ms, reaching its peak in as little as 200 μs and this produced the magnetic pulse (*ca.* 2 T), which, in turn, induced current flow in the underlying cortical tissue. The cycle of events is represented in figure 5. The technique is painless and safe as long as ethical and safety guidelines are followed (Wasserman 1998).

The clinical neuroscience community was quick to pick up on the importance of this discovery, and Barker's transcranial magnetic stimulation (TMS) was soon widely used to measure nerve conduction velocities in clinical and surgical settings (Murray 1992; Rothwell 1993). However, it is not in the clinical domain that TMS provides the most excitement; TMS is a tool with which to discover new facts about brain function and it has already delivered in many areas.

5. Reversibly disrupting brain function

I noted above that two of the problems with the lesion technique were that the process could not be reversed and that information about time was lost. With TMS, however, one can apply a single pulse (which lasts for less than 1 ms, see figure 5) at any time while a subject performs a task. The effect of the magnetic stimulation is to cause neurons to discharge at random in and around the area stimulated, and, thus, to impede the normal functioning of that area. Thus the subject 'suffers' from a temporary 'lesion effect', which lasts for a few tens of milliseconds. Theoretically, we are now able to disrupt information transmission in specific circuits at specific moments in time in the same way as a debugger needs to be able to access parts of a computer program at a particular point in its execution: a reverse engineer's dream. This has become known as the creation of 'virtual patients' (Walsh & Cowey 1998; Walsh & Rushworth 1999) and takes us into the realms that Penfield and Rasmussen could not enter—the elaboration areas. The first challenge for TMS, however, is to show that it can recreate the effects seen in real brain-damaged patients.

The patient L.M., mentioned above, suffered brain damage, caused by a thrombosis, which included those regions of her brain known to be important for the perception of movement (Allman & Kaas 1971; Zeki 1974; Zeki *et al.* 1991). According to the rationale of the 'virtual patient' approach, TMS applied to the visual motion areas of the brain should make subjects experience the same difficulties as

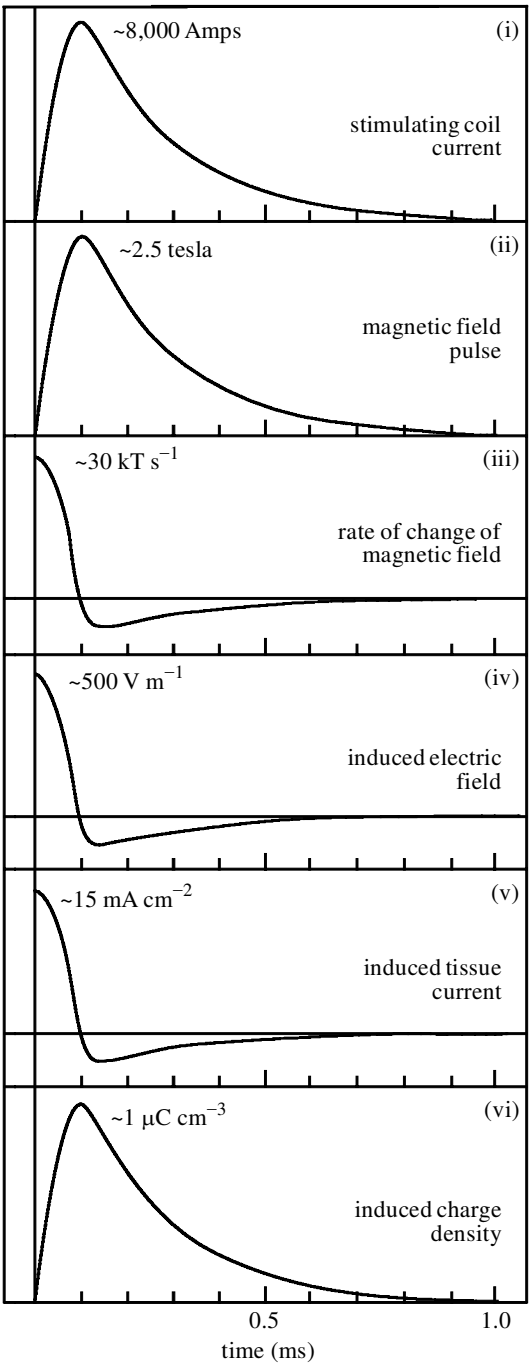

Figure 5. The sequence of events in TMS. An electrical current in the stimulating coil (i) produces a brief magnetic field (ii), which, because of the brevity of the pulse, is changing very rapidly (iii). The induced magnetic field in turn induces an electric field (iv), which causes neurons to discharge (v). The cycle produces no net change in electric charge (vi).

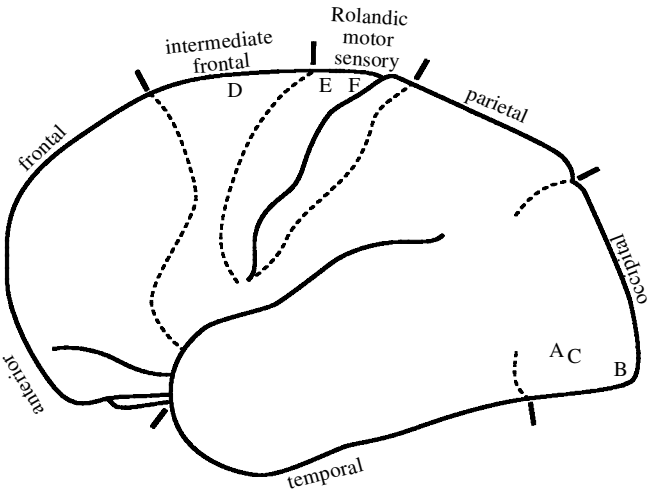

Figure 6. Sites A, B and C show areas where Penfield & Rasmussen (1950) obtained visual phosphenes. These areas also overlap the regions stimulated by Kammer (1999). Regions D, E and F represent the premotor cortex (D, an 'elaboration area'), the motor cortex (F) and an intermediate site. These three regions were stimulated by Rushworth and colleagues in order to delineate the temporal structure of the system responsible for selecting an action and actually producing it.

L.M. Indeed, several laboratories have now shown that TMS over human area V5 (approximately area A on figure 6) specifically impairs the perception of movement (see Amassian *et al*. (1998), Walsh & Cowey (1998) and Hotson & Anand (1999) for reviews). So, magnetic stimulation has the face validity conferred by replication of others' findings, but it also needs to be able to extend the findings of others.

6. A return to Penfield

In their investigations of the visual cortex in patients, Penfield & Rasmussen (1950) observed that stimulation of the posterior occipital cortex (figure 6) led patients to experience phosphenes, which they described in terms such as 'I saw just one star' (figure 6, area B), 'Silver things to the left of me' (figure 6, area C), or 'red and blue wheels'. Penfield & Rasmussen (1950, p. 208) were aware that seizures of the occipital lobe were associated with blindness in the parts of the visual field represented therein, and they surmised that with their more localized electrical stimulation, the patient 'may be blind only in that portion of the field where he seems to see the light'. This kind of focal blindness is known as a scotoma, and TMS has since been able to show that the prediction was correct. Kammer (1999) applied TMS to the occipital lobe (around the areas marked B and C in figure 6) and mapped the spatial distribution of the phosphenes experienced. He then gave subjects a task in which they were required to detect the presence of a target in different parts of the visual field and found that the location of the transient scotoma coincided with the location of the phosphene produced by TMS at the same site. Thus, in the case of the visual cortex, Kammer concludes that the mechanism of suppression appears to be excitatory. This is an important step forward because the production of a deficit does not, of itself, say anything about the neural mechanism.

7. Elaborating elaboration areas

Penfield called areas from which they could not elicit a response 'elaboration areas' and surmised that these could only be studied in action. In a recent series of experiments, Rushworth and colleagues have not only shown this to be true but have demonstrated the temporal structure of interactions between the motor cortex (which Penfield and Rasmussen could study) and the premotor cortex (an elaboration area that could not be studied by direct stimulation). Figure 6 shows the sites at which magnetic stimulation was applied (Schluter *et al*. 1999). Subjects were required to carry out a simple visual discrimination task (discriminating between large and small rectangles and circles) and to press an appropriate button. TMS was applied to one of three cortical areas at different times after the stimuli were presented. If TMS was applied to the motor cortex (site F in figure 6) *ca.* 300 ms after the stimuli were presented, subjects were slower to make their responses; if TMS was applied to the pre-motor cortex (D in figure 6) *ca.* 100 ms after stimulus onset, the subjects were slower to make their response; and if an area between these two sites was stimulated, the time to respond was slower when the magnetic stimulation arrived *ca.* 180 ms after the visual stimuli were presented. Here we have an example of three links in a chain of motor signals being segregated by TMS across a gap less than a fifth of a second. This millisecond-level power shows that the pre-motor elaboration area is important for selecting which movements to make over 100 ms before the lower level motor cortex is instructed to execute the movement.

8. The cheating brain

Correlating excitation with temporary blindness (Kammer 1999), recreating the effects of brain damage (Walsh & Cowey 1998; Walsh & Rushworth 1999), and elaborating the fine temporal structure of the interactions between different areas within a system; all seem to be reasons for brain engineers to be cheerful. But the brain cheats. Like no other machine, it changes the way it performs a task over time. One may have given a detailed and even accurate account of the function of an area, but the details of the function may change over time: an area that is crucial to learning a task may not be necessary once the task has been learned (Poldrack *et al*. 1998; Walsh *et al*. 1998*a*, *b*), and even if it is, its role may have changed. Studies using TMS have approached the issue of plasticity by either measuring the functional correlates of it or by actually manipulating it. A particularly pleasing example of charting the changing functions of the nervous system is shown in figure 7. Eyre *et al*. (1991) stimulated the motor cortex in over 300 subjects between the ages of 32 weeks and 52 years and recorded electrical activity in the biceps and the hypothenar muscle. They took notice of the time between applying stimulation and the arrival of signals at the muscle recording sites (a measure of neural conduction time), and also of the power required to produce muscle activity. As figure 7 shows, there was a sharp decrease in both delay time and power required during the first two years of life, and by the time the children had reached five years of age their delay time had reached the same level as that of adults. The importance of this is that the results correlate with the time taken for the muscle nerve fibres involved to reach their maximum diameter and, because diameter is a determinant of speed, their maximum conduction velocities. The TMS data also correlate with the time at which children develop good fine finger and prehension skills.

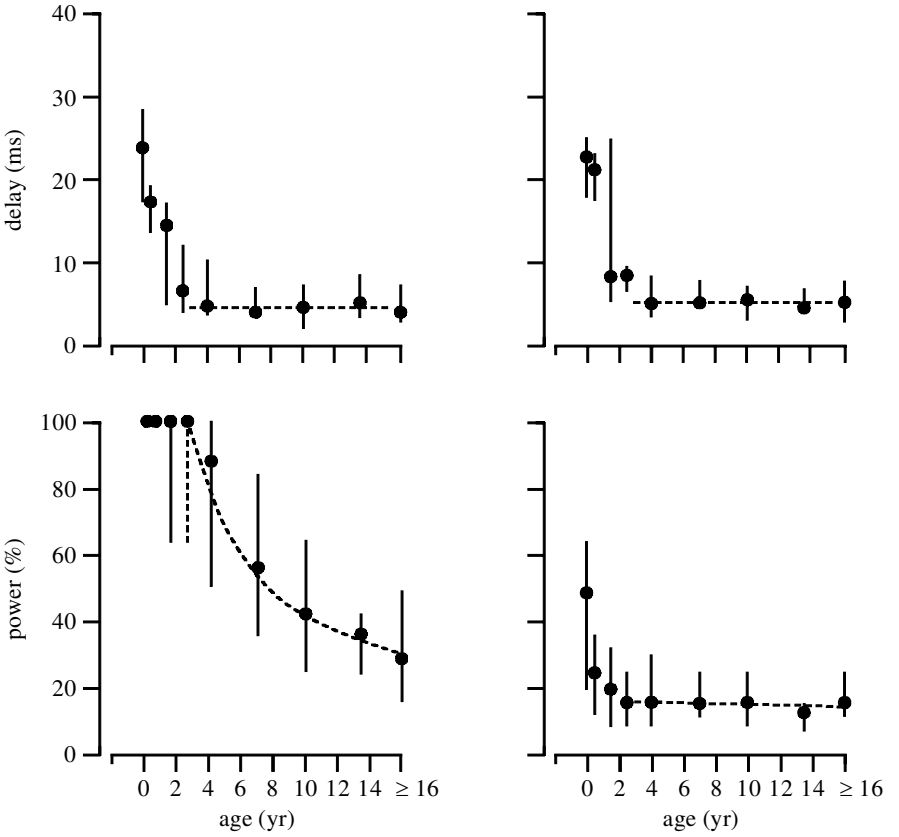

Figure 7. Charting the neural development. Eyre *et al.* (1991) stimulated the motor cortex in children and adults and measured its effects on two muscle groups. The bottom two figures show that the power required to elicit muscle activity decreases very rapidly over the first two years and reaches adult levels by the age of five. The top two figures show that the conduction time follows a similar pattern.

Recording change is impressive enough but change can also be produced. A recent study by Pascual-Leone *et al.* (1999) has shown that magnetic stimulation applied at different temporal rates can either impede or enhance one's ability to learn certain kinds of tasks. Remarkably low levels of stimulation (1 Hz) over the motor cortex slowed down learning on a visuomotor-association task, but learning on the same task was faster than normal when TMS was applied at 10 Hz. Similar results have also been obtained in the visual system (Stewart *et al.* 1999; O'Breathnach & Walsh 1999) and also in language (Töpper *et al.* 1998). The implications of this kind of manipulation of learning function are far reaching, and attempts to apply this in the clinic are already underway.

9. Predictions

Prediction is usually a veil for predilection, so I'll come clean and say what it is I would like to see happen in the near future with TMS. The emergence of TMS as a tool in neuropsychology has been slower than it should have been. Other techniques—

such as functional magnetic resonance imaging, multi-channel electroencephalography and magnetoencephalography—have all attracted more attention. They are, in themselves, exciting developments, and we have learned much about the human brain from them. However, they all record brain activity in one form or another and, thus, cannot reveal how the brain would function in the absence of a certain component. TMS offers a unique combination of component removal and timing and, for these reasons, has a special role in addressing psychological problems. So, my first prediction is that every psychology department in the world will have a TMS laboratory. My second prediction concerns the ability of TMS to influence cortical activity. We are already seeing signs that TMS may be able to replace electroconvulsive therapy in the treatment of depression (see, for example, George *et al.* 1995), and one can only hope for an acceleration in the development of this programme. In addition, there is potential for TMS to be used to influence the progress of those recovering from stroke if the ability for TMS to influence learning turns out to have real potential. My final prediction is that TMS will be used in all its modes and, in particular, in conjunction with the other imaging techniques to obtain a picture of the brain in action when TMS has been used to either impede or enhance processing. Indeed, there has already been some success in this area. Using positron emission tomography scanning, Paus *et al.* (1997) measured changes in cerebral blood flow after subjects had received TMS. The pattern of brain activation was not random: the areas activated by TMS included the site beneath the stimulating coil and several regions to which that area was anatomically connected. From here on, TMS will be used to assess which of those activations have a functional meaning by applying TMS and recording brain blood flow when subjects are performing a task. It may even lead to crossing one of the longest bridges in cognitive neuroscience: how do the functionally specialized regions of the brain act together to produce our experience of the world? The upshot of all this will be what science always aims for: counter-intuitive insights into a piece of the natural world.

Whatever happens, there is only one route that scientists can take to make it so and for a reminder we can go back to Faraday. In 1859, while trying to devise a means of measuring gravitational forces, he wrote in his diary, 'Let the imagination go, guiding it by judgement and principle, but holding it in and directing it by *experiment*'; good advice for the new millennium of science.

My work on TMS has been supported by MRC grants G971/397/B and G9711247, The Dr Hadwen Trust and The Royal Society.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

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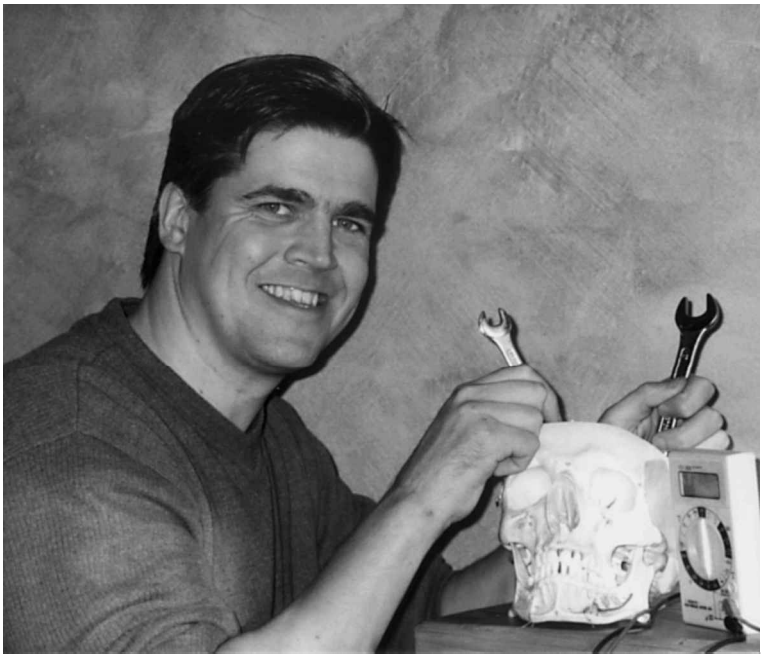
Born in Oldham, Greater Manchester, Vincent Walsh graduated in psychology from the University of Sheffield and studied at UMIST for his PhD in visual neuroscience, awarded in 1992. His early interests were in the brain mechanisms for the construction and perception of form and colour. He currently holds a Royal Society University Research Fellowship in the Department of Experimental Psychology, Oxford, where his work is concentrated on perceptual learning and mechanisms of brain plasticity. His recent initiatives using magnetic stimulation have been the first series of experiments to use the technique to investigate cognitive processes. He will be 1038 years old at the end of the third millennium.



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