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Our brains: transparency within bounds

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We already have considerable insight into the working of the brain, that part of our body which generates the mind, which makes us hope and wish and feel, and finally allows us to comprehend ourselves as 'Self'. However, the big questions about what thinking, consciousness and emotions really consist of cannot be answered yet. Continued research on the brain persists, tackling one of the greatest challenges for the human mind, namely: to discover its own preconditions, to unravel its own prerequisites. May we hope (or fear) that, in the future, brain research we will be able to give the final answer to that everlasting question of philosophy 'What makes us human?' Or is there an epistemological barrier when we look at the human brain and the subjectivity generated by it? There are fundamental cognitive problems regarding the extreme complexity of the brain's system and the brain–mind question. On the other hand, the findings of brain research are already so compelling that their interpretations should be guidelines for the humanities and the social sciences.

Introduction

The current state of astronomical knowledge tells us that we can only perceive baryonic matter, 'ordinary matter' so to speak. But the analysis of data sent by the satellite Wmap indicates that this is just 4.4% of the universe. Which leaves us with 95.6% of 'dark matter' and 'dark energy' whose existence and characteristics can only be assessed indirectly.

This seems a compelling metaphor for the brain. In brain research, are we not also limited to the objectively measurable part of our neuronal cosmos? The subjective part with which we experience mental conditions from the 'inside' remains in the dark, stays hidden from anyone who is not 'me'.

Apparently, evolution has limited the faculties of our brains to the requirements

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of life up to the Stone Age. What else should be necessary? We realise these restrictions when we play chess. Thinking ahead about our own strategies and those of our opponent, there arises a proliferating stream of variants that loses any contours with a third, fourth or fifth move. We may, however, be successful in the game even if we do not succeed in defining our decisions many moves in advance. Intuition comes to our assistance. And it is intuition that interferes when neuroscientists study the mechanisms that represent the most complex functional brain reactions. Sometimes everything seems to fall into place. However, such intuitive plausibilities may well blur our view. The fact is that, apart from certain correlations with some biological phenomena and some trivialities, we know hardly anything yet about mental processes in the human brain, which puts us into line with the astronomer: both of us can only recognize the recognizable.

The past and the present

Nowadays, it sounds trivial to say that the brain is the very locale or, even more appropriate, the generator of the soul, the place that produces the mind which in turn makes us hope, wish, feel and finally allows us to perceive ourselves as 'Self'. The brain and its activity have long been the objects of philosophical speculation. The first suggestion of interpreting the brain as the locale of the soul dates back to the Pythagorean Alcmaion of Kroton (around 500 BC), who dissected animals and, among other things, described the course which the optic nerve takes through our head. A hundred years later it was Hippocrates of Kos (460–370 BC) who reflected about the brain in a manner which seems surprisingly modern. He supposed that from our brain 'and exclusively from our brain' there derive our pleasures and also our fears, insomnia and any disturbances of consciousness. While this may be celebrated as a triumph of antique scholarship, it was really an intuitive guess. In contrast Aristotle (384–322 BC), a most shrewd observer of natural phenomena, considered the heart to be the seat of the mind, and this a hundred years after Hippocrates.

Today we know very much more about the brain, but the crucial questions of antiquity on what the soul, what thinking, consciousness, and feeling actually are, still cannot be answered. Under the keyword combination 'brain OR neuro', MEDLINE, a database on clinical and biological medicine, has offered about 28 000 original publication entries per year over the last decade. During that time, the tools of brain research have gained in refinement.

From roundworm to man

Like elsewhere in biology our neurobiological publications are increasingly dominated by genetic data, dull looking rows of letters and numbers. Decades ago

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such exactitude was barely present in physics. Now our knowledge of molecular interplay and cellular interrelation in nerve tissue is making rapid progress and precision, thanks to new laboratory techniques. Much of the progress has come from study of the rat, the mouse, the fruitfly *Drosophila* and the roundworm *Caenorhabditis*. These creatures are used simply because it is ethically unobjectionable to work with them, and their genetic make-up is relatively simple to manipulate; the relevance is because the structural and functional elements of the nervous system are similar in these animals and in man.

Many of the complex aspects of the brain can be studied in man using modern imaging techniques: nuclear spin tomography, positron-emission tomography and MRI, magnetic resonance imaging. Mental activity can be visualized as bright areas in virtual cerebral sections, even in 3D reconstructions, with resolution in the millimetre range. Thus, we are able literally to gather a picture of the mental conditions of a test person or a patient.

When we extrapolate these technical advances into an undefined – yet maybe not so very far – future, the question arises: will at some time the soul of man, 'the most sacred being we know of' (Hermann Hesse, 'Peter Camenzind', 1904) be laid open to the inquisitive eye of the scientist as totally as to that of the criminal psychologist or even the agent of any dictator to come? Can we hope or fear that there will, one day, be a conclusive answer to the perennial question of philosophy, 'What makes us human?' A question that is as profound as the answer to the question 'What is life?', a question which, over centuries and millennia, has been the object of philosophical speculation? There are good reasons to believe that, in the case of the brain and the subjectivity created by it, we are facing barriers of a fundamental kind due to the extreme complexity of the brain.

The issue of complexity

The human brain consists of about 100 billion nerve cells which, with thousands of synaptic informational contacts, form a very complex spatial net (Figure 1). Yet Gierer[1] has shown that a much simpler network of only 120 operational elements would already exhaust the capacity of the largest possible computer, should the machine run all the possible conditions of this model system. He has presented this notion in his 'finitist epistemology'. The 100 billion neurones in our brain, however, work in an analogue format, that is, they have an open number of conditions at their disposal. The determination of the state of such a system at any time would be astronomically far from a solution.[2]

In light of modern network theory, though, dealing with this problem may not be so hopeless. Obviously, the method of processing information in our brains is far more similar to modern artificial neuronal networks than to traditional computers with their serial operations. Such networks do not process numeral

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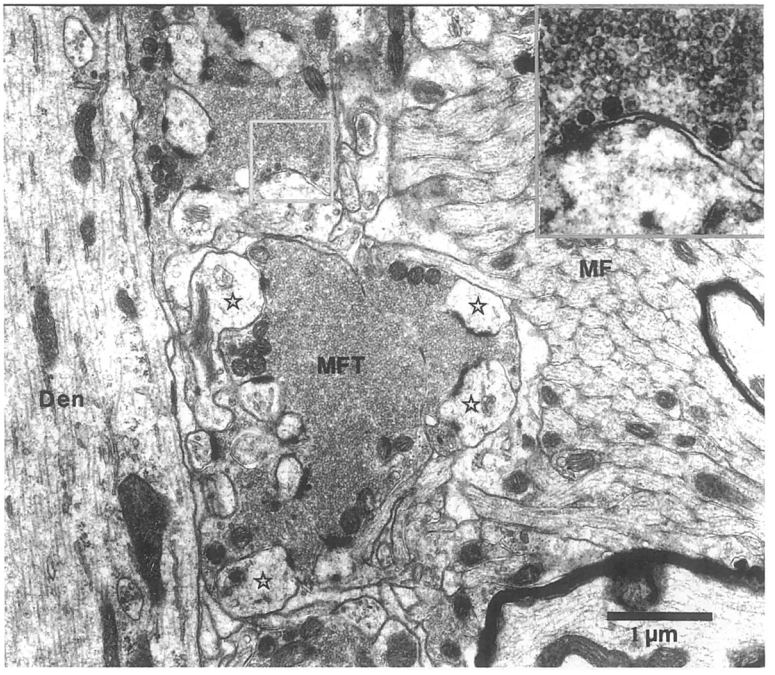


Figure 1. Electron micrograph of synaptic elements of the rat hippocampus, a phylogenetically old brain area. Left, a section through a dendrite (Den) is seen. Dendrites are processes of a nerve-cell-like antennae destined for synaptic information intake. A presynaptic ending of a so-called mossy fibre (mossy fibre terminal, MFT) is shown in the mid-position. Mossy fibres are axonal processes for information output, which form as presynaptic structures of complex synapses. The postsynaptic elements marked by an asterisk (*) show a membrane thickness at the synaptic area. The MFT element is endowed with small vesicles that contain a neuronal transmitter for signal transduction from the presynaptic to the postsynaptic element. Mitochondria are marked by black arrows. The insert (above, right corner) shows another synaptic structure, where transmitter vesicles appear to be 'empty' (amino acid transmitter?) or the larger ones form a dark core (transmitters of the monoamine or peptide type). The white arrow shows the synaptic cleft between the pre- and the postsynaptic area. (Kindly provided by Dr. G. Laube, Institute of Medical Neurobiology, University of Magdeburg.)

algorithms one at a time, but they form patterns, compare and combine them in an economical manner. Moreover, neuronal networks are self-organising and they adapt to many emerging requirements on the basis of an optimization process.

Despite arbitrary starting conditions, and under constant feedback from the outside, the networks generate their own rules of inner interlocking. An

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epistemological understanding of such regularities may drastically simplify an analysis of our mental network.

The evolution of this complexity

It would, however, be wrong in principle to assume that our brains are completely unstructured at the time of our birth. Genetics determines most of the complex activities of the nervous system. We can see this in other organisms; for instance, it dictates the specific flying technique to a newly hatched fly, and tells the weaverbird how to construct its artful net. The brains of different people look very much the same and this holds even at the microscopic level. Evolutionarily developed and genetically dictated construction plans are responsible for this phenomenon. However, there are even conspicuous differences due to the genetic diversity of individuals. For instance, regional variations in the thickness of the cerebral cortex are rather more similar in twins and especially in identical twins than in unrelated individuals[3] (Figure 2).

Whilst some cellular cross-connections may be determined quite precisely if necessary by their biological purpose, in other cases the synaptic connections of neuronal structures are adaptable to the modifications that are fundamental to learning.

The modular structure of brains made it possible to allocate more or less brain matter in relation to the required function as it developed with the evolution of the species. As a consequence, the olfactory brain area of animals with an exceptionally fine sense of smell is relatively large, as is the cortical region responsible for the auditory faculties in bats and dolphins, which navigate using echolocation.[4] In human beings, the pre-frontal cerebral cortex is specifically spacious; this is, the part of the brain concerned with higher mental faculties – the ability to act according to a preconceived plan, the awareness of 'self', directed attention and the coordination of emotion and reason. Evolution, and especially that of our cerebral abilities, has placed us on a markedly higher mental level than any other animal. But when we compare our brain with that of our nearest animal relatives, it is mostly a difference in quantity, chimpanzees have a mere quarter of our brain weight, but the basic structural components, however, are the same.

It has recently been reported by Chenn and Walsh[5] that mice in whom an additional gene for the membrane protein β-catenin has been inserted, develop a significantly larger cerebral cortex. In fact its surface has to fold up to fit into the tiny skull (Figure 3). Mice normally have a smooth brain surface, whereas these transgenic mice show a furrowed surface, like that of humans and many other animals. Whether this increase in the size of the mouse brain results in a higher cerebral performance, is still unclear. Equally unclear is the basis for the sharp

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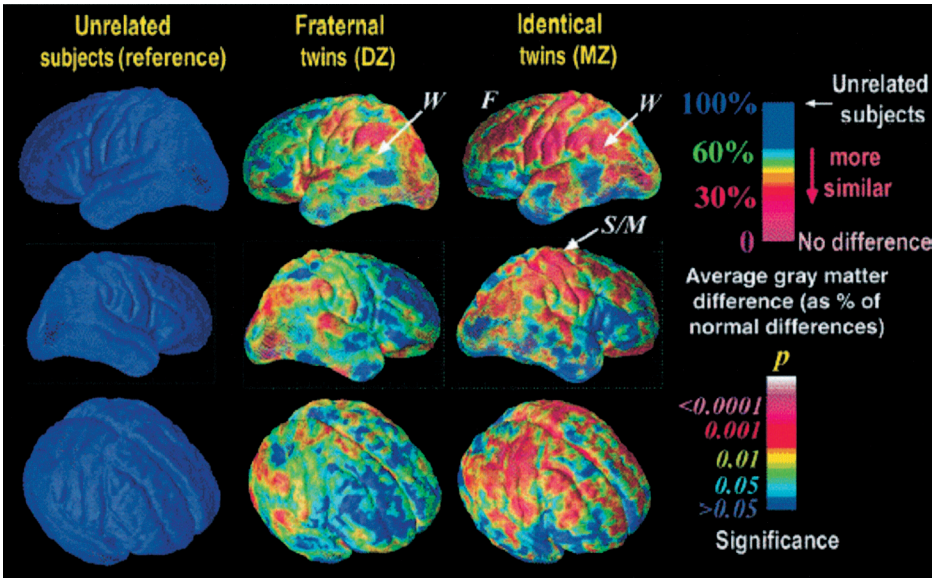


Figure 2. Three-dimensional maps of grey matter and models of cortical surface anatomy were derived from magnetic resonance images. Differences in the quantity of grey matter at each region of cortex were computed for identical and fraternal twins, averaged and compared with the average differences that would be found between pairs of randomly selected, unrelated individuals (blue, left). Colour-coded maps show the percentage reduction in intra-pair variance for each cortical region. Fraternal twins exhibit only 30% of the normal inter-subject differences (red, middle), and these affinities are largely restricted to language and spatial association cortices. Genetically identical twins display, in a large anatomical band, only 10–30% of normal differences (red and pink) suggesting strong genetic control of brain structure in these regions, but not others (blue: the significance of these effects is shown on the same colour scale). (P. M. Thompson *et al*., (2001) *Nature Neuroscience*, **4**, 1253–1258, reproduced with kind permission of the authors.)

increase in cerebral cortex during anthropogenesis. Does it really stem from changes in a few genes or even a single gene, for instance in the β-catenin gene?

The brain–mind issue

Our capacity to experience enables us to learn about the activities of our brain quite directly, without any necessity to know about the mechanisms of its working. We experience our cerebral conditions from a 'me'-perspective, that is we recognize them and sense them as a familiar face, a will, a pain or pleasure, as red or cold or quiet or beautiful. And all the while we need not even know that

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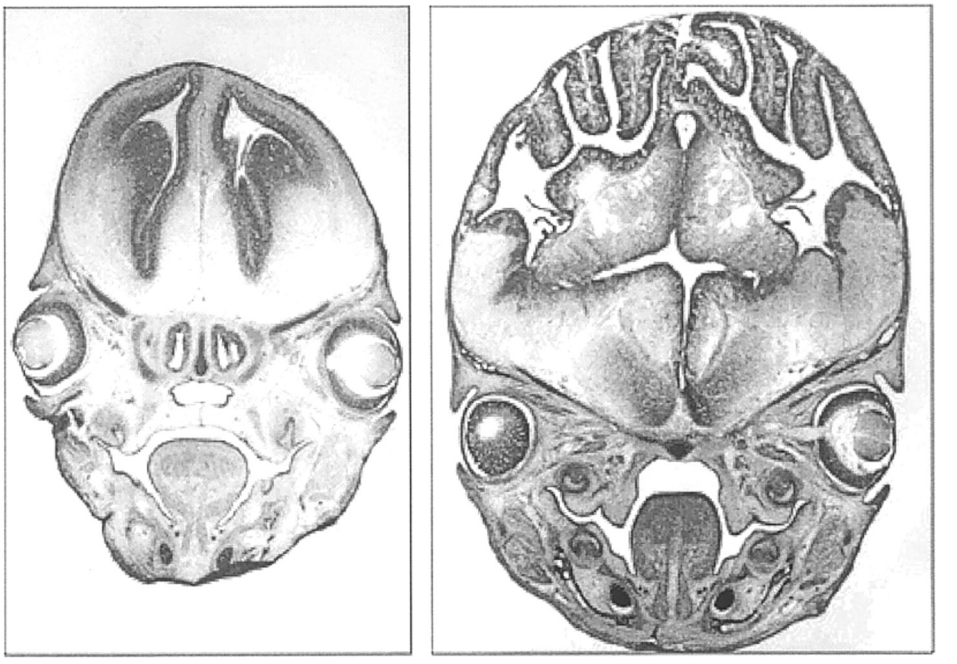


Figure 3. Coronal section through a brain of β-catenin transgenic mouse compared with wild-type littermate control. The brains from transgenic mice (right) are enlarged overall and have a greatly increased surface area without a corresponding increase in thickness (A. Chenn and C. A. Walsh (2002) *Science*, **297**, 365–369, reproduced with kind permission of the authors).

this experience happens inside our skull. If the reverse is equally true, namely that the knowledge of the cerebral mechanisms does not provide us with an understanding of what exactly experience is, then this would lead to the following implication. Brain research concerned with neuronal activity, may not be able to decode the complex aspects of the brain's activity. Indeed, what has been brought to light by neurobiology so far has strictly speaking been mere biological correlates of experience. Even the 'views into the life of the mind' by means of modern imaging techniques, do not offer more. Someone who has been colour-blind from birth would never be able just to guess at how a non-colour-blind person senses the colours, or how such a person feels about them. Likewise, it would be futile to explain the experience of a symphony to someone born deaf, or compassion to an unfeeling psychopath. And even if we had the most precise insight into the structure and mechanisms of the brains of a tit, a white

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shark or a female cross-spider we will never be able to feel how these animals experience nesting, the pleasure of tearing their prey apart, or the advances of the courting spider male. We would not even be in the position to gather from our scientific studies, whether these animals are capable of subjectivity. To use the metaphor of the computer, it is as if we were missing the monitor, which should translate the activities inside the micro-chip into a virtual, and thus directly perceivable, format, be it as a display of word processing, a game of chess or a flight simulation. Perhaps we could solve the problem if we constructed a kind of interface. By this we should be able to log directly into the brain of another human being or an animal, and thus experience their inner world in an entirely unmediated form, co-experiencing another being's world so to speak. Yet, as far as we can see this is just wishful thinking, and nothing feasible is in sight.

The correlation of the real and the virtual world

Since the brain is the scientifically perceivable base for any mental process, then modifying this material substratum should bring about modifications in the mental processes. This is beyond doubt the case. Strokes and brain tumours, neurotropic pharmaceuticals and electric stimulation of the brain show that this is so. On an experimental as well as on a clinical level the brain is accessible through an internal cerebral 'colloquial speech', i.e. membrane-electric and chemical 'languages'. The membrane-electric signalling mode is used by nerve tissue to encode information on the cell surface and to pass it on via the cell and its dendrites; the chemical mode serves to transmit messages to the subsequent cells via informational cell contacts, the synapses. Either of these communication modes provides us with a direct access to the virtual reality of the mind. A fine electrode positioned in the brain tissue accesses electric signals and can also be used for the stimulation of a targeted area. Depending on the location of the electrode's tip, motor actions, feelings or elements of more complex experiences can be retrieved. Likewise we can administer signal substances and thereby influence brain functions. Drugs may modify the effects of these signal substances: cocaine, for instance, blocks the mechanism necessary to reabsorb the neurotransmitter dopamine.

These possibilities of intervention also tell us something about the conditions of the natural substrate, the brain. In research this is often used as a principle of further investigation into any mechanisms of effects. Which brain sites are involved in specific mental or emotional conditions, can be studied, for instance, by electric stimulation of the suspected areas. Agents such as transmitters or intra-cellular signal molecules and their analogues allow us to trace their molecular receptors and to decode whole chains of effects. We have known for some time that transmitters of the monoamine type (dopamine, noradrenaline, and

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serotonin) play an important role in the formation of affect. This is the operating basis of most of the neuro- and psycho-tropic substances used in medicine.

Some research suggests that individual traits of character or temperament find their explanation in molecular peculiarities in transmitter receptors or membrane-related transmitter transport mechanisms. These findings seem to open up a pathway to the molecular-genetic understanding of an inheritance of personal traits, as has been argued by classical genetics. Twin studies have shown that differences in character are, to a substantial percentage, rooted in genetic factors.[6] Recently, it was found that people with a low proneness to anxiety differ in the control region of a serotonin transporter gene.[7]

The door seems to have opened to the definition of personality-determining genes. In the near future, the genes we are given will be made transparent for everybody on a chip and for the corresponding computer processing. We need to consider whether we would not prefer to claim our right to ignorance! On the other hand, the availability of this insight into individual genetic advantages or potential dangers provides us with enormous possibilities. We have here again the ethical ambivalence of scientific knowledge similar to that we encounter in biotechnology or nuclear physics.

Brain research and theory-formation of the humanities

The importance of our brain as the hardware correlate for the virtual world of our mind, will not be in doubt. And yet, the 'upper floors' of our structure of epistemology, the humanities and social sciences, and often philosophy too, show some reservations towards brain research. The sheer mass of findings explaining brain-physiological and mental phenomena, cannot be covered even by the neuroscientist. Specialization and sub-specialization are the consequence. For the non-neuroscientist, the extraction of the essentials of brain research is a formidable task. Inter- and trans-disciplinary action is needed. However, most of the time the 'doers' in scientific research do not escape their disciplinary area. Yet it goes without saying that besides our extraordinary learning capacity nature and the natural history of man have to be taken into account in the humanities and the social sciences, otherwise we end up with half-knowledge and incomplete images of the human being. The brain is not a kind of plasticine that can arbitrarily and unlimitedly be shaped and re-shaped by the environment, as some sociological approaches want to make us believe. On the contrary, the biological-genetic predispositions display specific, and at the same time individual, differences, which have emerged in the process of natural history and supply a distinct framework. To ignore this was the political doctrine of the countries of the former Eastern bloc; the attitude, however, is still to be found in many varieties of societies of any political or ideological colour. What we need is a sense of reality, first of all in the sciences, if we want to be more successful when dealing

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with human beings. But then this sense is equally important when we ponder our self-definition; that is, the question 'What makes us human?'

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