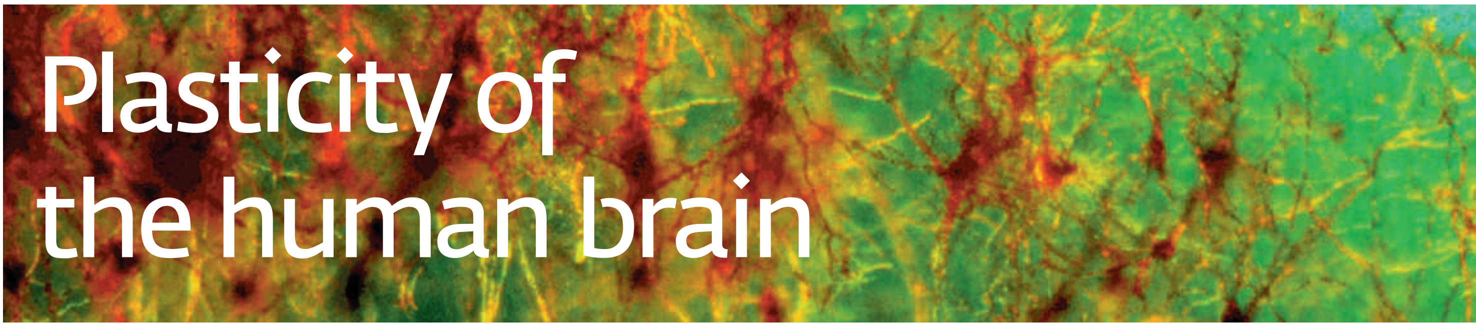


Plasticity of the human brain

"WE NEVER USE THE SAME BRAIN TWICE"

The human brain is constantly changing. Whether it is responding to experiences, learning skills or recovering from injury, the function and structure of the brain are in a continual state of flux that scientists refer to as plasticity, which continues throughout life.

Most of our understanding of plasticity comes from studies on animal brains. With advances in non-invasive brain imaging, however, the human brain has become accessible for investigations into plasticity. For example, we have seen that the area of the brain involved in navigation is larger in London taxi drivers than in control subjects[1] and that learning to juggle can reshape areas of the brain involved in movement. There is also indirect evidence that neurons can regenerate, even in adult human brains[2].

IMAGING PLASTICITY

In the past few decades, various non-invasive brain-imaging methods have been used in studies on brain plasticity.

Structural imaging. Certain types of magnetic resonance imaging (MRI) can reveal the structure of grey matter[3] and white matter[4]. These techniques allow scientists to probe neuronal density in various areas of the brain, to study the size and layout of connections linking regions, or to assess structural changes owing to learning (Fig. 1), injury or disease.

Functional MRI (fMRI). This technique logs changes in brain function by measuring changes in local blood flow or haemoglobin oxygenation (Fig. 2). fMRI can measure changes in the brain's pattern of activity after injury or learning[5].

Molecular imaging. Finding the molecular basis of plasticity in the human brain is a new idea. It involves, for example, looking for changes in the chemical receptors or transporters that induce or prevent plasticity. One approach, positron emission tomography (PET), uses radioactive tracers that attach to chemicals to track how they are made or distributed in the brain. Another, emerging approach is non-invasive optical brain imaging, which uses fluorescent tracers[6].

These techniques have helped reveal the plastic nature of structures in the human brain. However, our understanding of the underlying processes is still insufficient, and several challenges must be tackled before we can comprehend how the human brain changes with experience and time. To meet these challenges, new methodological developments will be necessary.

OUTSTANDING CHALLENGES

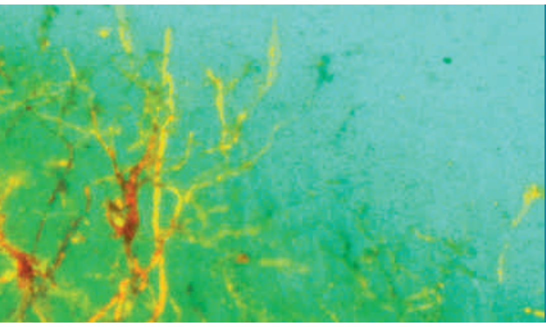
Linking to physiology. It is not easy to link brain-imaging studies to the underlying neurophysiology. For example, there is the so-called inverse problem of fMRI. This technique measures 'vascular signals' — changes in blood flow and haemoglobin oxygenation — that are assumed to be closely related to neuronal activity (for example, action potentials of neurons, and inhibitory or excitatory synaptic activity), but it is unclear how[7]. The problem is compounded by the fact that fMRI has a temporal resolution in the order of seconds, which is not fast enough to reflect the millisecond activity of individual neurons. How, then, to measure activity and be closer to neuronal processes? One way is to combine fMRI with other non-invasive tools with better temporal resolution, such as electroencephalography (EEG). Using fMRI and EEG together, recent studies have been able to identify neurons firing in human subjects and the potential underlying generator structures[8].

From single sites to networks. No brain area works in isolation. Cognitive functions are managed by networks of interconnected brain areas, some of which fulfil specialized subtasks. Although brain mapping — allocating functions to specific brain areas — is meaningful, it needs to take into account the role of the area within the entire network or 'connectome' of brain areas. Several new neuroimaging approaches can show the linkage of brain areas into networks; for instance, diffusion tensor imaging (DTI), which is a variant of MRI, allows imaging of structural connectivity, while functional connectivity can be assessed through resting-state fMRI.

Molecular underpinnings. In animals, researchers can examine the molecular processes that mediate plasticity by opening up the brain. In humans, there is a need for non-invasive methods. PET, for example, is already successfully employed in humans — but rarely for studies on brain plasticity. Integrating PET with MRI is one promising way forward for plasticity research, allowing simultaneous recording of blood dynamics and molecular responses in the brain[9].

Genetic roots. Geneticists are interested in finding links to plasticity in the brain; indeed, many studies have highlighted the molecular machinery behind Alzheimer's or Parkinson's disease. Whole-genome analysis is now technically possible and is decreasing in price; combining this both

Researchers at Max Planck Institute for Human Cognitive and Brain Sciences are studying how perceptual learning, as well as learning new motor skills, is associated with brain reorganization, which can be assessed non-invasively with structural and functional magnetic resonance imaging in human subjects. Recently, it has been shown that different brain areas are engaged sequentially, with prefrontal areas being associated with long-term learning (Taubert *et al.*, *J. Neurosci* 2010, in press).



- The human brain changes throughout life in response to experience — a process called plasticity.
- Several different techniques can be used to study brain plasticity, including measuring changes in brain structure, function and molecular events.
- Improvements in these techniques will help us understand how brain plasticity relates to learning or how to aid recovery in brain-injured patients.

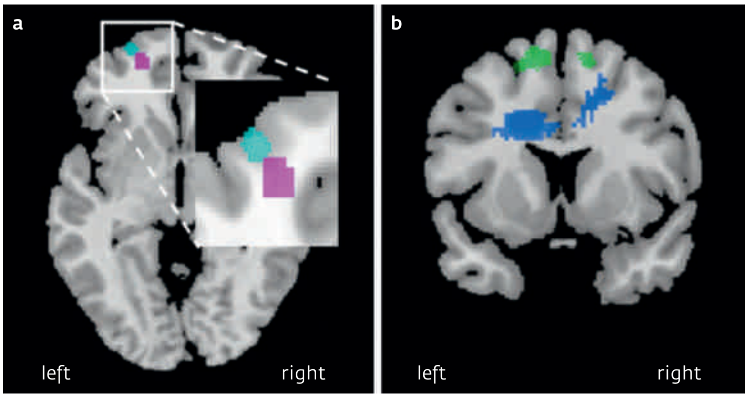
with tests of cognition or behaviour and with brain imaging could yield powerful insights into how genetic differences shape the brain, and to what extent the plasticity is programmed genetically.

Effects of ageing and social setting. The effects on brain plasticity of genetic and molecular factors cannot be disentangled from the effects of ageing. For instance, certain genes are expressed preferentially at certain ages. Disorders that are more prevalent at older ages, such as Alzheimer's and Parkinson's disease or stroke[10], can also affect the plastic capacity of the brain. An individual's social setting is also relevant to brain plasticity. Studies of the 'social brain' are becoming more widespread and will help us understand how our social world can influence our biology.

Theoretical advances. The field of plasticity research is still relatively new, and mainly involves accumulating data to test hypotheses. As the field matures, it will be important to formulate conceptual frameworks to cement findings into a larger scheme. Computational models of brain activity and plasticity are a promising way forward, developed in conjunction with empirical research.

Research into plasticity might result in many useful applications. Both individual learning and larger institutional educational courses could benefit from a better understanding of the underlying neural mechanisms. Moreover, there are potentially important clinical implications: new drugs and treatment protocols could boost brain plasticity and, hence, the recovery of brain function. With knowledge of the genetics of plasticity, we could organize patients or study subjects by genotype and test treatments accordingly. A fuller understanding of the brain's electrical rhythms might allow us to use electric or magnetic stimulation to change activity patterns in different areas, thus improving learning or aiding recovery from injury. The continuing improvements in brain-imaging techniques will allow these ambitions to be realized.

Fig. 1 | Brain MRI scans

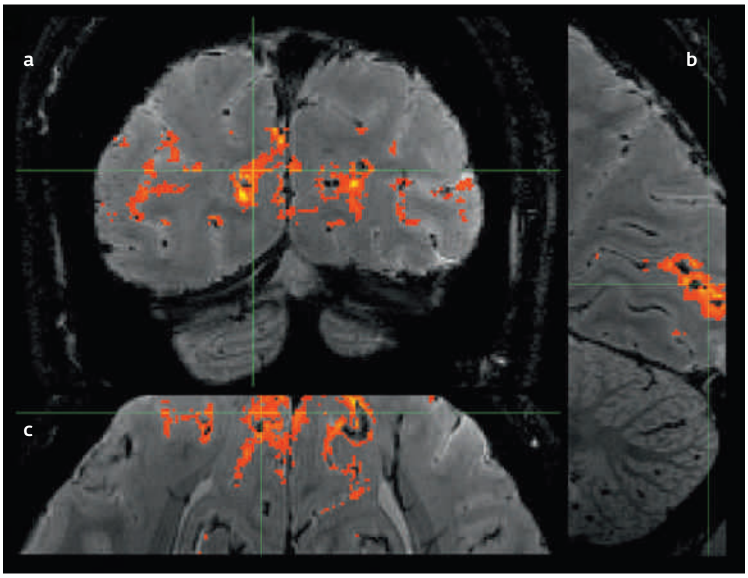


Training-induced structural changes observed in top-view (left) and front-view (right) brain MRI scans. With improving motor performance during the learning of a balancing task, structural changes in the grey (cyan, green) and white matter (magenta, blue) in the prefrontal cortex and the supplementary motor areas occur. Interestingly, some of these structural changes are only transient while other seem to be permanently linked to improved function.

(Adapted from ref. 11)

left | Electroencephalography (EEG) can be used in conjunction with fMRI to improve the latter's temporal resolution.

Fig. 2 | Examples of fMRI scans



Examples of (a) coronal, (b) sagittal and (c) transversal fMRI brain scans obtained at a field strength of 7 Tesla showing the technique's sensitivity to local changes in haemoglobin oxygenation. The spatial resolution is 0.65 x 0.65 x 0.65 millimeters.

Fig 2: courtesy of Robin Heidemann and Bob Turner, MPI, Leipzig

For references see pages 94 and 95