The role of magnetic resonance imaging in investigating brain function

Historical development and future perspectives

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Mijnheer de Rector Magnificus, geachte dames en heren,

Biomedical nuclear magnetic resonance (NMR) imaging, now more commonly known as MRI has undergone a significant development since its inception in the late 1970s. This encompasses both the technical capabilities and the breadth of application. This lecture will describe how we reached our present state of development and will make some predictions regarding future prospects.

Historically the NMR phenomenon was independently discovered by two groups: those of Purcell at MIT, and of Bloch at Stanford, who published their results in 1946. They were jointly awarded the Nobel prize for this discovery in 1952. Prior to this achievement important work was performed by the Dutch physicist Gorter, who only failed to demonstrate NMR due to an unfortunate choice of sample, and by the Russian physicist Zavoisky working in Kazan, who was the first to demonstrate the closely related phenomenon of electron spin resonance, and may have observed an NMR signal as early as 1941. Unfortunately the authorities in Moscow would not believe his results and the difficult circumstances of that time prevented their dissemination to the wider world.

What do you need to perform Nuclear Magnetic Resonance? As the name implies a magnetic field within which the sample is placed, and some method of developing a resonance amongst the nuclei of the sample. Not all nuclei will display NMR: for this to be possible they have to possess a magnetic moment, i.e. behave as small magnets. A necessary corollary of this is that they also have angular momentum, or spin. The natural motion of such spins in an external magnetic field is to precess, rather like the motion of a spinning child’s top in the earth’s gravitational field.

The nucleus with which we are concerned in this talk is the proton in the water molecule (or the ‘H’ in H2O), as this forms the basis for almost all imaging experiments. If you were to interrogate the state of an individual proton in a magnetic field then you would find it precessing about that field with a characteristic frequency called the Larmor frequency, which is directly proportional to the strength of the main magnetic field. The z-component of its angular momentum will be either parallel or anti-parallel to the direction of the main magnetic field. For a sample having many protons there will be more in the parallel than in the antiparallel state, as the former is energetically more favourable. The sample will hence
Figure 1
Schematic representation of proton spins precessing in an external magnetic field.

Figure 2
The application of a radiofrequency magnetic field at the Larmor frequency can be used to bring the magnetisation into the transverse plane by means of a 90° pulse.
possess nuclear magnetisation, with a magnetisation vector pointing parallel to that of the main magnetic field, as shown in figure 1. The external application of a circularly polarised magnetic field at the Larmor frequency, and perpendicular to the main field, will cause the magnetisation vector to precess about both fields. If the duration of this radio frequency pulse is chosen such that the magnetisation vector is rotated through $90^\circ$ (c.f. figure 2) then the magnetisation will induce a voltage in a coil placed adjacent to the sample in a similar way to the function of a dynamo. Once the magnetisation is in this transverse plane local differences in the frequency of rotation caused by inhomogeneities in the main magnetic field will cause the total signal to decay owing to a loss of phase coherence. The time constant for this decay is called $T_2^*$. The effects of these inhomogeneities can be reversed by the application of a second radio frequency pulse, typically of $180^\circ$ angle, at some time $\tau$ after the first. This will flip the magnetisation over, so that spins that developed a phase lead or lag of $\phi$ during the period $\tau$ will have a phase lead or lag of $-\phi$ immediately after the second pulse. Hence after a further period $\tau$ all spins will be in phase and give a maximum signal. This is known as a spin echo, and is illustrated in figure 3. The signal intensity at the centre of a spin-echo is attenuated with a time constant known as $T_s$, the spin-spin relaxation time, which reflects the degree to which the spins exchange energy, a process that is irreversible. The third relaxation time which is necessary to characterise a sample is known as $T_1$, and reflects the time required for the magnetisation to return to its original state prior to being perturbed. It does this by giving up energy to its surrounding, and hence $T_1$ is known as the spin-lattice relaxation time.

Two developments provided the impetus for the development of MRI: the first was the realisation in 1971 that the NMR relaxation characteristics of tumourous and healthy tissues differ markedly, the second was that it is possible to make simple projection images by means of interrogating the NMR signal in the presence of a magnetic field gradient. It was hence clear that the goal of in vivo imaging on the basis of NMR was desirable, and an indication was given as to how that goal could be achieved. The pioneers of MRI in the 1970s were confronted with the problem of how to get from a 1D projection or shadowgram to sectional images of diagnostic quality. This problem was compounded by the relatively poor homogeneity of the main magnetic field in whole-body magnets, which meant that the
Figure 3

After a 90° pulse the signal will decay with a time constant $T_2^*$ owing to the presence of main field inhomogeneities and to $T_2$ decay. The effects of the inhomogeneities can be reversed by using a 180° refocusing pulse to generate a spin-echo at the time $2t$ after the excitation.

Larmor frequency varied with position. A great deal of ingenuity was expended in the search for viable techniques: of note is the echo-planar-imaging (EPI) method of Mansfield, which embodied the then unrealisable dream of obtaining images within the timescale of tenths of seconds, and the slower but more robust spin-warp technique of Edelstein et al..

After spin-warp everything changed, and enormous amounts of money flowed into the methodological development of MRI from commercial companies that were afraid of missing out on a revolution. This meant that the technique was catapulted from the laboratory to the clinic within a few years, and that by the mid 1980s the majority of imaging techniques currently in use had been proposed if not yet implemented on commercial scanners. By the late 1980s MRI was established in the clinic for performing studies of anatomy, and technological developments had advanced sufficiently that a small number of scanners worldwide were capable of performing EPI. The dream that EPI would ever prove capable of providing anatom-
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ical images of diagnostic quality was not then to be realised. However the availability of EPI provided the ability to acquire large amounts of data within a short period of time making both parametric mapping and dynamic studies possible. At this point MRI moved beyond providing non-invasive images of anatomy that largely reflected what would be seen if the object under investigation were to be sectioned and viewed with the naked eye, and started to provide parametrical and functional information. Two major and exemplary developments of this nature were those of functional MRI and of diffusion MRI. The remainder of this lecture will be primarily concerned with these topics.

Diffusion Imaging

Most people have a vague idea of what diffusion is. For the physicist it is inextricably linked to the concept of Brownian motion: if smoke particles are observed under a microscope it will be seen that they are buffeted by invisible objects. These are the molecules in the air. The higher the temperature the greater the speed of the air molecules and the greater the diffusion driven displacements of the smoke particles. Diffusion occurs in both gases and liquids. MR experiments can be made sensitive to diffusion by using pulsed magnetic field gradients to impart a phase change to the spins that is proportional to position. At some later time the phase change is reversed, and stationary spins will be unaffected by the whole procedure. Diffusing spins will not in general have a phase change of zero, and the resulting loss of coherence with other spins will lead to a net loss of signal. Diffusion MRI was developed in the mid 1980s, but remained to a large extent a method without an application until Moseley et al. attempted to measure temperature changes in brain infarcts. They found dramatic increases in signal intensity, which were incompatible with changes in temperature. Since then it has been realised that diffusion MRI offers a very powerful probe of tissue microstructure. The mean displacement of water molecules in a diffusion MRI experiment is about 10 μm, and the signal intensity is exquisitely sensitive to changes in the displacement. In the case of brain infarction cell swelling of about 10% in volume occurs within minutes of the insult. It is now standard practice to scan patients with suspected infarcts using diffusion weighted imaging (DWI) upon arrival in hospital. The EPI imaging method is generally used for this, as it is largely insensitive to
motion. Although EPI has limited spatial resolution it is sufficient to detect large infarcts.

The biophysics underlying the contrast in diffusion imaging is fairly complex. It has to be considered that there is an intra- and an extra-vascular compartment, linked via the endothelium in the capillary walls, and furthermore that the extra-vascular compartment is further subdivided into intra- and extra-cellular spaces separated by a semi-permeable cell membrane. The contrast in all diffusion imaging is determined essentially by the molecular displacement, which in turn will depend on the specific diffusion environment within a compartment, the level of impediment presented by the barriers between compartments as well as the degree of exchange. In biological systems it is far from self-evident that the motion of water molecules will be solely Brownian in nature. In blood vessels there is directional flow, which can be randomised by the frequency at which the vessel changes orientation. These considerations have lead to the term apparent diffusion coefficient (ADC) to be widely used in measuring diffusion coefficients in tissue. For the diffusion of water it is generally assumed that the contribution of the intra-vascular compartment can be neglected. The most sophisticated mathematical models then consider a two compartment system with exchange, and are forced to make a number of simplifying assumptions regarding the nature of the tissue morphology. The change in ADC occurring due to infarction is then determined from an increase in extra-cellular tortuosity, combined with a shift in water to the more restricted intra-cellular compartment. The measured change in ADC is, however, still somewhat greater than predicted. The difference has generally been attributed to additional non-Brownian processes within the cell (micro-streaming) that would cease once the cell had been deprived of energy. There has been a recent report that diffusion within large cells at least is Brownian: if verified then there is still a component of the ADC change for which no known mechanism exists. This situation exemplifies many of the difficulties encountered in applying mathematical models to biophysical problems: simplifying assumptions have to be made in order to make the problem tractable. This applies for example to the assumed morphology of the cells. Furthermore some important parameters are not easily measured, such as the intracellular diffusion coefficient in the absence of restriction, whilst others are currently not quantifiable.
Although DWI has become of considerable importance in the clinic, it is another observation made early on in its development that has provoked the greatest interest amongst neuroscientists. Diffusion weighting is achieved by the application of pulsed magnetic field gradients, and implicit in the concept of a gradient is also that of an inherent direction: the mean displacement along a particular direction determines the signal attenuation. For an isotropic medium such as a glass of water the result is self evidently independent of this direction. However, it was found that the white matter of the human brain is sufficiently anisotropic to produce measurable effects in DWI, as shown in figure 4. This anisotropy arises because of the ordered nature of the arrangement of the cells on the spatial scale of an imaging voxel, i.e. of several millimetres. The myelinated axons that are a major constituent of white matter have an approximately cylindrical symmetry, and many thousands of these may be oriented approximately parallel to each other. Given that the cell membrane is semi-permeable it is clear that diffusion parallel to the long axis of the axons will be easier than in the perpendicular direc-

Figure 4
Molecules that diffuse freely will have an expectation value for the displacement given by a sphere. In the presence of restriction, for example within a cell, the diffusion will no longer be isotropic
tion, where barriers to diffusion are more likely to be encountered. The degree of attenuation recorded in a DWI experiment will hence be affected by the extent to which the orientation of the diffusion weighting gradient is parallel to the dominant direction of the axons.

Initially this anisotropy was regarded as an artefact, as it represented a confound for the reliable detection of infarcts. However it was soon realised that valuable information concerning the white matter could be gleaned from this data. The anisotropy is described in mathematical terms by the diffusion tensor, and with the development of diffusion tensor imaging (DTI) a method was developed whereby the full tensor for each pixel could be calculated, derived from the data acquired from at least six measurements of the diffusion induced attenuation along independent axes. Provided that there is only one dominant diffusion direction within a voxel the tensor provides a complete description of the anisotropy, and from it ellipsoids of constant displacement can be generated. A number of scalar values can be derived from the tensor with which the diffusion can be characterised. The simplest of these is the trace, which measures the average diffusivity along the three main axes of the tensor. This provides a measure of the diffusion, independent of the anisotropy, and may be measured most simply by averaging the diffusion attenuation along three orthogonal axes, without even needing to acquire sufficient information to calculate the full tensor. In this way the confounding influence of anisotropy can be removed from diagnostic images. The fractional anisotropy index (FAI) is also noteworthy in this context as it provides a scalar measure of the degree of anisotropy.

The importance of DTI is difficult to underestimate, as for the first time it is possible to examine the fibre pathways in living tissue. The culmination of this effort is tractographic imaging, which is no more than a post-processing method for DTI data. In most tractographic methods the direction of the major axis of the diffusion tensor is interpolated onto a fine matrix, and the course of the fibre tracts then estimated. The images produced are impressive, but it should be emphasised that there is no guarantee that the tracts shown correspond identically to those in the living object, they just represent a likely solution that is consistent with the measured data. The presence of a lesion in white matter will generally cause a disruption of the axonal tracts, and the degree of impairment can be measured with DTI. The
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extent to which the connection between grey matter regions has been disrupted can be correlated with loss of function. It has also been shown that some diseases such as schizophrenia which generate no obvious lesions give rise to a reduction in white matter anisotropy.

It is hence clear that an important aspect of DTI data is the information it provides regarding the connections between distant grey matter regions. This may be termed anatomical connectivity, and there is considerable evidence that this is related to the functional connectivity. Put simply, cells that fire together wire together, and so complete anatomical connectivity maps of the brain should be expected to provide a description of the functional connectivity, showing whether, for example, two regions are directly connected, or only via a third region. The effective connectivity describes how networks of regions work together to perform a specific task. If you are just interested in determining how well two grey matter regions are connected then you do not necessarily have to worry about the precise course of the white matter tract between them. It is possible to use the information contained in the DTI map in a probabilistic fashion, for example by allowing a large number of particles to take a random walk through the brain, with the probability of a jump in a given direction being determined on the basis of the diffusion tensor. In this way it is possible to obtain semi-quantitative values for the strength of the anatomical connectivity between regions of grey matter.

As we have seen DTI has advanced to a powerful tool for studying the living human brain. However it is not without its difficulties, both technical and fundamental. One of the foremost technical problems that confronts the experimentalist is that of bulk motion. Any diffusion weighting experiment is sensitised to molecular displacements on the scale of tens of micrometres. Diffusion is a stochastic process and results in a signal attenuation arising from the loss of phase coherence of the signal from molecules each having an individual history of motion in the presence of a magnetic field gradient. Bulk motion is coherent, and many molecules will experience the same effective motion. Consequently bulk motion results in a phase change of the signal. Translation gives rise to a phase shift, whereas rotation will give rise to a phase gradient that is perpendicular both to the axis of rotation and to the direction of the diffusion-weighting gradient. The effects of such phase changes on the imaging experiment can be catastrophic as almost all imaging
experiments use phase information to encode spatial information, and some rely heavily on a maintenance of phase coherence in order to function correctly. The result of bulk motion on many commonly used imaging experiments when they are combined with diffusion sensitisation is to scramble the spatial information, or to irreversibly extinguish signal. The post-hoc correction of scrambled spatial information is possible if the experiment is designed so as to additionally record the degree of phase change associated with bulk motion: the so-called navigator echo correction. However signal extinction may only be corrected if the experimentalist is in a position to intervene and correct the phase errors induced during the diffusion weighting prior to the imaging part of the experiment. This means that in the space of a few milliseconds an MR signal has to be digitised, the phase errors induced by the diffusion-weighting recorded, and the necessary phase modifications made via the application of an appropriate field gradient pulse to correct for phase gradients arising from rotation, and of a phase shift to correct for translation. A correction of this nature allows imaging methods with a much higher spatial resolution to be used than is currently the case.

The whole assumption upon which DTI is based is that there is a single dominant group of fibres sharing a common orientation throughout a voxel. If this is not the case then the tensor calculation will produce incorrect information. This situation may arise if fibres either cross or kiss. Kissing or abutting fibres may ultimately be resolved by improving the spatial resolution. However crossing fibres represent a more serious problem which may only be resolved by extending the tensor formalism. If the diffusion weighting gradient is applied in multiple directions then the resulting data may be analysed in terms of a linear superposition of the signal from individual fibre orientations, provided of course that the water molecules cannot diffuse between regions of differing orientation. Such experiments are generally performed with a very strong diffusion weighting in the belief that the signal most restricted in its diffusion, and hence least attenuated by the diffusion weighting, will express the greatest anisotropy.

So while great progress has been made with DTI and tractography there are still unresolved issues in data acquisition and analysis. It would be desirable to acquire data from the whole brain with a high spatial resolution and sensitivity, without motional artefacts, and with a large number of diffusion weightings. Once this has
been achieved we still need to find adequate means to express the degree of connectivity between grey matter regions. Furthermore we need to find experimental tests as to whether grey matter regions are really connected or whether there are multiple kissing fibres giving rise to the illusion of connection. Finally, we need some measure of certainty that the white matter tracts that we are depicting so beautifully, really run along these paths.

**Functional Magnetic Resonance Imaging**

Functional magnetic resonance imaging (fMRI) has become one of the workhorses of cognitive neuroimaging. Historically, observations made in the 19th century indicated that regions of the brain that are functionally active experience an increase in blood flow. It was also known that there are histological differences between different regions of the brain, ideas that culminated in the Brodmann atlas. It is now accepted wisdom that a degree of functional segregation exists within the brain, i.e. specific regions are required for specific functionalities, a concept supported by the close correlation between specific brain lesions and the absence of certain abilities, such as speech or motoric control. The fundamental paradigm of cognitive neuroimaging is for the brain to perform at least two tasks, one of which may be no more than being in a state of rest, and to measure differences in some parameter which may be spatially localised and changes its value with the degree of brain activation. If there were brain areas corresponding to all human activities then these would have long been identified, but while on the one hand functional segregation may be essential, particularly to process input from our senses, or to control our movements, on the other hand if it were the sole basis for functional architecture then this would be massively inefficient. Hence the brain requires structures that reflect abstraction, and when investigating the way in which the brain performs a given task it is desirable to understand how networks of activated regions interact. As with DTI we are again concerned with connectivity.

As a physicist one is also interested with how brain activation can be measured with fMRI, and what the characteristics of this technique are. As indicated earlier the origin of the fMRI signal is the change in blood flow that occurs in the proximity of an activated region. The change in signal intensity occurs as a result of the
change in magnetic properties of blood as a function of its oxygen content. There are three classes of magnetism, ferromagnetism as exhibited by iron, nickel and some other materials: here a strong attraction towards a magnet is generated, something we are all familiar with, and indeed the greatest hazard associated with MR-systems; paramagnetism, in which there is a weak attraction towards a magnet, and finally diamagnetism which generally expresses itself as a still weaker repulsion. Now most tissue is weakly diamagnetic, including oxyhaemoglobin, however deoxyhaemoglobin is paramagnetic. Hence, in going from the arteries, which deliver oxygenated blood to tissue, to the veins, which return deoxygenated blood to the heart and thence to the lungs, there is a gradient in the concentration of deoxyhemoglobin, which is illustrated in figure 5. The distribution of the deoxyhemoglobin in tissue is very fine, as the diameter of vessels in the capillary bed is of the order of micrometres, though the post-capillary vessels are larger. The presence of the deoxyhemoglobin disturbs the local homogeneity of the main magnetic field, and as the frequency of the MR signal is directly proportional to the field strength, nuclei that are close to a paramagnetic centre will have a different frequency. The

Figure 5
Functional magnetic resonance imaging is sensitive to the presence of deoxyhemoglobin which is to be found in the capillaries and the veins.
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magnitude of the MR signal that we record is dependent amongst other things on the coherence of the spins: if all spins have the same frequency then they remain in step and a larger signal is obtained than in the situation that there is a dispersion of frequencies. Although the deoxyhaemoglobin is confined to the venous compartment the region of changed local frequency can extend beyond this and into the tissue. If looked at in detail there are a number of mechanisms that can contribute to the signal loss. This contrast is termed blood oxygen level dependent (BOLD), and was discovered by Seiji Ogawa and colleagues in 1990. They found that the contrast in a T₂*-weighted image of a rat brain changed dramatically as a function of the oxygen content of the inhaled air. Within two years this principle had been used to demonstrate activation studies in humans.

The question then arises as to how activation affects BOLD contrast. If tissue is activated then by definition it will metabolise more oxygen than in the resting state, and so this will lead to an increase in the concentration of deoxyhaemoglobin and a reduction in signal. However, in order to supply the oxygen to the tissue the blood flow needs to increase locally, and an increase in blood flow will tend to reduce the concentration of deoxyhaemoglobin by washing it out of the tissue faster than in the resting state. Finally it should be considered that the increase in blood pressure associated with the increase in flow will cause an increase in the volume of the post-capillary vessels, a mechanism that will again tend to increase the deoxyhaemoglobin content. We hence see that in the activated state there are two mechanisms tending to increase the deoxyhaemoglobin content and only one that is tending to reduce it. However, contrary to your probable expectation it is the single mechanism that wins in healthy adults, with the result that activation leads to an increase in signal intensity.

Activation studies based on BOLD contrast are popular because of the widespread availability of MR-scanners, the fact that there are no known harmful side effects of MRI (provided of course that it is used properly!), and the use of blood as an endogenous contrast medium means that experiments can be repeated as often as required. As we have seen BOLD contrast is complex in origin, arising as it does from the interplay of three separate physiological parameters. Furthermore signal changes may have their origin in either the intra- or the extra-vascular compartment, and may arise from the capillary bed and from veins which may be far
downstream from the site of activation. If we consider the response to a short stimulus then the first thing to note is that any haemodynamic response commences seconds after the electrophysiological activity has terminated. The response may then be subdivided into three distinct phases, that are shown in figure 6:

First, the fast response or initial dip. This is a negative BOLD response that occurs a few seconds post stimulation. It is believed to occur as a result of increased oxygen consumption prior to the increase in blood flow. It is elusive, and probably only reliably detectable at field strengths in excess of 3 T. By being confined just to the region of increased neuronal activity it probably has the highest spatial resolution possible with fMRI.

Second, the main BOLD response. This is a positive going signal that reaches its maximum six to ten seconds post-stimulus. It is robust, and used for almost all studies. The signal contributions come primarily from post-capillary veins and their immediate vicinity. If signal from draining veins is measured then this can be far from the site of activation.

![Figure 6](image_url)

**Figure 6**

*Schematic representation of the BOLD response to a short stimulus. After an initial dip, the fast response the signal increases after a number of seconds to reach a maximum. Thereafter the post-stimulus undershoot returns to baseline about 45-60 seconds post-stimulus.*
Finally, the post-stimulus undershoot. This reflects the return of the system to equilibrium, primarily due to the long time constant for venous volume changes.

As the main magnetic field strength increases, the intravascular contribution diminishes, and the ability to detect extravascular signal changes about small vessels also improves. This has proven to be a major driving force for the development of very high field imaging systems for humans such as the 7 T whole body system at the Center for Magnetic Resonance Research in Minnesota and the 8 T whole body system at Ohio State University. The use of these systems for human imaging brings with it a host of technical problems, but it has already been clearly demonstrated that significant improvements in the attainable spatial resolution can be obtained, particularly by the use of T2*-weighted imaging methods. At lower field strengths like 1.5 T, T2*-weighted techniques are generally preferred because of their higher sensitivity. T2*-weighted images are only sensitive to a subset of the mechanisms responsible for BOLD contrast, and this results in an improved spatial localisation but a diminished sensitivity. Furthermore the image quality in EPI is improved if T2-contrast is used. Even at our humble field strength of 3 T it has proven possible to use these techniques to perform cognitive studies, and by using special techniques to eliminate the signal from the venous compartment it is possible to detect signal changes that should arise solely from the activated tissue.

In discussions regarding sensitivity it is natural to concentrate on the signal intensity, but it is of course the ratio of signal to noise that is decisive. For inanimate objects the noise sources are well understood: essentially thermal noise in the coil and inductive or capacitative losses arising from the interaction between the coil and the object. In living systems the noise can arise from a number of further sources: physiological noise arising directly or indirectly from respiration or the heartbeat. There are also spontaneous fluctuations in the BOLD signal independent of these. It could recently be shown that at 3 T the physiological noise dominates for T2*-weighted BOLD sequences and so further gains in functional sensitivity in going to higher field strengths will be diminished. We are currently exploring the question as to whether this is true for T2-weighted sequences or not.

Despite its enormous success BOLD imaging has limitations. In particular the reliance on an indirect measurement of neuronal activation, namely the blood flow changes, means that the temporal resolution is exceedingly poor. The spatial
resolution is better than other methods, but only in animal studies has it been possible to differentiate the layers of the cortex, which would provide a new quality of information for neuroscience. It remains however a permanent source of wonderment that someone thinking about a problem, or performing an everyday activity, starts a train of events that seconds later still manifest themselves in the nuclear characteristics of water protons.

The evergreen tree?

Some years ago I visited Kazan in Tartarstan, the place where Zavoisky performed his original experiment, and an old Russian professor whose two sons had become MR-physicists leant back and said to me: 'it's the evergreen tree'. If we look at the amazing range of NMR applications, from solid-state NMR, through high resolution protein analysis, medical application, pharmaceutical research, cognitive neuroscience and in the recent past quantum computing, we are tempted to think that there will always be new challenges and applications for the inventive. If we look however at the massive achievements which lie behind us, then we wonder what is left to do. This way of looking at science is guaranteed to achieve nothing more than a mood oscillating between elation and despair. The challenge is to look not at the set of all possible experiments, but at the subset of possible and relevant experiments. The ability to identify the latter often distinguishes the successful researcher. The question of relevance is of primary concern: you may be rewarded for doing the impossible, but never for doing the irrelevant! In a time of constantly changing challenges the relevant experiment represents a moving target. MRI and fMRI teaches us little in terms of physics, it is only the application that lends relevance to the experiment. As an example we can consider the excitation of a curved slice, rather than the planar slices commonly used in MRI. This requires some analytical skill and insight, and may be dismissed by outsiders as a typical physicist activity. It is only in realising that the cortex of the human brain can be found on a cylindrical surface and that acquisition from a single slice allows all information to be simultaneously and not sequentially acquired that an experiment of this nature gains value. In the more general sense developments that can seem pointless for many years suddenly acquire value when the right application presents itself. The EPI imaging experiment was touted throughout the 1980s by
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its protagonists as the future of diagnostic imaging: a role for which it was fundamentally unsuited owing to its limited spatial resolution and vulnerability to artefacts. However the whole boom in physiological types of measurement would have been unthinkable without EPI, i.e. it took fifteen years in a rapidly advancing field before it found its true application. In the early 1980s the Medical Research Council of Great Britain almost cut off the funding for EPI development, but were sufficiently far-sighted finally not to do this.

So what does the future hold? Which problems would we like to solve? If we confine ourselves to the areas examined in this talk then in DTI it would be great to build a bridge between anatomical, functional and effective connectivity. A generally neglected problem is that even when we have perfectly charted the course of the white matter tracts through the brain these disappear into the grey matter giving us only the crudest idea of where they ultimately terminate. In fMRI there is still scope for improving the spatial resolution, though unfortunately improvement of the temporal resolution seems a more intractable problem. There are also ideas for performing fMRI on a different basis than that of BOLD signal changes: for example the subtle NMR effects from frequency shifts arising from the magnetic fields associated with dendritic activity, or the possibility that a small neuronal cell swelling occurs as a result of activation, which expresses itself in a reduction in the diffusion coefficient. A pressing concern is the equivalence between activation recorded by different modalities, which goes to the core of cognitive neuroimaging. Does electrophysiological activity as recorded by other techniques such as MEG and EEG always lead to measurable changes in metabolic activity, which we indirectly detect with fMRI? Experiments performed recently, both in Nijmegen and elsewhere show that some relative increases in electrophysiological activity are coupled with relative decreases in the BOLD signal change.

The FC Donders Centre

I have lived in Nijmegen and worked at the FC Donders Centre for less than two years. I have found here a centre in which there is a genuine spirit of cooperation and scientific enterprise. The concept on which the Donders Centre is based is excellent, providing a balance between scientific independence of the Principal Investigators and collaboration: the sort of collaboration that arises spontaneously.
from a commonality of interests and not that which is imposed. There is always a considerable time lag between scientific activity and its manifestation in the form of peer-reviewed publications, and so I hope that the world outside the Netherlands will soon see what a dynamic and enterprising Centre for scientific research has been established here.

The ideal of academic life is that teaching and research go hand in hand. The question then arises as to how to teach multi-disciplinarity? If every multi-disciplinary area attempts to become a discipline in its own right then this will lead to enormous fragmentation. Furthermore there is the idea that in studying a discipline you learn a way of thinking that is powerful within that specific discipline: the student of physics does not attempt to learn all of known physics, they learn hopefully how to deal with physical problems. The power of multi-disciplinary research lies in bringing the strengths of each discipline together to solve a common problem. I still believe that people should study the classic disciplines, but they need additionally openness, flexibility and communication skills. Post-graduate training such as the Masters course in Cognitive Neuroscience now being established in Nijmegen provides the ideal opportunity for this.

As vital as teaching is finance. Most nations have now moved primarily to a grant-driven system as the fairest way of distributing resources. In an era in which scientific research is extraordinarily expensive this is understandable as it ensures direct accountability. In this talk I have tried to give a glimpse of the way in which progress in this field has been achieved; much of it would have been incompatible with the grant giving process, with its lengthy peer-review procedure. This is particularly true for the cumbersome and almost incomprehensible structures associated with obtaining funds from the European Union.

Acknowledgements

This Autumn it will be twenty years since I started working in biomedical NMR, and it is a pleasure for me to acknowledge the many people who have contributed to my development and who have continued to feed my enthusiasm for the subject. To start at the beginning in Aberdeen there were Tom Redpath and Jim Hutchison, my PhD supervisor, who between them put me on the right road towards my doctorate and ensured that I did not stray too far from it. My first head of department
was John Mallard who having built up the department of Biomedical Physics and Biomedical Engineering at Aberdeen successfully defended it from decimation during the Thatcher-period. Following my PhD I fled the uncertainties of the British University system for Dieter Leibfritz’s group at the University of Bremen. Having originally intended to stay there for one year or so I finally left after eight. In Bremen I was given the freedom to develop as an independent scientist and enjoyed working with Peter Börnert, Mathias Hoehn, Wolfgang Dreher, Uwe Böttcher, Thoralf Niendorf, Bernd Kühn, Torsten Reese and Axel Haase amongst others. I even obtained a German qualification, the habilitation, in 1995. My next position was as head of the MR-group of the Max-Planck-Institute for Cognitive Neuroscience in Leipzig, which provided a range of challenges both scientific and managerial. It also gave me a tremendous grounding in the application of MR methods in cognitive neuroscience. The size of the Institute makes it difficult to name all those I worked with, but I would like to particularly mention Yves von Cramon, one of the Directors who gave me invaluable insights into scientific management, all members of the MR group, which always had a special atmosphere, and outside of it Margret Hund-Georgiadis, Stefan Pollmann and Stefan Zysset with whom I enjoyed fruitful collaborations.

It is not easy to leave your own country after twenty seven years, and somewhat easier to leave a second country after fourteen, but for the last two years my home has been in the Netherlands, which in its language and culture contains elements familiar from both Britain and Germany (naturally only the best of these!), while retaining its own distinctive character. The person who persuaded me to join the Donders Centre was Peter Hagoort, and it is a pleasure to thank him for the friendly reception he has given me, and the open and honest way in which all discussions were conducted. I should like to thank the ‘snuf’ for establishing the Chair. I would also like to thank Tildie Stijns, Erik van den Boogart and Arthur Willemsen for the warmth with which they received me upon my arrival here, and express my enjoyment in working with Laura Parkes, Christian Kerskens, Paul Gaalman and Hubert Fonteijn in the MR-group. The other PIs at the Donders Centre are a formidable team and I should like to thank them for the tremendous scientific atmosphere they have generated within the Donders Centre. Outside the Donders Centre I have hatched many plans with a wide range of other groups: Berend Hillen (Anatomy),
Arno Kentgens (Physical Chemistry), Eric Roubos (Biology), Mark van Buchem (Leiden), Frans Verstraten (Utrecht) and especially Arend Heerschap (Radiology), hopefully these will bear fruit in the coming years.

Scientific endeavour at whatever level is not an impersonal activity, but is highly individual. Through my interactions with many colleagues I have seen how both character and intelligence play their respective roles in science, and how each of us develops their own method and style of approaching problems. For myself I can say that I learnt the value both of perseverance and of education from my parents.

The mainspring of my own life is my family, and managing (as best I can) to be a husband a father and a scientist, often seems to hold me in a state of near permanent activity. I owe a tremendous debt in all of these to Sandra, my wife, without whose support this juggling act would long ago have become impossible.

Amongst my failings has been an inability to become fluent in the Dutch language, but one thing I have learnt to say with considerable relish is...

*Ik heb gezegd.*
The role of magnetic resonance imaging in investigating brain function

Literature


