IN AUGURAL LECTURE
13TH SEPTEMBER 2012

HOW MAGNETIC RESONANCE IMAGING OPENS A WINDOW ON HUMAN BRAIN FUNCTION

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INAUGURAL LECTURE GIVEN TO MARK THE ASSUMPTION OF THE POSITION AS PROFESSOR OF

NEUROIMAGING

AT THE FACULTY OF SCIENCE AND TECHNOLOGY AT THE UNIVERSITY OF TWENTE ON THURSDAY 13TH SEPTEMBER 2012

BY

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13TH SEPTEMBER 2012
INTRODUCTION

MIJNHEER DE RECTOR MAGNIFICUS, GEACHTE DAMES EN HEREN,

This lecture is about the regional changes in blood flow that occur when our brain is performing a task, or even when idling at rest. I will show how magnetic resonance imaging (MRI) is privileged amongst current imaging techniques in its ability to detect and characterise this response. I will explain how MRI can detect signal changes at the spatial scale of the building blocks of brain function: the cortical columns and laminae, but also how it is possible to draw very general conclusions about the connectivity of the brain on the basis of group studies carried out with a more modest spatial resolution. I will show how the measurement techniques of MRI are rapidly changing, driven by new technical insights and new methodologies, and how these developments can contribute to improved measurement of brain function.

MRI IN A NUTSHELL

Before embarking on a discussion of brain activation we shall engage in a short digression on the basics of MRI. Magnetic resonance imaging has its roots in the earlier discovered technique of nuclear magnetic resonance (NMR). In NMR a sample is magnetised when placed in a strong static magnetic field ($B_0$, oriented along the z-axis). The equilibrium state of the bulk magnetisation is that it is oriented parallel to the static magnetic field. The application of a circularly polarised radio-frequency field at the Larmor frequency causes the bulk magnetisation to precess. If the angle of precession is $90^\circ$ then transverse magnetisation is generated which can produce a detectable signal. If the precession angle is $180^\circ$ then the longitudinal magnetisation
is inverted and no detectable signal is produced. If the magnetisation is perturbed then its return to the equilibrium state is governed by three relaxation times: $T_1$, which determines the recovery rate of the longitudinal magnetisation; $T_2$, which determines the decay rate of the transverse magnetisation under ideal conditions; and $T_2^*$ which gives the effective relaxation time of the transverse magnetisation in the presence of inhomogeneities in the static field. These relaxation times form the basis for the most commonly used contrasts in MRI, and the latter two, as we shall see below, can be used in brain activation studies. A $T_1$ contrast can be generated by initially applying a $180^\circ$ inversion pulse, followed by a delay conventionally known as TI (the inversion time) during which the magnetisation recovers, and then an excitation pulse to readout the signal. A $T_2$ contrast is typically generated by a spin-echo experiment. In this a $90^\circ$ excitation pulse is followed at an interval TE/2 later by a $180^\circ$ refocusing pulse, which has the effect of eliminating the effect of static field inhomogeneities at a time TE (the echo time) after the initial excitation. Finally and most straightforwardly a $T_2^*$ contrast is generated by acquiring the signal TE after the initial excitation pulse, but in this instance without any intervening refocusing pulse. Examples of these contrasts are shown in Figure 1.

Figure 1. Anatomical images of the brain. From left to right a $T_1$-weighted image; a $T_2$-weighted image; and a $T_2^*$-weighted image of the occipital pole.
The major step from NMR to MRI was the introduction of pulsed magnetic field gradients. These made slice selective excitation possible and are the essential components in producing images. If we consider a two dimensional MRI experiment then the data are acquired in the inverse space of the object being imaged. This inverse space is generally known as k-space, and the instantaneous k-space coordinate at any time is given by the time-integral of the pulsed magnetic gradients up to that point. In recent years spatial localisation has also been achieved by using the sensitivity profiles of radio-frequency receiver coils, generally placed in an array. The use of such multi channel receiver coils has made it possible to significantly reduce the amount of gradient encoding required to produce an image and hence to considerably accelerate image acquisition.

The imaging method most commonly used for brain activation studies is EPI (Echo Planar Imaging). This is capable of producing an image as the result of a single excitation. It achieves this by a raster-like coverage of k-space that requires strong and rapidly switchable pulsed magnetic field gradients. If the image data are acquired after an excitation pulse, then this is known as gradient-echo EPI and the images have a $T_2^*$ contrast. It is also possible to generate a spin-echo, and acquire the EPI image at the centre of the spin-echo, in which instance the image will primarily have a $T_2$-contrast with some degree of $T_2^*$-weighting which will be greatest at the highest spatial frequencies.

THE BIG BOLD PICTURE

In 1990 Seiji Ogawa and colleagues (Ogawa et al., 1990) published a paper in which they demonstrated that the contrast in a $T_2^*$-weighted images of a rat brain changed dramatically dependent on whether the rat was breathing air or pure oxygen. They named this blood oxygenation level dependent (BOLD) contrast. This discovery formed
the basis for functional magnetic resonance imaging (fMRI) which has become one of the work-horses of cognitive neuroimaging. The next step in the process was to show that regional changes in brain activity produced a measurable change in BOLD contrast: something that was demonstrated nearly simultaneously by groups working in Minnesota and at MGH (Massachusetts General Hospital). (Kwong et al., 1992; Ogawa et al., 1992)

BOLD contrast arises as a result of the change in magnetic properties of blood as a function of oxygen content. Most tissue is weakly diamagnetic, including oxyhaemoglobin, however deoxyhaemoglobin is paramagnetic. Hence, in going from the arteries to the veins, there is a gradient in the concentration of deoxyhemoglobin. 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 magnitude of the MR signal that we record is dependent on the coherence of the spins: if all nuclei 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.

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. Historically, observations made in the 19th century indicated that regions of the brain that are functionally active experience an increase in blood flow. This increase 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 may cause an increase in the volume of the post-capillary vessels, a mechanism that will again tend to increase the deoxyhaemoglobin concentration. We hence see that in the activated state there are two mechanisms tending to increase the deoxyhaemoglobin concentration and only one that is
tending to reduce it. However, it is the single mechanism that wins in healthy adults, with the result that activation leads to a higher value of $T_2$ and $T_2^*$, and a concomitant 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, and the use of blood as an endogenous contrast medium means that experiments can be repeated as often as required. In the vast majority of cases BOLD experiments are performed using gradient-echo EPI as the acquisition method, as the $T_2^*$-weighted signal shows the greatest signal changes.

Because 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 arise in either the intra- or the extra-vascular compartment, and may have their origin in the capillary bed but also in veins which may be far downstream from the site of activation. To be more specific there are four contrast mechanisms that contribute to the BOLD signal increase: an increase in intravascular $T_2$ caused by the reduction in intravascular deoxyhemoglobin; a reduced dephasing of the signal coming from within blood vessels, caused by differences in offset frequency of blood vessels dependent upon deoxyhemoglobin content and the orientation of the vessel relative to the static magnetic field; the static dephasing of extra-vascular signal around larger vessels caused by differences in Larmor frequency as a result of the bipolar field distortion about the vessel is reduced; and finally the dynamic averaging effect caused by the dephasing of spin signals diffusing through the bipolar field surrounding smaller vessels is also reduced. As the main magnetic field strength increases, the intravascular contribution diminishes because the $T_2$ of venous blood falls off rapidly with increasing static magnetic field strength, whereas the strength of the dynamic averaging contribution increases with the second power of $B_0$. This has proven to be a major driving force for the development of very high field imaging systems, because the spatial localisation of the BOLD signal change can be expected to significantly
improve at higher field strengths owing to the increased weighting of the dynamic averaging mechanism. It has also given a considerable impetus to the use of spin-echo BOLD at very high field strength because the two static dephasing mechanisms will not contribute to this contrast, and when the short $T_2$ of venous blood is taken into consideration this will also make no contribution, which means that potentially high field spin-echo BOLD will exclusively reflect the signal contribution from dynamic averaging, and will hence be better localised to the site of the underlying neuronal activity (Lee et al., 1999).

Hitherto we have discussed how the BOLD signal change may increase with increasing static magnetic field strength, 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, for example physiological noise arising directly or indirectly from respiration or the heartbeat. There are also fluctuations in the BOLD signal that are independent of these, and are believed to arise from spontaneous fluctuations in neuronal activity and in blood flow. The BOLD and non-BOLD physiological noise is not truly random, and may be coherent over a range of spatial scales, depending on its origin. The frequency spectra are also different. The strength of the physiological noise is proportional to the signal intensity, and hence its relative importance increases with the static magnetic field strength. Once a main field strength of 3T has been reached the physiological noise is already the dominant noise source at standard spatial resolutions of about 3 mm isotropic (Krüger and Glover, 2001). It is hence only possible to obtain an increase in sensitivity at 7T if sufficiently small voxels are used that thermal noise is still the dominant mechanism (Triantafyllou et al., 2005).
MESA-LEVEL IMAGING

In the last decade it has become generally accepted that the regional increase in blood flow accompanying brain activation is not a direct consequence of increased oxygen consumption, but is rather due to the release of vasodilators as a result of excitatory synaptic activity (Lauritzen, 2005; Logothetis et al., 2001). It remains an open question as to the spatial scale on which the blood flow response is coupled to the underlying neuronal activity. There is some evidence that it is tightly coupled even at the level of the cortical laminae and columns, whereas some of the earlier optical imaging literature claims that we are watering the entire garden for the sake of one thirsty flower (Malonek and Grinvald, 1996).

The grey matter of the human neocortex is divided up into six histological layers, which are believed to fulfil different functions. In particular certain layers are associated with either the input or the output to a given region. There are also four vascular layers, characterised by differing capillary densities. The blood supply to the neocortex is characterised by both the arterial and the venous supply originating from the external surface, closest to the CSF, and known as the pial surface. Thus the veins that drain the neocortex increase in diameter as they approach the cortical surface, and the larger vessels are to be found at the pial surface abutting the CSF. The neocortex is typically 2.5 to 3 mm thick and hence acquiring data at the level of the laminae requires submillimetre spatial resolution and will only be possible if the haemodynamic point spread function is sufficiently narrow. This compares with a standard fMRI experiment which will typically have a spatial resolution of about 3 mm isotropic. Given the complex interactions between the neurons of the different laminae it may well only be possible to obtain laminar information by performing experiments that utilise differential paradigms so that two activated states are compared with each other, rather than comparing activation with rest.
Following earlier work in animal models the past few years have witnessed an increase in interest in pursuing layer specific studies in humans. To date we have concentrated on exploring the utility of gradient echo sequences for layer specific fMRI. This approach has the advantage of greater sensitivity and a lower dependence on the static magnetic field strength. It is also considerably easier to acquire data with this contrast. The main disadvantage of course is the reduced spatial specificity. Our hope was that if we used sufficiently small voxels then the signal change could be localised unambiguously to grey matter and the contribution from larger vessels eliminated on the basis of their position at the pial surface. Initial experiments were confined to the visual cortex because this is easy to identify, can be strongly stimulated, and there is a clear expectation that the maximum signal should occur in layer IV. Furthermore layer IV in human primary visual cortex (V1) coincides with the stripe of Gennari, a layer of more heavily myelinated tissue, that can be distinguished in anatomical images. Hence the greatest activation should coincide with this anatomical landmark, providing an independent verification of the success of the experiment. The low SNR at the single voxel level makes this technique only feasible if the cortical depth of each voxel can be accurately determined, and the signal then integrated over a number of voxels at the same depth. In this way layer dependent activation profiles can be obtained for pre-defined regions of the cortex, on the basis of anatomical definition, or activation patterns. We examined a group of seven subjects using a simple gradient echo acquisition technique at the commonly used field strength of 3 Tesla (Koopmans et al., 2010). The results were highly reproducible at the individual level, consistently showing a peak in signal change coincident with the stripe of Gennari. The group average shows a highly convincing pattern of activation through the cortex with a peak coinciding with layer IV and the largest signal change at the surface of the cortex where the pial vessels reside as shown in Figure 2.
We then went on to explore differential activation using a faster imaging technique also at 3 Tesla. Here a monochromatic stimulus and two colour stimuli were included. Hence the differential activation between achromatic, red-green and blue-yellow stimuli could be assessed. The colour stimuli were hypothesised to be processed more in the histological layers II and III, owing to the presence of so-called colour blobs in these layers: groups of cells that respond selectively to colour input. Hence the maxima of activation should occur in the supra-granular layers above the stripe of Gennari. In this study eleven subjects were scanned and the layer specific activation in V1 assessed. Greater activation was found for the colour stimulus in the supra-granular layers, in line with expectation.

As outlined above the greatest sensitivity and spatial specificity for laminar fMRI will be obtained at high static magnetic field strengths, irrespective of whether a gradient or a spin echo sequence is used.
However, the laminar results obtained with gradient echo approaches that were to be found in the literature, showed a diversity of recorded profiles. We hence turned our attention to a full characterisation of the laminar gradient echo response at 7 Tesla (Koopmans et al., 2011). In order to achieve this we developed a multi-echo gradient echo technique that was not only capable of examining the activation as a function of depth but also as a function of echo time (TE). The echo time dependence is particularly relevant at 7 Tesla because of the divergence in the $T_2/T_2^*$ relaxation times of venous blood and grey matter. Given that the optimum TE for fMRI is equal to the relevant relaxation time ($T_2/T_2^*$) of the tissue in question, it can hence be expected that the maximum signal change for the venous compartment will be recorded at a shorter TE than for the grey matter. A further advantage of a multi-echo acquisition is that it makes it possible to compute the $T_2^*$ relaxation time as a function of cortical depth. Finally, the ability to measure layer dependent signals over extended regions of the neocortex makes it possible to assess the limit at which physiological noise starts to dominate.

In terms of results we found that the $T_2^*$ value was shortest adjacent to white matter, and with the exception of the stripe of Gennari then increased when going from the white matter boundary to CSF. Thus the $T_2^*$ value would appear to reflect the myelinisation of the tissue, rather than the deoxyhemoglobin concentration. The signal variance however showed a different dependence, being greatest in the layers with the highest blood volume. This is unsurprising when considering that BOLD noise should be a major contributor to total physiological noise at 7 Tesla. The activation pattern showed as expected that the maximum pial activation occurs at a considerably shorter TE than that of the grey matter. What was however surprising was that the $T_2^*$-variation in grey matter was sufficiently large that the optimum TE differed as a function of cortical depth. It was hence possible to explain many of the divergent results found hitherto in the literature on the basis of these previously unknown differences.
in relaxation times. With the insights gained from this study it is possible to proceed with more confidence in using GE methods for layer specific activation at high static magnetic field strengths.

FAST, FASTER, FASTEST

There is a constant desire to accelerate the acquisition speed in MRI in general because this increases patient throughput, reduces the sensitivity to motion and opens up access to dynamic processes. Even fMRI, which samples the rather slow hemodynamic response function can benefit from accelerated acquisition, because this response needs to be sampled at about 0.5 Hz, which if combined with whole brain coverage leads to a requirement of approximately 15 slices per second at moderate spatial resolution of 3 mm, but about 50 slices per second for studies at laminar resolution. The main tool for achieving this goal is to use multi-channel receiver coils to accelerate the acquisition in two of the three dimensions. This can be done for 3D imaging sequences by accelerating along both phase-encoding directions. Benedikt Poser and Markus Barth in Nijmegen used this to develop a 3D EPI imaging sequence capable of acquiring whole brain data at 1 mm isotropic resolution within 3 seconds at 7 Tesla (Poser et al., 2010). We have also worked successfully with a single shot 3D-GRASE sequence. In this method an entire plane of kx-ky data are acquired, as in standard 2D spin-echo EPI, but now this is done at a given value of kz. The signal is then refocused using a radiofrequency pulse and the next kx-ky plane is readout under the next spin-echo, but at a different kz value. This procedure continues until a full volume of k-space has been sampled. The total length of the readout train in this method is limited by T2 relaxation, which in the brain means that about 200 ms are available. Within this time it has proven possible to obtain over 20 slices. It is also possible to accelerate 2D imaging
sequences along the slice direction by simultaneously exciting multiple slices. This technique goes under various names: multiband; multiplex; and simultaneous multi-slice, and was first discovered over a decade ago (Larkman et al., 2001). Interest in this technique increased dramatically when it was realised that it could be combined with EPI for performing fMRI (Moeller et al., 2010). Currently a typical repetition time (TR) for standard fMRI is of the order of 2 seconds: the ability to accelerate by a factor four or more would mean that physiological processes, particularly cardiac pulsation would not be under-sampled, and could be directly regressed out of the subsequent analysis.

Multiplexing has traditionally relied on the linear superposition of phase-modulated radio-frequency pulses in order to simultaneously excite the slices. This means that the power deposition increases linearly with the number of slices which can be prohibitive for large numbers of slices, high pulse angles, and high static magnetic field strengths. Our approach has been to use periodic excitation pulses that simultaneously excite a potentially infinite number of equidistant slices but where the power deposited is independent of the number of slices, which has given rise to the acronym PINS (Norris et al., 2011). The basic idea is to intersperse a series of short RF pulses with pulsed magnetic field gradients. Excitation will then occur periodically where the gradient pulse induces phase changes that are multiples of $2\pi$. More specifically, any known non-adiabatic RF pulse can be transformed into a periodic pulse simply by multiplying its RF envelope by a comb function. This multiplication in the time domain is the equivalent of a convolution in the frequency domain. It is hence subject to the same constraints as any other digitisation process and therefore the sampling must at least fulfil the Nyquist condition with respect to the highest modulation frequency present in the RF envelope. More commonly the sampling frequency will be determined by the ratio of the periodicity of the excitation to the slice thickness, $N$. For example a Gaussian pulse has a slice thickness defined by its FWHM bandwidth: $N$ is then given directly by the number of sampling periods of the comb
that occur between the FWHM values of the pulse in the time domain. An alternative approach is to follow that of Hore and to generate the RF pulse as a Fourier series expansion (Hore, 1983). Consider a periodic function \( h(\omega) \), with period \( 2\pi \), such that \( h(\omega) \) has the value of unity in the range \(-\pi/N \leq \omega \leq \pi/N\), and zero elsewhere within the period, and hence corresponds to an ideal slice profile. The Fourier expansion of \( h(\omega) \) is then an even function given by

\[
h(\omega) = \frac{1}{N} + \sum_{m=1}^{\infty} \frac{2}{nm} \sin \frac{mn}{N} \cos m\omega \tag{1}
\]

The time domain representation of equation [1] is

\[
H(t) = \frac{1}{N} \delta(t) + \sum_{m=1}^{\infty} \frac{1}{nm} \sin \frac{mn}{N} \{\delta(m-t) + \delta(m+t)\} \tag{2}
\]

Which is a sinc-modulated string of delta functions that will be truncated at \( m=M \). We implemented PINS pulses in a spin-echo sequence and demonstrated their application on the head of a healthy volunteer as shown in Figure 3.

[A] Gold Standard (slices acquired separately)

[B] PINS acquisition (left) and its reconstruction (right)

Figure 3. In vivo results of 4-fold PINS acceleration obtained in sagittal section from the head of a healthy volunteer. Four individually scanned slices (a) serve as a gold standard reference to the PINS data in (b).
The reduced power deposition has been exploited to make experiments possible, particularly at 7 Tesla that were previously deemed unattainable. As an example we have recently been able to implement one of the most power intensive sequences, RARE (also known as fast spin echo and turbo spin echo) with a near order of magnitude reduction in power deposition. This development will effectively mean that almost all standard methodologies available at clinical field strengths will now become available at 7 Tesla.

JOINING UP THE DOTS: CONNECTIVITY STUDIES

Modern brain imaging is much concerned with networks of brain regions and hence connectivity analysis plays an increasingly important role. Here MRI data are important in a number of different ways: structural or anatomical connectivity can be investigated using diffusion weighted imaging (DWI) which is capable of probing the anisotropy in the displacement of water molecules caused by myelinated nerve fibres. The measurement of anisotropy in each voxel indicates the directions of nerve fibres within the voxel. The information from neighbouring voxels can be combined to generate tractograms of the nerve fibres through the brain, and hence to examine the structural connectivity between brain regions. Resting state fMRI also probes connectivity, but in this instance so called functional connectivity which is determined from the correlation in the time-course of BOLD-weighted signals. Resting state fMRI is unbelievably simple to perform: the subject just has to lie still in the scanner, typically for a period of about 10 minutes, while BOLD-weighted data are continuously acquired. Resting state fMRI and DWI do not measure identically the same properties, as regions of the brain may exhibit a strong functional connectivity with each
other that is in fact mediated by a third region. However, following the Hebbian principle, that put loosely states that cells that wire together fire together, it is clear that both methodologies measure very similar characteristics of the brain. When the whole brain is parcellated into some hundreds of regions then the matrix of connections between the regions has become known as the connectome. Enormous resources are now being invested worldwide in investigating the characteristics of the connectome. It is a natural extension of connectivity analysis to consider the brain as a network in which the grey matter regions represent the nodes, and the connections between them are the edges. This approach makes it possible to identify and characterise the hubs of the brain: those nodes that have a large number of local connections are local hubs, whereas those situated strategically between different modules are connector hubs (Hagmann et al., 2008).

Some years ago we initiated a study of nearly eighty healthy subjects that were imaged for anatomy, DWI and resting state fMRI, using an acquisition protocol that was then considered ‘state of the art’. By acquiring over a thousand volumes of resting state data per subject it was possible to perform analyses on a single subject level. These data have provided the basis for a number of ongoing studies, particularly in collaboration with the group of Christian Beckmann. In an early study we utilised these advantages to examine the characteristics of the default mode network (DMN). The DMN was identified about a decade ago as a set of brain regions that deactivates during the performance of a task. It was later shown that in an independent component analysis (ICA) that the regions of the DMN form a separate IC, and further, that some regions of the DMN are also major connector hubs in the brain. Our aim was to investigate whether there was a distinctive hub-structure within the regions of the DMN, and how these were related to the pattern of anatomical connectivity. The large number of time points in the data set made it possible to perform an ICA analysis at the single subject level with 75 ICs. Each identifiable region within the DMN was then used as a region of interest for a subsequent
partial correlation coefficient (PCC) analysis. The thresholded PCCs were used as the weighted edge strengths in a single subject graph-theoretical analysis. Averaging over the whole group then identified hot-spots of betweenness centrality and node degree, which could be used to identify local and connector hubs. If the graph theoretical analysis was restricted to just two regions, then the position of the connector hubs corresponded well to the locations at which anatomical fibres (as measured with DWI) joined the said regions.

We have also used this dataset to investigate the distribution of hubs in the whole brain: in this instance on the basis of deterministic fibre-tractography. Here the entire neo-cortex was parcellated into a 1000 ROIs for each subject on the basis of a k-means algorithm. This was performed 20 times per subject to remove parcellation bias. The ROIs were used as seed regions for the tractography, and the unthresholded connectivity pattern used as input to the graph-theoretical analysis. Averaging across parcellations and subjects produced maps of local and connector hubs. These revealed that there is a sparse and lateralised distribution of connector hubs, which include a number of regions known to be important for particular brain functions, as shown in Figure 4.

**Figure 4.** Distribution of nodes of connector hubs as determined by average of betweenness centrality. (a) mapped onto a standard brain, and (b) on a flattened brain.
As an example of how techniques and applications interact, we have used PINS to implement spin-echo EPI at 7 Tesla with whole brain coverage of 84 slices, a repetition time of less than 2 seconds and a voxel volume of 1.6 mm (Koopmans et al., 2012). We used this technique to perform the first spin-echo resting state fMRI study on a limited group of six subjects from whom 500 volumes of data were acquired over a time period of 15 minutes. A group level ICA analyses was performed on these data in order to verify that the standard networks known from gradient echo could be replicated. Indeed the data were so powerful that an analysis with 70 ICs could be performed of which we were confident that 24 represented genuine networks. It was thus possible to detect the major networks, but also a number of hitherto undetected, but neuro-scientifically plausible ones. Dual regression was then used to show the ICs at the single subject level, revealing an excellent localisation to grey matter. The potential advantage of this approach is that it is highly sensitive, the signal is well localised to the parenchyma, and the use of a spin-echo avoids the signal drop-outs that occur in gradient-echo techniques. This could hence ultimately become the method of choice for performing resting state brain connectivity studies.

VISION

In this lecture I have tried to convey some of the excitement that I still feel for performing MRI, even though I am nearing the end of my third decade in this field. The interaction between methodological advance, biophysics and the underlying physiology mean that this is an area that is constantly evolving in the eternal circle of new techniques generating new applications, and new challenges driving the development of novel methods. We have also just celebrated twenty years of fMRI, with the field having moved from identifying activated regions in its early years to now mainly examining network performance and
characteristics. My goal in all of this is to develop methods that reliably and accurately measure brain function at the scale of the relevant brain structures in the brain, the layers and ultimately the columns, and then to determine how these are structurally and functionally connected with each other. In the last decade the community has come appreciably closer to attaining this goal in that both column- and layer-specific imaging have been demonstrated. Furthermore, advances in methodology, such as multiplexing, make it easier to acquire large amounts of data at high spatial and temporal resolution. There remains however considerable work to do in methods development and analysis before we are able to transform proof of principle experiments into tools that are of value to cognitive neuroscience.

MIRA

This inaugural lecture has come about because of the strong ties between the MIRA institute at the University of Twente and the Donders Institute at the Radboud University. This manifests itself in many different ways. Initially there was an interest in Twente being an external participant in the Donders Centre for Cognitive Neuroimaging (DCCN), which also led to some teaching on Neuroimaging being performed in Twente, notably by Markus Barth. To function effectively as a participant it is essential in the DCCN model that there is a principal investigator (PI) actively representing the scientific interests of the participating institution. The search for a suitable PI was long and arduous but after several abortive attempts Christian Beckmann was appointed, and took up his position in the autumn of 2011. There were other notable successes: first the PIDON project, VIP brain networks, was a successful joint enterprise which has funded a number of joint projects between the two Institutes. There is also the advent of the centre for medical imaging (CMI) in Twente, which increases the scope
for scientific collaborations. This whole endeavour would not have been possible without the support of the directors of MIRA: Clemens van Blitterswijk, and more recently Vinod Subramaniam, as well as that of the Dean, Gerard van der Steenhoven. The main credit as the architect and visionary behind this successful collaboration has to go to Peter Vooijs, who worked tirelessly to make a success of this endeavour.

ACKNOWLEDGEMENTS

It is a pleasure for me to conclude this lecture by acknowledging the many people who have contributed to my development and who have continued to feed my enthusiasm for the subject. Right at the beginning in Aberdeen there were Tom Redpath and Jim Hutchison, my PhD supervisor, who helped me take my first faltering steps in what was then known as NMR-imaging. My first head of department was John Mallard who was responsible for building up the department of Biomedical Physics and Biomedical Engineering at Aberdeen and for initiating the program of MRI. Following my PhD I joined Dieter Leibfritz’s group at the University of Bremen. In Bremen I developed as an independent scientist, working on diverse themes such as $^{13}$C and proton spectroscopy, fast imaging and diffusion. 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. During this period I gained a good understanding of the application of MR methods in cognitive neuroscience.

I have now been based in Nijmegen for over a decade and have greatly enjoyed, and profited from the special atmosphere at the Donders Institute, and particularly at the Centre for Cognitive Neuroimaging. The unique atmosphere owes a great deal to Peter Hagoort and the non-hierarchical structures that he established at the
outset. The attractive structure and the great resources have attracted a string of high-powered PIs who have together made the Donders the success story that it now is. Since 2005 we have also enjoyed a unique partnership with the University of Duisburg-Essen, which led to the establishment of the Erwin L. Hahn Institute, centred around a whole-body 7 T scanner, that has put us in the privileged position of having access to three different static magnetic field strengths. Again, the atmosphere at the Hahn Institute is supportive and collaborative, and I am grateful to my fellow directors Matthias Brand and Mark Ladd for their part in this. Over the years I have gradually been able to build up a group that is internationally competitive in a number of research areas. This is in great part due to the ability to recruit good people who contribute to a dynamic and stimulating environment. There is not sufficient space or time to acknowledge all members of the group past or present, but I would like to say a special word of thanks to Markus Barth for his selfless commitment to the group and its ideals.

Finally I should like to say a few words about my family. I am indebted to my parents for their support and encouragement in early life, and in particular for their realisation of the value of education, even though their generation did not enjoy the access to higher education that we currently have. My close family have made a number of sacrifices over the years, from barely seeing me at breakfast, to enduring my occasional absences at conferences and my periodic drifting off into deep thought. Our children, Tim and Suzanne have given us great energy which has carried over into my working life, and Sandra your knowledge of the scientific life has always made you perceptive and understanding of the environment that I work in. Without you all this whole endeavour would lose much of its attraction and dynamism.

In short, I am a lucky man both professionally and privately.

Ik heb gezegd.
LITERATURE


