Chapter 1

Introduction

1.1 Probing the Secrets of the Brain

The brain is the most fascinating, and least understood, organ in the human body. For centuries, scientists and philosophers have pondered the relationship between behaviour, emotion, memory, thought, consciousness, and the physical body. In the Middle Ages there was much controversy as to whether the soul was located in the brain or in the heart. As ideas developed however, it was suggested that mental processes were located in the ventricles of the brain. According to this theory 'common sense' was located in the lateral ventricles, along with imagination accommodated in the posterior part. The third ventricle was the seat of reasoning, judgement and thought, whilst memory was contained in the fourth ventricle.

It was in the 17th century that Thomas Willis proposed that various areas of the cortex of the brain had specific functions, in particular the circle of vessels at the base of the brain which now bear his name. In the 19th century, Gall put forward his 'science' of phrenology, where the presence or absence of bumps on the skull revealed the strength or weakness of various mental and moral faculties. Despite the dubious method he used, Gall put forward two very important concepts: that the brain was the seat of all intellectual and moral faculties; and that particular activities could be localised to some specific region of the cerebral cortex.

The study of brain function progressed in the late 19th century through work involving the stimulation of the cortex of animal brains using electrical currents. This lead to the mapping of motor function in animals and, later, in humans. These results however contained many inconsistencies. More reliable work was carried out in the mid 20th century by Penfield, who managed to map the motor and somatosensory cortex using cortical stimulation of patients undergoing neurosurgery. In the latter half of this century, most progress in the study of brain function has come from patients with neurological disorders or from electrode measurements on animals. It has only been in the last decade or so that brain imaging techniques have allowed the study of healthy human subjects.

1.2 Pictures of the Mind

The impact of medical imaging on the field of neuroscience has been considerable. The advent of x-ray computed tomography (CT) in the 1970's allowed clinicians to see features inside the heads of patients without the need for surgery. By making the small step of placing the source of radiation within the patient, x-ray CT became autoradiography, so that now not only structure but also blood flow and metabolism could be followed in a relatively non-invasive way. A big step forward was made by choosing to use a positron emitter as the radioisotope. Since a positron almost immediately annihilates with an electron, emitting two photons at 180 degrees to each other, much better localisation of the radioisotope within the scanner is obtained. Using labelled water, positron emission tomography (PET) became the first useful technique which allowed researchers to produce maps of the mind, by measuring blood flow during execution of simple cognitive tasks. Since local blood flow is intimately related to cortical activity, regions of high regional blood flow indicate the area in the cortex responsible for the task being performed.

At around the same time, another technique which promised even better anatomical pictures of the brain was being developed. Magnetic resonance imaging (MRI), based on the phenomenon of nuclear magnetic resonance, produces images of the human body with excellent soft tissue contrast, allowing neurologists to distinguish between grey and white matter, and brain defects such as tumours. Since MRI involves no ionising radiation, the risks to the subject are minimised. The development of contrast agents suitable for dynamic MRI studies, and improvements in the speed of imaging, opened up the possibility of using the technique for functional brain studies. In 1991 the first experiment using MRI to study brain function was performed, imaging the visual cortex whilst the subject was presented with a visual stimulus. A contrast agent was used in this first study, but it was not much later when the first experiment was carried out using the blood as an endogenous contrast agent. The haemoglobin in the blood has different magnetic properties depending on whether it is oxygenated or not; these differences affect the signal recorded in the MR image. By imaging a subject at rest and whilst carrying out a specific task, it became possible to image brain function in a completely non-invasive way.

The 'pictures of the mind' that have been produced over the past few years have started to make a big impact on the way neuroscience is approached. There are, however, still areas of the technique of functional MRI that require refinement. The fast imaging method of echo planar imaging, which is essential for fast dynamic studies, can suffer from poor image quality. In addition some areas of the brain are not visible on its scans. The mechanisms behind the observed activation response are not well understood, and there are issues involved in the way that the data from such experiments are analysed. However, the potential of fMRI, alongside that of PET, means that the study of the human brain has entered a new era, offering new insights into neurology, psychiatry, psychology and perhaps even contributing to the philosophical debate about the relationship between mind and brain.

1.3 The Scope of this Thesis

The material presented in this thesis covers a number of the aspects concerning the technique and application of functional MRI.

The second chapter covers the theory of magnetic resonance imaging, including the classical and quantum mechanical descriptions of nuclear magnetic resonance, and the variety of techniques that can be used to image biological samples. The origin of contrast in MRI is then described and the sources of image artefacts discussed. The chapter ends with two sections on practical imaging, one on the hardware that is required for MRI and another on the safety aspects of putting human volunteers inside MR scanners.

Chapter Three is concerned primarily with brain function. An outline of the main techniques used for functional neuroimaging, including positron emission tomography, magnetoencephalography and magnetic resonance spectroscopy, is given. Some basic aspects of neuroscience are then covered, and the main structures in the brain, its biochemistry and functional organisation are described. The technique of fMRI is covered in detail, describing how brain activity affects the contrast in the MR image, how experiments are performed and how the data are analysed.

The three chapters that follow cover improvements in the technique of fMRI. Chapter Four deals with the optimisation of MRI for functional brain imaging. Experiments that determine the optimum image echo time (TE) to use in an fMRI study are described. These use a technique that acquires six images, each with a different echo time, in a single shot. The reduction of image artefact is the subject of the next section. A number of post-processing techniques that reduce the Nyquist or N/2 ghost are compared for effectiveness on fMRI data sets and a method for removing the bands on images that result from external r.f. interference is demonstrated. Finally in this chapter, a technique for the fast acquisition of inversion recovery anatomical reference scans is described.

The implementation of the technique of interleaved echo planar imaging is the subject of the fifth chapter. The reasons for using the technique are explained, and the problems that have arisen in its use for high resolution, low distortion fMRI are discussed. Chapter Six covers aspects relating to the analysis of fMRI data to produce statistically robust results. The theory and implementation of a number of image pre-processing techniques is described and the statistical techniques that can be used to detect regions of activation are outlined. Two new statistical analysis methods are described, both of which make no assumptions as to the shape of the activation response that is expected. The theory behind software that is used to draw inference from the resulting statistics is explained and ways of presenting the final data are described.

Chapter Seven presents the results from an fMRI study of motor function in normal volunteers and patients with Parkinson's disease. Aspects of the stimulus paradigm design and implementation are covered, as is the optimisation of the imaging and experimental protocol.

1.4 References

The material on the history of the study of brain function comes from:

- Clarke, E. and Dewhurst, K. (1972) 'An Illustrated History of Brain Function', Sandford Publications, Oxford.

Detailed references on the history of PET and fMRI are given in Chapter 3, however basic introductions to these topics are given in:

- Ter-Pogossian, M. M., Raichle, M. E. and Sobel, B. E. Positron Emission Tomography. *Scientific American* October 1980.
- Pykett, I. L. NMR Imaging in Medicine. *Scientific American* May 1982.
- Raichle, M. E. Visualizing the Mind. *Scientific American* April 1994.