Imaging the Brain in Mental Illness

Yale University, New Haven, Connecticut, USA
and
National Institute of Mental Health, Bethesda, Maryland, USA

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(November 2007)

A report for the Winston Churchill Memorial Trust
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Acknowledgements

I would like to thank the Winston Churchill Memorial Trust for funding my visit to USA to observe imaging technologies for studying the brain in mental illness. I am indebted to Professor Philip Cowen and Dr Trevor Sharp for supporting my application to the Trust. In addition, I would like to thank Berkshire Healthcare NHS Foundation Trust for granting me 4 weeks study leave to be able to undertake this Fellowship.

Furthermore, I would like to thank my hosts at Yale University and National Institute of Mental Health (NIMH):

Yale University: I am very grateful to Dr Zubin Bhagwagar who acted as my main host at Yale University and helped to facilitate my Fellowship there. I am particularly grateful to Dr Graeme Mason for explaining some of the Magnetic Resonance Spectroscopy protocols that they use at Yale. In addition, I am grateful to Dr Robert Malison, who was kind enough to allow me to attend the Psychiatric Residents Educational Programme while at Yale. Innumerable thanks also go to the other members of staff who were very helpful and incredibly generous with their time. These include Dr Jonas Hannestad and Dr Gerard Sanacora as well as Research Fellows Barbara Ruf, Kathleen Maloney, and Dr Aybala Saricicek.

NIMH: I thank Ms Amy Blackburn of the NIH Visitors Information Centre for giving me a tour of the NIH main campus with a very good commentary on the functions of many of the units. I am very grateful to Dr Husseini Manji Director of the Mood and Anxiety Disorders Program at the NIMH and to Dr Wayne Drevets for giving me their time in answering many of my questions about their research. I also thank Dr Giacomo Salvadore for showing me around the Imaging Facilities at NIMH.
SECTION 1

Introduction

I have always believed that broadening one’s horizons can be very beneficial at both the personal and the professional levels. This is how I came to find out about the Winston Churchill Memorial Trust Travelling Fellowship. I had initially come across the Fellowship several years ago, but did not feel that I was ready to apply until the Autumn of 2006. As a psychiatrist I was fully aware that the causes of mental illness were multi-factorial and included psychosocial aspects. Nevertheless, I needed to be specific in terms of what I wanted to learn and observe if I was to be awarded the Travelling Fellowship. In particular, I had noticed that the ‘Science and Technology’ category recurred every year. I knew that my interests lay in applying science and technology to answer research questions in the field of medicine. I had also always been impressed by the use of imaging technologies to study the brain. As a psychiatrist, I was most interested in how the brain might be altered in psychiatric disorders and how imagining techniques might help us to understand the pathology behind mental illnesses by visualising alterations in the structure or function of the brains of patients suffering from mental disorders.

As an avid reader I knew that Sir Winston Churchill had suffered from instabilities in his mood including phases of depression, which he had referred to as his ‘Black Dog’. This had conjured up images of suffering in my head as well as an admiration for how he was able to become an extraordinary leader in a very difficult time in history, in spite of his depression and perhaps because of his will to overcome it. I was therefore determined to apply for a Winston Churchill Memorial Trust Travelling Fellowship to study ‘Brain Imaging in Mental Illness’. I felt that I would gain the most by visiting a country that was at the forefront of this type of technology, and so I chose to visit USA. Due to many other commitments, I felt that I would probably only be able to spend a maximum of 4 weeks away on study leave in USA. I knew from the scientific literature and from colleagues that there were a number of centres in USA that were investigating psychiatric disorders with imaging techniques. In the end I decided upon visiting the Department of Psychiatry at Yale University, New Haven and the National Institute of Mental Health (NIMH), Bethesda, Maryland. It was clear that investigators at Yale University were at the forefront of using Magnetic Resonance Spectroscopy (MRS) to study brain biochemistry in psychiatric patients, while many seminal images studies, including those using Positron Emission Tomography (PET), had emerged from units based at NIMH.

I decided that I would spend 3 weeks at Yale University and the Connecticut Mental Health Centre in New Haven as I was keen to observe or understand the set up with regards to the MRS studies there. Nevertheless, I believed that it was also important for me to visit the prestigious NIMH in Bethesda even if it was for 1 week. Here I could find out about both clinical and preclinical cutting-edge studies in the field of biological psychiatry. I planned my visit for the month of November 2007. I made my departure for 5th November 2007 and my return back to UK for 2nd December 2007.
My Background

My first degree was in Biochemistry at the University of Surrey. As I was enrolled on a Sandwich course I undertook the 3rd year of my degree at the National Poisons Unit in London. Here, I studied how lethality of overdose with antidepressants may be related to their membrane-stabilising properties. This spurred me on to specialise in Toxicology in the final year of my degree.

I then joined the Department of Pharmacology at the London Hospital Medical College in Whitechapel for a year where I was involved in carrying out research in basic neuropharmacology. However, I knew that I also wanted to become a doctor and so I left this post to study medicine at The Medical College of St Bartholomew’s Hospital. I was close enough to both the Royal London Hospital and Queen Mary Westfield College to be able to continue with some neuropharmacological research during my medical school vacations. After house jobs I knew that I wanted to specialise in Psychiatry. I did my Basic Speciality Training in London. However, after attaining my MRCPsyCh and MSc at University College London, I decided to move to Oxford. I was initially at Oxford University for Clinical Research Fellowships in biological psychiatry and basic neuroscience, but in recent years have resumed my Higher Speciality Training in General Adult Psychiatry in Oxfordshire, Buckinghamshire and Berkshire.

Mental Illness

Mental disturbance and its associated behaviours have been described since ancient times. However, it was not until the 20th century when expert-agreed definitions and classifications of different mental disorders or mental illnesses came into their own. As new clinical discoveries are made and as society has changed, then so has the way that mental disorders are classified. The two manuals that are currently in use are the ‘International Classification of Diseases’ and ‘Diagnostic and Statistical Manual of Mental Disorders’. Examples include mood disorders such as major depressive disorder and bipolar disorder, anxiety disorders such as obsessive compulsive disorder, and psychotic disorders such as schizophrenia.

Mood disorders and in particular depression, are a major cause of disability and may be increasing in prevalence, although this is disputed (Hafizi 2006). A number of complex factors come together to result in a mood disorder. Alterations in the structure or function of the brain are thought to subserve the symptoms of mood disorders. It is thought by biological psychiatrists that by understanding these alterations, then better treatments may become available. Brain imaging techniques have thus been employed to help identify the brain areas that may be altered in psychiatric disorders such as depression.

Brain Imaging

Many studies in neuroscience require the use of experimental animals or post-mortem human brains. These types of studies are very valuable and can in some instances lead to ideas that then bear fruit in future clinical studies. However, there are obvious limitations to both animal studies and human post-mortem studies. Brain imaging
techniques are therefore a great advance as they allow researchers to gather information on the living brain including those of human beings. These types of data can greatly add to the knowledge that is acquired through traditional neuroscience research.

Imaging technologies are used to visualise the structure of the brain or to examine its function, as well as study the effects of pathology or drugs on the brain. Some of these technologies and their applications to the study of mental disorders, in particular mood disorders such as depression, are described below:

**Structural Imaging**

**Computed Tomography**

Computed Tomography (CT) uses a series of x-rays with high resolution and computing to create cross sectional images of the brain. CT is often used in clinical settings to visualise brain pathology including injury to the brain. CT has allowed researchers to examine and quantify changes in the volume of the cerebral ventricles, or the ventricular to brain ratios. CT allows visualisation of deep brain structures. Some of the limitations of CT include exposure to ionising radiation and the relative lack of sensitivity in distinguishing gray matter (cellular brain substance) and white matter (tracts) from each other.

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) is considered an advance on CT as it does not require the use of x-rays to visualise the brain and is in some ways easier to operate. MRI technology uses a large magnet to create a magnetic field through which radio waves are passed. Radiofrequencies then emitted by each point in the brain are detected by sensors and converted to images by computer. The idea is that hydrogen atoms have different magnetic properties across different biological tissues (Paushter et al 1984). MRI has emerged as the pre-eminent imaging modality for visualising neurologic diseases in the central nervous system. MRI can be used to produce high-resolution anatomically-based images. However, the use of MRI is limited in a patient with an intracranial metallic implant or clip, or with a cardiac pacemaker. Nevertheless, using MRI technology, volume reductions have been observed in depression in the basal ganglia, prefrontal cortex and hippocampus (Konarski et al 2007).

**Functional imaging**

Beyond simple structural imaging, a number of imaging techniques are used to acquire data on brain function and dynamics. Analyses of blood perfusion allows for evaluation of brain function at the regional level, while metabolic indices and ligand binding studies provide information at the cellular and intracellular levels respectively. The techniques used include functional magnetic resonance imaging (fMRI), Magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single photon emission computed tomography (SPECT).
**Functional Magnetic Resonance Imaging**

Modifications in MRI techniques have provided us with fMRI which can provide functional and dynamic data rather than purely static data. fMRI measures rely on the paramagnetic properties of oxygenated and deoxygenated hemoglobin. Images of changing blood flow in the brain are created that are thought to be associated with activity in nerve cells. These signals are detected as blood-oxygen-level dependent (BOLD) contrast. fMRI is non-invasive, not associated with radiation exposure and allows repeat scanning. fMRI provides fairly good spatial and temporal resolution, but is sensitive to head movements.

**Magnetic Resonance Spectroscopy**

Magnetic resonance spectroscopy (MRS) is a technique that can provide metabolic information that can easily be integrated with MRI. With MRS one can measure brain biochemical metabolites *in-vivo*. MRS uses a resonant radiofrequency pulse and a magnetic field to detect within the sample of interest a nuclear signal, most commonly from a proton \([^1H]\) (Stanley 2002). Examples of other types of spectroscopy include \(^{31}P\) spectroscopy and \(^{13}C\) spectroscopy with different MR signal sensitivities.

\(^1H\) spectroscopy allows detection of N-acetylaspartate (NAA), amino acids such as glutamate (Glu), glutamine(Gln) and gaba-aminobutyric acid (GABA) and the simple sugar myo-inositol. \(^{31}P\) spectroscopy can detect the levels of adenosine triphosphate (ATP), phosphocreatinine and inorganic phosphate. Some of these and other compounds are described in more detail below.

**Compounds Detected by MRS in the Human Brain:**

**Lactate**

Lactate is the end product of glycolysis and is elevated in the brain if the tissue becomes ischaemic or if there are activated inflammatory cells such as macrophages present.

**N-Acetylaspartate**

N-acetylaspartate (NAA) has also been detected using proton MRS and has been suggested to be a neuronal marker, although approximately equal concentrations of NAA are found in white and gray matter, which may mean that NAA might be a marker of axonal integrity as well. Recent studies suggest that NAA changes might also be reversible.

**Amino acids**

The determination of the individual concentrations of the amino acids glutamine (Gln), glutamate (Glu), and GABA using \(^1H\) MRS has been difficult due to the complex spectral appearance of Glu/Gln (Glx). However, the use of higher field strengths above 1.5T has helped to improve the quantitation of these compounds (Srinivasan et al 2006).
Glutamate is the most abundant brain neurotransmitter in the brain, while Gln and Glu cycling accounts for 80% of glucose use by the brain (Magistretti et al 1999). Recent studies with the drug topiramate has shown that this drug leads to increases in brain Gln levels and this may be related to its role in the treatment of disorders such as bipolar disorder, eating disorders and alcohol dependence (Moore et al 2006). Similarly, GABA in the brain is thought to play a role in depression and schizophrenia. Its measurements require higher field strengths than 1.5 T or special spectral editing sequences.

**Creatine**

Creatine (Cr) is often used as an internal standard, because its levels are fairly constant across the brain and change little with pathology. Cr and phosphocreatine are found in rapid exchange with each other.

**Choline**

Choline (Cho) resonance is seen with compounds such as Cho, phosphocholine, glycerophosphocholine, and betaine. The levels of Cho in gray and white matter differ from each other and high concentrations are found in glial cells (Kotitschke et al 1994). Increases in the Cho peak are found with inflammation, myelin breakdown and malignancy.

**Myo-inositol**

Myo-inositol (mI) is a simple sugar that acts as glial marker, and is seen to be increased in inflammatory processes and with myelin breakdown.
Diffusion Tensor Imaging

It has been hypothesised that alterations in the connecting tracts of the brain may play a role in mood disorders. These tracts are often covered by myelin and are described as white matter. Some studies in the depressed elderly or in treatment-resistant depression have shown up white matter hyperintensities (Regenold et al 2005).

Diffusion tensor imaging (DTI) is able to measure the microscopic diffusion of water and hint at the microstructure of the brain including white matter bundles. DTI has revealed abnormalities in white tracts in some schizophrenic patients, but more studies on mood disorders are awaited.

Positron Emission Tomography

Positron Emission Tomography (PET) is a highly sensitive and quantitative imaging technique used in both clinical and research settings. It can be used to scan many different organs in the body including the brain. PET can provide a means of examining regional glucose metabolism, cerebral blood flow and pharmacology in vivo, both at rest and under activating conditions (Brooks 2005). Neuronal glucose metabolism can be monitored with \(^{18}\)F-2-fluoro-2-deoxyglucose, while regional cerebral blood flow can be observed with \(^{15}\)O-H\(_2\)O.

The study of brain receptors requires the use of selective radioligands. These radioligands are labelled with positron emitters (e.g. carbon-11, \(t_{1/2}=20.4\) min; fluorine-18, \(t_{1/2}=109.7\) min; bromine-76, \(t_{1/2}=6\) hr) produced within a cyclotron. For a radioligand to be useful in PET studies, its labelling needs to be stable, it needs to have sufficient affinity and high selectivity for the receptor under investigation and low non-specific binding, rapid permeation into the brain, and few metabolites, if any. If metabolites are present in plasma, then ideally they should be polar so that they cannot cross the blood-brain barrier easily.

A positron is a positively-charged electron which upon emission from the nucleus of for example an \(^{11}\)C or \(^{18}\)F combines with an electron. This process results in the production of two high energy gamma rays (511 keV) released from the site of annihilation at 180° from each other. These gamma rays exit the body and are detected using a series of highly sensitive external radiation detectors placed in parallel rings around the head. Individual detectors are constructed from scintillating crystals and have an amplification circuit. On entering the crystal detector the gamma rays are converted into visible photons which are amplified by a photomultiplier tube and are then converted into an electrical impulse. If the detectors linked in electronic coincidence pick up two emissions within a very short space of time one is able to make an estimate of an annihilation that occurred somewhere along a line joining the two detectors. With sufficient sampling of lines of events and angles, it is possible to reconstruct a 3 dimensional tomographic distribution of positron annihilation and hence radioactivity in the body. Reconstruction techniques are then used to create the PET emission scan.
Single Photon Emission Computerised Tomography

Single Photon Emission Computerised Tomography (SPECT) has a coarser spatial and temporal resolution and lesser sensitivity compared to PET. It uses commercially available gamma-emitter radionuclides with relatively long half-lives (e.g. iodine-123, $t_{1/2}=13.2\text{ hr}$; technetium-99m, $t_{1/2}=6\text{ hr}$). This means that SPECT scanners do not need to be located on the same site as the cyclotron. Early studies of depressed subjects with SPECT showed correlations between the severity of depression and reduced activity in frontal brain regions (George et al 1993).

Imaging in Mood disorders

In general, the results of functional imaging studies suggest that there may be regional alterations in the brain function of patients with major depressive disorder and bipolar disorder. In particular, an abnormal interaction between two neural systems within the brain may subserve dysfunctions in mood. These systems are the ventral system that comprises brain regions including the insula, the amygdala, ventral anterior cingulate and prefrontal cortex, and the dorsal systems which includes brain regions such as the hippocampus, dorsal anterior cingulate and prefrontal cortex (Phillips et al 2003).

Furthermore, MRS technology can detect levels of lithium in the brain (Soares et al 2001) and has also revealed abnormalities in the basal ganglia, thalamus and fronto-temporal regions of the brains of bipolar patients (Silverstone et al 2005).

Brain Imaging in UK

All of the imaging technologies described above have been used or are in used in UK. CT and MRI are used throughout the UK for diagnostic purposes, but also used in psychiatric research. fMRI is used in a number of centres including in Oxford, Cambridge and London, to study functional alterations in the brain of psychiatric patients. In addition, fMRI is used to investigate the brain regions that subserve emotions, memory etc. in normal healthy controls upon challenge with neuropsychological tests. PET research is currently conducted in the Hammersmith Hospital, Imperial College, London and Manchester University, Manchester. Proton MRS is currently being used at Oxford University to study cortical amino acid levels in patients with mood disorders.
SECTION 2

Aims of the Fellowship

The aims of my Winston Churchill Travelling Fellowship were to gain an understanding of:

1. Brain imaging studies conducted at Yale University including dynamic $^{13}\text{C}$-MRS within a dedicated clinical research unit
2. Pre-clinical studies and their link to clinical brain imaging studies including PET imaging at National Institute of Mental Health.

Itinerary

Dates: 5th November-2nd December

Yale University: First 3 weeks

National Institute of Mental Health: Last week

1. Yale University

Over my 3 week visit to New Haven, I was able to visit a number of sites at Yale University and was also able to interview a number of researchers there. My main point of contact at Yale University was Dr Zubin Bhagwagar, who is an Assistant Professor there. He is responsible for running the Clinical Neuroscience Research Unit.

Clinical Neuroscience Research Unit

The Clinical Neuroscience Research unit (CNRU) is a unique setting in that it brings together Yale research, clinical, educational, and public psychiatry missions. The CNRU is based within the Connecticut Mental Health Centre (CMHC). The mission of the CNRU is to teach psychiatric residents excellence in clinical care while answering important research questions. This is in order to further understanding of the field of neuroscience while improving patient care.
The programme at the CNRU included Research Meetings with Principal Investigators, Case Conferences, Psychiatry Grand Rounds, Neuroscience Research Training Program (NRTP) Seminars and Advanced Psychopharmacology PGY III Classes. I was able to observe how clinical case conferences were conducted for inpatient clinical research patients. The inpatients are all admitted with a clinical research protocol in mind, including brain imaging protocols for MRS or PET. At the same time they are clinical patients with clinical complaints that also have to be addressed.

Yale MR Imaging Research Centre

The new Yale MR Imaging Research Centre is part of a research and teaching facility at Yale University School of Medicine. The imaging facilities include both laboratory and imaging space. There is dedicated space for electrophysiological and psychological testing, for computing, and image and data analysis. It houses the research magnets and the personnel in one contiguous facility and thus contains all the resources for integrated studies of human brain.

Fig.4. Yale MR Imaging Research Centre

$^{13}$C Magnetic Resonance Spectroscopy

I was fortunate enough to have discussions with Dr G Mason who was able to explain to me the science behind $^{13}$C MRS protocols. $^{13}$C MRS allows for a dynamic picture of brain metabolism, does not produce radioactivity, provides a high spectral resolution, and allows for the simultaneous measurement of the rates of several metabolic pathways. Relative to the $^{12}$C atom, the $^{13}$C isotope is in low abundance (about 1%) and consists of 6 protons and 7 neutrons. Although it is an isotope it is not radioactive. In MRS studies, $^{13}$C is often administered as $^{13}$C glucose or $^{13}$C acetate. The $^{13}$C label can be introduced into the glucose molecule on different carbon atoms. For example, the use of glucose at the C1 position has helped to yield rates for glucose oxidation, glutamate-glutamine transmitter cycling and GABA synthesis, while that at the C2 position has helped to yield estimates of the relative flow of the Krebs cycle to glutamine synthesis in astrocytes.
In $^{13}$C MRS glucose studies, glucose is administered as an infusion that should be sterile and free from pyrogens and kept frozen at minimum -20 °C. All volunteers or patients have baseline investigations including an ECG and are screened for a history of cardiovascular disease, cerebrovascular accidents or diabetes mellitus. Patients are fasted overnight, and then on the day of the study they have an intravenous catheter inserted in each forearm. One is used to infuse $^{13}$C glucose over a 2 hour period, while the other is for drawing blood samples. This is so that blood glucose levels are closely monitored to make sure that they are in the required range and at steady level of 180 mg/dL. Glucose is metabolised into a number of products in the brain including glutamate and GABA which can then be detected via MRS imaging and further spectral editing.

One of the findings generated from $^1$H MRS in depression has been that of lowered levels of cortical GABA. However it has been $^{13}$C MRS studies that have shown that GABA levels may be lower in depression by 30-50% due to the synthesis of GABA being slower in depression (Mason and Krystal 2006). $^{13}$C MRS studies of glutamate/glutamine cycling and GABA thus permit an examination of the interactions between neurons and glia.

![Fig.5. Molecular forms of D-glucose and acetate](image)

![Fig.6. Metabolism of Glucose and Glutamate/Glutamine cycling](image)
PET Centre

I visited the PET Centre at Yale University. This is actually a new and growing Centre and its primary focus is to conduct scientific research in humans and experimental animal and some imaging for clinical patient management. The Yale PET Centre has 2 scanners: a CTI HR+ and a HRRT scanner. There is also space for a dedicated animal PET scanner. On site there is also a state-of-the-art radiochemistry facility with Mini hot cells and automated radiochemistry modules for the development and use of PET radiopharmaceuticals labelled with $^{11}$C, $^{15}$O, $^{13}$N, and $^{18}$F. Other important sections of the PET Centre include the PET physics and data analysis group and the biology group. The PET psychics and data analysis group oversees the operation of the PET scanners, develops new methods to optimise acquisition of data and also runs an image analysis laboratory. The biology group is comprised of scientists with a purpose to design new radiotracers, and to evaluate and validate them as in vivo agents. The PET Centre has scientific collaborations with other School of Medicine departments, but is keen to develop ties to basic science departments and with industry partners. While I was in New Haven radiotracers were being used to study noradrenaline reuptake transporters in cocaine users, 5-HT$_{1B}$ receptors and serotonin reuptake transporters in mood disorders.

Lectures

While at Yale, I also attended a number of lectures. These included lectures on MRI physics entitled ‘Nuclei and their applications’, ‘Safety and MRI scanning’ and ‘Scalar coupling and spectral editing’. Another was a guest lecture given by Professor J. Gabrieli from Harvard University and was on the topic of ‘Development of Declarative Memory in Human Brain’. Data obtained from studies with children suggest that the prefrontal cortex continues to be pruned with age, while the medial temporal lobe develops early on and remains constant in volume after age of 8. Grand Round lectures attended were: ‘Human laboratory model of smoking lapse behaviour’, ‘Cognitive control and Cocaine dependence’. The NRTP seminars included Journal Club meetings where scientific papers were presented, discussed and appraised. Topics discussed included the validity of a mouse model of premenstrual dysphoric disorder. I also attended an NRTP psychopharmacology seminar entitled ‘extra-pyramidal effects of antipsychotic drugs’. I was also invited to present some of my own research for the NRTP residents on 16th November 2007. I thought that I was well received and a number of probing questions were asked that I found to be very helpful afterwards.

Neuroscience and Psychoanalysis Conference

While I was in New Haven I attended a conference on Neuroscience and Psychoanalysis. This conference was in memory of F. Morton Reiser and held in St Thomas More Chapel on 15th November 2007. A number of notable speakers including Noble Laureate Professor Gerald M. Edelman presented their research findings at this conference. The topics included ‘From Brain Dynamics to Consciousness: How Matter Becomes Imagination’, ‘Local and Global Brain Activity’ and ‘Language in Dreams and Other Things’. The afternoon conference was followed by an evening talk at Davenport College entitled ‘Freud meets his porcupine: Sigmund Freud, James Jackson Putnam and the American Dream’.
2. **National Institute of Health**

The National Institutes of Health (NIH) is a part of the US Department of Health and Human Services and is the primary Federal Agency for conducting and supporting medical research. It is composed of 27 Institutes and Centres, and also provides leadership and funding for other institutions around the world. The NIH Bethesda Campus is home the Clinical Centre which is the world’s largest clinical research hospital. Some of the research eventually translates from laboratory discoveries to better clinical treatments, therapies and interventions for patients. The types of research conducted at NIH are varied and range from molecular biochemistry to clinical trials and veterinary research.

**NIH Visitor Information Centre**

I was initially looking for an overall understanding of the organisation of NIH. I therefore went on a couple of tours conducted by the staff of the NIH Visitor Information Centre. This centre provides tours and overviews of NIH for individuals and groups including school children, university students and health and science professionals. I found the tours very informative and the staff extremely helpful.

**National Institute of Mental Health**

The National Institute of Mental Health (NIMH) is part of the NIH and is the world’s largest scientific organisation that is dedicated to research on mental disorders. Its focus is on understanding the causes of mental disorders, finding better treatments and preventative strategies as well as promoting mental health. NIMH is organised into a number of divisions. These are listed as follows:

- Division of Neuroscience and Basic Behavioral Science (DNBBS)
- Division of Adult Translational Research and Treatment Development (DATR)
- Division of Developmental Translational Research (DDTR)
- Division of AIDS and Health and Behavior Research (DAHBR)
- Division of Services and Intervention Research (DSIR)
- Division of Extramural Activities (DEA)
- Division of Intramural Research Programs (DIRP)

**Mood and Anxiety Disorders Program**

My visit focused on the Mood and Anxiety Disorders Program (MAP) of the Division of Intramural Research Programs (DIRP). My main point of contact here was Dr Husseini K. Manji, who is the Chief of the Laboratory of Molecular Pathophysiology and the Director for MAP at NIMH. My other point of contact was Professor Wayne Drevets who is the Chief of the Section on Neuroimaging for MAP. MAP is the largest research program focused on mood and anxiety disorders in the world. Researchers here investigate the diagnosis, treatment and prevention of serious mood and anxiety disorders. The program is divided into groups studying in depression, bipolar disorder, anxiety disorders, posttraumatic stress disorder and obsessive compulsive disorder. A range of research methods are used here including neurochemical, neuroendocrine, neurophysiological and neuroimaging techniques.
Laboratory of Molecular Pathophysiology

The focus of the Laboratory of Molecular Pathophysiology is the study in mood disorders of changes in gene and protein expression profiles regulating neuroplasticity and cellular resilience. An integrated preclinical and clinical strategy is utilised with the focus on understanding the molecular and cellular mechanisms of action of mood stabilizing drugs. Current preclinical projects include genomics and proteomics strategies to study brain signaling networks, morphometric and histochemical analyses of brain tissue from transgenic and knockout mice, as well as human postmortem brain tissue. Current clinical studies involve the use of signal transduction modifiers (e.g. protein kinase C inhibitors) as potential novel agent for the treatment of mood disorders. Another clinical study is the use of morphometric brain imaging to examine the neurotrophic effects of mood stabilisers.

In a recent study funded by NIH, but carried out at Stony Brook University Medical Center, Brookhaven National Laboratory and Cold Spring Harbor Laboratory has shown that it is possible to use MRS to image a biomarker of neural stem and progenitor cells (NPCs) in the living human brain and thus monitor neurogenesis, the development of new neurons (Manganas et al 2007). This is the first non-invasive approach to identify NPCs in the human brain. The signal processing method used, allowed researchers to separate the biomarker from other signals in the brain in the MRS data. The researchers observed major differences in the concentrations of the biomarker between two human brain regions, the hippocampus and cortex. They also found that the biomarker decreased with age. The technology may prove to be a major discovery leading to better treatments for disorders such as depression.

Fig.7. Magnetic resonance spectroscopy to detect stem/progenitor cells in the live human brain. Also detected are other cells in the brain, such as neurons (NAA), and glial cells (Cho, ml) and their functional state (Cr).

Dr H Manji explained that this was an exciting discovery and it has led his group to develop a mouse model that allows suppression of neurogenesis. Their plan is to observe if this suppression could lead to behavioural changes, including depressive behaviours, and to see if suppression of neurogenesis would stop antidepressants from being effective. They plan to use the spectroscopic measures developed above to examine these hypotheses.
Section on Neuroimaging

The Mood and Anxiety Disorders Neuroimaging Section at NIMH uses imaging to study the neurobiological bases of mood and anxiety disorders. The same subjects are studied using multiple techniques to provide complementary data. PET and MRS are applied to measure brain receptor pharmacology, chemistry and neurotransmitter function. PET and fMRI are used to map brain regions showing physiology changes in both normal and pathological emotional states. Structural MRI is used to examine brain structure and localise pathology in mood and anxiety states secondary to brain lesions. These assessments are also integrated with genetic, clinical and laboratory data.

Studies are conducted with several aims including:

1) To characterise mood and anxiety disorder phenotypes using biological markers rather than by nonspecific, subjective, clinical symptoms alone.
2) To determine how the brain normally modulates stress responses.
3) To delineate the neural circuits manifesting depressive and anxiety disorders.
4) To identify abnormalities of brain receptors and chemistry in mood and anxiety disorders.
5) To assess the effects of sex hormones on brain chemistry and function, in order to understand the greater risk of depressive and anxiety disorders in women, post partum depression and premenstrual dysphoric disorders.
6) To elucidate the mechanisms of drug treatments to help in the development of better therapies. more effective therapies.
7) To characterise neuroimaging abnormalities in samples at high familial risk for developing mood disorders.

Professor W Drevets explained that the variability seen with PET data may be partially explained with correlations with data obtained from receptor genotypes. He also explained how glutamate/Gaba abnormalities in mood disorders as suggested by preclinical and neuroimaging, how recently led them to test the anti-glutamate receptor drug riluzole as a possible psychotropic agent in the treatment of depression in patients.
National Library of Medicine

While at NIH, I visited the National Library of Medicine (NLM). This is a library that has served scientists, lecturers and doctors for centuries, but has also begun to provide information services for the general public via the world wide web. ‘Medline Plus’ and ‘PubMed’ represent examples of free internet-based resources provided by the NLM. Medline Plus is a free and up-to-date health information website, while PubMed is a web-based literature database that provides free access to MEDLINE, a database of more than 15 million bibliographic citations and abstracts in the fields of medicine, nursing, dentistry, veterinary medicine, healthcare systems and preclinical sciences. At the time, the NLM had an interesting interactive exhibition called ‘Visible Proofs-Forensic views of the body’. There were exhibits on the history and the rise of forensic medicine and on how recent advances in DNA analysis have helped in solving criminal cases. The exhibition included information on the use of x-rays and imaging technologies such as CT and MRI in forensic investigations.

NIH News in Health

NIH ‘News in Health’ is a monthly newsletter produced by NIH. One of the editions was particularly interesting in that it had a number of articles on mental health research. These included a pilot study on the use of an NK\textsubscript{1} receptor antagonist in the treatment of post traumatic stress disorder. I was interested as some of my own research has been on NK\textsubscript{1} receptors in the brain. Another article was on why some alcoholics benefit from medication and counselling and some don’t. Research at NIH’s national Institute on Alcohol Abuse and Alcoholism had shown that sufferers can be grouped into different alcoholism subtypes depending on family history, personality and other factors which could then help to predict response to treatments. Finally another article that I noticed which was most relevant to my visit was entitled ‘Brain Imaging Reveals Joys of Giving’. It appears that volunteers given an online account of $100 would show activations in pleasure-related centres of the brain when they received money, saw money go to a good cause or donated money. This was thought to be related to the ‘warm glow’ that some people get when they donated money to a good cause. This shows that imaging studies in normal healthy volunteers can also be very valuable in understanding the mechanism of brain processes including the pleasure centres.
SECTION 3

Conclusions

It appears that at both Yale University and NIMH, having a dedicated inpatient clinical research facility is extremely useful for conducting clinical research. Also at both institutions there is an emphasis on translational medicine. In recent years, UK has followed USA in providing more funding towards translational research.

Future Directions

While structural imaging techniques are used to rule out organic causes of mental disturbances, at present, functional neuroimaging methodologies are not used to help with the management of patients with psychiatric disorders. However, these techniques hold great promise for understanding the neuroanatomical substrates for psychiatric disorders. In mood disorders at least, neuroimaging approaches are being combined and correlated with cognitive measures, neuroendocrinology and genotyping (Konarski et al 2007). Furthermore, PET ligand studies are being increasingly used by the Pharmaceutical industry to guide with medication dosing. Therefore, technological developments in MRS and PET are likely to aid in gaining a better understanding of the pathology behind psychiatric disorders and in the development of drugs for these disorders.

Future neuroimaging studies will also benefit from advances in MR magnet strength. One group has shown excellent spectra from human brain at 7 T (Tkac et al 2001). For higher field proton MRS, optimal signal-to-noise ratio gains may be achievable at smaller voxel sizes than are currently being used at 1.5 T. A further benefit might be the use of oral glucose with $^{13}$C MRS studies. If the loss in sensitivity could be minimised, then this would be more tolerable for patients and volunteers than intravenous glucose. Other useful technical advances would be with tissue segmentation techniques, diffusion tensor imaging, simultaneous analyses of the findings of functional and structural neuroimaging and longitudinal analysis of the same patients in the acutely depressed and recovered states (Konarski et al 2007).

Follow up

On my return to UK in December 2007, I reported back some of my findings to Professor Grasby at the PET unit, MRC Clinical Sciences Centre, Hammersmith Hospital, London. In addition, I was asked to give a talk on emerging options in bipolar disorder at Prospect park Hospital, Reading. I was able to incorporate some of what I had learnt on my Churchill Fellowship in USA. My visit and my funding by the Winston Churchill Memorial Trust was also described in a short article in the February 2008 edition of ‘Newsline’, the monthly bulletin produced by the Berkshire Healthcare NHS Foundation Trust. I have arranged to speak about my fellowship to the Thameslea Association in September 2008.
References


