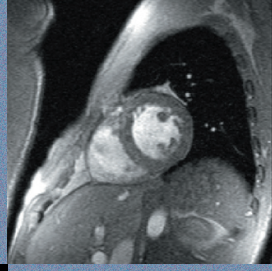
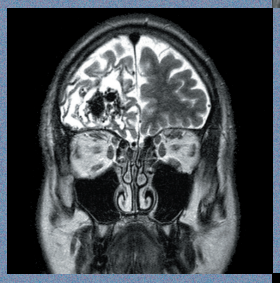
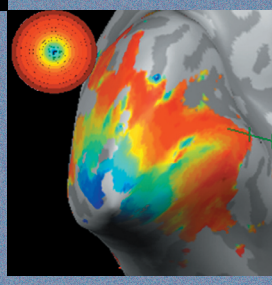
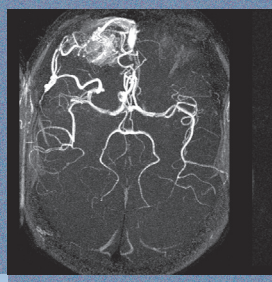


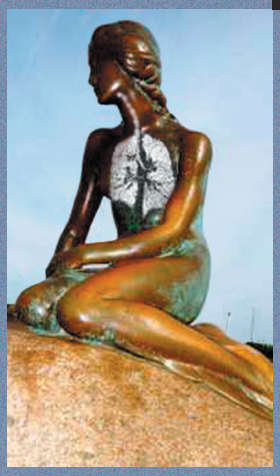




DRCMR

Annual Report 2004





Danish Research Centre for Magnetic Resonance

Introduction

This report summarizes the aims and organization of the Danish Research Centre for Magnetic Resonance (DRCMR), also known as the Department of Magnetic Resonance, at Hvidovre Hospital and describes the accomplishments of the DRCMR Staff during 2004.

The main aim of the DRCMR is to advance the use of magnetic resonance as a clinical and investigative tool in biomedical science. Consequently, DRCMR Staff employ state-of-the art instrumentation and bioinformatics tools for the diagnosis and management of medical patients and for a range of biomedical investigations. The clinicians and investigators of the DRCMR are active participants at national and international level in the community of biomedical scientists. In the last year, the Centre has continued to thrive and grow. The continued growth and the anticipation of continued development and expansion of our scientific activities requires that the DRCMR maintains a flexible internal organizational structure that facilitates both focused and integrative activities within the Centre. We are proud to present the Centre's recent accomplishments in our 2004 annual report.

Finally, I would like to express our gratitude towards the foundations and institutions that have supported us financially over the years and whose support has enabled the Centre to achieve and maintain its frontline position in MR research.

Olaf B. Paulson
Head of the DRCMR

DRCMR Profile

The Danish Research Centre for Magnetic Resonance (DRCMR), also known as the Department of Magnetic Resonance, is located in the middle of Hvidovre Hospital, in sections 340A and 340B. The Centre has 3 Siemens whole-body scanners. The newest, a Magnetom Trio (3.0 tesla) was installed in 2002 following a generous donation by the Simon Spies Foundation. Two other systems, a Magnetom Vision (1.5 tesla) and a Magnetom Impact (1.0 tesla), were installed in 1994. The two latter scanners have since been upgraded and continue to perform at a high level for the Centre's clinical and research needs. All three scanners are located in 340A which also includes facilities for clinical work and a conference room. To complement the clinical research, the Centre also has an experimental imaging and spectroscopy system, a Varian 4.7 Tesla scanner. This scanner was upgraded towards the end of 2004 to provide a modern system suitable for MR studies of small animals. The experimental scanner is located in section 340B which also holds facilities for data analysis and research.

Contents

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Dansk Resumé

Denne rapport giver et indblik i målene, visionerne og organisationen af MR-afdelingen på Hvidovre Hospital og beskriver afdelingens aktiviteter i 2004. Én af afdelingens styrker er netop tværfagligheden af aktiviteterne, der spænder fra et aktivt klinisk miljø med en lang række diagnostiske MR-tjenester til et omfattende forskningsprogram, der dækker klinisk MR såvel som basal forskning. Centret blev grundlagt efter en stor donation fra Simon Spies i 1984 og allerede fra starten var der lagt lige vægt på såvel forskning som kliniske anvendelser. I 2002 sikrede Simon Spies Fonden med donationen af landets første højfeltsskanner, at afdelingen er forblevet i front. Afdelingen råder således i dag over 3 humane MR-skannere med feltstyrker på hhv. 3,0, 1,5 samt 1,0 tesla. Derudover råder afdelingen over en 4,7 tesla dyreeksperimentel skanner, der blev gennemgribende opgraderet i 2004.

Dette har sikret international anerkendelse i form af blandt andet projektstøtte fra EU, samarbejde med udenlandske forskningsinstitutioner, omfattende publikationsaktivitet i internationale tidsskrifter og udvælgelsen af afdelingen til MR-evalueringscenter ved internationale medicinafprøvninger. Det er lykkedes afdelingen at fastholde en udenlandsk topforsker, professor i psykiatri og radiologi, Terry Jernigan, i en delt stilling mellem MR-afdelingen og en stilling som centerleder i San Diego.

Det glæder os overordentligt at denne indsats også er blevet bemærket i Danmark, hvilket blandt andet i 2004 har givet anledning til at afdelingens chef, professor Olaf B. Paulson, er blevet tildelt én af landets fornemste priser, Mogens Fogs Jubilæumspris, som anerkendelse for en enestående indsats for fremme af dansk neurologi og neurologisk forskning både nationalt og internationalt.

Overview of 2004

A unique strength of the Danish Research Centre for Magnetic Resonance (DRCMR) is the multidisciplinary nature of its activities. The Centre is home to an active clinical department providing a full range of diagnostic MRI services. Patient referrals come from a broad range of referral sources, including other hospitals in Copenhagen and throughout the eastern parts of Denmark in addition to Hvidovre Hospital. The clinical services of the department are performed alongside the investigative imaging, providing valuable integration between primary clinicians and clinical researchers.

Distinguishing the DRCMR from other academic radiology settings in Denmark is the juxtaposition within the Centre of a vigorous basic research program with the patient-oriented activities of the department. This ensures the highest level of scientific support for the Centre's biomedical mission, and places it at the forefront of MR method development. Through interaction with partners in the Copenhagen Brain Research Center, the DRCMR also participates in groundbreaking research in neuroinformatics, neuropharmacology, and cognitive science.

Imaging facilities

The Centre has 3 Siemens whole-body clinical scanners. The newest, a Magnetom Trio (3.0 tesla), was installed in 2002 after a generous donation from the Simon Spies Foundation. This new equipment is state-of-the-art as further enhancements and upgrades have been performed since. The two other clinical scanners, a Magnetom Vision (1.5 tesla) and a Magnetom Impact (1.0 tesla), were installed in 1994. These scanners have since been upgraded and continue to perform at a high level in support of the Centre's clinical and research needs. All three clinical scanners are located in area 340A of the hospital, where there are also facilities for clinical work and conferences.

In addition, the Centre has an experimental Varian 4.7 tesla scanner, suitable for MR studies in small animals. The experimental scanner is located in area 340B where there are also facilities for data analysis and other research activities. In 2004 a complete upgrade of the experimental animal scanner took place. Only the old magnet and a newer gradient coil remains from the old instrument, so in effect the result is a new scanner with state-of-the art hardware and software. This 4.7 tesla system is the only modern MR scanner in Copenhagen for studies of small experimental animals. It has fast imaging capabilities necessary for special studies such as functional imaging. Funding contributions from several sources, including Hvidovre Hospital, have made the planned upgrade possible. The scientific group, working mostly in preclinical research (including two senior researchers, a PhD student and two technicians), have started to implement the new techniques essential for their future studies.

Departmental organization

With new and upgraded MR systems and increasing numbers of staff, the department has undergone a restructuring and a new organizational arrangement implemented. Four (overlapping) groups of investigators have begun to meet regularly to exchange information and review the progress of their projects: a group of investigators focused on method development (Methods Group), a group of investigators conducting preclinical research in the animal facility (Preclinical Group), a group conducting human brain research (Brain Research Group), and a group conducting rheumatology research (Rheuma Group). Each group has a group leader charged with organizing the agenda and chairing the sessions, and this individual represents the group of investigators on the Research Coordinating Committee (RCC). The RCC is comprised of the DRCMR research leaders, and the committee meets weekly to review the progress of the research and to discuss issues of general interest, regarding both scientific and administrative matters.

Clinically orientated activities

The Centre's is a provider of local and national radiological services and compared with 2003, this last year has seen an almost 5% increase in the numbers of patients investigated. The department's radiological expertise is also in demand as the Centre becomes more established as a reading and MR-coordination site for several large clinical trials. An essential component of these trials is data analysis and the Centre has made considerable effort and progress in establishing a "configurable" analysis pipeline. MR images acquired using sequences designed to obtain differing morphological, physiological or functional information can be entered into the 'pipeline' and automatically analyzed using a wide range of methods including alignment, intensity correction and segmentation. There is little doubt that this will be of major benefit to most patient studies in the future.

2004 and the future

The Danish Research Centre for Magnetic Resonance is led by Prof. Olaf Paulson, a scientist whose contributions to neuroscience have been recognized again this year by the 2004 Mogens Fog Prize for his outstanding contribution to neuroscience. The Centre would like to take this opportunity to congratulate him on another prestigious award.

The new 3 tesla whole body system provides a demanding environment where researchers continue to invest significant effort developing new powerful imaging and spectroscopy methods. The high quality of morphological and functional images obtained at 3 tesla ensures that the system will continue to have an important future in the department's research activities. It is the department's hope that it will be possible to continue the implementation of new hardware and remain in the international frontline.
The accomplishments of the year, described within this report, illustrate the depth and breadth of expertise within the department. Prof. Terry Jernigan continues to function in the department as a visiting professor bringing her experience as a clinical neuropsychologist and as co-director of the Laboratory of Cognitive Imaging to the Centre. The Centre, therefore, continues to attract scientists from abroad to make the DRCMR a truly international environment in which to work. The interaction between radiologists, clinicians, psychologists, physicists and engineers together with other scientists from different disciplines both within the department and collaborating centres continues to create a rich multi-disciplinary environment to pursue MR research and apply it to clinical problems.

With the anticipated expansion of the facilities and staff numbers over the next year, the department is confident that it will continue to make significant scientific contributions and remain at the forefront of MR research at an international level.

Professors Olaf Paulson (DRCMR) and Jes Olesen (Copenhagen University Hospital, Glostrup) receive the Mogens Fog Jubilee Award. The awards were given by the Neurological Research Foundation on the occasion of Mogens Fog's 100-year birthday as recognition of exceptional efforts in the advancement of Danish neurology and neurological research, both nationally and internationally.

Organisation and Staff

Department Chair

Olaf B. Paulson, DMSc, Professor

Senior staff, Clinical

Margrethe Herning, MD, Senior Physician and Clinical Chief
Anne-Mette Leffers, MD, Senior Physician
Sussi Larsen, Head Technologist

Senior Staff, Research

Irene K. Andersen, PhD, Clinical Physicist
William Baaré, PhD, Psychologist
Ellen Garde, MD, PhD
Lars G. Hanson, PhD, Chief Physicist
Maria J. Miranda, MD, PhD
Poul Ring, Engineer
Egill Rostrup, MD & Human Biologist
James Rowe, MD, PhD
Ian J. Rowland, PhD, Chemist
Karam Sidaros, PhD, Engineer
Lise Vejby Søgaard, PhD, Physicist

Junior Staff, Clinical

Annika Reynberg Langkilde, MD, PhD
Camilla Gøbel Larsen, MD
Henrik Meelby, MD
In addition residents from the Department of Radiology rotate through DRCMR for periods of 2 months.

Junior Staff, Research

PhD students
Daniela Balslev, MD
Mark Schram Christensen, Engineer
Tim Dyrby, Engineer
David Alberg Holm, MSc
Elizabeth Kalowska, MD
Katja Krabbe, MD
Henrik Lund, Human Biologist
Torben Ellegaard Lund, Engineer
Kristoffer Hougaard Madsen, Engineer
Henrik Kahr Mathiesen, MD
Annette Skræp Nielsen, MD
Kirsten Nielsen, MD
Robin de Nijs, Hospital Physicist
Dorthe Pedersen, MD
Thomas Z. Ramsøy, Psychologist
Charlotte Ryberg, Biologist
Trine Stavngaard, MD
Jon Wegener, MSc

Junior Researchers
Niels Broberg, Engineer
Matthew Liptrot, Engineer
Arnold Skimminge, Physicist
Martin Skov, MA Nordic Languages and Litterature
Kathrine Skak Madsen, Student

Research Assistants
Andreas Hansen, Medical Student

Technologists

Nina Hansen, Laboratory Technician
Sascha Gude, Laboratory Technician
Pia Olsen, Radiographer
Forough Sadolin, Radiographer
Helle Juhl Simonsen, Research Technician
Hanne Schmidt, Radiographer
Rune Mau, Computer Technician

Secretarial Staff

Laila Andersen
Jeannette Beck
Lotte Hansen
Lisa Juhl Simonsen
Ina Tech
Sussie K. Volkmann

Cleaning Assistants

Ruth Kielstrup
Elsebeth Nielsen

Visiting and Associated Staff

Senior Staff

Peter Born, MD, PhD
Terry L. Jernigan, PhD, Psychologist and Visiting Professor
Mikkel Østergaard, DMSc, PhD

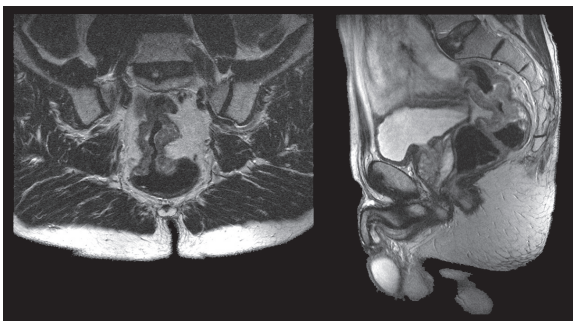
Junior Staff

Bo Ejbjerg, MD
Katrine Pagsberg, MD, PhD
Mikkel B. Stegmann, Engineer, PhD
Marcin Szkudlarek, MD, PhD
Susette Krohn Therkelsen, MD

Clinical Imaging

In 2004, 2496 patients underwent MR investigations. Of these, 1456 were referred from Hvidovre Hospital while the remaining patients were referred from other counties outside Copenhagen. Investigations of neurological diseases, e.g. suspicion of stroke, multiple sclerosis, intracranial tumours, intracranial haemorrhage, dementia and epilepsy are an important part of daily clinical radiology.

The Centre is a member of the 'EPI-KIR' group, a national organisation responsible for national epilepsy patient management that selects patients suitable for surgical intervention and is responsible for post-operative patient management. Consequently, many patients with epilepsy have been imaged for the presence of structural brain lesions causing seizures. Many of the patients with epilepsy were investigated with a specific protocol including volumetric measurements of the hippocampus regions, T2-relaxation measurements and, where appropriate, proton spectroscopy.



59-year old patient with rectal carcinoma.

MRI of patients with traumatic brain injury has been a growing part of our MR investigations. MRI applied in the sub-acute or early chronic phase, following severe head trauma, is a promising prognostic tool in this type of patient for whom long-term clinical outcome is very difficult to predict.

Patients with suspected intracranial vascular diseases such as arteriovenous malformations and aneurysms are regularly referred to the department for investigation with MRI and MR angiography. MR imaging and angiography are also used as screening methods in patients with "warning leaks" from cerebral aneurysms, in patients with manifest subarachnoidal haemorrhage and patients with a family history of cerebral aneurysms. MR angiography can be a valid supplementary investigation preoperatively. Tumours in the pituitary gland, vestibular schwannomas, meningiomas and other intracranial tumours are best investigated with MRI. Clinically suspected sinus thrombosis or tumours near the venous sinuses are now investigated using slow-flow MR-angiography as interventional x-ray based cerebral angiography is replaced as the modality of choice.

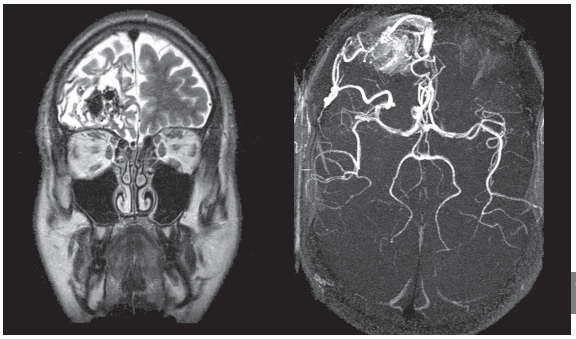
In paediatric radiology, MRI is used successfully in neonates with hypoxic complications that occur before, during or after delivery. Many children with seizures in the postnatal period were investigated since congenital malformations and metabolic diseases are well described with MRI.

Patients with suspected cervical spinal stenoses or suspected cervical disc herniation are also preferentially investigated with MRI. Suspicion of lumbar disc herniation, post-operative recurrent disc herniation, or infection, MRI is the preferred diagnostic method. Also, intradural pathology such as tumours of the spinal cord, intradural meningiomas and neurinomas are well characterised by MRI.

Musculoskeletal MRI is an important clinical area and is rapidly replacing diagnostic arthroscopy in the evaluation of meniscal lesions, lesions in the cruciate ligaments, collateral ligaments and damage to the cartilage. In the shoulder, MRI is used in diagnosing labral lesions, rupture of the rotator cuff and so forth. Preoperative investigation of musculoskeletal tumours can determine the extent of disease and help treatment planning potentially resulting in limb-saving operations. Metastatic bone disease is also best diagnosed with MRI.

Increasing numbers of scans are being performed at the DRCMR on the abdomen. MRCP is the investigation of choice concerning the bile ducts and pancreatic duct when gallstones and obstruction are suspected. The alternative diagnostic ERCP is an invasive method associated with risk of morbidity and mortality.
MRI of perineal fistulas and rectal cancer are well established and the department has become a regional centre for rectal cancer MRI. It is the diagnostic method of choice for focal tumour staging thereby facilitating patient management.

In the coming year, we expect the 3T MR scanner to continue to bring new and better diagnostic imaging especially in the head and abdomen.



Arteriovenous malformation in the right frontal lobe.

Collaborations

The DRCMR collaborates and works closely with many institutions both nationally and internationally. Primary collaborators in 2004, especially those with whom common funding was obtained and those who participated in supervision of PhD students, are listed below.

National Collaborations

Basic Research

Informatics and Mathematical Modelling, The Technical University of Denmark
Department of Physics, The Technical University of Denmark
Department of Psychology, University of Copenhagen
Department of Physical Exercise and Sport Science, University of Copenhagen.
Department of Clinical Physiology, Copenhagen University Hospital, Rigshospitalet
Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet
Center of Functionally Integrative Neuroscience, University of Aarhus

Pre Clinical Research

August Krogh Institute, University of Copenhagen
BioCentrum-DTU, The Technical University of Denmark
Institute for Molecular Pathology, University of Copenhagen
Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet
Statens Serum Institut

Clinical Brain Research

Department of Psychology, University of Copenhagen
Department of Medical Physiology, Panum Institute, University of Copenhagen
Copenhagen University Hospitals
Department of Clinical Chemistry, Hvidovre
Department of Pediatrics, Hvidovre
Department of Neurorehabilitation, Hvidovre
Department of Neurology, Bispebjerg
Department of Psychiatry, Bispebjerg
Department of Neurology, Glostrup
Neurobiology Research Unit, Rigshospitalet
Sclerosis Research Unit, Rigshospitalet
The Memory Disorders Research Unit, The Neuroscience Centre, Rigshospitalet
The Neonatal Department, Rigshospitalet
Department of Psychiatry, Rigshospitalet

Clinical Body Research

Research Department of Human Nutrition, The Royal Veterinary and Agricultural University
Copenhagen University Hospitals
Department of Cardiology, Hvidovre
Department of Clinical Nutrition, Hvidovre
Department of Clinical Physiology, Hvidovre
Department of Respiratory Medicine, Hvidovre
Department of Respiratory Medicine, Gentofte
Department of Clinical Physiology, Rigshospitalet
Department of Rheumatology, Copenhagen University Hospital, Hvidovre
This department is one of the centre's main collaborators and Professor. Mikkel Østergaard is the leader of the rheumatology research group at the MR department. Through the rheumatology research group there is a broad and established collaboration with several rheumatological and radiological departments in hospitals both within and outside Denmark.

International Collaborations

Basic Research

Department of Radiation Physics, Lund University Hospital, Sweden
Institute for Clinical Neuroscience, Göteborg University, Göteborg, Sweden
Laboratory of Cognitive Imaging, University of California, San Diego, USA
Center for fMRI, University of California, San Diego, USA
Centre for Magnetic Resonance, University Hospital, Trondheim, Norway
Department of Clinical and Experimental Epilepsy, Institute of Neurology, London, United Kingdom
Center of Cognitive Neuroscience, Nijmegen, The Netherlands.
University Laboratory of Physiology, Oxford University, UK
Prism Lab, School of Psychology, University of Birmigham, UK

Clinical Brain Research

Laboratory of Cognitive Imaging, University of California, San Diego, USA
Robert Steiner Magnetic Resonance Unit, ICSM Hammersmith Hospital, London, United Kingdom
Wellcome Department of Imaging Neuroscience, London, United Kingdom
Institute of Clinical Radiology, Munich, Germany
Department of Woman and Child Health, Karolinska Institutet, Stockholm, Sweden

Clinical Body Research

Clinic for Anesthesiology, Radiology, Johannes Gutenberg-University, Mainz, Germany
Institute of Physics, Johannes Gutenberg-University, Mainz, Germany
Section of Academic Radiology, University of Sheffield, United Kingdom

International Multi-Centre Research Collaborations

The EU project: Automated Removal of Partial Volume Effects (PVEOut). Chaired by Prof. Bruno Alfano, Centro per la Medicina Nucleare, Naples, Italy.
The EU project: Leukoaraiosis and Disability in the elderly (LADIS). Chaired by Prof. Domenico Inzitari, Department of Neurological and Psychiatric Sciences, University of Florence, Italy.
European Task Force on Age-Related White Matter Changes. Chaired by Prof. Philip Scheltens, PhD, Academisch Ziekenhuis Vrije Universiteit, Amsterdam, The Netherlands.
The EU Polarized Helium to Image the Lungs (PHIL) project. Chaired by Prof. M. Leduc, PhD, Department de Physique Ecole Normale Superieure, Paris, France.
The EULAR and OMERACT collaborations concerning imaging in rheumatoid arthritis.

Copenhagen Brain Research Center

In April 2002, the Danish Research Centre for Magnetic Resonance entered a co-ordinated collaboration with other brain research institutions in the Copenhagen area, in the form of the Copenhagen Brain Research Center (CBRC). The centre consists of the following institutions:

- Department of Medical Chemistry, The Royal Danish School of Pharmacy
- H. Lundbeck A/S, Copenhagen
- Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital, Hvidovre
- The PET and Cyclotron Unit, Copenhagen University Hospital, Rigshospitalet
- Informatics and Mathematical Modelling, Technical University of Denmark
- Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet
- Department of Psychology, Faculty of Humanities, University of Copenhagen

Copenhagen Brain Research Center is established as a platform for interdisciplinary collaboration in brain research with a high international impact. In order to achieve this goal the partners of CBRC regularly meet, present, and discuss new projects. Numerous projects are carried out in collaboration between two or more of the partners, e.g. in form of combined supervision of PhD students in projects. Projects of interdisciplinary nature form the basis for joint grant applications.
(from the CBRC website: www.cbrc.dk)

Basic Research

Methodological innovations arise naturally in an environment where cutting-edge techniques are used to address problems in biomedical science. At the DRCMR, technical research projects invariably serve two specific roles. Firstly, the development of new advanced techniques is necessary to remain competitive, i.e. to provide first class research for the benefit of patients and society. Secondly, the methodological research, which is funded mostly from external sources, provides part of the Centre's basic infrastructure for the benefit of both the individual projects and the DRCMR.

For people who are new to medical imaging research, the level of technical complexity and necessary workload associated with MRI-based clinical research is normally quite surprising. As an example, consider a functional MRI investigation, where a series of brain images are acquired while the subject performs a specific task. Planning of the optimal task or paradigm requires understanding of the cognitive processes required to solve the given task as well as understanding how the actual neural activation is reflected in the measured signals. Once the paradigm that will be presented to the subject during the scan has been designed, it must be programmed on the computer that controls the stimulus presentation. Furthermore, optimising the image acquisition requires understanding the physical principles governing the image attributes. Once the data have been collected, a major part of the work still remains, namely post-processing of the thousands of images acquired during the investigation. This is performed on a separate computer system and typically involves several steps, such as realignment of the measured images to compensate for subject motion during the investigation, registration of the 3D images of different subjects to a common coordinate space, so that the measurements can be compared, and automatic grey and white matter segmentation of the brain performed. Finally, statistical analysis of the millions of pixel time series is needed to locate areas activated by performing the presented task.

This significant data analysis requirement was for the example of functional scanning only. Other MR techniques require similar levels of technical investment on a per-project basis. This requires highly skilled and specialised personnel with expertise in engineering, physics and computer programming.

The basic research at the Centre can be divided into four categories: development and optimisation of new MR sequences (MR physics), development of novel post-processing strategies and experimental design (MR informatics), investigation of the basic physiological factors reflected in MR images (physiology) and mapping of the cognitive functions in the brain (brain mapping). The activities of the Centre within each of these categories are described in the following.

MR Physics

Although numerous clinical MR sequences are provided with the MR scanners by the scanner manufacturers, there are a variety of research projects at the Centre that rely on sequences that are either written in-house or are modified versions of provided sequences. The Centre therefore has agreements with Siemens and Varian that give researchers access to the source code of the manufacturers' sequences. This eases the process of modifying and optimising MR pulse sequences.

In February 2004, Robin de Nijs started his PhD-project funded by a grant from the Danish Medical Research Council. He will be developing fast MR spectroscopic imaging (MRSI) for the 3T system using parallel imaging and other fast techniques together with Lars G. Hanson. The high field offers enhanced sensitivity but the methodological challenges are numerous. Quantitative single voxel spectroscopy (SVS) is another field of interest. Software to analyze SVS-spectra with low concentrations of phenylalanine

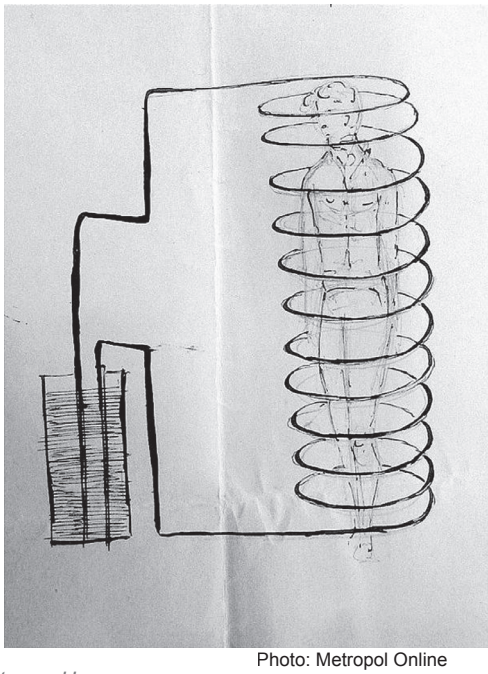


Photo: Metropol Online

The link between electricity and magnetism was first demonstrated in 1820 by the Danish scientist Hans Christian Ørsted, who found that a compass needle was influenced by an electrical current in a nearby wire. The findings were described in detail in a paper published in the same year entitled "Experimenta Circa Effectum Conflictus Electrici in Acum Magneticam" (translated "Experiments on the Effect of the Electric Conflict on the Magnetic Needle").

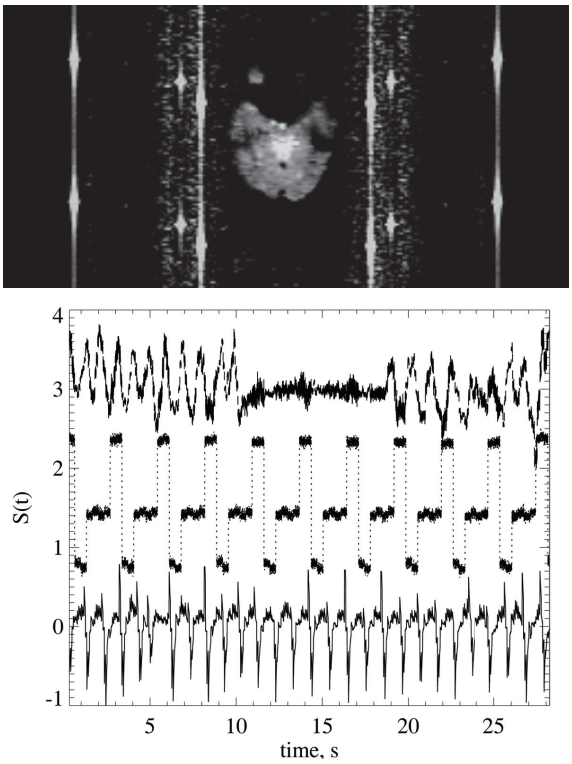
Recently, a previously unknown drawing believed to be made by Hans Christian Ørsted was found in a collection of 300 letters from the period that also included correspondence between other notabilities such as fairy tale writer Hans Christian Andersen. The drawing has a remarkable resemblance to present day Magnetic Resonance Imaging systems. However, the drawing pre-dates the invention of MRI by 150 years and rather reflects Ørsteds interest in the possible effects of magnetism on the body.

(Phe) in the brain has been developed successfully. Phe is (globally) present in the brain of people who suffer from phenylketonuria (PKU). Since Phe is harmful to the brain, PKU patients are typically kept on a strict Phe-free diet. SVS is used to measure the effect of the diet together with promising new treatments with Phe-poor diets in combination with medicine.

A so-called q-space imaging sequence was developed to probe the microscopic motion of water molecules in living tissue and to monitor subtle changes in the molecular motion due to disease. The same sequence, developed by Lars G. Hanson, is also capable of producing rapid multi-point T1 relaxation measurements and RF field mapping. The analysis software is being developed with Henrik Lund, for the characterization of normally appearing, but possibly challenged, brain tissue of patients with multiple sclerosis.

Another main area of sequence development at the Centre has been in the development of arterial spin labelling (ASL) sequences. ASL is the only completely non-invasive method of measuring regional blood flow in vivo. Karam Sidaros has been working on the methodological development of ASL at the DRCMR for several years and is responsible for maintaining and optimising the ASL sequences on the 3T Trio scanner. Considerable effort has been put into implementing a highly flexible version of the sequence that incorporates several ASL techniques with online post-processing on the scanner. The flexibility of the sequence makes it suitable for both exploratory investigations of ASL techniques as well as incorporating ASL perfusion measurements in clinical research protocols. ASL has been incorporated in neonatal imaging studies as well as in collaborative studies in demented patients. David Holm joined the Centre in 2004 and has worked on ASL optimisation on the 3T Trio scanner for his Master's thesis project.

There has been an increase in the number of research projects that incorporate functional MRI (fMRI) whereby blood flow changes related to neural activation can be detected. The 3T scanner at the Centre is especially suited for fMRI, and has yielded impressive results. This has been mainly due the increased sensitivity at higher field, but also in part due to the faster imaging gradients available on the 3T scanner. One disadvantage, though, of fMRI at high field is that there are increased image distortions and signal loss in areas of the brain that are close to tissue-air boundaries such as in the orbitofrontal cortex. Specialized in-house sequences that compensate for these effects are now used routinely in several fMRI projects.



Monitoring electrophysiology with MRI: Results from a pilot experiment where the newly developed method was used for recording physiological signals during MR-scanning. The image at the top shows a rapidly acquired MR image (10 images per second) of a single slice through the brain and eyes. The white lines next to the head are physiological signals encoded into the image with equipment developed at DRCMR. These signals can be extracted from the images as shown in the curves below the image. The curves are simultaneous measurements of eye muscle activity (EOG, top), calibration signal (middle) and electrocardiac signal (ECG, bottom). A goal of the project is to refine this method to a level where it can be used for simultaneous recording of neuronal electrical activity (EEG) and fMRI.

Furthermore, Torben Lund at the DRCMR has found that the analysis of functional studies is more robust and consistent when information about respiration and blood circulation is included in the analysis. Specific features were therefore added to the fMRI pulse sequences to enable the recording of respiration and pulse time series during the scan.

Another area that has seen substantial progress in 2004 is the simultaneous acquisition of functional images and electro-encephalogram (EEG) recordings. This is a highly difficult task due to the interference between the two recordings. The acquisition of MR images causes an artefact signal in the EEG recordings that is about 3 orders of magnitude higher than the actual EEG signal. This sets very high demands of both the hardware used to record the EEG signals and the software used in their analysis. Torben Lund has pioneered analysis methods that resulted

in several presentations at international meetings in 2004. Based on the experienced difficulties with EEG and fMRI acquisition, Lars G. Hanson has headed a group looking at a novel method for recording the two simultaneously. As a result, a patent application was submitted in 2004 by Hvidovre Hospital after advice from external consultants. In addition to the above mentioned people, the group involves Christian G. Hanson, who has developed prototype electronics providing very promising pilot data.

Working with contrast-based perfusion measurements, Irene K. Andersen has been implementing and optimizing perfusion quantification using T1-weighted dynamic measurements. Contrast-based perfusion measurements often rely on T2*-weighted imaging to monitor the susceptibility effects of the paramagnetic contrast agents used. However, T1-weighted imaging, albeit less sensitive, offers a number of other advantages over T2*-weighted imaging, especially when quantifying perfusion. Irene moved to Gothenburg in 2004 and has now initiated a close collaboration between the DRCMR and the Institute of Clinical Neuroscience at Gothenburg University where she continues to work on T1-weighted perfusion imaging.

A new development in 2004 has been in the field of fast T1 mapping, where Karam Sidaros has developed a novel approach for overcoming the effects of inhomogeneities in the radiofrequency fields that are used in MRI. Such inhomogeneities affect the accuracy of T1 estimation, and the new technique aims at extracting both the T1 values and the field map from the measurements.

MR Informatics

For each patient, MRI provides several sets of images with differing contrast. These are aligned and analysed together by a set of available methods, appropriate for the individual project. In order to do this efficiently and reproducibly, a configurable analysis “pipeline” has been established that will be of major benefit to the majority of patient studies in the future. MR-images are fed into the pipeline and are automatically analysed using a selection of the available methods, such as alignment, intensity correction and segmentation. Maintaining such a pipeline is a major task which has mainly been undertaken by Arnold Skimminge and Tim Dyrby. The functionality of the pipeline is steadily increasing as new methods are added.

Vision is studied intensively with fMRI because knowledge of the levels of visual processing gives general insight into the organisation of the brain and the process of perception. For each location in the visual field, there is a dedicated part of the brain that performs basic analysis and relays the visual inputs to other parts of the brain. In both research and clinical diagnosis it is highly relevant to map this so-called retinotopic organisation. A technique for this was implemented by Kristoffer Madsen as part of his Master’s thesis project, supervised by Torben Lund, Per Skafte Hansen and Lars Kai Hansen. This concluded Kristoffer’s graduate study of applied physics at DTU in the summer of 2004 after which he commenced a PhD project in collaboration between the DRCMR and the DTU.

Classification of tissue types and anatomical structures based on MRI images are tasks often performed with little conscious effort by trained radiologists. Automating the process, however, is highly challenging, but is needed to obtain quantitative results without the exceptionally labour intensive task of manually classifying tissue types on the hundreds of images resulting from modern MRI examinations. Important progress was made within the area of brain and heart segmentation by Mikkel Stegmann who received his PhD degree from the Technical University of Denmark in 2004. In context of the EU LADIS project focusing on the aging population, Tim Dyrby made important improvements in automated brain tissue classification that accounts for white matter lesions.

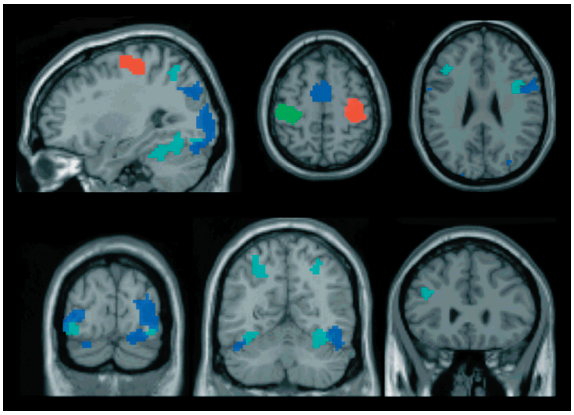
Basic Physiology

Functional MRI (fMRI) relies on the sensitivity of certain MRI sequences to regional changes in either cerebral blood flow or in blood oxygenation during neural activation. Blood flow changes can be measured directly using the ASL methods described above while blood oxygenation changes can be measured using sequences with BOLD (blood oxygenation level dependent) contrast. Although ASL measurements have a number of theoretical advantages over BOLD measurements, they are less commonly performed due to their reduced sensitivity.
There are several physiological parameters that are affected by neural activation including oxygen consumption, glucose metabolism, blood flow or perfusion, blood volume and blood oxygenation. These parameters interact through complex relationships and are affected by other parameters such the blood’s haemoglobin content and oxygen saturation. Egill Rostrup is currently heading a project that aims

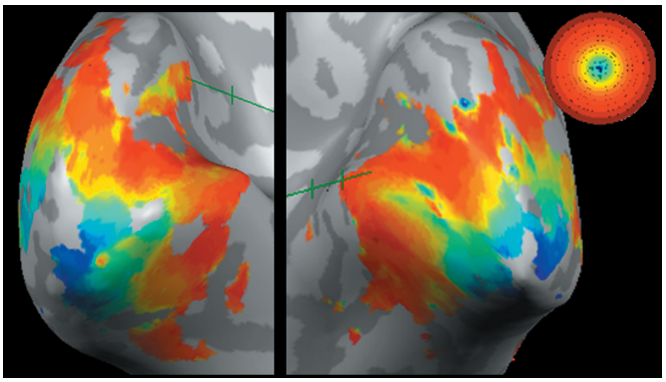
to develop a mathematical model that can describe the relation between regional blood oxygenation and a number of other physiological parameters, such as blood flow, haemoglobin content and the blood levels of oxygen and carbon dioxide in the brain. The model was used to predict the BOLD response from physiological data based entirely on PET measurements in normal volunteers. By using PET measurements it was possible to obtain reference values for both blood flow and volume in the brain. It was shown that the BOLD response is less sensitive to blood flow changes when the initial flow is elevated and how this effect is modulated by the concomitant changes in blood volume and oxygenation. The model has, for example, been used to confirm an exponential relationship between the cerebral blood flow and the arterial concentration of CO_2. Furthermore, the model has been used to probe the non-linear relationship between blood flow and oxygenation changes. A thorough understanding of the physiological parameters underlying the measured fMRI signals is essential in interpreting brain mapping experiments such as those described in the following section.

Brain Mapping

A DTU student, Mark Schram Christensen, finalised his Master's degree in applied physics under supervision of Torben Lund, Karam Sidaros and Rodney Cotterill. The subject of the thesis was an experimental study of visual perception, and very interestingly it was found that not only are visual areas of the brain involved in perception, but also the premotor cortex, which is normally attributed motor planning abilities, seems to be involved in visual perception. The experiment also showed that there are different patterns of activity in the brain when a visual stimulus suddenly appears and when it is sustainly perceived. One of our collaborators, Rodney Cotterill has suggested that human consciousness relies on mechanisms



Areas in cyan show regions that are involved in the sudden perception of a visual stimulus, whereas the areas in dark blue are areas involved in sustained perception of the visual stimulus. Areas in red and green are due to left and right hand finger presses.



The image shows how the visual field is mapped into the visual cortex. The color coding corresponds to different eccentricities in the visual field as shown on the radial colorscale. Note that points near the center of the visual field are represented more strongly than points in the periphery.

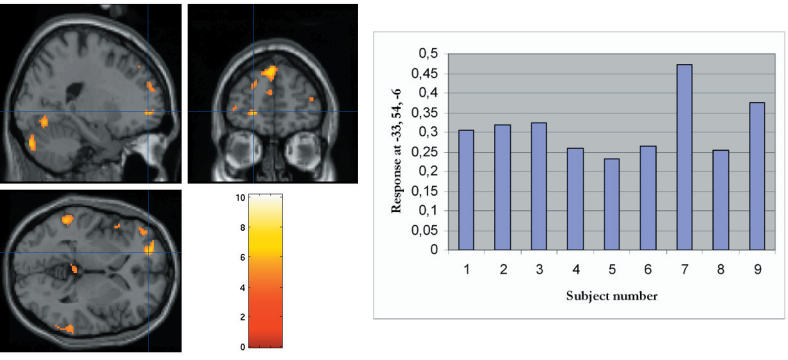
that simulate motor interaction with the environment. The results from the Master's thesis by Mark strongly support that view. Mark is now enrolled as a full-time PhD student, his project deals with how we perceive our own movements and is done in collaboration with Jens Bo Nielsen's motor control group at the Department of Physical Exercise and Sport Science at the University of Copenhagen.

Supervised by Torben E. Lund, Kristoffer Hougaard Madsen has finalised his MSc degree in applied physics. The project was concerned with fMRI and visual experiments, in particular the retinotopic mapping paradigm which is now used in a clinical project to investigate vision in patients suffering from optic neuritis. This paradigm is especially interesting from a technical point of view because problems concerning the delay of the BOLD response and effects of slice acquisition times can be eliminated. Due to the clinical utility of retinotopic mapping, considerable effort has been devoted to the reduction of the time needed to obtain a retinotopic map. Kristoffer Madsen is now enrolled as a PhD student at IMM, DTU. His project deals with fMRI methodology and is supervised by Lars Kai Hansen IMM, DTU and Torben E. Lund.

Supervised by William Baaré and Torben E. Lund, Jon Wegener has finished his MSc in Communication and Molecular Biology. The title of the thesis was "In Search of the Cheater Detection Module in Human Brain: An fMRI investigation" Evolutionary models suggest that developing and maintaining successful social exchange within a species requires that individuals are able to successfully identify social non-reciprocators. This has led researchers to hypothesize that an extensively social species such as humans have evolved specialized cognitive mechanisms for

identifying social contract violators. A recent lesion-study found neurological support for this hypothesis, indicating that the identification of social contract violators could be selectively impaired compared to the identification of non-social rule (precaution rule) violators in a patient suffering from bilateral damage to the anterior PFC (BA 10/11) and temporal poles (BA38) extending to more posterior temporal areas in the left hemisphere (BA 20/21/22/27). Consequently, the aim of the MSc study was to test the hypothesis that some or all of these brain areas are activated in healthy controls during the detection of social contract violators compared to precaution rule violators using a similar experimental design. The findings of the study indicate that the detection of social contract violators activates a network of areas implicated in social reasoning. Temporal areas included in this network have previously been found activated in "Theory of Mind" tasks, while anterior PFC were activated in altruistic punishment and in the observation of intentional social norm violations. Jon Wegener is now enrolled as PhD student at the Faculty of Health Science investigating Neuroeconomics. This project is carried out under the supervision of Christian Gerlach (LLD) and Olaf B. Paulson.

In a new project, Martin Skov is using fMRI to investigate aesthetic emotions. A distinct system of structures in the brain is dedicated to computing the importance or value of any perceived object (such as whether or not the object is 'attractive' or 'repulsive'). The aesthetic emotions – 'beauty', 'ugliness', 'dull', 'interesting', etc. – form a subset of this system. Not much is known, however, about which neural structures underlie these emotions or what triggers them into activation. To test whether or not aesthetic emotions are unique or just piggyback-rides on more basic emotions, subjects were asked to rate 300 photographs on an aesthetical



Left: Left anterior PFC activation from the identification of social contract violators relative to the control task (WSTsoc>WSTpre) (n=9)
Right: Corresponding percent increase in BOLD response within the peak voxel from each individual subject (n=9).

Example of a landscape painting used in functional MRI studies of neuroaesthetics. The subjects are asked to rate a large number of paintings from an aesthetic viewpoint while being scanned.

scale ('beauty', 'ugly', 'neutral'). The affective content of these photos were known to the experimenter but not to the subjects, making it possible to contrast affective content and aesthetic rating. The results show that it is possible to experience affectively repulsive photos as beautiful, or affectively pleasing photos as ugly, thus supporting the contention that aesthetic emotions to some degree differ from more basic emotions. In collaboration with clinics at Rigshopitalet we are now testing how patients with uni-lateral brain lesions in important emotion-related structures (amygdala and orbitofrontal cortex) perform on the same test. In addition, together with Semir Zeki's group at the Wellcome Laboratory of Neurobiology in London, we are further exploring how the aesthetic response to language (literature) and sound (music) differ, if at all, from the aesthetic response to visual stimuli.

The ability to recognize visual feedback from own movement as opposed to someone else's movement is important for motor control and social interaction. The neural processes involved have centered around two hypotheses. The stimulus is compared with a) the proprioceptive feedback or with b) the efferent copy of the motor command and if they match, then the external stimulus is identified as feedback. Hypothesis a) predicts that the brain areas involved in distinguishing self from other during passive and active movement are similar, whereas hypothesis b) predicts that they are different. Daniela Balslev and colleagues' fMRI results show that identifying visual feedback during active and passive movement activates similar brain areas and probably engages a similar mechanism - detecting visuo-proprioceptive synchrony. In collaboration with the University of Birmingham, Daniela is currently testing whether an rTMS-induced reduction in proprioception results in a decreased ability to identify visual feedback.

Clinical Body Research

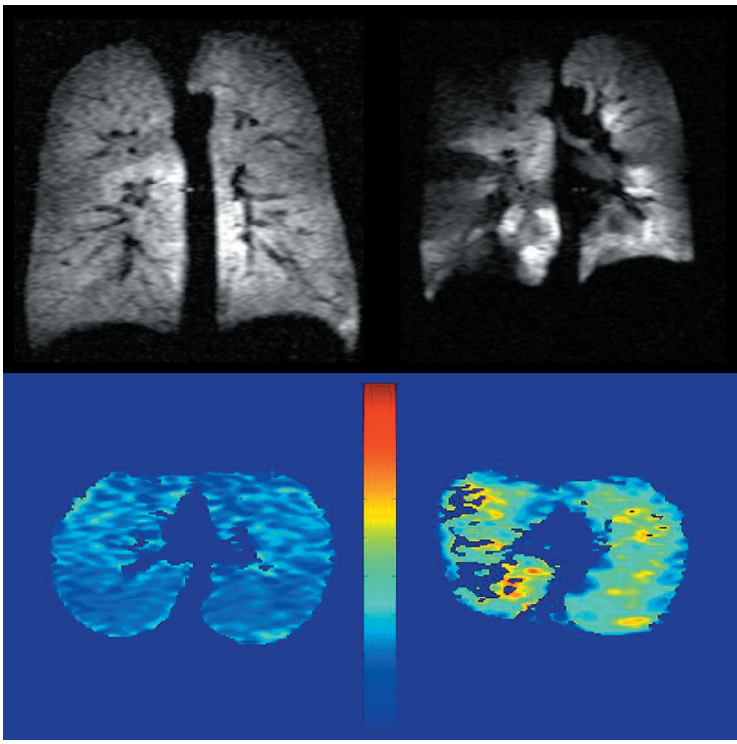
Pulmonary Function

Imaging of the lungs poses a number of difficulties with respect to traditional MRI. Large susceptibility differences at the air-tissue interfaces causes the MRI signal to decay very rapidly and, in addition, the proton density of the lung tissue is low compared to other tissues. During recent years, a new MR method based on imaging an inhaled hyperpolarized gas has emerged.

The DRCMR is one of three clinical centres involved in the EU PHIL project on hyperpolarized ^{3}He MR lung imaging methodology and applications. The technique is unique in Denmark and relies on the inhalation of magnetised helium, which is a harmless gas. The aim of the PHIL project was to validate this new lung imaging method by comparing to conventional lung examination techniques: lung function test, CT scan and Krypton scintigraphy. The included subjects were patients diagnosed with chronic obstructive pulmonary disease (COPD) and lung healthy volunteers.

The hyperpolarized ^{3}He gas for the studies was produced by another PHIL partner in Germany and shipped to Copenhagen by air freight. The MR protocol included morphological imaging providing information about the ventilation distribution and diffusion imaging which has been shown to correlate with the alveolar sizes in the lung.

The Little Mermaid with her lungs visualized using ^{3}He-imaging. This was the logo used for the final EU-PHIL meeting held in Copenhagen in 2004.



Helium images aquired by MR imaging of inhaled hyperpolarized ^{3}He. Morphologic images (top row) show the ventilation distribution for a healthy volunteer (left) and a smoker with chronic obstructive pulmonary disease (COPD), (right). ADC maps (axial view) for the same subjects are shown in the bottom row. The colourscale indicates ADC values from 0 to 0.9 cm²/s. Enlargement of alveolar airspaces from normal values (~0.17 cm²/s) is readily apparent for the COPD patient.

The project was very successful in 2004. Patient inclusion was completed in February and altogether 35 subjects were scanned at the DRCMR, nearly all resulting in very high quality images. The results have been analyzed together with results from the other participating centres. Specialists in radiology and nuclear medicine scored the MR images as well as the images from CT and Kr scintigraphy studies in order to make detailed comparison of the techniques. Parts of the results have already been published, others are still being analysed. The DRCMR, together with the Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet, hosted the final 3 days dissemination meeting of the EU project. Nearly 80 people participated including project partners, scientific collaborators as well as representatives from pharmaceutical companies and the gas industry.

A new project using the MR lung imaging technique has been started, studying patients with alpha-1-

antitrypsin deficiency. Lise Vejby Søgaard and Trine Stavngaard are locally responsible for MR lung imaging techniques at DRCMR.

Rheumatoid Arthritis

An increasingly aggressive therapeutic strategy, improved treatment options, and encouraging preliminary results have attracted growing attention to the potential of MRI in the diagnosis, prognostication and monitoring of rheumatoid arthritis (RA). MRI offers multiplanar imaging with unprecedented soft tissue contrast and high spatial resolution. Synovitis, the primary joint lesion in RA, can be detected and monitored, as can early bone destruction. In contrast, conventional radiography only shows the late signs of preceding synovitis.

A PhD study, conducted by Bo Ejbjerg, is moving towards its final phase. In this study, MRI methodology is applied with special focus on small extremity joints, especially in the hand, which are often affected in rheumatoid arthritis. Specific aims, which are evaluated in a series of studies involving comparisons with clinical, radiographic and histopathologic parameters, include investigation of the following: 1) Which MRI sequences are the most sensitive for evaluating joint inflammation and destruction; 2) Whether qualitative or semi-quantitative methods can provide information similar to more time-consuming quantitative methods; 3) Whether very detailed examination of a few joints is more sensitive to changes in rheumatoid inflammation and destruction than less detailed examination of many joints: 4) Whether a low-cost dedicated extremity MRI unit can provide similar information as “conventional” expensive high-field MRI units. The PhD study will be defended by Dr. Ejbjerg on May 20th, 2005. More PhD studies within the area of MRI and ultrasonography in RA and other inflammatory arthritides, building on these experiences, are currently being planned.

In addition to research undertaken in the context of PhD projects, the rheumatology group participates in an important international collaboration concerning MRI definitions, scoring methods and validation in rheumatoid arthritis. In general MRI scoring methods of RA joints are insufficiently validated and as a consequence of this, an “OMERACT-MRI” study group have since 1999 worked on developing definitions of RA changes and on developing and testing scoring methods. OMERACT is an international forum with expertise in MRI in RA and in scoring methodology which performs validation studies and seeks consensus within Outcome MEasures in Rheumatoid Arthritis Clinical Trials. In 2003-2004, the main task has been to develop “the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas”. Using this, MR images of wrist and metacarpophalangeal joints of patients with rheumatoid arthritis can be scored for synovitis, bone oedema and bone erosion, guided by standard reference images. It will be published as a supplement to the Annals of Rheumatic Diseases in 2005. The Rheumatology group is also involved in international collaborations concerning MRI of other inflammatory arthritides.

Finally, the group participates in 3 Danish multi-centre studies of RA and spondyloarthritides. In a longitudinal multi-centre study of 160 early RA patients (“CIMESTRA”), the aim is to investigate the value of MRI as an outcome measure and prognostic marker in early RA, compared with routine clinical, biochemical and radiographic parameters. MRI-data from this study has been analysed in 2004 and is expected to be presented in 2005.

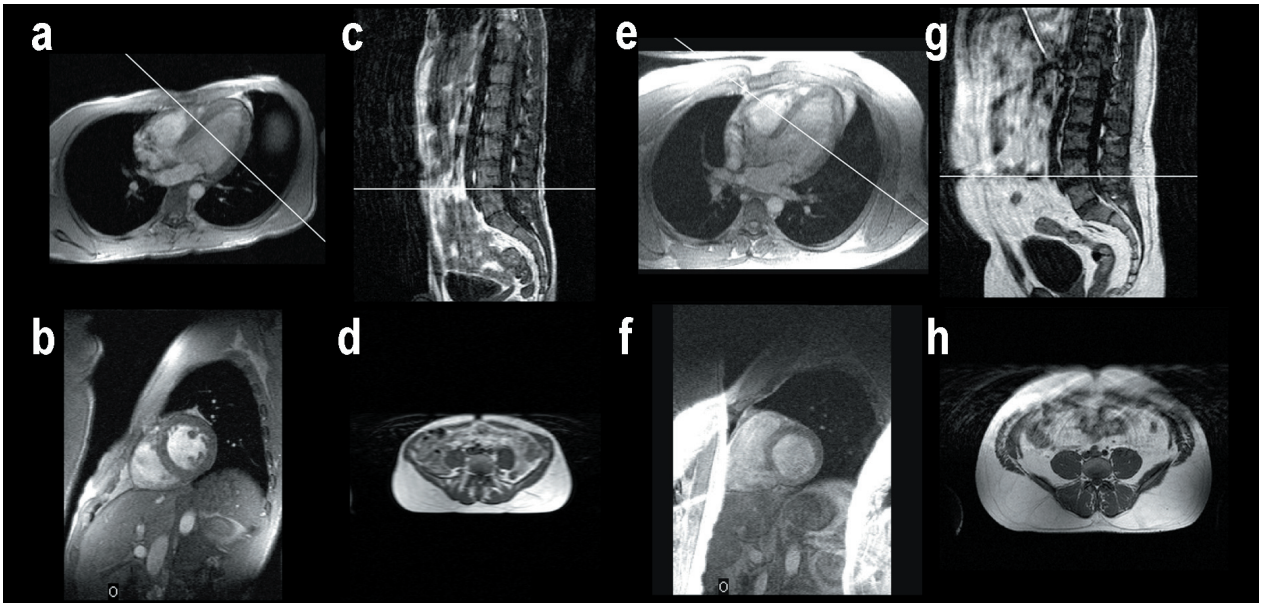
Cardiac Function

The influence of simple obesity on heart function is being studied by Dorthe Pedersen. Currently, two projects are being conducted. One investigating left ventricular function, geometry and potential anti-remodelling effects following weight loss in obese men and women. This project aims to investigate the influence of simple obesity, body composition and weight reduction on left ventricular mass, function and neurohormonal activation. It also investigates whether there is a correlation between neurohormonal activation and left ventricular mass in obese people. Neurohormonal activation is an activation of different neuroendocrine systems as in, for example, the renin-angiotensin-aldosterone system and sympathetic nervous system. A second project is directed at investigating left ventricular mass and endothelial function to elucidate the pathophysiology underlying increased left ventricular mass in simple obesity, which is only partly explained by increased blood volume and increased lean body mass. In myocardial hyperthrophy/increased left ventricular mass, due to conditions such as arterial hypertension and haemodialysis, an association is found with decreased endothelial function, which again is correlated to an increased risk of cardiovascular events. It has not so far been investi-

gated if increased left ventricular mass and decreased endothelial function is correlated in simple obesity.
In the first project 58 obese men and women, with a body mass index (BMI) above 33kg/m^2, participated. All were examined initially and after 8 weeks following a 7% reduction in bodyweight. Forty-two came back for a final examination one year later. At every visit, cardiac MRI, abdominal MRI and DEXA scanning were carried out and blood samples were drawn. The blood samples will be analysed for component of the neuroendocrine systems and other markers known to be predictors for cardiovascular disease.

The second study is a cross-sectional study where 30 obese men and women, with a BMI above 30 kg/m^2, and 26 subjects with normal weight underwent cardiac MRI, abdominal MRI, DEXA scanning and endothelial function test and had blood samples taken. As in the first study, the blood samples will be analysed for neuroendocrine activation and cardiovascular and endothelial markers including hsCRP, homocystein, BNP, endothelin, selectin I-CAM , V-CAM.
All MRI data will be acquired by the end of January 2005. Data is now being processed and evaluated, and will form the basis for a PhD thesis to be submitted at the end of 2005.

Susette Krohn Therkelsen is also working in this area of research and has been using MRI to study the atria and the left ventricle in middle-aged normal subjects, in patients with permanent atrial fibrillation and in patients with persistent atrial fibrillation before and after cardioversion. In collaboration with the cardiology laboratory at the University of Copenhagen, the study aims at measuring right and left atrial as well as left ventricular dimensions and systolic function by cardiac MRI in normal subjects, in patients with permanent atrial fibrillation (AF) and in patients with persistent AF before and after conversion to sinus rhythm. In addition, a range of neurohumoral substances are measured along with atrial measures acquired with echocardiography and signal-averaged-p-wave duration, which is an estimate of the intra-atrial conduction time of the sinus node impulse. The normal subjects will serve as controls for the patients with AF, and will also form the basis of a small introductory evaluation study to estimate the accuracy of the atrial measures. Whilst being primarily descriptive, the study aims to evaluate whether the cardiac measures or the plasma level of the neurohumoral substances possess any potential as prognostic markers for the risk of recurrent AF after successful cardioversion. Inclusion and examination of all 20 healthy volunteers, 60 patients with persistent atrial fibrillation and 20 with permanent atrial fibrillation is completed. Evaluation of the data is completed. The work has so far resulted in three submissions of original articles and it forms the basis for a PhD thesis to be submitted in January 2005.



The images from a-d were acquired from a 29 year old man, 1.77 m tall and a BMI of 22 kg/m^2
The images from e-h were acquired from a 36 year old man, 1.77 m tall and a BMI of 36 kg/m^2
The images a-b and e-f are examples of cardiac scanning using an electrocardiogram-triggered, breath-hold, gradient-echo technique with an imaging plane in the true short axis of the left ventricle. This technique gives cinematographic images with a temporal resolution of 55 milliseconds during the cardiac cycle with a slice thickness of 6 mm, a field-of-view of 263 x 350 mm^2 and a matrix size of 126 x 256. The entire ventricle is enclosed by a stack of imaging planes without inter-slice gaps. From the end-diastolic and end-systolic frames, left ventricle mass and ejection fraction can be calculated.
The images c-d and g-h represent scout T1 weighted images in the sagital plane and axial T1 weighted at the level of L4-L5 in the abdomen. The axial images are acquired with a 5 mm slice thickness, a field-of-view of 500 mm2 and a matrix size of 256 x 256.

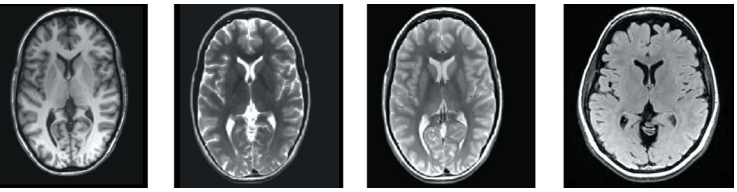
Clinical Brain Research

Neuropsychiatric Disorders

In this area of the program, research is directed at the longitudinal investigation of brain structure and function in prodromal and early stages of affective disorder (e.g., in monozygotic and dizygotic twins with very high risk of developing an affective disorder) and in different stages of schizophrenia (e.g., in drug-naïve first episode patients, in patients with disease onset in childhood and adolescence or adulthood, and in chronic patients).

Major depressive and bipolar disorder (MDD; BPD) are common and severe psychiatric illnesses affecting respectively 4% to 8 % and 1.3% to 1.6 % of the general population. The risk of recurrence is high and 15% to 20 % of patients commit suicide. Although the aetiology of affective disorder is unknown, genetic factors as well as environmental, especially stress-inducing, factors are involved. Heritability estimates for MDD range between 31% and 66%. The heritability of BPD is approximately 70%. The underlying pathophysiology of affective disorders is largely unknown. However, recent post-mortem and functional and structural in vivo neuroimaging studies have provided accumulating evidence for the presence of functional and structural abnormalities in the brains of patients with affective disorder as compared to healthy controls.

Schizophrenia is a complex, chronic, and debilitating disease, in which different aspects of cognition and behaviour, including attention, perception, thought processes, emotion and volition are affected. The disorder afflicts approximately 1% of the general population and typically has its onset in young adulthood. Although its etiology is not known, genetic factors (~80% heritability) as well as environmental, such as intrauterine and perinatal, factors are involved. In vivo imaging studies have been pivotal for our understanding of schizophrenia as a brain disease. Studies of first-episode (drug-naïve) schizophrenia patients are important as they control, to a large extent, for effects of factors such as long-term hospitalization, neuroleptic treatment and disease chronicity.



Differing MR techniques are used to obtain morphological information in the different projects: T1-, proton density-, T2-weighted, FLAIR.

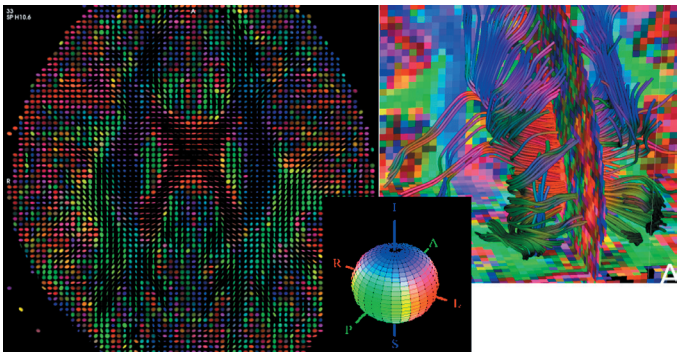
Predominantly, our MR investigations address the following questions: (a) which brain abnormalities are present before onset of an affective disorder? (b) Which abnormalities are related to an increased (genetic) risk to develop affective disorder? (c) Which abnormalities are present at illness onset? (d) Which abnormalities emerge during the course of the illness? (e) Which abnormalities progress in the first years of the illness? (f) How are these abnormalities and changes related to cognitive functions, pharmaceutical treatment, behavioural symptoms, and social and medical history? (g) Which abnormalities and changes are predictive of treatment response and clinical outcome? Questions (c) through (g) pertain to both psychiatric syndromes.

The following MR techniques are used in the different projects: structural MRI including T1, proton density and T2 weighted, FLAIR and diffusion tensor imaging (DTI) sequences. The latter is a novel technique that permits investigation of white matter microstructure. Additionally, in the schizophrenia projects, fMRI is used to investigate (frontal) brain function using a verbal working memory (N-back) task.

The senior researcher at the DRCMR responsible for coordinating the MR investigations is William Baaré. Patients and healthy controls are recruited and clinically evaluated by the psychiatry departments at the university hospitals of Rigshospital (Affective disorders: Principal investigator: Prof. Dr. Lars Kessing) and Bispebjerg (Schizophrenia: Principal investigators: Professor Ralf Hemmingsen, Dr Birte Glenthoj and Professor Tove Aarkrog). There is currently 1 project investigating affective disorders (A1) and 6 projects investigating schizophrenia (S1-S6).

Psychiatrist Maj Vinberg is the clinical researcher responsible for the affective disorder project (A1). In this project healthy mono– and dizygotic twins (age > 18 years) with a high and a low risk of developing affective disorder are investigated. The degree of risk depends on zygosity and the diagnostic status of the co-twin (e.g., diagnosed with affective disorder or never received a psychiatric diagnosis). Four hundred potential subjects were identified by linking the Central Psychiatry Registry and the Danish Twin Registry, a possibility which is unique to Denmark. To date, 145 twins have undergone MR scanning.

Clinical researchers responsible for the different schizophrenia projects are the psychiatrists Birte Glenthøj



Images of fractional anisotropy and fibres crossing the corpus callosum were created with software developed at MGH Martinos NMR Center.

(S1: "Structural and functional brain abnormalities in drug naïve adult onset schizophrenia") and (S2 "Structural and functional brain changes in drug-naïve first-episode schizophrenia patients: relation to cognitive function and anti-psychotic medication") , Katrine Pagsberg (S3: "Structural and functional brain abnormalities in early onset first-episode schizophrenia") and (S4: "First episode psychotic children and adolescents: a 5 year follow-up study of brain structure and function"), Bettina Søholm (S5: "Pharmacological treatment of cognitive deficits in schizophrenic patients: The effects of central cholinergic augmentation on cognitive deficits, and psychopathology") and Hannah Bro (S6: 5-10 year follow-up of schizophrenia patients: "Skizofreni: Sygdomsprocessens kliniske, psykofysiologiske og neurobiologiske manifestationer"). Data acquisition for projects S1 and S3 was completed by the end of 2002. For projects S2, S4 and S5 data acquisition started in 2003 and is ongoing. Project S6 started towards the end of 2004.

In project S2 we have shown that abnormalities in ventricular and frontal white matter volumes are already present at the early onset of non-affective and non-organic psychosis in minimally medicated children and adolescents. Also, our finding of smaller intracranial

The verbal working memory task (NBack), characteristically, activates the parietal, (pre)frontal, and cingulate cortices

volume in the subgroup of patients with schizophrenia suggests alterations in early brain development and supports current hypotheses implicating neurodevelopment in the pathophysiology of schizophrenia. In contrast to findings in adults, grey matter abnormalities appear not to be a key feature when the onset of illness occurs during childhood/adolescent brain maturation.

Brain Aging and Neurodegenerative Disorders

The Centre is the site of several studies of normal aging and the neurodegenerative disorders that afflict the elderly; and is a participating site in a broader multisite investigation by European Union collaborators entitled, "Leukoaraiosis and Disability in the Elderly" (LADIS). The latter is an ongoing structural MRI study of the known changes that occur with aging in the white matter of the brain. The objective is to better describe the predictors and consequences of these changes. Older volunteers are scanned at entry into the study and again 3 years later and abnormalities in the white matter are measured. These measures are correlated with extensive neurobehavioral assessments. Egill Rostrup is the senior DRCMR investigator most closely involved with the LADIS studies.

As part of the LADIS project, Charlotte Ryberg is focusing on studies of the corpus callosum, which is the major cerebral white matter structure carrying most interhemispheric connections. Initial studies in the Danish LADIS cohort have revealed a relationship between corpus callosum atrophy and cognitive decline, as well as an association between corpus callosum abnormality and the severity of white matter damage elsewhere in the cerebral hemispheres. This work resulted in reports at several conferences in 2004, including the 9th International Conference on Alzheimer's disease and Related Disorders and the meeting of the International Society for Magnetic Resonance in Medicine.

Two important DRCMR subprojects have developed from the LADIS initiative, both involving the development of advanced methods for automated measurement of abnormalities in cerebral white matter. Tim Dyrby is developing and validating tissue segmentation methods that rely on artificial neural network algorithms. Other tissue segmentation methods are available that permit automated tissue segmentation of the normal tissues in the brain (grey

matter, white matter, and cerebrospinal fluid). The new method under development at the DRCMR extends these by identifying and segmenting the white matter hyperintensities in the brain as well as the normal tissue types, thus providing a much more informative result in older individuals and patients, in whom such abnormalities are prevalent.

A second subproject of the LADIS investigation is led by Mikkel Stegmann, a collaborator from the Technical University of Denmark. This project involves the development and application of mathematical models for parameterisation of shape and appearance of MR data from corpora callosa. The resulting automated methods can then be used to examine, in a completely objective way, the variability in callosal morphology that occurs in the elderly LADIS subjects. Further development of these new mathematical techniques was presented in 2004 at the 2nd International Workshop on Generative Model Based Vision and at the annual SPIE meetings.

Ellen Garde and collaborators from DRCMR and from other University of Copenhagen hospitals (Glostrup and Rigshospitalet) continue their long-term (longitudinal) MRI investigation of elderly individuals. This study also focuses on white matter hyperintensities and recent findings confirm that increases in these abnormalities are associated with intellectual decline over a five-year period in 85 year olds. These results were published in 2004 in the Neurobiology of Aging.

In addition to these large projects investigating normal aging, the DRCMR is involved in several other clinically-oriented projects investigating neurodegenerative disorders. Katja Krabbe of the DRCMR, together with collaborators from Bispebjerg Hospital, is completing a study of patients with Parkinson's disease and the related disorder, multiple system atrophy. This project employs several MR modalities with the aim of finding better methods for differential diagnosis of the disorders. During 2004 the work in this project has focused on new information obtained from novel diffusion-based imaging techniques that have increased sensitivity to the disease effects on cerebral fibre tracts. Other work on this project identified patterns of grey matter degeneration in these disorders and reported evidence for increased intracranial volume in Parkinsonism. These findings were reported at the 10th International Conference on Functional Mapping of the Human Brain and at the meeting of the International Society of Magnetic Resonance in Medicine.

Terry Jernigan, who joined the DRCMR in 2003, directs a project that aims to develop clinically applicable functional MRI paradigms for probing brain systems affected early in several target neuropsychiatric disorders. In 2004, Thomas Ramsøy initiated a new PhD project within this program that focuses on methods for detecting early changes associated with Alzheimer's disease. During this year he has developed a new fMRI paradigm that evokes activity in the perirhinal and entorhinal parts of the temporal lobe that show the earliest pathological changes in dementing patients. The results obtained with this new paradigm will be presented at two upcoming meetings. Of particular interest is evidence that the new high-field fMRI method appears to evoke activity in the target region that is detectable consistently in individual subjects. This augers well for the use of this new paradigm for detection of early dysfunction in individuals at-risk to develop Alzheimer's disease. Other results suggest that individual differences exist in the anatomical distribution of the activation within the rhinal cortices. These observations are important because they may have implications for the design of optimal methods for probing the functional integrity of rhinal regions for clinical purposes.

Terry Jernigan has also continued to be involved in several studies of brain morphology in aging and dementia. Through her participation in the multi-site Brain Morphometry BioInformatics Research Network (BIRN) she has contributed to studies related to the ethical issues that arise from data-sharing initiatives, and to defining the differences in the patterns of neurodegeneration that occur in individuals with early vs. later onset of Alzheimer's Disease. The results of these studies were presented at the 10th International Conference on Functional Mapping of the Human Brain and at the 9th International Conference on Alzheimer's disease and Related Disorders. Her work has also focused increasingly on the effects of aging and dementing disorders on cerebral white matter. She recently published work describing and highlighting the protracted adult course of ongoing myelination in cerebral white matter and evidence for regional variability in age-related white matter volume loss in the elderly. Related work contrasting the distribution of white matter loss in Alzheimer's disease was also presented at the 9th International Conference on Alzheimer's disease and Related Disorders. With others, she also published evidence of specific cerebral white matter loss and cerebellar atrophy in Huntington's disease in the journal, Neurology. Finally, she continues to contribute to studies of the neurode-

generation that accompanies chronic HIV-infection. In 2004, evidence that white matter abnormalities detectable on MR are strongly related to subsequent autopsy findings in these patients was published in Archives of Neurology.

Prefrontal lesions

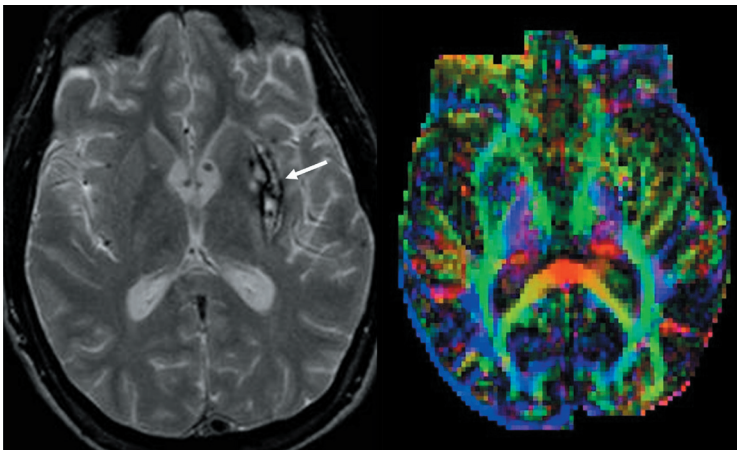
Our prefrontal cortex is essential for normal everyday behaviour and thought. Dysfunction of this region is both common and disabling. The region is vulnerable to injury by stroke, trauma or tumours, and to neurodegeneration in fronto-temporal dementias. Prefrontal cortical dysfunction is also a feature of other common illnesses like Parkinson's disease. However, the normal functions of this region remain controversial. Neuropsychological studies of patients with prefrontal lesions, and functional neuroimaging studies of healthy humans have lead to diverse proposed functions, including working memory, organization of behaviour, planning, attention, top-down control of perception and monitoring of internal cognitive and motor processes.

Recent functional neuroimaging studies by Katz Sakai and colleagues have shown that activity in prefrontal cortex can 'preconfigure' cognitive processes in other regions, in expectation of future events. Activity in healthy prefrontal cortex is also associated with protection of memories against the effects of distraction (Sakai et al., 2002a), reactivation of memories after distraction and selection of one item out of several possible alternatives. However, functional imaging can inform us about activation of a region in association with performance of a task, but not whether a specific brain region is essential. To understand whether a brain region is necessary requires the study of the effects of damage to a brain region. By studying patients with focal damage to the prefrontal cortex, using neuropsychological and functional imaging techniques, we can learn much more about the essential functions of this brain region, and learn about the brain's ability to adapt and compensate following an injury. Consequently, an international collaborative project has been established including James Rowe (DK) Dick Passingham (UK), Katz Sakai (Japan), Flemming Gjerris (DK), Torben Lund (DK,) Thomas Ramsøy (DK), Mark Christensen (DK) and Olaf Paulson (DK). Patients have been recruited from Rigshospitalets departments of neurosurgery and epilepsy, together with a group of healthy control subjects for comparison. All subjects have been studied using a special working memory task in which they must remember letters or spatial locations. Both types of memory tasks (letters and locations) are repeated many times during a 20 minute functional MRI investigation, to determine an average picture of brain activity for each type of memory.

The Trio scanner at Hvidovre has given high quality data, from which we will be able to determine how we use advanced information to prepare to remember information, how we remember the information itself, how we use such memories to make a decision, and what happens to each of these processes after brain damage. Due to the relationship between general intelligence and the extent of prefrontal cortex activation, we have used two additional tests to estimate the IQ of patients and healthy volunteers. It is expected that the full analysis of this large and complex study will take several months.

Traumatic Brain Injury

Severe traumatic brain injury (TBI), predominantly caused by motor vehicle accidents, is the leading cause of death and long-term morbidity among younger age groups in Western countries. The final outcome of severe TBI is highly variable, ranging from almost full recovery to persistent vegetative state. Outcome prediction is extremely difficult, giving rise to clinical problems particularly in cases of prolonged unconsciousness. One type of brain lesion often found in these patients is diffuse axonal injury, caused by axonal shear. In the acute trauma setting, episodes



A T_2-weighted gradient echo image (left) and a diffusion tensor image (right) of a 19-year old patient who had sustained severe head injury in a traffic accident 8 weeks previously. On the left image, small black dots represent diffuse axonal injury caused by shear; the arrow indicates remains of a haematoma. On the right image, water diffusion directionality is depicted in colour (red: x=lateral, green: y=anterior-posterior, blue: z=superior-inferior).*

of low blood pressure or lack of oxygen often occur, which might cause additional hypoxic-ischemic brain injury. These diffuse type injuries are not always well visualised by conventional imaging but may be important determinants of outcome.

A project on TBI is headed by Annette Skræp Nielsen in collaboration between the DRCMR and the Department of Neurorehabilitation, Division of Traumatic Brain Injury at Hvidovre Hospital. In this project adult patients with severe TBI, transferred from neurosurgical units to Hvidovre Hospital for rehabilitation, are scanned 6-10 weeks post-injury and again at follow-up after 6 months. The project applies newer MRI methods with the aims of obtaining a better characterisation of TBI patients in the sub-acute phase and identifying key imaging parameters that are predictive to outcome. Of particular interest are diffusion tensor imaging for quantification of diffuse axonal injury, contrast-based perfusion imaging for assessment of the hemodynamic status, and spectroscopy with whole-brain coverage for detection of hypoxic-ischemic changes.

A total of 25 TBI patients, out of 30 planned, have been included. In addition, a few patients that have been resuscitated from cardiac arrest are also included in order to characterise and compare changes caused by 'pure' hypoxic-ischemic events. The association between imaging results and clinical outcome will be analysed taking into account other possible prognostic indicators. The results of this project could provide important diagnostic, prognostic and pathophysiological information useful in the clinical management of brain-injured patients. An additional benefit of the project is that it offers a detailed radiological investigation of each patient which is often requested by the clinicians as well as the relatives.

Multiple Sclerosis

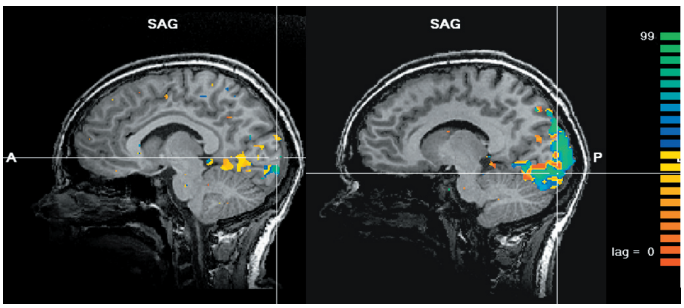
The DRCMR has a long tradition of combining MR research with research in multiple sclerosis (MS). In 2004 this tradition was not only continued but the MS research programme was significantly extended in several areas. Currently, two researchers at the DRCMR are working full time in this field. A major part of this research is performed in collaboration with external groups and thus has an extensive multidisciplinary input ranging from molecular biology and pathophysiology to psychiatry. In general, the research projects aim towards improving the diagnostic value of magnetic resonance investigations. This could be highly beneficial to the individual patient suffering from multiple sclerosis. In addition, a more accurate means of disease monitoring will improve the quality of clinical trials and thus help assessing whether new treatments can prevent or deter disease development.
Henrik Kahr Mathiesen finished his PhD thesis on MR spectroscopy in relapsing remitting MS in 2004. The aims of his thesis were to develop, validate and implement new MR techniques with higher specificity for pathological changes seen in lesions and in normal appearing brain tissues in MS.

MR spectroscopy can provide information about neuronal loss or dysfunction by measuring changes in N-acetyl-aspartate (NAA), a metabolite widely believed to reflect neuronal viability. A number of previous imaging studies have demonstrated that conventional measures, such as total number and volume of white matter lesions in the brain, are only able to predict patient symptoms to a very limited extent. Also the correlations between cognitive dysfunction and conventional MRI (e.g. lesion load) have been moderate. During his PhD studies, Henrik Kahr Mathiesen included a total of 20 patients with relapsing remitting MS. These patients were scanned serially at five time points over a 2 year period. The first results from this large body of acquired data have now been published and important methodological improvements documented. It was possible, for the first time, to obtain simultaneous whole-brain and regional measures (distinguishing cortical grey matter, normal appearing white matter and white matter lesions) of neuronal metabolites. This approach, using multi-slice echo planar spectroscopic imaging (EPSI), was shown to be reproducible and to possess some unique advantages compared to conventional non-localised or single-voxel-spectroscopy. Comparing spectroscopic measures with neuropsychological measures, a high correlation was found between global NAA/creatine ratio and an overall cognitive dysfunction factor suggesting that global NAA measured by multi-slice EPSI can be used as a surrogate marker for cognitive impairment in early MS.

The new high-field scanner (Siemens Trio, 3 T), installed in the department in 2002, is now showing its worth in MS projects also. Initially, a radiological comparison of scans obtained at 1.5 T and 3 T was performed by Kirsten Nielsen. In this project, 28 patients with acute optic neuritis (ON) (14 with clinically isolated acute ON and 14 with acute optic neuritis and MS) from the Department of Neurology, Glostrup, were scanned sequentially on the same day

in both scanners. Quantitative data including T2 lesion load as well as enhancing lesions were gathered and compared. On comparing scans at 3 T with scans at 1.5 T, a statistically significant increase in the number of lesions detected on FLAIR images was found. We investigated whether the difference in number of lesions could have an impact on the diagnosis of the fourteen patients with clinically isolated acute optic neuritis. According to the new MS diagnostic criteria for conversion of clinically isolated syndromes, e.g. optic neuritis, to clinically definite MS there must be objective evidence of dissemination of the disease in time and in space. We found that five of the fourteen patients fulfilled the criteria for dissemination in space at 1.5 T and six fulfilled these criteria at 3 T. As this could have an impact on patient diagnosis we suggest that the diagnostic sensitivity at 3 T is considered in large scale trials of ON - or MS patients.
In acute ON, an effective recovery is often observed which has been interpreted by some as adaptive changes. This hypothesis will be investigated further using retinotopic mapping. This project, also in collaboration with the Department of Neurology, Glostrup, has commenced, and twenty patients with acute optic neuritis have been included. The patients are scanned serially at four time points over a six month period, the first scan taking place in the acute phase of the disease and the remaining scans performed during recovery.

In one of the MS projects at the DRCMR, Henrik Lund uses MR techniques to quantitatively investigate aspects of the pathological mechanisms of MS. From these studies we hope to learn important details on the breakdown of myelin sheaths as well as of the blood-brain-barrier. At the time of writing 20 patients have been included and we expect to include 60 patients in total. All patients are scanned three times – just before start of treatment, after 3 months and after 6 months. The MR determined outcomes will subsequently be correlated to a vast range of immunological and neurological measures collected by our collaborators Pameli Datta and Martin Krakauer at Copenhagen University Hospital, Rigshospitalet. Three different approaches are being utilised in the exploration of the structural changes caused by the pathological mechanisms.



Activation in the visual cortex during stimulation with the expanding ring in the acute phase of optic neuritis (left) and after 14 days of recovery (right).

By applying so-called q-space analysis to diffusion data, it is possible to acquire structural information on the various biological barriers and compartments influencing diffusion. The problem with traditional diffusion tensor imaging (DTI) is that the calculated diffusion coefficients are expected not to depend on the diffusion weighting. However, this is correct only in perfectly homogenous media and not in vivo where the diffusion of water is hindered by tissue structures. q-Space analyses are based on several diffusion weightings and hence give more detailed information on the structures and the sizes of the tissue compartments. For example, this technique will be used to analyse the water diffusion orthogonal to the fibres since this is thought to reflect a direct immunological breakdown of the myelin and/or axons as well as anterograde (Wallerian) and terminal axonal degeneration as a response to focal lesions. This approach will, therefore, provide information on both diffuse as well as focal pathologies. The data analysis and interpretation will be performed in collaboration with physicist, Sara Brockstedt, physicist Jimmy Lätt, Lund University, Sweden and physicist, Lars G. Hanson, DRCMR.
Additionally, two methods have been implemented to gain insight into the breakdown of the blood-brain-barrier. After contrast injection, focal enhancing lesions appear hyperintense on T1-weighted scans because the contrast agent, which increases the signal, accumulates where the blood-brain-barrier is broken down. It is hypothesized that a subtle breakdown of the barrier in regions that do not appear as a discrete lesion can still give rise to a measurable change in the signal intensity. This diffuse increase in signal intensity is measured quantitatively and compared to brain tissue of healthy subjects. Finally, in collaboration with Irene K. Andersen, physicist, University of Gothenburg, Sweden, methods are set up to investigate the water exchange over the blood-brain-barrier. Compared to traditional T1-weighted imaging following injection of contrast agent, these methods are potentially much more sensitive to changes in the integrity of the blood-brain-barrier.

The DRCMR participates in a number of international drug trials for the treatment of MS and is the MR-analysis centre for the MECOMBIN and NORMIMS studies. Both of these studies are investigator driven trials assessing the therapeutic effect of simultaneous treat-

ment with methylprednisolone and interferon-beta-1a (IFN). In the MECOMBIN study, low dose IFN and methylprednisolone is given to previously untreated patients, whereas in the NORMIMS study, high-dose IFN and methylprednisolone is given to patients with residual disease activity in spite of IFN-treatment.
The studies include hundreds of subjects scanned at multiple MR centres. Image data from both studies are processed at DRCMR using in-house developed software to delineate regions and calculate lesion load as one major MRI outcome variable. Other variables such as brain volume and brain parenchymal fraction are calculated following meticulous pre-processing to minimize the effect of inter-centre variability.
In addition to the analysis centre function, the department participates in a total of four international trials predominantly focusing on relapsing-remitting multiple sclerosis, and two trials investigating the treatment of clinically isolated syndromes.

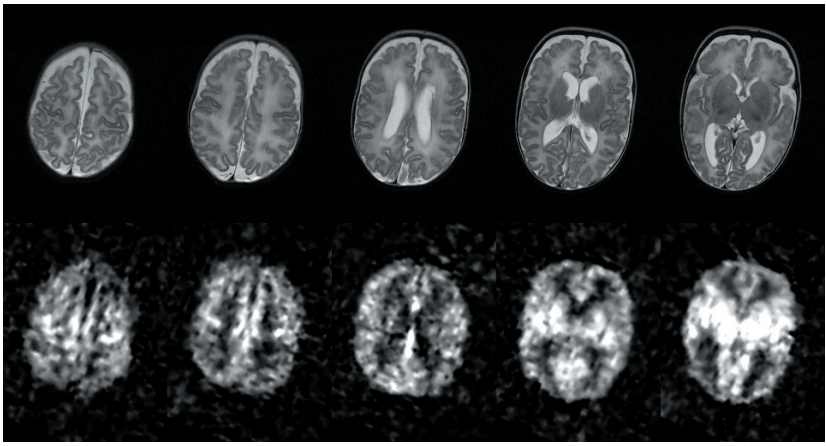
Cerebral Stroke

Stroke is the third most common cause of death in western countries. The first-year mortality is about 25% and many survivors suffer major disability. In one third of the patients, stroke in progression (SIP) is noted. This type of patient has an even worse prognosis with respect to mortality and clinical outcome. At present there is no effective treatment for patients with SIP, probably reflecting limited knowledge of the underlying pathophysiological mechanisms.
Elizabeth Kalowska submitted her PhD thesis in 2004 regarding a study on stroke in progression. A total of 41 patients recruited from the Department of Neurology, Hvidovre Hospital were investigated acutely (<24 hours), after one week and at follow-up after 3 months, using a protocol including spectroscopy, perfusion and diffusion measurements. Extensive clinical data was acquired at the same time points. The results confirmed the correlation between lesion size and clinical severity (Scandinavian Stroke Scale) in the acute stage and at subsequent scans. Clinical recovery in the first week was seen predominantly in those in whom lesion size decreased, while increases in lesion size were associated with adverse clinical status. The final clinical outcome, however, was not predictable by the initial lesion size or by the presence of non-infarcted areas with compromised blood supply (mismatch zones). These findings are of relevance for future therapeutic strategies such as thrombolysis, and suggest that clinical recovery is a multi-factorial process, influenced by a variety of factors and not just lesion and mismatch volumes.

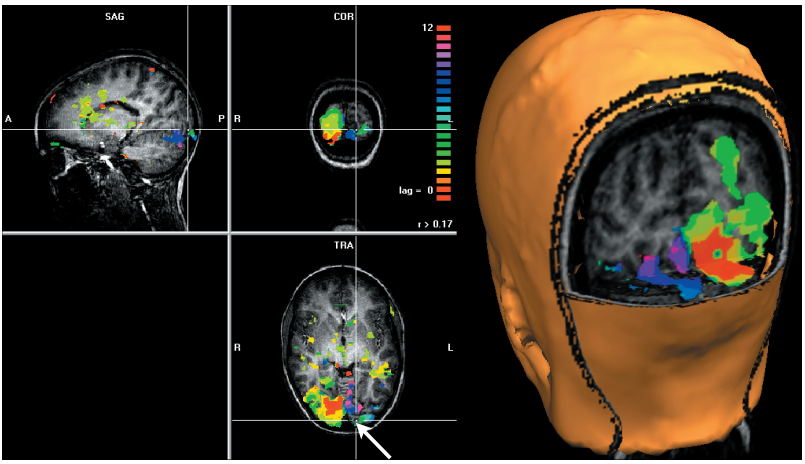
Neonatal Brain Maturation

Infants born prematurely are at risk of brain injury and neurodevelopmental deficits in later life. The pathogenesis of brain lesions is still controversial but apparently both infection in pregnancy and perinatal ischemia influence the development of white matter damage (WMD). Large epidemiological studies support the hypothesis that infection in pregnancy causes WMD in the immature brain. On the other hand, several studies support the ischemia hypothesis. Recent studies with single voxel spectroscopy have demonstrated that levels of lactate (an indicator of insufficient oxygen supply to the brain) are significantly higher in premature infants with WMD at term-equivalent age compared with premature infants at the same age with normal white matter.

In an ongoing collaboration with the department of Paediatrics, a study headed by Maria J. Miranda aims to demonstrate an association between infection in pregnancy and white matter damage in the immature brain at term-equivalent age. The study commenced using the Centre's 1.5T scanner but was moved to the 3T scanner when it became available. The study aims at including 200 premature infants born at either Hvidovre Hospital or Rigshospitalet at a gestational age (GA) less than 33 weeks. The placenta is histologically and microbiologically examined by a pathologist, while blood from the umbilical cord is examined for bacterial endotoxins and several inflammatory cytokines. These data will be compared with the number and extent of brain lesions and lactate accumulation found in MR scans performed at term-equivalent age. Other



Neonatal perfusion imaging. Top row shows five axial T2-weighted images of a 2-month old girl. She was born 2 months prematurely, and the MRI exam was thus performed at term-equivalent age. The bottom row shows cerebral blood flow maps acquired non-invasively using Arterial Spin Labelling (ASL). The images indicate a high perfusion level in the basal ganglia compared to the cortical grey matter and deep white matter.



The figure shows the result of a retinotopic mapping experiment in an 11 year old girl with epilepsy. In spite of substantial motion during the examination, it can be observed from the maps that the activity in the left visual cortex is reduced and, in particular, the small malformed area marked with the crosshair and the white arrow is not activated. This is useful information as this area was under suspicion of causing the seizures.

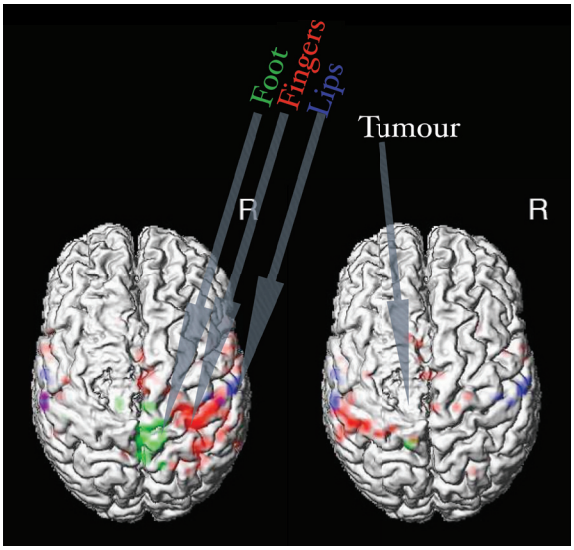
studies include Diffusion Tensor Imaging (DTI), a technique that enables white matter microstructure to be investigated. Histological correlates such as the size, cross sectional density and organization of axons as well as degree of myelination can be studied with this method. Both MR spectroscopy (MRS) and DTI data are being analyzed for the first 100 infants from Hvidovre hospital.

In 2005, infants born at a GA less than 28 weeks at Righospitalet will be included in the study and will undergo MR examination at term-equivalent age. Infants with signs of inflammation of the umbilical cord and infants without will be selected and matched for the purposes of comparison. Unpublished data from the first 100 infants show that approximately 12% of unselected infants born under 33 weeks of gestation have signs of placental inflammation, which makes it difficult to get significant results between inflammation and brain lesions.

A unique tool available at the DRCMR is the arterial spin labelling (ASL) technique able to non-invasively measure perfusion. Sick premature and term neonates have a vulnerable cerebral circulation. Impaired autoregulation of the cerebral blood flow may be a major factor contributing to the development of brain damage in these infants. In the past years, studies of the cerebral circulation have been done using different invasive methods such as xenon-clearance, PET and SPECT while other non-invasive approaches for estimating CBF, e.g. Doppler ultrasonography and near infrared spectroscopy have not accomplished the primary expectations. Maria J. Miranda and Karam Sidaros have therefore headed a study to evaluate the feasibility of using ASL to measure neonatal cerebral perfusion. As this MR method is entirely non-invasive and safe, even in very young infants, serial measurements are possible, which might be essential for understanding the pathogenetic mechanisms of brain damage in sick neonates. The initial results of this study have indicated that, with a minor modification of the ASL technique, the method is indeed suited for measuring neonatal perfusion. These results have been presented at several international meetings in 2004.

Presurgical Planning

Pioneered by Torben E. Lund a number of pilot investigations on presurgical mapping have been performed in collaboration with neurosurgeons at Rigshospitalet, neurologists at Epilepsiklinikken and Dianalund together with researchers and radiologists at DRCMR. The best results have been obtained with tumour patients whom are typically better at lying still in the scanner. Patients with epilepsy are, in this respect, more challenging to examine as they typically have difficulties with keeping still. The paradigms used are: motor-mapping, language lateralisation and visual field mapping. We are currently looking into combining fMRI with tractograpy. This combination is challenging because lack of anisotropy in the case of a tumour does not necessarily imply lack of connecting fibres.



The figure shows the result of a language mapping experiment in a 36 year old father who had two attacks of aphasia during reading for his children. The tumour is clearly located close to the areas involved in word generation.

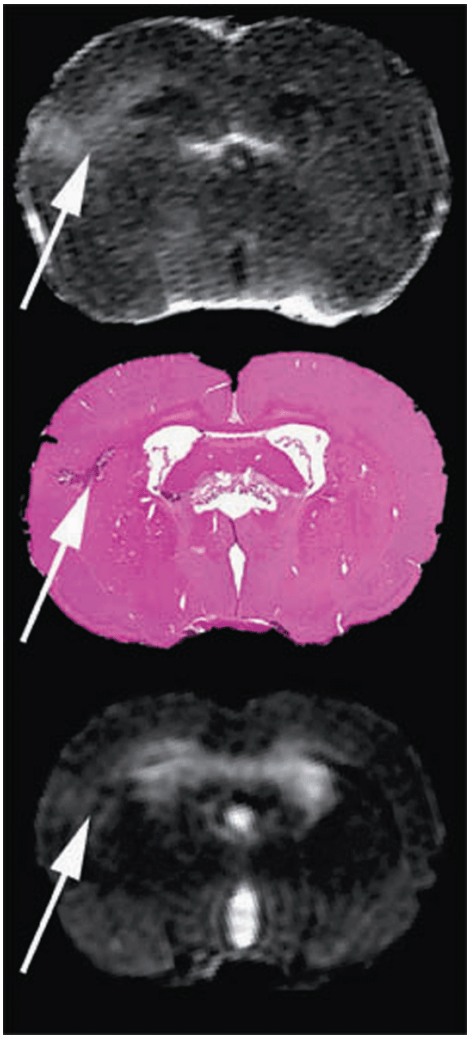
Preclinical Research

For an MR research group to remain competitive, the group should strive to keep up with the continuing technological advances achieved by the MR manufacturers. In September, the preclinical research group was fortunate to have the 4.7 T MR system upgraded by Varian to provide a modern and highly capable MR imaging and spectroscopy system. Originally installed in 1989, the 4.7T magnet is now the only surviving piece of hardware with all other components including gradients, amplifiers, computers etc having been replaced with modern components. The magnet has proved itself over the years and has, until the upgrade, remained at essentially the same magnetic field. During the upgrade process the magnet field had to be increased slightly so that the proton resonant frequency would shift from 200 to 200.5 MHz. When 'ramping' the magnet field, the potential for catastrophic quenches (a quench is when the superconducting properties of the magnet are lost, resulting in a spectacular boil-off of the liquid nitrogen and helium used to cool the magnet) is very much increased and is certainly an exciting time. Fortunately, this went very smoothly. Looking through old records from when the machine was installed it was discovered that the magnet field had remained exceptionally stable over 15 years and had changed by less than 0.007%. The upgrade has enabled, for example, the implementation of many new techniques including arterial spin labelling and fast imaging sequences that are essential to the success of future studies.

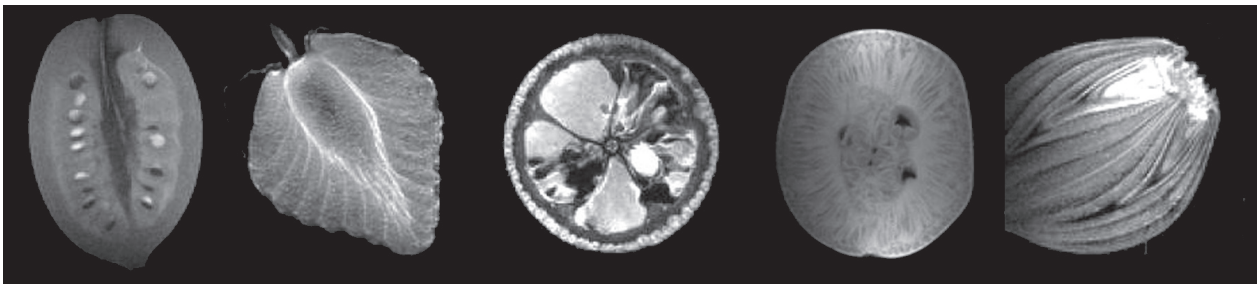
Currently, the group has two senior post-doctoral, one PhD student and two technical staff that focuses, primarily, on longitudinal investigations of small animal models of disease. The group collaborates with a number of other groups within the Copenhagen area with a focus on cancer and brain disease and function. This provides the opportunity for exciting multi-disciplinary projects to be performed with contributions from researchers with different scientific expertise and experience.

The group has been working in collaboration with the Institute for Molecular Pathology, University of Copenhagen, on two related projects. One project is designed to develop MR methodology in order to investigate early vascular changes following administration of a drug targeted to tumour vasculature. The other project has been directed at developing a reproducible model of angiogenesis that could be readily investigated using MR.

For a tumour to develop beyond approximately 1 mm^3, new blood vessels able to supply nutrients etc must also develop. The development of new blood vessels, known as angiogenesis, is obviously an essential step in tumour progression and is also an obvious target in cancer treatment. The aim of the first study is to develop a method of assessing early vascular changes following administration of a drug targeted to tumour vasculature. When used with a cytotoxic agent, the combined efficacy is likely to depend on the timing between agent administrations. To optimize the timing, the time course of the vascular effects should be characterized. To this end, arterial spin labelling perfusion techniques will be implemented on the scanner together with fast T1 measurements able to follow bolus contrast agent administration. This is the subject of a PhD study that commenced towards the latter part of 2004.



Visualization of brain damage (arrowed) in a meningitis infected rat using (top) post contrast T1W imaging, (middle) H&E histology and (bottom) T2W imaging.



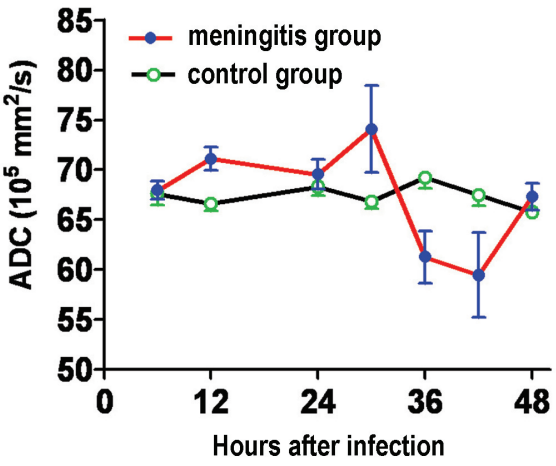
To evaluate the upgraded 4.7T system, a variety of different items were selected for imaging. From left to right: plum tomato, strawberry, kumquat, grape and onion

An in vivo angiogenesis assay that could be studied using MR methods would be of significant value in the screening and evaluation of anti- and pro-angiogenic agents. Such a model would facilitate the investigation of the influence of physiological factors upon angiogenesis and the validation of MR methods used to assess vasculature. Consequently, in the second project, a Matrigel angiogenesis assay has continued to be developed and has been refined via the use of superparamagnetic iron oxide contrast agent. This ongoing work has demonstrated that the Matrigel implant model could be used to assess and quantify the effects of vascular-targeted agents. In addition, the model could also be used to investigate drug mechanism. Data from this study has been presented at international meetings.

In collaboration with the Technical University of Denmark, we have started work on the development of new iron oxide contrast agents. Initial work has been promising and a new perfusion agent based on the internal labelling of red blood cell ghosts has been developed. Red blood cell ghosts containing superparamagnetic iron oxides have been shown to be detectable using T2* sensitive MR sequences in vitro and in vivo. This work is being expanded to label other cell types and peptides for use in cell and molecular imaging applications.

In 2004 we have continued to work closely with the State Serum Institute with the aim of exploring the use of MRI as a means of monitoring experimental pneumococcal meningitis. In a study following rats for a period of up to 48 hours after infection, we have been able to use MR to grade the severity of disease. T2W and post contrast T1W images were found to be most useful in this regard. In addition, we have also investigated the evolution of the disease using quantitative diffusion measurements and found, over the 48 hour period that the appearance of vasogenic oedema is followed, at around 36 hours, by cytotoxic oedema. These studies have shown that it is possible to evaluate a wide range of therapeutic strategies designed both to cure the bacterial infection and minimise disease sequelae. Data from this study has been presented at international meetings.

Work has also commenced on probing brain function using manganese enhanced MRI (MEMRI). In collaboration with the August Krogh Institute, an MSc project is now underway designed to explore the regions in a rat brain associated with contextual fear conditioning. Using mannitol to open up the blood brain barrier, manganese chloride is slowly infused, via a cannulated artery, into the brain. Manganese is analogous to calcium and is preferentially taken up in activated regions. Since manganese is paramagnetic, activated regions may appear hyperintense in T1 weighted images. Currently, the project is in the design phase.



Plot showing the evolution of vasogenic oedema (an increase in water ADC) followed by cytotoxic oedema approximately 36 hours after infection with pneumococcal meningitis.

Other Activities

Consultation

The following staff members have acted as consultants for national and international agencies, boards and societies:

Olaf B. Paulson:
- Chairman of the Department of Clinical Neuroscience and Psychiatry, University of Copenhagen
- Chairman of the Research Committee of the Neuroscience Centre at Rigshospitalet
- Secretary of the Danish Society of Neuroscience
- Member of the board of the Danish Alzheimer Association
- Member of the Danish Alzheimer Research Foundation
- Member of the Neurology Committee of the Copenhagen Hospital Corporation
- Member of the committee for implementation of clinical neuroscience and psychiatry in the new curriculum for the physician education at the University of Copenhagen
- Chairman of the methodology session – reviewer on the Swedish “Brain Power” project

Terry L. Jernigan:
- Member of the Editorial Advisory Boards of the following journals: Neuropsychology; Journal of the International Neuropsychological Society; Psychiatry Research: Neuroimaging; Developmental Neuropsychology
- Consultant to the U.S. National Institute of Mental Health Board of Scientific Counselors for Intramural Research Programs
- Member of U.S. National Institute of Mental Health Special Emphasis Panel – Molecular Markers and Mechanisms of HIV-Associated Dementia (RFA)
- Invited Speaker at the International Conference on Applications of Neuroimaging to Alcoholism, Sponsored by the U.S. National Institute on Alcohol Abuse and Alcoholism

Thomas Zöega Ramsøy:
- Managing Editor: Science and Consciousness Review: www.sci-con.org
- Member of the board, secretary: Nordic Neuropsychological Society
- Administrator: Nordic Network for Consciousness Studies

Journal Review

During 2004, DRCMR staff members have been reviewers for the following journals:

- Alcoholism
- American Journal of Geriatric Psychiatry
- American Journal of Psychiatry
- Anesthesiology
- Archives of General Psychiatry
- Archives of Neurology
- Cerebral Cortex
- Clinical and Experimental Research
- Human Brain Mapping
- International Congress on Schizophrenia Research
- Journal of Abnormal Psychology
- Journal of the American Medical Association
- Journal of the International Neuropsychological Society
- Klinisk neurologi og neurokirurgi
- Neurobiology of Aging
- NeuroImage
- Neuropsychologia
- Neuropsychology
- Proceedings of the National Academy of Sciences
- Psychiatry
- Psychiatry Research
- Psychological Bulletin
- Science
- Stroke
- The Boundaries of Consciousness: Neurobiology and Neuropathology, Progress in Brain Research
- Ugeskrift for Læger

Training Activities

Received Training

The centre strives to maintain a vigorous continuing-education program for staff at all levels within the centre. Staff members are actively encouraged to attend relevant scientific and other professional conferences, and particular emphasis is given to sponsorship of PhD students and junior staff at international symposia and workshops focusing on advanced theory and techniques.

Formal Instruction by DRCMR Staff

Throughout the year, many courses are organized and run locally for the benefit of staff, collaborators and other interested external researchers. In addition, staff contribute each year to a number of external training activities:

Outside Instruction:

- Daniela Balslev and Olaf B. Paulson: Teaching "PET and fMRI for studies of the functional activation of the brain", European Society of Neurology - Functional neuroimaging
- Lars G. Hanson: Teaching "Hospitalsfysikerpraktik", students from Rigshospitalet and University Hospital Odense.
- Lars G. Hanson: Teaching "Medical Imaging Course", "Biophysics Course" and "Medical Image Processing"at the Technical University of Denmark
- Lars G. Hanson: Teaching "Quality Assurance", at Radiografskolen
- Annette Skræp Nielsen: Teaching "Neurological Diseases", Københavns Brandvæsen
- Annette Skræp Nielsen: Teaching "Neurorehabilitation", University of Southern Denmark
- Egill Rostrup: Teaching "Tracerkinetics", PhD-course at University of Copenhagen
- Mark Schram Christensen and Kristoffer Madsen: Teaching "fMRI analysis", Neurobiology Research Unit, Rigshospitalet
- Karam Sidaros: Teaching "Tracerkinetics", PhD-course,University of Copenhagen
- Karam Sidaros: Teaching "Magnetic Resonance 3", University of Aarhus
- Martin Skov: Teaching "Neuroæstetik", Department of Art and Culture Research, University of Copenhagen

Individual Supervision of graduate students by DRCMR Staff:

- William Baaré was supervisor for medical student Andreas Glenthøj, University of Copenhagen, OSVAL 2 project
- Daniela Balslev was supervisor for medical student Tanja Korfitsen, University of Copenhagen, OSVAL 1 project
- Lars G. Hanson, Henrik Kahr Mathiesen and Olaf B. Paulson were supervisors for medical student Shanu F. Rømer, University of Copenhagen, OSVAL 2 project
- Torben Lund was supervisor for student Kristoffer Madsen, Technical University of Denmark, Master's project.
- Torben Lund and Karam Sidaros were supervisors for student Mark Schram Christensen, Technical University of Denmark, Master's project
- Torben Lund and William Baaré were supervisors for student Jon Wegener, Roskilde University, Master's project
- Olaf B. Paulson was supervisor for Medical student Matias Vested, University of Copenhagen, OSVAL 1 project
- Karam Sidaros was supervisor for Medical student Nicolai Hasse, University of Copenhagen, OSVAL 1 project
- Karam Sidaros was supervisor for student David A. Holm, University of Aarhus, Master's project.

Congress Organization

- Olaf B. Paulson organized teaching Courses of the European Society of Neurology with the title "Functional neuroimaging"
- Olaf B. Paulson was a member of the programme committee for the Federation of European Neuroscience Society's annual meeting in Lisbon
- Olaf B. Paulson was a member of the Executive Board of the European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) and chairman of the local organizing committee of ESMRMB's annual meeting in Copenhagen, September
- Lise Vejby Søgaard and Trine Stavngaard organized and carried out the last meeting regarding the PHIL project. The meeting took place in Copenhagen.

Awards

We are pleased to announce the following awards to DRCMR Staff in 2004:

- The Neurological Research Foundation awarded Professor Olaf B. Paulson with the Mogens Fog Honorary Prize on March 19th. The award was given for his outstanding research and his contribution to Danish neurology.
- Research Technician Helle Juhl Simonsen received on May 15th, 2004 the 3rd place award in the category of Research Focus Proffered Paper at the Thirteenth Annual Meeting in Kyoto, Japan of the ISMRM - SMRT (Section for Magnetic Resonance Technologists). The paper was titled Pathogenesis of Corticospinal Tract Degeneration in ALS Patients by Diffusion Tensor Imaging.

Publications

A large number of publications has resulted from the work performed by the research staff at the DRCMR during 2004. The most important of these publications are listed here according to category:

PhD and Doctoral Theses

- Pagsberg K. Structural Brain Abnormalities in 10-18 Year Old Children and Adolescents with First-Episode Psychosis. University of Copenhagen, Faculty of Health and Sciences, 2004. (PhD)
- Stegmann MB. Generative Interpretation of Medical Images. Technical University of Denmark, DTU, 2004. (PhD)
- Søndergaard L. Quantitative assessment of aortic regurgitation and stenosis using magnetic resonance velocity mapping: Technical aspects and clinical evaluation. University of Copenhagen, Faculty of Health Science, 2004. (Doctoral)

Peer Reviewed Journal Articles

1. Adams KH, Pinborg LH, Svarer C, Hasselbalch SG, Holm S, Haugbol S et al. A database of [(18)F]-altanserin binding to 5-HT(2A) receptors in normal volunteers: normative data and relationship to physiological and demographic variables. Neuroimage 2004; 21(3):1105-1113.
2. Archibald SL, Masliah E, Fennema-Notestine C, Marcotte TD, Ellis RJ, McCutchan JA et al. Correlation of in vivo neuroimaging abnormalities with postmortem human immunodeficiency virus encephalitis and dendritic loss. Arch Neurol 2004; 61(3):369-376.
3. Balslev D, Christensen LO, Lee JH, Law I, Paulson OB, Miall RC. Enhanced accuracy in novel mirror drawing after repetitive transcranial magnetic stimulation-induced proprioceptive deafferentation. J Neurosci 2004; 24(43):9698-9702.
4. Broholm H, Andersen B, Wanscher B, Frederiksen JL, Rubin I, Pakkenberg B et al. Nitric oxide synthase expression and enzymatic activity in multiple sclerosis. Acta Neurol Scand 2004; 109(4):261-269.
5. Cohen ER, Rostrup E, Sidaros K, Lund TE, Paulson OB, Ugurbil K et al. Hypercapnic normalization of BOLD fMRI: comparison across field strengths and pulse sequences. Neuroimage 2004; 23(2):613-624.
6. Conaghan PG, Ostergaard M, McGonagle D, O'Connor P, Emery P. The validity and predictive value of magnetic resonance imaging erosions in rheumatoid arthritis: comment on the article by Goldbach-Mansky et al. Arthritis Rheum 2004; 50(3):1009-1011.
7. Dzik-Jurasz AS, Leach MO, Rowland IJ. Investigation of microenvironmental factors influencing the longitudinal relaxation times of drugs and other compounds. Magn Reson Imaging 2004; 22(7):973-982.
8. Ejbjerg B, Narvestad E, Rostrup E, Szkudlarek M, Jacobsen S, Thomsen HS et al. Magnetic resonance imaging of wrist and finger joints in healthy subjects occasionally shows changes resembling erosions and synovitis as seen in rheumatoid arthritis. Arthritis Rheum 2004; 50(4):1097-1106.
9. Fennema-Notestine C, Archibald SL, Jacobson MW, Corey-Bloom J, Paulsen JS, Peavy GM et al. In vivo evidence of cerebellar atrophy and cerebral white matter loss in Huntington disease. Neurology 2004; 63(6):989-995.
10. Gerlach C, Law I, Paulson OB. Structural similarity and category-specificity: a refined account. Neuropsychologia 2004; 42(11):1543-1553.
11. Hulshoff Pol HE, Brans RG, van Haren NE, Schnack HG, Langen M, Baare WF et al. Gray and white matter volume abnormalities in monozygotic and same-gender dizygotic twins discordant for schizophrenia. Biol Psychiatry 2004; 55(2):126-130.
12. Humphreys GW, Kyllingsbaek S, Watson DG, Olivers CN, Law I, Paulson OB. Parieto-occipital areas involved in efficient filtering in search: a time course analysis of visual marking using behavioural and functional imaging procedures. Q J Exp Psychol A 2004; 57(4):610-635.
13. Jensen J, Langkilde AR, Fenst C, Nicolaisen MS, Roed HG, Christiansen M et al. CD4 T cell activation and disease activity at onset of multiple sclerosis. J Neuroimmunol 2004; 149(1-2):202-209.
14. Jernigan TL, Fennema-Notestine C. White matter mapping is needed. Neurobiol Aging 2004; 25(1):37-39.
15. Karlsborg M, Rosenbaum S, Wiegell M, Simonsen H, Larsson H, Werdelin L et al. Corticospinal tract degeneration and possible pathogenesis in ALS evaluated by MR diffusion tensor imaging. Amyotroph Lateral Scler Other Motor Neuron Disord 2004; 5(3):136-140.
16. Knudsen GM, Karlsborg M, Thomsen G, Krabbe K, Regeur L, Nygaard T et al. Imaging of dopamine transporters and D2 receptors in patients with Parkinson's disease and multiple system atrophy. Eur J Nucl Med Mol Imaging 2004; 31(12):1631-1638.
17. Knudsen GM, Rostrup E, Hasselbalch SG. Quantitative PET for assessment of cerebral blood flow and glucose consumption under varying conditions. Int Congr Ser 2004;(1265):189-200.
18. Kyhn M, Herning M, Prause JU, Heegaard S. Orbital involvement in multifocal fibrosclerosis. Acta Ophthalmol Scand 2004; 82(3 Pt 1):323-324.
19. Murphy PS, Viviers L, Abson C, Rowland IJ, Brada M, Leach MO et al. Monitoring temozolomide treatment of low-grade glioma with proton magnetic resonance spectroscopy. Br J Cancer 2004; 90(4):781-786.

20. Nielsen FA, Hansen LK, Balslev D. Mining for associations between text and brain activation in a functional neuroimaging database. Neuroinformatics 2004; 2(4):369-380.
21. Nielsen G, Fritz-Hansen T, Dirks CG, Jensen GB, Larsson HB. Evaluation of heart perfusion in patients with acute myocardial infarction using dynamic contrast-enhanced magnetic resonance imaging. J Magn Reson Imaging 2004; 20(3):403-410.
22. Nielsen JE, Johnsen B, Koefoed P, Scheuer KH, Gronbech-Jensen M, Law I et al. Hereditary spastic paraplegia with cerebellar ataxia: a complex phenotype associated with a new SPG4 gene mutation. Eur J Neurol 2004; 11(12):817-824.
23. Østergaard M, Duer A, Moller U, Ejbjerg B. Magnetic resonance imaging of peripheral joints in rheumatic diseases. Best Pract Res Clin Rheumatol 2004; 18(6):861-879.
24. Pinborg LH, Adams KH, Yndgaard S, Hasselbalch SG, Holm S, Kristiansen H et al. [18F]altanserin binding to human 5HT2A receptors is unaltered after citalopram and pindolol challenge. J Cereb Blood Flow 2004, 24(9), 1037-1045.
25. Ramsoy TZ, Overgaard M. Introspection and subliminal perception. Phenomenol Cogn Sci 2004; 3(1):1-23.
26. Rowland IJ. Biomedicinske fluor-NMR-studier på mennesker. Dansk Kemi 2004; 84:22-28.
27. Szkudlarek M, Court-Payen, Strandberg C, Klarlund M, Klausen T, Ostergaard M. Ultrasonographic assessment of finger and toe joints in rheumatoid arthritis - reply to letter by Scheel et al. Arthritis Rheum 2004; 50:1008-1009.
28. Szkudlarek M, Narvestad E, Klarlund M, Court-Payen, Thomsen HS, Ostergaard M. Ultrasonography of the metatarsophalangeal joints in rheumatoid arthritis: comparison with magnetic resonance imaging, conventional radiography, and clinical examination. Arthritis Rheum 2004; 50(7):2103-2112.
29. Szkudlarek M, Ostergaard M. Diagnostic value of Doppler ultrasonography in rheumatoid arthritis: comment on the article by Weidekamm et al. Arthritis Rheum 2004; 50(2):676-677.
30. Taskiran M, Rasmussen V, Rasmussen B, Fritz-Hansen T, Larsson HBW, Jensen GB et al. Left ventricular dysfunction in normotensive Type 1 diabetic patients: the impact of autonomic neuropathy. Diabet Med 2004; 21(6):524-530.

Conference Proceedings

The DRCMR was represented at 28 meetings and conferences during 2004 with 85 abstracts.

- The 12th Scientific Meeting of The International Society for Magnetic Resonance in Medicine (14 abstracts)
- Perfusion Workshop arranged by The International Society for Magnetic Resonance in Medicine (4 abstracts)
- The 10th Annual Meeting of The Human Brain Mapping (7 abstracts)
- The 21st Meeting of The European Society of Magnetic Resonance in Medicine and Biology (6 abstracts)
- The 45th Meeting of The European Society of Pediatric Research (1 abstract)
- The Annual Meeting of Pediatric Academic Societies (PAS) (1 abstract)
- The 9th International Conference on Alzheimer's Disease and Related Disorders (7 abstracts)
- The 32nd Annual Meeting of The International Neuropsychological Society (2 abstracts)
- Schizophrenia Research Meeting, Davos in Switzerland (1 abstract)
- Neuroeconomics Meeting, South Carolina (1 abstract)
- Neuroday, Panum Instituttet, Copenhagen (1 abstract)
- The European Committee for Treatment and Research in Multiple Sclerosis, Vienna (1 abstract)
- The 5th Annual European Congress of Rheumatology (EULAR) (8 abstracts)
- The 11th Annual Meeting of The European Society of Musculoskeletal Radiology (ESSR) (2 abstracts)
- The 68th National Scientific Meeting of The American College of Rheumatology (ACR) (9 abstracts)
- Neuroscience Day, Segerfalk Symposium, Lund (1 abstract)
- Annual Meeting of The Society for Neuroscience (4 abstracts)
- The 8th Conference of The Association for The Scientific Study of Consciousness (1 abstract)
- The 2nd International Workshop on Generative Model Based Vision (1 abstract)
- European Association for Nuclear Medicine (1 abstract)
- Workshop in Boston arranged by The International Society for Magnetic Resonance in Medicine (1 abstract)
- Research Day, Hvidovre Hospital (2 abstract)
- Scandinavian Neuropediatric Society (1 abstract)
- European Society of Magnetic Resonance in Neuropediatrics (2 abstracts)
- International Society and Conference Series on Medical Image Computing and Computer-Assisted Intervention (1 abstract)
- European Federation of Neurological Societies (1 abstract)
- The International Society for Optical Engineering (2 abstracts)
- Society for Cardiovascular Magnetic Resonance (2 abstracts)
- Annual Danish NMR Meeting (2 abstracts)

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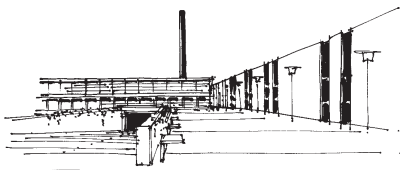

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