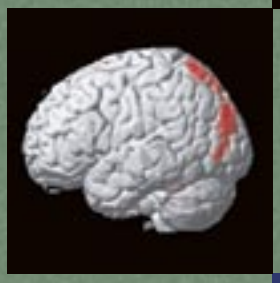
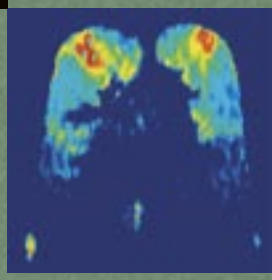
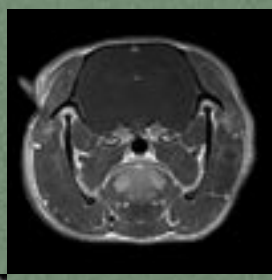
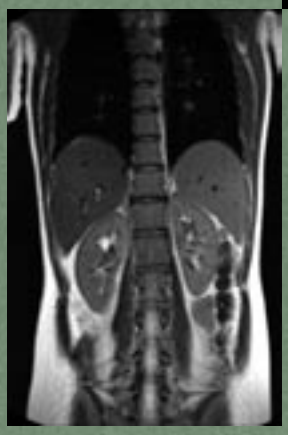




DRCMR

Annual Report 2006





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 2006. The main aim of the DRCMR is to advance the use of magnetic resonance as a clinical and investigative tool in biomedical science.

The year 2006 was a year of major changes at the DRCMR. In brain research the DRCMR became a major partner in the established “Center for integrated molecular brain imaging” (Cimbi) sponsored by the Lundbeck Foundation. In the clinical setting several physicians and technicians have been replaced and an essentially new staff has taken over. These changes occurred at a time well suited to meet the new demands formed by a new structure of the University of Copenhagen and by a new organisation of the hospitals and the university hospitals in the capital region of Denmark. In the coming year the organisation of the DRCMR will continue towards further strengthening the department as one of the most dynamic, flexible and innovative MR clinical and research units in this part of Europe.

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

Olaf B. Paulson
Head of the DRCMR

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 2006. 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 tre 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.

Året 2006 blev et år med store ændringer på MR afdelingen. I løbet af året har afdelingen således fået et næsten nyt klinisk personale med ny klinisk profil, og inden for forskningen er MR-afdelingen blevet etableret som en vigtig samarbejdspartner i ”Center for integrated molecular brain imaging” (Cimbi), som blev bevilget i slutningen af 2005 af Lundbeckfonden. Disse nyskabelser vil få stor betydning for afdelingens fortsatte virke inden for klinik og forskning. En reorganisering, som er i gang, vil fortsætte i år 2007 mhp. yderligere at styrke afdelingen. MR-afdelingen står således vel rustet til at møde de nye udfordringer, der ligger i Københavns Universitets nye organisation og i Region Hovedstadens reorganisering af sundhedsvæsenet. Afdelingens fortsatte reorganisering har således netop til formål at sikre afdelingen som en af de førende kliniske og forsknings MR-centre i denne del af Europa.

DRCMR at a Glance

A unique strength of the Danish Research Centre for Magnetic Resonance (DRCMR) is the multi-disciplinary 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 research partners in the Copenhagen Brain Research Center and elsewhere, the DRCMR also participates in groundbreaking research in neurology, neuroinformatics, neuropharmacology, neuropsychiatry, cognitive science, and rheumatology.

Imaging facilities

The Centre has three Siemens whole-body clinical scanners. A Magnetom Trio (3.0 tesla), scanner was installed in 2002 after a generous donation from the Simon Spies Foundation. This 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 also are 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 advanced 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. The preclinical group is involved in a set of promising new studies, using a pig model, that aim to create direct links between the results of new methods for visualizing fibre connections within the human brain and the "gold standard" results acquired using precise anatomical methods possible only when using post-mortem specimens. These studies are important in defining and extending the limits of new MR methods and illustrate the advantages of combined high-field human and animal imaging facilities (and the scientists who use them) in one site.

Clinically orientated activities

The Centre is a provider of local and national radiological services in response to physician referrals. The department's radiological expertise is also in demand as a reading and MR coordination site for several large clinical trials. An essential component of these trials is image analysis, and the Centre continues to make considerable effort and progress in establishing a "configurable" analysis pipeline. MR images acquired using sequences designed to obtain differing morphological, physiological or functional information are entered into the 'pipeline' and automatically analyzed using a wide range of methods including alignment, intensity correction and segmentation. In the last year, continuing development of this pipeline has narrowed the gap between traditional radiological practices and the informatics approaches of the future.

Organization of Departmental Research

Current research is organized around four themes by (overlapping) groups of investigators who meet regularly to exchange information and review the progress of their projects. These groups include investigators focused on method development (Methods Group), investigators conducting preclinical research in the animal facility (Preclinical Group), investigators conducting human brain research (Brain Research Group), and investigators 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 leaders of the DRCMR and meets weekly to review the progress of the research and to discuss issues of

general interest, regarding both scientific and administrative matters.

2006 and the future

In 2006 a new profile of the clinical section of the DRCMR was established. In the fall Per Åkeson, who came from a position as chief radiologist in Malmö, Sweden, took over the leadership of the clinical section of the department. Together with an essentially new clinical staff this secured dynamic and innovative changes in the clinical work rendering the department ready to meet new challenges with the establishment of the new hospital organisation in the capital region of Denmark and with the continuous rapid evolution of clinical MR.

In the research one of the most exciting developments of the year was the department's role in the implementation for a new Center for Integrated Molecular Brain Imaging (Cimbi). This center is funded by the Lundbeck Foundation and drew applications from many major neuroscience groups within Denmark. The Cimbi group is led by Professor Gitte Moos Knudsen of the Neurobiology Research Unit at Rigshospitalet and included contributions from principal investigators at the Danish University of Pharmaceutical Sciences (led by Professor Mikael Begtrup), the Technical University of Denmark (led by Professor Lars Kai Hansen) as well as the DRCMR (led by Professors Paulson and Jernigan). The research in Cimbi focuses on the neural bases of personality dimensions that predispose individuals to affective and substance use disorders, with special emphasis on the serotonergic neurotransmitter system. Both PET and MRI will be employed in studies of human subjects, and these will be complemented with relevant studies using animal models. Advanced informatics techniques, new tracer compounds, and novel serotonergic challenge paradigms will also be developed within the Center. The work will also involve collaborating laboratories in Europe and the US.

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. The interaction between radiologists, clinicians, psychologists, physicists and engineers together with other scientists from different disciplines within both 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 new clinical and research initiatives over the next year, the department is confident that it will continue to make significant clinical and scientific contributions and remain at the forefront of MR research at an international level.

Organisation and Staff

Department Chair

Olaf B. Paulson, DMSc, Professor

Senior staff, Clinical

Marianne Daslgaard, Head Technologist (from October 2006)
Margrethe Herning, MD, Senior Physician and Clinical Chief (until June 2006)
Sussi Larsen, Head Technologist (until March 2006)
Anne-Mette Leffers, MD, Senior Physician (until April 2006)
Michel Nemery, MD, Senior Physician (from September 2006)
Forough Sadolin, Head Technologist (Radiographer) (March - September 2006)
Per Åkeson, MD, Senior Physician and Clinical Chief (from October 2006)

Senior Staff, Research

William Baaré, PhD, Psychologist
Lars G. Hanson, PhD, Chief Physicist
Terry L. Jernigan, Professor, PhD, Psychologist
Torben Ellegaard Lund, PhD, Engineer
Julian Macoveanu, PhD, Engineer
Maurice Ptito, Guest Professor, PhD, DMSc
Poul Ring, MSc, Engineer
Egill Rostrup, MD, DMSc & Human Biologist
Ian J. Rowland, PhD, Chemist
Fabien Schneider, PhD, Engineer
Karam Sidaros, PhD, Engineer
Lise Vejby Søgaard, PhD, Physicist
Xingchen Wu, PhD, MD

Junior Staff, Clinical

Annika Reynberg Langkilde, PhD, MD
Camilla Gøbel Larsen, MD
Erland Magnusson, MD (from December 2006)
Jakob Marstrand, PhD, MD
Henrik Meelby, MD (until May 2006)
Peter Magnusson, PhD, Physicist
Xiong Xie, MD (until May 2006)

In addition residents from the Department of Radiology rotate through the DRCMR for periods of 2 months.

Junior Staff, Research

PhD students
Mark Schram Christensen, MSc, Engineer
Sadia Asghar Butt, MSc, Biochemist
Tim Dyrby, MSc, Engineer
David Alberg Holm, MSc, Engineer
Bettina Hornbøll, MSc, Biologist
Elizbieta Kalowska, MD
Katja Krabbe, MD
Astrid Lou, MD
Kristoffer Madsen, MSc, Engineer
Kathrine Skak Madsen, MSc, Biologist
Henrik Kahr Mathiesen, MD
Annette Sidaros, MD
Kirsten Korsholm, MD
Robin de Nijs, MSc, P.D. Engineer, Medical Physicist
Dorthe Pedersen, MD
Thomas Z. Ramsøy, MSc, Psychologist
Charlotte Ryberg, MSc, Biologist
Arnold Skimminge, MSc, Physicist
Jon Wegener, MSc, Life Sciences and Chemistry

Junior Researchers
Matthew Liptrot, MSc, Engineer
Henrik Lund, MSc, Human Biologist
Jens Bundgaard, MSc, Physicist
Martin Skov, MA Nordic Languages and Literature

Research Assistants and Students
Henrik Lundell, Engineering Student
Anders Dæhli Skjolding, Medical Student

Technologists

Siri Eggum, Radiographer
Sascha Gude, Laboratory Technician
Leif Børgesen, Radiographer
Nina Hansen, Laboratory Technician
Pia Olsen, Radiographer
Hanne Schmidt, Radiographer
Helle Juhl Simonsen, Research Technician
Jesper Rohde, Radiographer

Secretarial Staff

Jeanette Beck
Lotte Hansen
Lisa Juhl Simonsen
Ina Tech
Sussie K. Volkmann

Cleaning Assistants

Ruth Kielstrup
Elsebeth Nielsen

Conscientious Objectors

Rasmus Hasenfuss
Rune Morten Larsen
Thomas Bach

Visiting Staff

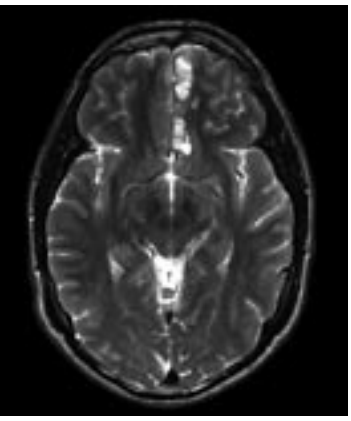
Bo Ejbjerg, PhD, MD
Maria J. Miranda, PhD, MD
Trine Stavngaard, PhD, MD
Mikkel Østergaard, DMSc, PhD

Clinical Imaging

The clinical section of the DRCMR underwent a major reorganisation during 2006. New personnel was employed and the knowledgebase among the clinical doctors was further expanded. Per Åkeson, who came from a position as chief radiologist in Malmö, was recruited to take over the leadership of the clinical section. The number of radiographers was also increased and dynamic and innovative changes in the clinical work were introduced, making the department well-prepared for future changes. During the reorganisation the patient throughput was unavoidably reduced due to lack of personnel. Despite this, 2882 examinations were performed in 2006, the majority of these being referrals from Hvidovre Hospital. A substantial amount of patients was, however, referred from other counties inside or outside Copenhagen as well.

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. But also investigations of orthopaedic cases, e.g. intraarticular diseases such as meniscal tears or osteoarthritis, extraarticular diseases such as tenditis and soft tissue diseases as well as soft tissue tumours are a growing part of the daily workload. Different types of abdominal examinations have also become a more important area for MR-scanning. However, spinal examinations are still a large part of the daily work.

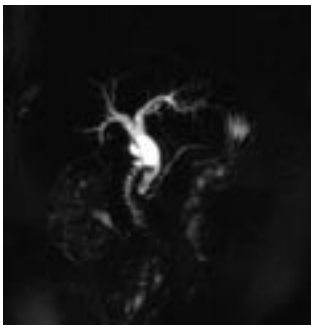
One of the senior radiologists is a member of the 'EPIKIR' group, an organisation responsible for national epilepsy patient management that selects patients suitable for surgical intervention and is responsible for postoperative patient management. Consequently, many patients with epilepsy have been 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 etc. Patients are received from all over Denmark for these examinations.



MRI is very sensitive to pathology, but also to non-critical abnormalities. This example shows a condition known as DNET in the left frontal lobe (right side of image). Even though it may look dramatic, the imaged person is healthy. Findings unrelated to symptoms is one of the challenges in clinical radiology. The employed technique known as parallel imaging allows 19 such brain slices to be imaged at 3 tesla field strength in less than two minutes.

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 performed both without and with contrast agents. The use of the 3T scanner for these examinations has further improved the results due to the very high resolution that can be achieved.

MRI of patients with traumatic brain injury has been a research field at the department and is becoming 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.



Dilatation of, and gallstones in the common bile duct of a 43 year old patient shown well at 3 tesla.

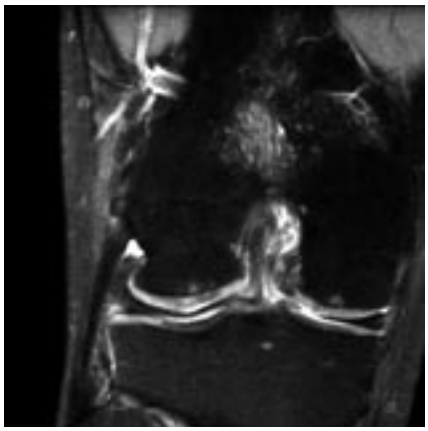
In paediatric radiology, MRI is used successfully both in neonates and older children with different neurological diseases such as hypoxic complications occurring around delivery and seizures in the postnatal period. For the investigation of congenital malformations, both cerebral and spinal, as well as metabolic diseases MRI is the method of choice readily visualizing most diseases. One of the senior radiologists is also a member of a Copenhagen network meeting regularly to evaluate difficult cases of neurological malformations and paediatric diseases.

Many examinations of mainly children are performed in general anaesthesia and the department is now with the help of the department for anaesthesia performing MR-scanning under general anaesthesia two days per week.

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

Musculoskeletal MRI is an important clinical area and is rapidly replacing diagnostic arthroscopy in the

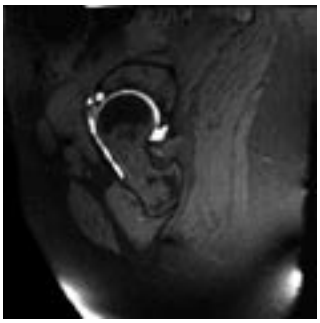
Clinical Imaging



Very early osteoarthritis changes in the knee-cartilage of a 42 year old patient seen well at 3 tesla.

evaluation of meniscal lesions, lesions in the cruciate ligaments, collateral ligaments and damage to the cartilage in the knees. During the year the increasing use of the 3T scanner has improved the diagnostic accuracy quite a lot mainly concerning cartilage evaluation. In the shoulder, MRI is used in diagnosing labral lesions, rupture of the rotator cuff and so forth. In the hip MRI is used to diagnose labral lesions, cartilage diseases and sometimes to find difficult hip fractures. MR-arthrography of both shoulder and hip joints has been applied and has improved the results in these joints. Other areas where MRI is used are tendon tears around the ankle, different diseases in the foot and inflammatory diseases in the spine and the sacro-iliac joints. Preoperative investigation of musculoskeletal tumours can determine the extent of disease and help treatment planning. Metastatic bone disease is also best diagnosed with MRI.

The trend of increasing numbers of abdominal scans being performed at the DRCMR has been further accentuated. MRCP has become a routine investigation for the bile ducts and pancreatic duct. MRI of perineal fistulas in patients with inflammatory bowel disease has become the standard method for preoperative evaluation. MRI of rectal cancer is a well-established method 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. During the year the bulk of these examinations have been moved to the 3T scanner with much improved accuracy as a result.



Arthrography of hip with lesion of labrum and subchondral cysts in a 35 year old patient.

Collaborations

The DRCMR collaborates and works closely with many institutions both nationally and internationally. Primary collaborators in 2006, especially those with whom common funding was obtained and those who participated in supervision of PhD students are listed below.

National Collaborations

In the area of Neuroscience, an important formal national collaboration has been established for some years in form of the Copenhagen Brain Research Centre (www.cbrc.dk). In 2005, new funding has been obtained from the Lundbeck foundation to establish a new Center for Integrated Molecular Brain Imaging (Cimbi). The participants are the Neurobiology Research Unit at Rigshospitalet, the Danish University of Pharmaceutical Sciences, the Technical University of Denmark, as well as the DRCMR.

National Collaborations

Centre of Functionally Integrative Neuroscience, University of Aarhus

Centre for Integrated Molecular Brain Imaging (CIMBI), Rigshospitalet

Department of Physics, The Technical University of Denmark

Informatics and Mathematical Modelling, The Technical University of Denmark

Department of Exercise and Sport Sciences, University of Copenhagen

Department of Psychology, University of Copenhagen

Department of Neuroscience and Pharmacology, Panum Institute, University of Copenhagen

Hammel Neurocenter, Aarhus University Hospital
Institute for Molecular Pathology, University of Copenhagen
The Parker Institute, Copenhagen University Hospital Frederiksberg
Research Laboratory for Stereology and Neuroscience, Bispebjerg Hospital
Research Department of Human Nutrition, The Royal Veterinary and Agricultural University
Statens Serum Institut

Copenhagen University Hospitals

Departments at Hvidovre Hospital
Department of Neurorehabilitation
Department of Paediatrics
Department of Radiology
Department of Respiratory Medicine
Department of Rheumatology

Departments at Rigshospitalet
Danish Multiple Sclerosis Center
Department of Clinical Physiology
Department of Neurosurgery
Department of Radiology
Department of Rheumatology
The Memory Disorders Research Unit
The Neurobiology Research Unit
The Neonatal Department
University Clinic of Neurosurgery, The Neuroscience Centre

Departments at other Copenhagen University Hospitals
Center for Neuropsychiatric Research, Psychiatric University Centre Glostrup
Department of Neurology, Bispebjerg Hospital
Department of Neurology, Glostrup Hospital
Department of Psychiatry, Bispebjerg
Department of Psychiatry, Glostrup Hospital
Department of Respiratory Medicine, Copenhagen University Hospital, Gentofte

International Collaborations

Center for fMRI, University of California, San Diego, USA
Centre for Medical Image Computing, University College London, United Kingdom
Department of Clinical and Experimental Epilepsy, Institute of Neurology, London, United Kingdom
Department of Clinical Radiology, Klinikum Grosshadern der Universität München, Germany
Department of Neurology and Brain Imaging Center, Johann Wolfgang Goethe-University, Frankfurt, Germany
Department of Radiation Physics, Lund University Hospital, Sweden
Image Science & Biomedical Engineering, University of Manchester, United Kingdom
Institute for Clinical Neuroscience, Göteborg University, Göteborg, Sweden
Laboratory of Cognitive Imaging, University of California, San Diego, USA
Medical Imaging Research Institute, Heidelberg, Germany
Medical Research Council, Cognition and Brain Sciences Unit, University of Cambridge, United Kingdom
Neuroscience and Psychiatry Department, The University of Manchester, United Kingdom
Robert Steiner Magnetic Resonance Unit, ICSM Hammersmith Hospital, London, United Kingdom
School of Psychology, The University of New England, Armidale, Australia
The Dementia Research Centre, National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom
The Neuroscience Institute, San Diego, USA
University of Arizona, Center for Consciousness Studies, Arizona, USA
University Laboratory of Physiology, Oxford University, United Kingdom
Clinic for Anesthesiology, Radiology, Johannes Gutenberg-University, Mainz, Germany
Institute of Physics, Johannes Gutenberg-University, Mainz, Germany

International Multi-Centre Research Collaborations

The DiMI Project: An international network of excellence for the advancement of diagnostic molecular imaging (DiMI).
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.

Basic Research

A key component of the research chain is what is called Basic Research. Unlike blue sky research, which has no immediate application in mind, Basic Research is a required stepping-stone on the way to any clinical application or applicative research, and so can also be considered as 'Foundation Research'. Once this concept is understood, it is easy to see how the clinician's evaluation of a particular treatment's outcome, or the discovery of new knowledge about a physiological system by researchers, both depend upon the integrity of the Basic Research building block. Basic Research is therefore a key focus area within the DRCMR.

So what constitutes Basic Research? Although it is quite common to divide the vague, all-encompassing term 'research' into clinical (e.g. evaluating X vs Y in the treatment of Z) and knowledge-enhancing (e.g. probing of a particular physiological system, or developing a new quantification method), it can be more informative to think of research divided along different lines. For example, classification into 'development', 'evaluation' and 'application' emphasizes the multistage nature of the research path, and also has the advantage of unifying the research in the clinical and research sections, an area which the DRCMR is coming to set even more focus upon in the next years. It also highlights the importance of Basic Research, which quite simply constitutes the first two steps. Without it, achieving the final step of applicative research would not be possible. Thus we can think of Basic Research as either:

- Developing of new methods which can provide quicker results, more accurately, and more robustly. Example areas would include hardware (new scanner technology, combination of existing technologies, etc), software (usually specialized in-house code) or analysis methods (statistical calculations, optimization, mathematical modelling etc),
- Evaluating such newly-developed methods. This is extremely important for in-house developments, but also for 'keeping up to date' with the latest advances by scanner and equipment manufacturers, and by other research groups around the world. This includes a vast range of software code (e.g. SPM, FSL, Camino), and the related algorithms and mathematical models associated with them.

As a major MR research facility, the DRCMR has a responsibility to ensure it is as up-to-date as possible. Only then can it contribute to the advancement of MR methods and techniques on an international scale, and hence also offer the best quality care to its patients.

The basic research at the Centre can be divided into five categories:

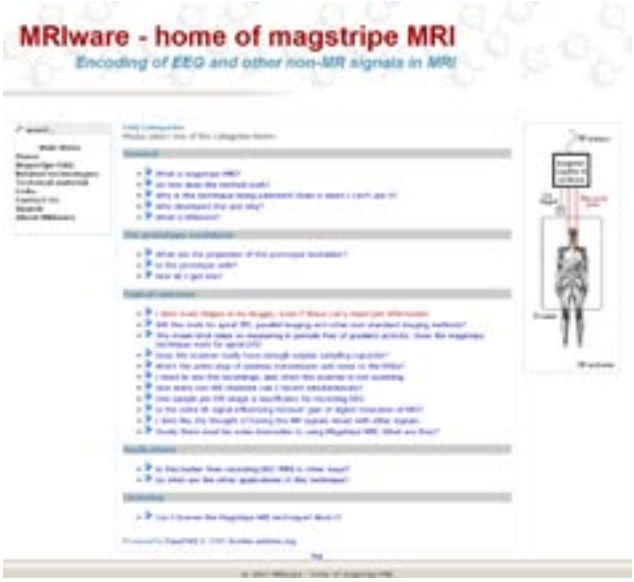
1. Development and optimisation of new MR sequences and methods (MR physics and methodology)
2. Development of novel post-processing strategies and experimental design (MR informatics)
3. Investigation of the basic physiological factors reflected in MR images (physiology)
4. Mapping of the cognitive functions in the brain (brain mapping)
5. Investigation of the neural bases of personality dimensions with special emphasis on the serotonergic neurotransmitter system (Cimbi)

The activities of the Centre within each of these categories are described in the following.

MR Physics and Methodology

Although numerous clinical MR sequences are provided with the MR scanners by the scanner manufacturers, there are a variety of research projects within 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.

Diffusion tractography is a new method which non-invasively allows for studies of the complex connections in the brain. Neural fibres connect the different regions of the brain that process inputs giving rise to perception and appropriate output. Tim Dyrby, Lise Vejby Søgaard and William Baaré have continued the important process of understanding the basics of the diffusion process and how optimal MR scanner parameters can be selected to obtain high quality datasets for validating tractography. By doing scans in vitro most of the problems known to hamper in vivo measurements, e.g., patient movement and physiological noise (respiration and cardiac), are overcome. The possibility of increasing the scanning time furthermore results in high quality datasets superior in resolution and signal-to-noise ratio compared to scans acquired in vivo. Tim Dyrby performed the analysis comparing different diffusion tractography methods and their validity in collaboration with Daniel

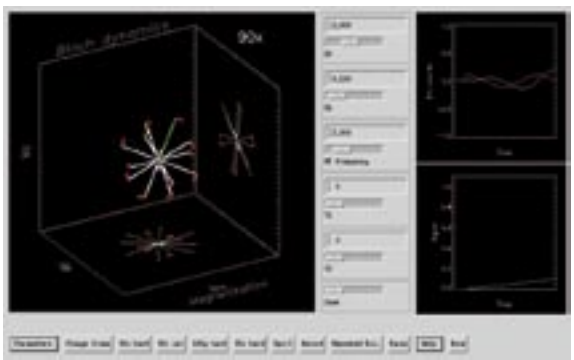


An independent spin-off company MRIware was founded to make the Magstripe MRI technique developed at the DRCMR available to a broader audience. Here is a sample from the company homepage at http://www.MRIware.com/.

Alexander and Geoffrey Parker (UK). This collaboration is reflected in the presence of DRCMR data on the Camino Diffusion MRI Toolkit Homepage on http://www.cs.ucl.ac.uk/research/medic/camino/.

Arterial spin labelling (ASL) has been a main area of sequence development in the past years at the Centre. ASL is the only completely non-invasive method of measuring regional blood flow in vivo. Karam Sidaros continues to develop ASL methodology and is responsible for maintaining and optimising the ASL sequences on the 3T Trio scanner. This requires continuous effort since regular scanner software updates ensure that all in-house sequences need updating too. Recently, a new 3D ASL sequence was acquired from a collaborator in Heidelberg. The new sequence which is currently being tested offers much higher signal-to-noise ratios. David Holm has been working on implementing ASL at 4.7T as a tool for his PhD project on measuring angiogenesis in tumours, i.e. the formation of new blood vessels as a tumour grows.

Another activity of the DRCMR is the simultaneous acquisition of functional MRI (fMRI) and electrical signals coming from brain activity (electroencephalography, EEG recording). The combination of the two techniques can improve both source localisation in EEG and temporal resolution in fMRI. Briefly, EEG can measure when there is brain activity and fMRI can measure where it happens. Hence EEG-fMRI is widely believed to be a technique that will increase the understanding of processes and networks in the brain, and will provide improved diagnosis of particular diseases, for example, when used for pre-surgical planning in epilepsy. However, measuring EEG and fMRI simultaneously 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 trace that is about 3 orders of magnitude larger than the actual EEG signal. This is highly demanding both for the hardware used to record EEG signals during scanning and for the analysis software. Brothers Lars and Christian G. Hanson have headed a group developing a novel method for recording EEG and fMRI simultaneously. The approach uses a special modulator together with the scanner for recording both EEG and fMRI data. Similar to the so-called “Magstripe technique” used for encoding of soundtracks in movies, the EEG signals are encoded in the MR images outside the visible region. A proof-of-concept study has been accepted for publication in Journal of Magnetic Resonance Imaging. The technique and especially the developed hardware has matured much since the initial studies and in 2006 alpha-EEG recording was demonstrated using the method. The electronics developer of the group, Christian G. Hanson, has constructed a highly flexible 8-channel modulator for the purpose. The method is simple to use, sensitive, inexpensive and more robust than traditional methods. The analysis is also suitable for integration on the scanner, even as the data are being acquired (real-time EEG-fMRI). PhD student Arnold Skimminge enrolled in the ITMAN graduate school at the Technical University of Denmark is working on these issues. The patent rights for the Magstripe method are now claimed by an independent spin-off company MRIware founded for that purpose (http://www.MRIware.com/).



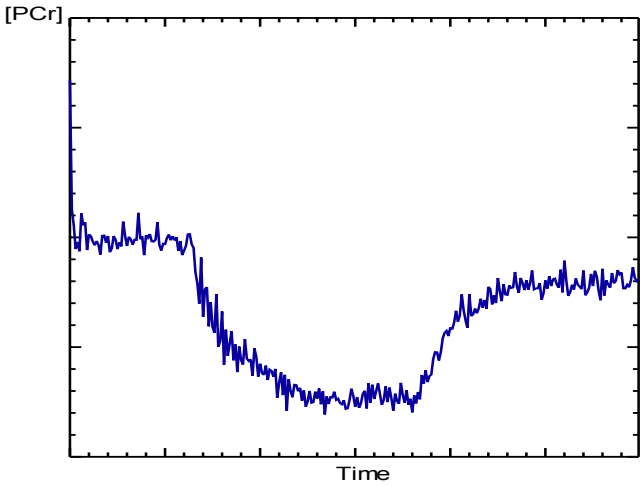
Software for illustrating and teaching the essentials of basic MRI was developed at the DRCMR and can be downloaded from the Centre homepage free of charge. The software runs on most platforms (Windows, Linux and more).

Basic Research

The staff of the DRCMR provides teaching in many contexts as described elsewhere in this annual report. Examples are the courses in Basic MRI given by Lars G. Hanson. In order to aid the teaching of this difficult subject, software that demonstrates many essential MRI techniques has been developed by Lars. A beta-version has been available for download for some time but in 2006 the software was significantly enhanced and the first official release was made. The program runs on most platforms (Windows, Linux and more) and can be downloaded from the DRCMR homepage and used free of charge.

Contrast-based perfusion measurements have long been an area of research at the DRCMR. Lately, focus has been on implementing and optimising perfusion quantification using T_1-weighted dynamic measurements. Contrast-based perfusion measurements often rely on T_2*-weighted imaging to monitor the susceptibility effects of the paramagnetic contrast agents used. However, T_1-weighted imaging, albeit less sensitive, offers a more direct relation between the amount of contrast agent used and the change in image intensity. This is an advantage over T_2*-weighted imaging, especially when quantifying perfusion. A former member of the department, Irene K. Mikkelsen moved to Sweden in 2004 thereby initiating collaboration between the DRCMR and the Institute of Clinical Neuroscience at Gothenburg University. The collaboration also includes related aspects of data acquisition and analysis, and it involves Henrik Lund, Karam Sidaros, Arnold Skimminge and Lars G. Hanson.

Magnetic resonance spectroscopy can be used to measure the concentrations of phosphorous metabolites in vivo and this was a subject of research at the DRCMR in the early days of MRI. It has not been performed locally for many years, however. There are simply too many interesting MR techniques, so phosphorous spectroscopy was left out of focus for while. The techniques recently got a renaissance at the Centre due to interest expressed by external collaborators, Luke Haseler and Bengt Saltin from the Copenhagen Muscle Research Centre. Flemming Jessen designed and built an MR-compatible ergometer for the scanner and with a coil borrowed from the Radiological Department at Rigshospitalet, we were ready to go. Lars G. Hanson programmed automated calibration and scanning, and a number of successful pilot experiments were performed towards the end of the year. The setup is ready for use in a series of experiments planned for 2007.



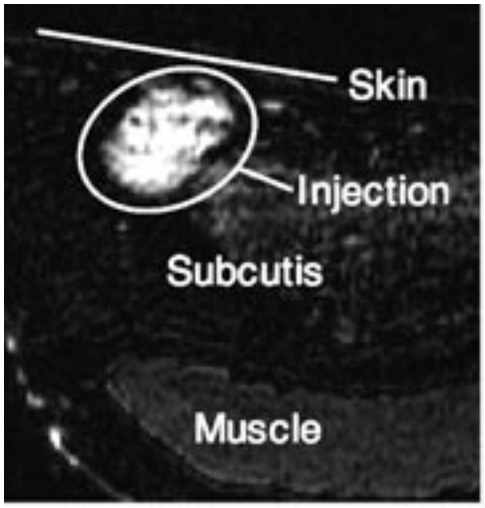
The phosphocreatin concentration and the corresponding MR signal changes during exercise as shown in this graph. A subject in the scanner is resting for a two minute period followed by 4 minutes of exercise and 4 minutes of rest. During the exercise period the phosphocreatin pool is depleted and subsequently re-established.

In 2006 a new line of research was initiated at the DRCMR. Henrik Lundell, a student from the Technical University of Denmark supervised by Bjørn G. Nielsen and Lars G. Hanson, investigated visualisation by MRI of injections. Henrik's Masters project supported by the Novo Scholarship Programme was aimed at characterising normal injections and injections made with needle-free devices that apply liquid drugs to the skin at such high pressure that the liquid penetrates the skin. Needle-free injections have advantages with respect to safe handling and psychological factors, but it is very important that the injection characteristics are well understood and controlled. Pharmacokinetics are highly influenced by the structure of the deposition and MRI was applied to visualise the overall morphology of the deposition. Diffusion Tensor Imaging (DTI) was used to reveal microstructures within the area of deposition. MRI based methods may also improve the understanding of the biomechanics of the subcutis.

MR Informatics

For each patient, MRI provides several sets of images with differing contrast. These are aligned and further analysed together by a series of processing methods chosen in accordance with the aims of the individual project. In order to do this efficiently and reproducibly, configurable analysis "pipelines" have been established and are now used in almost all studies. MR-images are fed into the pipelines and are automatically analysed using a selection of the available methods, such as alignment, intensity correction and segmentation. Designing and implementing the basic framework as well as extending the functionality with new methods are major tasks undertaken by Arnold Skimminge and Tim Dyrby for the benefit of both

ongoing and future studies. In the EU LADIS project that is a multi-centre project focusing on the aging population, Tim Dyrby has succeeded in standardising the image processing of hundreds of brains in such a "pipeline" for automatic classification of brain tissue into white matter lesions, grey matter, white matter and cerebrospinal fluid.

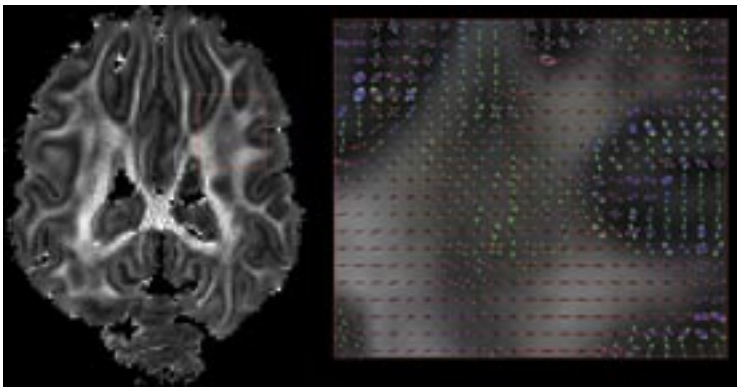


A T_2-weighted image of a subcutaneous saline injection. Visualisation of injections can assist the development of new user-friendly injection methods. This injection is made with a needle free jet device.

Robin de Nijs is funded by a grant from the Danish Medical Research Council. His work in 2006 was mostly directed towards analysis of existing neonatal spectroscopy data acquired with the 3 tesla scanner. Challenges include analysis of data from highly sensitive multi-element coils, quantification of metabolite concentrations and enhancement of the data quality that is often compromised by subject motion during the examination. In single voxel spectroscopy of the infant brain, motion artefacts are frequent. In order to get reliable data, acquisitions with motion artefacts need to be rejected. This can be achieved by postponing averaging of the individual repetitions within one measurement. These can be analysed automatically with independent component analysis where the dominant component represents motionless acquisition. The motion rejection was successfully applied on single voxel spectroscopy data of preterm infants at both short and intermediate echo time.

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, a part of the brain is dedicated to performing 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. An efficient technique developed by Kristoffer Madsen for mapping both polar and eccentricity information is now being used in clinical projects.

Working at the crossroads of mathematical modelling, statistics and medical image analysis, Ph.D. student Karl Sjöstrand and associate professor Rasmus Larsen from the Technical University of Denmark have in cooperation with the DRCMR developed a series of generic methods for analysing the shape of the brain and its substructures. In a mainly theoretical effort, they developed a new method for finding unrepresentative samples of anatomy from large data sets. The method generalises a statistical method for one-class classification known as the support vector domain description. This work was presented at the conference for Medical Image Computing and Computer-Assisted Intervention (MICCAI) in Copenhagen, where it was elected best student paper in the image analysis category. Working together with Dr. Colin Studholme from the University of California San Francisco (UCSF), techniques for relating localised characteristic deformations of anatomy to clinical outcome were developed. The methodology was applied to the LADIS data set of the corpus callosum with promising clinical and theoretical results. The project resulted in a journal paper that has been accepted for publication in Transactions on Medical Imaging (IEEE TMI). The collaboration with UCSF was established



High quality diffusion weighted datasets acquired post mortem provide unique opportunities for validation and development of new mathematical models for tractography. The figure shows an example. The fractional anisotropy (FA) (left) is widely used for quantifying the anisotropy in, e.g., white matter. The FA calculation, however, is typically based on a single-fibre model. In complex regions containing crossing fibres, the FA maps are therefore misleading as they indicate artificially low anisotropies (dark region in red square). Instead, more complex models such as PAS-MRI that are capable of modelling crossing fibres can be used. The figure to the right shows a PAS-MRI calculation corresponding to the red region in the left figure. This way of modelling detects crossing fibres in regions where the FA maps incorrectly indicates a low anisotropy.

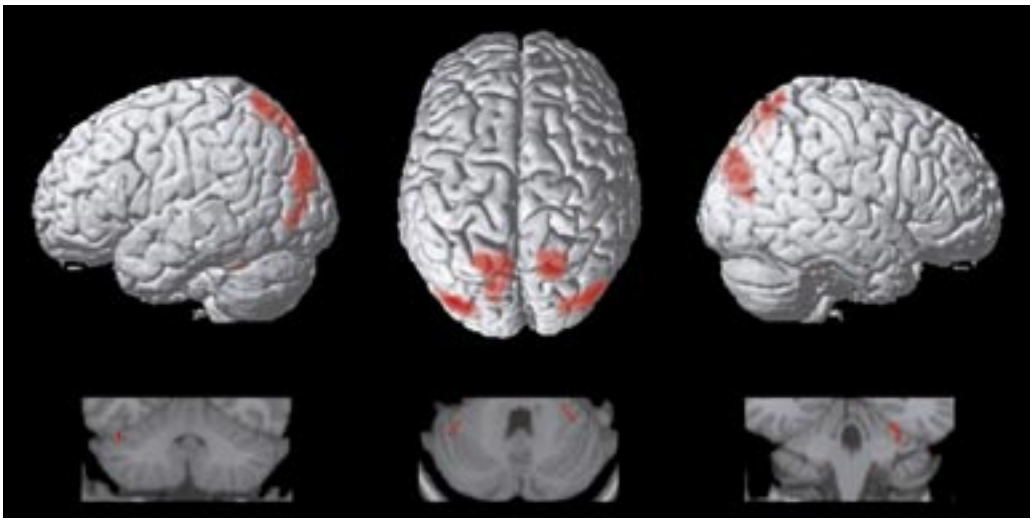
through a six-month study abroad program conducted by Karl Sjöstrand at UCSF. The work of the DRCMR and the Technical University of Denmark was widely acknowledged by researchers at and around UCSF. A confirmation of this came in the form of an invited talk at the statistics department at Stanford University. The collaboration with UCSF is carried on, currently through a joint study on whole-brain morphometry.

Kristoffer Madsen is funded by a PhD scholarship from the Technical University of Denmark (DTU). In 2006 his work was primarily centred on development of algorithms for time series analysis, in particular Bayesian statistical methods to improve estimation and detectability in presence of arbitrary correlated noise. These methods may be used to improve the reproducibility of results from fMRI time series from retinotopic mapping experiments. In collaboration with co-workers Torben Lund and Morten Mørup from DTU, Kristoffer Madsen is also developing methods for unsupervised multi-way analysis of fMRI data. The methods use constrained parallel factor analysis algorithms and are aimed at estimating signals in multi-subject data even when the type of stimulation is not known.

Kristoffer Madsen and Torben Lund have previously developed techniques to extract physiological noise parameters such as respiration and pulse from MRI data and used these to improve the analysis of functional MRI studies. Along the same line of work, Karam Sidaros and Torben Lund have in 2006 been estimating the effects of respiration and pulsation-induced motion on perfusion images using Arterial Spin Labelling (ASL). They found that, both respiration and pulsation have a significant effect on the perfusion-weighted images produced by this technique. Using the same methods described above for fMRI as well as new methods that don't require physiological recordings, it is possible to reduce these effects in ASL as well.

Basic Physiology

One of the very fascinating applications of MRI is mapping the functional anatomy of the human brain. During the last decade the brain mapping methodologies have developed tremendously, and the majority of current studies relies on the BOLD (blood oxygenation level dependent) technique, rather than radiotracer based methods. In 2006 Egill Rostrup successfully defended his doctoral dissertation on the basic physiology of brain activation as described here. During brain activation the supply of oxygen is known to increase more than its use, resulting in a decrease of deoxy-haemoglobin levels. Since deoxy-haemoglobin is paramagnetic, this results in a more homogeneous magnetic field, as can be detected by appropriate MR techniques. These techniques are primarily sensitive to the total amount of deoxy-haemoglobin pr. unit of tissue, which is determined from a balance between oxygen supply and use, but also depends on blood volume and other properties such as haematocrit, pH and PaO_2. The BOLD effect is therefore not specific to neural activation. In his dissertation, Egill Rostrup used the term $BOLD_A$ for BOLD responses caused by neural activation, and $BOLD_B$ for those caused by factors such as hypercapnia, hypoxia or other changes in blood composition or supply. These non-neural factors are very relevant both because they represent a tool by which basic brain physiology can be studied, and because they interact with the $BOLD_A$ responses, thereby adding to their intra- and inter-subject variability. The dissertation reviewed the literature regarding the basic physiological mechanisms common to $BOLD_A$ and $BOLD_B$ responses with a special emphasis on the influence of variations in arterial blood gases. Furthermore, a mathematical model of the BOLD response was introduced. It included, as a novel feature, the contributions from both the arterial, capillary and venous compartments. The model was used to guide the interpretation of experimental results obtained by the author and other experimenters. From the modelling results it appeared that the level of tissue oxygenation in the brain is critically dependent on the permeability of the blood-brain barrier to O_2 diffusion, and it was suggested that O_2 metabolism under some, but not all conditions may be limited by arterial O_2 delivery. In BOLD measurements the baseline signal increases with arterial CO_2-tension as suggested by several studies, and this is mainly due to increased blood flow and brain oxygenation. These findings are confirmed by the present modelling results, which further indicate that the $BOLD_B$ response may be influenced by pH and PaO_2 changes in addition to the haemodynamic changes during hypercapnia. During hypoxia the $BOLD_B$ signal decreases in spite of regulatory CBF increases that minimise the change in oxygen delivery to the brain. Haemodilution also influences the $BOLD_B$ signal, and this effect seems to be related to an accompanying increase in flow. The magnitude of the $BOLD_A$ response detected after neural activation is dependent on several baseline parameters. Conditions with high baseline flow, such as hypercapnia, generally diminish the response magnitude. Hypoxia has also been shown to diminish



The top row shows regions of the posterior parietal cortex with increased activation when subjects perform self-generated foot movements and they produce the visual feedback by themselves. The bottom row shows regions of the cerebellum affected by the same task. The direct effects of visual feedback and from self-generated movements have been subtracted, which means that the activation in these regions is only present when subjects perform the movement with visual feedback themselves.

the $BOLD_A$ response, and the effect of arterial deoxyhaemoglobin was proposed as an additional factor in hypoxia. Decreased baseline flow may enhance the $BOLD_A$ response, as long as O_2 metabolism is uncompromised. In conclusion, several physiological factors influence the magnitude and detectability of BOLD responses, and should be accounted for in order to minimise variability between experimental groups. A quantitative understanding now seems possible, due to recent progress in modelling and data acquisition techniques. In quantitative terms the inter-individual variability is unknown, and this is an area that should be pursued further.

Brain Mapping

As a part of his PhD project, Mark Schram Christensen has, together with Jesper Lundbye-Jensen, Svend Sparre Geertsen, Nicolas Petersen and Jens Bo Nielsen, all from the Department of Exercise and Sport Sciences, and Olaf B. Paulson, compared self and externally generated foot movements with and without visual feedback of how much the foot moved. They showed that activation of the posterior parietal cortex and the cerebellum was increased when the subjects themselves produced the visual feedback. This suggests that the aforementioned regions are very important for the integration of motor command signals and visual feedback. Furthermore, the group showed that different regions of the cerebellum displayed activation differences depending on whether the movements and visual feedback were self generated or externally generated. The work is in press in the journal Cerebral Cortex.

Daniela Balslev has, together with Finn Å. Nielsen, Torben E. Lund, Ian Law, and Olaf B. Paulson investigated how motor and proprioceptive signals contribute to the recognition of visual feedback from own movements. They found that similar brain areas were activated by a temporal mismatch between movement and its visual feedback regardless whether the movement was active or passive. This suggested that the motor command may be less important for the recognition of the visual feedback than previously thought. This study has been published in Neuroimage. Following up on this experiment, Daniela together with Jonathan Cole from the University of Bournemouth and Chris Miall from the University of Birmingham tested whether a man with chronic proprioceptive deafferentation was able to recognize his own movements when these movements were presented visually. The patient was able to perform the task. However, his performance was less accurate than that of healthy controls. Thus, although proprioception is not critical for self-recognition, in its absence the recognition of visual feedback is impaired. This work has been accepted for publication in the Journal of Cognitive Neuroscience.

Together with Mark Schram Christensen and Ulrich Kirk from the University College in London, DRCMR investigator Martin Skov conducted two new fMRI experiments in 2006 on the formation of aesthetic preferences. In the first study they scanned a group of architects and a group of non-architects as they rated a series of pictures of buildings and human faces. The assumption was that, while the two groups would react similarly to the faces, the architects would have a different neural reaction to the buildings due to their expertise on this type of object. A comparison of the two groups showed that this was indeed the case: In assessing the aesthetic appeal of the build-

ings the architects activated orbitofrontal cortex and the anterior part of the cingulate cortex more than the non-architects. In the second study a group of subjects without any formal interest in art was asked to rate a series of abstract paintings while being scanned. However, they were informed that half of the paintings were on loan from Louisiana Museum, the most famous fine arts museum in Denmark, while the other half was manufactured by the experimenters themselves. Prompted by this top-down modulation the subjects rated the "Louisiana" paintings as more appealing than the "Experimenter" paintings, and also exhibited elevated activity in the right medial orbitofrontal cortex associated with their preference for the "Louisiana" paintings. This result demonstrates that people's aesthetic experiences can be influenced by semantic knowledge.

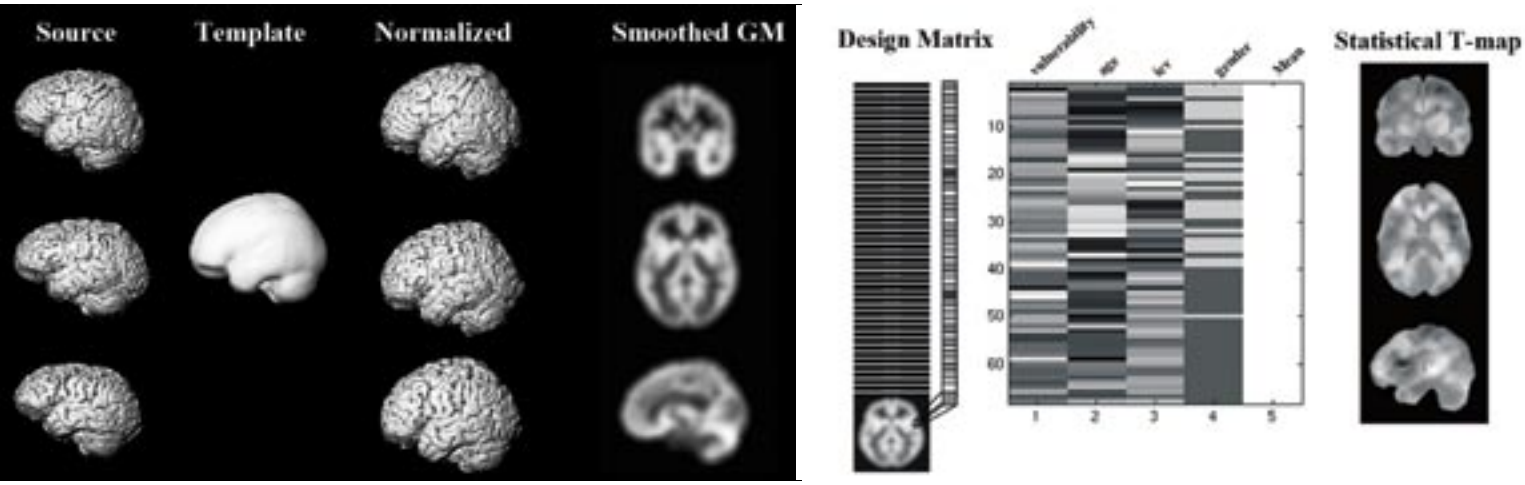
PhD student Jon Sigurd Wegener, together with Kristoffer Madsen and Mark Schram Christensen from the DRCMR, and Julian Jamison from UC Berkeley, investigated how the healthy human brain evaluates immediate rewards, versus larger future rewards. These evaluations, termed inter-temporal choices, exhibit large individual differences and have important implications for outcomes in health such as substance-abuse. The main objective was to identify a graded relationship between the processing of time delay and brain activation as measured with fMRI. Subjects were asked to perform a series of 200 binary choices between a fixed immediate reward and larger rewards in either one week, one month, or one year. The results show that, independently of reward, posterior parts of bilateral parietal and temporal cortices become increasingly activated the closer the two options are in time, indicating a network for the processing of time in intertemporal choices. This work was presented at the 12th annual meeting of the Organisation for Human Brain Mapping.

Cimbi

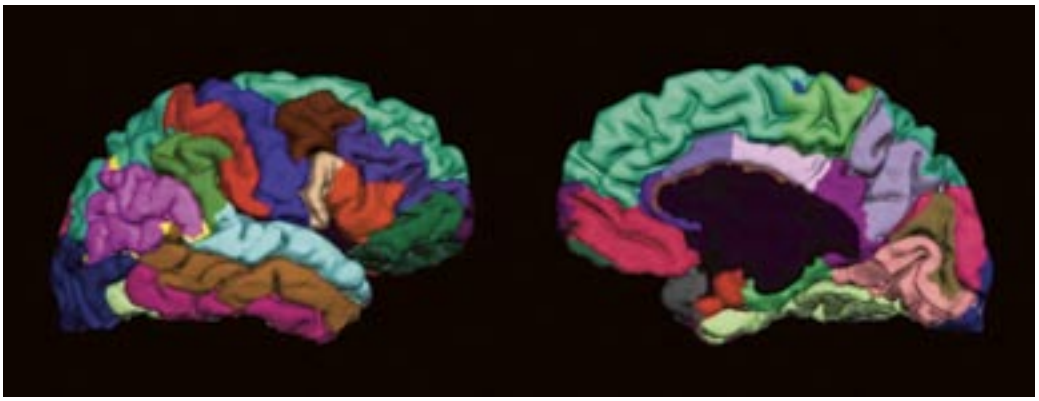
In January 2006, the Center for Integrated Molecular Brain Imaging (Cimbi) was founded as a new research centre funded by the Lundbeck Foundation with the DRCMR being a main participant. The research in Cimbi focuses on the neural bases of personality dimensions that predispose individuals to affective and substance use disorders, with special emphasis on the serotonergic neurotransmitter system. Both PET and MRI are employed in studies of human subjects, and these are complemented with relevant studies using animal models. Advanced informatics techniques, new tracer compounds, and novel serotonergic challenge paradigms are also being developed within the Centre.

The role of the DRCMR in Cimbi is twofold: Terry Jernigan leads a project focusing on the relation between personality, biochemistry and brain structure while Olaf B. Paulson heads a group focusing on functional brain imaging under serotonergic challenges.

One of the important issues addressed in Cimbi is the influence on human behaviour of genes that



Voxel based morphometry (VBM) allows for a comprehensive assessment of anatomical differences throughout the brain by means of a voxel by voxel statistical analysis of regional structural differences and structure/function relationships. As such VBM allows for testing and as well as generating of hypotheses. Shortly, individual brain images (Source) are spatially normalized into a standard space (Template). After tissue classification and smoothing, different models (Design Matrix) can be used to estimate how much of the variance in gray matter (GM) volume can be explained by different variables of interest such as for example the vulnerability score on the NEO-P-IR.



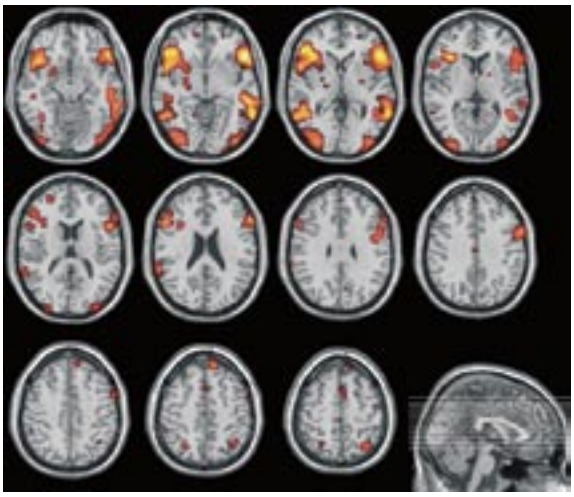
The Freesurfer software generates high resolution cortical surface maps that can be used in calculating cortical thickness. Moreover, cortical surface maps can be segmented automatically in specific anatomical brain regions as shown in the figure. Left: lateral view of the brain, right: medial view of the brain.

affect the brain serotonin system. Previous brain imaging research suggests that one of the ways that these genes may act is through their influence on the structure of the brain, perhaps during the process of brain development. That is, genetic polymorphisms may influence the size of certain cell populations in the brain, or the numbers of connections that are established, or preserved, between specific brain structures. This may lead to differences in brain morphology. Structural neuroimaging methods continue to improve in sensitivity and anatomical resolution, and it is now possible to examine brain morphology, and even the physical connections between brain areas in remarkable detail. The major aim of this project is to apply these new structural neuroimaging approaches to volunteer subjects, so that differences in anatomy can be linked to genetic variability on the one hand, and to personality traits, cognitive functions, and other functional parameters on the other. Thus it may be possible to determine to what extent genetic influences on serotonin function and behaviour may be mediated by their effects on the brain's anatomical structure.

The aim of the functional studies is to investigate the relationship between the cerebral activation responses and the serotonergic system using fMRI. Attention will be directed towards functions where the serotonergic system is known to be involved, such as in emotion and decision. The activation responses will be correlated to the presence of receptor density and to genetic polymorphism. Further it is planned to study the activation responses under challenge of the serotonergic system by drug intervention and tryptophan depletion.

In launching these studies in Cimbi, we have so far focused on recruiting and training the scientific personnel needed to accomplish the studies, on fine-tuning the MRI measurement protocol to ensure that we collect the most valuable MRI data, designing the paradigms to be used in the functional studies, performing pilot studies and on identifying the best approaches for representing and modelling these complex data once they have been collected.

We have made excellent progress in constructing our team: William Baaré has accepted the position as MRI imaging scientist on the morphometry project while Julian Macoveanu has joined the group focusing on the functional studies. Fabien Schneider joined the team for a few months, but unfortunately had to leave for France. Three PhD students, Kathrine Skak Madsen, Bettina Hornbøll and Jon Sigurd Wegener have been recruited to work on these projects along with Jens Bundgaard who will provide critical support to the project as an image processing specialist.



Results from one subject doing an emotion face processing task. The subjects are shown faces of women and men in blocks of four that could be neutral, fearful and angry. They have to press different buttons if the photo is of a woman or a man. Images show activation during fearful and angry faces compared with neutral faces.

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 cause the MR signal to decay very rapidly and, in addition, the proton density of lung tissue is low compared to other tissues. During recent years, a new MR method based on imaging an inhaled hyperpolarized gas has emerged.

Lise Vejby Søgaard and Trine Stavngaard are locally responsible for MR lung imaging at the DRCMR. The technique is unique in Denmark and relies on the inhalation of magnetised helium, which is a harmless gas. The DRCMR was first involved in hyperpolarized ^{3}He imaging as one of three clinical centres involved in the EU PHIL project. 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 at the DRCMR is produced at the Physics Department at Johannes Gutenberg-University in Mainz, Germany and shipped to Copenhagen as air freight. The MR protocol includes morphological imaging providing information about the ventilation distribution and diffusion imaging that has been shown to correlate with the alveolar sizes in the lung. It has been suggested that the lung ADC values can be used as a sensitive marker for the progression of emphysema.

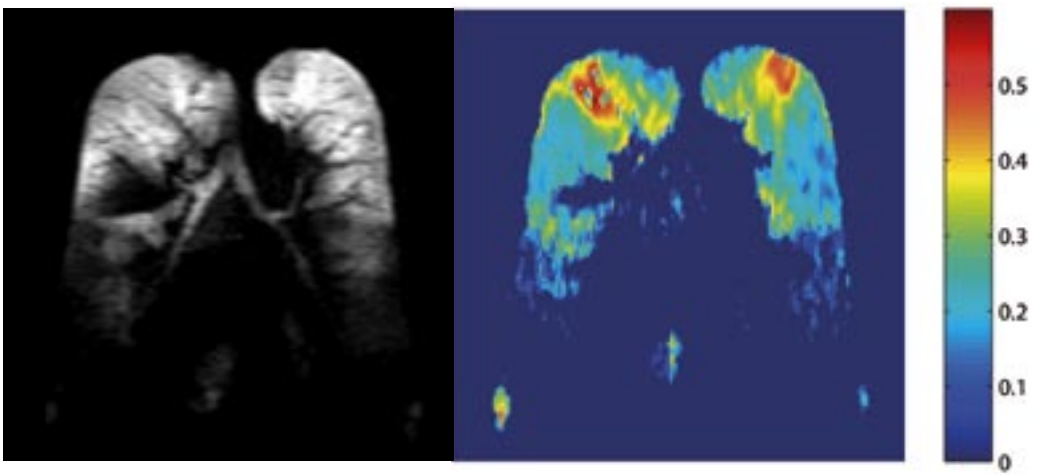
This hypothesis has been investigated in a recent longitudinal study in patients with known alpha-1-antitrypsin deficiency. The patients have been imaged with hyperpolarized ^{3}He three times at one-year intervals. The final follow-up scan after two years was conducted in 2006. Preliminary data analysis reveals that the mean ADC values do indeed increase with time in these patients with progressive emphysema.

The partners from the PHIL project and a few additional organisations have formed a research network PHELINET that has obtained funding from the EU 6th Framework Programme as a Marie Curie Research Training Network. The PHELINET project will commence in 2007 and will support one PhD student to be employed at the DRCMR.

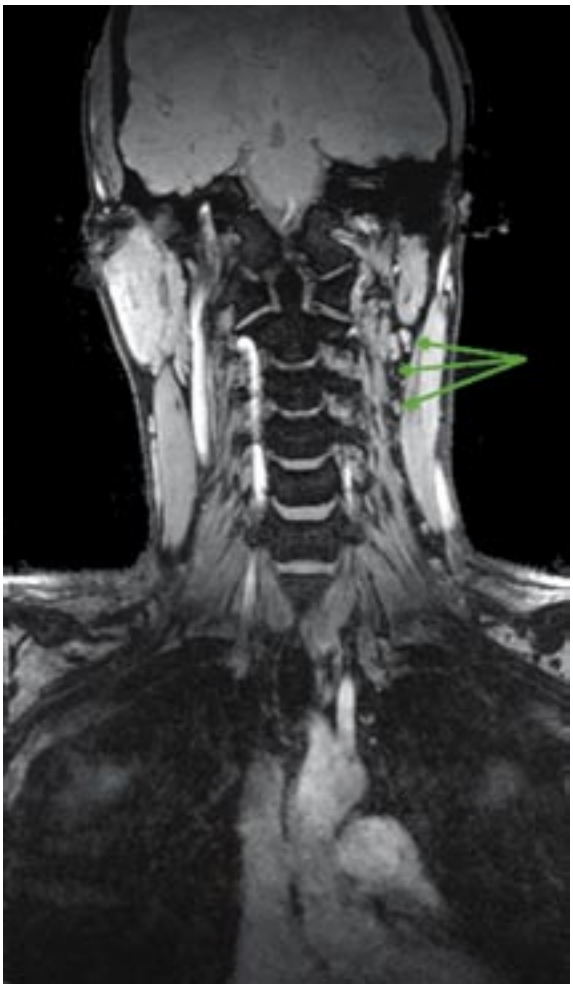
Clinical Trials

In 2006 the department designed and conducted an MRI-study as part of a phase one trial of a new drug for lung diseases. An important part of the development of new drugs is to test them for side effects in healthy volunteers under extremely controlled circumstances. The company PhaseOne Trials that is located at, and partly owned by Hvidovre Hospital, specialises in this kind of trials and organised the study for the pharmaceutical company Schering-Plough.

The study involved 16 volunteers who were scanned before and twice after administration of the new drug. The overall aim of the rather extensive MR-examination was formulated by the company, but the specific design was left to the local physicists, Peter Magnusson and Lars G. Hanson, who also conducted the study. The protocol was quite demanding in terms of sequence adaptation and scanning as it should be sensitive to changes in the lymph system, the liver, the spleen and the bone marrow in the hip region. Also the subsequent radiological evaluation performed by Chief MD Per Åkeson was correspondingly demand-



Left: coronal morphology image showing the ventilation distribution after inhalation of approximately 200 ml hyperpolarized ^{3}He. The ventilation distribution shows the typical pattern of lower lung destruction in a patient with alpha-1-antitrypsin deficiency. Right: corresponding colorcoded ^{3}He ADC map (units cm^2/s). Clearly elevated ADC values are apparent in this patient as a characteristic sign of emphysema. For comparison, healthy lungs typically have ADC values in the range 0.16-0.22 cm^2/s.



Coronal fat saturated 3D MEDIC sequence (voxel size 0.64x 0.64x1.00 mm^3) clearly delineating the anatomy of the neck. Normal lymph nodes can be seen on the left side (green arrows).

ing. Besides providing the images needed for the trial, the study also resulted in the development of new sequences targeted at the mentioned regions, which can now be used for the diagnostic purposes in clinical patients. As an example and for the assessment of lymph node size changes, high resolution images of the neck region were acquired with a high SNR, using a 3D MEDIC sequence.

Inflammatory joint diseases

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.

In addition to research undertaken in the context of PhD projects dealing with RA, spondyloarthritis an psoriatic arthritis (PsA), the rheumatology group participates in an international collaboration concerning MRI definitions, scoring methods and validation in RA and PsA. 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 was 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. This atlas was published as a supplement to the Annals of Rheumatic Diseases in 2005. The international group has subsequently focused on validation of dedicated extremity MR units and development of a scoring system for psoriatic arthritis. The Rheumatology group is also involved in international collaboration concerning MRI of ankylosing spondylitis and other spondyloarthritis.

Furthermore, the group participates in four Danish multi-centre studies of RA and spondyloarthritides. In one of these, a longitudinal multi-centre study of 160 early RA patients (“CIMESTRA”), the aim is to investigate the value of MRI as outcome measure and prognostic marker in early RA, compared with routine clinical, biochemical and radiographic parameters.

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 in, for example, monozygotic and dizygotic twins with a very high risk of developing an affective disorder). The same investigative approach is directed at different stages of schizophrenia, for example, in drug-naïve first episode patients, in patients with disease onset in childhood and adolescence or adulthood, and in chronic patients.

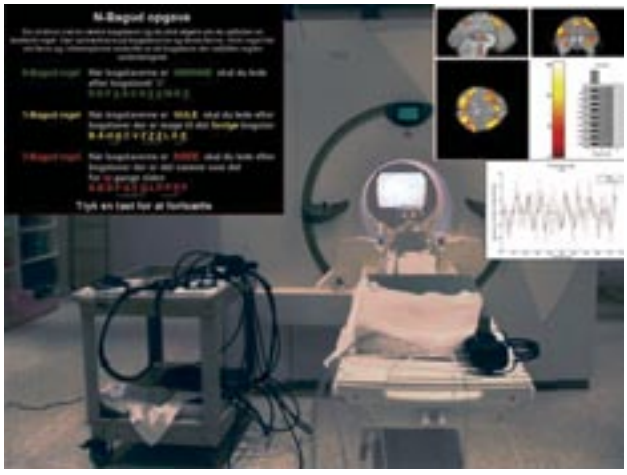
Major depressive and bipolar disorder (MDD; BPD) are common and severe psychiatric illnesses affecting respectively 4% to 8% and 1.3% to 1.6% of the general population. The risk of recurrence is high and 15% to 20% of patients commit suicide. Although the aetiology of affective disorder is unknown, genetic 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.

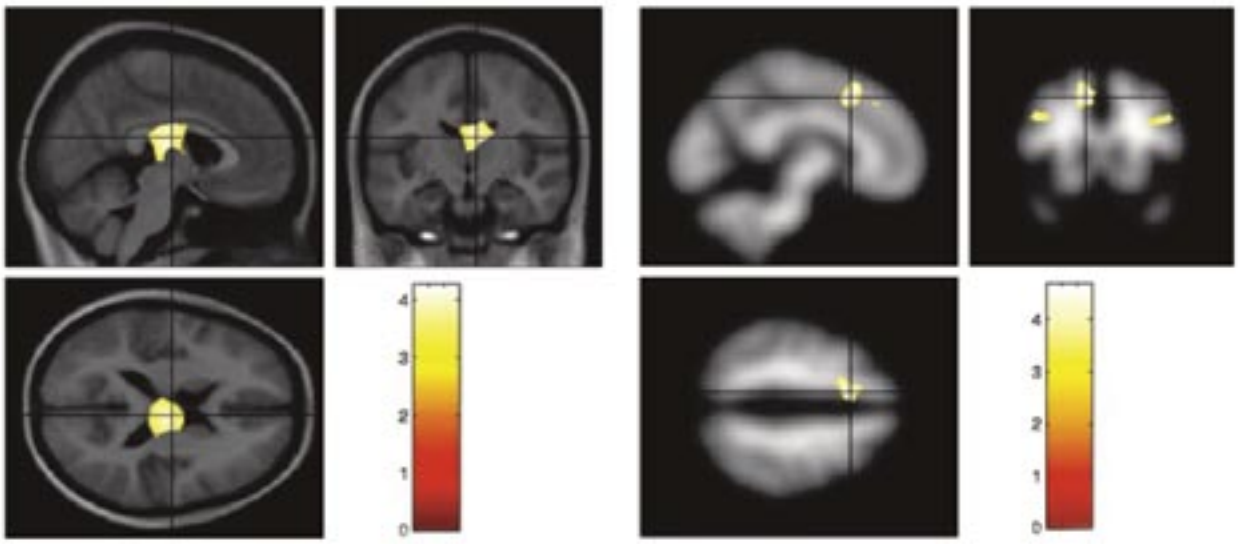
Predominantly, our MR investigations address the following questions: (a) which brain abnormalities are present before onset of an affective disorder? (b) Which abnormalities are related to an increased (genetic) risk to develop affective disorder? (c) Which abnormalities are present at illness onset? (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? These questions are addressed to both psychiatric syndromes.

The following MR techniques are used in the different projects: structural MRI including T_1, proton density and T_2-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 Rigshospitalet (Affective disorders: Principal investigator: Prof. Dr. Lars Kessing), and Bispebjerg and Glostrup Hospitals (Schizophrenia: Principal investigators: Professors Ralf Hemmingsen, Birte Glenthoj and Tove Aarkrog). There is currently one project investigating affective disorders (A1) and five projects investigating schizophrenia (S1-S5).



Typical setup for an fMRI experiment. An N-Back working memory task is shown as an example. The task is projected on a screen in the magnet, visible to the subject through a mirror attached to the head coil. In the upper right corner, a typical activation map of a healthy subject is shown, depicting brain regions that are significantly activated with increasing working memory load.



Left: Schizophrenia patients (n=15) compared to healthy controls (n=29) had larger CSF volume in right body of the lateral ventricle. Right: Patients (n=29) compared to controls (n=29) had smaller white matter volume in left superior frontal gyrus.

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 that is unique to Denmark. Inclusion of subjects finalized in the end of 2005. MR scans are available for 173 subjects. Data analysis is currently ongoing.

Clinical researchers responsible for the different schizophrenia projects are the psychiatrists: Birte Glenthøj (S1: "Structural and functional brain abnormalities in drug naïve adult onset schizophrenia") and Bjørn Ebdrup (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"); and Trine Bjørg Hammer (S5: 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. In 2003, data acquisition commenced for projects S2 and S4 and remains ongoing. Project S5 started towards the end of 2004 and is ongoing.

In project S1, 16 antipsychotic drug-naïve and 3 minimally medicated first-episode schizophrenic patients and 19 matched controls participated. Patients were randomly assigned to treatment with either low doses of the typical antipsychotic drug, zuclopenthixol, or the atypical compound, risperidone. High resolution MRI-scans were obtained in patients before and after 12 weeks of exposure to medication and in controls at baseline. Caudate nucleus, nucleus accumbens, and putamen volumes were measured. Compared to controls, absolute volumes of interest (VOIs) were smaller in patients at baseline and increased after treatment. However, when controlling for age, gender and whole brain or intracranial volume, the only significant difference between patients and controls was a Hemisphere x Group interaction for the caudate nucleus, with controls having larger left than right caudate nuclei and patients having marginally larger right than left caudates. Within patients, the two medication groups did not differ significantly with respect to volume changes over time in any of the VOIs. Nevertheless, when examining medication groups separately, a significant volume increase in the putamen was evidenced in the risperidone group. In conclusion, the altered asymmetry in caudate volume in patients suggests intrinsic basal ganglia pathology in schizophrenia, most likely of neurodevelopmental origin. No significant differences between the effects of the two medications on

basal ganglia volumes could be demonstrated after 3 months of low dose treatment. This study is currently in press in Psychiatry Research: Neuroimaging.

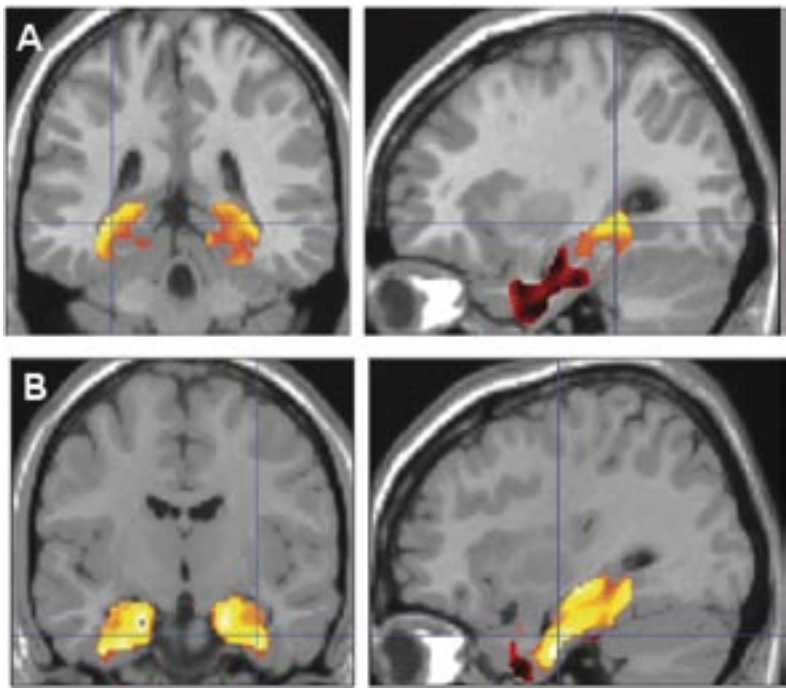
In project S2, it was shown that abnormalities in ventricular and frontal white matter volumes are already present at the early onset of non-affective and non-organic psychosis in minimally medicated children and adolescents. In addition, our finding of smaller intracranial volume in the subgroup of 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. This study was published in 2006 in the Journal of Neural Transmission

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 multi-site 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. Elderly volunteers were scanned at entry into the study and a 3-year follow-up scan has now been completed. These measures are correlated with extensive neurobehavioural assessments. Egill Rostrup is the senior DRCMR investigator most closely involved with the LADIS studies.

As part of the LADIS project, PhD-student Charlotte Ryberg is focusing on studies of the corpus callosum, which is the major cerebral white matter structure carrying most interhemispheric connections. Data analysis is performed in collaboration with the group of Prof. Rasmus Larsen at the Technical University of Denmark, especially regarding an automated method to recognise and quantify the volume of this structure. The full dataset of 569 subjects has been analysed, and correlations with several measures of cognitive and motor performance were demonstrated. Notably, these effects seem to be additive to the effect of age related white matter changes per se. In 2006 two papers were published describing the correlation with clinical and neuropsychological performance.

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. PhD-student Tim Dyrby is developing and validating tissue segmentation methods that rely on artificial neural network algorithms. Thanks to the efforts of Dutch colleagues, a full set of manually delineations of the white matter abnormalities is available, and it turns out that the automated methods perform very well compared to these expert-based results. Sources of disagreement stem just as much from anatomical bias in the human observer, as from inaccuracies of



Age-effects on two cognitive paradigms as measured with fMRI. (A) shows areas with increased (orange and yellow) brain activity in young relative to old healthy subjects during an object naming task. This difference shows that young subjects tend to recruit more posterior regions of the hippocampus and parahippocampal areas than older subjects on this task. (B) shows that a large proportion of the medial temporal lobe is more activated (orange and yellow) during an object encoding task relative to older subjects. These figures were part of a presentation of age effects on cognition and brain activation at the 2006 Society for Neuroscience conference.

the automated method. When strict control of between centre differences in MRI quality is controlled for the method performs very well.

Based on the automated shape detection, it is possible to apply mathematical models for parameterization 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. A sophisticated method for shape analysis was developed by Karl Sjöstrand, as described in the Basic Research section.

Thomas Ramsøy heads a project on the healthy aging of the brain. Using both structural and functional MRI methods, complemented by neuropsychological tests, the main focus is on the medial temporal lobe (MTL) structures including the amygdala, hippocampus and rhinal cortices. This year, the team presented their findings at the Annual Meeting of the Organization for Human Brain Mapping, demonstrating that MTL structures make different contributions to object vs. position encoding, as well as gross hemispheric differences on the same tasks. The team also reported at the International Society for Magnetic Resonance in Medicine conference that standard spatial normalization of MTL regions led to a highly variable fitting to a template brain, a problem relevant to group analysis and comparison of both structural and functional data in this region. Finally, at the Annual Meeting for the Society for Neuroscience, the team reported the effects of aging on three functional MRI paradigms; memory, visual categorization and processing of aversive faces. The results showed pronounced changes in MTL structures between age groups, lending support to prominent theories of age-related changes and compensative functions in the brain. The methods developed in the current research project, including structural and functional protocols, will be applied on the study of the effects of ecstasy (MDMA) abuse, and on the effect of degenerative disease such as Alzheimers Disease.

Parkinson's disease (PD) and the related disorder, multiple system atrophy (MSA) may be difficult to diagnose clinically. Katja Krabbe of the DRCMR, together with collaborators from Bispebjerg Hospital, has completed a study of patients with these diseases employing segmentation of conventional MR images and MR diffusion measurements. Visual evaluation of diffusion colour maps turned out to be more sensitive in the differential diagnosis between the two diseases than conventional imaging. Substantia nigra volume was decreased in both patient groups compared to normal controls but the segmentation studies did not prove useful in the differential diagnosis between the diseases. These results have been submitted for publication.

The investigators at the Centre continue to be active contributors to the international literature on normal aging and disorders of aging. This year, Terry Jernigan, with collaborators from other universities participating in the multi-site Brain Informatics Research Network (BIRN), coauthored an article describing the reliability and validity of skull-stripping methods for automated analyses of brain MRI data. She also coauthored a chapter describing the use of functional MRI in the evaluation of neuropsychiatric disorders, appearing in the 3rd Edition of Clinical Magnetic Resonance Imaging, Eds: Edelman, Hesselink, Zlatkin, & Crues. Finally, with Drs. Gamst and Wolfson, she presented work describing the advantages of quasi-likelihood statistical methods for modelling volumetric imaging data, at the annual meeting of the Organization for Human Brain Mapping.

Multiple Sclerosis

The DRCMR has a long tradition of combining MR and multiple sclerosis (MS) research, and 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 neuropsychology. In general, the research projects aim towards improving the diagnostic value of magnetic resonance investigations. 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. The projects in this area are carried out by PhD-student Kirsten Korsholm, working with optic neuritis (a common precursor of MS) and Henrik Lund, working with MS patients. Additionally, in 2006 the MS group could welcome Dr. Xingchen Wu, who has extensive experience within the areas of both clinical and experimental MS research.

Optic neuritis (ON) typically causes symptomatic visual impairment and retrobulbar pain developing over hours or days due to demyelineation and inflammation of the optic nerve. The disease mainly affects young people and is associated with decreased visual acuity, abnormal colour vision, decreased contrast

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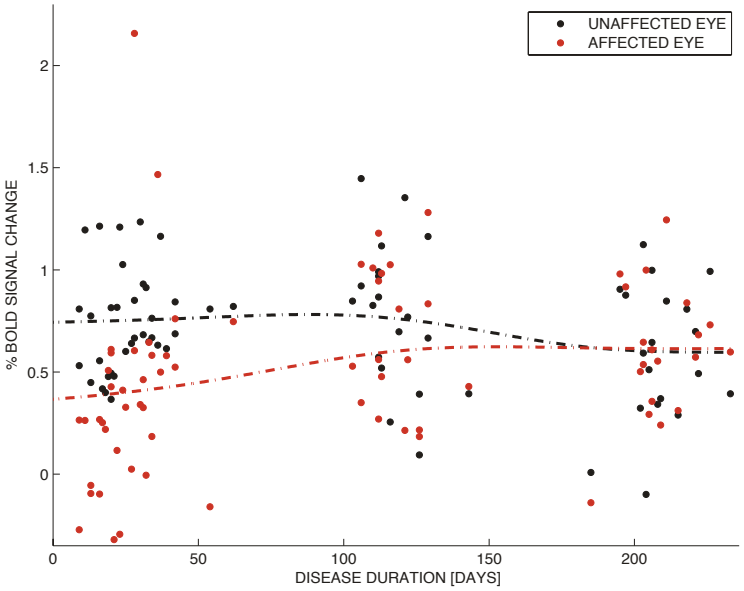
sensitivity, visual field defects, and delayed or broadened visual evoked potentials (VEP). Within weeks or months after onset of symptoms, a spontaneous recovery of vision occurs and patients usually regain good vision. However, ON is associated with a high risk of developing multiple sclerosis (MS) and is the presenting symptom in approximately 20% of patients with MS.

In patients with MS adaptive cortical changes to visual, motor and cognitive tasks have previously been demonstrated with fMRI, and these cortical changes have been interpreted as compensatory mechanisms helping in maintaining normal function in spite of structural neuronal damage.

In patients with ON evidence of cortical adaptations taking place in early and higher visual areas (especially in the lateral occipital complexes) and also outside the occipital cortex has been reported. However, no studies have serially investigated activation in subcortical structures, in particular in the lateral geniculate nucleus (LGN), a thalamic relay nucleus in the visual pathway, during recovery from ON.

With current functional MRI techniques and visual stimulation it is possible to map the activation in LGN. PhD-student Kirsten Korsholm heads an investigation of this in a group of patients during recovery from ON in addition to analyses of activation in both early and higher visual cortices. This study has now been finished and the results have been submitted to an international journal. One of the main findings of this study was a normalisation of LGN activation upon stimulation of the affected eye during recovery

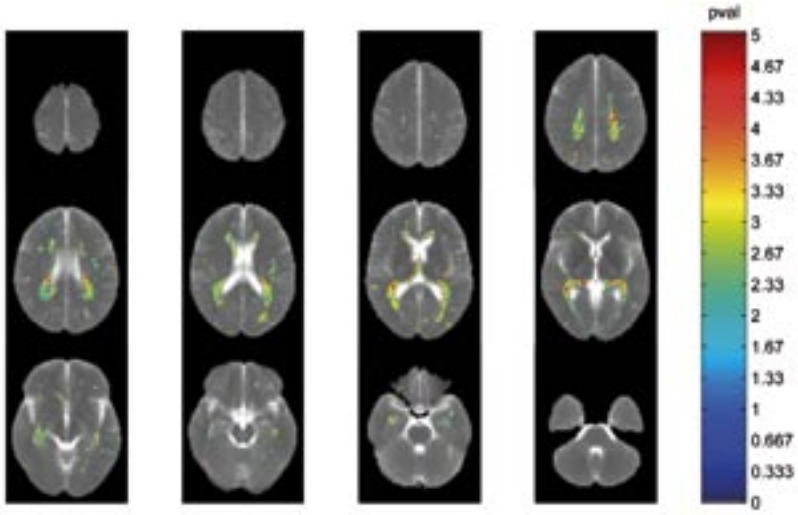
Another study in the field of ON deals with a voxel-based analysis of whole brain activation during recovery from ON to assess whether adaptive changes take place outside the visual cortex. In addition, the group is working on methods to analyse changes in retinotopic organisation during resolution of scotomas in patients with ON. Both projects are carried out in collaboration with the Department of Neurology at Glostrup Hospital.



Mean LGN activation during stimulation of the affected and unaffected eye in patients with optic neuritis. During recovery there is a significant increase in LGN activation from stimulation of the affected eye (red). The activation of LGN from stimulation of the unaffected eye (black) decreases over time in a stepwise fashion with a significant decrease between three and six months. It is seen that the activation of LGN for the affected and unaffected eye levels of at a similar positive level as time increases pointing to normalisation of the LGN activation elicited by the affected eye.

The pathological mechanisms of MS are investigated quantitatively by applying different MR techniques to two groups of MS patients. From these studies Henrik Lund and his collaborators hope to learn important details on the breakdown of myelin sheaths as well as of the blood-brain-barrier. The participating patients in one of the groups were newly diagnosed at entry and have been scanned three times – just before start of treatment, after 3 months and again after 6 months. This longitudinal study gives us an excellent opportunity to monitor the effects of different treatments. The patients in the other group have had MS for at least half a year and are volunteering in a cross-sectional study. For both groups the outcomes are correlated to a vast range of immunological and neurological measures collected by our collaborators at Copenhagen University Hospital, Rigshospitalet.

The different MR-techniques all aim at the exploration of structural changes caused by the pathology of MS. For example, applying so-called q-space analysis to our diffusion data, it is possible to acquire structural information on the various biological barriers and compartments. The problem with traditional diffusion tensor imaging (DTI) is that the calculated diffusion coefficients are not expected to depend on the diffusion weighting or diffusion time. This is correct only in perfectly homogenous media and not in vivo where the diffusion of water is hindered by tissue structures. Normal DTI analysis gives one (apparent) diffusion coefficient (ADC) based on the assumption that the



Clusters of minimum 10 voxels illustrating the correlation between the T_2 relaxation time and a composite measure of cognitive dysfunction in a group of 50 patients. Focal lesions as delineated manually on T_2-weighted images were excluded from the analysis. Our results show that subtle changes in the normal appearing white matter are partly responsible for the highly disabling cognitive deterioration seen in MS.

sample behaves as a perfect Gaussian distribution. However, an increased ADC does not tell us whether the viscosity is lowered or whether the sample has fewer barriers. The q-space analysis, which is based on several diffusion weightings provides a size distribution of the tissue compartments and thus potentially gives clinically relevant information on the breakdown of the structures. This technique will be used to analyse the water diffusion orthogonal to the fibres since an alteration in this diffusion is hypothesized to reflect a direct immunological breakdown of the myelin and/or axons. Additionally, anterograde (Wallerian) and terminal axonal degeneration as a response to focal lesions possibly gives rise to more diffuse changes. Hence, the approach is expected to provide information on diffuse as well as focal pathologies and we aim at showing that q-space imaging can provide clinically relevant information in MS at scanning times suitable for the clinic. The data analyses and interpretation will be performed in collaboration with Finn Sellebjerg, Rigshospitalet and Lars G. Hanson, DRCMR.

In addition, methods are currently being implemented to gain insight into the breakdown of the blood-brain-barrier. After contrast injection, focal enhancing lesions appear hyperintense on T_1-weighted scans because contrast agent accumulating in the tissue that surrounds a broken blood-brain-barrier increases the MR signal. It is hypothesized that a subtle breakdown of the barrier in regions that do not appear as focal enhancing lesions still gives 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.

For a separate group of MS patients we have been able to show that the cognitive performances of the patients are correlated to subtle pathological changes in the CNS. As focal lesions delineated using T_2-weighted images are often used for the diagnosis and monitoring of MS we decided to investigate the voxelwise correlation between quantitative T_2-values and a large battery of cognitive measures. Rather intriguingly, excluding focal T_2-lesions from the analysis we show that subtle changes in the so-called normal appearing white matter are partly responsible for the highly disabling deterioration of the cognitive function. This project has been carried out in close collaboration with Per Soelberg Sørensen and Agnete Jønsson, both at Rigshospitalet.

Recent studies have suggested that clinically important information about the status of the brain can be obtained by functional MRI (fMRI), in addition to that obtained from structural scans of the brain.
Studies of cerebral activation in MS patients have successfully been carried out using the BOLD fMRI technique, which allows to dynamically follow metabolic and haemodynamic consequences of brain activity. Furthermore, it is now believed that processing of a functional task by the brain can only be performed through interaction of segregated regions within a complex network. Functional connectivity MRI (fcMRI) is a new method of assessing neuronal connectivity in the human brain by mapping brain regions with synchronous, regional fluctuations in cerebral blood oxygenation. These techniques have recently been refined by our Centre by increasing the signal-to-noise ratio and improving data analysis. We plan to investigate the recovery mechanism of multiple sclerosis patients by evaluating the cerebral activation and neural connectivity.

Traumatic Brain Injury

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. In survivors of severe TBI the final outcome is both highly variable, ranging from

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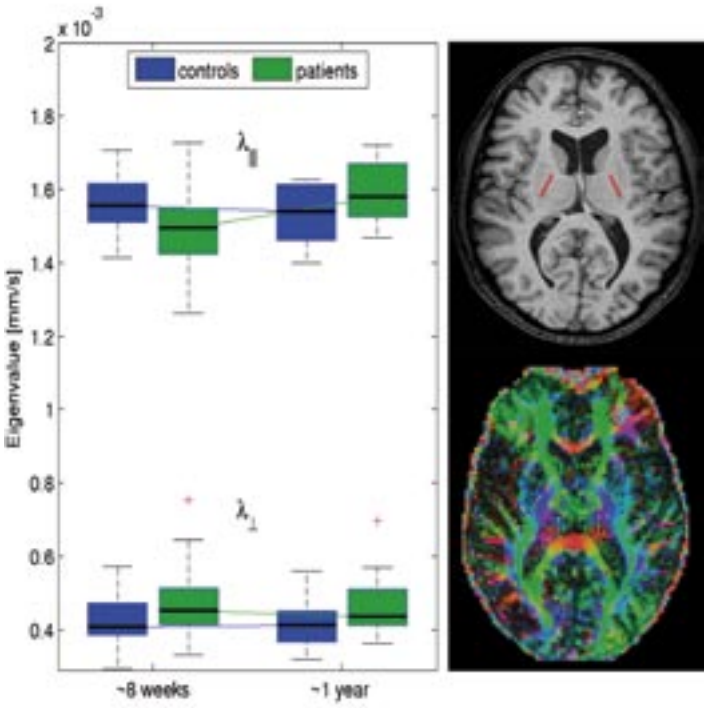
almost full recovery to persistent vegetative state, and extremely difficult to predict, especially in cases of prolonged unconsciousness. Several different types of lesions can occur in TBI, but diffuse primary and secondary lesion types are thought to be major prognostic determinants. However, these diffuse lesions are highly underestimated by conventional imaging. Advanced quantitative MR techniques, such as diffusion tensor imaging (DTI) and spectroscopic imaging, have the potential to improve detection of these important lesions and provide useful clinical tools for outcome prediction.

A PhD project on TBI is headed by Annette Sidaros in collaboration between the DRCMR and the Department of Neurorehabilitation, Brain Injury Unit, at Hvidovre Hospital. In this prospective longitudinal study, adult patients with severe TBI are scanned at mean 8 weeks and 1 year post-injury. Healthy controls are scanned for comparison. In addition to conventional MRI sequences the project applies DTI and spectroscopic imaging. Clinical outcome of patients is evaluated at 1 year post-trauma.



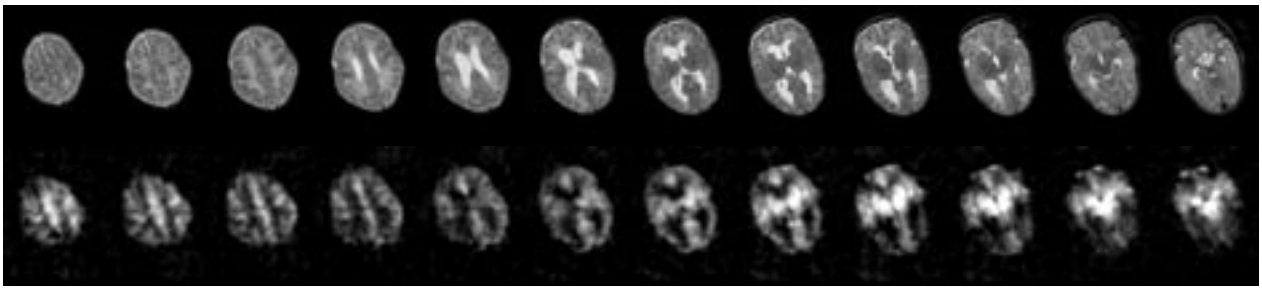
Diffusion tensor imaging (DTI) is sensitive to microstructural changes during recovery from severe traumatic brain injury. An example from the posterior limb of the internal capsule (PLIC) is shown. Left: Plot of diffusivity parallel ($\lambda_{||}$) and perpendicular ($\lambda_{\perp}$) to axonal fibre direction. In patients (n=22) $\lambda_{||}$ selectively increased during late functional recovery ($p<0.00001$). Right: The results were derived from the region delineated on conventional T_1-weighted images (top). A DTI colour map illustrates the predominant direction of water diffusion. The PLIC appears blue, representing diffusion in the superior-inferior direction (bottom).

Data collection was completed in 2006. Thirty patients have been included and scanned in the late subacute phase; of these 23 completed the 1-year follow-up scan. DTI data has been evaluated, and findings suggest severe and widespread diffusion abnormalities at the late subacute stage. Interestingly, at 1-year follow-up diffusion had partly or completely normalised in some brain regions, particularly so in patients with good clinical outcome. These findings provide in vivo indications that axonal repair may be among the mechanisms underlying clinical recovery following severe TBI. The results of this project might provide important diagnostic, prognostic and pathophysiological information useful in the clinical management of brain-injured patients.

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 1.5 tesla scanner but was moved to the 3 tesla scanner when it became available. The study aimed 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



Anatomical T_2-weighted MR images of a 54-day old preterm infant scanned at term (top row) and corresponding quantitative perfusion weighted images measured non-invasively using arterial spin labeling (bottom row).

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.
The study was temporarily stopped after the first 100 infants studied, born with a GA ≥ 28 weeks. The analysis of these data has revealed that inflammation (chorioamnionitis or funicitis) can only be demonstrated in a minor proportion (10-12%) of the placenta of infants born ≥ 28 weeks of gestation. The plan is to continue the study with infants born at Rigshospitalet with a GA below 28 weeks, where inflammation is expected to be much higher. However, the MR spectroscopy (MRS) data from these 100 infants (analysed by Robin de Njis), reveals other important findings in the metabolic pattern of the brain of premature infants at term-equivalent-age as compared with healthy term-born controls. Choline/Creatine ratios were significantly different between the groups (preterm at term-equivalent age vs. term controls). The decreased Choline-levels likely indicate delayed or poorer quality of myelination in preterm infants (not seen on MRI), at least in some areas of the brain, even in preterm infants at term without brain lesions. The hypothesis of concomitant inflammation and hypoxia-ischemia was not supported by the data of these first 100 infants born at a GA ≥ 28 weeks.

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

In the next 1-2 years we would like to include infants born at a GA less than 28 weeks at Righospitalet and they will undergo MR examination at term-equivalent age. Infants with and without signs of inflammation of the umbilical cord will be selected and matched for 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 measure perfusion non-invasively. 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. Maria J. Miranda and Karam Sidaros have therefore headed a study to evaluate the feasibility of using ASL to measure neonatal cerebral perfusion. They have studied a group of healthy preterm born infants and a group of healthy term born controls for comparison. Results of this study show a higher perfusion in premature infants at term equivalent age in both cortical grey matter and basal ganglia, when compared with term-born controls indicating that perfusion may be influenced by both developmental and postnatal ages. 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 in future studies. The results on healthy infants have indicated that, with a minor modification of the ASL technique, the method is indeed suited for measuring neonatal perfusion.

Cerebral white matter is especially sensitive to damage as a consequence of prematurity, causing significant morbidity despite improved neonatal care. In addition, survivors of prematurity can have more subtle developmental problems including learning

and behavioural difficulties, even though their brains look normal on conventional imaging. Diffusion Tensor Imaging (DTI) is a powerful tool that may be used to study white matter tract changes during development in very young infants. The technique has the potential to depict subtle changes in brain development not visible in conventional imaging. Maria Miranda, with the help of collaborators from Sweden and Spain, has systematically acquired diffusion tensor images in a cohort of premature infants, born after 28-33 weeks of gestation, and in infants born at term after an uncomplicated pregnancy. When comparing the groups using an approach where white matter structures of interest are traced manually, no differences between the groups were found. However, comparing the whole brain statistically with voxel based morphometry (VBM), an advanced development of white matter regions in occipital white matter was found. This is in contrast to current belief, where a delayed white matter development is expected due to the detrimental effects of prematurity. These data have been submitted for publication.
The DTI data analysis was done in cooperation between paediatricians, Maria Miranda & Peter Born and Egill Rostrup, DRCMR, with the collaboration of Zoltan Nagy, Karolinska Institute, Sweden and Lars G. Hanson, DRCMR, on the ROI analysis. For the VBM analysis, we collaborated with psychologist Monica Gimenez from Barcelona University and Terry Jernigan, DRCMR and University of California.

Clinical perfusion imaging

Investigation of the blood supply to different regions of the brain is central to the diagnosis of several neurological diseases. However, it is a practical obstacle that such perfusion measurements typically require very specialised scanning procedures, such as PET or especially SPECT, as well as injection of radioactive tracers. Therefore, perfusion measurements are not widely used in spite of the potentially useful information they provide. As an example, perfusion changes seen in demented patients that provide a means of distinguishing between different forms of dementia such as Alzheimer's disease, vascular dementia and fronto-parietal dementia. The distinction is important because these diseases have different prognoses and different therapeutic options.

In a collaborative project with the memory clinic at Rigshospitalet, Karam Sidaros and Egill Rostrup are involved in non-invasively acquiring perfusion weighted MR images using a method called Arterial Spin Labelling (ASL). In this study, patients with Mild Cognitive Impairment (MCI) and healthy age-matched controls are scanned using both MRI and SPECT. The aim is to compare the perfusion measurements using the two techniques where ASL has the advantage of being non-invasive and non-ionizing. The scans are compared visually and quantitatively using region analyses. Data acquisition has now been completed, and analysis is underway. Preliminary results have sprung off a separate study to reduce pulsation-induced artefacts in the ASL measurements as described in the Basic Research section.

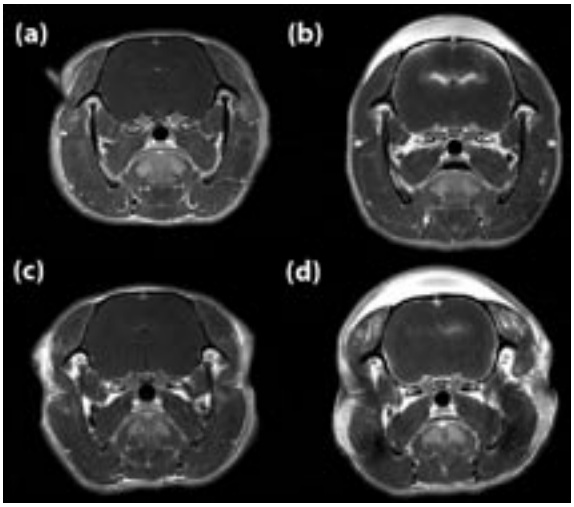
Preclinical Research

The preclinical research group utilizes a 4.7T Varian scanner designed for small animal imaging and spectroscopy research. Upgraded in 2004, the system is used, primarily, for the longitudinal investigations of small animal models of disease. Brain disease and cancer are two areas currently under investigation with basic research into mechanistic aspects of disease progression and treatment being performed. The majority of the pre-clinical work is undertaken in collaboration with other research groups within the Copenhagen area, providing the opportunity for exciting multi-disciplinary projects to be performed with contributions from researchers with different scientific expertise and experience.

In continued close cooperation with the Statens Serum Institut, work investigating Streptococcus pneumoniae (pneumococcal) meningitis in a rat model has continued. These studies are motivated by the fact that bacterial meningitis remains a life threatening disease with significant mortality and morbidity. Previous work from the preclinical group has demonstrated the power of MR imaging methods to follow the evolution of the disease and the group has expanded these studies investigating two closely related projects:

The first project has used MR to study perfusion dependent cerebral oedema formation during the course of the disease. In healthy humans, a constant blood supply to the brain despite changes in cerebral perfusion pressure (CPP) is secured by cerebral blood flow (CBF) autoregulation. Bacterial constituents as well as specific mediators of the inflammatory response are known to be potent vasodilators and cause oedema, increasing CBF, cerebral blood volume, and intracranial pressure (ICP); moreover, this vasodilatation may impair normal cerebrovascular reactivity, affecting the regulation of cerebral blood flow. Previous studies using the pneumococcal model have shown that CBF autoregulation, i.e., the ability to preserve CBF in the face of changes in CPP, is lost. Patients with meningitis are often hypotensive with increased ICP, resulting in a critical reduction in CPP. Consequently, the time course of cerebral oedema formation in the face of changes in CPP within the normal range of CBF autoregulation has been investigated. Using diffusion imaging methods, oedema formation was measured using acquired apparent diffusion coefficient (ADC) maps. The hypothesis is that both vasogenic and cytotoxic oedema are present at baseline and that an increase in CPP will influence cytotoxic oedema formation. Initial results are promising and will be validated against the standard wet-to-dry method for estimating the amount of water in the brain.

A second project has commenced where the role of sepsis in the evolution of meningitis is being investigated. In patients, the development of hydrocephalus is a well-known disease characteristic complicating the course of bacterial meningitis and is associated with a mortality of around 50%. This study builds upon previous work where it has been shown that the development of hydrocephalus is also a characteristic of the animal model. It is thought that the production and re-absorption of cerebrospinal fluid is compromised in bacterial meningitis probably due to obstruction by bacteria/pus leading to acute hydrocephalus. In the pneumococcal model, expansion of the ventricles occurs at an early stage of disease and appears to be closely correlated with the deterioration of the animal as assessed using standard clinical and motor scoring measures. The role of sepsis in hydrocephalus has been investigated using a bacteria specific antibody administered intravenously immediately prior to infection (via the injection of bacteria directly into the brain). This provides a unique meningitis model where the bacterial infection is limited to the brain only. Comparison with control animals has shown the disease to be slowed as assessed using clinical and motor scoring. Examples of post contrast T_1-weighted MR images acquired from normal, infected, antibody treated and animals treated with additional intravenous bacteria demonstrate the significant role of sepsis in the disease process.

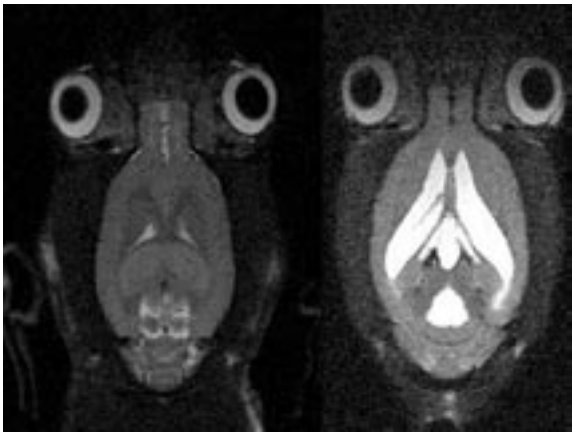


Post contrast T_1-weighted MR images acquired from (a) normal, (b) infected, (c) antibody treated and (d) animals treated with additional intravenous bacteria. The significantly reduction in blood brain barrier breakdown (areas of hyperintensity) clearly illustrates a significant effect of pre-treatment with antibody, showing sepsis to play a major role in the disease process.

Preclinical Research

As part of the meningitis studies, the group also contributes to the DiMI network. The goal of the Network of Excellence “Diagnostic Molecular Imaging” (DiMI) - Molecular Imaging for Diagnostic Purposes - is to integrate multidisciplinary research for the development of new probes and multimodal non-invasive imaging technology for early diagnosis, assessment of disease progression and treatment evaluation (www.dimi-net.org).

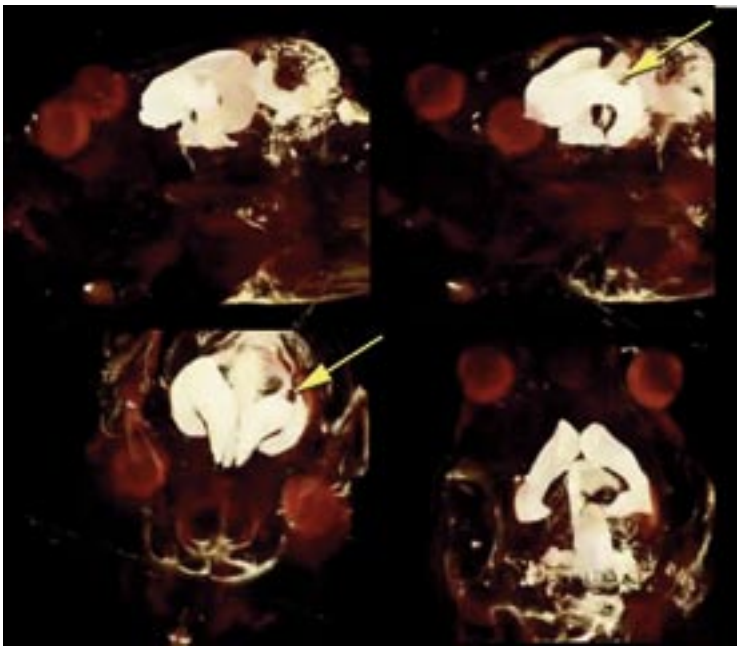
In collaboration with Rigshospitalet, an experimental animal model of hydrocephalus has been developed to explore the biomolecular basis of the condition. In this project, hydrocephalus is induced through percutaneus intracisternal injection of sterile kaolin suspension in Sprague-Dawley rats. Whilst the model will be utilized to investigate the role of cellular water channels (aquaporins) in the hydrocephalic brain, it also complements the meningitis studies. Using an optimized 2D axial T_2-weighted fast spin-echo sequence, the size of the lateral ventricles in the rat brain was determined confirming the validity of the model.



MR-images (T_2-weighted fast spin-echo sequence) of (left) normal rat brain (right) kaolin induced hydrocephalic rat brain.

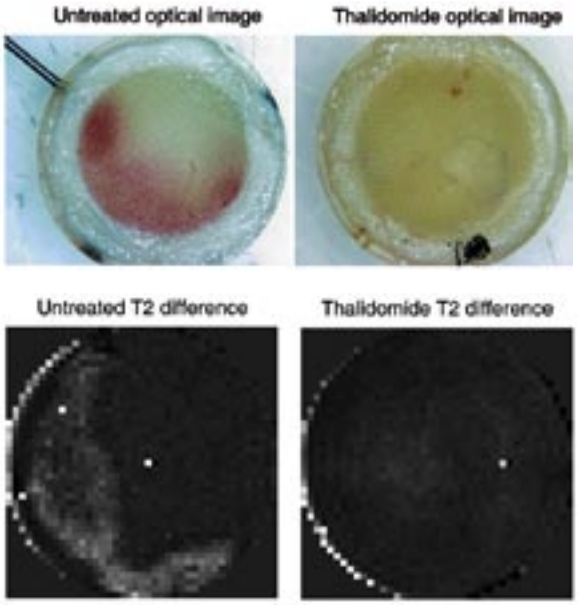
An alternative means of visualizing the hydrocephalic ventricular system is shown following intracisternal administration of GdDTPA. Using a standard 3D gradient echo T_1-weighted sequence, 3D representations of the contrast agent filled ventricles may be obtained.

As mentioned above, the group is involved in a number of different projects. In a cancer related project, an MR compatible assay to assess the efficacy of new anti-cancer agents is being developed. 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 group has continued to work on the development of a reproducible model of angiogenesis that could be readily investigated using MR. Such a model would also facilitate the investigation of the influence of physiological factors upon angiogenesis and the validation of MR methods used to study angiogenesis in vivo. Consequently, Matrigel containing specific angiogenesis promoters, held within a Perspex support was implanted sub-cutaneously in nude mice. The anti-angiogenic properties of thalidomide was used to demonstrate the validity of this approach. T_2 was determined before and after injection of a vascular contrast agent (Endorem). Optical images were acquired ex vivo using a stereomicroscope. The extent of new blood vessel formation was estimated by thresholding T_2 difference images as well as quantifying the amount of red pixels in the optical images. Treatment with thalidomide resulted in a significant drop in the number of pixels detected with either method.



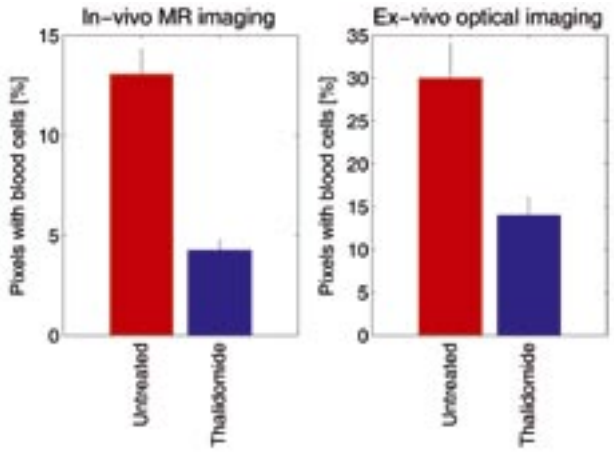
3D representations of the ventricular system in a hydrocephalic rat. Images were acquired using a 3D T_1-weighted gradient echo sequence following intracisternal administration of GdDTPA. Note incomplete filling of the ventricles (arrowed).

In a further project, the group has utilised electroporation methodology to deliver contrast agents intracellularly in vivo. Using Magnevist (GdDTPA)

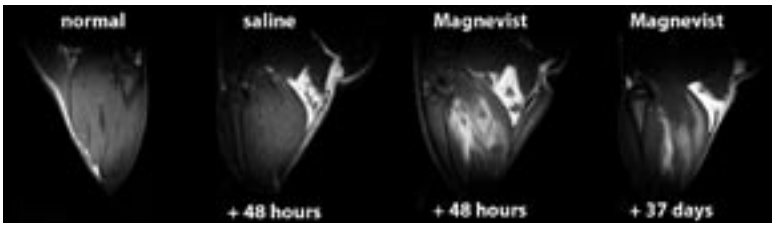


Optical image from an untreated animal (top left), optical image from a thalidomide-treated animal (top right). Post contrast T_2 difference in an untreated animal (bottom left), Post contrast T_2 difference in a thalidomide-treated animal (bottom right). Both methods clearly show the anti-angiogenic effects of the drug treatment.

injected intravenously prior to the application of high voltage electric pulses to rat thigh muscle, contrast agent remains trapped within the tissue for several weeks. The intracellular delivery of contrast agent allows metabolite compartmentalisation to be probed since the incorporation of the contrast agent into the cytoplasm enables direct interaction of the contrast agent and any cytoplasm containing metabolite.



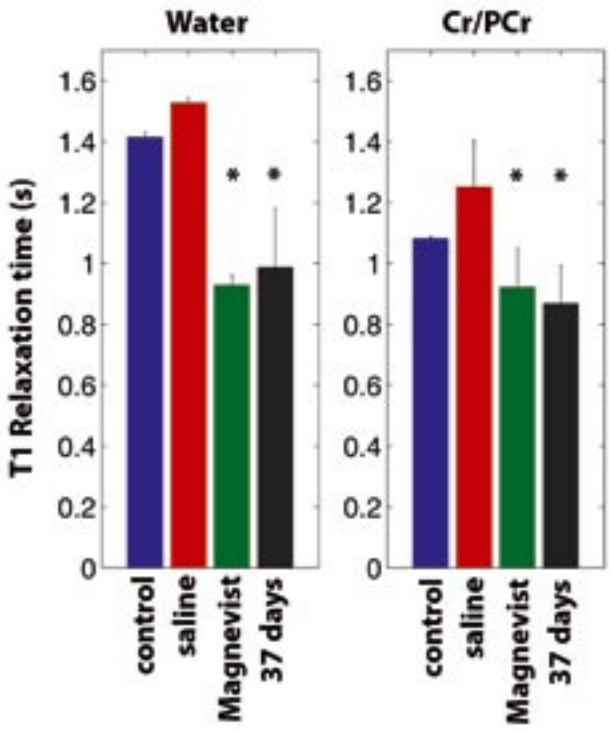
Comparison of MR and optical imaging methods for assessing angiogenesis in the Matrigel assay Percentage of pixels containing significant blood volume estimated using in vivo MR imaging (left) and optical imaging methods (right) clearly show the anti-angiogenic effects of thalidomide.



T_1-weighted MR images of rat thigh muscle. Regions of hyperintensity are due to trapped Magnevist contrast agent (GdDTPA) following electroporation of the muscle. Note that contrast agent remains trapped for prolonged periods of time.

So far, the resonance attributable to creatine/phosphocreatine has been investigated and the metabolite's longitudinal relaxation time has been shown to be significantly influenced by the trapped gadolinium chelate.

This is in accord with creatine/phosphocreatine being thought to reside within the cytoplasm. The exact nature of the trapped gadolinium chelate is currently unknown and requires further investigation. However, the prolonged trapping of the gadolinium chelate clearly demonstrates the successful delivery of the contrast agent and its effect on metabolite relaxation times, validating the methodology.



Effects of trapped Magnevist contrast agent on T_1 relaxation times of (left) water and (right) creatine/phosphocreatine (Cr/PCr). The trapping of intracellular contrast agent significantly reduces water and metabolite relaxation times 48 hours (Magnevist) and over 5 weeks (37 days) after electroporation when compared to control and saline administered control animals.

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
- President 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 Research Committee of Hvidovre Hospital

Michel Nemery:
- Representative of Danish Society of Radiology in the Danish Medical Society
- Member of workgroup on Teleradiology under the Danish Society of Radiology

Terry L. Jernigan:
- Co-Director of Laboratory of Cognitive Imaging
- Section Editor of Neurobiology of Aging
- Member of the Editorial Advisory Board of Neuropsychology
- Member of the Editorial Advisory Board of Journal of the International Neuropsychological Society
- Member of the Editorial Advisory Board of Psychiatry Research: Neuroimaging
- Member of the Editorial Advisory Board of Developmental Neuropsychology
- Ad Hoc Reviewer, US National Institute of Drug Abuse, Treatment Research Subcommittee
- Program Committees, 2007 Annual and 2007 Mid-year Meetings of the International Neuropsychological Society
- Invited Participant, “The First Neuro-Math Educational Research Symposium”. Sponsored by US National Science Foundation/George Mason University, Learning Lab Denmark, Danish University of Education, OECD-CERI, 2006.
- Invited Participant, “The Neural Basis of Mathematical Cognition: A Conference on Using Brain Imaging to Understand Mathematical Milestones, Obstacles to Expertise, and the Impact of Education.” Sponsored by Vanderbilt University, the Sackler Institute of Weill Cornell Medical College; George Mason University; and the National Science Foundation. 2006.

Thomas Zöega Ramsøy:
- Managing Editor: Science and Consciousness Review: www.sci-con.org
- Administrator: Nordic Network for Consciousness Studies

Journal Review

During 2006, DRCMR staff members have been reviewers for the following journals:
- Acta Neurologica Scandinavia
- American Journal of Psychiatry
- Clinical Physiology and Functional Imaging
- Future Neurology
- Human Brain Mapping
- IEEE transactions on medical imaging
- Journal of Cerebral Blood Flow
- Journal of Cerebral Blood Flow and Metabolism Magnetic Resonance in Medicine
- Journal of Child Psychology and Psychiatry
- Magnetic Resonance in Medicine
- MICCAI Conference
- Neurobiology of Aging
- NeuroImage
- The Journal of Physiology

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:
- Karam Sidaros: Teaching course: Tracer kinetics, University of Copenhagen
- Karam Sidaros, Kirsten Korsholm, Torben E. Lund and Egill Rostrup: Teaching at DSMMR course: 3T MR-scanning, technique and fMRI
- Mark Schram Christensen: Teaching Neurophysics, Department of Physics, Technical University of Denmark

- Mark Schram Christensen: Teaching Human Motor Functions, Department of Exercise and Sport Sciences, University of Copenhagen
- Mark Schram Christensen: Teaching Motor Control Neuroscience PhD course, Graduate School of Neuroscience, University of Copenhagen
- Lars G. Hanson (local organizer), Karam Sidaros, Per Åkeson, Margrethe Herning, Xiong Xie and Lise Vejby Søgaard: "MR-temadage", biannual, Sygepleje- og Radiografskolen
- Lars G. Hanson (local organizer), Michel Nemery, Arnold Skimminge: Teaching: Medical Imaging Systems, Technical University of Denmark
- Lars G. Hanson: Teaching: PhD course on Functional Imaging, Bispebjerg Hospital
- Kristoffer H. Madsen, Torben E. Lund (local organizers), Lars G. Hanson: Teaching: Medical Imaging Analysis, Danish Technical University
- Michel Nemery: Teaching DTU students and medical students (6th term) at the Copenhagen University
- William Baaré: Teaching: Brain imaging in schizophrenia, Danish Clinical Intervention Research Academy Schizophrenia Clinical Intervention in Schizophrenia

Courses Organized at the DRCMR:
- Karam Sidaros was the local organizer and teacher at: ESMRMB Lectures on MR – perfusion and flow
- Lars G. Hanson (course organizer), Lise Vejby Søgaard, Karam Sidaros taught: Fundamentals of MRI

Individual Supervision of graduate students by DRCMR Staff:
- Kirsten Korsholm was supervisor for medical student Sara Maria Dalbjerg (OSVAL 1)
- Kirsten Korsholm was supervisor for medical student Jonas Vestergård Iversen (OSVAL 1)
- Mark Schram Christensen was supervisor for medical student Katja Sørensen (OSVAL 1)
- Mark Schram Christensen was co-supervisor on MSc Thesis by Kasper Kragh Andersen, Tue Hvass Petersen & Svend Sparre Geertsen, Department of Exercise and Sport Sciences, University of Copenhagen
- Lars G. Hanson was supervisor for MSc.Eng. student and Novo Nordisk Scholarship recipient Henrik Lundell, Danish Technical University
- Lars G. Hanson was an external examiner at a MSc project , Ingeniørhøjskolen Århus
- Torben E. Lund was supervisor for PhD student Kirsten Korsholm, MD
- Torben E. Lund was supervisor for PhD student Kristoffer H. Madsen, Engineer
- Lise Vejby Søgaard was external examiner: MR1 course and MR3 course, Aarhus University
- Lise Vejby Søgaard and Ian J. Rowland were supervisors for biology student Kathrine Skak Madsen and scholar recipient Anders Dæhli Skjolding
- William Baaré was supervisor for PhD student Thomas Ramsøy, Tim Dyrby, Randi Starfelt and Bjørn Ebdrup

Invited speaker activity

- Olaf B. Paulson was invited speaker at Symposium for Albert Gjedde's 60 years birthday: Retinotopic mapping in fMRI studies
- Olaf B. Paulson was invited speaker at The neuroscience meeting, Atlanta
- Tim B. Dyrby was invited speaker at The Center for Functionally Integrative Neuroscience, Aarhus University Hospital
- Tim B. Dyrby was invited speaker at a Matlab workshop: Matlab for Large-Scale Problems: NeuroImaging, The Technical University of Denmark

Terry Jernigan:
- "Studies of Brain Maturation and Academic Skill Development in School-Aged Children." NSF/OECD Conference on Neuroscience of Math Education. Copenhagen, Denmark.
- "Studies of Brain Maturation in School-Aged Children and Adolescents" Department of Psychiatry, Copenhagen University Hospital, Bispebjerg
- "The Inconstant Brain: MR Imaging of the Lifespan" Harvard/MIT BrainMap Seminar, Cambridge, MA
- "The Inconstant Brain: MR Imaging of the Lifespan" Keynote Address, Annual Meeting of the Medical Imaging and Computer-Assisted Interventions Society, Copenhagen, Denmark
- "The Inconstant Brain: Magnetic Resonance Imaging of the Lifespan" Lectures on the priority research area, "Body and Mind", University of Copenhagen, Denmark

Congress Organization

- Tim B. Dyrby organized a minor DTI workshop at the Danish Centre of Magnetic Resonace with international guest speakers.
- Terry Jernigan was co-organizer, with Christian Gerlach, of a Symposium on Cognition and Brain Development at the meeting of the European Societies of Neuropsychology in Toulouse, France.

Awards

- We are pleased to announce that Mark Schram Christensen received the first prize at the Neuroday Presentation Competition on November 3rd, at Rigshospitalet
- Student Rasmus Engholm, Technical University of Denmark, supervised by Lars G. Hanson, was awarded with the Novo Scholarship Program Award for Best Popular Science Article
- NeuroImage Editors Choice Award, Methods and Modelling was given to Torben E. Lund, Kristoffer H. Madsen, Karam Sidaros, WL Luo and TE Nichols for the article "Non-white noise in fMRI: does modelling have an impact?"
- Annette Sidaros was awarded for the best oral presentation at Hvidovre Hospital Research Day and the best poster presentation at the 4th Academy of Multidisciplinary Neurotraumatology Congress

Publications

A large number of publications has resulted from the work performed by the research staff at the DRCMR during 2006. The most important of these publications are listed here according to category:

PhD and Doctoral Theses

1. Henrik K. Mathiesen. MR Spectroscopy in Relapsing Remitting MS. PhD Thesis, Faculty of Health Sciences, University of Copenhagen, 2006.
2. Egill Rostrup. Basic Physiology of BOLD Imaging. DMSc Thesis, Faculty of Health Sciences, University of Copenhagen, 2006.

Peer Reviewed Journal Articles

1. Balslev D, Nielsen FA, Lund TE, Law I, Paulson OB. Similar brain networks for detecting visuo-motor and visuo-proprioceptive synchrony. Neuroimage 2006; 31(1):308-312.
2. Brandt CT, Frimodt-Moller N, Lundgren JD, Pedersen M, Skovsted IC, Rowland IJ et al. Evaluation of anti-pneumococcal capsular antibodies as adjunctive therapy in experimental pneumococcal meningitis. J Antimicrob Chemother 2006; 58(6):1291-1294.
3. Christensen MS, Ramsoy TZ, Lund TE, Madsen KH, Rowe JB. An fMRI study of the neural correlates of graded visual perception. Neuroimage 2006; 31(4):1711-1725.
4. Fennema-Notestine C, Ozyurt IB, Clark CP, Morris S, Bischoff-Grethe A, Bondi MW et al. Quantitative evaluation of automated skull-stripping methods applied to contemporary and legacy images: effects of diagnosis, bias correction, and slice location. Hum Brain Mapp 2006; 27(2):99-113.
5. Gerlach C, Law I, Paulson OB. Shape configuration and category-specificity. Neuropsychologia 2006; 44(7):1247-1260.
6. Glenthoj BY, Mackeprang T, Svarer C, Rasmussen H, Pinborg LH, Friberg L et al. Frontal dopamine D(2/3) receptor binding in drug-naive first-episode schizophrenic patients correlates with positive psychotic symptoms and gender. Biol Psychiatry 2006; 60(6):621-629.
7. Habekost T, Rostrup E. Persisting asymmetries of vision after right side lesions. Neuropsychologia 2006; 44(6):876-895.
8. Haugbol S, Pinborg LH, Arfan HM, Frokjaer VM, Madsen J, Dyrby TB et al. Reproducibility of 5-HT(2A) receptor measurements and sample size estimations with [(18)F]altanserin PET using a bolus/infusion approach. Eur J Nucl Med Mol Imaging 2006.
9. Holm DA, Sidaros K. Slice profile optimization in arterial spin labeling using presaturation and optimized RF pulses. Magn Reson Imaging 2006; 24(9):1229-1240.
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11. Hulshoff Pol HE, Schnack HG, Mandl RC, Brans RG, van Haren NE, Baare WF et al. Gray and white matter density changes in monozygotic and same-sex dizygotic twins discordant for schizophrenia using voxel-based morphometry. Neuroimage 2006; 31(2):482-488.
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14. Larsen A, Madsen KH, Lund TE, Bundesen C. Images of illusory motion in primary visual cortex. J Cogn Neurosci 2006; 18(7):1174-1180.
15. Linde R, Hasselbalch SG, Topp S, Paulson OB, Madsen PL. Global cerebral blood flow and metabolism during acute hyperketonemia in the awake and anesthetized rat. J Cereb Blood Flow Metab 2006; 26(2):170-180.
16. Lindegaard HM, Vallo J, Horslev-Petersen K, Junker P, Ostergaard M. Low-cost, low-field dedicated extremity magnetic resonance imaging in early rheumatoid arthritis: a 1-year follow-up study. Ann Rheum Dis 2006; 65(9):1208-1212.
17. Liston AD, Lund TE, Salek-Haddadi A, Hamandi K, Friston KJ, Lemieux L. Modelling cardiac signal as a confound in EEG-fMRI and its application in focal epilepsy studies. Neuroimage 2006; 30(3):827-834.
18. Lund TE, Madsen KH, Sidaros K, Luo WL, Nichols TE. Non-white noise in fMRI: Does modelling have an impact? Neuroimage 2006; 29(1):54-66.
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20. Mathiesen HK, Jonsson A, Tscherning T, Hanson LG, Andresen J, Blinkenberg M et al. Correlation of global N-acetyl aspartate with cognitive impairment in multiple sclerosis. Arch Neurol 2006; 63(4):533-536.
21. Miranda MJ, Olofsson K, Sidaros K. Noninvasive measurements of regional cerebral perfusion in preterm and term neonates by magnetic resonance arterial spin labeling. Pediatr Res 2006; 60(3):359-363.
22. Nielsen FA, Christensen MS, Madsen KH, Lund TE, Hansen LK. fMRI neuroinformatics. IEEE Eng Med Biol Mag 2006; 25(2):112-119.
23. Nielsen K, Brask D, Knudsen GM, Aznar S. Immunodetection of the serotonin transporter protein is a more valid marker for serotonergic fibers than serotonin. Synapse 2006; 59(5):270-276.
24. Nielsen K, Rostrup E, Frederiksen JL, Knudsen S, Mathiesen HK, Hanson LG et al. Magnetic Resonance Imaging at 3.0 Tesla Detects More Lesions in Acute Optic Neuritis Than at 1.5 Tesla. Invest Radiol 2006; 41(2):76-82.
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Conference Proceedings

The DRCMR was represented at 23 meetings and conferences during 2006, presenting 64 abstracts.

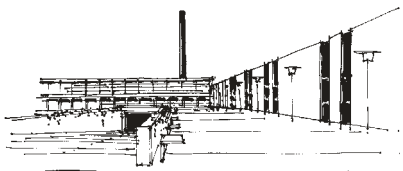
Acknowledgements

National Research Funding

Copenhagen University: Faculty of Science
Copenhagen University Focus Area: Body and Mind
Copenhagen University Hospital, Hvidovre
Copenhagen University Hospital, Rigshospitalet
Danish Multiple Sclerosis Society
Danish Rheumatism Association
Elsass Foundation
Lundbeck Foundation
Novo Nordisk Scholarship Programme
Research Fund of Copenhagen Hospital Corporation
Savværksejer Jeppe Juhl og Hustru Ovita Juhls Foundation
Scleroseforeningen
Technical University of Denmark
The Danish Medical Research Council
The Velux Foundation

International Research Funding

EU 5th framework. LADIS project
Nordic Network symposium on Imaging in Medicine and Biology 2006



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Hovedstadens Sygehusfællesskab