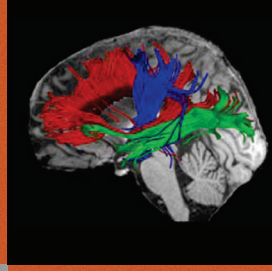
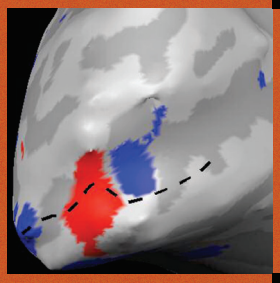
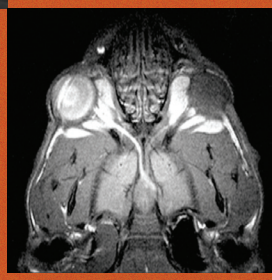
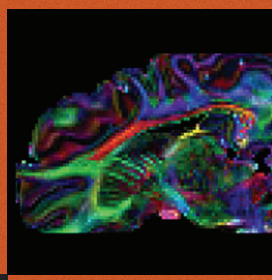


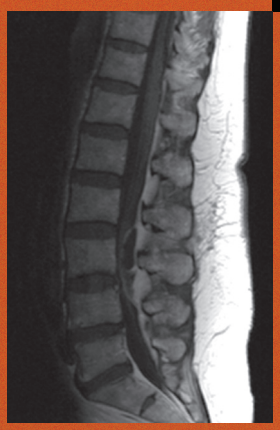




# DRCMR

## Annual Report 2005





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 2005.
The main aim of the DRCMR is to advance the use of magnetic resonance as a clinical and investigative tool in biomedical science. Consequently, DRCMR Staff employ state-of-the art instrumentation and bioinformatics tools for the diagnosis and management of medical patients and for a range of biomedical investigations. The clinicians and investigators of the DRCMR are active participants at national and international level in the community of biomedical scientists. In the last year, the Centre has continued to thrive and grow. The continued growth and the anticipation of continued development and expansion of our scientific activities requires that the DRCMR continues to maintain a flexible internal organizational structure that facilitates both focused and integrative activities within the Centre. We are proud to present the Centre's recent accomplishments in our 2005 annual report.
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*

# DRCMR Profile

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

# Contents

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**Layout**
Karam Sidaros




# Dansk Resumé

Denne rapport giver et indblik i målene, visionerne og organisationen af MR-afdelingen på Hvidovre Hospital og beskriver afdelingens aktiviteter i 2005. 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, Terry Jernigan, der netop i 2005 er blevet tildelt et professorat ved Københavns Universitet med ansættelse på MR-afdelingen på Hvidovre Hospital.

MR-afdelingen kunne fejre sit 20-års jubilæum i 2005 hvilket blev fejret den 25. august ved en velbesøgt ceremoni med gæster fra den akademiske og medicinske verden. Afdelingens leder, professor Olaf B. Paulson præsenterede afdelingens historie samt højdepunkter fra de sidste to årtier og begivenheden tiltrak sig også mediernes opmærksomhed.

Et af højdepunkterne i 2005 var MR-afdelingens succesfulde medvirken i at sikre dannelsen af et nyt forskningscenter: Center for integreret molekylær billeddannelse af hjernen, forkortet Cimbi. Centeret er finansieret af Lundbeckfonden, og er dannet som et samarbejde mellem en række forskningsinstitutioner i København, heraf MR-afdelingen samt en række internationale samarbejdspartnere.

# Overview of 2005

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 are also facilities for clinical work and conferences.
In addition, the Centre has an experimental Varian 4.7 Tesla scanner, suitable for MR studies in small animals. The experimental scanner is located in area 340B where there are also facilities for data analysis and other research activities. In 2004, a complete upgrade of the experimental animal scanner took place. Only the old magnet and a newer gradient coil remains from the old instrument, so in effect the result is a new scanner with 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. Funding contributions from several sources, including Hvidovre Hospital, made the planned upgrade possible. The pre-clinical 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.

## 2005 and the future

This year, the Danish Research Centre for Magnetic Resonance reached an important milestone and saw a number of major new developments. The Centre celebrated its 20th anniversary on August 25th with a ceremony attended by many in the academic and medical communities. Prof. Olaf Paulson reviewed the history and some of the highlights of the last two decades, and the ceremony was also the occasion for the inaugural lecture by Prof. Terry Jernigan in association with her appointment in the Centre as Professor in Neuroimaging. These events were spotlighted in national media coverage, including a television piece on the evening news broadcast by DR1. Prof. Jernigan's work on brain effects of methamphetamine use and HIV-infection was also featured in the international news media in 2005 and was, for example, covered by the British Broadcasting Company. Local news coverage was also given to work within the Centre by Torben Lund and Karam Sidaros on Fibromyalgia and by Jon Wegener on emotion processing.

As a sign of the growing integration of the work of the DRCMR with other disciplines, the department hosted a quarterly meeting of the Danish Neuropsychological Society in May. Thomas Ramsøy of the Centre arranged this meeting, which was well attended by Society membership, with the program included lectures by several Centre investigators.

*In 2005, the DRCMR celebrated its 20th anniversary and Professor Terry Jernigan was appointed as Professor of Neuroimaging at the University of Copenhagen and the DRCMR.*

One of the most exciting developments of the year was the department's role in the successful competition for a new centre for Integrated Molecular Brain Imaging (Cimbi). This competition was sponsored by the Lundbeck Foundation and drew applications from many major neuroscience groups within Denmark. The Cimbi group was led by Prof. Gitte Moos Knudsen of the Neurobiology Research Unit at the Rigshospital and included contributions from principal investigators at the Danish University of Pharmaceutical Sciences (led by Prof. Mikael Begtrup) and the Technical University of Denmark (led by Prof. Lars Kai Hansen) as well as the DRCMR (led by Profs. Paulson and Jernigan). The research in the new Center will focus on the neural bases of personality dimensions that predispose individuals to affective and substance use

*Members of the DRCMR taking a short break during the annual departmental Christmas symposium*

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

# Organisation and Staff

## Department Chair

Olaf B. Paulson, DMSc, Professor

## Senior staff, Clinical

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

## Senior Staff, Research

William Baaré, PhD, Psychologist
Lars G. Hanson, PhD, Chief Physicist
Terry L. Jernigan, Professor, PhD, Psychologist
Maria J. Miranda, MD, PhD
Poul Ring, MSc, Engineer
Egill Rostrup, MD & Human Biologist
Ian J. Rowland, PhD, Chemist
Karam Sidaros, PhD, Engineer
Lise Vejby Søgaard, PhD, Physicist

## Junior Staff, Clinical

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

## Junior Staff, Research

**PhD students**
Mark Schram Christensen, MSc, Engineer
Tim Dyrby, MSc, Engineer
David Alberg Holm, MSc
Katja Krabbe, MD
Elizbieta Kalowska, MD
Torben Ellegaard Lund, MSc, Engineer
Kristoffer Madsen, MSc, Engineer
Henrik Kahr Mathiesen, MD
Annette Skræp Nielsen, MD
Kirsten Nielsen, MD
Robin de Nijs, MSc, P.D. Engineer, Medical Physicist
Dorthe Pedersen, MD
Thomas Z. Ramsøy, Psychologist
Charlotte Ryberg, MSc, Biologist
Randi Starrfelt, MSc, Psychologist
Jon Wegener, MSc, Life Sciences and Chemistry

**Junior Researchers**
Niels Broberg, BSc, Engineer
Matthew Liptrot, MSc, Engineer
Henrik Lund, MSc, Human Biologist
Kathrine Skak Madsen, Student
Arnold Skimminge, MSc, Physicist
Martin Skov, MA Nordic Languages and Litterature
Signe Vangkilde, Student

**Research Assistants**
Andreas Hansen, Medical Student

## Technologists

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

## Secretarial Staff

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

## Cleaning Assistants

Ruth Kielstrup
Elsebeth Nielsen

## Conscientious Objectors

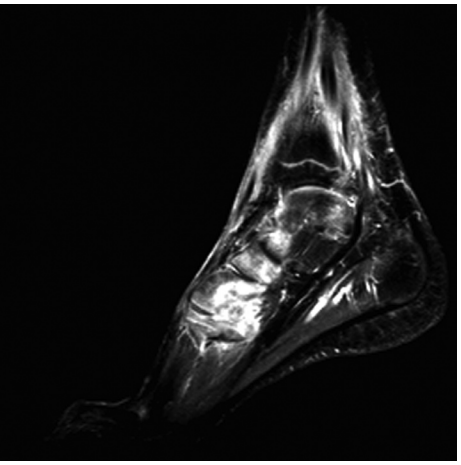
Brian Donati
Rasmus Hasenfuss

## Visiting Staff

Daniela Balslev, MD, PhD
Peter Born, MD, PhD
Bo Ejbjerg, MD, PhD
Jens Christian Nilson, MD, PhD
James Rowe, MD, PhD
Trine Stavngaard, MD, PhD
Mikkel B. Stegmann, PhD
Mikkel Østergaard, DMSc, PhD

# Clinical Imaging

In 2005, 3411 patients underwent MR investigations. Of these, 1951 were referred from Hvidovre Hospital while the remaining patients were referred from other counties outside Copenhagen. Investigations of neurological diseases, e.g. suspicion of stroke, multiple sclerosis, intracranial tumours, intracranial haemorrhage, dementia and epilepsy are an important part of daily clinical radiology.



*12 year old boy with tuberculosis in the middle of the left foot*

The chief radiologist is a member of the 'EPI-KIR' group, a national organisation responsible for national epilepsy patient management that selects patients suitable for surgical intervention and is responsible for 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, T2-relaxation measurements and, where appropriate, proton spectroscopy.

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

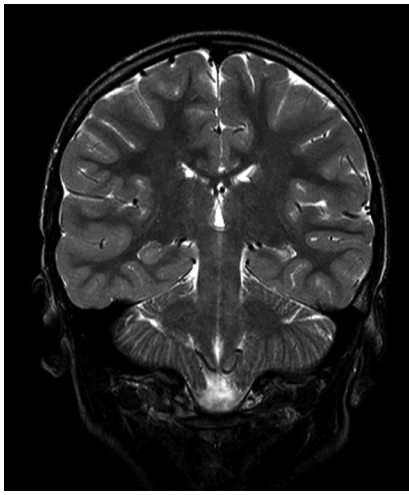
Patients with suspected intracranial vascular diseases such as arteriovenous malformations and aneurysms are regularly referred to the department for investigation with MRI and MR angiography. MR imaging and angiography are also used in patients with suspicion of "warning leaks" from cerebral aneurysms,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

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

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

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

The 3 Tesla MR scanner has proved to provide better diagnostic imaging especially in the evaluation of the brain and particularly in knee joints, where meniscal tears are often readily delineated and the cartilage is well visualised.



*Severe atrophy of the left hippocampus in a patient with medically intractable epilepsy*

# Collaborations

The DRCMR collaborates and works closely with many institutions both nationally and internationally. Primary collaborators in 2005, 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). The CBRC consists of the Neurobiology Research Unit and the PET and Cyclotron Unit at Rigshospitalet, Informatics and Mathematical Modelling at The Technical University of Denmark, the Center for Visual Cognition, Department of Psychology, University of Copenhagen, the Department of Medical Chemistry, The Danish University of Pharmaceutical Sciences, H. Lundbeck A/S, and the MR department at Hvidovre Hospital. 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
Department of Physics, The Technical University of Denmark
Informatics and Mathematical Modelling, The Technical University of Denmark
Institute of Exercise and Sport Sciences, University of Copenhagen
Department of Psychology, University of Copenhagen
Department of Medical Anatomy, University of Copenhagen
Department of Medical Biochemistry and Genetics, Panum Institute, University of Copenhagen
Department of Medical Physiology, Panum Institute, University of Copenhagen
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 Cardiology*
*Department of Clinical Chemistry*
*Department of Clinical Nutrition*
*Department of Clinical Physiology*
*Department of Neurorehabilitation*
*Department of Orthopaedic Surgery*
*Department of Pathology*
*Department of Paediatrics*
*Department of Radiology*
*Department of Respiratory Medicine*
*Department of Rheumatology*

Departments at Rigshospitalet
*Danish Multiple Sclerosis Center*
*Department of Nephrology*
*Department of Clinical Physiology*
*Department of Radiology*
*Department of Rheumatology*
*The Memory Disorders Research Unit*
*The Neurobiology Research Unit*
*The Neonatal Department*

Departments at other Copenhagen University Hospitals
*Department of Clinical Chemistry, Bispebjerg Hospital*
*Department of Neurology, Bispebjerg Hospital*
*Department of Neurology, Glostrup Hospital*
*Department of Neurophysiology, Glostrup Hospital*
*Department of Psychiatry, Bispebjerg*
*Department of Radiology, Aarhus University Hospital, Århus Kommunehospital*
*Department of Radiology, Gråsten Gigthospital*
*Department of Radiology, Herlev Hospital*
*Department of Radiology, Odense University Hospital*
*Department of Respiratory Medicine, Copenhagen University Hospital, Gentofte*
*Department of Rheumatology Odense University Hospital*
*Department of Rheumatology, Gråsten Gigthospital*
*Department of Rheumatology, Herlev Hospital*
*Department of Rheumatology, Aarhus University Hospital, Århus Kommunehospital*
*Department of Ultrasonography, Herlev Hospital*

## International Collaborations

Center of Cognitive Neuroscience, Nijmegen, The Netherlands.
Center for fMRI, University of California, San Diego, USA
Centre for Magnetic Resonance, University Hospital, Trondheim, Norway
Centre for Medical Imaging 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 Radiation Physics, Lund University Hospital, Sweden
Departments of Rheumatology and Radiology, Leeds General Infirmary, United Kingdom.
Department of Radiology, University of California San Francisco, USA.
Departments of Radiology and Rheumatology, St. George Hospital, Sydney, Australia.
Departments of Radiology and Rheumatology, University of Auckland, New Zealand.
Image Science & Biomedical Engineering, University of Manchester, United Kingdom
Institute for Clinical Neuroscience, Göteborg University, Göteborg, Sweden
Institute of Clinical Radiology, Munich, Germany
Laboratory of Cognitive Imaging, University of California, San Diego, USA
Robert Steiner Magnetic Resonance Unit, ICSM Hammersmith Hospital, London, United Kingdom
Section of Academic Radiology, University of Sheffield, United Kingdom
The Neuroscience Institute, San Diego, USA
University Laboratory of Physiology, Oxford University, United Kingdom
Wellcome Department of Imaging Neuroscience, London, 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: Automated Removal of Partial Volume Effects (PVEOut)
Chaired by Prof. Bruno Alfano, Centro per la Medicina
Nucleare, Naples, Italy.
The EU project: Leukoaraiosis and Disability in the elderly (LADIS)
Chaired by Prof. Domenico Inzitari, Department of
Neurological and Psychiatric Sciences, University of
Florence, Italy.
European Task Force on Age-Related White Matter Changes
Chaired by Prof. Philip Scheltens, PhD, Academisch Ziekenhuis Vrije Universiteit, Amsterdam, The Netherlands.
The EULAR and OMERACT collaborations concerning imaging in rheumatoid arthritis.

Cimbi
Center for integrated molecular brain imaging

The DRCMR is a core institution in the Center for Integrated Molecular Brain Imaging (Cimbi). Cimbi is a new research centre whose funding by the Lundbeck Foundation was announced in 2005. The research in the new Center 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 Center. The work venues span several institutions in Copenhagen as well as several collaborating laboratories in Europe and the U.S.

# Basic Research

The basic research at the DRCMR addresses both methodological and physiological questions. The aim of developing faster, more sensitive and more specific MR methods is, ultimately, to answer important physiological questions about, for example, the neural basis of consciousness. To answer this big question, brain function must be understood in detail at a variety of levels ranging from biochemical and cellular levels, over structure and connectivity, all the way to social behaviour since personal interactions during individual development influence the formation of consciousness. All these pieces of the puzzle need to be assembled to reveal the big picture behind this unanswered question regarding the unique nature of human brain function. Together with researchers from all over the world, DRCMR staff collect pieces of the puzzle and occasionally find a few that fit together. Most basic research, therefore, seems to target questions at a rather mundane level. It is easy to formulate the big questions, but the answers are only provided piecewise by focused studies of very specific aspects of physiology and behaviour.

In order to perform clinical and basic research at an international level, cutting-edge techniques need to be developed and enhanced continuously. At the DRCMR, technical research projects invariably serve two specific roles. Firstly, the development of new advanced techniques that are necessary to remain competitive, i.e. to provide first class research for the benefit of patients and society. Secondly, the methodological research, funded mostly from external sources, provides part of the Centre's basic infrastructure for the mutual benefit of individual projects and the DRCMR.

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

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

When the methods are used to address biomedical problems, new needs invariably arise and new possibilities open, thus fuelling continued methodological research.

The basic research at the Centre can be divided into four categories:
1. Development and optimisation of new MR sequences (MR physics)
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)

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

## MR Physics

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

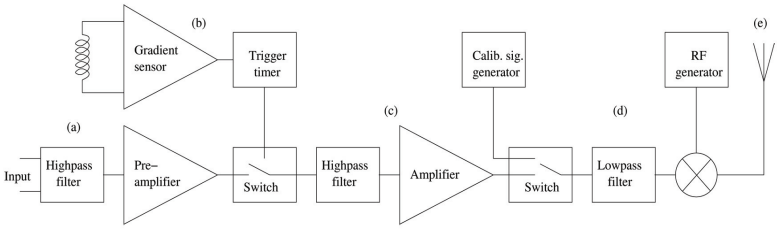
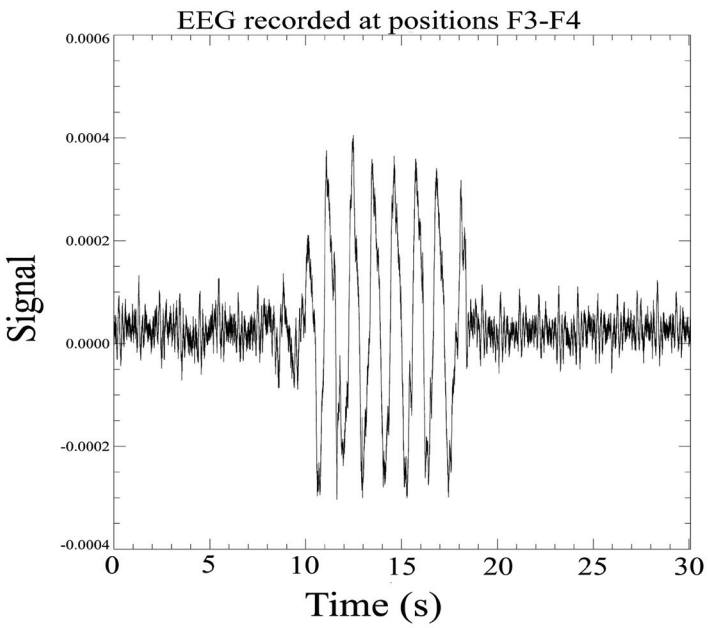



*Diagram showing the developed 8-channel modulator for encoding EEG in MRI. The EEG signal is high-pass filtered and pre-amplified (a). A gradient-activity sensor consisting of a simple coil near the opening of the scanner can, optionally, be used to trigger a sample-hold circuit (b). Subsequently the signals are high pass-filtered and amplified (c). The EEG or a calibration signal generated internally in the modulator are selectively filtered and are mixed with an RF carrier near the Larmor frequency (d). The high-frequency output is amplified and emitted into the scanner room by a simple aerial (e). It is detected by the RF coil of the scanner and is extracted from the MR raw data. Oversampling ensures that the MR images are unaffected.*

Tim Dyrby, Lise Vejby Søgaard and William Baaré have optimised diffusion measurements ex vivo. The aim has been to ensure that the data quality for diffusion tractography is optimal. Tractography is a technique that maps the white matter fibre bundles (the wiring of the brain) connecting brain structures responsible for different aspects of perceiving and thinking. Hence, the combination of functional imaging (fMRI) and diffusion tractography is of major interest when exploring brain function. Reference datasets acquired over long time and consequently of extremely high quality have been acquired for the purpose of validating tracking algorithms. This is achieved by comparing maps derived from normal quality data and from the high quality reference data, for which the fibre tracking algorithms are less challenged. Tim Dyrby performs the analysis of these data sets in collaboration with Daniel Alexander and Geoffrey Parker (UK).

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 ensures that all in-house sequences have need of updating too. 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. Torben Lund pioneered this field at the DRCMR and triggered by the challenges Torben experienced, Lars G. Hanson has 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 encoding of soundtracks in movies, the




*EEG recorded from positions F3-F4 on the forehead of a volunteer with the new, patented EEG-fMRI recording method. The subject in the scanner is performing left/right eye movements, interrupting the middle 8 seconds of a 30 second resting period. Rapid MR imaging is performed throughout the acquisition period. If normal EEG-equipment had been used, the recordings would be flooded with scanner-generated noise much larger than the signal. In contrast, the EEG signal shown that is free of gradient artifacts, was extracted from the MR raw data. The EEG reflecting the eye movement looks normal except for small pulse artifacts of magnitude comparable to those of normal EEG signals. The 0.5 kHz bandwidth is unusually high.*

# Basic Research

EEG signals are encoded in the MR images outside the visible region. A patent application submitted in 2004 by Hvidovre Hospital, was published in 2005 and a proof-of-concept study received considerable attention at conferences even though the developed prototype was not sensitive enough for the weak electrophysiological signals coming from the brain (EEG). The electronics developer of the group, Christian G. Hanson, subsequently constructed and built a new, much improved and highly flexible 8-channel version of the equipment. It is now clear that the method is simple to use, sensitive, inexpensive and more robust than other methods. The analysis is also suitable for integration on the scanner, even as the data are being acquired (real-time EEG-fMRI). During 2005, Arnold Skimminge was increasingly involved in the project and was, at the end of the year, awarded a PhD grant to pursue these ideas from the ITMAN graduate school at the Technical University of Denmark.

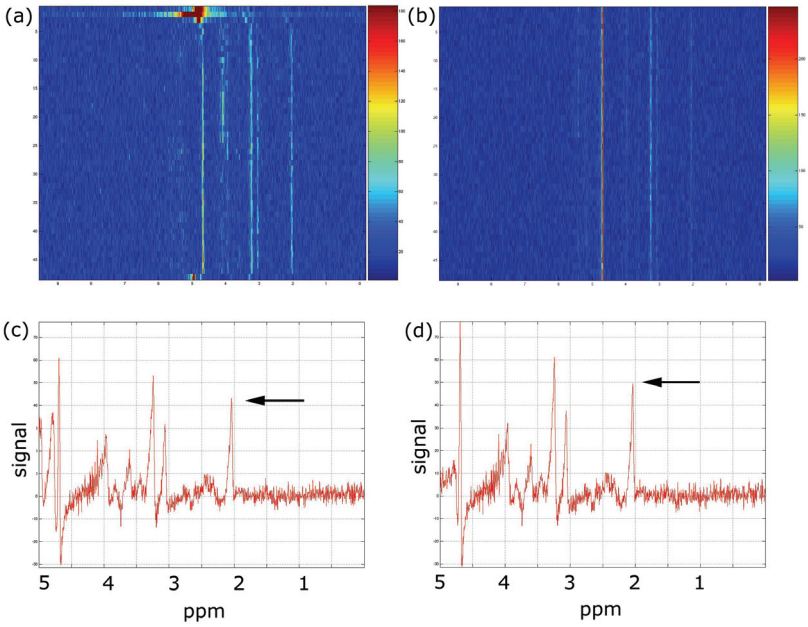
Working with contrast-based perfusion measurements, Irene K. Andersen has been implementing and optimizing perfusion quantification using T1-weighted dynamic measurements. Contrast-based perfusion measurements often rely on T2*-weighted imaging to monitor the susceptibility effects of the paramagnetic contrast agents used. However, T1-weighted imaging, albeit less sensitive, offers a number of other advantages over T2*-weighted imaging, especially when quantifying perfusion. A former member of the department, Irene K. Mikkelsen moved to Sweden in 2004 thereby initiating a 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.

## MR Informatics

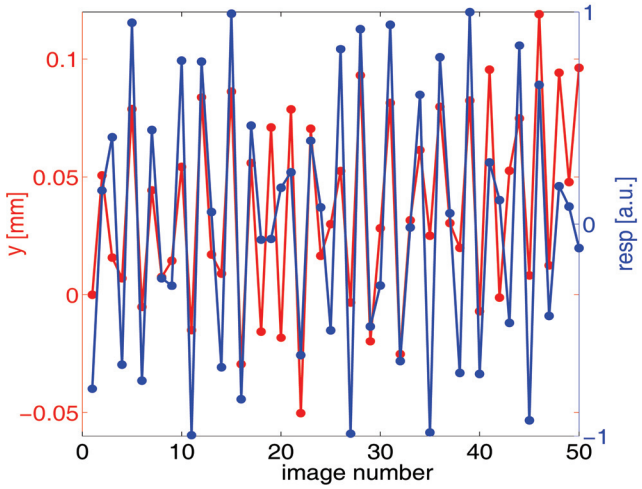
For each patient, MRI provides several sets of images with differing contrast. These are aligned and further analysed together by a series of processing methods chosen in accordance with the aims of the individual project. In order to do this efficiently and reproducibly, configurable analysis “pipelines” have been established that 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. Tim Dyrby has also made important improvements in automated brain tissue classification of white matter lesions as used in the EU LADIS project focusing on the aging population.

Robin de Nijs is funded by a grant from the Danish Medical Research Council. His work in 2005 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 analyzed automatically with independent component analysis, and the dominant components represent motionless acquisition.

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,




*Spectrograms (a & b) of the metabolite signal from an 8 ml voxel in two different infant brains showing 48 individual repetitions as rows with a horizontal frequency axis in parts per million (ppm). The colour depends on the intensity of the signal at a specific frequency. The partially suppressed water signal and the metabolite signals are visual as vertical stripes, as seen for water at 4.7 ppm and NAA (arrowed) at 2 ppm. The spectrograms show measurements with (a) and without motion artifacts (b). Proton spectra obtained by averaging all repetitions (c) and obtained by only averaging the motionless repetitions as determined by independent component analysis (d). The “double” water peak apparent in (a&c) disappears and the metabolite signal, as illustrated by the NAA resonance at 2 ppm (arrowed), increases.*




*A high degree of correlation between the apparent motion in ASL images (red) and the respiration measured using a respiration belt (blue) is demonstrated.*

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.

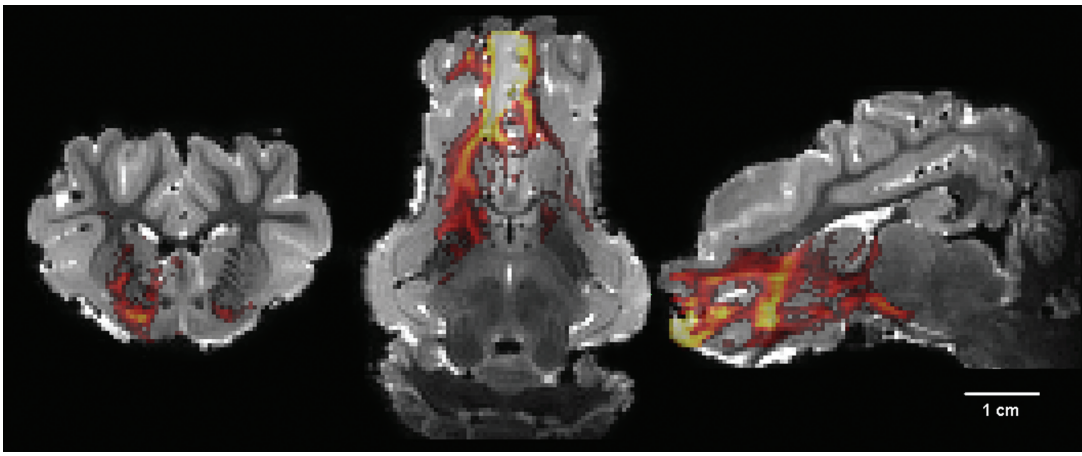
Classification of tissue types and anatomical structures based on MRI images are tasks often performed with little conscious effort by trained radiologists. Automating the process, however, is highly challenging but is necessary to obtain quantitative results without the exceptionally labour intensive task of manually classifying tissue types on the hundreds of images resulting from modern MRI examinations. Important progress was made within the area of brain segmentation in a collaboration involving students Casper Børgesen and Thomas Hammershaimb Mosbech from the Technical University of Denmark. Using a statistical model of typical brain geometry and its variations, the intracranial volume can be estimated accurately from MRI images of the head in a mostly automatic fashion.

Associate professor Rasmus Larsen, assistant professor Mikkel B. Stegmann and Ph.D student Karl Sjöstrand from the Technical University of Denmark, have developed new ways of treating shape information from medical images. This makes, for example, correlation analyses between descriptions of form and clinical/cognitive parameters more accurate and reliable. A series of innovative statistical methods have also been investigated and applied to exploratory analyses of fMRI data as well as to the decomposition of shape and texture data. The results have received much attention from an international and interdisciplinary audience.

Methodology for identifying the high intensity brim of subcutaneous lipids was introduced by Rasmus Engholm, who was granted a Novo Scholarship for developing automated measurement of the volumes of subcutaneous and visceral lipids in pigs based on abdominal MR images. The visceral lipids are of main importance for the development of insulin resistance in diabetes. The developed method was demonstrated to give results correlating closely to those obtained when the pigs were slaughtered. Rasmus Larsen and Lars G. Hanson supervised the work whilst Berit Christoffersen and Dorthe Pedersen collected the data.

In December, Torben Lund defended his PhD thesis on analysis of functional brain imaging. He found that the analysis of functional studies is more robust and consistent when information about respiration and blood circulation is included in the analysis. The method relied on sequence features added to the fMRI pulse sequences to enable the recording of respiration and pulse time series during the scan. Together with Kristoffer Madsen, a new method was developed in 2005 for estimating respiration and pulse directly from the MR imaging data. The method performs well and may

*A high quality, optimized diffusion weighted dataset of a pig brain examined ex vivo using the 4.7T experimental scanner. Compared to the in vivo situation, the scanning time is not limited. A region in the prefrontal cortex was chosen as a seed point for the tractography and different pathways were found in agreement with results based on histology and staining. A prefrontal corticothalamic projection was found using probabilistic tractography based on the the PICo method. Sequence parameters were optimized for tractography without interfering physiological noise or motion artifacts commonly pronounced on datasets acquired in vivo.*



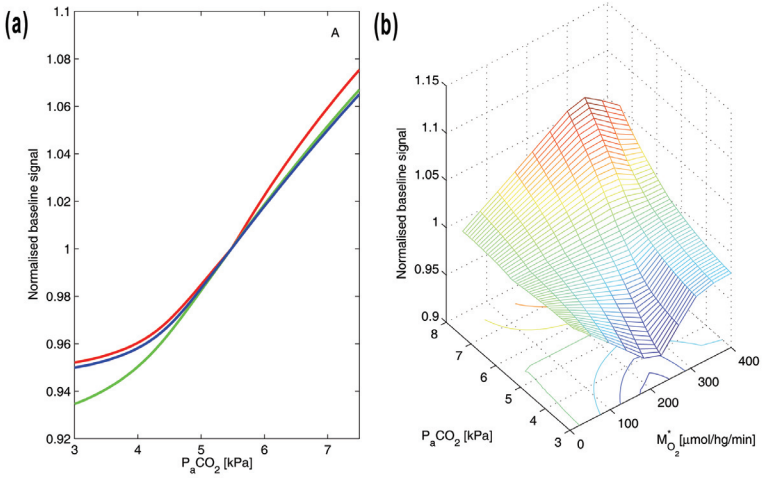
also be applied to data acquired before it was feasible to perform imaging simultaneously with pulse and respiration measurements.

Along the same line of work, Karam Sidaros and Torben Lund have been estimating the effects of respiration and pulsation-induced motion on perfusion images using Arterial Spin Labelling (ASL). They found that, in particular, respiration has a significant effect on the perfusion-weighted images produced by this technique. Using the same methods described above for fMRI, these effects may also be reduced in ASL.

## Basic Physiology

Functional MRI (fMRI) relies on the sensitivity of certain MRI sequences to regional changes in either cerebral blood flow or in blood oxygenation during neural activation. Blood flow changes can be measured directly using ASL methods while blood oxygenation changes can be measured using sequences with BOLD (blood oxygenation level dependent) contrast. Although ASL measurements have a number of theoretical advantages over BOLD measurements, they are less commonly performed due to their reduced sensitivity.

Several physiological parameters are affected by neural activation, including oxygen consumption, glucose metabolism, blood flow or perfusion, blood volume and blood oxygenation. Changes in the BOLD MR signal may occur when these basic parameters change as a direct consequence of changes in the physiological baseline state (e.g. inhalation of $CO_2$, hemodilution etc.) or as a consequence of neural activation. This gives rise to two distinguishable forms of the BOLD response. However, these forms are not independent, and the level of activation obtained in a brain mapping experiment therefore depends on the physiological baseline state of the subject. This fact has particular importance when comparing different groups of subjects to each other.

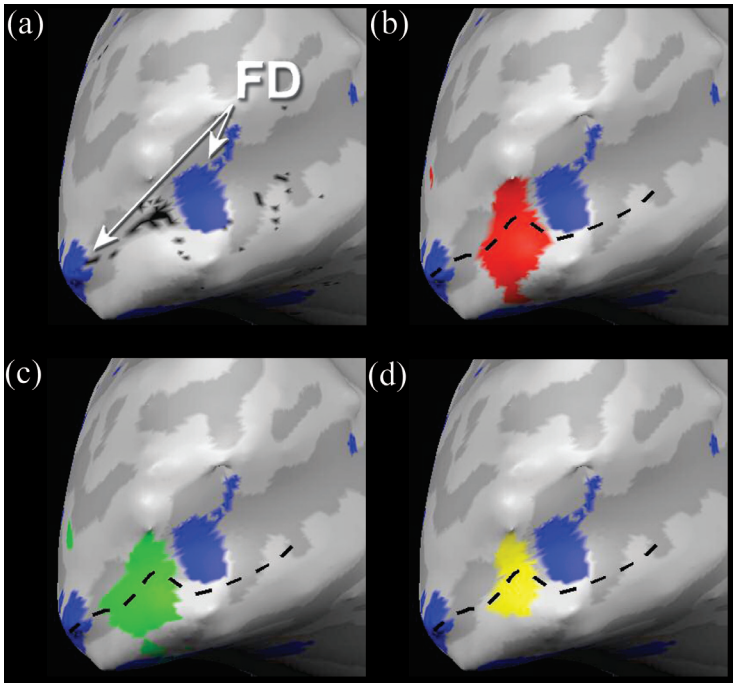



*(a) Predicted BOLD response (in normalised units) as a function of arterial $PCO_2$, green curve shows the relationship when only flow changes are assumed; for the blue curve pH has been included, whereas the red curve also incorporates the effect of oxygen changes. (b) The relationship between BOLD signal and $PCO_2$ is influenced by the magnitude of brain metabolism ($CMRO_2$).*

The details of the interrelationship have been explored quantitatively using a numerical compartment model. It was shown that current knowledge predicts a monotonous relation between BOLD signal and arterial $PCO_2$, which however, was influenced on the concomitant changes in arterial pH and $PO_2$. Furthermore, BOLD signal reactivity is also influenced by the brain's basic metabolic rate, due to the balance between oxygen delivery and oxygen use in the cerebral tissue. Combinations of high metabolism and low flow lead to an oxygen limitation regime, in which further increases of metabolism cannot occur without flow increases, whereas in other situations the two parameters are independent. In general, current experimental evidence is not precise enough to determine which regime is most prevalent. The arterial haematocrit is another factor that has been shown experimentally to influence the BOLD response. Since hematocrit varies systematically between selected groups of subjects (e.g. men and women) this may have large practical implications. Current modelling shows that the effect of haematocrit itself is minor but that BOLD magnitude may be affected by concomitant flow changes.

## Brain Mapping

Together with Axel Larsen and Claus Bundesen from the Department of Psychology Kristoffer H. Madsen and Torben E. Lund have been working on a project entitled: "Images of Illusory Motion in Primary Visual Cortex". By presenting two stationary successively flashing visual stimuli at different spatial locations it is possible to generate illusory visually perceived motion. Even though this phenomenon is well known and accepted, little is known about the neurophysiological origins. Using fMRI and presentation of visual stimuli, as described above, it was possible to show that cortical activation, similar to that of real motion, is observed along the path of illusory motion in the primary visual cortex. The results suggest that a feedback mechanism in the brain helps us to perceive



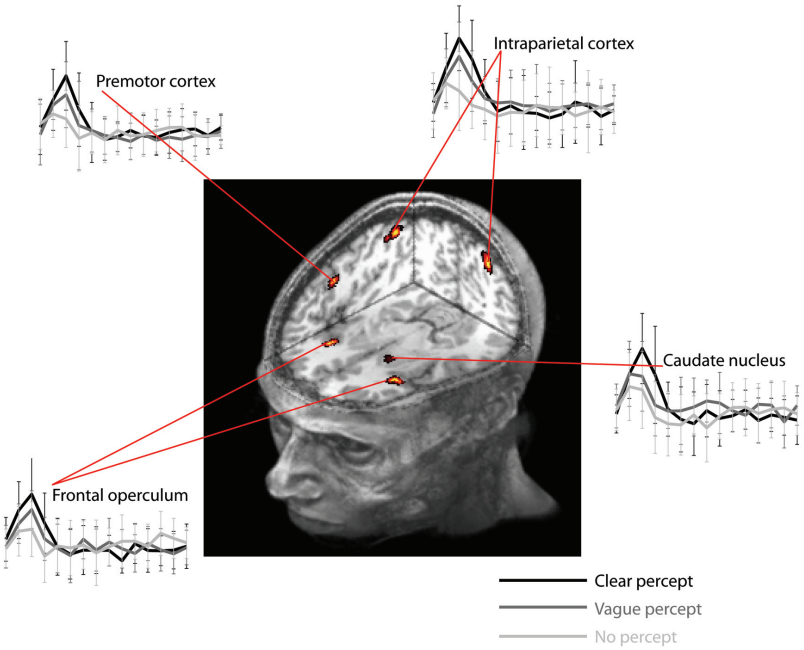

*The figures (a-d) are left occipital cortex activation maps of a single subject. Figure (a) shows activation related to two simultanously flashing dots (marked FD) (no illusory motion), the black dotted line shows the calcarine sulcus as determined by a retinotopic mapping experiment. Figure (b) shows activation related to a flashing bar connecting the two dots in red (blue activation is related to the two simultaneously flashing dots), the dotted black line once again denotes the calcarine sulcus. Similarly, figures (c) and (d) show activation related to real motion between the dots (green) and illusory motion (yellow).*

illusory motion in a way similar to how a real movement would have been perceived. This work has been accepted for publication in the Journal of Cognitive Neuroscience.

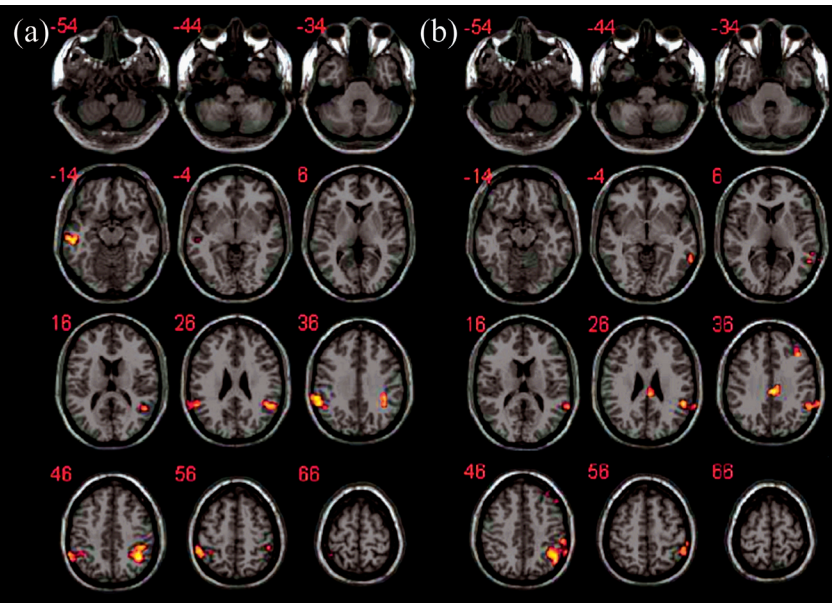
As a part of his PhD project, Mark Schram Christensen has, together with Thomas Z. Ramsøy,Torben E. Lund, Kristoffer H. Madsen and James B. Rowe, investigated visual perception using fMRI. They have shown how activation of brain structures in intraparietal cortex, premotor cortex, and the basal ganglia correlates with the subjective experience of conscious perception of visual objects. Activation in these areas increased gradually when percepts changed from being absent to vague to clear. This work has been accepted for publication in NeuroImage.

As a follow up on experiments in her PhD project, Daniela Balslev has, together with Finn Årup Nielsen, Torben E. Lund, Ian Law, and Olaf B. Paulson investigated the ability to recognize feedback from one's own movements as opposed to others' movements. This is important for motor control and social interaction. The neural processes involved in feedback recognition are incompletely understood. Two competing hypotheses have been proposed: the stimulus is compared with either (a) the proprioceptive feedback or with (b) the motor command, and if they match, then the external stimulus is identified as feedback. Hypothesis (a) predicts that the neural mechanisms or brain areas involved in distinguishing self from other during passive and active movement are similar, whereas hypothesis (b) predicts that they are different. In an fMRI study, healthy subjects saw visual cursor movements that were either synchronous or asynchronous with their active or passive finger movements. The aim was to identify the brain areas where the neural activity depended on whether the visual stimulus was feedback from one's own movement and to contrast the functional activation maps for active and passive movement. The investigators observed activity increases in the right temporoparietal cortex in the condition with asynchronous relative to synchronous visual feedback from both active and passive movements. However, no statistically significant difference was found between these sets of activated areas when the active and passive movement conditions were compared. These results do not support the hypothesis that recognition of visual feedback during active and passive movement relies on different brain areas. This work has been accepted for publication in NeuroImage.

This year, DRCMR investigator Martin Skov has continued working on the neurobiology of aesthetic preferences. Aesthetic preferences are emotions




*Single subject structural MRI with functional overlay of areas showing a gradual increase in activation when visual objects are perceived more clearly.*




*Clusters of voxels showing significant activity increase in the asynchronous compared with the synchronous condition during active (a) and passive (b) movement.*

that guide behaviour in a variety of situations, chiefly reproductive and hedonic. Darwin was the first biologist to recognize, in The Descent of Man (1871), how, in many species, members often evolve extraordinary traits in order to attract the other sex. The ability of traits such as tails, colours, or vocalization to function as attractors rests on their ability to arouse feelings of aesthetic preference. We now know the main outline of the system responsible for establishing aesthetic preferences in the human brain, but exactly how its sub-components interrelate is still unclear. Are aesthetic feelings such as "beautiful" or "ugly", for instance, rooted in more basic emotions such as positive and negative valence? Together with Mark Schram Christensen, James Rowe, and Olaf B. Paulson, Skov tested this question in an fMRI paradigm where subjects were asked to rate affective photographs according to how "beautiful", "ugly" or "neutral" they found them to be. Since the scenes depicted in the photos displayed either a very positive, a neutral, or a very negative affective valence, it was possible to tell if the subjects' aesthetic judgments were conditioned by this valence or not. It turned out that all subjects found some of the photos with a positive affective valence "ugly", and some of the negative photos "beautiful". Furthermore, the imaging data indicate that the experience of a photo with a negative affective valence as "beautiful" requires activation of a different neural network than the experience of a positive photo as "beautiful" (see Figure). This work was presented at the 11th annual meeting of the Organization for Human Brain Mapping.

Safety Evaluation

It is imperative that MR examinations are performed safely. In 2005, the DRCMR took on an assignment for Coloplast, a company that makes chemically active dressings for wounds. Customers were questioning the MR safety and compatibility of dressings containing silver. Consequently, Lars G. Hanson, Lise Vejby Søgaard and Karam Sidaros conducted relevant analyses and tests for specific Coloplast products. In order to establish whether the dressings were MR safe and compatible, a risk assessment was made based on the chemical and physical properties of the dressings and on the worst-case conditions under which they might be used. The risk assessment eliminated safety concerns. Experimental testing verified the predictions and demonstrated preservation of image quality, even for sensitive sequences. Hence, the dressings in question were found to be safe and MR compatible under the considered worst-case conditions.

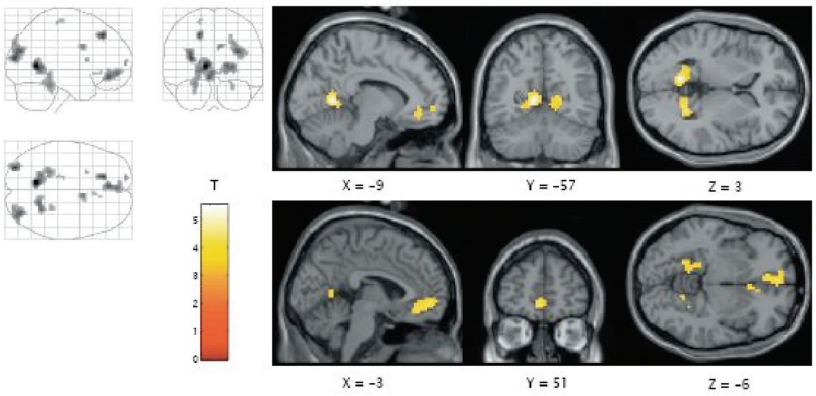



*Figure illustrating activation related to making a judgment of affective photos as beautiful, regardless of the affective valence.*

# Clinical Body Research

## Pulmonary Function

Imaging of the lungs poses a number of difficulties with respect to traditional MRI. Large susceptibility differences at the air-tissue interfaces causes the 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.

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

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

The PHIL project was very successful. The project finished in 2004 and altogether 35 subjects were scanned at the DRCMR, nearly all resulting in very high quality images. The results have been analyzed together with results from the other participating centres. Specialists in radiology and nuclear medicine scored the MR images as well as the images from CT and Kr scintigraphy studies in order to make detailed comparison of the techniques. Trine Stavngaard defended her PhD thesis in October 2005. The thesis entitled “New imaging techniques in COPD” included the locally acquired PHIL results.

Lise Vejby Søgaard and Trine Stavngaard are locally responsible for MR lung imaging techniques at DRCMR and are in an ongoing project, investigating the development of the apparent diffusion coefficient (ADC) in patients with alpha-1-antitrypsin deficiency. The ADC measured with hyperpolarized $^{3}$He is indicative of the alveolar sizes in the lung. The patients have been so far been imaged at baseline and after one year. A final follow-up scan after two years will be conducted in 2006. In addition, studies in lung-healthy volunteers are performed to investigate the long-term reproducibility of ADC measurements as well as the relationship of ADC with inspiration state.

## Cardiac Function

The influence of simple obesity on heart function is being studied by Dorthe Pedersen. Two projects are now in their final stages. In one study, left ventricular function, geometry and potential anti-remodelling effects are measured following weight loss in obese men and women. This project aims to investigate the influence of simple obesity, body composition and weight reduction on left ventricular mass, function and neurohormonal activation. It also investigates whether there is a correlation between neurohormonal activation and left ventricular mass in obese people. Neurohormonal activation is an activation of different neuroendocrine systems as in, for example, the renin-angiotensin-aldosterone system and sympathetic nervous system. A second aim is to evaluate left ventricular mass and endothelial function to elucidate the pathophysiology underlying increased left ventricular mass in simple obesity, which is only partly explained by increased blood volume and increased lean body mass. In myocardial hyperthrophy/increased left ventricular mass, due to conditions such as arterial hypertension and haemodialysis, an association is found with decreased endothelial function, which again is correlated to an increased risk of cardiovascular events. It has yet to be investigated if increased left ventricular mass and decreased endothelial function is correlated in simple obesity. In this project 58 obese men and women, with a body mass index (BMI) above 33kg/m$^2$, participated. All were examined initially and after 8 weeks following a 7% reduction in bodyweight. Forty-two came back for a final examination one year later. At every visit, cardiac MRI, abdominal MRI and DEXA scanning were carried out and blood samples were drawn. The blood samples will be analysed for component of the neuroendocrine systems and other markers known to be predictors for cardiovascular disease.

The second study is a cross-sectional study where 30 obese men and women, with a BMI above 30 kg/m$^2$, and 26 subjects with normal weight, underwent cardiac MRI, abdominal MRI, DEXA scanning and endothelial function test and had blood samples taken. As in the first study, the blood samples were analysed

for neuroendocrine activation and cardiovascular and endothelial markers including hsCRP, homocystein, BNP, endothelin, selectin I-CAM , V-CAM. The last MR data were acquired in 2005. Data are now being processed and evaluated, and will form the basis for Dorthe Pedersen's PhD thesis.

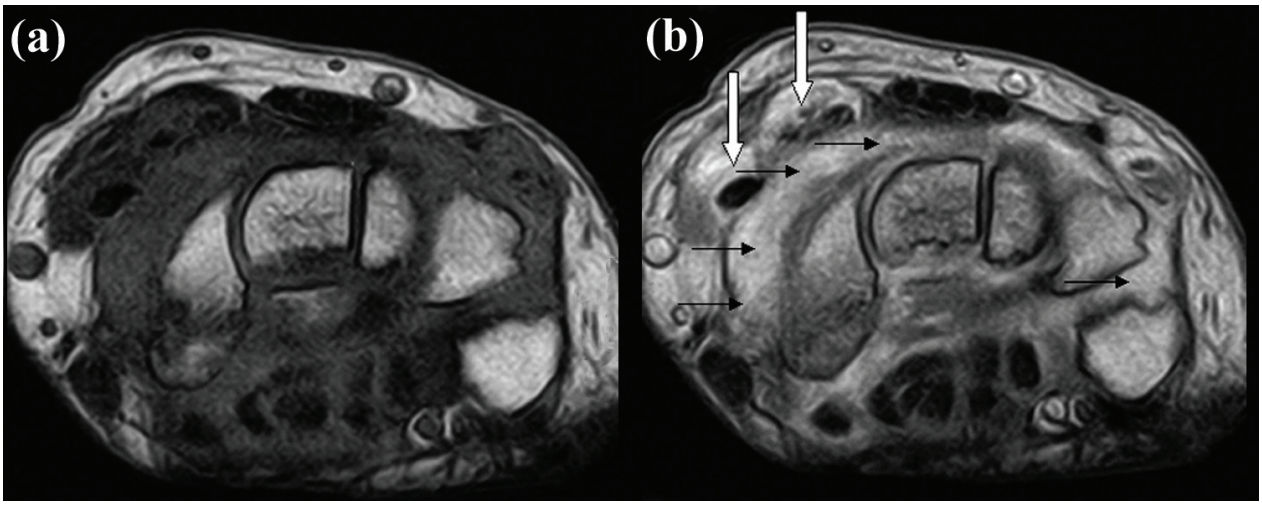
In 2005, Susette Krohn Therkelsen defended her PhD thesis where MRI was used to study the atria and the left ventricle in middle-aged normal subjects, in patients with permanent atrial fibrillation and in patients with persistent atrial fibrillation before and after cardioversion. In collaboration with the cardiology laboratory at the University of Copenhagen, right and left atrial as well as left ventricular dimensions and systolic function were measured by cardiac MRI in normal subjects, in patients with permanent atrial fibrillation (AF) and in patients with persistent AF before and after conversion to sinus rhythm. In addition, a range of neurohumoral substances were measured along with atrial measures acquired with echocardiography and signal-averaged-p-wave duration, which is an estimate of the intra-atrial conduction time of the sinus node impulse. The normal subjects served as controls for the patients with AF, and also formed the basis of a small introductory evaluation study to estimate the accuracy of the atrial measures. Whilst being primarily descriptive, the study was designed to evaluate whether the cardiac measures or the plasma level of the neurohumoral substances possess any potential as prognostic markers for the risk of recurrent AF after successful cardioversion.

## Inflammatory joint diseases

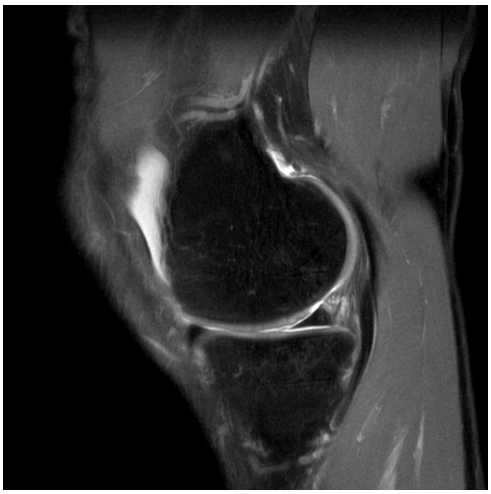
An increasingly aggressive therapeutic strategy, improved treatment options, and encouraging preliminary results have attracted growing attention to the potential of MRI in the diagnosis, prognostication and monitoring of rheumatoid arthritis (RA). MRI offers multiplanar imaging with unprecedented soft 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.

A PhD study, conducted by Bo Ejbjerg, was finalized is 2005. In this study, MRI methodology was applied with special focus on small extremity joints, especially in the hand, which are often affected in rheumatoid arthritis. Specific aims, which are evaluated in a series of studies involving comparisons with clinical, radiographic and histopathologic parameters, include investigation of the following:

1) Which MRI sequences are the most sensitive for evaluating joint inflammation and destruction
2) Whether qualitative or semi-quantitative methods can provide information similar to more time-consuming quantitative methods
3) Whether very detailed examination of a few joints is more sensitive to changes in rheumatoid inflammation and destruction than less detailed examination of many joints




*Pre- (a) and post-contrast (b) T1-weighted MR images of a rheumatoid arthritic wrist, showing synovitis and tenosynovitis.*

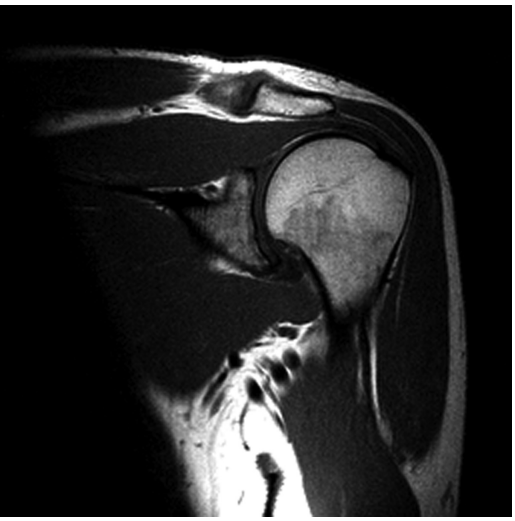


*Sagital slice through a knee with cartilage degeneration, acquired at 3T.*

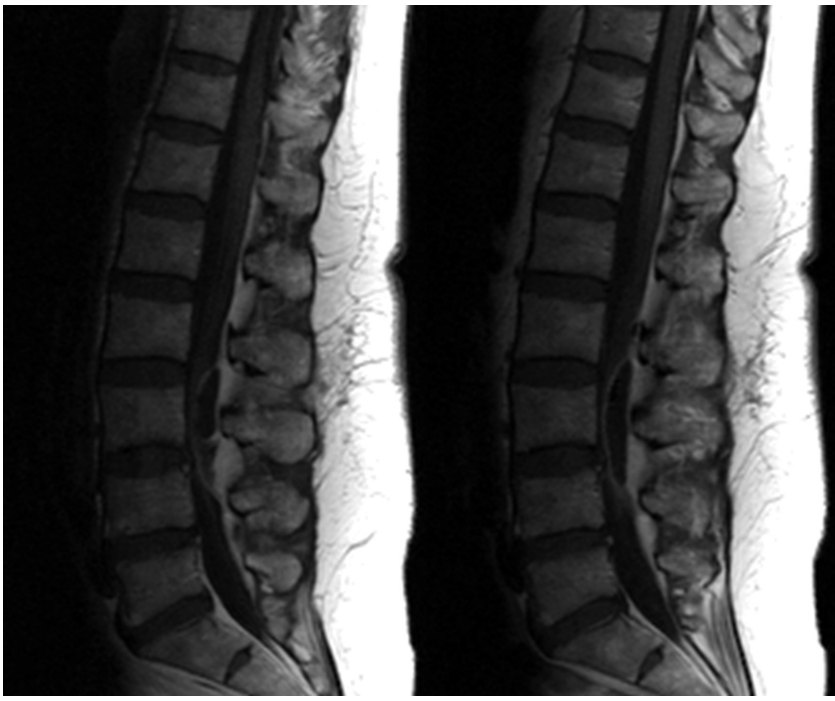
4) Whether a low-cost dedicated extremity MRI unit can provide similar information as "conventional" expensive high-field MRI units
More PhD studies within the area of MRI and ultrasonography in RA and other inflammatory arthritides, building on these experiences, are ongoing.

In addition to research undertaken in the context of PhD projects, the rheumatology group participates in an international collaboration concerning MRI definitions, scoring methods and validation in rheumatoid arthritis. In general MRI scoring methods of RA joints are insufficiently validated, and as a consequence of this an "OMERACT-MRI" study group have since 1999 worked on developing definitions of RA changes and on developing and testing scoring methods. OMERACT is an international forum with expertise in MRI in RA and in scoring methodology, which performs validation studies and seeks consensus within Outcome MEasures in Rheumatoid Arthritis Clinical Trials. In 2003-2004, the main task has been to develop "the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas". Using this, MR images of wrist and metacarpophalangeal joints of patients with rheumatoid arthritis can be scored for synovitis, bone oedema and bone erosion, guided by standard reference images. 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 3 Danish multicentre studies of RA and spondyloarthritides. In a longitudinal multi-centre study of 160 early RA patients ("CIMESTRA"), the aim is to investigate the value of MRI as outcome measure and prognostic marker in early RA, compared with routine clinical, biochemical and radiographic parameters.



*Typical appearance of muscle and bone in a normal left shoulder*



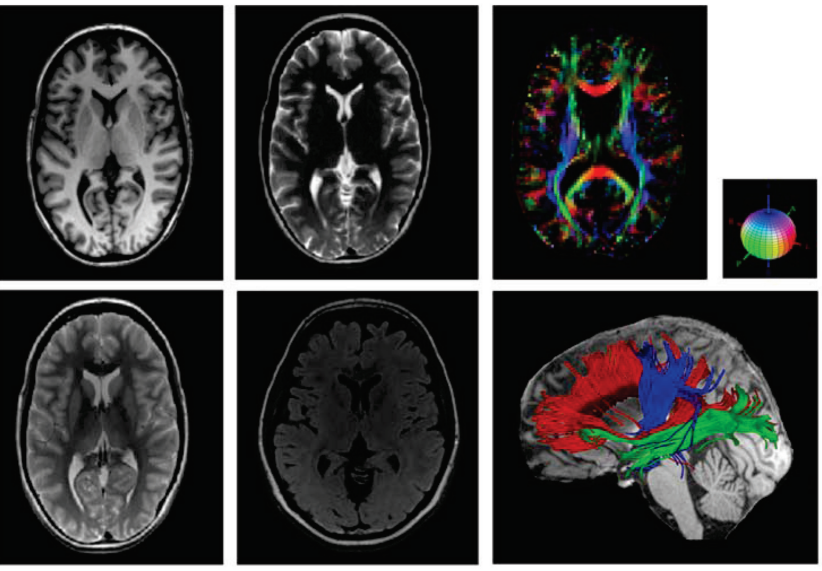
*Example of an epidural lumbar abscess*

# 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.



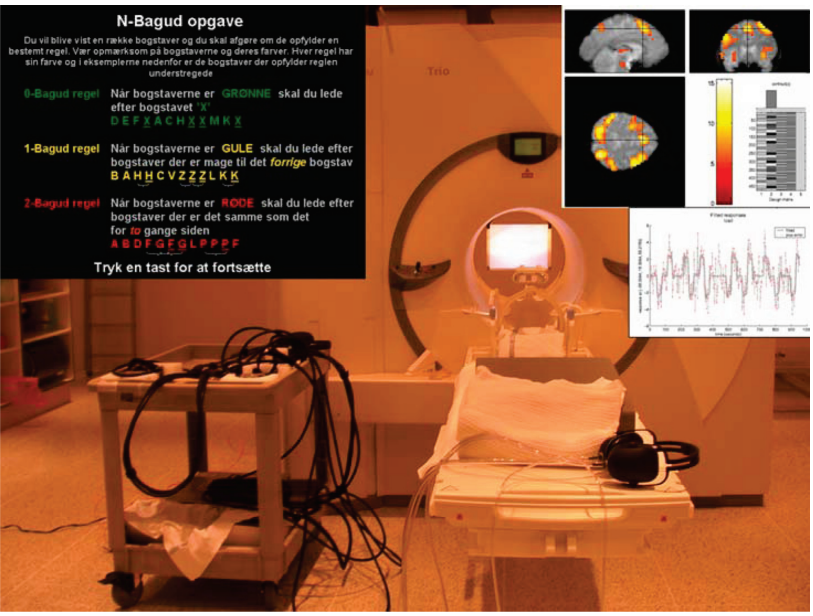
*First row from left to right: T1 weighted, T2 weighted, and diffusion tensor: fibre directions: red = left-right, blue =top-down, green = front-back. Second row from left to right: proton density weighted, FLAIR, and fibre tracks.*

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

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

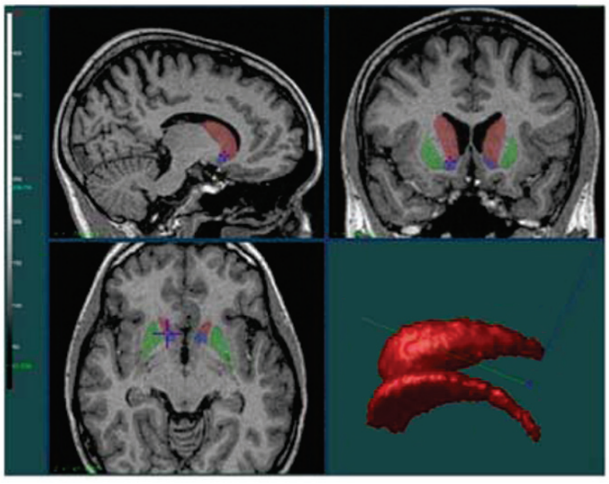



*Typical setup for an fMRI experiment. A N-Back working memory task is shown as an example. The task is projected on a screen in the magnet, visible to the subject through a mirror attached to the head coil. In the upper right corner, a typical activation map of a healthy subject is shown, depicting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

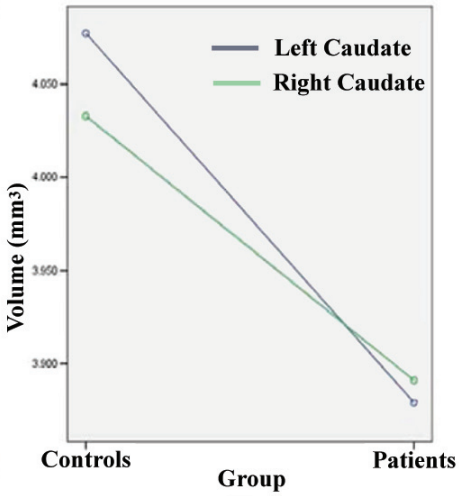
Psychiatrist Maj Vinberg is the clinical researcher responsible for the affective disorder project (A1). In this project healthy mono– and dizygotic twins (age > 18 years) with a high and a low risk of developing affective disorder are investigated. The degree of risk depends on zygosity and the diagnostic 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. To date, 176 twins have undergone MR investigation.

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 (S2 "Structural and functional brain changes in drug-naïve first-episode schizophrenia patients: relation to cognitive function and anti-psychotic medication"); Katrine Pagsberg (S3: "Structural and functional brain abnormalities in early onset first-episode schizophrenia") and (S4: "First episode psychotic children and adolescents: a 5 year follow-up study of brain structure and function"); Bettina Søholm (S5: "Pharmacological treatment of cognitive deficits in schizophrenic patients: The effects of central cholinergic augmentation on cognitive deficits, and psychopathology") and Hannah Bro (S6: 5-10 year follow-up of schizophrenia patients: "Skizofreni: Sygdomsprocessens kliniske, psykofysiologiske og neurobiologiske manifestationer"). Data acquisition for projects S1 and S3 was completed by the end of 2002. Project S5 was completed in the middle of 2005. In 2003, data acquisition commenced for projects S2 and S4 and remains ongoing. Project S6 started towards the end of 2004 and is ongoing.

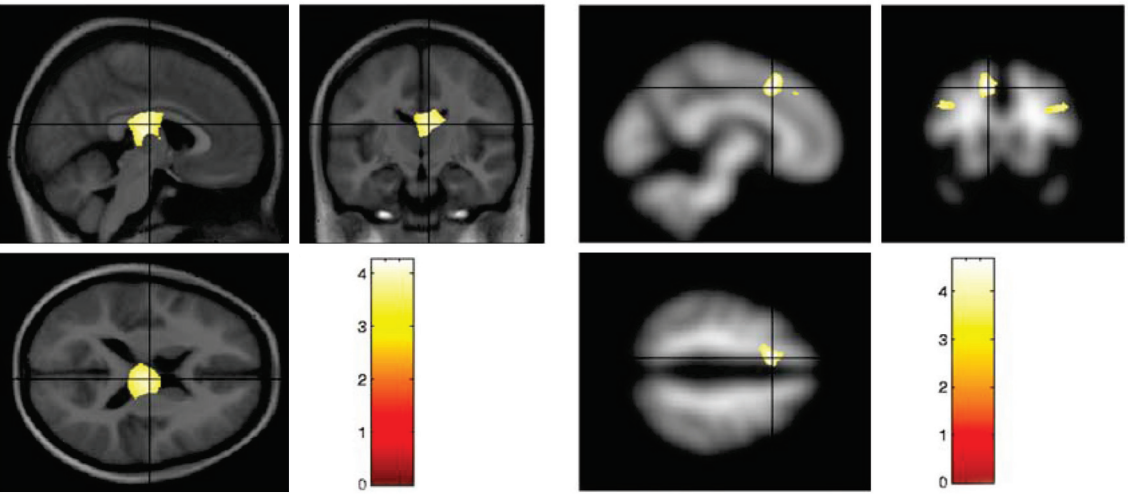
In project S1, 16 antipsychotic drug-naïve and 3 minimally medicated first-episode schizophrenic patients and 19 matched controls participated. Patients were randomly assigned to treatment with either low doses of the typical antipsychotic drug, zuclopenthixol, or the atypical compound, risperidone. 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.



*Left: delineation of volumes of interest was done in DISPLAY, which allows simultaneous tracing in 3 planes: Red = caudate nucleus, green = putamen, and blue = nucleus accumbens. Right: Group x Hemisphere interaction, with controls having larger left than right caudate nuclei and patients having marginally larger right than left caudate volumes.*



# Clinical Brain Research




*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.*

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 an 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.

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.

## Brain Aging and Neurodegenerative Disorders

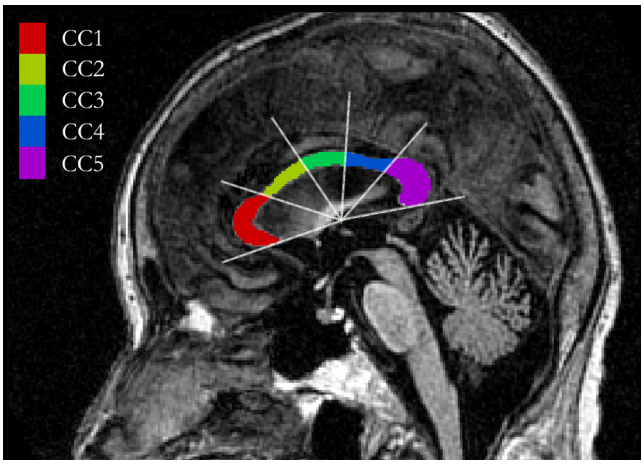
The Centre is the site of several studies of normal aging and the neurodegenerative disorders that afflict the elderly; and is a participating site in a broader multi-site investigation by European Union collaborators entitled, “Leukoaraiosis and Disability in the Elderly” (LADIS). The latter is an ongoing structural MRI study of the known changes that occur with aging in the white matter of the brain. The objective is to describe better the predictors and consequences of these changes. Older volunteers were scanned at entry into the study and most of them have now been scanned again for their 3-year follow-up. 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, 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 Mikkel Stegmann at the Technical University of Denmark, who developed an automated method to recognise and quantify the volume of this structure. The full dataset of 569 subjects have been analysed, and correlations with several measures of cognitive and motor performance were demonstrated. Notably, these effects seems to be additive to the effect of age related white matter changes per se. The results have been presented at the international congress of vascular dementia (“VASCOG 2005”), and have been submitted for full publication. The DRCMR also con-

tributed to a related study of white matter changes in relation to medial temporal lobe atrophy and memory in the LADIS population.

Two important DRCMR subprojects have developed from the LADIS initiative, both involving the development of advanced methods for automated measurement of abnormalities in cerebral white matter. Tim Dyrby is developing and validating tissue segmentation methods that rely on artificial neural network algorithms. 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 the automated method. The high variability in quality of this very large multi-centre image dataset is a significant obstacle and is the subject of current efforts.

A second subproject of the LADIS investigation is derived from the work of Mikkel Stegmann, 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. Further development of these new mathematical techniques include automated methods for determining the mid-sagittal plane of a 3D acquisition was presented at a 2005 SPIE meeting.




*Segmentation of corpus callosum (CC) areas obtained from a mid-sagittal MRI section. A variant of the Witelson radial partitioning schemes was used for regional analyses of the corpus callosum. CC1: rostrum and genu, CC2: rostral body, CC3: midbody, CC4: isthmus, CC5: splenium.*

Thomas Ramsøy is leading a project in the Centre that focuses on the function of an area of the brain often affected very early in Alzheimer's disease. This year, the team working on this project presented their findings at the Annual Meeting of the Organization for Human Brain Mapping showing that specific fMRI methods can be used to investigate the function of these small regions. A second report at the Conference on the Prevention of Alzheimer's Disease described the range of variability observed among different people in the exact site of brain activation, and explained the implications of this observation for designing a new method for detecting dysfunction in these regions for clinical purposes in the future.

Katja Krabbe of the DRCMR, together with collaborators from Bispebjerg Hospital, is completing a study of patients with patients with Parkinson's disease (PD) and the related disorder, multiple system atrophy (MSA). This project employs several MR modalities with the aim of finding better methods for differential diagnosis of the disorders. Findings of increased intracranial volume in PD and decreased volumes of substantia nigra and basal ganglia in both PD and MSA have been published. Furthermore significant differences in diffusion characteristics between the two diseases have been found.

This year, Terry Jernigan and her colleague Anthony Gamst contributed to a discussion published in the international journal, Neurobiology of Aging, integrating the results of several studies of brain structure changes associated with normal aging. The contribution by Jernigan and Gamst drew attention to the many consistencies among the studies and described some of the reasons that earlier findings appeared to provide discrepant findings. Key among the reasons was the lack of appreciation by many investigators that the effects across the age-range were in some cases nonlinear, and thus the results were strongly influenced by the particular age range that was examined in the studies.

The investigators at the Centre continue to be active contributors to the international literature on normal aging and disorders of aging. Of note, at the end of 2005, Terry Jernigan was named as Section Editor of a new section on Imaging for the Neurobiology of Aging, a leading international journal on aging. This appointment underscores both the increasing role of brain imaging in aging research, generally, and the Centre's key role in this research.

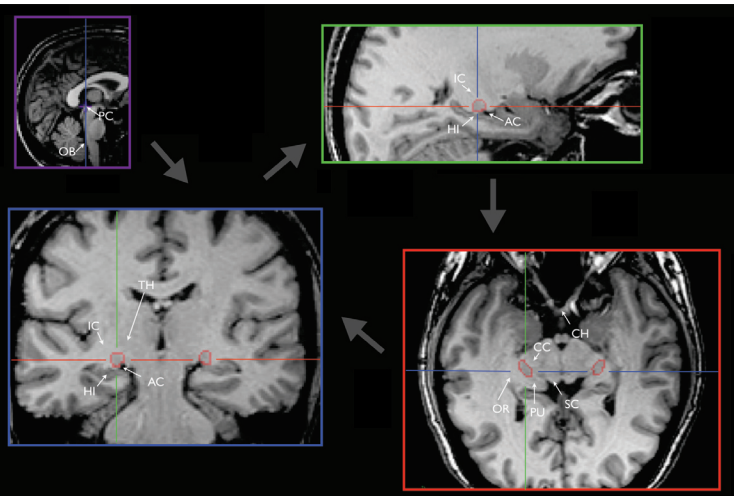
# Clinical Brain Research

## Multiple Sclerosis

The DRCMR has a long tradition of combining MR and multiple sclerosis (MS) research. In 2005, Henrik Lund and Kirsten Nielsen were working full time in this field. A major part of this research is performed in collaboration with external groups and thus has an extensive multidisciplinary input ranging from molecular biology and pathophysiology to 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 high-field scanner (Siemens Trio, 3 T), installed in the department in 2002, is showing its worth in MS projects, and both the projects by Henrik Lund and by Kirsten Nielsen are carried out on this scanner. Initially, a radiological comparison of scans obtained at 1.5 T and 3 T of patients with acute optic neuritis (ON) was performed by Kirsten Nielsen. This project has been completed and the results have been published in a special issue on 3 Tesla MR in Investigative Radiology.

Acute ON is the onset manifestation in 20% of patients later diagnosed with multiple sclerosis.




*To investigate the activation in the lateral geniculate nucleus (LGN) during visual stimulation of patients with optic neuritis, the LGN was delineated on structural images. The posterior commissural (PC)-Obex plane is the preferred coronal plane for visualisation of LGN. On T1-weighted images LGN is a region of the same or slightly higher signal-intensity than cortex, located above the hippocampus (HI) and the ambient cistern (AC), and beneath and lateral to the thalamus (TH). Laterally, LGN is bordered by the optic radiations (OR). After delineation of the LGN borders, statistical analysis of the ROIs, co-registered to the functional images, was performed.*

Symptoms include impaired vision and pain on eye movement, and typical signs are abnormal colour vision, decreased contrast sensitivity, abnormal visual evoked potentials and decreased visual acuity. The disease mainly affects young people and median age of onset is 30 years.

In acute ON, an effective recovery is often observed weeks or months after onset of symptoms, however, this recovery still remains mainly unexplained. Factors like remyelination of the optic nerve and adaptive changes taking place in the visual cortex, may contribute. To investigate this recovery process in more detail, Kirsten Nielsen and collaborators are performing a study on functional activation in patients with acute ON. Thirty patients have been included (inclusion finished in November 2005). Patients are scanned serially at four time points over a six month period, the first scan taking place in the acute phase of the disease and the remaining scans performed during recovery. Twenty-five patients have received their final scan and a large mass of data has been collected. Two different paradigms are used for visual stimulation: a full-field black and white flickering checkerboard, and a retinotopic mapping paradigm consisting of a rotating wedge and an expanding/contracting ring of flickering checkerboard.

With current functional MRI techniques and full-field visual stimulation, it is possible to map the activation in the lateral geniculate nucleus (LGN), which is a small nucleus in the visual pathway receiving inputs from both eyes, and in turn projecting to the visual cortex. The first subproject deals with investigations of the activation in the LGN during recovery from ON, and to accomplish this, the LGN is delineated on high-resolution structural MR images prior to the statistical analysis of the functional low-resolution images. Our preliminary results suggest that during recovery of vision, the activation in LGN returns to normal, indicating that the input reaching the LGN returns to normal during recovery. This might suggest that at least part of the recovery process takes place in the optic nerve.

The second subproject deals with the retinotopic (re)-organization in the visual cortex to investigate the hypothesis that cortical adaptive changes take place during recovery from acute ON. Data analysis is about to commence. Both projects are carried out in collaboration with the Department of Neurology, Glostrup.

In another project, the pathological mechanisms of MS are investigated quantitatively by applying three different MR-techniques to a group 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. All patients are newly diagnosed and will be scanned three times – just before start of treatment, after 3 months and again after 6 months. The outcomes are subsequently correlated to a vast range of immunological and neurological measures collected by our collaborators at Copenhagen University Hospital, Rigshospitalet.

The three different MR-techniques all aim at the exploration of structural changes caused by the pathology of MS. First, 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. However, this is correct only in perfectly homogenous media and not in vivo where the diffusion of water is hindered by tissue structures. q-Space analyses are based on several diffusion weightings and hence give more detailed information on the structures and the sizes of the tissue compartments. For example, this technique will be used to analyse the water diffusion orthogonal to the fibres since 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 will possibly give rise to more diffuse changes. Hence, the approach is expected to provide information on diffuse as well as on focal pathologies. The data analysis and interpretation will be performed in collaboration with Sara Brockstedt and Jimmy Lätt, both at Lund University, Sweden and with Lars G. Hanson, DRCMR.

In addition, two methods are being implemented to gain insight into the breakdown of the blood-brain-barrier. After contrast injection, focal enhancing lesions appear hyperintense on T1-weighted scans because the contrast agent accumulates in tissue surrounding a broken blood-brain-barrier, increasing the MR signal. It is hypothesized that a subtle breakdown of the barrier in regions that do not appear as a focal lesion 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. Finally, in collaboration with physicist Irene K. Mikkelsen from the University of Gothenburg, Sweden, methods are set up to investigate the water exchange over the blood-brain-barrier. Simply due to the water molecule's much smaller size compared to the contrast agent, these methods are potentially much more sensitive to changes in the integrity of the blood-brain-barrier.

## Prefrontal lesions

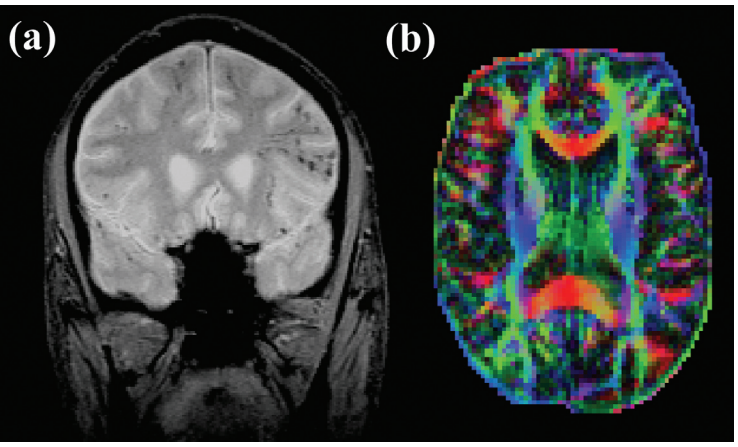
Our prefrontal cortex is essential for normal everyday behaviour and thought. Dysfunction of this region is both common and disabling. The region is vulnerable to injury by stroke, trauma or tumours, and to neurodegeneration in fronto-temporal dementias. Prefrontal cortical dysfunction is also a feature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

Recent functional neuroimaging studies by Katz Sakai and colleagues have shown that activity in prefrontal cortex can "preconfigure" cognitive processes in other regions, in expectation of future events. Functional imaging can provide information about activation of a region in association with performance of a task but not if a specific brain region is essential. To understand whether a brain region is necessary requires the study of the effects of damage to a brain region. By studying patients with focal damage to the prefrontal cortex, using neuropsychological and functional imaging techniques, we can learn much more about the essential functions of this brain region, and learn about the brain's ability to adapt and compensate following an injury.

In 2004, an international collaborative project was established, which included the DRCMR, to investigate the normal functions of the prefrontal cortex and the changes that follow injury to the prefrontal cortex. Five patients from RH volunteered, together with a control group of 19 healthy adults.

The Trio scanner at DRCMR provides high quality data, from which we will be able to determine how we use advanced information to prepare to remember information, how we remember the information itself, how we use such memories to make a decision, and

# Clinical Brain Research




*In severe head trauma, a common type of brain lesion is microscopic diffuse axonal injury. When diffuse axonal injury is accompanied by haemorrhage, it appears as scattered black dots on a conventional T2*-weighted gradient echo MRI sequence (a). However, the vast majority of these microlesions remain undetected by conventional imaging. Diffusion tensor imaging (DTI) allows for the quantitative measurement of the degree and directionality of water diffusion, providing a means of studying tissue microstructure (b). This advanced technique might provide a sensitive tool for quantifying diffuse axonal injury.*

what happens to each of these processes after brain damage. Due to the relationship between general intelligence and the extent of prefrontal cortex activation, we have used two additional tests to estimate the IQ of patients and healthy volunteers. The data from this large and complex study is currently being analysed by the principal investigator James Rowe. Results are expected mid 2006, focusing on the relationships between brain activity, working memory and cognitive control in healthy subjects, and the brain plasticity that allowed successful task performance following localized damage to the prefrontal cortex.

## Traumatic Brain Injury

Severe traumatic brain injury (TBI), predominantly caused by motor vehicle accidents, is the leading cause of death and long-term morbidity among younger age groups in Western countries. The final outcome of severe TBI is both highly variable, ranging from almost full recovery to persistent vegetative state, and extremely difficult to predict, especially in cases of prolonged unconsciousness. The most important type of primary neuronal injury in severe blunt TBI is diffuse axonal injury, a microscopic lesion type caused by axonal shear. One of the predominant sites of this injury type is the corpus callosum, where a high number of axons cross the midline connecting the cerebral hemispheres. In the acute trauma phase, episodes of low blood pressure or lack of oxygen often occur, adding to hypoxic-ischemic brain injury resulting in a poorer outcome. Together, these two diffuse type brain lesions are thought to be the major determinants of outcome following severe TBI. However, the extent of both lesion types is highly underestimated by conventional imaging. Advanced quantitative MR techniques have the potential to improve detection of these important lesions and provide useful clinical tools for outcome prediction.

Annette Skræp Nielsen heads a PhD project on TBI in collaboration between the DRCMR and the Department of Neurorehabilitation, Brain Injury Unit, at Hvidovre Hospital. In this project, adult patients with severe TBI, previously transferred from other neurosurgical units in the Copenhagen area to Hvidovre Hospital for rehabilitation, are scanned at 5-10 weeks and 1 year post-injury. The project applies advanced MRI methods with the dual aims of better lesion characterization in the post-acute phase and the identification of key imaging parameters that can be used to predict long-term outcome. Of particular interest are diffusion tensor imaging (DTI) for quantification of diffuse axonal injury, and spectroscopy, with whole-brain coverage, for detection of hypoxic-ischemic changes. During rehabilitation, patients are regularly assessed and their clinical status rated. Clinical outcome is evaluated at 1-year post-trauma using the Glasgow Outcome Scale. Thirty patients, together with a similar number of healthy controls, are being studied. In addition, a few patients that have been resuscitated from cardiac arrest are also included in order to characterize and compare changes caused by 'pure' hypoxic-ischemic events. Preliminary results from DTI investigations strongly indicate diffusion abnormalities in the corpus callosum of TBI patients. Interestingly, these diffusion abnormalities significantly change between the two scan time points, suggesting progressive axonal degeneration occurring several months following severe TBI. The relevance of these findings to long-term clinical outcome is currently being evaluated. 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

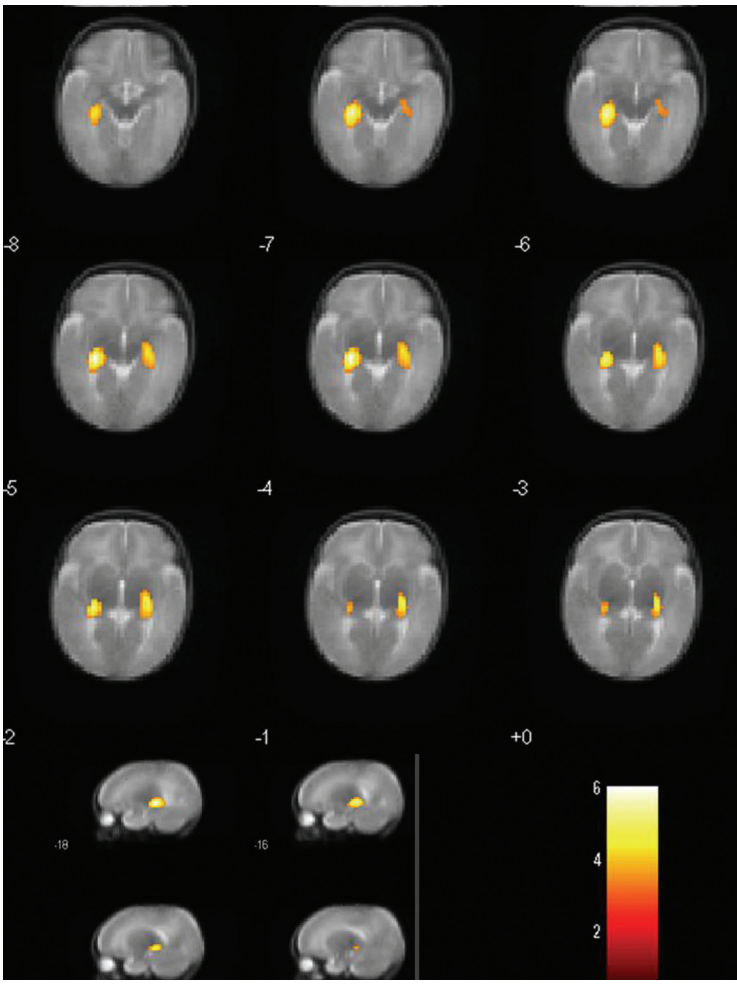
Infants born prematurely are at risk of brain injury and neurodevelopmental deficits in later life. The pathogenesis of brain lesions is still controversial but apparently both infection in pregnancy and perinatal

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 aims at including 200 premature infants born at either Hvidovre Hospital or Rigshospitalet at a gestational age (GA) less than 33 weeks. The placenta is histologically and microbiologically examined by a pathologist, while blood from the umbilical cord is examined for bacterial endotoxins and several inflammatory cytokines. These data will be compared with the number and extent of brain lesions and lactate accumulation found in MR scans performed at term-equivalent age. Other 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 MR spectroscopy (MRS) and DTI data are being analyzed for the first 100 infants recruited from Hvidovre hospital.

In 2006-07, infants born at a GA less than 28 weeks at Righospitalet will be included in the study and will undergo MR examination at term-equivalent age. Infants with signs of inflammation of the umbilical cord and infants without will be selected and matched for 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.




*As the neonate brain matures the nerve fibres are myelinated, i.e. they are covered by a protective layer of 'insulation'. Diffusion tensor imaging makes it possible to follow this process because myelinisation restricts water diffusion across the nerve fibres. In one project, diffusion images from prematurely and normally born children are compared, and mathematical analysis highlights areas where the diffusion is very asymmetric. Both groups are scanned shortly after normal time of delivery. The coloured areas show that diffusion was found to be more asymmetric (i.e. the tissue more mature) in preterm than in normal infants. It is likely that this difference reflects the increased stimulation of the preterm infants during their weeks of extra-uterine life, in which the term-born infants had only experienced for a few days at the time of scanning.*

Impaired autoregulation of the cerebral blood flow may be a major factor contributing to the development of brain damage in these infants. In the past years, studies of the cerebral circulation have been performed using different invasive methods such as xenon-clearance, PET and SPECT while other non-invasive approaches for estimating CBF, e.g. Doppler ultrasonography and near infrared spectroscopy have not accomplished the primary expectations. Maria J. Miranda and Karam Sidaros have therefore headed a

study to evaluate the feasibility of using ASL to measure neonatal cerebral perfusion. 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. 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. These results have been presented at several international meetings in 2004 and are now submitted for publication.

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. Both parts of the study have sent to international conference for presentation, and are currently under preparation for publication.

DTI data analysis was made 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

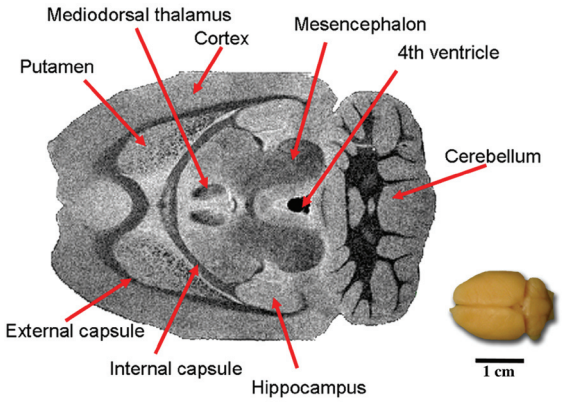
Investigation of the blood supply to different regions of the brain is central to the diagnosis of several neurological diseases. However, it is a practical obstacle that such perfusion measurements typically require very specialised scanning procedures, such as PET or especially SPECT, as well as injection 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.

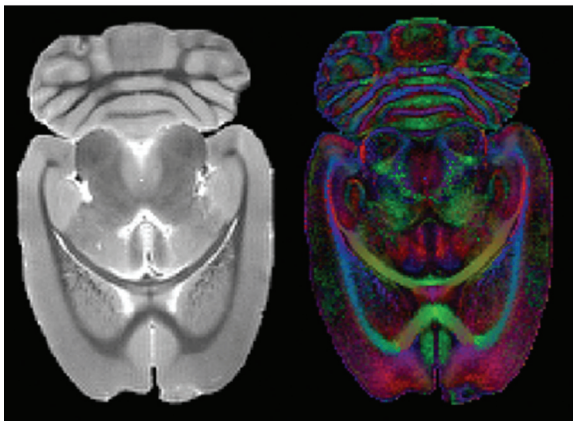
In a collaborative project with the memory clinic at Rigshospitalet, Karam Sidaros and Egill Rostrup are involved in non-invasively acquiring perfusion weighted MR images using a method called Arterial Spin Labelling (ASL). In this study, patients with Mild Cognitive Impairment (MCI) and healthy age-matched 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.

# Preclinical Research

In 2005, the Preclinical group consisted of two senior post-doctoral fellows, one PhD student, one MSc student and a technical staff member. This small group focuses, primarily, on longitudinal investigations of small animal models of disease. The group collaborates with a number of other groups within the Copenhagen area with an emphasis on brain disease and function, and cancer. This provides the opportunity for exciting multi-disciplinary projects to be performed with contributions from researchers with different scientific expertise and experience. In September 2004, the 4.7 Tesla MR system was upgraded by Varian to provide a modern and highly capable MR imaging and spectroscopy system. Since then, the system has been used in variety of projects as described below. To obtain the highest quality data, it is essential to refine the methods supplied by the manufacturer and to develop new ones. This has been an important aspect of the group's work in 2005.

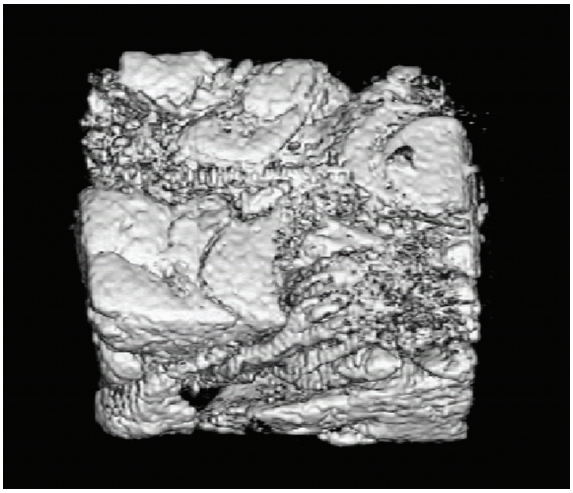
The group has been working in collaboration with the Institute for Molecular Pathology, University of Copenhagen investigating tumour angiogenesis. For a tumour to develop beyond approximately 1 $mm^3$, new blood vessels able to supply nutrients etc must also develop. The development of new blood vessels, known as angiogenesis, is obviously an essential step in tumour progression and is also an obvious target in cancer treatment. One aim of the work is to develop a method of assessing early vascular changes following administration of a drug targeted to tumour vasculature. When used with a cytotoxic agent, the combined drug efficacy is likely to depend on the timing between drug administrations. To optimize the timing, the time course of the vascular effects should be characterized. To this end, arterial spin labelling perfusion techniques have been implemented on the scanner together with fast T1 measurements able to follow bolus contrast agent administration. This is the subject of a PhD study that commenced towards the latter part of 2004. Components of the study will be performed in collaboration with the Johns Hopkins University School of Medicine, Baltimore during a planned visit in 2006.



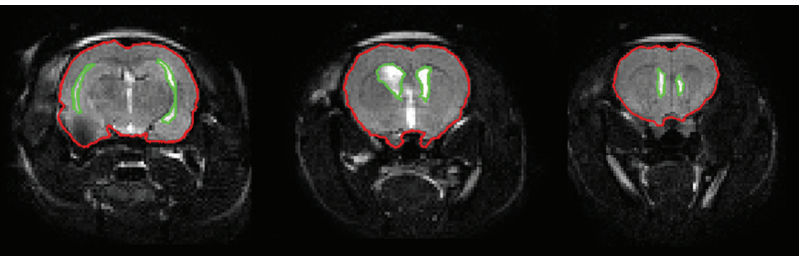
*High resolution ex vivo images acquired from a fixed rat brain. Detailed structure is apparent in the standard MR images (top and bottom left) and in the colour coded diffusion map (bottom right).*

The group is also involved with a number of other ongoing projects. Work has continued on the internal labelling of red blood cell ghosts. Red blood cell (RBC) ghosts containing commercially available super-paramagnetic iron oxides (Endorem) have been prepared and shown to be detectable using T2* sensitive MR sequences in vitro and in vivo. The use of commercially available iron oxides has the advantage of already being recognized as clinically safe if, for example, RBC ghosts released their contents prior to be taken up by the liver and spleen. Another project includes the study of amber with the aim of obtaining insight into the degradation of museum specimens. Preliminary studies have shown that it is possible to image amber that is relatively 'young'. Unfortunately, it has not proven possible to obtain sufficient signal from the museum artefacts. Investigations into the

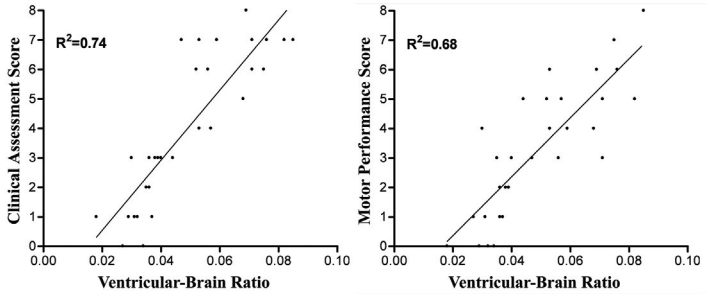


*3D representation acquired from a sample of amber. It is unusual to be able to obtain images from solids.*

# Preclinical Research



*Ventricular-brain ratios, calculated as the ratio of the areas of the ventricles (delineated in green) divided by the area of the brain (delineated in red), determined for three slices acquired using a T2W sequence in a meningitis rat model.*



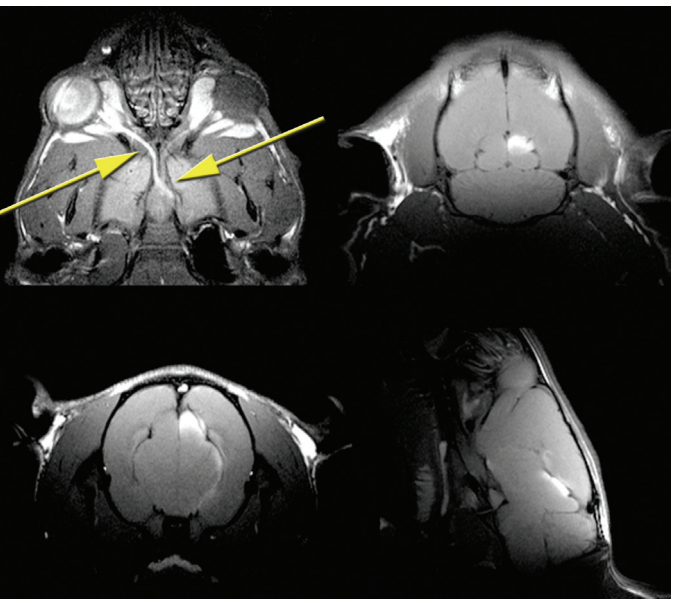

*Plots showing a relationship between the size of the ventricles and (left) clinical assessment and (right) motor scores. Expansion of the ventricles (hydrocephalus) with time during disease evolution would be expected to be a significant factor in the observed clinical status.*

nature of the origin of the MR signals will commence in the near future.

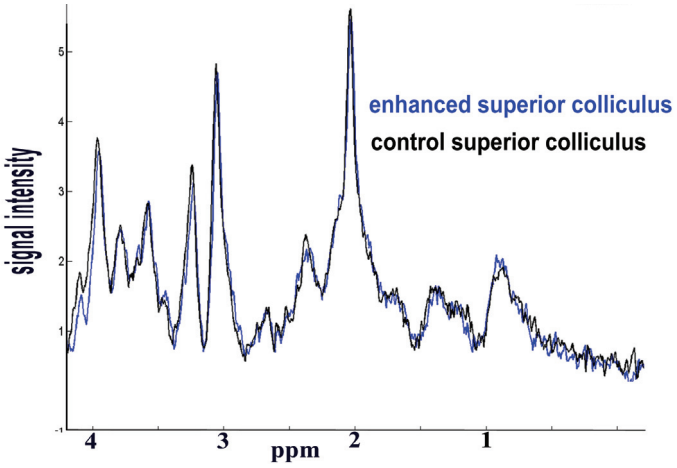
In 2005, the group has continued to work closely with the State Serum Institute with the aim of exploring the use of MRI as a means of monitoring experimental pneumococcal meningitis. Bacterial meningitis remains a life-threatening disease with significant mortality and morbidity. Development of acute hydrocephalus is a well-known disease characteristic complicating the course of bacterial meningitis and is associated with a mortality of ~50%. Consequently, we have continued to explore data acquired from rats studied for a period of up to 48 hours after infection. Using morphological images to measure the size of the ventricles in infected and control animals, we have compared these measurements with clinical scores. Clinical scoring involves assessment of the physical appearance and clinical characteristics of the animals such as, for example, the ability of an animal to grip a surface and hear a specific frequency noise. It is thought that production and re-absorption of cerebrospinal fluid is compromised in bacterial meningitis probably due to obstruction by bacteria/pus leading to acute hydrocephalus. In this experimental model of meningitis, expansion of the ventricles is detected at an early stage of the disease. The observed gradual increase in ventricular size was closely associated with the deterioration in clinical assessment and motor performance. As shown in the figures, this fascinating data shows a close relationship between the MR appearance of the animal's brain and its clinical status as the disease evolves.

As part of the meningitis work, the preclinical group also contributes to the DiMI project. The goal of this 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. The group has shown that the disease model developed at the Statens Serum Institut is a good model of the clinical disease and that MR methods are ideally suited to follow the course of the disease and identify key pathological processes. Consequently, the combination of the model and MR methodology is expected to be of significant use in quantitatively evaluating new therapeutics, such as antibiotics, in addition to other therapeutic strategies.

The paramagnetic properties of divalent manganese cations ($Mn^{2+}$) and their in vivo resemblance to calcium cations ($Ca^{2+}$) has led to their use in morphological and neural pathway imaging. $Mn^{2+}$ is taken up through $Ca^{2+}$-channels during neural activity and subsequently transported anterograde along microtubules at a velocity equivalent to fast axonal transport



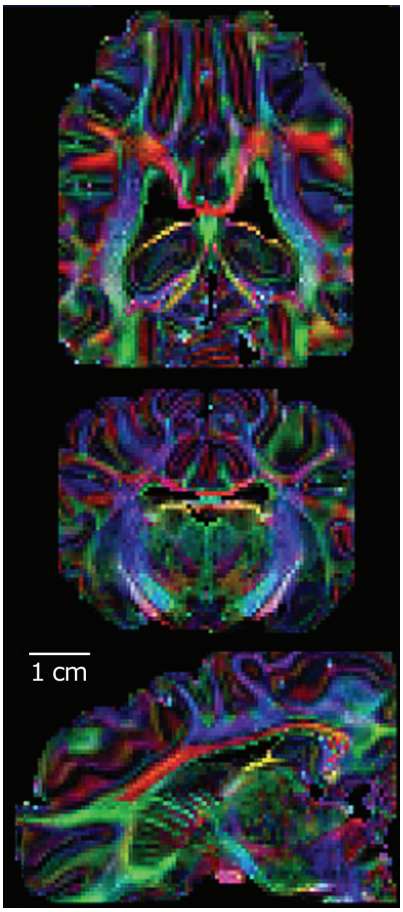
*T1W images acquired 24 hours after intravitreal injection of 3 µl of 50 mM $MnCl_2$ into the left eye of a rat. Note the transport of $Mn^{2+}$ from the left eye (arrowed, top left) crossing to the right superior colliculus (arrowed, top right) appearing as a hyperintense region (also in bottom left and right). The enhanced region in the right superior colliculus and the unenhanced left superior colliculus provides two adjacent regions to compare the effects of Mn on 1H MRS. The enhanced region possessed a mean T1 of 901±50 ms (n=5) whilst the contralateral region possessed a mean T1 of 1254±25 ms (n=5).*



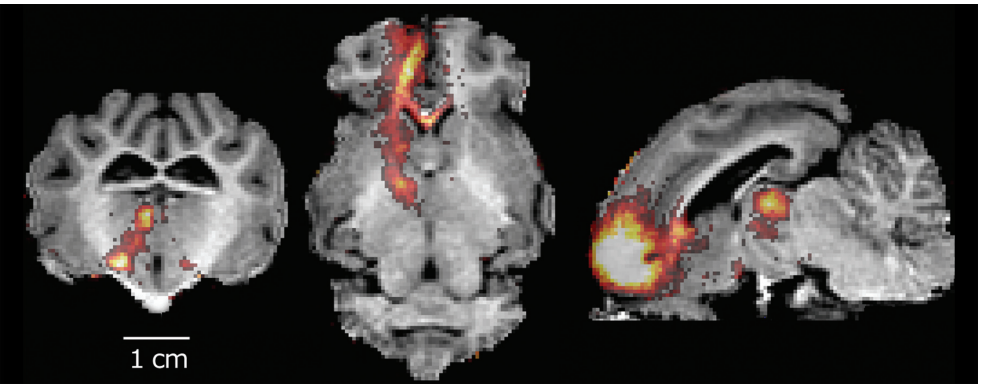

*Typical proton MRS spectra acquired in vivo from adjacent 2.5 mm isotropic voxels in the (blue) Mn-enhanced and (black) adjacent, control and unenhanced superior colliculus. The effect of the Mn appeared negligible when TR=4s and TE=17ms suggesting that 1H MRS may be used to obtain metabolic information that is not significantly influenced by the relaxation effects of the paramagnetic $Mn^{2+}$ cations.*

thereby making the metal suitable for neural tract tracing. However, the administration of Mn to observe neural pathways may be toxic and influence those same pathways due to the abnormal concentrations of Mn required to provide MRI contrast. As a result, the use of $^{1}$H MRS to obtain a metabolic profile of the brain may be influenced by both manganese-induced metabolic changes and the effect of the paramagnetic metal ion on the relaxation of the metabolites themselves if the Mn cations and metabolites are in the same cellular compartment. Consequently, the group has investigated the effect of Mn on 1H MR spectroscopy using an in vivo Mn enhanced optic tract imaging model together with phantom experiments. This is the subject of a Masters degree study that will be completed in 2006.

In collaboration with the Research Laboratory for Stereology and Neuroscience, Bispebjerg University Hospital, the use of manganese as a tracer to validate MR tractography has been investigated at 3 and 4.7 Tesla. Following injection of manganese directly into the brain of a mini-pig, manganese cations are transported anterograde via a 'fast' transport mechanism inside the axons and can be visualized on T1 weighted MR images. A Siemens TRIO 3 Tesla MR scanner was used for in vivo investigations and compared with ex vivo tractography at 4.7 Tesla system. In collaboration with University College London, and the University of Manchester, MR diffusion sequences have been optimized at 4.7 Tesla. Compared to in vivo data, ex vivo studies have significant advantages including the possibility of acquiring data over longer time periods and, therefore, obtain high resolution images without artefacts due to motion or physiological noise.




*A high quality, optimized diffusion weighted dataset of a pig brain examined ex vivo at 4.7 Tesla. Compared to the in vivo studies, scanning time is not limited. The colour coded tensor map shows the main fibre direction within each volume element. The colour illustrates the measured fibre direction (Green: front-back; Red: Left-right and Blue: top-bottom). A region in the prefrontal cortex was chosen as a seed point for the tractography and different pathways were found in agreement with results based on histology and staining. A prefrontal corticothalamic projection was found using probabilistic tractography based on the the PICo method. Sequence parameters were optimized for tractography without interfering physiological noise or motion artifacts commonly pronounced in datasets acquired in vivo.*




*Following injection of the paramagnetic tracer into to the prefrontal cortex of a young Göttingen mini pig brain, the movement of manganese cations may be visualized using a T1 weighted sequence at 3 Tesla. A difference map (colour) overlaid on a baseline images reveals the prefrontal corticothalamic projection with projection site in MD thalamus.*

# Other Activities

## Consultation

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

Olaf B. Paulson:
- Chairman of the Department of Clinical Neuroscience and Psychiatry, University of Copenhagen
- Chairman of the Research Committee of the Neuroscience Centre at Rigshospitalet
- Secretary of the Danish Society of Neuroscience
- Member of the board of the Danish Alzheimer Association
- Member of the Danish Alzheimer Research Foundation
- Member of the Neurology Committee of the Copenhagen Hospital Corporation
- Member of the committee for implementation of clinical neuroscience and psychiatry in the new curriculum for the physician education at the University of Copenhagen
- Chairman of the Research Committee of Hvidovre Hospital

Terry L. Jernigan:
- Co-Director of Laboratory of Cognitive Imaging
- Co-Director of VA Research Enhancement Award Program (REAP) – Cognitive Imaging
- Member of the Executive Committee, UCDS Department of Psychiatry
- Member of the Academic Advising Committee, UCDS Department of Psychiatry
- Member of the K-award Committee, UCDS Department of Psychiatry
- Member of the Faculty Search Committee, At the UCSD Department of Radiology
- 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
- Member of the Editorial Advisory Board of Neuroimaging
- Member of the Editorial Advisory Board of Developmental Neuropsychology
- Section Editor of Neurobiology of Aging
- Ad Hoc Reviewer, NIDA-K, The Training and Career Development Review Committee & Conflict of Interest Special Emphasis Panels
- Member of University-Wide Committee on Scholarly Communications, the subcommittee on Academic Personnel issues

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

## Journal Review

During 2005, DRCMR staff members have been reviewers for the following journals:
- Acta Paediatrica
- Acta Physiology Scandinavia
- Alcoholism
- American Journal of Geriatric Psychiatry
- American Journal of Psychiatry
- Annals of the Rheumatic Diseases
- Anesthesiology
- Archives of General Psychiatry
- Archives of Neurology
- Arthritis and Rheumatism
- Arthritis Research and Therapy
- Cerebral Cortex
- Clinical and Experimental Research
- Current Psychiatry Reviews
- Future Neurology
- Human Brain Mapping
- International Congress on Schizophrenia Research
- Journal of Abnormal Psychology
- Journal of Cerebral Blood Flow and Metabolism Magnetic Resonance in Medicine
- Journal of the American Medical Association
- Journal of the International Neuropsychological Society
- Journal of Magnetic Resonance Imaging
- Journal of Neurology, Neurosurgery & Psychiatry
- Klinisk neurologi og neurokirurgi
- Neurobiology of Aging
- NeuroImage
- Neuropsychologia
- Neuropsychology
- Physics in Medicine and Biology
- Proceedings of the National Academy of Sciences
- Psychiatry
- Psychiatry Research
- Psychological Bulletin
- Rheumatology
- Scandinavian Journal of Rheumatology
- Science
- Stroke
- Technology in Cancer Research and Treatment
- The Boundaries of Consciousness: Neurobiology and Neuropathology, Progress in Brain Research
- The Journal of Rheumatology
- Ugeskrift for Læger

## Training Activities

**Received Training**

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

**Formal Instruction by DRCMR Staff**

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

Outside Instruction:

- Karam Sidaros: Teaching course: Magnetic Resonance 3, University of Aarhus
- Karam Sidaros: Teaching course: Tracer kinetics, University of Copenhagen
- Lars G. Hanson, Karam Sidaros Anne-Mette Leffers, Margrethe Herning and Lise Vejby Søgaard: Teaching course: Magnetic Resonance, Sygepleje- og Radiografskolen
- Lars G. Hanson: Teaching: Medical Imaging course, Technical University of Denmark
- Lars G. Hanson: Teaching: MR Quality Assurance, Radiografskolen
- Terry L. Jernigan, Lars G. Hanson, Karam Sidaros, Thomas Z. Ramsøy: Teaching: Introduction to MRI for Psychology Students, University of Copenhagen
- Ian J Rowland: Teaching: Molecular brain imaging with MR, possibilities and limitations in: Multimodal Brain Imaging, Copenhagen Graduate School of Neuroscience, Copenhagen University
- Lise Vejby Søgaard: External examiner: MR3 course, University of Aarhus
- Mark S. Christensen: Teaching: Introduction to functional MRI and Consciousness, Human Neurobiology course, Institute of Exercise and Sport Sciences, University of Copenhagen
- Mark S. Christensen: Experimental instructor in the course Human Motor Control, Institute of Exercise and Sport Sciences
- Mark S. Christensen, Lars G. Hanson, Kristoffer Madsen, Martin Skov and Karam Sidaros: Teaching: Neuro Physics, Dept. of Physics, Technical University of Denmark
- Terry L. Jernigan: Teaching course: Linking Maps: “Understanding Effects Across Different Modalities” (Examples from NeuroAIDS and Substance Abuse Research) in, Multimodal Brain Imaging, Copenhagen Graduate School of Neuroscience, University of Copenhagen
- Thomas Z. Ramsøy. Teaching course: Consciousness: The Webcourse, Center for Consciousness Studies, University of Arizona

Courses Organized at DRCMR:

- Annette Skræp Nielsen and Kirsten Nielsen: Teaching “Neuroanatomy Study Group”
- Lars G. Hanson: Teaching course: MR Techniques, Danish Research Centre for Magnetic Resonance
- Martin Skov: Teaching course: Functional Imaging Seminar, Danish Research Centre for Magnetic Resonance

Individual Supervision of graduate students by DRCMR Staff:

- Lars G. Hanson was supervisor for MSc student Rasmus Engholm at Technical University of Copenhagen
- Lars G. Hanson was supervisor for Silja Heilmann, Thilde Kofoed and Emil Enemærke, whilst writing their Physics Bachelor Project at the University of Copenhagen
- Ian J. Rowland and Lise Vejby Søgaard were supervisors for MSc student Kathrine Skak Madsen
- Mark S. Christensen was co-supervisor for three MSc students, Svend Sparre Geertsen, Tue Hvass Petersen, and Kasper Kragh Andersen from the Institute of Exercise and Sports Sciences, University of Copenhagen
- Mark S. Christensen was supervisor for medical student Rie Harboe Nielsen, University of Copenhagen, OSVAL 1
- Maria Miranda was supervisor for medical student Anne Pieper, OSVAL 1
- Martin Skov was supervisor for MSc student Klaus Smedegaard, Filmvidenskab, University of Copenhagen
- Terry L. Jernigan was clinical supervisor for graduate practicum students
- Thomas Z. Ramsøy was supervisor teaching practice for psychology student Signe Vangkilde
- William F.C. Baaré was supervisor for medical student Andreas Glenthøj: Pregraduate research fellow

## Congress Organization

- Lars G. Hanson was the local organizer of the Annual Meeting of the Danish Magnetic Society held at The Danish Research Centre for Magnetic Resonance
- Martin Skov was the organizer of a Neuroaesthetics session held at the Mind and Brain conference, arranged by the Institute of Exercise and Sport Sciences, University of Copenhagen
- Thomas Z. Ramsøy was the local organizer of the quarterly meeting for the Danish Society for Neuropsychologists held at The Danish Research Centre for Magnetic Resonance.

## Awards

We are pleased to announce that Mikkel Stegmann received The Nordic Award for the best PhD Thesis in Image Analysis and Pattern Recognition in the years 2003-2004, at SCIA 2005

# Publications

A large number of publications has resulted from the work performed by the research staff at the DRCMR during 2005. The most important of these publications are listed here according to category:

## PhD and Doctoral Theses

- Balslev D. Proprioception - an obstacle for motor control in conditions with visuoproprioceptive conflict. Faculty of Health Sciences, University of Copenhagen, 2005.
- Ejbjerg B. Magnetic resonance imaging in rheumatoid arthritis. A study of aspects of joint selection, contrast agent use and type of MRI unit. Faculty of Health Sciences, University of Copenhagen, 2005.
- Habekost T. Deficits in visual attention after right side brain damage TVA based patient studies. Faculty of Humanities, University of Copenhagen, 2005.
- Lund TE. Advanced Methods in Functional MRI. Faculty of Health Sciences, University of Copenhagen, 2005.
- Stavngaard T. New imaging techniques in COPD. Faculty of Health Sciences, University of Copenhagen, 2005.
- Therkelsen SK. Atrial and Ventricular Volume and Function In Atrial Fibrillation - A Magnetic Resonance Imaging Study. Faculty of Health Sciences, University of Copenhagen, 2005.

Missing in the 2004 report:

- Taskiran M. Myocardial function in type 1 diabetic patients with cardiovascular autonomic neuropathy assessed with magnetic resonance imaging and echocardiography. Faculty of Health Sciences, University of Copenhagen, 2004.

## Peer Reviewed Journal Articles


1. Balslev D, Nielsen FA, Paulson OB, Law I. Right Temporoparietal Cortex Activation during Visuo-proprioceptive Conflict. Cereb Cortex 2005; 15(2):166-169.
2. Bird P, Conaghan P, Ejbjerg B, McQueen F, Lassere M, Peterfy C, Edmonds J, Shnier R, O'Connor P, Haavardsholm EA, Emery P, Genant H, Ostergaard M. The development of the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. Ann Rheum Dis 2005; 64 Suppl 1:i8-i10.
3. Conaghan P, Bird P, Ejbjerg B, O'Connor P, Peterfy C, McQueen F, Lassere M, Emery P, Shnier R, Edmonds J, Ostergaard M. The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas: the metacarpophalangeal joints. Ann Rheum Dis 2005; 64 Suppl 1:i11-i21.
4. Conaghan PG, McQueen FM, Peterfy CG, Lassere MN, Ejbjerg B, Bird P, O'Connor PJ, Haavardsholm E, Edmonds JP, Emery P, Genant HK, Ostergaard M. The evidence for magnetic resonance imaging as an outcome measure in proof-of-concept rheumatoid arthritis studies. J Rheumatol 2005; 32(12):2465-2469.
5. Daurignac E, Toga A, Jones D, Aronen H, Hommer D, Jemigan T, Krystal J, Mathalon D. Applications of morphometric and diffusion tensor magnetic resonance imaging to the study of brain abnormalities in the alcoholism spectrum. Alcohol Clin Exp Res 2005; 29(1):159-166.
6. Ejbjerg B, McQueen F, Lassere M, Haavardsholm E, Conaghan P, O'Connor P Bird P, Peterfy C, Edmonds J, Szkudlarek M, Genant H, Emery P, Ostergaard M. The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas: the wrist joint. Ann Rheum Dis 2005; 64 Suppl 1:i23-i47.
7. Ejbjerg BJ, Narvestad E, Jacobsen S, Thomsen HS, Ostergaard M. Optimised, low cost, low field dedicated extremity MRI is highly specific and sensitive for synovitis and bone erosions in rheumatoid arthritis wrist and finger joints: comparison with conventional high field MRI and radiography. Ann Rheum Dis 2005; 64(9):1280-1287.
8. Ellekvist MB, Nielsen AS. [Traumatic dissection of the internal carotid artery]. Ugeskr Laeger 2005; 167(14):1533-1534.
9. Friston KJ, Stephan KE, Lund TE, Morcom A, Kiebel S. Mixed-effects and fMRI studies. Neuroimage 2005; 24(1):244-252.
10. Garde E, Lykke ME, Rostrup E, Paulson OB. Decline in intelligence is associated with progression in white matter hyperintensity volume. J Neurol Neurosurg Psychiatry 2005; 76(9):1289-1291.
11. Jelsing J, Rostrup E, Markenroth K, Paulson OB, Gundersen HJ, Hemmingsen R, Pakkenberg B. Assessment of in vivo MR imaging compared to physical sections in vitro-A quantitative study of brain volumes using stereology. Neuroimage 2005; 26(1):57-65.
12. Jernigan TL, Gamst AC, Archibald SL, Fennema-Notestine C, Mindt MR, Marcotte TL, Heaton RK, Ellis RJ, Grant I. Effects of methamphetamine dependence and HIV infection on cerebral morphology. Am J Psychiatry 2005; 162(8):1461-1472.
13. Jernigan TL, Gamst AC. Changes in volume with age--consistency and interpretation of observed effects. Neurobiol Aging 2005; 26(9):1271-1274.
14. Krabbe K, Karlsborg M, Hansen A, Werdelin L, Mehlsen J, Larsson HB, Paulson OB. Increased intracranial volume in Parkinson's disease. J Neurol Sci 2005; 239(1):45-52.
15. Landewe RB, Hermann KG, van der Heijde DM, Baraliakos X, Jurik AG, Lambert RG, Ostergaard M, Rudwaleit M, Salonen DC, Braun J. Scoring sacroiliac joints by magnetic resonance imaging. A multiple-reader reliability experiment. J Rheumatol 2005; 32(10):2050-2055.

16. Lim ET, Sellebjerg F, Jensen CV, Altmann DR, Grant D, Keir G, Thompson EJ, Giovannoni G. Acute axonal damage predicts clinical outcome in patients with multiple sclerosis. Mult Scler 2005; 11(5):532-536.
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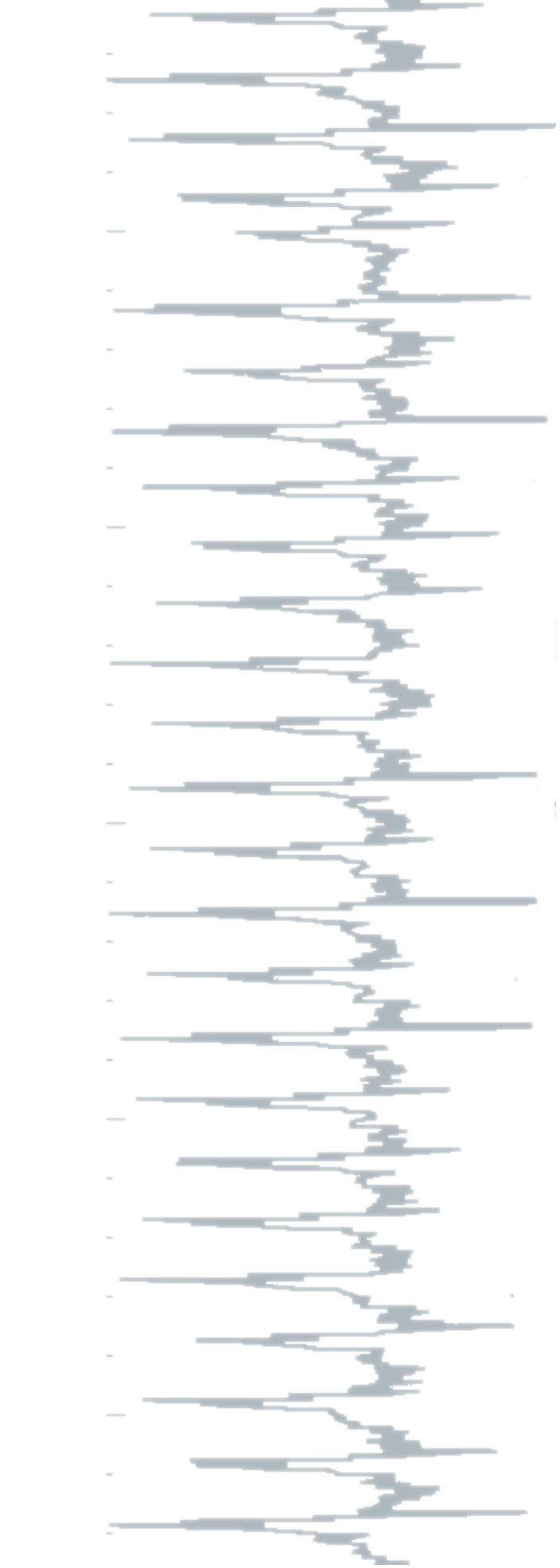
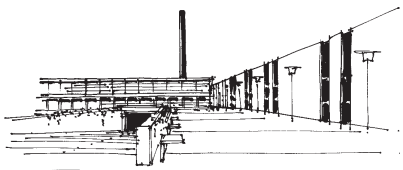
Missing in the 2002 report:

- Taskiran M, Fritz-Hansen T, Rasmussen V, Larsson HB, Hilsted J. Decreased myocardial perfusion reserve in diabetic autonomic neuropathy. Diabetes 2002, 51(11), 3306-3310.

## Conference Proceedings

The DRCMR was represented at 24 meetings and conferences during 2005, presenting 73 abstracts.





Hvidovre Hospital

Hovedstadens Sygehusfællesskab

# Acknowledgements


## National research funding

Biolanalytikernes Udviklings- og Forskningsfond
Center for Biomedical Optics and New Laser Systems
Risø National Laboratory, Optics and Plasma Research Department
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 Research Agency
Danish Rheumatism Association
Elsass Foundation
Grosserer Sigurd Abrahamson og hustru Addie Abrahamsons mindelegat
Lundbeck Foundation
Novo Nordisk Scholarship Programme
Research Fund of Copenhagen Hospital Corporation
Savværksejer Jeppe Juhl og Hustru Ovita Juhls Foundation
Scleroseforeningen
Speciallæge i neurologi Jørgen Wendelboe-Jørgensen og Laura Wendelboe-Jørgensens Fond
Technical University of Denmark
The Danish Medical Research Council
The Velux Foundation

## International research funding

EU 5th framework, LADIS project