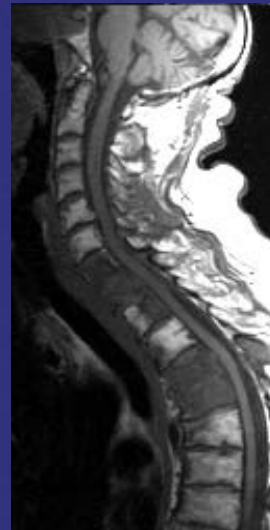


DRCMR

Annual Report 2001



Foreword



The year 2001 has been an interesting year for the Danish Research Centre for Magnetic Resonance. A DMSc and several PhD theses were defended in 2001. Naturally, this means that several projects have been completed as students and staff finish their studies and move on. Many research activities have continued and some exciting new research projects started. However, the year has not been without problems. In the clinical diagnostic section there was, unfortunately, a shortage of physicians (a current problem in Denmark) which, combined with the limited capacity of the department's oldest scanner (installed in 1989), resulted in reduced clinical activity. This decline, however, appears temporary since at the time of writing (Spring 2002), the department is again fully staffed. The year has also been kind to us. One of the most exciting events in 2001 was the purchase of a new high field (3 Tesla) Siemens Trio Scanner, made possible through a generous donation from the Simon Spies Foundation. The new scanner will be installed by the end of the summer of 2002. By that time, the modernisation of other parts of the department will also be completed. The new scanner will be of major significance during the coming years both for the clinical work and the centre's research. The acquisition of the new machine will benefit all of the research activities at the centre involving methodology, brain and heart research together with other areas such as rheumatology research.

Olaf B. Paulson

Background

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 two newest scanners, Magnetom Vision (1.5 Tesla) and Magnetom Impact (1.0 Tesla) were installed in 1994. These two scanners have since been upgraded and continue to perform at a high level for the centre's clinical and research needs. They are located in area 340A which also includes facilities for the clinical work and a conference room. The oldest scanner, a 1.5 Tesla Magnetom SP from 1989 is located in area 340B which holds facilities for data analysis and research as well as the centre's experimental scanner, a Sisco 4.7 Tesla scanner. This experimental scanner is suitable for MR studies of small animals and was upgraded in 1998.

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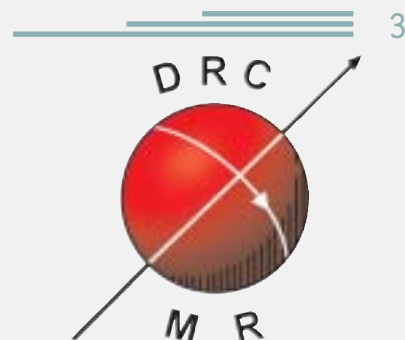
Dansk Resumé

Stigende internationalisering, stigende internationalt samarbejde og MR-afdelingens ønske om at udbygge dette i de kommende år har gjort det naturligt, at årsrapporten i år er udarbejdet på engelsk.

2001 blev et interessant år for MR-afdelingen. Der udkom hele 6 phd- og disputatsafhandlinger. Projekter blev afsluttet, og nye blev igangsat. I den kliniske diagnostiske sektion var der beklageligvis en mangel på læger, et generelt problem i Danmark som sammenholdt med, at afdelingens ældste skanner fra 1989 har en begrænset kapacitet, førte til et let fald i antallet af undersøgelser. Imidlertid er afdelingen igen godt bemandet, og man regner med, at man igen er oppe på fuld kapacitet i 2002. Den største begivenhed for afdelingen i 2001 var indkøbet af en ny højfelts 3 Tesla skanner, som blev doneret af Simon Spies Fonden, og som installeres i løbet af 2002. Med denne nye skanner vil afdelingen igen være i frontlinien med mulighed for at tage nye udfordringer op inden for klinisk diagnostik og forskning.

MR-afdelingens forskning omfatter både metodologisk udvikling og forskning relateret til normal fysiologi og til sygdomme relateret til flere organsystemer. Forskningen omfatter flere områder inden for hjernens funktioner og sygdomme, hjerteforskning, led- og bindevævsforskning samt lungeundersøgelser. Desuden udføres der på afdelingen geologisk forskning på afdelingens skanner til eksperimentel forskning.

Afdelingen modtager væsentlig fondsstøtte til sikring af forskningen (se bagsiden).



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Organisation and Staff

The centre has both clinical and research responsibilities and is organized accordingly. The centre is chaired by Professor DMSc Olaf B. Paulson. The director of the clinical functions is Head Radiologist Margrethe Herning. The Head Physicist is PhD Lars Hanson and the Head Technologist is Sussi Larsen.

Staff

Senior Staff, Clinical

Margrethe Herning, 'Overlæge'
Anne-Mette Leffers, 'Overlæge'

Senior Staff, Research

William Baaré, psychologist, PhD
Ellen Garde, MD, PhD
Henrik Gesmar, Chemist, PhD
Lars G Hanson, Physicist, PhD
Henrik BW Larsson 'Overlæge', DMSc
Olaf B Paulson, Professor, DMSc
Poul Ring, Engineer
Egill Rostrup, MD & Human Biologist
Ian John Rowland, Chemist, PhD
Lise Vejby Søgaard, Physicist, PhD

Junior Staff, Clinical

Ali A. Muhamad, MD
Mette Nordling, MD
Gulla Søby Rathje, MD

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

Junior Staff, Research

PhD Students

Irene Klærke Andersen, Engineer
Bjørn Grønning, MD
Elizbieta Kalowska, MD
Katja Krabbe, MD
Annika Reynberg Langkilde, MD
Jacob Rørbech Marstrand, MD
Henrik Kahr Mathiesen, MD
Jens Christian Nilsson, MD
Sverre Rosenbaum, MD
Karam Sidaros, Engineer

Junior Researchers

Mikael Boesen, MD
Torben Ellegaard Lund, Engineer
Dorthe Pedersen, MD
Stefan Wolff, Engineer

Technologists

Steen Ahlmann Nielsen, Laboratory Technician
Lill Andreasen, Laboratory Technician
Nina Hansen, Laboratory Technician
Sussi Larsen, Laboratory Technician
Pia Olsen, Laboratory Technician
Hanne Schmidt, Laboratory Technician
Helle Juhl Simonsen, Laboratory Technician
Marlene Soelberg, Laboratory Technician
Anne-Marie Vind, Laboratory Technician

Secretarial Staff

Lotte Grønbech Hansen
Anette Servé
Lisa Juhl Simonsen
Marianne Rønn

Cleaning Assistants

Ruth Kielstrup
Elsebeth Nielsen

Students

Minna Nørgaard, Human biology
Annette Schneider, Physics
Tim Dyrby, Engineer
Andreas Hansen, Medicine
Niels Broberg, Engineer

Visiting Staff

Senior Staff

Peter Born, MD, PhD
Thomas Fritz-Hansen, MD
Mette Klarlund, MD, PhD
Maria Miranda, MD, PhD
Dan Olsen, Geologist
Anders Stensgaard, Engineer
Lars Søndergaard, MD
Mette Regin Wiegell, Chemist, PhD
Mikkel Østergaard, MD, PhD, DMSc

Junior Staff

PhD Students

Bo Ejbjerg, MD
Elisabeth Hildebrandt-Eriksen, Human biologist
Torben Mackeprang, MD
Gitte Nielsen, MD
Katrine Pagsberg, MD
Mustafa Taskiran, MD
Susette Krohn Therkelsen, MD
Mikkel B. Stegmann, Engineer
Marcin Szkudlarek, MD

Junior Researchers

Helle Andersen, MD
Trine Stavngaard, MD

In 2001, 5076 clinical investigations were performed on 2049 patients, many investigations were performed before and after intravenous contrast media. 1224 patients were referred from Hvidovre Hospital, 825 patients referred from other counties. Most of the diagnostic work involved the investigation of neurological diseases, e.g. suspicion of stroke, multiple sclerosis, intracranial tumours, intracranial hemorrhages and dementia.

Many epileptic patients have been investigated concerning structural brain lesions causing seizures. Many of the epileptic patients were investigated before surgery with a special program including volumetric measurements of the hippocampus regions and T2-relaxation measurements.

Intracranial vascular diseases such as arteriovenous malformations and aneurysms were investigated with MR-imaging and MR-angiography. MR-imaging and MR-angiography are used as screening methods in patients with "warning leaks" from cerebral aneurysms, in patients with manifest subarachnoidal hemorrhage and patients with a family history of cerebral aneurysms. MR-angiography can be a valid supplementary investigation preoperatively.

Tumours in the pituitary gland, acoustic neuromas, meningiomas and other intracranial tumors are best investigated with MRI. Traditional cerebral arteriographies are replaced by slow-flow MR-angiography in suspicion of sinus thrombosis or tumours near the venous sinuses.

In pediatric radiology, MRI is used in neonates with hypoxic complications before, during or after delivery. Congenital malformations and metabolic diseases are well described with MRI.

Conventional cervical myelography is an invasive and uncomfortable investigation for patients. Today patients with suspected cervical spinal stenoses or suspected cervical disc herniation are investigated with MRI. Suspicion of lumbar disc herniation is primarily diagnosed



Gallstones in the gallbladder and the common bile duct. Dilatation of the biliary tree. MIP reconstruction from a set of coronal HASTE sections.

with CT, but in the case of post operative recurrent disc herniation, or in the case of infection, MRI is the preferred diagnostic method. In cases of negative CT and strong suspicion of disc herniation, as well as suspicion of high lumbar herniation, MRI is also indicated.

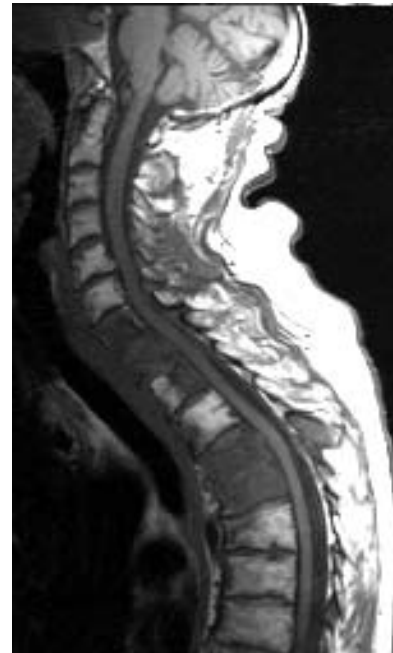
In patients with metastatic spinal disease, MRI is the diagnostic method of choice.

Structural heart disease such as tumours, structural changes in connection with some kinds of arrhythmias and heart valve disease are best diagnosed with MRI. In the near future it is likely that heart function will be described with MRI and MRA.

Musculoskeletal MRI is a growing clinical area. Diagnostic arthroscopy is more and more frequently replaced by MRI 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 and thereby limb-saving operations. Metastatic bone disease is well and best diagnosed with MRI.

In Sports Medicine the use of MRI will increase for visualising soft tissue regions, joints and bone structures.

In the abdominal area, MRCP is the investigation of choice concerning the bile ducts and pancreatic duct, when gall stones and obstruction are suspected. The alternative diagnostic ERCP is a method associated with morbidity and risk of some mortality. MRI of perineal fistulas and rectal tumours are well established methods. We hope to expand liver and pancreas investigations. In the coming year, a 3T MR-scanner will be installed at our centre. We expect it will bring new and better diagnostic imaging.



Cervical and upper thoracic spine with metastases in several vertebral bodies. Sagittal T1-weighted scan.

Collaborations

The DRCMR collaborates with many institutions both nationally and internationally. In the following only main collaborators in 2001 are listed, especially those with whom common funding was obtained and those who participated in supervision of PhD students.

National Collaborations

Brain Research

Copenhagen University Hospitals

Division of Neurological Rehabilitation, Hvidovre
Department of Neurology, Rigshospitalet
Sclerosis Research Unit, Rigshospitalet
Neurobiology Research Unit, Rigshospitalet
The Memory Disorders Research Unit, The Neuroscience Centre, Rigshospitalet
Department of Neuropaediatrics, John F. Kennedy Institute, Glostrup
Department of Neurology, Glostrup
Department of Neurophysiology, Glostrup
Centre of Preventive Medicine, The Glostrup Population Studies, Glostrup
Department of Neurology, Bispebjerg
Department of Psychiatry, Bispebjerg
Department of Clinical Physiology and Nuclear Medicine, Bispebjerg
Department of Neurology, Gentofte

Department of Psychology, University of Copenhagen
Department of Health Psychology, Institute of Public Health, University of Copenhagen
Laboratory of Neuropathology, Institute of Molecular Pathology, University of Copenhagen
Department of Medical Anatomy, University of Copenhagen
Department of Medical Biochemistry and Genetics, The Panum Institute, University of Copenhagen
Informatics and Mathematical Modelling, The Technical University of Denmark

Heart Research

Department of Cardiology, Copenhagen University Hospital, Hvidovre
Department of Endocrinology, Copenhagen University Hospital, Hvidovre
Department of Cardiology and Endocrinology, Copenhagen University Hospital, Frederiksberg
Department of Paediatrics, Copenhagen University Hospital, Rigshospitalet
Department of Cardiology B, Copenhagen University Hospital, Rigshospitalet
Research Department of Human Nutrition, The Royal Veterinary and Agricultural University

Department of Medical Physiology B, University of Copenhagen
Team Danmark Test Centre, Copenhagen University Hospital, Bispebjerg
Informatics and Mathematical Modelling, The Technical University of Denmark

Lung Research using Hyperpolarized Gasses

Department of Respiratory Medicine, Copenhagen University Hospital, Hvidovre Hospital
Department of Clinical Physiology, Copenhagen University Hospital, Rigshospitalet
Department of Respiratory Medicine, Copenhagen University Hospital, Gentofte
CISMI, Department of Chemistry, University of Copenhagen
Niels Bohr Institute, University of Copenhagen

Rheumatology Research

Copenhagen University Hospitals
Department of Rheumatology, Hvidovre
Department of Radiology, Hvidovre
Department of Orthopaedic Surgery, Hvidovre
Department of Clinical Physiology, Hvidovre
Department of Pathology, Hvidovre
Department of Rheumatology, Rigshospitalet

Department of Rheumatology, Herlev Hospital
Department of Radiology, Herlev Hospital
Department of Ultrasonography, Herlev Hospital
Department of Rheumatology, Gråsten Gighthouse
Department of Rheumatology Odense University Hospital
Department of Radiology, Odense University Hospital
Department of Rheumatology, Aarhus University Hospital, Århus Kommunehospital
Department of Radiology, Aarhus University Hospital, Århus Kommunehospital

International Collaborations

Brain Research

Centre for Magnetic Resonance, University Hospital, Trondheim, Norway
Massachusetts General Hospital, NMR-centre, Boston, USA
Department of Radiology, University of California, San Diego, USA
Centre for Magnetic Resonance Research, University of Minneapolis, Minnesota, USA.

Heart Research

The GUCH Unit, Middlesex Hospital, London, United Kingdom
 Centre for Magnetic Resonance Imaging, University of Trondheim, Norway
 Clinical Research Initiative in Heart Failure, Department of Cardiology, Western Infirmary, Glasgow, United Kingdom

Lung Research using Hyperpolarized Gasses

Klinik für Anesthesiologie, Radiologie, Johannes Gutenberg-University, Mainz, Germany
 Section of Academic Radiology, University of Sheffield, United Kingdom

Rheumatology Research

Department of Radiology, University of California San Francisco, USA.
 Rheumatology Research Unit and Department of Radiology, Leeds General Infirmary, United Kingdom.
 Departments of Radiology and Rheumatology, St. George Hospital, Sydney, Australia.
 Departments of Radiology and Rheumatology, University of Auckland, New Zealand.

International Multi-Centre Research Collaborations

The NIH funded Human Brain Project
Chaired by Prof. David Rottenberg, VA Medical Centre, University of Minnesota, Minneapolis, USA.

The EU Polarized Helium to Image the Lung (PHIL) project
Chaired by Prof. M. Leduc, PhD, Department de Physique Ecole Normale Supérieure, Paris, France.

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.

Research Projects

- Multiple Sclerosis
- Functional Brain Imaging
- Stroke
- Ageing and Dementia
- Other Degenerative Diseases
- Psychiatry
- Image Segmentation and Visualization
- Perfusion
- Cardiology
- Rheumatoid Arthritis
- Respiratory Medicine
- Pre-Clinical Studies
- Geology

Multiple Sclerosis

Conventional MRI techniques have proven important in the diagnosis and the follow-up of patients with multiple sclerosis (MS). However, these techniques have low specificity for the pathological changes in the MS lesions, and the correlation between conventional MRI and disability is poor.

During the last decade new techniques with improved sensitivity and increased pathological specificity have been developed, such as magnetic resonance spectroscopy (MRS), diffusion weighted imaging, and functional magnetic resonance imaging (fMRI). MRS has demonstrated neuronal dysfunction or loss as well as pathological changes in normal appearing white matter (NAWM). Diffusion weighted imaging demonstrates demyelination and fibre architecture, and by using fMRI, it is possible to detect which areas of the brain that are activated in response to a neuronal stimulus.

Research-group at DRCMR:

Annika R Langkilde, Henrik Kahr Mathiesen, Egill Rosstrup, Lars Hanson and Olaf B Paulson.

Functional MRI (fMRI) in Optic Neuritis

Patients with acute monosymptomatic optic neuritis (ON), which is often the harbinger of multiple sclerosis, were investigated with fMRI using visual stimuli. Both eyes were stimulated together and separately, and the activation in the visual cortex was detected and quantified. The patients were followed serially with four fMRI investigations, neuro-ophthalmologic testing and visually evoked potentials during one year. The aim was to study if and how the visual cortex shows an adaptive change in function in order to overcome the attack of ON. The hypothesis was that the healthy eye would have an increased activation during the period of impaired visual acuity compared to the affected eye. Status: The results are presently being calculated. Binocular stimulation studies indicate that a dynamic adaptive change occurs.

contact: Annika R. Langkilde

A Longitudinal Study with Conventional and Non-Conventional MRI Techniques in Patients with Optic Neuritis and RR-MS

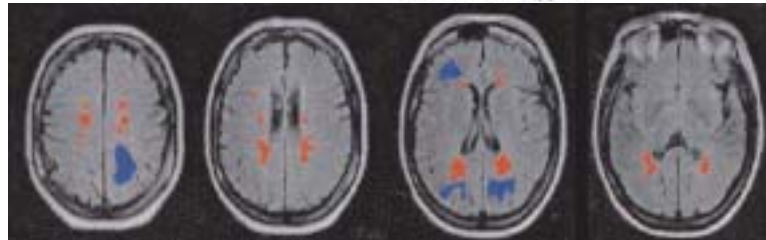
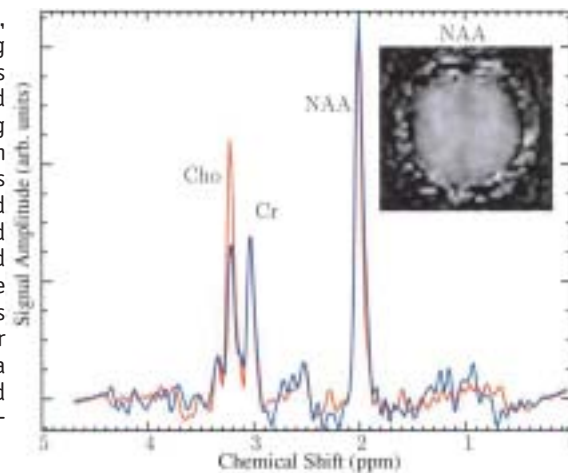
15 patients with optic neuritis and 24 patients with relapsing-remitting MS will be examined with conventional MRI as well as MR spectroscopy and diffusion weighted imaging serially. The project is designed to answer questions such as:

Can these new techniques be used to monitor disease activity? Can they predict the development of MS from optic neuritis? Can they be used to predict the course of the disease and will we get new pathophysiological knowledge?

Status: 21 patients were included by the end of 2001.

contact: Henrik K. Mathiesen

Two MR spectra, acquired by analyzing data from MS lesions (shown in red) and normal appearing white matter (shown in blue). The lesions show increased choline (Cho) and slightly decreased NAA peaks while the creatine (Cr) peak is unchanged. The upper right image shows a map of NAA measured using MR spectroscopic imaging.



A Longitudinal Study on The Effect of Interferon-beta Antibodies on The MRI Activity in RR-MS Patients

40 patients with relapsing-remitting MS (RR-MS) will be scanned 4 times over a 3 month period with conventional MRI including the administration of double dose contrast agent (gadolinium-DTPA 0.2 mmol/kg).

The patients are divided into 2 groups: patients with many antibodies and patients with few or none. The aim of the project is to determine whether there will be different MRI-observable activity in the two subgroups and whether patients with high antibody production are less protected by the treatment with interferon-beta.

Status: 28 patients were included by the end of 2001.

contact: Henrik K. Mathiesen

Clinical and Immunological Effects of Treatment with IVIG in Patients with Optic Neuritis

In this randomized, placebo-controlled study the effect of treatment with intravenous immunoglobulin (IVIG) on the visual function in patients with optic neuritis

is investigated. Testing of the visual function, immunological effects and MRI are performed serially.

Status: Until now 33 of 60 patients are included.

contact: Annika R. Langkilde

Functional Brain Imaging

Functional Magnetic Resonance Imaging (fMRI) is a method of acquiring MR images of brain activity. With proper design of MR-sequences, it is possible to acquire MR images weighted with, for example, perfusion, blood-oxygenation (BOLD) and several other physiological parameters. By acquiring thousands of such images during a cognitive task or sensory stimulation, it is possible to construct statistical maps locating, for example, regions of increased blood-flow during sensory stimulation or with increasing task difficulty. The fMRI-group at DRCMR has widespread activities ranging from investigations of the composition of the BOLD response to fMRI on patients suffering from sclerosis or schizophrenia.

Research Group at DRCMR:

Torben Lund, Minna Nørgaard, Karam Sidaros and Egill Rostrup

Event Related fMRI

Event related fMRI is a way of performing fMRI focusing on neural events rather than a neural condition. The potential of the method lies in imaging much more specific patterns of brain activity. The drawback (or challenge) is a much weaker and sometimes nonlinear signal. In 2001, a small study group was started with the goal of being able to understand the phenomena that occur when the paradigm consists of several different events whose lengths are shorter than the characteristic dimensions of the haemodynamic response, and to find out how this may be modelled accurately. Until now, two pilot experiments have been carried out, with some success but further investigations e.g. on paradigm-design are needed before event-related fMRI is a standard examination. With the introduction of the 3T system event-related fMRI becomes more feasible since the BOLD signal grows with the field strength squared.

contact: Torben Lund

Reduction of Physiological Noise in fMRI

Motion due to physiological pulsation is a major contributor to the noise in fMRI. A method for reduction of physiological noise in fMRI has recently been developed at DRCMR, which uses signal curves from vessels and ventricles as covariates in a general linear model. This approach is now being tested in a number of different situations to see when it has a significant impact. A major effect has been hypothesized in images of functional connectivity, and recent studies were able to confirm this. It is also very likely that this filtering scheme is superior to band-pass filtering, in event related fMRI where the signal is spread over a large range of fre-

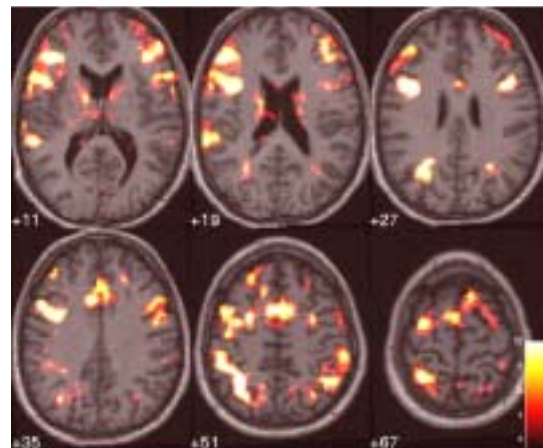
quencies, as opposed to block design where the signal induced by the paradigm is roughly periodic.

contact: Torben Lund

Localization and Lateralization of Language Functions by Functional Magnetic Resonance Imaging (fMRI)

Imaging of the human language function has a great theoretical interest because of the fundamental importance of language in all human activities. Furthermore, localization of language with fMRI may become of specific clinical importance in the presurgical assessment of neurosurgical patients, as an alternative to the highly invasive procedures used until now. Previous studies have shown the feasibility of this approach, but the accuracy and precision of the technique are unknown. In the present study we investigated ten healthy subjects using fMRI during three word generation tasks. Brain areas associated with the processing of these tasks were identified and the hemisphere which comprised the largest volume of activation was determined by means of a laterality index in six predefined regions. Two subjects were scanned repeatedly ten times, and the robustness of the location of activation, and laterality determined. The results will be used to integrate fMRI in clinical use.

contact: Minna D. Nørgaard



Functional activation during a phonetic language task with one subject scanned repeatedly 10 times. The bright regions correspond to areas activated in all of the 10 scans.

Estimation of Brain Metabolic Rate using fMRI

In an ongoing collaboration with the Centre for MR Research in Minneapolis, we have investigated the relationship between cerebral blood flow (CBF) and oxygenation weighted (BOLD) MRI during different respiratory conditions (the "graded hypercapnia" experiment). The purpose of this is to increase the quantitative understanding of the techniques used to acquire the CBF and BOLD weighted MR images, and to provide a calibration against which a regular brain activation experiment can be compared. Assuming that hypercapnia induces changes in blood flow only, and not brain metabolism, brain metabolism in the activation experiment can be estimated. New studies were undertaken in 2001 with the aim of comparing results obtained at 1.5 T with those obtained in Minneapolis at 3 and 7 T.

Status : 6 volunteers were scanned.

contact: Egill Rostrup

Research Projects

- Multiple Sclerosis
- Functional Brain Imaging
- **Stroke**
- **Ageing and Dementia**
- **Other Degenerative Diseases**
- Psychiatry
- Image Segmentation and Visualization
- Perfusion
- Cardiology
- Rheumatoid Arthritis
- Respiratory Medicine
- Pre-Clinical Studies
- Geology

Stroke

Stroke is the third most common cause of death in western countries. The first-year mortality is about 25% and many survivors suffer major disability. In one third of the patients, stroke in progression is noted. These patients have an even worse prognosis with respect to mortality and clinical outcome. At present there is no effective treatment for patients with stroke in progression, probably reflecting limited knowledge of the underlying pathophysiological mechanisms.

Research Group at DRCMR:
Elizabeth Kalowska and Sverre Rosenbaum

Stroke In Progression Study using MRI

The present prospective and consecutive study includes 50 patients with ischemic stroke within the last 24 hours of symptoms. All patients are examined with a routine CT scan. After informed consent the patients are scheduled for an MRI investigation within 24 hours after debut of symptoms. Another scan is scheduled after one week and finally the patients are investigated after 3 months. The MR investigation includes measurements of apparent diffusion coefficient, diffusion weighted imaging, cerebral blood flow and MR-angiography. Also echo planar imaging is performed aiming to study haemorrhagic transformation in the infarct. Finally, the measurements include spectroscopy to study the amount of metabolites in the brain, i.e. N-acetylaspartate (NAA), choline, creatine and lactate. Patients with stroke in progression are compared to patients with completed stroke, investigating pathophysiological differences between patients in the initial phase and during follow-up. This study is designed to identify those patients at risk of progressive stroke. This may in the future enable the identification of a more efficient treatment of patients with acute stroke than that available today.

Status: 45 patients should be included by the end of March 2002.

contact: Elizabeth Kalowska

Ageing and Dementia

There is strong evidence of an overall age-related degeneration of structures in the white matter. In particular, focal white matter hyperintensities (WMH), or leukoaraiosis, is a noticeable radiological observation often seen in the elderly. There are indications that WMH may reflect a localised exacerbation of degenerating processes in the white matter, and that these alterations may be involved in the transition to disability.

MRI offers detailed topographic images due to unique contrast resolution. Particularly in the evaluation of cerebral white matter changes, the combined application of conventional imaging with newer MRI techniques makes it possible to visualise the structural changes and elucidate the pathophysiological mechanisms behind WMH. The overall aims of the projects described below are to provide valuable information on the dynamics of normal cerebral ageing as opposed to diseases such as dementia.

Research group at DRCMR:
Ellen Garde, Jacob Rørbech Marstrand, Egill Rostrup, Lars Hanson and Olaf B Paulson.

Identification of Risk Factors for WMH and Cognitive Decline Based on 30 Years Follow-up

With 30 years follow-up data, the Glostrup population study offers an unique opportunity for the evaluation of the association between risk factors and WMH. The aim of this study is to evaluate the impact of cardiovascular risk factors occurring during a 30 year period on 1) changes in intelligence from age 50 to 80 and 2) the extent of WMH at age 80.

Status: Potential parameters have been chosen based on the literature, and evaluated for coherence from the 50, 60, 70, and 80 year studies. Preliminary results suggest that blood pressure dysregulation in the elderly, e.g. type and effect of treatment, may be related to the presence and extent of WMH changes.

contact: Ellen Garde

Progression of MRI White Matter Hyperintensities and Decline in Intelligence; a 5-Year Follow-up Study of 85 Year Old Subjects from The Glostrup Population Study

Considering the substantial amount of literature on WMH, very few studies on the progression of WMH and cognitive impairment have been published. Furthermore, those studies report contradictive results.

The purpose of this study is to describe the temporal relation between changes in WMH and cognitive function in a group of community-dwelling elderly, and explore the predictive value of WMH in relation to development of cerebrovascular disease and dementia. Status: A follow-up MRI examination has been performed on twenty six 85 year old subjects and an eval-

uation of the extent of WMH progression performed. Data from the medical examinations and neuropsychological tests are currently being compared to the MRI data.

contact: Ellen Garde

Cerebral Perfusion and Cerebral Reactivity is Reduced in White Matter Hyperintensities

Previous studies comparing subjects with WMH to normal controls have reported global reductions in cerebral blood flow and cerebral vascular reactivity. In this study we examined localized haemodynamic status in order to compare WMH to normal appearing white matter (NAWM).

Status: A group of 21 normal 85 year old subjects were studied using dynamic contrast enhanced MRI together with administration of acetazolamide (ACZ). When comparing WMH to NAWM, measurements showed significantly lower cerebral blood flow (CBF) and longer mean transit time (MTT) and the increases in CBF and cerebral blood volume (CBV) induced by ACZ were significantly smaller in WMH than in NAWM.

contact: Jacob R. Marstrand

AD 2000 Project

Patients suffering from Mild Cognitive Impairment (MCI) have an increased risk of developing Alzheimer's disease (AD). Volumetric and metabolic values obtained using MRI and MR spectroscopy are measured in MCI patients to examine the prognostic value of these measurements. In addition, MR spectroscopy or cerebral vascular reactivity (CVR) has been obtained in AD and vascular dementia (VD) patients.

Status: A group of 47 MCI patients and 15 normal control persons have been examined. CVR has been measured in 6 AD and VD patients, and 3 AD patients have been examined by MR spectroscopy.

contact: Jacob R. Marstrand

Leukoaraiosis and Disability in the Elderly - LADIS

Lesions in the white matter of the brain become more common with increasing age, but the pathological significance of these changes is unknown. The purpose of this project is to reveal the impact of the white matter changes on the transition to disability in elderly subjects. A group of elderly subjects with normal or nearly-normal daily function (a normal activity of daily living score), but significant white matter changes, are recruited from the Memory Disorders Research Unit at Rigshospitalet. All subjects go through an extended neuropsychological evaluation. At DRCMR structural and diffusion weighted scans are obtained. It is hoped that about 60 Danish subjects will be included in the project, which is part of a concerted action project under the 5th European framework programme. Together, the participating centres are to include a total of 800 patients.

Status: 22 subjects have been included.

contact: Egill Rostrup

Other Degenerative Diseases in the Nervous System

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), also known as "Lou Gehrig's disease" or motor neurone disease, is a progressive, fatal neurodegenerative disease that affects nerve cells in the brain and the spinal cord. The average age of ALS onset is 55 but can affect people at any age. 80% of ALS cases begin between the ages of 40 to 70.

Research group at DRCMR:
Sverre Rosenbaum

Diffusion Tensor Imaging of the Corticospinal Tracts in ALS

The pathogenesis of cerebrum involvement in Amyotrophic Lateral Sclerosis (ALS) is unknown. Using diffusion tensor imaging we aim to examine the corticospinal tracts in nine patients suffering from ALS compared to healthy controls at three levels determining if the process is an anterograde or a retrograde degeneration. The Apparent Diffusion Coefficient (ADC) and the fractional anisotropy were decreased respectively increased at the low level of pons and ADC was increased at the level of the internal capsule. This indicates a pathogenesis of retrograde degeneration, "dying backwards", starting in the axonal terminals spreading up towards the soma in the motor cortex progressing from a shrinkage of axons to a complete degradation or demyelination.

Status: Article under preparation.

contact: Sverre Rosenbaum

Parkinson's Disease

Multiple System Atrophy (MSA) is a neurodegenerative disease characterized by extrapyramidal, pyramidal and cerebellar symptoms along with signs of autonomic dysfunction. Clinically it can be difficult to distinguish between MSA and Parkinson's disease.

Research group at DRCMR:
Katja Krabbe, Egill Rostrup, Lars Hanson and Olaf B Paulson

Multiple System Atrophy (MSA) and Parkinson's Disease

The aim of this study is to find out which MR techniques are suitable to establish the diagnosis of MSA. 20 patients with Parkinson's disease, 10 patients with MSA and 20 normal age and sex matched controls will be enrolled in the project. All participants will be scanned with the following MR techniques: Conventional MRI, MR spectroscopy, MR diffusion weighted imaging and relaxation-time measurement. Furthermore, patients and controls will undergo neuropsychological testing with a test battery specifically designed for patients with Parkinson's disease.

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All patients will be examined clinically and disease state will be rated with Hoehn and Yahr scale and Unified Parkinson's Disease Rating Scale (UPDRS). All patients will be tested for autonomic dysfunction.

Status: 20 patients with Parkinson's disease, 10 patients with MSA and 10 controls have been MR scanned. All MSA patients have been tested for autonomic dysfunction.

contact: Katja Krabbe

Psychiatry

Schizophrenia is a complex, chronic and invalidating disease in which different aspects of cognition and behaviour, including attention, perception, thought processes, emotion and volition are affected. The study of first-episode schizophrenia patients is of importance since factors such as hospitalization, neuroleptic treatment, and disease chronicity will have minimal influence. Using structural and functional magnetic resonance imaging techniques, the project addresses the following questions: (a) which functional and structural abnormalities are present in (drug-naïve) first-episode schizophrenic patients? (b) how are these abnormalities and changes related to cognitive functions, behavioural symptoms, and social and medical history? (c) which abnormalities emerge during the course of the illness? and (d) how do these abnormalities evolve over the first years of illness?

Status: 53 patients and 45 healthy controls, matched on age, sex and socioeconomic status of the parents, have been scanned. Inclusion of subjects will be concluded in the spring of 2002.

Research group at DRCMR:

Anne Katrine Pagsberg, Torben Mackeprang, William Baaré and Torben Lund

Functional MRI in First-Episode Schizophrenia Patients

The most frequently studied and reported functional abnormality, as measured with SPECT, PET and fMRI, is the diminished ability of schizophrenia patients to activate the frontal lobes, particularly, when they are

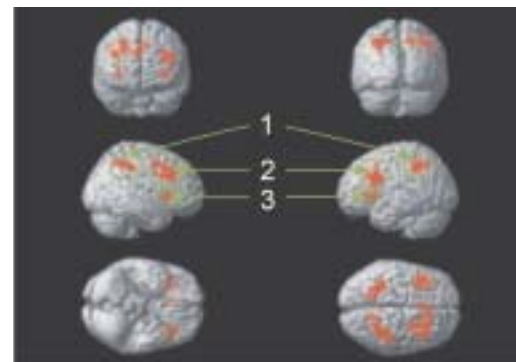
engaged in tasks in which the frontal lobes are assumed to play an important role. Until now most studies have been performed on chronic schizophrenia patients.

In the present project, gradient-echo echo-planar imaging pulse sequences, sensitive to the BOLD signal, are employed. Subjects are scanned while performing a working memory task (the N-back task). This task reliably activates the frontal and parietal lobes, and the cingulate gyri in healthy controls.

Preliminary results suggest that first-episode schizophrenia patients show an attenuated response, comparable to that reported in chronic patients, in frontal and parietal brain areas under conditions of increased working memory load (see figure). This suggests that the neural network underlying working memory is already compromised at an early stage of schizophrenia. Importantly, this diminished reactivity does not seem to reflect differences in task performance.

contact: Anne Katrine Pagsberg

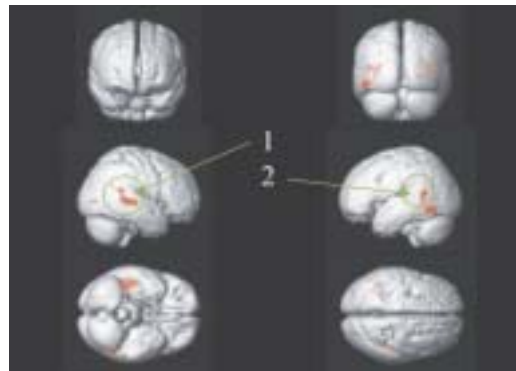
First-episode schizophrenia patients showed an attenuated response, bilaterally, in parietal (1), dorsolateral prefrontal (2) and inferior frontal (3) brain regions under conditions of increased working memory load, as compared to healthy controls.



Structural Brain Abnormalities in Schizophrenia

Structural brain abnormalities that are most consistently found in schizophrenia patients as compared to healthy controls in both postmortem and in-vivo imaging studies include enlarged ventricles, reduced grey matter volume, and smaller medial temporal lobe structures (i.e. amygdala-hippocampal complex, parahippocampal gyrus). Frontal, (superior) temporal, and thalamic abnormalities are also found. Grey matter seems to be more affected than white matter. The theoretical and clinical significance of these pathophysiological findings in schizophrenia is by no means clear. Disturbances in early (pre- and perinatal) as well as late (adolescence) brain developmental processes have been implicated. Neurodegenerative processes might also be involved after illness onset. Furthermore, the relationship between structural abnormali-

Increased severity of positive symptoms was significantly related to smaller grey matter volumes in right (1) and left (2) superior temporal sulci.



ties, clinical variables (e.g. positive and negative symptoms, clinical outcome) and cognitive functioning is still poorly understood.

In a subgroup of patients we investigated the relationship between grey matter volume and clinical symptomatology (e.g. positive symptoms including reality distortion and disorganized behaviour, and negative symptoms) using voxel based morphometry. This technique allows for a voxel by voxel statistical analysis of regional structure/function relationship. Preliminary results suggest that an increase in the severity of positive symptoms is related to a decrease in grey matter volume in especially the right and (to a lesser extent) left superior temporal sulci. This finding underlines the involvement of especially superior temporal abnormalities in the early course of schizophrenia and corroborates earlier findings.

contact: Anne Katrine Pagsberg

Image Segmentation and Visualization

MRI generates vast amounts of data, and methods for data reduction and visualization are therefore of great importance. Such methods include segmentation, where regions of interest may be detected automatically to measure, for example, volumes of white and grey matter in the brain, thus deriving a few valuable parameters from full a 3D data set. This task is inherently difficult, due to noise, unwanted signal variation and limited spatial resolution. Another approach to handling the very large MRI datasets is to use tools that detect regions of special interest (e.g. pathology), and present those to the clinicians in a way that facilitates reliable diagnosis.

Research group at DRCMR:

Lars G. Hanson, Torben Lund, Margrethe Herning, and Henrik B.W. Larsson.

Simultaneous Segmentation and Coil Inhomogeneity Correction

Radio waves are transmitted and received using antennas (coils) during MR imaging. Differences in coil sensitivity cause unwanted intensity variations across the resulting images. This is a major problem for automatic detection of anatomical structures (segmentation). Correction methods exist that rely on the intensity variation being smooth. This is not fulfilled at tissue boundaries, and improved segmentation methods are expected as a result of going beyond this assumption. Status: Coil sensitivity measurement and a method relying on calibration has been implemented and tested successfully. Algorithms for simultaneous segmentation and inhomogeneity correction is under development.

contact: Lars G. Hanson

Automatic Detection and Visualization of Cortical Dysplasias

Detecting cortical dysplasias associated with epileptic seizures is a major problem. Cortical dysplasias occur as a subtle local thickening of the cortex accompanied by a blurred grey/white matter junction. The manual detection of these features in 3D datasets is very time consuming. A tool has been developed to facilitate the detection of focal cortical dysplasias by extending the conventional means of visualization and by automatically pointing out potential "trouble spots" to the radiologist.

Status: Software has been developed and described in Stefan Wolff's MSc thesis. Practical tests continue in 2002.

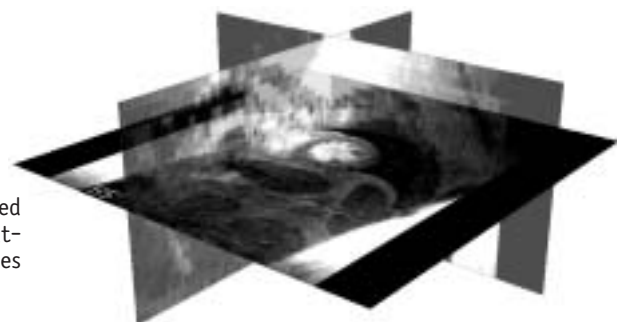
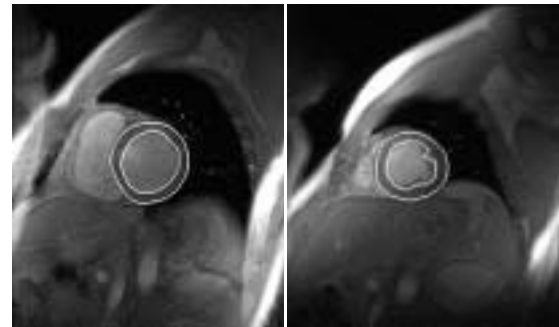
contact: Margrethe Herning

Automated Segmentation and Analysis of Cardiac MRI using Statistical Image Analysis

The purpose of this project is two-fold; a) to develop a method for 3D segmentation of the left ventricle in short-axis cine MRI over the heart cycle in order to automatically obtain functional parameters of the human heart (e.g. ejection fraction) in a fast and objective manner and b) to develop a method for single-slice left ventricle segmentation in short-axis perfusion MRI during the bolus passage in order to obtain functional parameters of the human heart for tissue viability estimation. Automation of currently resource demanding routine post processing by employing and developing computerized segmentation methods using advanced statistical image analysis is undergoing further development (see figures below). This project is performed in collaboration with IMM at the Technical University of Denmark and forms part of MSc Mikkel Stegmanns PhD project.

contact: Henrik B.W. Larsson

Examples of automated delineation of the endo- and epicardial contours of the left ventricle in a single slice of short-axis cardiac MRI. Each image shows the right ventricle to the left of the contours and the dark region to the right is the lung.



Cardiac MRI volume visualized using three orthogonal cutting planes (secondary planes are semi-transparent).

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Perfusion

Perfusion weighted imaging is used in everyday clinical imaging, but inter-subject comparisons and patient follow-up require quantitative perfusion imaging methods. This group works with technical aspects of perfusion imaging to improve quantification. The research areas span from the development of scanner sequences and signal processing for improved perfusion measurements (with or without contrast agent infusion), over investigation of brain reactivity to diamox, investigation of the perfusion/diffusion mismatch in rats and humans with stroke, to the latest evolving research of lung ventilation with hyperpolarized gases. Perfusion measurements are used in the department to investigate heart disease and multiple sclerosis.

Research-group at DRMR:

Irene K. Andersen, Karam Sidaros, Jacob R. Marstrand, Sverre Rosenbaum, Ellen Garde, Lisa Hildebrandt-Eriksen, Lise Vejby Søgård, Egill Rostrup and Lars Hanson.

Relationship between Cerebral Perfusion and Internal Carotid Blood Flow

As part of his PhD study, Marstrand made an investigation in 18 normal subjects of the relation between cerebral perfusion and internal carotid blood flow for two commonly used scanner sequences. Perfusion changes in response to acetazolamide showed linear correlation with the carotid blood flow changes when measured with the GE-EPI technique, but did not correlate when measured with the SE-EPI technique.

contact: Jacob R. Marstrand

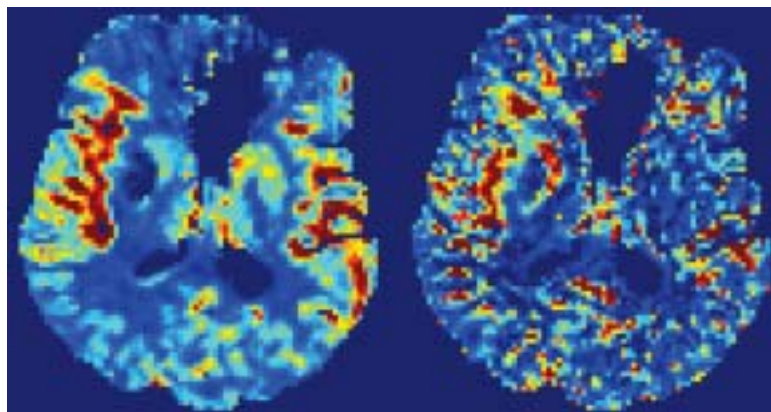
Perfusion Quantification using Gaussian Process Deconvolution

To quantify the perfusion from bolus tracking experiments, the tissue concentration curves have to be corrected for the non-ideal shape of the arterial concentration curve that acts as input to the tissue. This is achieved using deconvolution, which is non-trivial due

to the noise-level of the measurements. In this study, a new method for regression was tested as a deconvolution technique for perfusion quantification via simulations on artificial curves. The performance of the new deconvolution method on healthy subjects is comparable to present methods. The new method automatically adjusts the filtration of the noise and thus performs better on patients than the present methods that are optimized for healthy subjects.

The study also includes optimization of scanner sequences to improve the perfusion estimate (see figure).

contact: Irene K. Andersen



The perfusion level of a stroke patient measured simultaneously with two different scanner sequences during passage of a bolus of contrast agent. The methods supply information about different parts of the vascular tree.

Offset Correction in Arterial Spin Labelling

Arterial spin labelling uses blood water as a natural tracer. It relies on the difference between a perfusion-sensitive and a perfusion-insensitive image. If the scanner sequence is not carefully optimized, perfusion quantification may become biased. An apparent perfusion is then registered even when there is no perfusion. This study shows, that the bias or offset may be corrected mathematically. Offset correction is a good supplement to scanner sequence optimization, since the sequence optimization alone reduces sensitivity.

contact: Karam Sidaros



A non-invasive perfusion image acquired using PICORE QUIPSS II, a quantitative arterial spin labelling technique. The image was acquired in five minutes.

Filtering of Perfusion Measurements using Training Data

Perfusion measurements are sensitive to system and physiological noise. A method was developed to reduce this problem. It detects time curve features which are reproducible across tissues and subjects. These trends derived from example data are used to separate signal from noise.

contact: Lars G. Hanson

Cardiology

The Cardiology Research Group at the DRCMR has a long tradition for broad involvement in cardiovascular MR research. MRI is extremely well suited for cardiac examinations allowing for detailed studies of chamber structure and function, as well as high-precision measurements of flow and perfusion. Within the past year, the group has been engaged with projects covering a variety of pathological conditions such as congenital heart disease, hypertensive heart disease, acute myocardial infarction, heart failure, atrial fibrillation and heart afflictions related to diabetes mellitus and obesity. Various aspects of these conditions have been investigated using a range of MRI techniques, among which some are well established, whereas others are more experimental. The specific projects are described in detail below.

Research group at DRCMR:

Helle Andersen, Mikael Boesen, Thomas Fritz-Hansen, Bjørn A. Grønning, Gitte Nielsen, Jens C. Nilsson, Dorthe Pedersen, Lars Søndergaard, Mustafa Taskiran and Susette Krohn Therkelsen.

Neurohumoral Prediction of Left-Ventricular Morphologic Response to β -blockade With Metoprolol in Chronic Left-Ventricular Systolic Heart Failure

In order to tailor therapy in heart failure, a solution might be to develop sensitive and reliable markers that can predict response in individual patients or monitor effectiveness of therapy. The aim of the study was to evaluate a range of neurohumoral factors as markers for left-ventricular (LV) antiremodelling as measured by cardiac MR from metoprolol treatment in patients with chronic LV systolic heart failure. Pre-treatment levels of atrial (ANP) and brain (BNP) natriuretic peptides were identified as powerful predictors of LV antiremodelling during the 6-month study period.

contact: Bjørn A. Grønning

Diagnosis of Heart Failure by Neurohumoral Plasma Concentrations

Heart failure is a detrimental condition with a dismal prognosis, comparable to several forms of cancer. Diagnosis of heart failure still relies mainly on clinical evaluation and an echocardiographic measure of left ventricular systolic function. In an attempt to facilitate diagnosis of this important disease, biochemical substances have been suggested as alternative markers. The aim of the present study was to compare the potential of a range of neurohumoral substances as diagnostic markers for LV dimensions and ejection fraction as measured by cardiac MR in patients with symptomatic heart failure in NYHA classes II-IV; and, in addition, to examine whether any supplementary information is gained by comprehensive neurohumoral profiles. Brain natriuretic peptide (BNP) as well as N-terminal pro BNP came out as the strongest markers for LV dimensions and ejection fraction. However, a comprehensive neurohumoral evaluation (by ANP (LV volumes), endothelin-1 (LV myocardial mass) and aldosterone (LV ejection fraction)) may add some information to the diagnosis.

contact: Bjørn A. Grønning

Left Ventricular Dysfunction in Obese Subjects and Potential Antiremodelling Effects Following Weight Loss – an MRI Study (an Amendment to the Topiramate Study)

Objectives: To evaluate the degree of left ventricular dysfunction and left ventricular hypertrophy as well as potential cardiac effects from weight reduction in obese subjects. Furthermore, the study aims at investigating whether obese subjects have elevated plasma levels of neurohumoral substances (BNP, ANP, N-terminal pro BNP, endothelin, epinephrine, norepinephrine, renin, aldosterone, arginine-vasopressin), and whether there is a correlation with the cardiac findings before and after weight loss. Fifty-eight obese subjects with a BMI $\geq 33 \text{ kg/m}^2$ and $< 40 \text{ kg/m}^2$ have been included and cardiac examinations and blood samples have been performed twice, before and after 8 weeks of diet and 8% weight loss. The subjects will be examined again after one year. The acquisition of MRI data will be completed in the summer of 2002. The data will form the basis for a PhD thesis, which is expected to be submitted in the end of spring 2004.

contact: Dorthe Pedersen

Early Assessment in the Acute Phase of Myocardial Infarction using MRI with Focus on Infarct Size, Myocardial Oedema and Haemodynamic Condition

Important diagnostic and prognostic variables in the postacute myocardial infarction patient include infarct size, LV function and the presence of myocardial oedema. 48 patients with a first transmural myocardial infarction have been included. All 48 patients underwent MRI examinations on days 3, 5, and 7 after the myocardial infarction. Patients had daily ECG's

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performed and serum markers were obtained hourly during the first 4 hours after admission, every 4 hours the following 12 hours and after 36 and 48 hours after admission. The aim was to study early phases of myocardial infarction. To quantify infarct size, left ventricular end diastolic and systolic volume and myocardial oedema, measurements were performed using MRI. These results will be validated by ECG, estimated infarct size and enzymatic indices of myocardial necrosis, myocardial scintigraphy and late coronararteriography. Status: Data processing has been completed and the results are presently being evaluated.

contact: Gitte Nielsen

Myocardial Perfusion by MRI in Patients with First Myocardial Infarction, in Early Phase

MRI can be used to non-invasively assess myocardial perfusion in patients with acute myocardial infarction. (MI)

20 patients with MI were included. MRI examinations were performed in 4 patients before and 90 min after thrombolytic treatment. The other 16 patients had MRI examinations from hours to 3 days after the MI. Furthermore the patients were examined on days 3, 5 and day 7 after the acute MI. The aim was to use MRI for quantitative assessment of myocardial perfusion in relation to other non-invasive methods for assessment of reperfusion and late coronary angiography for vessel patency.

Status: Data processing has been completed and the results are presently being evaluated.

contact: Gitte Nielsen

Ventricular Characteristics in Patients with Transposition of the Great Arteries Corrected by Mustard's Procedure

Previously, transposition of the great arteries was treated by atrial switch procedures after which the right ventricle served the systemic circulation. Although these patients are generally considered asymptomatic, it is well established that mortality rates are increased, which may be explained by the inability of the right

ventricle to adapt sufficiently to the much higher systemic pressure. The purpose of the study was to characterize patients who have undergone atrial switch by the Mustard procedure in terms of right ventricular dimensions and function, neurohumoral profile, heart rate variability and maximum oxygen consumption. Approximately twenty patients have been examined with MRI, blood sampling, 24-hour Holter monitoring and exercise testing. The data are still being evaluated.

contact: Helle Andersen

14-year old female with transposition of the great arteries corrected by the Mustard-procedure. Long-axis section of the right and left ventricles. Notice the characteristic hypertrophy of the right ventricle and the parallel course of the great arteries with abnormal origin. AO, aorta; LV, left ventricle; PA, pulmonary artery; RV, right ventricle.



MRI of the Atria and Left Ventricle in Middle-Aged Normal Subjects and Patients with Persistent Atrial Fibrillation Before and After Conversion to Sinus Rhythm

The purpose of this study is to measure right and left atrial as well as left ventricular dimensions and systolic function by cardiac MRI in normal subjects and in patients with persistent (> 48 hrs) atrial fibrillation. In addition, a range of neurohumoral substances will be measured along with atrial measures acquired with echocardiography and signal-averaged p-wave duration (SAPD), which is an estimate of the intra-atrial conduction time of the sinus node impulse. The normal subjects will serve as controls for the patients with persistent atrial fibrillation, and will also form the basis for a small introductory evaluation study to estimate the accuracy of the atrial measures. Whilst being primarily descriptive, this study aims to evaluate whether the cardiac measures or the plasma level of the neurohumoral substances possess any potential as prognostic markers for the risk of relapse of atrial fibrillation after successful DC-conversion to normal sinus rhythm.

The normal controls have all been examined, and initial data evaluation has been performed. Furthermore, twenty-five patients with persistent atrial fibrillation have been examined (target: 40-50 patients). Patient inclusion is expected to be complete by the summer of 2002. The project is expected to form the basis for a PhD thesis.

contact: Susette K. Therkelsen

Left Ventricular Remodelling in the First Year Following Acute Myocardial Infarction

Remodelling of the left ventricle (LV) is a detrimental complication to myocardial infarction (MI) characterized by progressive deterioration of ventricular function. The purpose of the study was to establish the frequency and extent of LV remodelling in a modern infarct population offered medical treatment in compliance with daily clinical practice. Furthermore, the study sought to evaluate the predictive value of N-terminal pro brain natriuretic peptide (NT-proBNP). Forty-two patients with a first transmural MI were examined after 1 week, 1 month, 3 months, 6 months and 1 year with blood sampling and MRI. Approximately 1/3 of the patients developed significant LV remodelling during follow-up; these patients could be identified with high diagnostic accuracy by an elevated level of NT-proBNP one week after the MI.

contact: Jens C. Nilsson

Evaluation of Left Ventricular Dimensions and Function in Hypertensive Patients During Treatment with Losartan or Atenolol (a Substudy to the Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study)

The purpose of the study is to evaluate potential effects on left ventricular (LV) dimensions and function from treatment with losartan or atenolol in hypertensive patients with electrocardiographic signs of LV hypertrophy. Approximately 30 patients randomized to either treatment in the LIFE-study have been submitted to cardiac MR examinations before and approximately 5 years after randomization, in order to measure LV volumes, myocardial mass and systolic function. The MR images are currently being analysed.

contact: Mikael Boesen

Myocardial Perfusion Reserve in Type 1 Diabetes

The pathophysiological mechanisms responsible for increased cardiovascular mortality in patients with diabetic autonomic neuropathy are unknown. In order to investigate the effect of autonomic neuropathy on myocardial perfusion, magnetic resonance first pass perfusion imaging was performed before and after Dipyridamole-induced vasodilation in 10 type 1 diabetic patients with autonomic neuropathy (defined by cardiovascular tests), in 10 age- and gender-matched type 1 diabetic patients without autonomic neuropathy and in 10 healthy controls.

Status: Data are expected to form the basis of a PhD thesis.

contact: Mustafa Taskiran

Myocardial Function in Type 1 Diabetes

In addition to the perfusion measurements, patients and normal controls were examined with cine-MRI and echocardiography in order to evaluate the impact of autonomic neuropathy on left ventricular systolic and diastolic function. It has been reported that diabetics often develop some degree of left ventricular diastolic dysfunction, but it is unknown whether autonomic neuropathy is related to this. Status: The data have been evaluated statistically, and are expected to form the basis of a PhD thesis.

contact: Mustafa Taskiran

Rheumatoid Arthritis

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

Based on experiences from two PhD dissertations and a doctoral thesis, current main research efforts of the arthritis research group are divided into the 4 main projects described below.

Research group at DRCMR:

Bo Ejbjerg, Marcin Szkudlarek, Mette Klarlund and Mikkel Østergaard

MRI of Small Extremity Joints in Rheumatoid Arthritis

This PhD study investigates the value of different MRI-methods in RA, particularly early RA. 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 semiquantitative methods can provide information similar to more time-consuming quantitative methods; 3) Whether very detailed examination of a few joints is more sensitive to changes in rheumatoid inflammation and destruction than less detailed examination of many joints; 4) Whether a low-cost dedicated extremity MRI unit can provide similar information as "conventional" expensive high-field MRI units.

Status: Studies were initiated 1/1-2001. Preliminary results suggest comparable sensitivities of low-field and high-field units. Most studies are still in progress.

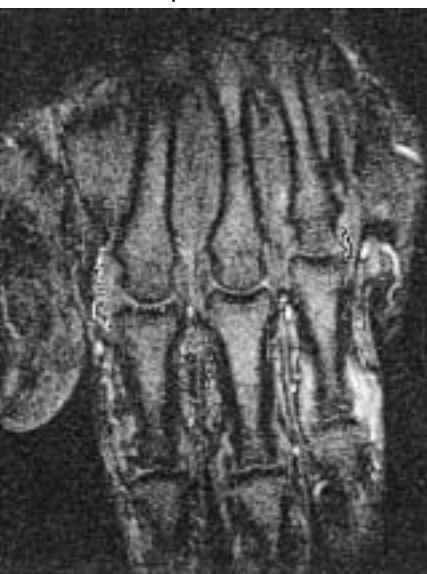
contact: Bo Ejbjerg

Research Projects

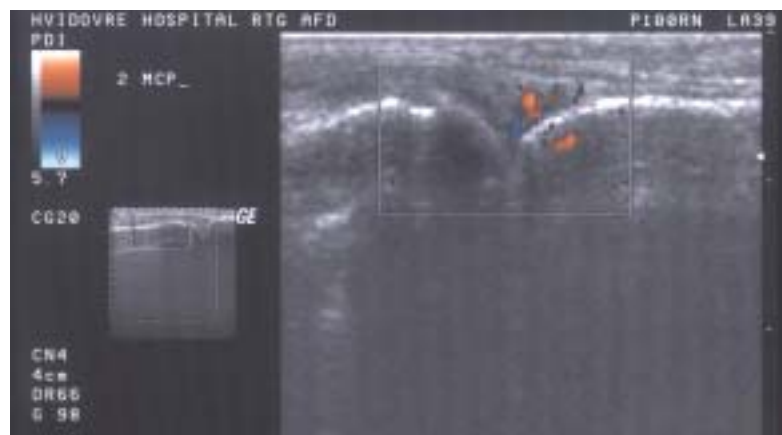
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Ultrasonography of Small Extremity Joints in Rheumatoid Arthritis

Ultrasonography (US) is more available and less expensive than MRI. Novel high-frequency transducers allow high-resolution assessment of the small joints of the hands and feet. The projects in the PhD study focus on ultrasonography, including the flow-sensitive Power Doppler technique, of the joints of the hands and feet in RA, including early RA. The projects include a number of methodological studies, comparison with clinical, histopathologic, radiographic and MRI findings, as well as longitudinal studies to investigate the sensitivity to change.



Dynamic post.-contrast MR examination of a patient with 3-year-old rheumatoid arthritis T1-weighted FLASH image of the patients' dominant hand after injection of Gd-DTPA, showing swollen synovium in the 2nd and 4th MCP-joints and in the 4th PIP-joint.



Ultrasound image of the same patient's 2nd MCP-joint with power Doppler signal in swollen and hypoechogenic synovium.

Status: The PhD-study was initiated 1/1-2000. Data acquisition in the cross-sectional studies is completed. Main results so far include a generally good inter-observer agreement on US-findings and a very high agreement between Power Doppler US and dynamic contrast-MRI (published 2001). This indicates that US is reliable for assessment of finger joint synovitis. Most data remain to be analysed.

contact: Marcin Szkudlarek

International Collaboration on MRI Definitions, Scoring Methods and Validation

As a consequence of the fact that MRI scoring methods of RA joints are insufficiently validated, an "OMERACT-MRI" study group with expertise in MRI in RA and in scoring methodology have, since 1999, worked on developing definitions of RA changes and on developing and testing scoring methods. OMERACT is an international forum which performs validation studies and seeks consensus within Outcome MEasures in Rheumatoid Arthritis Clinical Trials.

Status: Based on biannual meetings and a number of validation exercises, MRI definitions of important RA joint pathologies and preliminary scoring methods have been suggested. Further validation studies, particularly concerning longitudinal data, are required.

contact: Mikkel Østergaard

MRI of Wrist and Finger Joints as Outcome Measure and Prognostic Marker in Early Rheumatoid Arthritis - a Longitudinal Multi-centre Study of 160 Early RA Patients

Through sequential MRI of wrist and finger joints of patients included in a Danish multicentre 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.

Status: 116 patients are included.

contact: Bo Ejbjerg

Respiratory Medicine

Conventional MR imaging does not provide functional information on the lungs. Neither does it offer detailed structural information, as only the outline of the lungs can be visualized using conventional MRI. This is due to the enormous surface area, causing rapid signal loss. Instead, the clinicians rely on radionuclear techniques for imaging of lung diseases. Unfortunately, these give relatively poor spatial resolution even for high dose radiation.

It has recently become possible to magnetize certain gasses using strong lasers and techniques relying on fundamental atomic physics. The magnetic gas can be inhaled by patients, and be used for forming detailed MR images of lung function and structure. The most promising gas for this purpose is an inert and non-radioactive Helium isotope, He-3, which is completely harmless to the body.

The gas can stay magnetised for days, when kept in special containers, and it can consequently be shipped over large distances. This is important, since it is immensely complicated to reach high grades of magnetisation of the gas. It is therefore only performed at few institutions worldwide.

Research-group at DRCMR:

Trine Stavngaard, Lise V. Søgård, Lars G. Hanson and Olaf B. Paulson

Polarized Helium to Image the Lung

The DRCMR is one of three European clinical centres involved in the EU sponsored Polarized Helium to Image the Lung (PHIL) project, which aims at evaluating the potential of this new technique.

The Helium is magnetized in Mainz, Germany, and is shipped to Hvidovre Hospital and Sheffield University to be used for lung imaging. The lung MR images will be compared to conventional lung examinations to evaluate whether the new technique offers the expected clinical advantage. Other centres in the project are involved in improving the techniques for magnetising and imaging the gas.

The patient population selected for the PHIL project suffers from COPD (chronic obstructive pulmonary disease). The cohort encompasses 120 patients with chronic bronchitis and emphysema. These diseases can be caused, for example, by genetic disorders (such as alpha1-antitrypsin-deficiency) and smoking. It is hoped that the new non-invasive technique will provide a means of early diagnosis and treatment monitoring for these widespread diseases.

Further information on the PHIL project homepage, <http://www.phil.ens.fr/>.

Status: The project started December 2000. The first year was used for planning the patient study, obtain-

ing necessary permissions and performing hardware upgrades to allow controlled helium imaging on a clinical scanner. Patient and volunteer scans will commence in year 2002.

contact: Trine Stavngaard

Pre-Clinical Studies

The pre-clinical studies performed at DRCMR are designed primarily to support the clinical work performed within Hvidovre Hospital. The pre-clinical work aims to develop, evaluate, refine and implement new MR techniques in order to measure the biochemical (metabolic), physiological and morphological characteristics of disease states. The acquired parameters could then be used to monitor therapeutic interventions and facilitate the development of new therapeutic agents and strategies both in pre-clinical development and in clinical trials. Ultimately, developed techniques should be applied routinely in clinical diagnosis, prognosis and monitoring.

Research group at DRCMR:

Elisabeth Hildebrandt-Eriksen, Ian Rowland, Niels Broberg and Helle Simonsen

Metabolite Compartmentalisation: Preliminary Studies in Normal Brain

Previous clinical studies have revealed significant effects of contrast agents on brain proton MR spectra. Signal loss of approximately 15% has been observed for choline following administration of Gd-DTPA using T2-weighted (T2W) spectroscopy. In addition, T1-weighted (T1W) spectroscopic studies have shown minimal choline line-broadening effects. In the normal brain Gd-DTPA would be expected to act as intravascular blood pool agent. An intact blood brain barrier would prevent direct interaction between the contrast agent and metabolite. Hence the effect of the contrast agent on the predominantly intracellular metabolites, choline (Cho), creatine (Cr) and N-acetylaspartate (NAA) would be expected to be dependent on the vascular properties of the tissue. Preliminary studies on normal brains and brains with infarcts have been performed using T1W single voxel spectroscopy at doses higher than can be used clinically. Under these conditions, significant contrast induced chemical shifts were observed for all metabolites. This was attributed to changes in the bulk susceptibility of the brain tissue. Future studies will investigate the effects of contrast agents on spectra acquired from pathological brain tissue.

contact: Ian Rowland

Research Projects

- Multiple Sclerosis
- Functional Brain Imaging
- Stroke
- Ageing and Dementia
- Other Degenerative Diseases
- Psychiatry
- Image Segmentation and Visualization
- Perfusion
- Cardiology
- Rheumatoid Arthritis
- Respiratory Medicine
- Pre-Clinical Studies
- Geology

Investigation of the Glutamate Antagonist SPD-502

SPD-502, an antagonist to the glutamate receptor of the AMPA subtype, was tested in a model of mild focal cerebral ischaemia in the rat. This animal model of human stroke yields cortical infarcts (100 mm³ on average) after reversible occlusion of both carotid arteries and the distal part of the middle cerebral artery for 30 minutes. Treatment with the antagonist was initiated 2 hours after reperfusion as a bolus and infusion for 24 hours, both given intravenously. The control group received saline analogously. SPD-502 reduced infarct size by almost 50%. The MR characteristics (T2 (transverse relaxation constant) and Apparent Diffusion Coefficient) of the developing and final infarct area and the remaining healthy brain tissue, respectively, were similar between the control and the SPD-502 group. Reperfusion was verified in all animals with the non-delayed passage of a bolus of MR contrast agent.

Delayed treatment with SPD-502 is effective in reducing cortical infarct volume in this animal model of mild focal cerebral ischaemia. This is the first report of effectiveness of this drug in a model of focal cerebral ischaemia.

contact: Elisabeth Hildebrandt-Eriksen

MR imaging of Vascular Casts

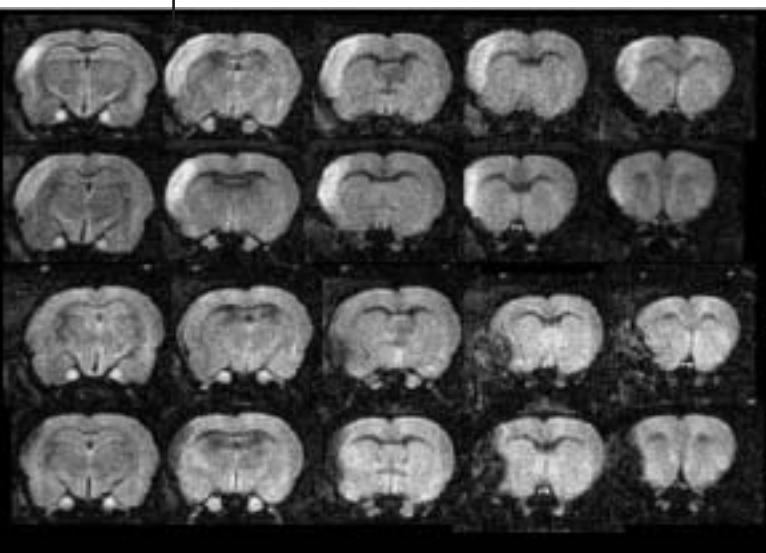
The aim of this study was to establish an ex vivo method of investigating tissue vasculature directly using MRI. Using standard corrosion casting methods, a variety of materials were assessed for their suitability for casting and MRI. The study revealed that a silicone-based material exhibited properties suitable for both casting and obtaining 2D and 3D images. Furthermore, paramagnetic gadolinium containing complexes could be incorporated into the casts enabling the production of phantoms of differing magnetic susceptibilities suitable for assessing and validating direct and indirect methods of obtaining vascular information.

contact: Ian Rowland

Development of an Electroporation System for Use within an MR Scanner

In vivo electroporation is an established means of increasing cellular permeability to drugs and other agents by applying strong pulsed electric fields to tissue to increase intracellular drug uptake as in the case for electrochemotherapy. Successful clinical application of this approach requires identification of the tissue to be electroporated with subsequent monitoring of treatment efficacy. Consequently, an electrode system suitable for use within a MR scanner has been developed and applied successfully in vivo. Standard MR methods have been used to monitor the effects of high voltage pulses performed within the bore of a MR scanner. Results from this study indicate that MR methods could be applied to treatment planning, dosimetry and monitoring of electroporation based gene and chemotherapeutic strategies.

contact: Ian Rowland



Day 1

Day 3

Day 7

Day 14

Infarct development monitored non-invasively by MRI within the same animal. On these coronal sections through the brain of a saline-treated rat, the lesioned side shows edema at first, then tissue changes progress finally yielding cystic cavitation of the diseased tissue.

MR Imaging of Plastinated Tissue

Plastination is an established technique for the long-term preservation of tissue. In this process, water and lipid is removed and replaced by a curable polymer thereby providing hard and durable anatomical specimens. Methyl groups within the polymeric silicone are known to rotate freely at room temperature and possess relaxation properties making it possible to image the methyl protons. Our studies have shown that human kidney together with human and animal brain tissue, plastinated using a silicone S10 standard technique, can be imaged using MR. Furthermore, the specimens provide images that exhibit contrast between, for example, white and grey matter. This ongoing work suggests that plastinated specimens may be used as MR phantoms and that their study may provide further insight into MR contrast mechanisms in vivo.

contact: Ian Rowland



Spin echo image of a plastinated human brain slice at 4.7T, showing contrast between grey and white matter.

Geology

Natural rocks have a porous structure, where the pore space may constitute anything from 0 to 50 % of the total rock volume. If the pore space contains one or more hydrogen-containing fluids, the fluid distribution may be imaged by proton MR imaging, provided the rock has acceptable magnetic characteristics. Geological Survey of Denmark and Greenland (GEUS) uses MR imaging to study the distribution of oil and water in a variety of experiments, where the ultimate goal is to optimise the recovery of oil and gas from Danish oil and gas fields. The experiments are typically flooding experiments, where water or oil is pumped through a rock sample under controlled conditions, and the production of water and oil is recorded.

Research group at DRCMR:

Dan Olsen, in collaboration with GEUS (Geological Survey of Denmark and Greenland)

GEUS Activities at DRCMR in 2001

In 2001 Geological Survey of Denmark and Greenland (GEUS) utilised the SISCO 4.7 T scanner at Danish Research Centre for Magnetic Resonance in the project "Three-Phase Immiscible WAG Injection: Transport Mechanisms and Multiscale Reservoir Models", which is financed by Energiforskningsprogrammet (EFP) under the Ministry of Economic and Business Affairs. The project investigated transport mechanisms during WAG injection (water-alternating-gas injection) at pore scale as well as macroscopic scale, with special emphasis on the chalk lithology. WAG injection is used in certain hydrocarbon fields to increase the oil production, but has so far not been used in the Danish hydrocarbon fields. A pilot study on the SISCO scanner evaluated to what extent NMR may be used for quantitative determination of fluid saturations in a WAG model system by investigating the fluid system water-decane-benzyl alcohol in the pore space of a chalk sample from the Tyra field. At room temperature and low pressure, this system is a three-phase fluid system with approximately 5% mutual solubility between water and benzyl alcohol. The pilot project used a 2D CSI technique to separate the signals from the three fluid phases, and succeeded in producing quantitative 2D saturation maps with a reproducibility of 1.5-4 p.u. (porosity units) (1 sigma) at pixel level. The mean fluid saturation of the sample was determined with an accuracy of 3 p.u. or better. It was concluded that the method could be used as an experimental model system of a WAG injection process.

contact: Dan Olsen

Doctoral and PhD Theses

The DRCMR has over many years, provided facilities for PhD students in various research projects in the field of MR. In 2001, one doctoral (DMSc) thesis and four PhD theses based on research carried out at DRCMR were defended successfully.

Magnetic Resonance Investigations of the Human Infant Brain Peter Bjerre Toft, MD, DMSc

Thesis defended August 17th, 2001.

This doctoral thesis was based on MR investigations of the normal and sick human infant brain. The methods used were proton magnetic resonance spectroscopy, magnetic resonance imaging, magnetic resonance diffusion measurements, and mapping of vascular reactivity to changes in carbon dioxide by using functional magnetic resonance imaging.

Concentrations of choline, total creatine, N-acetyl-L-aspartate and lactate were estimated by proton magnetic resonance spectroscopy in healthy infants less than one year of age, and in infants born preterm - with and without intrauterine growth retardation. The concentration of lactic acid in a volume of interest including the striatum was shown to be independently associated with the severity of intrauterine growth retardation and with the degree of prematurity. In preterm infants with germinal matrix haemorrhage the concentration of lactic acid was highest in the side of the brain with the (largest) germinal matrix haemorrhage. At the corrected age of three months the concentration of choline was highest in the side with the (largest) lesion, possibly indicating a more persisting damage or delay of maturation.

The volume of the total brain and of some of its larger nuclei was determined by magnetic resonance imaging volumetry. In a group of newborn infants with various

severity of intrauterine growth retardation it was found that postnatal brain growth is primarily due to cortical growth. It was also found that brain volume is less affected than total body weight in intrauterine growth retardation.

Using diffusion weighted magnetic resonance imaging the apparent diffusion coefficient for water was measured in the newborn brain, and maps of these values could depict unmyelinated tracts of nerve fibres before they became apparent on T1 and T2 weighted magnetic resonance images.

By means of gradient echo magnetic resonance imaging, changes of the magnetic resonance signal in the brain, was observed during hyperventilation of the sick infant brain.

In a separate article the significance of the observed elevation of the lactate level was discussed. The hypothesis that perinatal striatal injury may play a role in the development of behavioural disorders with hyperactivity and deficit of attention was proposed and discussed.

In conclusion, an elevated level of lactate and hereby a disturbance of the oxidative metabolism in the brain is the result of several perinatal disorders.

Age-Related White Matter Changes in MRI. Evaluation of a Possible Relation to Changes in Cognitive Function in a Population of Normal 80 Year Old Subjects.

Ellen Garde, MD, PhD

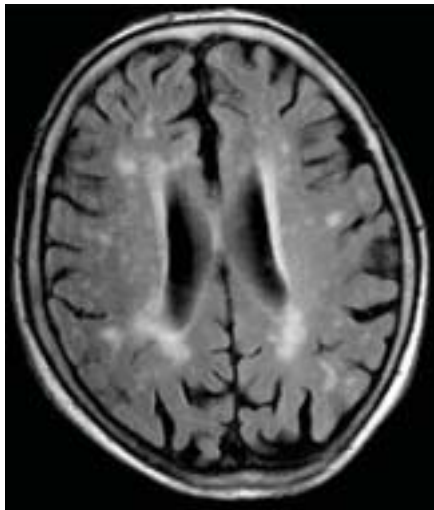
Thesis defended May 8th, 2001

The process of ageing is not homogeneous and familiarity with the range of normal findings is crucial in order to be able to recognize abnormal conditions.

Magnetic resonance imaging (MRI) offers detailed topographic images due to unique contrast resolution. Particularly in the evaluation of white matter changes in the elderly, MRI might provide valuable information regarding the dynamics of normal cerebral ageing.

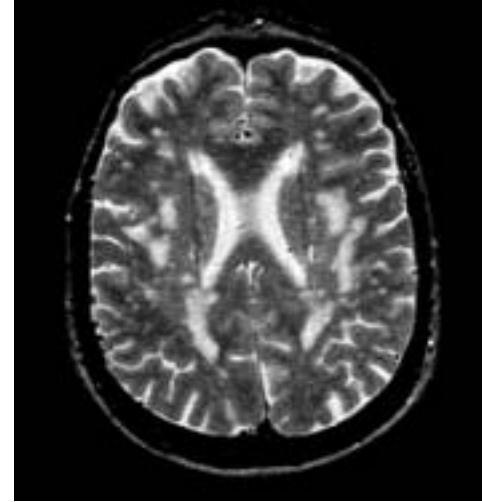
A survey of the current literature on MRI detectable white matter hyperintensities (WMH) points toward WMH as a predominantly small-vessel disease associated with blood pressure dysregulation, and repeated episodes of transient decrease in CBF as a main factor contributing to the formation of WMH. Previous studies also indicate that WMH, as one of several factors, may eventually affect abilities such as gait and global as well as selective cognitive functions.

This view is supported by our longitudinal study which show that even in a sample of community-dwelling Danish octogenarians, a significant correlation exists between WMH and changes in intelligence from age 50 to age 80. In particular, a correlation with specific subtests reflecting speed of mental processing and attention corroborates with findings from the literature that WMH mainly affect functions related to the frontal lobe.



MR image (FLAIR) of the brain of an 85 year old man who has been participating in the Glostrup Population Study for 35 years. This axial slice shows periventricular and deep white matter hyperintensities.

80-year old non-demented woman with moderate WMH. Walks with a cane due to periodic imbalance but no subjective complaints of cognitive impairment.



Even though a very low frequency of silent infarcts suggest that cerebrovascular disease was absent or mild in most of our participants, the incidence of risk factors was in accordance with data from a Danish health survey. In our sample of octogenarians the presence of WMH was significantly associated with the use of anti-hypertensive drugs.

In a diagnostic context, WMH could be regarded as a warning that preventive measures are called for, especially directed towards dysregulated blood pressure in the elderly.

Our future research in age-related white matter changes will be directed towards the study of progression of WMH in relation to cognitive function and neurological disabilities, as well as an evaluation of the association with risk factors, e.g. the role of blood pressure dysregulation in the elderly. In addition, newer MRI techniques will be applied in order to visualize the structural changes and elucidate the pathophysiological mechanisms behind WMH.

Cerebral Magnetic Resonance Imaging (MRI) and Ultrasound (US) in Preterm Infants: Prospective Comparison Study and Correlation with The Neurodevelopmental Status (at 1 and 2 yr. of Age)

María J. Miranda, MD, PhD

Thesis defended August 15th, 2001

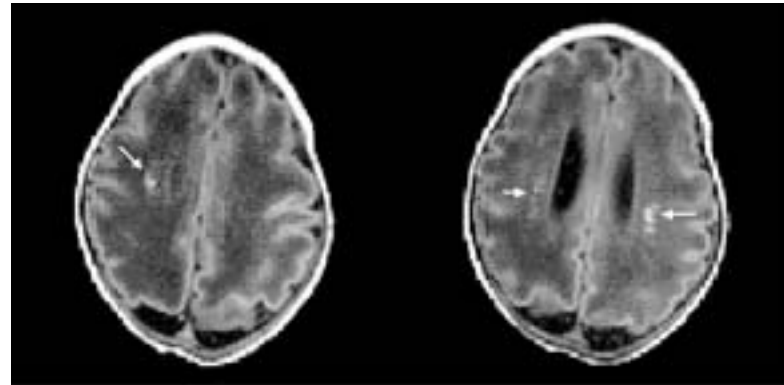
Background:

Epidemiological and pathology studies of preterm infants indicate that subtle lesions may occur in the immature brain without being diagnosed by ultrasound. These studies demonstrate a high incidence of neurodevelopmental problems and MRI brain abnormalities in later life.

Aims:

(1) To describe normal maturational findings in the immature brain, (2) to compare early brain ultrasound and MRI; and (3) to evaluate the prognostic value of neonatal MRI and US with regard to neuropsychological outcome at 1 and 2 years of age.

Early neonatal cerebral MRI and US were performed on 60 preterm neonates with a median birth weight of 1270 g, at a median postmenstrual age (PMA) of 32.4 weeks (range 28.3-38.6). A 1.5 Tesla Siemens Vision scanner was used. A scoring system was used registering normal and abnormal findings in the brain. Abnormal findings were grouped in 3 scores: (1) Germinal matrix haemorrhage score, (2) Periventricular Leukomalacia (PVL) spectrum score, and (3) other brain lesions score. The neuropsychological status was assessed using the Griffiths scales (GQ = General Quotient) at age 1 and 2 years. MRI & US Scores were correlated to neurodevelopmental results.



T1-weighted images showing punctate white matter lesions in the periventricular white matter of the brain in a preterm infant born 9 weeks before term.

Results and conclusions:

MRI revealed a significant number of punctate white matter lesions (n= 10 (16%)) not seen by US (see table score 2a and figure).

From this study we can conclude that neurodevelopment at 2 years of age, measured by the Griffiths GQ, is related to neonatal MRI and US scores. MRI is superior to US in determining the total PVL spectrum of lesions (see table);, and MRI is more precise in predicting neurodevelopment (GQ) at 2 years of age by all 3 MRI scores

	<u>Score 1:</u>		<u>Score 2:</u>
	GM/IVH & Ventricular size score (1a)	Large white matter hemorrhages (1b)	Punctate white matter lesions (2a) & cystic PVL(2b)
Total infants US/MRI	60/59 (100%)	60/59 (100%)	60/59 (100%)
Total lesions US	N=20 (33%)	N=7 (11.5%)	N= 0 (0%)(2a) N= 2 (3%)(2b)
Total lesions MRI	N=24 (40%)	N=6 (10%)	N= 10 (16%) (2a) N= 2 (3%) (2b)

Number (%) of infants with abnormal findings on MRI and US in Scores 1 and 2.

Evaluation of Human Stroke by MR Imaging

Sverre Rosenbaum, MD, PhD

Thesis defended March 30th, 2001

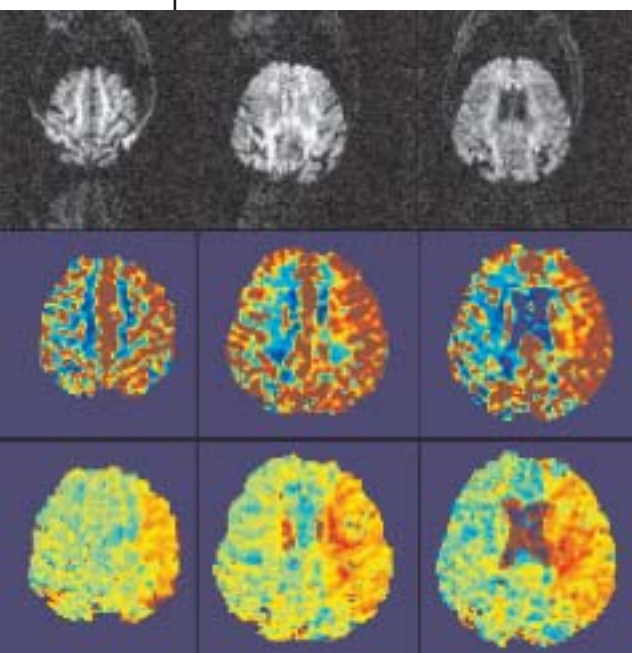
Ischemic brain tissue can be visualized by diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI). The combination of DWI and PWI has been shown to be promising in identifying potentially salvageable ischemic areas. Implementation of fast T2*-weighted (T2*W) echo planar imaging (EPI) has made it possible to detect haemorrhages, in the acute phase. These advances have turned attention to the possible use of MRI for rational stratification of patients with stroke to thrombolytic or neuroprotective treatment, from a knowledge of the metabolic status and from the exclusion of haemorrhages.

T2*W-EPI based detection of acute haemorrhages is a more sensitive method than other MR-techniques. However, further studies are needed to compare the sensitivity to that of CT.

Identification of haemorrhagic infarcts (HI) is important prior to thrombolytic therapy – in order to minimise the risk of inducing additional haemorrhages.

In 43 patients suffering from ischemic stroke, it was examined whether T2*W-EPI was more sensitive than T1-weighted (T1W) MRI in detecting HI. It was found that T2*W-EPI detected HI with very low sensitivity compared to conventional T1W-MRI. It was hypothesized that this was caused by a higher oxygenation state than in space-occupying haemorrhages. Disruption of the blood brain barrier was associated if HI was identified on both T2*W-EPI and T1W-MRI. This group of patients was hypothesized to have an increased risk of bleeding after thrombolysis or anticoagulant treatment.

Nine patients suffering from acute ischemic stroke were examined serially by DWI and PWI. Two patterns were interpreted as identifying viable tissue. The identification of these patterns was found valuable in stratifying acute stroke patients either to thrombolytic or neuroprotective treatment.



MR imaging in acute ischemic stroke performed within 24 hours from onset of symptoms. The left panel shows diffusion-weighted images of the brain (upper row), blood volume images (middle row) and images of showing the transit delay needed for Gd-DTPA to reach the brain (bottom row). There is a mismatch between the area in which Gd-DTPA is delayed (red) and the sparsity of lesions seen in the diffusion-weighted images. At follow-up at 3 days (right panel), a lesion had developed in the mismatch area.

Postmenopausal Hormone Replacement Therapy and Cardiovascular Disease – Effects on Blood Pressure and Velocity-encoded Magnetic Resonance Measures of Aortic and Cerebral Blood Flow

Morten Beck Sørensen, MD, PhD

Thesis defended September 21st, 2001.

This PhD thesis is based on research performed during a fellowship at the Department of Obstetrics and Gynaecology, Hvidovre Hospital, University of Copenhagen, Denmark and the Cardiovascular MR Unit, Royal Brompton Hospital, London, England. The studies were conducted in cooperation with Danish Research Centre for Magnetic Resonance and Departments of Cardiology and Nuclear Medicine at Hvidovre Hospital.

Cardiovascular disease is the most common cause of death in women, and is a disease where the female sex hormones play an important role. Menopause is regarded as an independent risk factor for coronary disease in women and several studies have demonstrated positive effects of postmenopausal oestrogen replacement on risk markers for coronary disease and stroke. In the experimental part of the dissertation, vascular effects of sequential hormone replacement therapy (HRT) were studied by velocity encoded magnetic resonance with emphasis on two issues: Temporality and progestogen addition. Cerebral blood flow, systemic vascular resistance, stroke volume, blood pressure and markers of changes in coronary blood flow and aortic compliance were studied in a crossover study in healthy postmenopausal women, randomised to oestradiol and cyclic norethisterone acetate or placebo.

Reduced cardiac workload (reduced blood pressure and systemic vascular resistance) and compensatory increase in stroke volume as well as reduced blood pressure response to mental stress, were constant throughout the three months of therapy. Progestogen did not negate the vasodilatory properties of oestrogen. The mentioned effects are firmly established as coronary risk reducing measures and have, in long term studies, been shown to reduce coronary morbidity and mortality. The findings were accompanied by reductions in the estimate of change in coronary blood flow. Overall, cerebral blood flow was unaffected by HRT after three months of combined HRT. The progestogen caused significant cerebral vasodilation and a rather unexpected drop was seen after 9 weeks of combined therapy, which could be related to norethisterone withdrawal. In addition to changes in cholesterol metabolism and insulin sensitivity, the vascular effects of hormone replacement are likely to prevent cardiovascular morbidity and mortality. Large prospective and randomised studies of the effects of oestradiol and norethisterone acetate on cardiovascular morbidity and mortality endpoints are needed.



Measurement of cerebral blood flow by velocity-encoded magnetic resonance
Left: Sagittal gradient echo magnetic resonance image used for piloting of the cross sectional plane (line) used for MR flow measurement. Right: Cross sectional magnitude cine image for assessment of cerebral blood flow. Flow velocity and vessel area is measured in the 4 cerebral arteries (arrows) and total cerebral volume flow is calculated.

Diffusion Tensor MRI of Brain Anatomy in Health and Disease

Mette R. Wiegell, PhD

Thesis defended May 30th, 2001

Diffusion tensor imaging (DTI) is a magnetic resonance imaging method to measure the molecular self-diffusion of water in three dimensions. Given the microscopic scale of diffusion in biological tissue, DTI provides an exquisitely sensitive probe of the tissue structure including the orientation and anisotropic organization of the diffusion compartments. Traditionally, DTI studies have reported scalar measures of diffusion, such as anisotropy and mean diffusivity, neglecting the rich geometric information available in the full eigenstructure of the diffusion tensor. Under the belief that the geometry of the diffusion tensor could provide greater insight into neural tissue structure and architecture, we undertook a detailed DTI study of human white matter anatomy in health and disease. The background and the results of the DTI analysis form the major sections of the thesis as described below.

Background:

The anatomy of the human brain is reviewed from the cellular to the gross anatomical levels. Particular emphasis is placed on the cellular properties which influence diffusion contrast such as the cellular length scales and membrane characteristics. The experimental basis of DTI is described in detail including diffusion theory, the diffusion MRI experiment, and calculation of diffusion tensor. The influence of sequence parameters such as diffusion time and diffusion weighting are discussed.

Cross-fibre anatomy:

We developed an approach for imaging intravoxel white matter fibre inhomogeneity, i.e. fibre crossing and divergence, by referencing the full eigenstructure of the diffusion tensor including the major, medium and minor eigenvectors. The model revealed planar fibre anatomy in regions of fibre crossing such as the intersection of

the corona radiata with the corpus callosum, and the divergence of the superior longitudinal fascicle. The principal eigenvector picture, on the other hand, incorrectly assigned these areas an intermediate fibre direction inconsistent with the component fibre anatomy.

Thalamus:

DTI of the thalamus revealed anisotropic diffusion aligned with the corticothalamic and thalamocortical projections. Incorporating the full diffusion tensor into an unsupervised k-means clustering algorithm provided segmentation of the thalamic nuclei based on the fibre/sheet orientation of the white matter projections. The automatic segmentation agreed well with stereotyped histological atlases.

Pathology:

The influence of pathology on diffusion was considered for multiple sclerosis and the long-term effects of radiotherapy, two pathologies characterized predominantly by extensive demyelination. The results were reported with respect to diffusion coefficients, anisotropy and structural changes. An interesting result consistent across both studies was diffuse white matter changes in the normal appearing white matter. We hypothesized that this effect was due to subtle changes in the extracellular medium and/or fibre specific degeneration. In the white matter lesions of both pathologies the dominant effect was an increase in diffusion accompanied by a decrease in anisotropy, which we attributed to the demyelinating effects of the pathologies. Despite extensive abnormalities on T2-weighted MRI, DTI showed intact fibre orientations with reduced anisotropy. Remarkably, fibre specific degeneration was observed in both pathologies in terms of an increase in anisotropy associated with structural changes.

Other Activities

Congress and Workshop Participation

The staff of DRCMR have participated in the following international meetings and congresses related to their research fields.

- Integrated Functional Imaging Workshop, University of Pittsburgh, Pennsylvania, USA, March 2001. (2 delegates)
- Joint Annual Meeting of the International Society of Magnetic Resonance in Medicine and the European Society for Magnetic Resonance in Medicine and Biology, Glasgow, Scotland April 2001. (18 delegates)
- International Congress on Schizophrenia Research, Whistler, British Columbia, Canada. April/May 2001. (1 delegate)
- 50th Scientific Session of the American College of Cardiology, Orlando, USA. March 2001. (1 delegate)
- Europace, Copenhagen, June 2001. (1 delegate)
- Human Brain Mapping, Brighton, United Kingdom, June 2001. (5 delegates)
- Heart Failure, Barcelona, June 2001. (2 delegates)
- First International workshop of the white matter study group, Bordeaux, France, June 2001. (2 delegates)
- Advances in Diagnostic Methods and Complications of Epilepsy, Århus, June 2001. (1 delegate)
- Scientific Sessions 2001 of the European Society of Cardiology, Sweden, September 2001. (1 delegate)
- Nordic MATLAB Conference, Oslo, October 2001. (1 delegate)
- Workshop on Minimum MR Data Acquisition Methods: Making More with Less, Marco Island, Florida, USA, October 2001. (1 delegate)

Congress Organization

Olaf Paulson is a member of the local organizing committee for the European Society for Magnetic Resonance in Medicine and Biology 21st Meeting, Copenhagen 2004.

Pre- and Postgraduate Teaching

Organization of Courses and Symposia

- Functional Imaging Techniques II: Tracer Kinetics in Nuclear Medicine and Magnetic Resonance Imaging, December 3-7, 2001 (Gitte Moos Knudsen, Henrik B.W. Larsson, Jacob R. Marstrand, Egill Rostrup and Claus Svarer).
- On January 17, 2001 DRCMR organized a one-day public symposium.

Pregraduate Supervision

- Christoffer Torrendrup, high school student. Final-year project in physics. Supervisor: Lars G. Hanson (DRCMR).
- Minna Nørgaard, MSc student (human biology). Graduate thesis: An fMRI Study on Hemispheric Dominance of Language Activation. Supervisor: Egill Rostrup (DRCMR). Co-supervisors: Torben Lund (DRCMR) and Bjørn Quistorff (Department of Medical Biochemistry and Genetics, University of Copenhagen).
- Stefan Wolff, MSc student (software engineering). Graduate thesis: Computer Aided Analysis of MR Brain Images. Supervisor: Per Skaftø Hansen (Informatics and Mathematical Modelling, Technical University of Denmark). Co-supervisors: Lars G. Hanson, Margrethe Herning, Torben Lund (DRCMR).
- Tim Dyrby, MSc student (software engineering). Graduate thesis: Brain segmentation in the presence of coil inhomogeneity (in preparation). Supervisor: Lars Kai Hansen (Informatics and Mathematical Modelling, Technical University of Denmark). Co-supervisor: Lars G. Hanson (DRCMR).
- Annette Schneider, MSc student (physics). Graduate thesis: Advanced spectroscopic methods (in preparation). Supervisor: Stig Steenstrup (Niels Bohr Institute for Astronomy, Physics and Geophysics (NBI-AFG), University of Copenhagen). Co-supervisor: Lars G. Hanson (DRCMR).
- Niels Broberg, BSc student (electrical engineering). Graduate thesis: Design, optimisation and assessment of an electrode system for in vivo electroporation within an MR scanner. Supervisor: Ian Rowland (DRCMR).

Pregraduate Teaching

- Nonlinear Signal Processing, Technical University of Denmark (Irene K. Andersen, Karam Sidaros).
- Applied Statistics and an Introduction to SAS and S+, Technical University of Denmark (Irene K. Andersen).

Postgraduate Teaching

- Specialist training course (A-course) in neurology: Demyelinating Diseases and Neuro Infections: Diagnostic Challenges in Multiple Sclerosis: MRI aspects (Annika Langkilde)
- Specialist course in neurology: MR in Stroke (Sverre Rosenbaum)
- Specialist course in psychiatry: The Application of Magnetic Resonance Imaging in Biological Psychiatry (Katrine Pagsberg)
- PhD course in functional imaging: Magnetic Resonance Imaging (Lars G. Hanson)
- Specialist course in rheumatology: MRI in Rheumatic Disease (Mikkel Østergaard)

- Course in Musculoskeletal Ultrasonography: "Arthritis: Clinic appearance and diagnostic" (Mikkel Østergaard)
- Postgraduate Course in Imaging in Rheumatology: Magnetic Resonance Imaging (Mikkel Østergaard)
- Postgraduate Course in Imaging in Rheumatology: Ultrasonography (Marcin Szkudlarek)

National and International Committees

National Committees

- Chairman, Department of Clinical Neuroscience and Psychiatry, University of Copenhagen (Olaf B. Paulson)
- Secretary of the Danish Society for Neuroscience (Olaf B. Paulson)
- Board Member of the Danish Alzheimer Association (Olaf B. Paulson)
- Board Member of the Research Council of the Copenhagen Hospital Corporation (Katrine Pagsberg)

International Committees

- Past President of the International Society of Cerebral Blood Flow and Metabolism (Olaf B. Paulson)
- Board Member of the World Federation of Neurology, Research Group on Dementia (Olaf B. Paulson)
- Member of the European Federation of Neurological Societies Working Group on Brain Imaging (Olaf B. Paulson)

- Country Coordinator for Denmark in the European Task Force on Age-related White Matter Changes (Ellen Garde)

Evaluation

- Member of the European Commission 5th Framework Programme expert panel 2001, Brussels (Olaf B. Paulson)
- Evaluator of one PhD-thesis (Olaf B. Paulson)
- Evaluator for a position as Professor of neurology at Helsinki University (Olaf B. Paulson)
- Evaluator for a position as Professor of neurology at Karolinska Institute (Olaf B. Paulson)
- Invited independent expert reviewing research projects for the University Research Plan, University of Siena, Italy (Ellen Garde).
- Finally, staff members of DRCMR regularly conduct peer-reviews for several international journals and at international congresses.

Awards

- Olaf B. Paulson: Niels A. Lassen Award 2000 (awarded on late Niels A. Lassen's 75 years birthday December 7th 2001).
- Marcin Szkudlarek: Margarethe Astrid Hedvig Schau-fuss grant.

Outlook . . .

A new year, a new scanner

The year 2002 will be a year of installation and expansion. The most important predictable event is expected to be the installation, by the end of the summer 2002, of the new 3 Tesla scanner, donated by the Simon Spies Foundation. This will significantly increase the capacity of the centre of both the clinical and research activities. During the first year, the new scanner will be used in research projects and for critical evaluation of the machine's clinical utility. This will give additional clinical capacity on the other scanners. Following the critical evaluation, the 3 Tesla scanner will be used more broadly for clinical diagnosis.

The centre's research activities cover many fields, brain, heart, joint, lung research and others. These areas will benefit from a number of grants to support the research work. For example, the department will utilise new equipment allowing electroencephalographic recording in the scanner, facilitating frontline brain research. The start of 2002 will also see the employment of a new clinical physicist whose duties will be to assist in the development and implementation of new and improved diagnostic MR techniques.

It is the hope of the department to strengthen collaboration both nationally and internationally. International collaboration is already well established, some of which is funded through the EU 5th Framework and we are looking to further broad-based collaboration in the future. Increased focus will be put on the collaboration with our partners: Informatics and Mathematical Modelling at the Technical University of Denmark, Neurobiology Research Unit, and the PET and Cyclotron Unit at Copenhagen University Hospital, Rigshospitalet; and the Department of Psychology, Faculty of Humanities at the University of Copenhagen. Together with the Department of Medical Chemistry at The Royal Danish School of Pharmacy and H. Lundbeck A/S, Copenhagen, all these centres will form a co-ordinated collaboration in the form of the Copenhagen Brain Research Center (<http://www.cbrc.dk/>) to be formally established in the spring of 2002.

With the employment of new staff and the acquisition of new facilities, we are well positioned to successfully meet the new challenges that the next scientific year will bring us.

Publications

A large number of publications has resulted from the research carried out at DRCMR during 2001. The most important of these publications are listed here according to category.

Dissertation

1. Toft, P.B. Magnetic Resonance Investigations of the Human Infant Brain 2001

PhD Theses

1. Garde, E. Age-related White Matter Changes in MRI. Evaluation of a possible relation to changes in cognitive function in a population of normal 80 year old subjects 2001;
2. Miranda, M.J. Cerebral Magnetic Resonance Imaging and Ultrasound in Preterm Infants: Prospective Comparison Study and Correlation with the Neurodevelopmental Status (at 1 and 2 Years of Age) 2001;
3. Rosenbaum, S. Evaluation of Human Stroke by MR imaging 2001;
4. Sørensen, M.B. Postmenopausal hormone replacement therapy and cardiovascular disease - effects on blood pressure and velocity-encoded magnetic resonance measures of aortic and cerebral blood flow 2001;
5. Wiegell, M.R. Diffusion tensor MRI of brain anatomy in health and disease 2001;

Peer Reviewed Journal Articles

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- Other Publications (Abstracts not Included)**
1. Groenning BA, Nilsson JC. "Multiple Regression: A Primer" by Paul D. Allison (book review). *Statistics in Medicine* 2001;20(12):1888-9.
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- Conference Proceedings**
- Oral Presentations**
- American College of Cardiology 50th Annual Scientific Session, Orlando, USA (1 presentation)
 - F Hoffmann-La Roche Workshop, Malta (1 presentation)
 - Heart Failure 2001, European Society of Cardiology, Barcelona, Spain (3 presentations)
 - European Society of Cardiology Scientific Sessions, Stockholm, Sweden, 2001 (2 presentations)
 - 9th Annual Meeting of the International Society of Magnetic Resonance in Medicine, Glasgow 2001. (3 presentations)
 - Årlige forskningsdag, H:S Hvidovre Hospital 2001. (1 presentation)
 - 8th Scientific Meeting of the European Society of Skeletal Radiology, 2001. (1 presentation)
- Posters**
- 9th Annual Meeting of the International Society of Magnetic Resonance in Medicine, Glasgow 2001. (5 posters)
 - International Congress on Schizophrenia Research, Whistler, 2001. (2 posters)
 - Arthritis Rheum 2001. (4 posters)
 - Heart Failure, Barcelona, 2001 (3 posters)
 - 50th Scientific Session of the American College of Cardiology, Orlando, 2001. (1 poster)
 - Scientific Sessions 2001 of the European Society of Cardiology, Stockholm, 2001. (2 posters)
 - Europace, Copenhagen, 2001. (1 poster)
 - Ann Rheum Dis 2001. (3 posters)
 - Human Brain Mapping, Brighton, 2001. (2 posters)
 - J Neurol Sci (1 poster)

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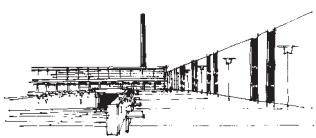
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