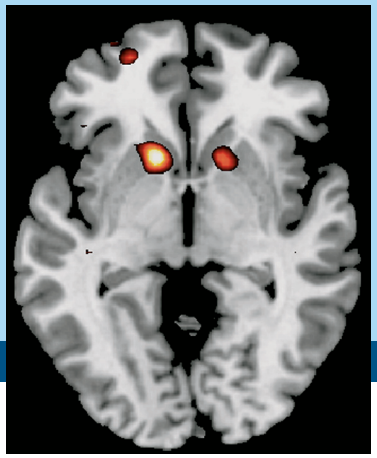

DRCMR Annual Report 2007

Danish Research Centre for Magnetic Resonance

Contents

Introduction

This report summarizes the aims and organization of the Danish Research Centre for Magnetic Resonance (DRCMR), also known as the Department of Magnetic Resonance, at Hvidovre Hospital and describes the accomplishments of the DRCMR staff during 2007.

The main aim of the DRCMR is to advance the use of magnetic resonance as a clinical and investigative tool in biomedical science. In the clinical section a new staff took over in the end of 2006 and beginning of 2007 and a major reorganization has taken place. In the research section the activities connected to the "Center for integrated molecular brain imaging" (Cimbi) established in 2007 and sponsored by the Lundbeck Foundation has been the major focus area and is gaining increasing impact for the department's research strategy. A reorganization of the research section has also started in 2007 and will continue in the coming year. Thus, a research manager has been appointed in a position where part of the time is devoted to the management of Cimbi. The department expects many new challenges in 2008 and is well prepared to meet these, and the DRCMR will continue towards further strengthening the department as one of the most dynamic, flexible and innovative MR clinical and research units in this part of Europe.

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

Olaf B. Paulson
Head of the DRCMR

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DRCMR at a Glance

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

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

Imaging facilities

The Centre has three Siemens whole-body clinical scanners. A Magnetom Trio (3 tesla), scanner was installed in 2002 after a generous donation from the Simon Spies Foundation. This equipment is state-of-the-art as further enhancements and upgrades have been performed since. The two other clinical scanners, a Magnetom Vision (1.5 tesla) and a Magnetom Impact (1.0 tesla), were installed in 1994 and are expected to be renewed in 2008. All three clinical scanners are located in area 340A of the hospital, where there also are facilities for clinical work and conferences.

In addition, the Centre has an experimental Varian 4.7 tesla scanner, suitable for MR studies in small animals. The experimental scanner is located in area 340B where there are also facilities for data analysis and other research activities. In 2004 a complete upgrade of the experimental animal scanner took place. Only the old magnet and a newer gradient coil remain from the old instrument, so in effect the result is a new scanner with advanced hardware and software. This 4.7 tesla system is the only modern MR scanner in Copenhagen for studies of small experimental animals. The pre-clinical group is involved in a set of promising new studies of cerebral connectivity using fixed brains scanned with a very high resolution for fibre-tracking. These studies are important in defining and extending the limits of new MR methods and illustrate the advantages of combined high-field human and animal imaging facilities (and the scientists who use them) in one site.

Clinically orientated activities

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

Organization of Departmental Research

Current research is organized around four themes by (overlapping) groups of investigators who meet regularly to exchange information and review the progress of their projects. These groups include investigators focused on method development (Methods Group), investigators conducting preclinical research in the animal facility (Preclinical Group), investigators conducting human brain research (Brain Research Group), and investigators conducting research using hyperpolarized substances, in 2007 only 3He. Each group has a group leader charged with organizing the agenda and chairing the sessions, and this individual represents the group of investigators on the Research Coordinating Committee (RCC).

2007 and the future

In 2007 a new profile of the clinical section of the DRCMR was established. In the fall of 2006 Per Åkeson, who came from a position as chief radiologist in Malmö, Sweden, took over the leadership of the clinical section of the department. Together with an essentially new clinical staff this secured dynamic and innovative changes in the clinical work rendering the department ready to meet new challenges with the establishment of the new hospital organisation in the capital region of Denmark and with the continuous rapid evolution of clinical MR.

In the research one of the most exciting developments of the year was the department's role in the continuous work with the Center for Integrated Molecular Brain Imaging (Cimbi), established in 2006 and funded by the Lundbeck Foundation. The Cimbi group is led by Professor Gitte Moos Knudsen of the Neurobiology Research Unit at Rigshospitalet and included contributions from principal investigators at the Faculty of Pharmaceutical Sciences, University of Copenhagen (led by Professor Mikael Begtrup), the Technical University of Denmark

(led by Professor Lars Kai Hansen) as well as the DRCMR (led by Professors Olaf Paulson and Terry Jernigan). The research in Cimbi focuses on the neural bases of personality dimensions that predispose individuals to affective and substance use disorders, with special emphasis on the serotonergic neurotransmitter system. Both PET and MRI will be employed in studies of human subjects, and these will be complemented with relevant studies using animal models. Advanced informatics techniques, new tracer compounds, and novel serotonergic challenge paradigms will also be developed within the Center. The work will also involve collaborating laboratories in Europe and the US.

The 3 tesla whole body system provides a demanding environment where researchers continue to invest significant effort developing new powerful imaging and spectroscopy methods. The high quality of morphological and functional images obtained at 3 tesla ensures that the system will continue to have an important future in the department's research activities. As mentioned earlier, new scanners are expected to be installed at the end of 2008.

The accomplishments of the year, described within this report, illustrate the depth and breadth of expertise within the department. The interaction between radiologists, clinicians, psychologists, physicists and engineers together with other scientists from different disciplines within both the department and collaborating centres continues to create a rich multi-disciplinary environment to pursue MR research and apply it to clinical problems.

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

Dansk Resumé

Denne rapport giver et indblik i målene, visionerne og organisationen af MR-afdelingen på Hvidovre Hospital og beskriver afdelingens aktiviteter i 2007. Én af afdelingens styrker er netop tværfagligheden af aktiviteterne, der spænder fra et aktivt klinisk miljø med en lang række diagnostiske MR-tjenester til et omfattende forskningsprogram, der dækker klinisk MR såvel som basal forskning. Centret blev grundlagt efter en stor donation fra Simon Spies i 1984 og allerede fra starten var der lagt lige vægt på såvel forskning som kliniske anvendelser. I 2002 sikrede Simon Spies Fonden med donationen af landets første højfeltsskanner, at afdelingen er forblevet i front. Afdelingen råder således i dag over tre humane MR-skannere med feltstyrker på hhv. 3,0, 1,5 samt 1,0 tesla. Derudover råder afdelingen over en 4,7 tesla dyreeksperimentel skanner, der blev gennemgribende opgraderet i 2004. Udskiftning af de ældste skannere forventes at finde sted ved årsskiftet 2008/09.

Dette har sikret international anerkendelse i form af blandt andet projektstøtte fra EU, samarbejde med udenlandske forskningsinstitutioner, omfattende publikationsaktivitet i internationale tidsskrifter og udvælgelsen af afdelingen til MR-evalueringscenter ved internationale medicinafprøvninger.

Året 2007 blev et år med væsentlige organisatoriske ændringer på MR afdelingen. I slutningen af 2006 og begyndelsen af 2007 fik afdelingens kliniske sektion i stort omfang nyt personale og har gennemgået en væsentlig reorganisation. I forskningssektionen er fokus i stigende grad blevet rettet mod aktiviteter knyttet til "Center for integrated molecular brain imaging" (Cimbi), som blev etableret i 2006 med støtte af Lundbeckfonden. En reorganisering i forskningssektionen er ligeledes påbegyndt med ansættelse af en "research manager" der ligeledes har administrative funktioner indenfor Cimbi. Reorganiseringen i forskningssektionen forventes at forsætte i det kommende år. Disse nyskabelser vil få stor betydning for afdelingens fortsatte virke inden for klinik og forskning. Afdelingen forventer store udfordringer i de kommende år og er vel rustet til at møde disse og til at sikre afdelingen som et af de førende kliniske og forsknings MR-centre i denne del af Europa.

Organisation and Staff

Department Chair

Olaf B. Paulson, DMSc, Professor

Senior staff, Clinical

Marianne Dalsgaard, Head Technologist
Michel Nemery, MD, Senior Physician
Per Åkeson, MD, DMSc, Senior Physician and Clinical Chief

Senior Staff, Research

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

Junior Staff, Clinical

Mariana Obreja Kristensen, MD
Camilla Gøbel Madsen, MD
Erland Magnusson, MD
Peter Magnusson, PhD, Physicist

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

Junior Staff, Research

PhD students

Sadia Asghar Butt, MSc, Biochemist
Mark Schram Christensen, MSc, Engineer
Anne-Marie Dogonowski, MD
Torsten Dorniok, MSc, Physicist
Tim Dyrby, MSc, Engineer
Bjørn Ebdrup, MD
Frederik Hengstenberg, MD
David Alberg Holm, MSc, Engineer
Bettina Hornbøll, MSc, Biologist
Kirsten Korsholm, MD
Astrid Lou, MD
Henrik Lundell, MSc, Engineer
Kathrine Skak Madsen, MSc, Biologist
Kristoffer Madsen, MSc, Engineer
Robin de Nijs, MSc, PDEng, Medical Physicist
Thomas Z. Ramsøy, MSc, Psychologist
Charlotte Ryberg, MSc, Biologist
Annette Sidaros, MD
Arnold Skimminge, MSc, Physicist
Jon Wegener, MSc, Life Sciences and Chemistry

The DRCMR staff at the retreat meeting held in March 2007 in Liseleje.

Magnetic Resonance Imaging relies on strong magnetic fields extending several meters from the scanners.
Photo by: Bo Tornvig

Secretarial Staff

Nana Siggard Andersen
Vibeke Andersen
Jeanette Beck
Anette Fallesen
Birgit Solá Gross
Lotte Hansen
Joan Husted
Tina Bo Kyong
Lisa Juhl Simonsen
Ina Tech

Cleaning Assistants

Ruth Kielstrup
Elsebeth Nielsen

Conscientious Objectors

Thomas Bach

Visiting Staff

Annika R. Langkilde, PhD, MD
Jakob Marstrand, PhD, MD
Maria J. Miranda, PhD, MD
Trine Stavngaard, PhD, MD

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

Research Assistants and Students
Christina Ursta Anghel
Brian Villumsen Broberg
Daniel Robert Chebat
Martin Vestergaard Hansen
Isabelle Matteau

Technologists

Siri Eggum, Radiographer
Sascha Gude, Laboratory Technician
Sussi Larsen, Research Technician
Pia Olsen, Radiographer
Jesper Rohde, Radiographer
Hanne Schmidt, Radiographer
Ann-Sofi Sjöqvist, Radiographer
Kristin Storli, Radiographer

COLLABORATIONS

The DRCMR collaborates and works closely with many institutions both nationally and internationally. Primary collaborators in 2007, especially those with whom common funding was obtained and those who participated in supervision of PhD students are listed below.

In the area of Neuroscience, an important formal national collaboration has been established for some years in form of the Copenhagen Brain Research Centre and from 2006 the Lundbeck Foundation Center for Integrated Molecular Brain Imaging (Cimbi).

National Collaborations

Center for Integrated Molecular Brain Imaging (Cimbi), Rigshospitalet
Center of Functionally Integrative Neuroscience, University of Aarhus
Department of Physics, the Technical University of Denmark
Department of Informatics and Mathematical Modelling, the Technical University of Denmark
Department of Exercise and Sport Sciences, University of Copenhagen
Department of Neuroscience and Pharmacology, Panum Institute, University of Copenhagen
Research Laboratory for Stereology and Neuroscience, Bispebjerg Hospital
Statens Serum Institut
Copenhagen Muscle Research Centre, CMRC
Learning Lab Denmark
Center for Semiotics, Aarhus University
Department of Arts and Cultural Studies, University of Copenhagen
Department of Nordic Studies, University of Copenhagen
Department of Psychology, University of Copenhagen
National center for Reading, Aarhus University
PhaseOne Trials A/S
The Niels Bohr Institute, University of Copenhagen
Research Department of Human Nutrition, Faculty of Life Sciences, Copenhagen University

Copenhagen University Hospitals

Departments at Hvidovre Hospital
Department of Neurorehabilitation
Department of Orthopedic Surgery
Department of Paediatrics
Department of Radiology
Department of Respiratory Medicine

Departments at Rigshospitalet
Danish Multiple Sclerosis Center
The Memory Disorders Research Unit
Department of Clinical Physiology
Department of Infectious Diseases
Department of Neurosurgery
Department of Radiology
Department of Psychiatry
Clinic for Spinal Cord Injuries
The Neurobiology Research Unit
Finsen Laboratory

Departments at other Copenhagen University Hospitals
Department of Psychiatry, Glostrup Hospital
Department of Clinical Physiology and Nuclear Medicine, Bispebjerg Hospital
Department of Clinical Physiology and Nuclear Medicine, Glostrup Hospital
Child and Adolescent Psychiatric Centre F, Bispebjerg Hospital
Department of Neurology, Glostrup Hospital

International Collaborations

Image Science & Biomedical Engineering, University of Manchester, United Kingdom
Laboratory of Cognitive Imaging, University of California, San Diego, USA
Medical Research Council, Cognition and Brain Sciences Unit, University of Cambridge, United Kingdom
Anatomy Department, Wellcome Department of Imaging Neuroscience, University College London, England
Buffalo Neuroimaging Analysis Center (part of the Jacobs Neurological Institute), New York State University at Buffalo
Centre for Medical Image Computing, Department of Computer Science, University College London, London, United Kingdom
Defence Research and Development Canada, Canada
Department of Clinical and Experimental Epilepsy, Institute of Neurology, London, United Kingdom
Department of Neurology and Brain Imaging Center, Johann Wolfgang Goethe-University, Frankfurt, Germany
Department of Interventional and Diagnostic Radiology, Johannes Gutenberg-University Medical School, Mainz, Germany
Department of Physics, Johannes Gutenberg-University Medical School, Mainz, Germany
Department of Psychology, University of the Balearic Islands, Spain
Department of Radiation Physics, Lund University Hospital, Sweden
Department of Radiology, University hospital MAS, Lund University, Sweden
Neuroscience and Psychiatry Department, The University of Manchester, United Kingdom
School of Psychology, The University of Birmingham, United Kingdom
School of Physiotherapy and Exercise Science, Griffith University, Queensland, Australia
Section for pulmonology, Department of Internal Medicine, University hospital MAS, Lund University, Sweden

International Multi-Centre Research Collaborations

The DiMI Project: An international network of excellence for the advancement of diagnostic molecular imaging (DiMI).
The EU project: Leukoaraiosis and Disability in the elderly (LADIS)
European Task Force on Age-Related White Matter Changes
EU 6th framework Program; Research and Training Network (RTN), Marie Curie Actions: Polarized Helium Lung Imaging Network (PHeLINet).

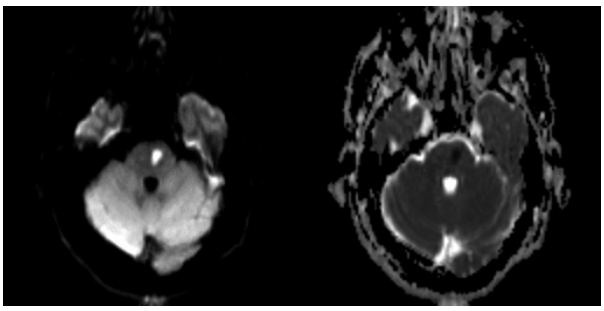
Collaboration in Clinical Trials

The DRCMR participates in national and international clinical phase I-III drug trials in collaboration with The Danish Multiple Sclerosis Center and The Memory Disorders Research Group at Rigshospitalet and with the PhaseOne Trial Center at Hvidovre Hospital. The pharmaceutical companies involved in our 2007 and current trials are Aventis, Biogen, BioMS, GSK, Merk Serono, Novartis, PPD Scandinavia, Roche, Schering, Schering-Plough, and Zymenex.

Clinical Imaging

The clinical section of the DRCMR underwent a major reorganisation during 2006 and has used 2007 to consolidate the department and to further establish new methods and routines. The patient throughput has been restored to a level higher than before the reorganisation and is now around 4000 examinations per year. The majority of the examinations are referrals from Hvidovre Hospital, although about half of them are referred from other hospitals or specialists inside or outside the Copenhagen area.

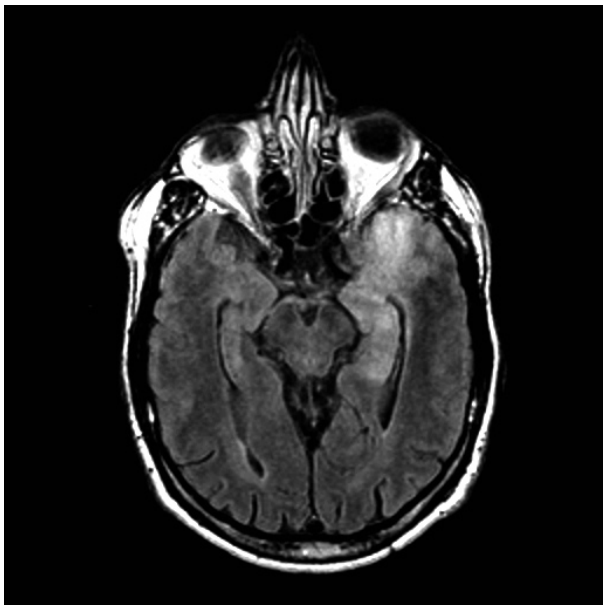
Investigations of neurological diseases, e.g. suspicion of stroke, multiple sclerosis, intracranial tumours, intracranial haemorrhage, dementia and epilepsy are an important part of daily clinical radiology and dominate the panorama of examinations together with spinal examinations. Investigations of orthopaedic cases, e.g. intraarticular diseases such as meniscal tears or osteoarthritis, extraarticular diseases such as tendinitis and soft tissue diseases as well as soft tissue tumours have increased in numbers. The fact that the radiology department at the Hospital has gotten an MR-scanner which is serviced by an abdominal radiologist has made the need for abdominal scannings less although some abdominal scanning is still performed. The clinical section also helps the department of radiology during vacation and sickness.



47 years old man with an acute infarct in the pons (brain stem). The infarcted area appears bright on a diffusion-weighted image (left) (trace with b=1000 s/mm^2) and dark on the Apparent Diffusion Coefficient (ADC) map (right) due to restricted diffusion.

The clinical section is represented in the 'EPI-KIR' group, an organisation responsible for national epilepsy patient management that selects patients suitable for surgical intervention and is responsible for postoperative patient management. Consequently, many patients with epilepsy have been imaged for the presence of structural brain lesions causing seizures. Many of the patients with epilepsy were investigated with a special protocol. Patients are received from all over Denmark for these examinations.

Patients with suspected intracranial vascular diseases such as arteriovenous malformations and aneurysms are regularly referred to the department for investigation with MRI and MR angiography. MR imaging and angiography are performed both without and with contrast agents. The use of the 3T scanner for these examinations has further improved the results due to the very high resolution that can be achieved and has become routine.

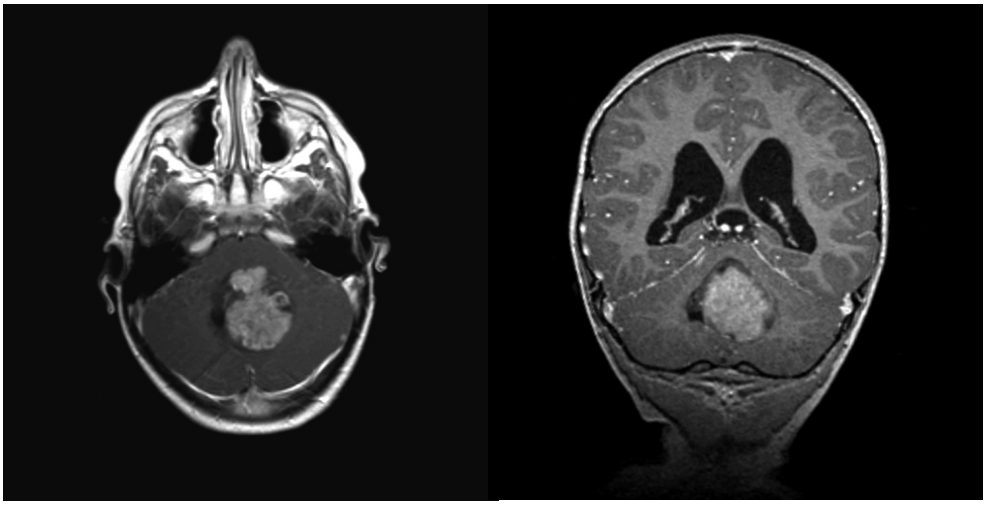


Axial FLAIR image of a 61 years old man with herpes encephalitis in the left temporal lobe.

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

Infectious diseases like encephalitis of different origins, central nervous system tuberculosis and different more or less seldom infections have also been a small but interesting part of the work.

In paediatric radiology, MRI is used successfully both in neonates and older children with different neurological diseases such as hypoxic complications occurring around delivery and seizures in the postnatal period. For the investigation of congenital malformations, both cerebral and spinal, as well as metabolic diseases MRI is the method of choice readily visualizing most diseases. This area has increased in importance during the year. The section is an active member of the Copenhagen network meeting regularly to evaluate difficult cases of neurological malformations and paediatric diseases.

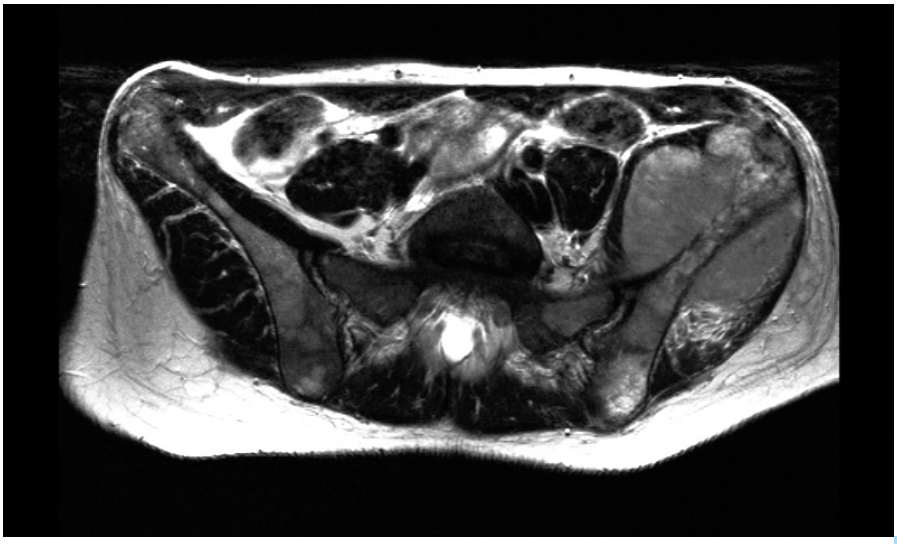


Axial (left) and coronal (right) T_1-weighted contrast-enhanced images of a 3-year old patient with a medulloblastoma in the 4th ventricle.

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

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

Musculoskeletal MRI is a clinical area which has increased in importance and is now a substantial part of the daily workload. The technique is rapidly replacing diagnostic arthroscopy in the evaluation of meniscal lesions, lesions in the cruciate ligaments, collateral ligaments and damage to the cartilage in the knees. During the year the examinations of the knee with the 3T scanner has become the standard of choice with valuable improvement of the investigative results. In the shoulder, MRI is used in diagnosing labral lesions, rupture of the rotator cuff and so forth. MR-arthrography of the shoulder has increased in numbers with good diagnostic results. In the hip MRI is used to diagnose labral lesions, cartilage diseases and sometimes to find difficult hip fractures. MR-arthrography of hip joints has improved the diagnostic results especially concerning labral lesions. 3D-imaging has also been applied with good results. Other areas where MRI is used are tendon tears around the ankle, different diseases in the foot and inflammatory diseases in the spine and the sacroiliac joints. Wrist examinations have also become an important group of examinations. Preoperative investigation of musculoskeletal tumours can determine the extent of disease and help treatment planning. Metastatic bone disease is also best diagnosed with MRI.



Axial T_2-weighted image of a 34 years old woman with a lymphoma in the left side of the pelvis.

Basic Research

Basic research is a key component of the research chain. Unlike research targeted at immediate application, basic research is the foundation for future clinical application or applied research, and it is therefore a key focus area within the DRCMR.

So what constitutes basic research? Classification into 'understanding', 'development', 'evaluation' and 'application' emphasizes the multistage nature of the research path. It also highlights the importance of basic research, which quite simply constitutes the first three steps. Without it, achieving the final step of applied research would not be possible. Thus we can think of basic research as either:

- Developing of new methods which can provide quicker results, more accurately, and more robustly. Example areas would include hardware (new scanner technology, combination of existing technologies, etc), software (usually specialized in-house code) or analysis methods (statistical calculations, optimization, mathematical modelling etc),
- Evaluating such newly-developed methods. This is extremely important for in-house developments, but also for 'keeping up to date' with the latest advances by scanner and equipment manufacturers, and by other research groups around the world. This includes a vast range of software code (e.g. SPM, FSL, Camino), and the related algorithms and mathematical models associated with them.
- Research that leads to a better biological understanding of the healthy human body and the interaction between biology and MRI methods. Example area would include understanding brain function or how physiological factors affect the MR images we acquire.

As a major MR research facility, the DRCMR must be up-to-date to advance MR methods and techniques on an international level, and hence also offer the best quality care to its patients.

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

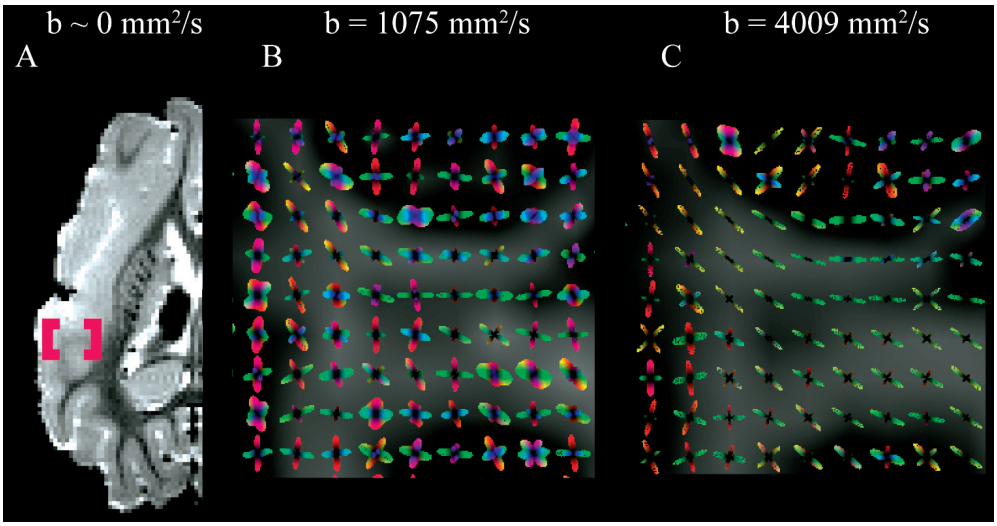
1. Development and optimisation of new MR sequences and methods (MR physics and methodology)
2. Development of novel post-processing strategies and experimental design (MR informatics)
3. Investigation of the basic physiological factors reflected in MR images (physiology)
4. Mapping of the cognitive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

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

MR Physics and Methodology

MR measurements involve complicated patterns of radio wave transmission, magnetic field changes and signal sampling. The measurement schemes programmed for the scanner are called sequences. Although numerous clinical MR sequences are provided with the MR scanners by the scanner manufacturers, there are a variety of research projects within the Centre that rely on sequences that are either written in-house or are modified versions of provided sequences. The Centre therefore has research agreements with Siemens and Varian that give researchers access to the source code of the manufacturers' sequences. This eases the process of modifying and optimising MR methods.

Diffusion tractography is a new method which non-invasively allows for studies of the complex connections in the brain. Neural fibres connect the different regions of the brain that process inputs giving rise to perception and appropriate output. Tim Dyrby, Lise Vejby Søgaard and William Baaré have continued the important process of understanding the basics of the diffusion process and how optimal MR scanner parameters can be selected to obtain high quality datasets for validating tractog-

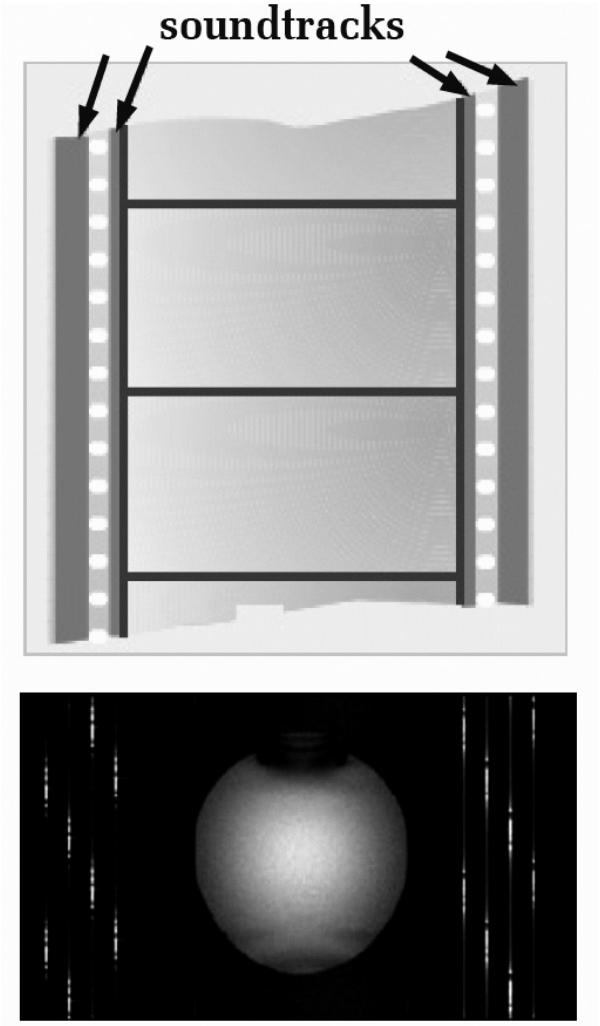


A series of diffusion weighted datasets with different sequence parameters (b-values) were acquired in one continuous scanning session on a perfusion fixated pig brain. A show an axial slice of a non-diffusion weighted image. The multi-fibre model PASMRI was used to reconstruct the (dominating) fibre directions in each voxel as shown in B and C (zoomed region marked in A). When a (too) low b-value of 1000 s/mm² is used to acquired the diffusion dataset the spatial coherence of reconstructed fibre directions is lower than if a higher b-value such as at 4009 s/mm² (B) have been used. Spatial coherence is believed to be important to obtain reliable tractography results.

raphy. By performing scans postmortem most of the problems known to hamper in vivo measurements, e.g., patient movement and physiological noise (respiration and cardiac) are overcome. The possibility of increasing the scanning time furthermore allows for acquisition of high quality datasets superior in resolution and signal-to-noise ratio compared to scans acquired in vivo. Tim Dyrby performed the analysis of optimal selection of diffusion parameters for postmortem and validated tractography against invasive in vivo neuronal tract tracers in collaboration with Dr. Daniel C. Alexander (London, UK) and professor Geoffrey Parker (Manchester, UK). This collaboration is reflected in the presence of DRCMR data on the Camino Diffusion MRI Toolkit Homepage on http://www.cs.ucl.ac.uk/research/medic/camino/.

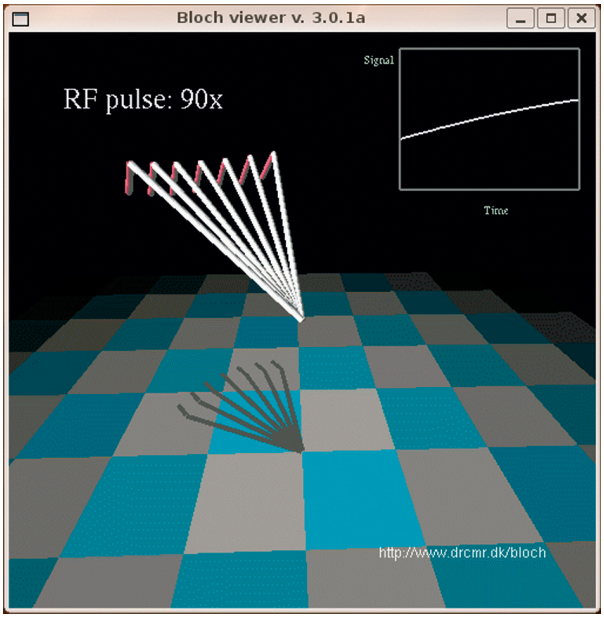
Arterial spin labelling (ASL) has been a main area of sequence development in the past years at the Centre. ASL is the only completely non-invasive method of measuring regional blood flow in vivo. Karam Sidaros is responsible for maintaining and optimising the ASL sequences on the 3T Trio scanner which requires continuous effort since regular scanner software updates requires in-house sequences to be updated too. Furthermore through collaboration with Dr. Mathias Günter, Heidelberg, the DRCMR has gained access to a 3D ASL sequence which offers significantly increased signal-to-noise ratio over the 2D-based sequences we have used previously. This greatly reduces the imaging time needed for quantitative perfusion imaging.

Another activity of the DRCMR is the simultaneous acquisition of functional MRI (fMRI) and electrical signals coming from brain activity (electroencephalography, EEG recording). The combination of the two techniques can improve both source localisation in EEG and temporal resolution in fMRI. Briefly, EEG can measure when there is brain activity and fMRI can measure where it happens. Hence EEG-fMRI is widely believed to be a technique that will increase the understanding of processes and networks in the brain, and may provide improved diagnosis of particular diseases, for example, when used for pre-surgical planning in epilepsy. Measuring EEG and fMRI simultaneously is a highly difficult task, however, due to the interference between the two recordings. The acquisition of MR images causes an artefact signal in the EEG that is about 3 orders of magnitude larger than the actual EEG signal. This is highly demanding both for the hardware used to record EEG signals during scanning and for the analysis software. A novel method for recording EEG and fMRI simultaneously was developed at the DRCMR by a team headed by Lars G. Hanson. An article demonstrating proof-of-concept was published in 2007 and the equipment was subsequently refined so it now provides high-quality EEGs even during rapid high-speed imaging at 3T field strength. The approach uses a special modulator to make it possible for the scanner to record both EEG and fMRI data. Similar to the so-called “Magstripe technique” used for encoding of soundtracks in movies, the EEG signals are encoded in the MR images outside the visible region. The electronics developer of the group, Christian G. Hanson, has constructed a highly flexible 8-channel modulator for the purpose. PhD student Arnold



A technique was developed at Hvidovre Hospital to make MR scanners record non-MR signals simultaneously with MR imaging (e.g. electrical signals from the brain, EEG). Similar to the way soundtracks are encoded in motion pictures, the non-MR signals are encoded outside the visible area. This is possible since modern MR-scanners acquire images wider than prescribed and shown (oversampling). The principle is here demonstrated with an MR-image of a water bottle. The stripes appearing in the edges of the image contain encoded electrical signals. These patterns are not visible on the scanner due to oversampling, but appear when the images are reconstructed from raw data. Likewise, the encoded signals can be extracted from raw data during a measurement.

Skimminge enrolled in the ITMAN graduate school at the Technical University of Denmark developed software for extracting the EEGs real-time on the scanner. This opens for alternative applications of the method, e.g. real-time EEG-fMRI and prospective motion correction based on motion sensors (any EEG electrode acts as a sensitive motion sensor in the magnetic field). The method is simple to use, sensitive, inexpensive and more robust than traditional methods. The analysis is also suitable for integration on the scanner, even as the data are being acquired (real-time EEG-fMRI). The patent rights for the Magstripe method are claimed by an independent spin-off company MRIware founded for that purpose (http://www.MRIware.com).

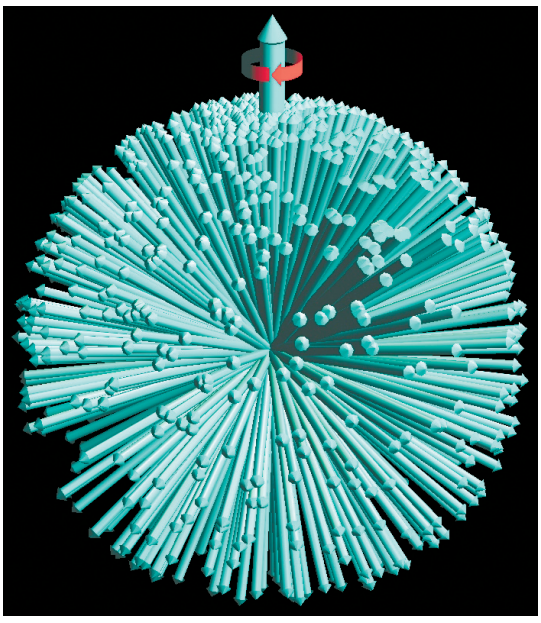


Screen dump from software developed at the DRCMR for visualization of basic and complicated MR methods. The figure shows how the magnetizations (white bars) of nuclei in varying magnetic fields are pushed by radio waves as indicated with red bars midway during a 90-degree pulse. Field inhomogeneity leads to a loss of signal, that can be reversed using the spin-echo technique. Animations illustrating this phenomenon and other MR-techniques are available on the DRCMR homepage. The software generating the animations can via a graphical user interface be used to manipulate virtual spin ensembles by application of radio waves and gradients as done during MR measurements. The software is freely available at http://www.drcmr.dk/bloch

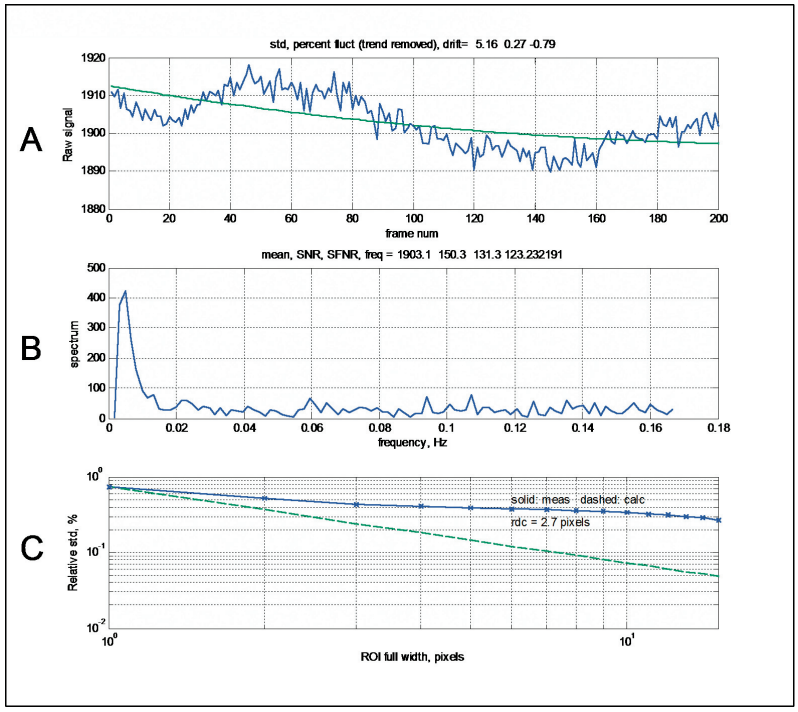
The staff of the DRCMR provides teaching in many contexts as described on the centre homepage. Examples are open, free and well-attended courses in Basic MRI. In order to aid the teaching of this difficult subject, interactive software that can be used to demonstrate many essential MRI techniques was developed by Lars G. Hanson. It runs on most platforms (Windows, Linux and more) and can be downloaded from the DRCMR homepage free of charge (http://www.drcmr.dk/bloch). Groups of nuclear spins can be visualized and manipulated via a graphical user interface that provides a unique insight into techniques that are normally perceived as highly challenging by students of MRI. An article describing the software was published in 2007 together with a number of educational animations available online on the Radiographics homepage with narrations describing basic concepts of MRI. Towards the end of 2007 a supplemental open-source software viewer was developed. It takes advantage of the capabilities of modern PC graphics cards and greatly enhances the visualization. Animations recorded with the new viewer are on the DRCMR homepage. These illustrate basic concepts of MRI.

Magnetic resonance spectroscopy can be used to measure the concentrations of phosphorous metabolites in vivo. Luke Haseler from *School of Physiotherapy and Exercise Science, Griffith University, Queensland, Australia* and Ylva Hellsten, Bengt Saltin from the *Copenhagen Muscle Research Centre, CMRC,* conducted exercise experiments in collaboration with Lars G. Hanson from the DRCMR. Healthy volunteers performed rhythmic leg motion in the scanner using an MR-compatible ergometer designed and built by Flemming Jessen, CMRC. Pharmocological intervention was used to study the muscle metabolism during exercise.

Henrik Lundell, a student from the Technical University of Denmark supervised by Bjørn G. Nielsen and Lars G. Hanson was awarded the Novo Scholarship prize for best scientific presentation for his talk on visualisation of injections by MRI of injections. Henrik's Master's project was aimed at characterising normal injections and injections made with needle-free devices that apply liquid drugs to the skin at such high pressure that the liquid penetrates the skin. Needle-free injections have advantages with respect to safe handling and psychological factors, but it is very important that the injection characteristics are well understood and controlled. Pharmacokinetics are highly influenced by the structure of the deposition and MRI was applied to visualise the overall morphology of the deposition. Diffusion Tensor Imaging (DTI) was used to reveal microstructures within the area of deposition. MRI based methods may also improve the understanding of the biomechanics of the subcutis. After finishing the project, Henrik continued as a PhD-student in collaboration with Jens Bo Nielsen at the Department of Exercise and Sport Sciences, University of Copenhagen.



The magnetization that is measured using MRI has contributions from the amazingly lage number of atomic nuclei in the body. During measurements, the nuclei are subject to different magnetic and radio wave fields. It is therefore quite challenging to teach MRI. The graph here was made for illustrating how the magnetization of individual nuclei in the body align along the direction of an applied field like compass needles. Simultaneously they rotate around the direction of the field. Due to nuclear interactions, the alignment is only partial. The capabilities of modern computer graphics cards has made the calculation of such scenes amazingly fast which was exploited to improve 3D, real-time visualization of MRI simulations for educational purposes.



A: Signal time course from a scanner stability measurement with a signal drift/trend of -0.79% as calculated form the polynomial fit (green line) and 0.27% signal fluctuation after polynomial de-trending. B: Frequency spectrum of the signal time course. C: Weisskoff-diagram with a corresponding short relative correlation distance (RDC) of 2.7 pixels, indicating a strong contribution from non-random noise to the signal fluctuations. Sources of such correlated noise are instabilities in e.g. the RF-amplifier, gradient amplifier and center frequency.

A new project was started in 2007 to assess the quality of functional MRI experiments. The approach taken in this project was to monitor the temporal and day-to-day stability of the MR-signal generated by the 3T Trio MR-scanner when performing rapid EPI-imaging over long image time series, as used for fMRI-experiments. The measurement and the analysis procedure were implemented by physicist Peter Magnusson. For assessment of the scanner stability, a dedicated cylindrical standard phantom is scanned in a standardized set-up using a 2D echo-planar pulse sequence. The scan consists of 200 consecutive EPI-image volumes and is performed twice at each measurement occasion. The measurements are performed twice a week. The acquired image time series are analysed with in-house developed software performing a fully automated analysis of a central slice in the image volume using regions of interest (ROI) as described by the FBIRN stability phantom quality assurance procedure (By G. H. Glover, Stanford University and FBIRN) and according to a method developed by Weisskoff (MRM 36:643, 1996). The analysis produces a time-series plot of the signal and estimates at what distance correlated noise starts contributing to the observed signal fluctuations over time. The larmor frequency is also monitored. Results compiled from nine example measurement occasions distributed over 13 days showed a largest change in drift from -1.03% to +0.97% from one day to the next, a largest fluctuation after de-trending of 0.3% and a smallest correlation diameter of 2.7 pixels. The signal changes caused by neural activation during an fMRI-experiment are in the range of a few percent which is also the range of the observed drifts from the example stability measurements. It is important to continue to monitor scanner instabilities according to the implemented protocol and to further study what implications it may have for fMRI-experiments.

MR Informatics

Many studies running at the DRCMR utilise images of different modalities and with differing contrasts. In order to perform tasks upon this multitude of images, including registration, normalisation, preprocessing and analysis in an efficient and reproducible manner, a common framework for these tasks is crucial. The major task of implementing a standardised environment for all studies based on the popular SPM5 software package was initiated by PhD-student Arnold Skimminge and co-workers. In particular recent developments such as physiological noise modelling for fMRI studies and methods for DTI data processing have been implemented into the standard workflow of ongoing studies, and hence these methods can now be easily incorporated into the analysis of MR data.

Neuroimaging often includes data from several modalities, e.g. structural MRI, functional MRI (fMRI), and PET as well as “metadata” such as age and gender. However, most analysis methods are modality-specific (considering only one modality at a time). Peter Mondrup, a DTU student making his MSc project, has initiated a project on “Statistical Analysis of Multimodal Brain Data”, where the focus is on integration of multiple modalities into a single analysis. Such multimodal analysis performed on voxel-level can be used to asses more complex questions in neuroscience.

PhD-student Kristoffer H. Madsen has focused mainly on unsupervised analysis of fMRI data. In particular this includes factor analysis type decompositions, independent component analysis and the extensions to higher order decompositions such as the canonical decomposition / parallel factor analysis model. The work has focused mainly on extending these simple linear decompositions in order to provide more realistic models for the analysis of fMRI signals. In particular extension of

these models to include shifts and imposing several constraints including temporal/spatial smoothness, sparseness and non-negativity have been developed together with Morten Mørup from the Technical University of Denmark. These methods can help in more accurately identifying activated regions in fMRI data as well as reduction of nuisance effects by explicitly modelling of these effects. The decomposition algorithms have been developed specifically with computational efficiency in mind making them suitable for large scale data sets such as multi-subject fMRI data.

Basic Physiology

One of the very fascinating applications of MRI is mapping the functional anatomy of the human brain. During the last decade the brain mapping methodologies have developed tremendously, and the majority of current studies relies on the BOLD (blood oxygenation level dependent) technique, rather than radiotracer based methods. Egill Rostrup has continually been working on modelling the basic physiology of brain activation. During brain activation the supply of oxygen is known to increase more than its use, resulting in a decrease of deoxy-haemoglobin levels. Since deoxy-haemoglobin is paramagnetic, this results in a more homogeneous magnetic field, as can be detected by appropriate MR techniques. These techniques are primarily sensitive to the total amount of deoxy-haemoglobin pr. unit of tissue, which is determined from a balance between oxygen supply and use, but also depends on blood volume and other properties such as haematocrit, pH and PaO_2. The BOLD effect is therefore not specific to neural activation, but can be caused by other factors such as hypercapnia, hypoxia or other changes in blood composition or supply. These non-neural factors are very relevant both because they represent a tool by which basic brain physiology can be studied, and because they interact with the neural BOLD responses, thereby adding to their intra- and inter-subject variability. Egill Rostrup introduced a mathematical model of the BOLD response in his doctoral work, which included, as a novel feature, the contributions from both the arterial, capillary and venous compartments. The model was used to guide the interpretation of experimental results obtained by the author and other experimenters. From the modelling results it appeared that the level of tissue oxygenation in the brain is critically dependent on the permeability of the blood-brain barrier to O_2 diffusion, and it was suggested that O_2 metabolism under some, but not all conditions may be limited by arterial O_2 delivery. In BOLD measurements the baseline signal increases with arterial CO_2-tension as suggested by several studies, and this is mainly due to increased blood flow and brain oxygenation. These findings are confirmed by the present modelling results, which further indicate that the BOLD response may be influenced by pH and PaO_2 changes in addition to the haemodynamic changes during hypercapnia. During hypoxia the BOLD signal decreases in spite of regulatory CBF increases that minimise the change in oxygen delivery to the brain. The magnitude of the BOLD response detected after neural activation is dependent on several baseline parameters. Conditions with high baseline flow, such as hypercapnia, generally diminish the response magnitude. Decreased baseline flow may enhance the BOLD response, as long as O_2 metabolism is uncompromised. In conclusion, several physiological factors influence the magnitude and detectability of BOLD responses, and should be accounted for in order to minimise variability between experimental groups. A quantitative understanding now seems possible, due to recent progress in modelling and data acquisition techniques. In quantitative terms the inter-individual variability is unknown, and this is an area that should be pursued further.

Brain Mapping

As mentioned in the previous section, an extremely useful aspect of MRI is its ability to measure functional activation of the brain based on the magnetic properties of oxy- and deoxy-haemoglobin. This technique of functional MRI (fMRI) is widely used to make functional maps of the brain. This is one of the key research areas at the DRCMR and a variety of projects rely on this technique to achieve a better understanding of brain function.

In one project PhD student Jon Sigurd Wegener, together with Kristoffer Madsen and Mark Schram Christensen from DRCMR, and Julian Jamison from University of Southern California, investigated how the healthy brain evaluates immediate rewards versus larger delayed rewards. These evaluations, termed inter-temporal choices, exhibit large individual differences and have important implications for outcomes in health such as substance-abuse. In order to process inter-temporal choices, an agent must imagine and predict decisions and mental states relating to him or herself in the future. Therefore, it was hypothesized that neural activation changes in areas known to be involved in attributing intentions to other agents, would correlate with the anticipation of future agents. The results support this hypothesis showing significant declining graded activations as the delay increased, in temporal and parietal areas bilaterally. Additionally, the relevance of these areas for time preference was confirmed via correlation analyses between a behaviourally measured discount factor and the graded activations in the parietal areas bilaterally. These results suggest that the slope of activation in parietal and temporal areas correlates significantly with the slope of the individual discount function. Results from this work were presented at the 13th annual meeting of the Organization for Human Brain Mapping.

As a part of his PhD project, which was successfully defended in November 2007, Mark Schram Christensen has, together with Jesper Lundbye-Jensen, Svend Sparre Geertsen, Tue Hvass Petersen and Jens Bo Nielsen, all from the Department of Exercise and Sport Sciences, and Olaf B. Paulson, investigated motor control without proprioceptive feedback from muscles and joints. They showed that in a situation where subjects performed voluntary ankle joint movements without proprioceptive feedback due to ischemic nerve block of the lower leg, activation in the somatosensory cortex was preserved. They further showed that the ventral premotor cortex seemed to modulate the activation in the somatosensory cortex in the absence of sensory feedback.

The work was published in the journal Nature Neuroscience.

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

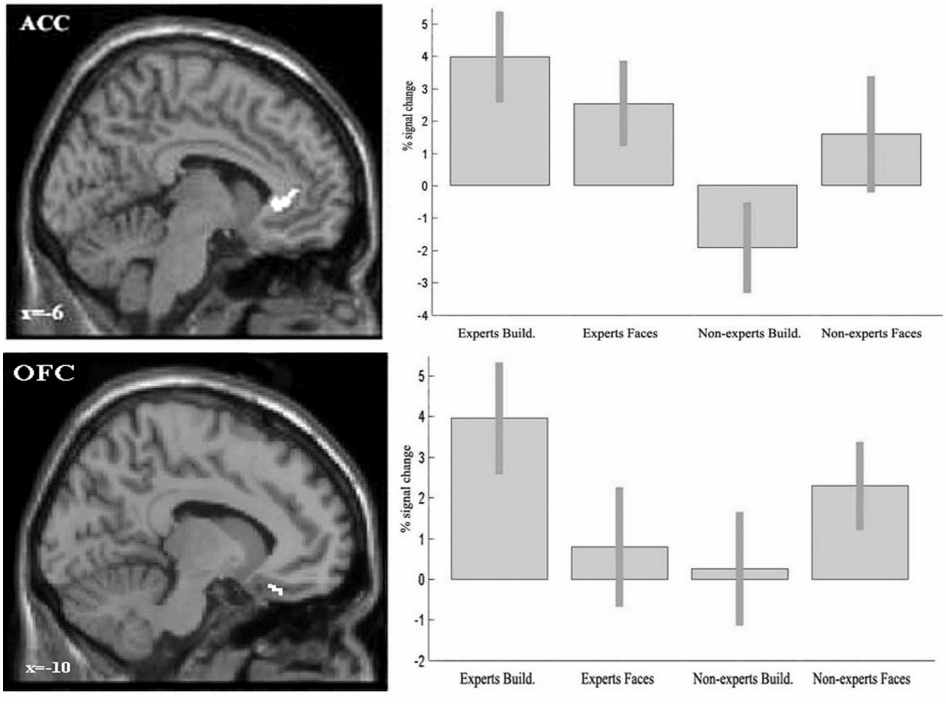
During visually guided movements both vision and proprioception inform the brain about the position of the hand, so interaction between these two modalities is presumed. Current theories suggest that this interaction occurs by sensory information from both hand locations. In the literature on perception, however, there is evidence that different sensory modalities interact which facilitates the processing of a stimulus in a different modality.

Daniela Balslev together with Prof. Chris Miall from the University of Birmingham and Jonathan Cole from the Poole Hospital and University of Bournemouth, UK investigated whether proprioception facilitates the processing of visual information during motor control. Subjects used a computer mouse to move a cursor to a screen target. In some of the trials, pseudorandomly, the cursor was rotated or the target jumped. Reaction time for the trajectory correction in response to this perturbation was compared under conditions with normal and reduced proprioception after 1Hz repetitive transcranial magnetic stimulation (TMS) over the hand-contralateral somatosensory cortex. Proprioceptive deafferentation slowed down the reaction time for initiating a motor correction in response to a visual perturbation in hand position, but not to a target jump. They conclude that intact proprioception is necessary for the rapid processing of visual feedback.

The supplementary use of TMS is becoming an increasingly important tool for the DRCMR staff, because it can answer questions directly at the neural level. TMS influenced neural electrical activity, which can be used to inhibit or excite neural circuitry. Another study, which was carried out in 2007 in a collaboration between Mark Schram Christensen, James Rowe, Lasse Kristiansen and Jens Bo Nielsen, showed that it is possible to block visual perception using TMS over the visual cortex but preserve the ability to perform visually guided goal directed movements towards a visual target. The effect is known as action-blindsight. The study has been published in the journal Proceedings of the National Academy of Sciences of the United States.

In 2007, Martin Skov continued work on his neuroaesthetics project. Data from three experiments acquired in 2006 were analyzed and written up for publication. This has so far resulted in three papers currently being submitted, but two more are expected to come out of the same data sets.

Parallel to his experimental work, Skov, together with Thomas Wiben Jensen of the University of Copenhagen, published the anthology *Følelser og kognition* (*Emotion and Cognition*) which was very positively received in the Danish press, generating reviews and profiles in, e.g., Jyllands-Posten, Weekendavisen, DR1's "Orientering" and Deadline 17.00, DR2's current affairs



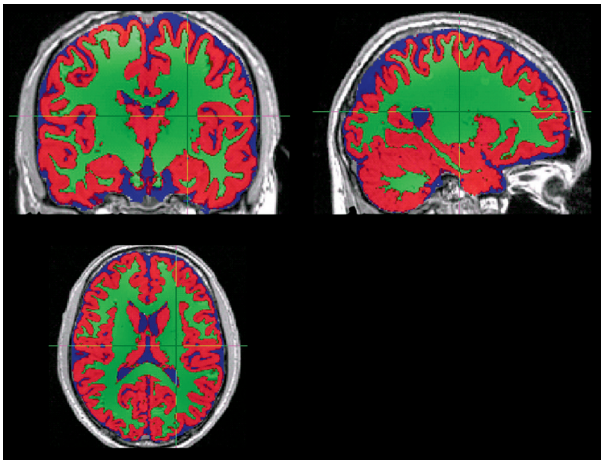
The orbitofrontal cortex (OFC) plays an important role in the formation of aesthetic preferences. For instance, the medial part of OFC exhibits higher activation in architects than in non-architects when these two groups assess the aesthetic value of buildings, but not when they assess the aesthetic value of faces. Data from U. Kirk, M. Skov, M.S. Christensen & N. Nygaard: "Brain correlates of aesthetic expertise. A parametric fMRI study" (in review).

program. Furthermore, together with Oshin Vartanian of the Defense and Research Development Canada, he also finished editing the first international anthology to present neuroaesthetics as a research field, *Neuroaesthetics*, which will published by Baywood Publishing Company in 2008.

The 'prefrontal set' study, a collaboration between James Rowe from University of Cambridge, Katsuyaki Sakai, University of Tokyo, Richard Passingham (London and Oxford) and DRCMR staff, came to fruition in November 2007 with its publication in the prestigious Journal of Neuroscience. The results were also warmly received at a presentation at the Society for Neuroscience annual meeting in San Diego in November 2007. The paper not only tells us about the role of the prefrontal cortex in a core cognitive function (cognitive set). It also tells us that important difference in brain function may only be revealed by more sophisticated analysis of the data - classical approaches to fMRI analysis would have lead us to the wrong conclusion. James Rowe believes that this lesson is applicable to many other areas of cognitive neuroscience, for studies of healthy brain function and neurological disease.

The paper was the subject of a 3 page commentary in the Journal of Neuroscience in March 2008. It was noted that the team at the DRCMR had "pioneered the combined use of human lesion and neuroimaging methods in the investigation of the functions subserved by this brain region" and that we "contribute valuable insights into the neural implementation of cognitive sets". This praise reflects the tremendous effort of the co-authors in Copenhagen, Oxford and Tokyo, and of the participants in the study in 2004-5. As principal investigator for the study James Rowe, is particularly grateful for the opportunity to have carried out this research at DRCMR.

Together with Helmut Laufs from Brain Imaging Center Frankfurt am Main, Torben Lund has collected a series of high quality simultaneous EEG/fMRI data. In this study the subjects were asked to relax with closed eyes, without trying to fight sleep. Even-though it was not the purpose of the study one of the subjects was able to go through all three stages of non-REM sleep during the 30 minutes of intensive EPI scanning. The results were published in Brain (Laufs et al. 2007) as part of a letter to the editor and demonstrated as the first brain imaging study thalamic activity related specifically to sleep spindles and k-complexes. The data from the subjects who did not fall asleep were published in Neuron as part of a larger study (Giraud et al. 2007). The findings in the paper suggest a connection between speech lateralisation and spontaneous oscillations in the EEG. Currently the data are being used so test a theoretical model suggested by James Kilner which connects the EEG activity with the BOLD signal.



Tissue segmentation: Red = Gray matter; Green = white matter, Blue = Cerebro Spinal Fluid

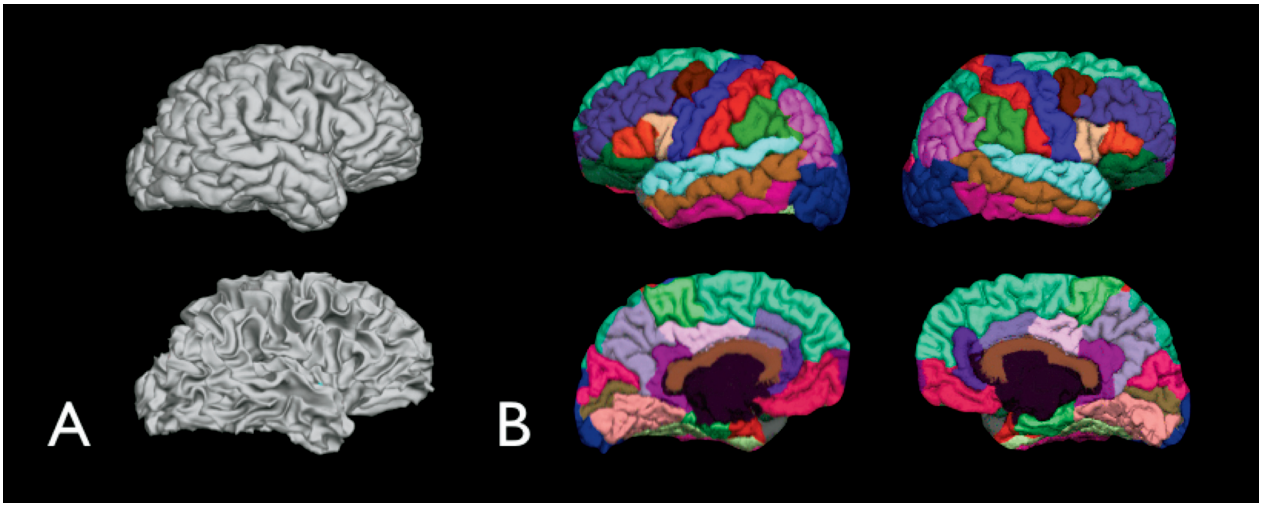
As a part of his PhD project, Henrik Lundell is, together with Dorothy Barthélemy and Jens Bo Nielsen, comparing cortical activity for patients with spinal cord injuries and normal controls. The aim of the study is to investigate the role of cortical plasticity after spinal cord injuries and to understand the role of subcortical networks in regeneration of locomotion after rehabilitation.

Cimbi

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

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

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



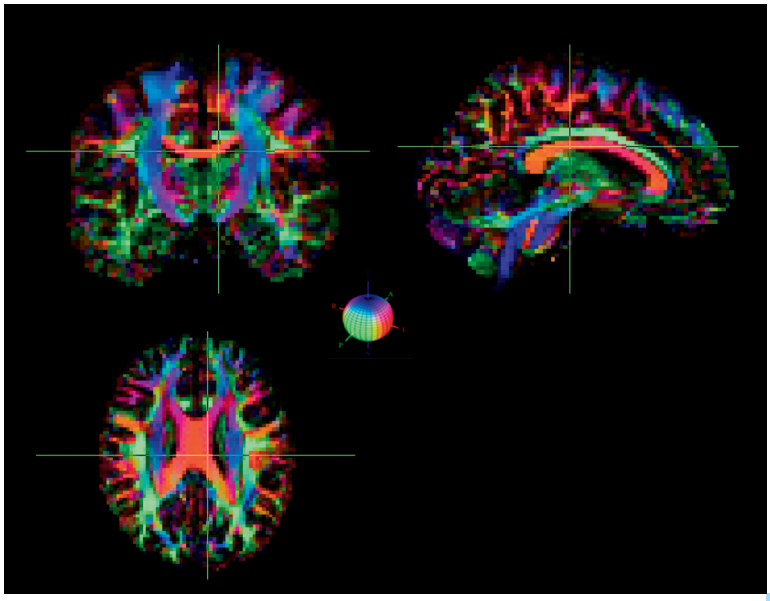
The Freesurfer software generates: A) high-resolution surface maps that can be used in calculating cortical thickness: Upper = Pial surface; Lower = white matter surface; B cortical surface maps that are automatically segmented in anatomical brain regions. Upper: lateral view of the left and right hemispheres; Lower: medial view of the left and right hemispheres.

influences on serotonin function and behaviour may be mediated by their effects on the brain's anatomical structure.

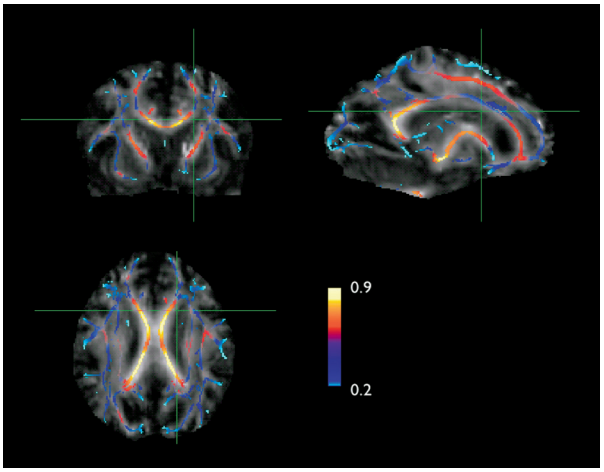
Senior researcher William Baaré and PhD-student Kathrine Skak Madsen are working on the morphological Cimbi project. Kathrine visited UC San Diego for 2 months in the fall of 2007 to obtain more intensive hands-on experience under the supervision of Professors Terrry Jernigan and Anders Dale. Jens Bundgaard joined the team for one an a half year as an image processing specialist. He made substantial progress in mastering relevant image processing and data handling skills relevant to the project aims. Unfortunately Jens had to leave the team for other career challenges.

Standardized procedures for acquiring phantom data and for image inspection have been developed and implemented and are now followed by project personnel. Automated pipelines have been developed to ensure uniformity in the basic postprocessing analyses applied to Cimbi datasets. This includes an entirely new pipeline for processing of the diffusion-weighted images. As part of this process, standardized, processed MR datasets are subjected to gradient non-linearity distortion and RF inhomogeneity correction and then tissue-segmented for use by NRU in analyses of the PET data.

A master Cimbi study template was constructed to provide optimal conditions for automated segmentation using SPM2. The template was based on a sample of 185 MR datasets from normal volunteers, selected from both Cimbi legacy data and prospectively acquired Cimbi cases. These cases were well distributed by age and gender, and the quality of the MR data was carefully controlled. The dataset was then analyzed to determine the effects of age on the tissue volumes and these effects were compared to those reported previously in the literature. These analyses suggest that the basic tissue segmentation methods applied in Cimbi compare favourably with those reported in other major centres, and that the methods should be reasonably sensitive to



Fractional anisotropy (an indicator of myelination and axon thickness), as well as colour-coded diffusion tensor maps showing the prevailing fiber direction in each voxel: Red: left -right direction; Blue: inferior -superior direction; Green: anterior -postrior direction.

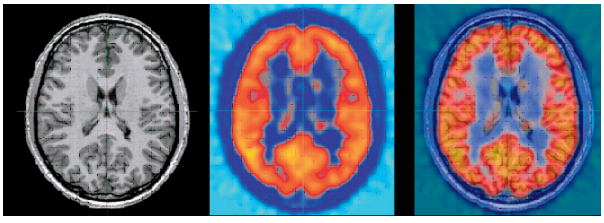


TBBS: individual FA images are high dimensionally warped to a target FA image. FA values for al subjects are next projected on a "skeleton", which represents the major fiber tracts common to all subjects. Here the mean skeleton FA-values over all subjects are overlaid on a mean group FA image. The colour bar depicts FA-values.

individual differences in brain morphology among Cimbi participants.

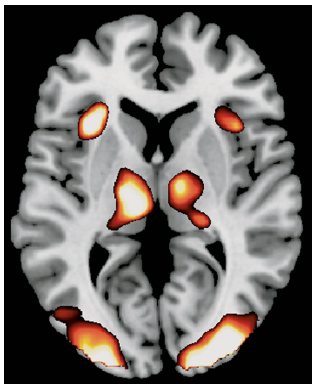
Our evaluation of segmentation methods continues. It is clear that results of different segmentation methods differ and that the choice of a method must be considered in light of the specific purpose for which the data are to be used. There are also differences in segmentation results between 1.5T and 3T datasets; however, it appears that these effects can be modelled reasonably well. It has been decided to augment the current voxel based morphometry (VBM)-based segmentation method used in Cimbi with segmentation of cortical parcels and subcortical gray matter structures using other software packages (Freesurfer and FSL). Project personnel have acquired specialty training in the application of these methods and will begin applying them to Cimbi data in the near future.

Tract-based spatial statistics (TBSS) is a method that supports voxel-wise analysis of DTI data, particularly fractional anisotropy (FA) maps by using FA to align the centres of major fibre tracts across individuals. This improves the sensitivity of voxel-wise methods for detecting alterations in fibre tract FA across groups (such as polymorphism groups) or in association with continuous variables (such as behavioural measures or biomarkers). Project personnel have obtained training in the use of this method and have begun to apply it to examine age (and polymorphism) effects on fibre tract microstructure.



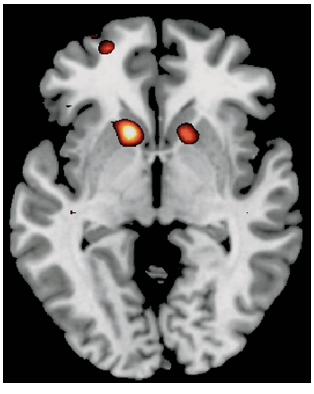
To enable a simultaneous voxel-wise analysis of structural (Left) and 5-HT$_{2A}$ receptor binding images (Middle), the binding images were automatically registered to structural images (Right).

Considerable time was spent this year attempting to map brain morphological correlates of those personality traits implicated in Cimbi 5-HT$_{2A}$ studies and to relate the findings to the neuroreceptor results. Traditionally, brain morphological information is embedded within the analysis of the PET data itself, in the form of ROI definition and partial volume correction of binding values. Therefore, in an attempt to gain a more complete picture of the separate and combined effects of brain morphology and receptor density on personality traits, we decided to apply a novel technique referred to as Biological Parametric Mapping (BPM). This method allows voxel-wise prediction of criterion variables (such as personality indices) using values from multiple imaging modalities simultaneously. This analysis, predicting personality traits from morphological and 5-HT$_{2A}$ maps, is in progress.



Bilateral insula and thalamus activations at group level during a decision making task.

The aim of the functional studies is to investigate the relationship between the cerebral activation responses and the serotonergic system using fMRI. The work is coordinated by post-doc Julian Macoveanu and involves two PhD-students, Bettina Hornbøll and Jon Wegener. The research focuses heavily on a set of behavioural constructs that have been linked to serotonergic function: self-discipline, vulnerability (and trait anxiety), and decision making. Activation paradigms for use with fMRI were designed to evoke, or probe, each of these behavioural dimensions, and they reliably produce activity in the fronto-limbic regions known to have high concentrations of 5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_{4}$ receptors (see figures). To elucidate the role of serotonergic func-



Ventral striatum and frontal areas reflect the level of risk undertaken by the studied group of subjects.

tion in these mental processes, brain activation patterns are being studied under challenge of the serotonergic system by different types of drug interventions. Additionally, the activation responses will be correlated to the receptor density and to genetic polymorphism of serotonin receptors and transporters, data provided by other Cimbi groups.

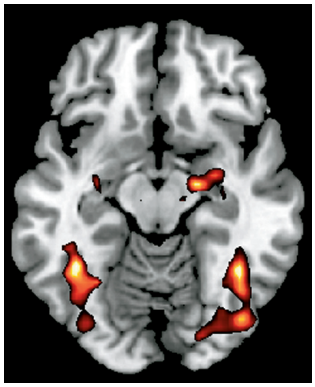


Image from a group level analysis from a gender discriminaiton task with emotional faces, showing bilateral amygdala activity. With the highest level of activation in the right side amygdala, also seen is activity in the FFA.

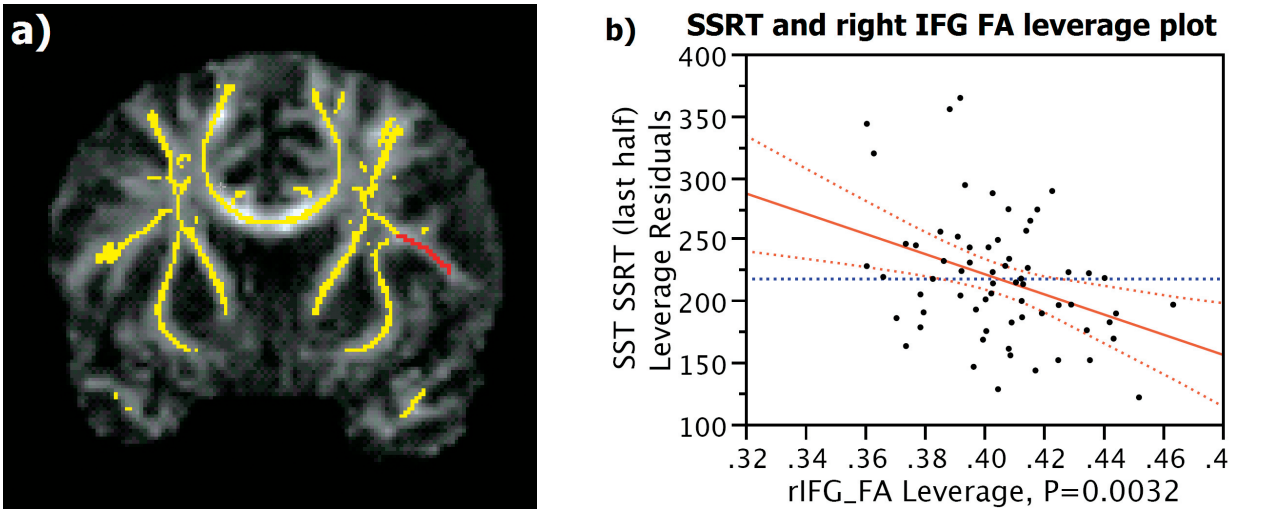
Brain Maturation

A new study of brain maturation in school-aged children was started in 2007. This project is led by Professor Terry Jernigan and represents a collaboration between the DRCMR and Learning Lab, Denmark of the Danish School of Education, Aarhus University. Also partnering in the project are three local schools, their students, and their families. The project involves two annual examinations with psychological and academic tests as well as structural brain imaging. Recent research has shown that biological maturation of brain tissues continues throughout childhood in the form of changes in cortical morphology, and particularly, in changing structure of the brain's fibre tracts. What is less well known is the degree of individual variability in the timing and pattern of these changes, and whether such variability has relevance for the developing mental functions of the child. These questions are the main focus of the new study.

Last year over 90 children, ranging in age from 7 to13 years, were studied at their baseline visits, and many completed their second visits to the department. Though it is too soon to examine the differences among the children in the rate of maturation, it has been possible to examine the variability among them at their entry to the study. There are already very interesting results and two research reports have been submitted for presentation at the Annual Meeting of the Organization for Human Brain Mapping. The two reports focus on measures of fibre tract organization in specific neural systems and the relationship with behavioural inhibition and working memory, respectively.

Both the capacity to successfully inhibit a "primed" response and the ability to keep in mind and use an accurate spatial model of the environment are functions that continue to develop substantially over the school-aged years. For both of these functions, specific neural systems have been implicated in adults. In the DRCMR study, measures of organization of fibre tracts in these systems were significantly correlated with the behavioural measures, and the analyses suggested that these associations were relatively specific to the organization of the implicated neural systems.

Though these are exciting results, the challenge is to interpret them correctly. Children may vary in the phase of maturation in the brain networks subserving response inhibition and working memory, and this variability may mediate these associations. This is plausible since both fibre tract maturation and these functions continue to develop during this age range. Alternatively, the associations could be mediated by stable individual differences reflecting underlying neural system connectivity. Longitudinal observations currently continuing in the DRCMR are needed to help distinguish between these, and other, explanations.



a) TBSS skeleton (yellow) with a region of interest in the right inferior frontal gyrus (IFG, red) overlayed a fractional anisotropy (FA) map. b) Response inhibition (SSRT) measured with the stop-signal task (SST) improves significantly with higher FA in the right IFG. The leverage plot shows the contribution of right IFG FA in predicting the SSRT, adjusted for the variation explained by age and whole skeleton FA

Clinical Research

Neuropsychiatric Disorders

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

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

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

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

The following MR techniques are used in the different projects: structural MRI including T_1, proton density and T_2-weighted, FLAIR and diffusion tensor imaging (DTI). The latter technique permits investigation of white matter microstructure. Additionally, in the schizophrenia projects, fMRI is used to investigate (frontal) brain function using a verbal working memory (N-back) task.

The senior researcher at the DRCMR responsible for coordinating the MR investigations is William Baaré. Patients and healthy controls are recruited and clinically evaluated by the psychiatry departments at the university hospitals of Rigshospitalet (Affective disorders: Principal investigator: Prof. Dr. Lars Kessing), and Bispebjerg and Glostrup Hospitals (Schizophrenia: Principal investigators: Professors Birte Glenthoj and Dr. Katrine Pagsberg). There is currently one project investigating affective disorders (A1) and five projects investigating schizophrenia (S1-S5).

Psychiatrist Maj Vinberg is the clinical researcher responsible for the affective disorder project (A1). In this project healthy mono- and dizygotic twins (age > 18 years) with a high and a low risk of developing affective disorder are investigated. The degree of risk depends on zygosity and the diagnostic status of the co-twin (e.g., diagnosed with affective disorder or never received a psychiatric diagnosis). Four hundred potential subjects were identified by linking the Central Psychiatry Registry and the Danish Twin Registry, a possibility that is unique to Denmark. Inclusion of subjects finalized in the end of 2005. MR scans are available for 173 subjects. A paper on grey matter changes in subjects at risk for Affective Disorders was submitted in the end of 2007. People at risk tended to have reduced hippocampal volumes as compared to healthy controls.

Clinical researchers responsible for the different schizophrenia projects are the psychiatrists: Birte Glenthøj (S1: "Structural and functional brain abnormalities in drug naïve adult onset schizophrenia") and Bjørn Ebdrup (S2 "Structural and functional brain changes in drug-naïve first-episode schizophrenia patients: relation to cognitive function and anti-psychotic medication"); Katrine Pagsberg (S3: "Structural and functional brain abnormalities in early onset first-episode schizophrenia") and (S4: "First episode psychotic children and adolescents: a 5 year follow-up study of brain structure and function"); and Trine Bjørg Hammer (S5: 5-10 year follow-up of schizophrenia patients: "Skizofreni: Sygdomsprocessens kliniske, psykofysiologiske og neurobiologiske manifestationer"). Data acquisition for projects S1 and S3 was completed by the end of 2002. In 2003, data acquisition commenced for projects S2 and S4 remains ongoing. Project S5 started towards the end of 2004 and is ongoing.

In project S1, 16 antipsychotic drug-naïve and 3 minimally medicated first-episode schizophrenic patients

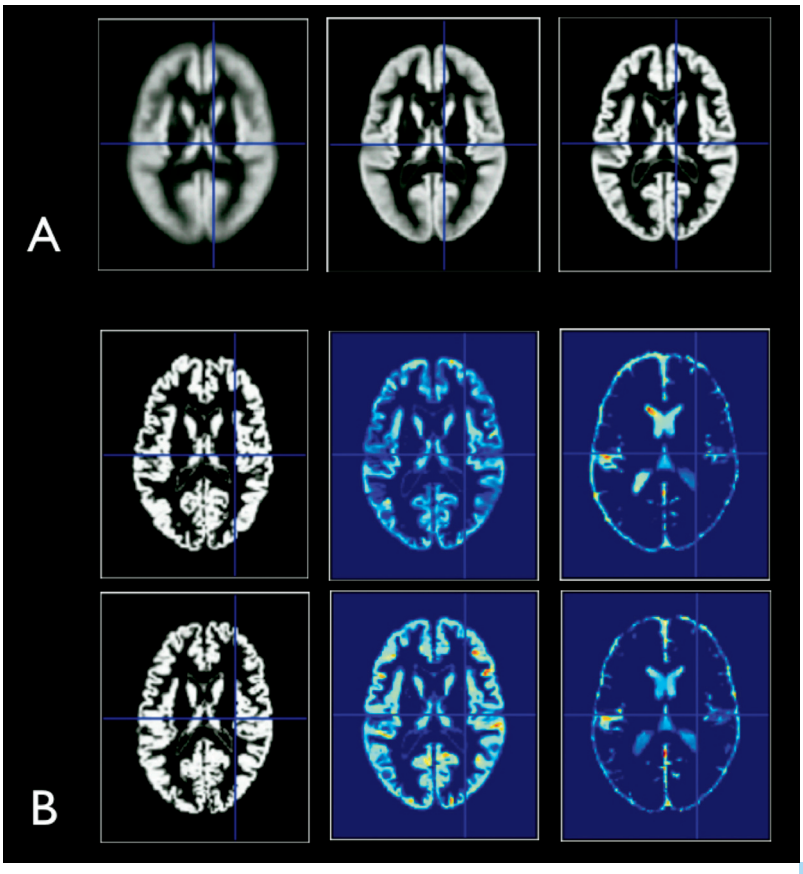
and 19 matched controls participated. Patients were randomly assigned to treatment with either low doses of the typical antipsychotic drug, zuclopenthixol, or the atypical compound, risperidone. High resolution MRI-scans were obtained in patients before and after 12 weeks of exposure to medication and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

In project S3, it was shown that abnormalities in ventricular and frontal white matter volumes are already present at the early onset of non-affective and non-organic psychosis in minimally medicated children and adolescents. In addition, our finding of smaller intracranial volume in the subgroup of patients with schizophrenia suggests alterations in early brain development and supports current hypotheses implicating neurodevelopment in the pathophysiology of schizophrenia. In contrast to findings in adults, grey matter abnormalities appear not to be a key feature when the onset of illness occurs during childhood/adolescent brain maturation. This study was published in 2006 in the Journal of Neural Transmission

In project S2 all baseline has been acquired and is currently analyzed. Preliminary results using DARTEL ("Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra") suggest that changes in grey matter volume in the drug naïve first episode schizophrenia subjects are minimal. Posters were presented at several conferences.

Brain Aging and Neurodegenerative Disorders

The Centre is the site of several studies of normal aging and the neurodegenerative disorders that afflict the elderly; and is a participating site in a broader multi-site investigation by European Union collaborators entitled, "Leukoaraiosis and Disability in the Elderly" (LADIS). The latter is an ongoing structural MRI study of the known changes that occur with aging in the white matter of the brain. The objective is to better describe the predictors and consequences of these changes. Elderly volunteers were scanned at entry into the study and a 3-year follow-up scan has now been completed. These measures are correlated with extensive neurobehavioural assessments. Egill Rostrup was the senior



DARTEL. A: individual brains are iteratively warped to refined group average images (e.g. templates). Left: start average; Middle: intermediate template; Right: final template. B: Two brains are depicted. Left: original grey matter; Middle: grey matter after warping to the last template. Right: CSF after warping to the last template. Note in the latter the similar shape of the ventricles. Finally, the intensities in the blue images are adjusted for the amount of warping and therefore reflect volume instead of concentration.

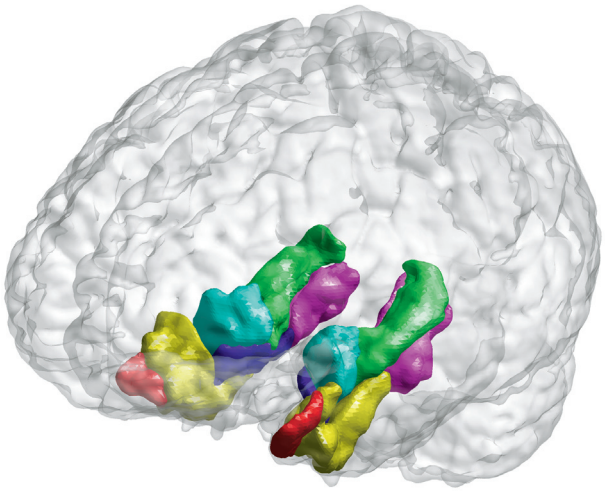
DRCMR investigator most closely involved with the LADIS studies.

As part of the LADIS project, PhD-student Charlotte Ryberg is focusing on studies of the corpus callosum, which is the major cerebral white matter structure carrying most interhemispheric connections. Data analysis is performed in collaboration with the group of Prof. Rasmus Larsen at the Technical University of Denmark, especially regarding an automated method to recognise and quantify the volume of this structure. The full dataset of 569 subjects has been analysed, and correlations with several measures of cognitive and motor performance were demonstrated. Notably, these effects seem to be additive to the effect of age related white matter changes per se. Two papers were published in 2007 based on the work from this study.

Based on the automated shape detection, it is possible to apply mathematical models for parameterization of shape and appearance of MR data from corpora callosa. The resulting automated methods can then be used to examine, in a completely objective way, the variability in callosal morphology that occurs in the elderly LADIS subjects. A sophisticated method for shape analysis was developed by Karl Sjöstrand and published in 2007.

Thomas Ramsøy heads a project on the healthy aging of the brain. Using both structural and functional MRI methods, complemented by neuropsychological tests, the main focus is on the medial temporal lobe (MTL) structures including the amygdala, hippocampus and rhinal cortices. This year, the project led to the submission of a PhD dissertation that focused on the effects of age on MTL activation during episodic memory processes. This work was also presented at the annual Neuroday conference in Copenhagen. This research demonstrated that age leads to dynamic and process-specific alterations in MTL activation. The observed age-related alterations were found to be dependent on processing stage (preparation, encoding, and rehearsal), suggesting that the effects of age on MTL activation is a mixture of loss of function (dedifferentiation) and top-down modulation (compensation). The project has led to the development of structural and functional imaging methods, and a protocol for drawing Regions of Interest of MTL structures. These advances will be applied on the study of the effects of ecstasy (MDMA) abuse, and on the effect of degenerative disease such as Alzheimers Disease.

Parkinson's disease (PD) and the related disorder, multiple system atrophy (MSA) may be difficult to diagnose clinically. Katja Krabbe of the DRCMR, together with collaborators from Bispebjerg Hospital, has completed a study of patients with these diseases employing segmentation of conventional MR images and MR diffusion measurements. Visual evaluation of diffusion colour maps turned out to be more sensitive in the differential diagnosis between the two diseases than conventional imaging. Substantia nigra volume was decreased in both patient groups compared to normal controls but the segmentation studies did not prove useful in the differential diagnosis between the diseases. Katja Krabbe successfully defended her PhD during 2007.



Regions of interest (ROI) of the extended medital temporal lobe. The figure shows a 3D reconstruction of ROIs drawn on one of the subjects in the study, and positioned within a transparent view of the native brain. Structures are indicated by colour, where red = temporopolar cortex, yellow = perirhinal cortex, blue = entorhinal cortex, cyan = amygdala, green = hippocampus, and pink/purple = parahippocampal cortex

Multiple Sclerosis

The DRCMR has a long history of doing MRI research on multiple sclerosis (MS), and a major part of this research is performed in collaboration with external groups and thus has an extensive multidisciplinary input ranging from neuroimmunology and neurophysiology to neuropsychology.

MS is an inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS). It is the leading cause of nontraumatic neurological disability among young adults. About 85% of MS patients initially experience a relapsing-remitting clinical course (RRMS) with transient symptoms followed by a secondary progressive course (SPMS) characterized by gradual progression of disability. In the majority of cases patients show episodes of neurological dysfunction (relapse, attack) separated by partial or complete recovery. MRI is a valuable tool for the diagnosis of MS and for monitoring the disease evolution. However, the correlation is limited between conventional MRI (T1, T2, and FLAIR) measures and clinical findings. There are several reasons for this mismatch: (a) The low pathological specificity of conventional MRI and the inability of conventional MRI to quantify the extent of damage in the so-called normal-appearing white matter (NAWM). (b) A relative mismatch between whole brain measures of lesion burden by MRI and the fact that clinical measures of disability are relatively pathway-specific. (c) The severity of clinical manifestations of MS does not result simply from the extent of tissue destruction, but rather represents a complex balance between tissue damage, tissue repair, cortical disconnection and reorganization. In general, the research projects aim towards improving the specificity and sensitivity of MR imaging to detect the heterogeneous pathological changes and cerebral adaptation in MS. In addition, we

also use MRI as a tool to evaluate the treatment effects of different immunomodulatory agents. The projects in this area are carried out by Henrik Lund, PhD-student Anne-Marie Dogonowski, senior researcher Xingchen Wu, who has extensive experience within the areas of both clinical and experimental MS research, and Kirsten Korsholm, who successfully defended her PhD thesis titled *Functional and structural MRI in optic neuritis*, in October 2007.

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

The different MR-techniques all aim at the exploration of structural changes caused by the pathology of MS. For example, applying so-called q-space analysis to our diffusion data, it is possible to acquire structural information on the various biological barriers and compartments. One limitation with traditional diffusion tensor imaging (DTI) is that the calculated diffusion coefficients are not expected to depend on the diffusion weighting or diffusion time. This is correct only in perfectly homogenous media and not in vivo where the diffusion of water is hindered by tissue structures. Normal DTI analysis gives one (apparent) diffusion coefficient (ADC) based on the assumption that the sample behaves as a perfect Gaussian distribution. However, an increased ADC does not tell us whether the viscosity is lowered or whether the sample has fewer barriers. The q-space analysis, which is based on several diffusion weightings provides a size distribution of the tissue compartments and thus potentially gives clinically relevant information on the breakdown of the structures. This technique will be used to analyse the water diffusion orthogonal to the fibres since an alteration in this diffusion is hypothesized to reflect a direct immunological breakdown of the myelin and/or axons. Additionally, anterograde (Wallerian) and terminal axonal degeneration as a response to focal lesions possibly gives rise to more diffuse changes. Hence, the approach is expected to provide information on diffuse as well as focal pathologies and we aim at showing that q-space imaging can provide clinically relevant information in MS at scanning times suitable for the clinic. The data analyses and interpretation will be performed in collaboration with Finn Sellebjerg, Rigshospitalet and Lars G. Hanson, DRCMR.

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

Functional MRI (fMRI) can give information on brain plasticity following MS-related structural injury, with the potential to limit the clinical manifestations of the disease. Studies of cerebral activation in MS patients have successfully been carried out using the blood oxygen level dependent (BOLD) fMRI technique, which allows to dynamically follow metabolic and haemodynamic consequences of brain activity. Furthermore, it is now believed that processing of a functional task by the brain can only be performed through interaction of segregated regions within a complex network. Functional connectivity MRI (fcMRI) is a new method of assessing cerebral connectivity by mapping regions with synchronous slow fluctuations in cerebral blood oxygenation and flow. Assessing functional cerebral connectivity of resting state BOLD appears to be an informative way to determine the clinical impact of the overall diffuse and focal injury in MS. These techniques have recently been refined by our Centre by increasing the signal-to-noise ratio and improving data analysis. Anne-Marie Dogonowski, Xingchen Wu and collaborators investigate the recovery mechanism of MS patients by evaluating the cerebral activation and functional cerebral connectivity in MS patients during acute relapse and after clinical recovery. In order to explore the correlation between cerebral connectivity and clinical disability, a separate group of MS patients with varying degrees of disability are investigated by using the same method.

Diffusion-weighted imaging (DWI), which can quantify the extent of microstructure changes within and outside conventional MRI visible MS lesions. There is increasing evidence showing that DWI is sensitive to detect subtle changes in the NAWM, and the fibre tracking capabilities of DWI are well suited for evaluation of fibre pathway changes associated with MS lesions. These two groups of MS patients included in fcMRI studies are also investigated using whole brain DWI in 61 directions. In addition detection of immunological markers from blood samples and clinical examinations is carried out at the same time points with MRI by collaborators at the Danish MS Center, Rigshospitalet. Patients are still being recruited for both projects.

MR spectroscopy (MRS) can provide information about neuronal loss or dysfunction by measuring N-acetyl aspartate (NAA), a suitable marker for neuronal integrity. Cognitive dysfunction can be seen in 50% of MS patients, and a substantial number of studies suggest that cognitive dysfunction is related to the overall disease burden of the brain. A group of patients with

early RRMS have been investigated using multi-slice echo planar spectroscopic imaging (EPSI) and a large battery of cognitive measures. The study showed that the cognitive performances of the patients were correlated to subtle pathological changes in the CNS. Rather intriguingly, we showed that subtle changes in the so-called normal appearing white matter were partly responsible for the highly disabling deterioration of the cognitive function. This project has been carried out by Henrik K. Mathiesen, Lars G. Hanson, and in close collaboration with Per Soelberg Sørensen and Agnete Jønsson, both at Rigshospitalet. The follow up study of the same group of patients are undertaken by Xingchen Wu and Lars G. Hanson, DRCMR and Morten Blinkenberg and Agnete Jønsson, Rigshospitalet.

Optic neuritis (ON) typically causes visual impairment and retrobulbar pain due to demyelineation and inflammation of the optic nerve. The disease is associated with decreased visual acuity, abnormal colour vision, decreased contrast sensitivity, visual field defects, and delayed or broadened visual evoked potentials (VEP). Within weeks or months after onset of symptoms, a spontaneous recovery of vision occurs and patients usually regain good vision. However, ON is associated with a high risk of developing MS and is the presenting symptom in approximately 20% of MS patients. After isolated acute ON the 10-year risk of developing MS has been reported to be approximately 40%.

There is evidence of cortical adaptation in patients with ON in early and higher visual areas (especially in the lateral occipital complexes) and also outside the occipital cortex. However, no studies have serially investigated activation in subcortical structures, in particular in the lateral geniculate nucleus (LGN). Kirsten Korsholm investigated what happens in the LGN during recovery from ON using fMRI and visual evoked potentials (VEP). The study showed that recovery of vision in the group of patients with ON is most likely due to resolution of inflammation and oedema in the optic nerve during the first months. In addition, a reduced activation of the LGN to stimulation of the unaffected eye is seen after recovery, and this has been interpreted as a shift away from early compensatory changes established in the acute phase in LGN. This may indicate very early plasticity of the visual pathways. This project was carried out in collaboration with the Department of Neurology at Glostrup Hospital, and the results were published in Brain in 2007.

Another study focusing on voxel-based analysis of whole brain activation during recovery from ON aims to assess whether adaptive changes take place outside visual areas as suggested by earlier studies. Previously the effect of the heterogeneity of scotomas in patients with ON has not been adequately addressed, and in this study we introduce a new method of modelling scotomas in fMRI to reveal a clearer pattern of neuroplasticity across a mixed patient-population. This project was also carried out in collaboration with the Department of Neurology at Glostrup Hospital, and the results of this study have been submitted to Neuroimage.

Traumatic Brain Injury

Traumatic brain injury (TBI), predominantly caused by motor vehicle accidents, is the leading cause of death and long-term morbidity among younger age groups in Western countries. In survivors of severe TBI the final outcome is both highly variable, ranging from almost full recovery to persistent vegetative state, and extremely difficult to predict, especially in cases of prolonged unconsciousness. Several different types of lesions can occur in TBI, but diffuse primary and secondary lesion types are thought to be major prognostic determinants. However, these diffuse lesions are highly underestimated by conventional imaging. Advanced quantitative MR techniques, such as diffusion tensor imaging (DTI) and spectroscopic imaging, have the potential to improve detection of these important lesions and provide useful clinical tools for outcome prediction.

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

Data collection has been completed and post-processing is ongoing. Thirty patients have been included and scanned in the late subacute phase; of these 23 completed the 1-year follow-up scan. DTI data has been evaluated and accepted for publication in Brain. The study findings demonstrate severe and widespread diffusion abnormalities at the late subacute stage. Interestingly, at 1-year follow-up diffusion had partly or completely normalised in some brain regions, particularly so in patients with good clinical outcome. These findings provide in vivo indications that axonal repair may be among the mechanisms underlying clinical recovery following severe TBI. Ongoing data-analyses focus on the brain atrophy that occurs during the 1-year follow-up period. Advanced morphological techniques are used to assess both global and regional atrophy. The results of this project might provide important diagnostic, prognostic and pathophysiological information useful in the clinical management of brain-injured patients.

Neonatal Brain Maturation

Infants born prematurely are at risk of brain injury and neurodevelopmental deficits in later life. The pathogenesis of brain lesions is still controversial but apparently both infection in pregnancy and perinatal ischemia influence the development of white matter damage. In an ongoing collaboration with the department of Paediatrics, a study headed by Maria J. Miranda aims to demonstrate an association between infection in pregnancy and white matter damage in the immature brain at term-equivalent age. The study aimed at including 200 premature infants born at either Hvidovre Hospital or Rigshospitalet at a gestational age (GA) less than 33

weeks. The placenta was histologically and microbiologically examined by a pathologist, while blood from the umbilical cord was examined for bacterial endotoxins and several inflammatory cytokines. These data are compared with the number and extent of brain lesions and lactate accumulation found in MR scans performed at term-equivalent age.

The study was temporarily stopped after the first 100 infants studied, born with a GA ≥ 28 weeks. The analysis of these data revealed that inflammation (chorioamnionitis or funicitis) can only be demonstrated in a minor proportion (10-12%) of the placenta of infants born ≥ 28 weeks of gestation. Studying a smaller group out of the originally 100 infants with a complete foetal inflammation profile revealed no correlation with MRI findings in this population. These results were published in Acta Paediatrica in 2007.

On the other hand, MR spectroscopy (MRS) data from these 100 infants (analysed by Robin de Njis), revealed other important findings in the metabolic pattern of the brain of premature infants at term-equivalent-age as compared with healthy term-born controls. Choline/Creatine ratios were significantly different between the groups. The decreased Choline-levels might indicate either earlier or slower myelination in preterm infants (not seen on MRI), at least in some areas of the brain, even in preterm infants at term without brain lesions.
Another modality that was used to examine the preterm infants is Diffusion Tensor Imaging (DTI) which can be used to study white matter microstructure as well white matter tracts. Comparing diffusion measures in the preterm infants with term-born controls revealed no differences between the groups where white matter structures of interest were traced manually. However, comparing the whole brain statistically with voxel based morphometry (VBM), an advanced development of white matter regions in occipital white matter was found. This is in contrast to current belief, where a delayed white matter development is expected due to the detrimental effects of prematurity. These data have recently been accepted for publication in Neuroimage. The DTI study was carried out by Maria J. Miranda in collaboration with Peter Born (a previous DRCMR researcher). Egill Rostrup, Lars G. Hanson and Terry Jernigan, DRCMR, as well as Zoltan Nagy, Karolinska Institute, Sweden and Monica Gimenez, Barcelona University, Spain.

Visual Plasticity

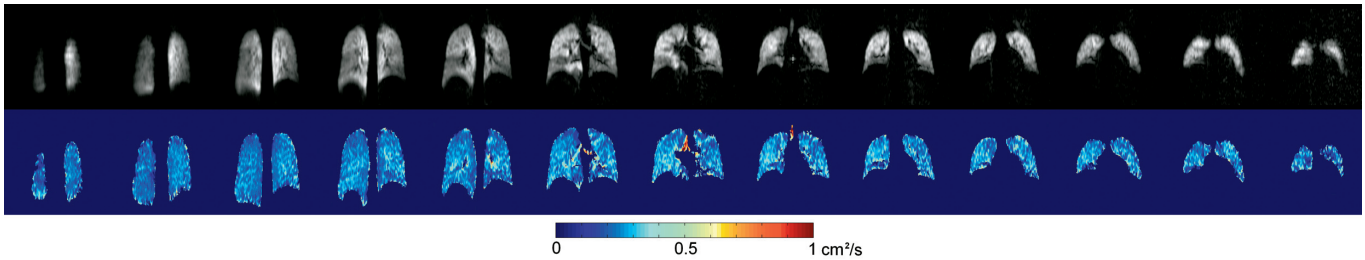
There is a strong tradition for investigating the visual system with fMRI at DRCMR. Several projects investigating human vision with fMRI are currently running dealing with how the visual system is affected in various disorders.

Visiting Professor Maurice Ptito is heading a research program on congenital blindness. The program is supported by the Danish Medical Research Council and the Harland Sanders Foundation in Canada. It deals mainly with the anatomic-functional re-organization of the brain in congenitally blind subjects. Maurice Ptito and coworkers published several papers on the subject in 2007. One example is research on how the afferent and efferent connections to the visual cortex of the blind's brain were largely atrophied. The visual cortex and its extrastriate connecting areas were also reduced in volume. However and interestingly enough, these areas were recruited during a 'visuo'-tactile task where a visual stimulus is converted into a tactile one and delivered to the tongue. This indicates that there is an increase in connections between the parietal and the occipital cortices.

Another project focusing on the visual system is a project on cataract headed by PhD-student Astrid Lou. Cataract is a very common disease of the eye lens severely degrading the ability to perceive visual input including decreased contrast sensitivity, reduced visual acuity and changed colour perception. The disorder typically has a gradual onset in the older population and is caused by the lens becoming more dense. By surgically replacing the eye lens with an artificial one the visual acuity, contrast sensitivity and colour perception can be normalised. In a study where cataract patients are followed before and after surgery we attempt to find out how such an abrupt change influences the brain processing of visual input.

Pulmonary Function

Imaging of the lungs poses a number of difficulties with respect to traditional MRI. Large susceptibility differences at the air-tissue interfaces cause the MR signal to decay very rapidly and, in addition, the proton density of lung tissue is low compared to other tissues. On conventional MR images the lungs appear as dark regions and only by using very sophisticated and advanced MR



MR-images of the lung of a healthy smoker, acquired using inhaled hyperpolarized ^{3}He-gas and the new 3D diffusion pulse sequence. The pulse sequence acquires two sets of base images over the entire lung: one set of images with a diffusion sensitizing gradient (not shown) and one set of images without diffusion sensitization gradient (top row). From the two sets of images the diffusivity of the ^{3}He-gas within the lung is calculated as the apparent diffusion coefficient (ADC) in units of cm^2/s on a pixel-by-pixel basis (bottom row). The base images shows where the inhaled gas has entered and hence reflects the regional ventilation. The sequence is adjusted so that the MR-signal is sensitive to diffusion in the restricted regime, making the calculated ADC-values reflecting the alveolar size. The ^{3}He-ADC has been shown to be a parameter sensitive to changes in alveolar size and is therefore useful for detecting emphysema and may also be useful for detecting the progression of emphysema over time.

methods can some information about the lung structure and function be extracted from the images. Another MR approach is based on imaging an inhaled hyperpolarized gas. DRCMR has been active in this field for a number of years now, starting with the very successful EU funded PHIL (Polarized Helium for Lung Imaging) project.

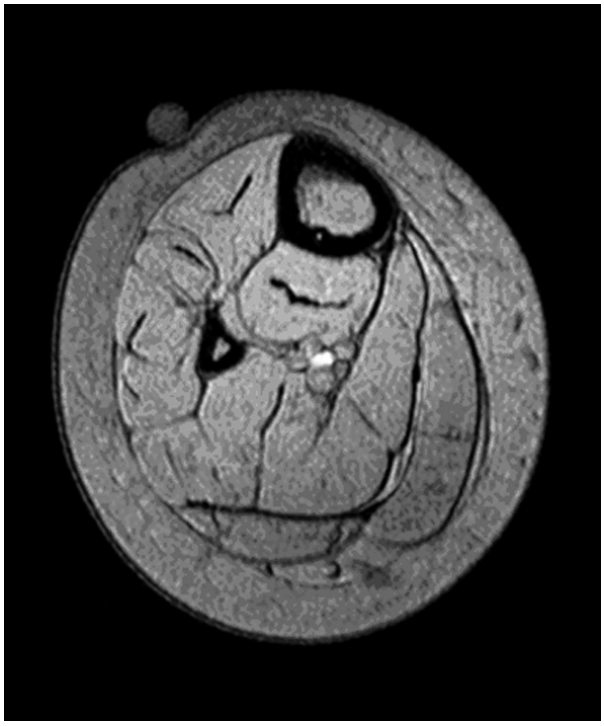
The partners from the PHIL project and a few additional organisations have formed a research network PHeLINet that has obtained funding from the EU 6th Framework Programme as a Marie Curie Research Training Network. The PHeLINet project commenced in 2007 and supports one foreign Early Stage Researcher employed at the DRCMR. Torsten Dorniok from Germany was recruited for this position and is working as a PhD-student.

Lise Vejby Søgaard and Peter Magnusson are locally responsible for MR lung imaging at the DRCMR. The technique is unique in Denmark and relies on the inhalation of magnetised helium, which is a harmless gas. The hyperpolarized ^{3}He gas for the studies at the DRCMR is produced at the Physics Department at Johannes Gutenberg-University in Mainz, Germany and shipped to Copenhagen as air freight.

In 2007 a new clinical study on COPD (chronic obstructive pulmonary disease) patients was initiated together with the Department of Cardiology and Respiratory Medicine. Thirty patients and 10 healthy smokers already participating in the ECLIPSE (non-drug study aiming at identifying relevant markers of the progression of COPD disease) study will be selected to be MR scanned 3 times with one year intervals in order to evaluate whether hyperpolarized ^{3}He MRI can be used to monitor disease evolution. PhD-student Frederik Hengstenberg is responsible for this clinical study.
The MR protocol includes morphological imaging providing information about the ventilation distribution and diffusion imaging that has been shown to correlate with the alveolar sizes in the lung. It has been suggested that the lung Apparent Diffusion Coefficient (ADC) values can be used as a sensitive marker for the progression of emphysema. The scanning protocol has been modified with new flip angle calibration procedures and a new 3D diffusion sequence has been developed.

Orthopaedics

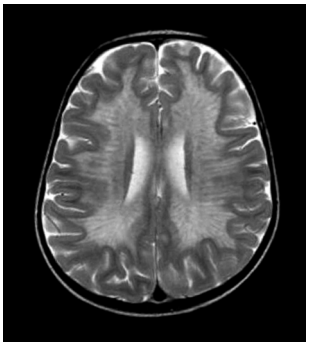
During 2007 measurements for an orthopedics research project were conducted at DRCMR in collaboration with the Gait Analysis Laboratory, Department of Orthopaedics Surgery at Hvidovre Hospital. The aim of the project was to study neurophysiological and biomechanical effects of focal anti spastic treatment of lower leg muscles (gastrocnemius and soleus) of children with cerebral palsy (CP) using Botulinum Toxin Type A (BTA). The relation between the dorsiflexor muscle cross-sectional area (CSA) as measured with MRI, and the dorsiflexor muscle thickness (MT) as measured with ultrasound, in children with CP was studied. The study was designed by PhD-student Thomas Bandholm from the Gait Analysis Laboratory and DRCMR physicist Peter Magnusson. The MR-measurements were performed on the 3T Trio MR-scanner with high in-plane resolution and involved multi-station scanning in order to cover the entire length of the lower legs. The requirement of large body coverage with moving-table multi-station scanning, limited the choice of RF-coil to the built-in body-coil with intrinsic low signal-to-noise-characteristics. This made the design of the MR-imaging protocol especially challenging in maximizing the signal-to-noise while maintaining a sufficiently high in-plane spatial resolution. The measurement results showed good correlation (r^2 = 0.778, P < 0.001) between the MT, as measured with ultrasound, and with the CSA, as measured with MRI, for the dorsiflexors. The dorsiflexor MT was 22% less in the affected compared to the non-affected leg in children with hemiplegia and the muscle group CSA was 32% less for the dorsiflexors in the affected compared to the non-affected leg accordingly. The study shows for the first time that the measurements of dorsiflexor MT reflects dorsiflexor CSA in children with CP and that measurements of dorsiflexor MT may be used to monitor changes in muscle size due to training or immobilization in CP.



High resolution MR-image (3D MEDIC multiple gradient-echo pulse sequence with three combined echoes and with a zero-filled in-plane resolution of 0.3 x 0.3 mm^2) of the lower leg as used for assessment of the dorsiflexor cross-sectional areas (CSA). The image slice position is 35% of the lower leg length, where the dorsiflexor muscle thickness (MT) was measured with ultrasound, as indicated by the oil-filled tablet.

Clinical Trials

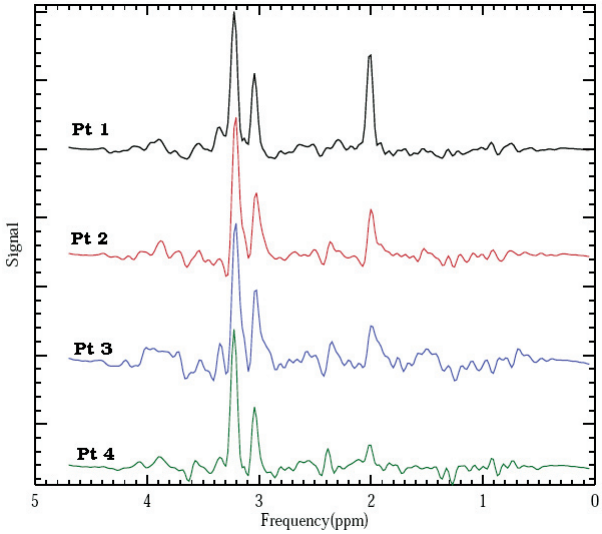
In 2007 a remarkable clinical trial was initiated at Hvidovre Hospital including the DRCMR: A potential treatment for the rare child disease Metachromatic Leukodystrophy (MLD) is currently being tested. In its late infantile form, MLD is a genetic disease that leads to demyelination of the brain. The children develop normally until approximately two years of age. Severe disabilities accumulate subsequently due to lack of an



The extremely rare and fatal disease MLD results in severe brain abnormalities. The white matter is subject to demyelination and is seen to appear bright with a characteristic stripe pattern. 13 patients from all over Europe were scanned several times at Hvidovre Hospital in 2007 as part of a drug trial. This study is the largest of its kind and it involves the use of new, promising methodologies.

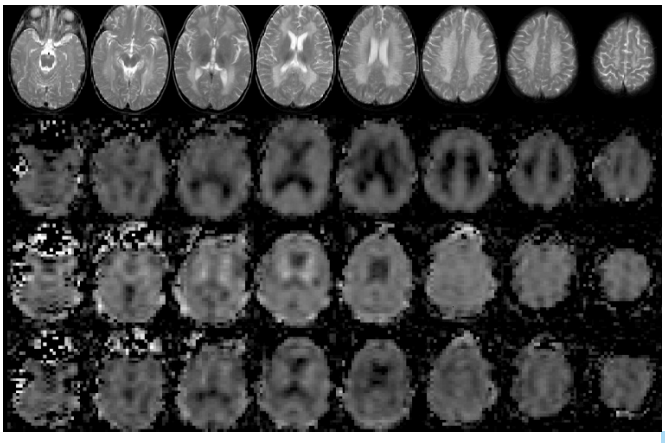
enzyme needed for sustained brain myelination. This horrible disease is normally fatal before age 10, but is luckily very rare: It affects only 1 out of 40,000 children. A Danish company *Zymenex* is now able to produce the missing enzyme and has initiated a clinical trial of treatment based on injection of the enzyme. In advance, it was far from clear that this would be sufficient for stopping the disease as the enzyme needs to move from the blood stream into the site of action to have any effect. Also, not all injected substances are tolerated by the body. The immune system can for example do away with the drug before it has any effect. The prospects, however, were sufficiently promising to warrant a try. A company *PhaseOne Trials* that is located at and partly owned by Hvidovre Hospital, was hired to conduct a clinical trial. Due to the low prevalence of the disease, this task is far from trivial: With two weeks interval, children from all over Europe that participate in the trial come to Hvidovre Hospital with their parents to get the treatment. This is necessary to ensure that the drug is used as intended and to monitor if there are effects (good or bad). Every half year, the stay is extended over two days that involve very extensive testing, including two hours of MR-scanning under anaesthesia. Making this possible is obviously a formidable challenge for the children, parents, the involved departments, the individual health care workers/scientists, companies and the study coordinators. It had not been possible without giving the project priority or without everybody demonstrating much more flexibility than normally possible in a busy environment.

Physicist Lars G. Hanson has been setting up the MRI protocols for the MLD study together with Ingeborg Krägeloh-Mann and Wolfgang Grodd from *University of Tübingen in Germany* who have investigated aspects of MLD on earlier occasions. Radiographers Siri Eggum and Ann-Sofi Sjøqvist conducted most of the scans



White matter spectra from four patiens with different severities of MLD. The NAA peak at 2 ppm is a measure of living neurons. It is seen to disappear during the course of the disease.

that involved structural imaging, diffusion tensor measurements, single voxel spectroscopy and spectroscopic imaging (short and long echo times). The practical aspects and the analysis have been discussed mainly with Christine Dali from *Rigshospitalet* who is the clinical investigator and the main paediatrician involved in all parts of the study. Though MRI studies of MLD have been performed before and though MRI plays an important role in the diagnosis of the disease, a relatively large patient group (thirteen patients) has never been examined longitudinally with MRI before (every half year). In particular, spectroscopic imaging was never reported for these rare patients despite the fact that this methodology can possibly offer the earliest sign of disease onset and provide unique insight into the progression of the disease of paramount importance for monitoring of treatment. It is particularly good that the measurements cover a large part of the brain using fast echo planar spectroscopic imaging techniques developed locally as part of Lars G. Hanson's PhD work years ago. Normally, spectroscopic imaging is not available, or covers just a single slice of brain within relevant acquisition times. Data are still being collected. These will give new insights into the nature of the disease and will demonstrate to which extent the drug is effective.



Apparently the first spectroscopic imaging results ever published for the disease MLD. The top row are T_2-weighted structural images while the three bottom rows show the distribution of NAA, choline and creatine, respectively. The three sets of metabolic images are normally quite similar but for this severely affected patient, the NAA image is basically reduced to a gray matter mask.

Preclinical Research

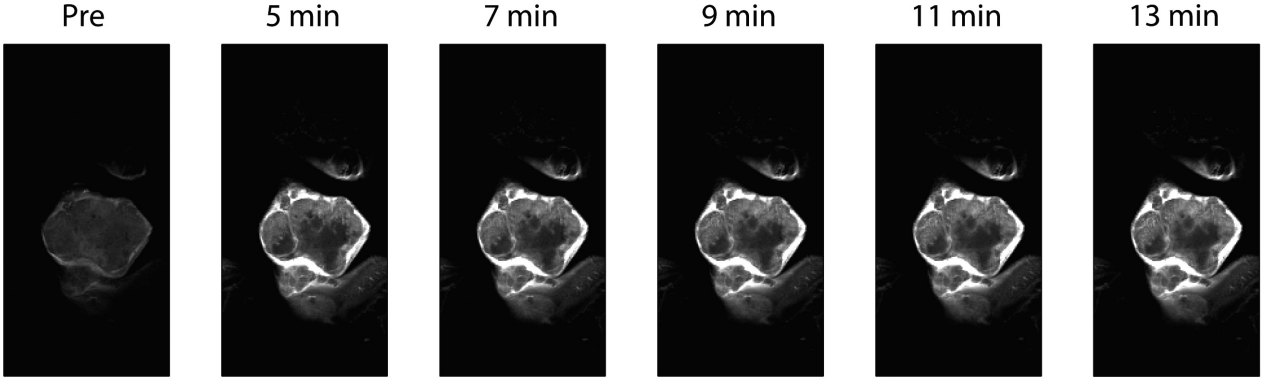
Working with animal models the preclinical research group studies anatomy, physiology and disease progression at a more fundamental level. The studies are mostly focused on brain disease and cancer. A 4.7T Varian scanner designed for small animal imaging and spectroscopy research is used for studying mice and rats, often in longitudinal studies where the same animal is imaged several times. The majority of the pre-clinical work is undertaken in collaboration with other research groups within the Copenhagen area, providing the opportunity for exciting multi-disciplinary projects to be performed with contributions from researchers with different scientific expertise and experience.

In cooperation with the Statens Serum Institut, work investigating Streptococcus pneumoniae (pneumococcal) meningitis in a rat model has continued. These studies are motivated by the fact that bacterial meningitis remains a life threatening disease with significant mortality and morbidity. Previous work from the preclinical group has demonstrated the power of MR imaging methods to follow the evolution of the disease and in 2007 a study to investigate the role of sepsis in meningitis was completed. Bacteremia is present in most patients with pneumococcal meningitis and plays an important role in the outcome. In the pneumococcal meningitis rat model the bacterimic component was modulated to investigate the effects on the disease progression. By intravenous administration of antipneumococcal antiserum at the time of the intracisternal meningitis infection the bacterial infection was limited to the brain only. This group of animals was compared to a group of rats infected intracisternally and another group infected both intracisternally and intravenously. Attenuation of the bacteremia improved the clinical disease symptoms and significantly reduced ventricle expansion and Blood-Brain-Barrier breakdown.

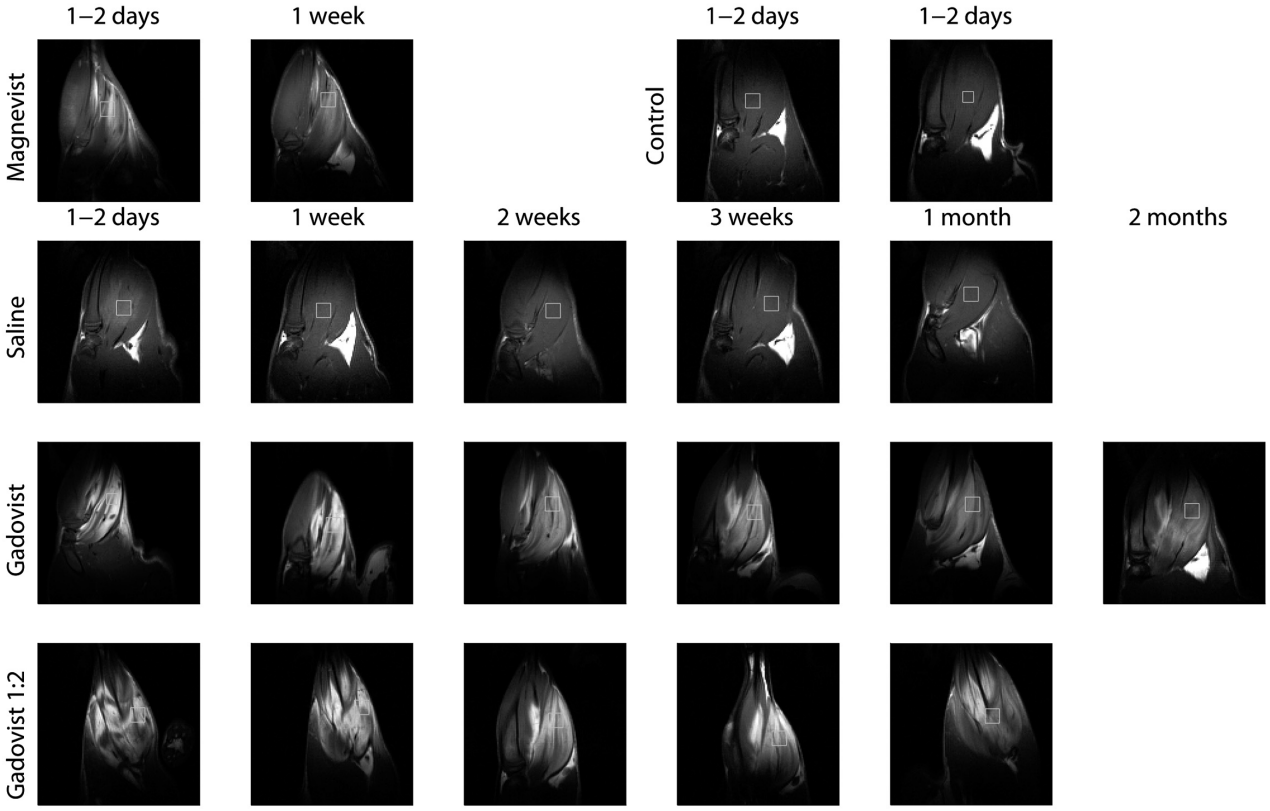
As part of the meningitis studies, the group also contributes to the DiMI network. The goal of the EU-funded Network of Excellence “Diagnostic Molecular Imaging” (DiMI) - Molecular Imaging for Diagnostic Purposes - is to integrate multidisciplinary research for the development of new probes and multimodal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

In 2007 we continued the collaboration with Rigshospitalet about the role of cellular water channels (Aquaporins) in hydrocephalus. In this project, hydrocephalus is induced through percutaneus intracisternal injection of sterile kaolin suspension in Sprague-Dawley rats. Three groups of animals (n=10 each) were studied at different timepoints (2 days, 1 week and 2 weeks) after induction of hydrocephalus. An optimized 2D axial T2-weighted fast spin-echo sequence allowed for determination of the size of the lateral ventricles which were all significantly enlarged compared to the control group. The apparent diffusion coefficient in periventricular tissue increased with time from kaolin injection, indicative of development of periventricular oedema as hydrocephalus develops with time. Brain tissue samples were analysed for aquaporins in collaboration with The Salt and Water Centre, Århus University. This has made it possible to correlate spatiotemporal expression of aquaporins to pathophysiology in the hydrocephalic brain examined through *in vivo* MRI.
In a future PhD study, the developed model will be used to examine the possible effect of aquaporin regulation through intrathecal drug administration in hydrocephalus.

Another study has been initiated utilising blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI) to study brain function across many brain areas implicated in schizophrenia within putative rat disease model(s) of schizophrenia. The outline is to examine brain regional effects in the disease model(s) following drug challenges (also referred to as pharmacological fMRI or phMRI). The drug challenges will include d-amphetamine and phencyclidine,



Tumour cross section in a transgenic mammary cancer mouse model (MMTV-PymT). The T_1-weighted images were aquired before (pre) and after intravenous administration of the contrast agent Magnevist. The distribution of the contrast enhancement shows that the tumour is well perfused in the outer parts surrounding a necrotic core.



T_1-weighted MR images of rat muscle after electroporation following intravenous injection of saline or Gd-based contrast agents. Hyperintense regions corresponding to intra-cellularly trapped contrast agent are visible up to two months after electroporation. The weak hyperintensity observed in the saline electroporated animal is due to initial edema formation. The blue box corresponds to the voxel chosen for subsequent spectroscopic measurements.

as effects of these have been studied extensively in human studies and, therefore, could further improve disease model validity. Other drugs may also be tested in order to examine, whether pharmacological induced behavioural changes (performed elsewhere) can be mirrored in a specific brain function signature in those brain areas associated with the psychotic symptoms and cognitive impairments found in schizophrenia.

A study aiming at characterising the tumour perfusion in a transgenic mouse model of mammary cancer was initiated in 2007. It is known that the energy and choline metabolisms in tumour cells are altered during cancer development from in vitro and in vivo studies on human breast cancers. The transgenic mouse model of breast cancer, expressing the polyoma middle T antigen (PymT) in the mammary epithelium under the control of mouse mammary tumour virus (MMTV) long terminal repeat, resembles human breast cancers in many ways. The transgenic mice form spontaneous tumours and are well-suited to study cancer progression and treatment and for characterization of metabolism by MR based methods. The transgenic model has kindly been provided by the Finsen laboratory at Rigshospitalet.

In a further project, the group has utilised electroporation methodology to deliver contrast agents intracellularly in vivo. Using Magnevist (Gd-DTPA) or Gadovist (Gd-BT-DO3A) injected intravenously prior to the application of high voltage electric pulses to rat thigh muscle, the contrast agent remains trapped within the tissue for several weeks. The intracellular delivery of contrast agent allows metabolite compartmentalisation to be probed since the incorporation of the contrast agent into the cytoplasm enables direct interaction of the contrast agent and any cytoplasm containing metabolite.

The T_1 values of different metabolites were measured at different time points (up to 2 months) after electroporation. Both creatine/phosphocreatine and trimethylammonium showed decreased T_1 values which gradually normalized as a function of time in the animals electroporated with Gd-based contrast agents. Relaxivity measurements in phantoms allowed for calculation of the intracellularly trapped contrast agent concentration. This method might be used for in vivo cell labelling studies of e.g. cancer metastasis or cell migration.

Other Activities

Consultation

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

Olaf B. Paulson:
- Vice-chairman of the Department of Clinical Neuroscience and Sensory Sences, University of Copenhagen
- Chairman of the Research Committee of the Neuroscience Centre at Rigshospitalet
- President of the Danish Society of Neurology
- Member of the Research Committee of Hvidovre Hospital

Per Åkeson:
- Member of the Scientific Advisory Board for the European Magnetic Resonance Foundation
- Member of the nominating committée for the European Magnetic Resonance Award

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

Terry L. Jernigan:
- Co-Director of Laboratory of Cognitive Imaging
- Section Editor of Neurobiology of Aging
- Member of the Editorial Advisory Board of Brain Imaging and Behaviour
- Member of the Editorial Advisory Board of Brain Structure and Function
- Member of the Editorial Advisory Board of Developmental Neuropsychology
- Member of the Editorial Advisory Board of Neuropsychology

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

Journal Review

During 2007, DRCMR staff members have been reviewers for the following journals:

- Acta Neurologica Scandinavia
- Acta Physiologica Scandinavia
- American Journal of Psychiatry
- Archives of General Psychiatry
- Archives of Neurology
- Cerebral Cortex
- Experimental Brain Research
- European Journal of Neurology
- Human Brain Mapping
- International Congress on Schizophrenia Research
- ISMRM conference
- Journal of Abnormal Psychology
- Journal of the American Medical Association
- Journal of Cognitive Neuroscience
- Journal of Mind and Behaviour
- Journal of Neurology
- Journal of the International Neuropsychological Society
- Neurobiology of Aging
- NeuroImage
- Neuropsychologia
- Neuropsychology
- NMR in Biomedicine
- Pediatrics
- Physiological Research
- Psychiatry
- Psychiatric Research: Neuroimaging
- Psychological Bulletin
- Studies in Ethics, Law and Technology
- The Journal of Physiology

Training Activities

Received Training

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

Formal Instruction by DRCMR Staff

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

Outside Instruction:
- Karam Sidaros: Teaching course: Tracer kinetics, University of Copenhagen
- Karam Sidaros: Teaching at Lund University: Scandinavian MR physics course
- Karam Sidaros: Giving ESMRMB Lectures on MR: Quantitative Perfusion Imaging, Freiburg
- Lars G. Hanson: Teaching of Quality Assurace, School of Radiography
- Lars G. Hanson (local coordinator and lecturer), Karam Sidaros, Per Åkeson, Michel Nemery, Mark Schram Christensen and Lise Vejby Søgaard: "MR-temadage", biannual, Sygepleje- og Radiografskolen
- Lars G. Hanson acting as MRI lecturer and exercise coordinator: Medical Imaging Course at Technical University of Denmark
- Lars G. Hanson co-planning Biomedical Engineering Course, Technical University of Denmark
- Lars G. Hanson acting as external consultant for students at the School of Radiography
- Lise Vejby Søgaard: Teaching "NMR & MRI: Physical principles, imaging and contrast", PhD course: Functional Imaging: Clinical and Research Applications of MR, SPECT and PET, at Bispebjerg Hospital
- Mark Schram Christensen: Teaching Neurophysics, Department of Physics, Technical University of Denmark

- Kristoffer H. Madsen: Lecture on Biophysics at the Danish Technical University
- Kristoffer H. Madsen: Lecture on Medical Image Processing at DRCMR
- Per Åkeson, Teaching at Advanced Imaging Research Center, Southwestern Medical Center, University of Texas Southwestern, Dallas, USA
- Michel Nemery: Teaching "MR af CNS" at the Technical University of Denmark
- Terry L. Jernigan: Lecture on Magnetic Resonance Imaging in Neuropsychology, University of Copenhagen
- Torben E. Lund: Teaching SPM at DRCMR

Courses Organized at the DRCMR:

- Lars G. Hanson was the organizer and lecturer on MR-techniques, Open Course at DRCMR

Individual Supervision of graduate students by DRCMR Staff:

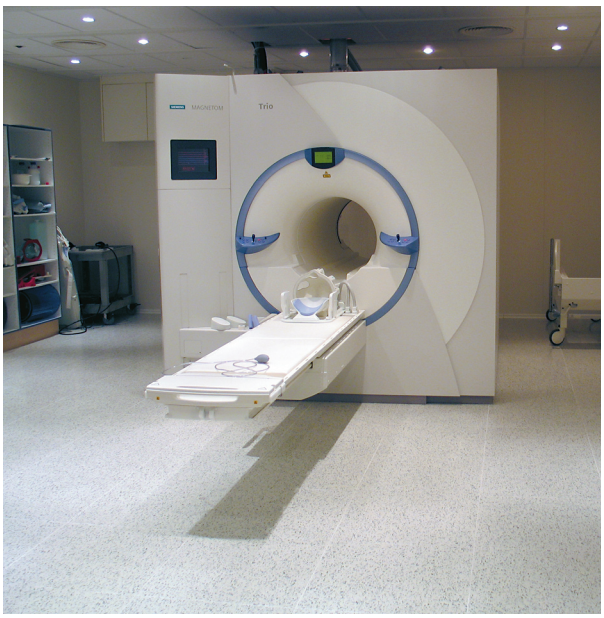
- Julian Macoveanu was supervisor for PhD students Bettina Hornbøll and Jon Wegener
- Kathrine Skak Madsen was supervisor for psychology student Martin Vestergaard Hansen
- Lars G. Hanson was supervisor for MSc.Eng. student and Novo Nordisk Scholarship recipient Henrik Lundell, Danish Technical University
- Lars G. Hanson was supervisor of junior researcher Henrik Lund
- Lars G. Hanson was supervisor of PhD student Arnold Skimminge
- Lars G. Hanson was supervisor of PhD student Robin de Nijs
- Lars G. Hanson was external examiner: MSc project, University of Lund
- Lars G. Hanson was external examiner: MSc project, University of Århus
- Lise Vejby Søgaard was external examiner: MR1 and MR 2 course, Aarhus University
- Lise Vejby Søgaard was external examiner: MSc project, Aarhus University
- Lise Vejby Søgaard was supervisor for Early Stage Researcher Torsten Dorniok
- Lise Vejby Søgaard and Ian J. Rowland were supervisors for scholar recipient Anders Dæhli Skjolding
- Mark Schram Christensen was supervisor for medical student Katja Sørensen (OSVAL 1)
- Per Åkeson was supervisor of Sandra Diaz, MD, student for doctoral thesis, Lund University, Sweden
- Per Åkeson was supervisor of Ingrid Casselbrant, MD, student for doctoral thesis, Lund University, Sweden
- Thomas Zöega Ramsøy was supervisor for psychology student Martin Vestergaard Hansen
- Torben E. Lund was supervisor for PhD student Kirsten Korsholm, MD
- Torben E. Lund was supervisor for PhD student Kristoffer H. Madsen, Engineer
- Terry L. Jernigan was supervisor for PhD student Thomas Zöega Ramsøy
- Terry L. Jernigan was supervisor for PhD student Kathrine Skak Madsen
- Terry L. Jernigan was member of the doctoral supervisory committee for PhD student Annette Sidaros
- Torben E. Lund was supervisor for PhD student Anne-Marie Dogonowski
- Torben E. Lund was supervisor for PhD student Arnold Skimminge
- William Baaré was supervisor for PhD student Bjørn Ebdrup, Kathrine Skak Madsen, Tim Dyrby and Trine Hammer

Congress Organization

- Mark Schram Christensen was a member of the organising committee of Brain and Mind Forum 2007.
- Martin Skov, Olaf B. Paulson & Karam Sidaros organized the XXI meeting of the Danish Society for Neuroscience: "Neuroimaging of human cognition". May 6-8, 2007.

Awards

- We are pleased to announce that PhD-student Henrik Lundell received an award for the best presentation at the Novo Nordisk Scholarship Symposium in 2007.



The 3T Siemens Magnetom Trio MR scanner at DRCMR was the first 3T scanner to be installed in Denmark. It is today used for the majority of the research projects at the centre.

Publications

A large number of publications has resulted from the work performed by the research staff at the DRCMR during 2007. The most important of these publications are listed here according to category:

PhD and Doctoral Theses

1. Christensen MS. Investigations of movement perception and visual perception with functional neuroimaging and transcranial magnetic stimulation. Faculty of Science, University of Copenhagen, 2007.
2. Kalowska EM. Cerebral blood flow in patients with stroke-in-progression. Faculty of Health Sciences, University of Copenhagen, 2007.
3. Korsholm K. Functional and Structural MRI in optic neuritis. Faculty of Health Sciences, University of Copenhagen, 2007.
4. Krabbe K. MR investigations in Parkinsonism. Faculty of Health Sciences, University of Copenhagen, 2007.

Peer Reviewed Journal Articles

1. Balslev D, Braet W, McAllister C, Miall RC. Inter-individual variability in optimal current direction for transcranial magnetic stimulation of the motor cortex. J Neurosci Methods 2007; 162(1-2):309-313.
2. Balslev D, Cole J, Miall RC. Proprioception contributes to the sense of agency during visual observation of hand movements: evidence from temporal judgments of action. J Cogn Neurosci 2007; 19(9):1535-1541.
3. Balslev D, Miall RC, Cole J. Proprioceptive deafferentation slows down the processing of visual hand feedback. J Vis 2007; 7(5):12-17.
4. Bischoff-Grethe A, Ozyurt IB, Busa E, Quinn BT, Fennema-Notestine C, Clark CP et al. A technique for the deidentification of structural brain MR images. Hum Brain Mapp 2007; 28(9):892-903.
5. Christensen MS, Lundbye-Jensen J, Geertsen SS, Petersen TH, Paulson OB, Nielsen JB. Premotor cortex modulates somatosensory cortex during voluntary movements without proprioceptive feedback. Nat Neurosci 2007; 10(4):417-419.
6. Christensen MS, Lundbye-Jensen J, Petersen N, Geertsen SS, Paulson OB, Nielsen JB. Watching Your Foot Move--An fMRI Study of Visuomotor Interactions during Foot Movement. Cereb Cortex 2007; 17(8):1906-1917.
7. Dyrby TB, Sogaard LV, Parker GJ, Alexander DC, Lind NM, Baare WF et al. Validation of in vitro probabilistic tractography. Neuroimage 2007; 37(4):1267-1277.
8. Giraud AL, Kleinschmidt A, Poeppel D, Lund TE, Frackowiak RS, Laufs H. Endogenous Cortical Rhythms Determine Cerebral Specialization for Speech Perception and Production. Neuron 2007; 56(6):1127-1134.
9. Glenthoj A, Glenthoj BY, Mackeprang T, Pagsberg AK, Hemmingsen RP, Jernigan TL et al. Basal ganglia volumes in drug-naive first-episode schizophrenia patients before and after short-term treatment with either a typical or an atypical antipsychotic drug. Psychiatry Res 2007; 154(3):199-208.
10. Gollan TH, Fennema-Notestine C, Montoya RI, Jernigan TL. The bilingual effect on Boston Naming Test performance. J Int Neuropsychol Soc 2007; 13(2):197-208.
11. Habekost T, Rostrup E. Visual attention capacity after right hemisphere lesions. Neuropsychologia 2007; 45(7):1474-1488.
12. Hanson LG. A graphical simulator for teaching basic and advanced MR imaging techniques. Radiographics 2007; 27(6):e27.
13. Hanson LG, Lund TE, Hanson CG. Encoding of electrophysiology and other signals in MR images. J Magn Reson Imaging 2007; 25(5):1059-1066.
14. Haugbol S, Pinborg LH, Arfan HM, Frokjaer VM, Madsen J, Dyrby TB et al. Reproducibility of 5-HT(2A) receptor measurements and sample size estimations with [(18)F]altanserin PET using a bolus/infusion approach. Eur J Nucl Med Mol Imaging 2007; 34(6):910-915.
15. Hogh P, Garde E, Mortensen EL, Jorgensen OS, Krabbe K, Waldemar G. The apolipoprotein E epsilon4-allele and antihypertensive treatment are associated with increased risk of cerebral MRI white matter hyperintensities. Acta Neurol Scand 2007, 115(4), 248-253.
16. Inzitari D, Simoni M, Pracucci G, Poggesi A, Basile AM, Chabriat H et al. Risk of rapid global functional decline in elderly patients with severe cerebral age-related white matter changes: the LADIS study. Arch Intern Med 2007; 167(1):81-88.
17. Johnson TR, Bayrhof N, Huber A, Kuijer JP, Luechinger R, Dietrich O, Stoevesandt D, Pedersen D, Reiser MF, Schoenberg SO.Myocardial tagging with steady state free precession techniques and semi-automatic postprocessing--impact on diagnostic value. Eur Radiol. 2007; 17(9):2218-24.
18. Jokinen H, Ryberg C, Kalska H, Ylikoski R, Rostrup E, Stegmann MB et al. Corpus callosum atrophy is associated with mental slowing and executive deficits in subjects with age-related white matter hyperintensities: the LADIS Study. J Neurol Neurosurg Psychiatry 2007; 78(5):491-496.
19. Korf ES, van Straaten EC, de Leeuw FE, van der Flier WM, Barkhof F, Pantoni L et al. Diabetes mellitus, hypertension and medial temporal lobe atrophy: the LADIS study. Diabet Med 2007; 24(2):166-171.
20. Korsholm K, Mathiesen HK, Lund TE. [Functional magnetic resonance imaging in multiple sclerosis]. Ugeskr Laeger 2007; 169(26):2518-2520.
21. Korsholm K, Madsen KH, Frederiksen JL, Skimminge A, Lund TE. Recovery from optic neuritis: an ROI-

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Conference Proceedings

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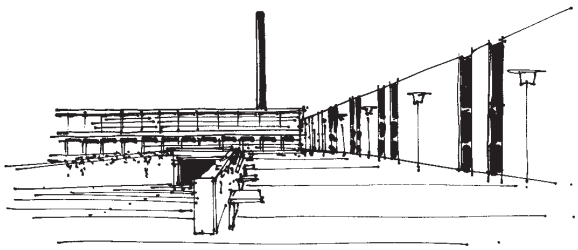

REGION H

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