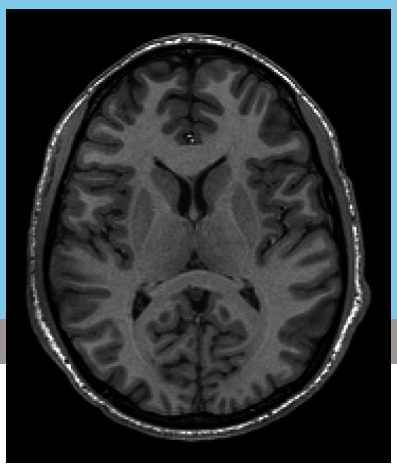

DRCMR

Annual Report 2009-2010

Danish Research Centre for Magnetic Resonance

Edited by: Karam Sidaros, Olaf B. Paulson, Majken L. Møller and Hartwig R. Siebner
Layout by: Majken L. Møller and Karam Sidaros

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DRCMR retreat at the Helene Elsass Center in Charlottenlund, April 2010

INTRODUCTION

Olaf B. Paulson

Hartwig R. Siebner

The years 2009 and 2010 have been some of the most exciting in the history of the Danish Research Centre for Magnetic Resonance (DRCMR). Public funding had already been obtained in 2008 for two new scanners for clinical use, a 3 and a 1.5 Tesla scanner to replace two older scanners dating back to 1994. In connection with the installation of the new scanners the department was completely reconstructed and is now a modern user-friendly department with good facilities for the patients. We would like to take the opportunity to thank all who were involved in the installation of the new scanners and the rebuilding of the MRI-facilities. Our special thanks go to the clinical team who showed great commitment and flexibility during the period of reconstruction. The 'new' department with its new scanners was officially inaugurated at the end of 2010. The reconstruction of the department further involved that the Department of Radiology's MR scanner was integrated in the MR Department and a closer collaboration between the two departments was established. The clinical scanners at the MR department now consist of two 3 Tesla and two 1.5 Tesla whole-body scanners.

Funding was also obtained in 2008 for upgrading of the department's small bore 4.7 Tesla MR-scanner used for experimental studies. This upgrade took place in 2009. Although the magnet is two decades old the scanner is now a modern completely up to date scanner. The upgrade of the scanner is also of utmost importance for the department's research activities with hyperpolarized Carbon-13.

The excitement in the department's history reached a new milestone in December 2009 where the Danish Agency for Science, Technology and Innovation granted 40% of the budget to establish a national 7 Tesla centre for human studies at the MR department. In June 2010 The John & Birthe Meyer Foundation gave a substantial grant covering the rest of the budget. The funding for the 7 Tesla centre now became a reality. The 7 Tesla scanner is expected to be installed in 2013.

In October 2010 the DRCMR received a major research grant. A "grant of excellence" was awarded by the Lundbeck Foundation to Professor Hartwig R. Siebner for a project entitled "control of actions" (ContAct). The mission of the ContAct group is to investigate how the human brain flexibly integrates relevant contextual dimensions into appropriate actions. Further the Lundbeck Foundation prolonged the Center for Integrated Molecular Imaging (CIMBI) headed by Prof. Gitte Moos Knudsen (Neurobiological Research Unit, Department of Neurology, Rigshospitalet) with major funding for additional five years in which the DRCMR is a major partner.

2009 and 2010 were years with new initiatives in the research organisation at DRCMR. In the fall 2010 a change in the leadership took place. Hartwig R. Siebner took over as Head of the Department after Olaf B. Paulson. Moreover, the previous structure with a research coordinating group was replaced in 2010 by twelve research groups. Each group focuses on a specific research theme and is headed by a research group leader (RGL). The motivation behind establishing a new organisational structure is to sharpen the neuroscientific and methodological profile of the DRCMR and to give the senior researchers more responsibility. The activities of the research groups and their interactions are highlighted in this rapport. Some overlap obviously takes place as many researchers have activities in more than one group.

The last two years have also witnessed a boost in the scientific output of the DRCMR with a marked increase in the number of published scientific papers of more than 70% as compared to the two preceding years (2007-2008).

We would like to express our gratitude towards the foundations and institutions whose support and collaboration over the years has enabled the Danish Research Centre for Magnetic Resonance to advance the use of magnetic resonance imaging as an investigative tool in biomedical science and to secure the DRCMR's frontline position in MR research.

Olaf B. Paulson and Hartwig R. Siebner

The magnet of one of the new MR scanners being lowered into the hospital building in March 2010.

DANSK RESUMÉ

Denne rapport giver et indblik i målene, visionerne og organisationen af MR afdelingen på Hvidovre Hospital og beskriver afdelingens aktiviteter i 2009-2010. MR afdelingen har i denne periode gennemgået en voldsom udvikling, som afspejles i flotte resultater i flere forskellige af afdelingens produktionskanaler og som ligeledes kan ses på afdelingens nye struktur.

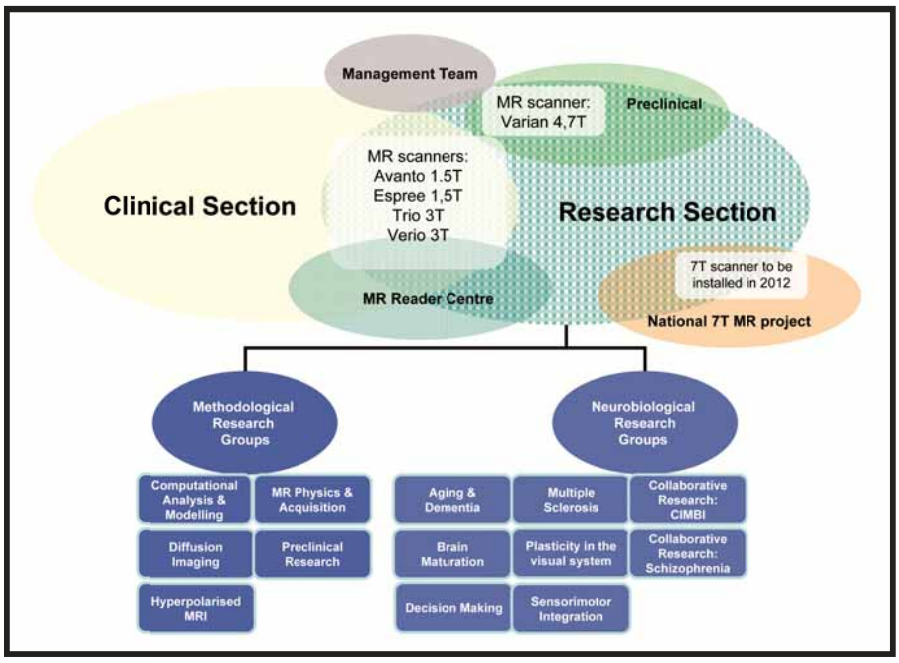
En bevilling af to nye skannere i 2008 førte til en større ombygning af den kliniske sektion, som stod klar til indvielse i sensommeren 2010. I forbindelse med ombygningen overgik ansvaret for Røntgenafdelingens MR skanner til MR afdelingen. MR afdelingen råder således nu over to stk. 3 Tesla og to stk. 1,5 Tesla MR skannere, der sammen med forbedrede vente- og patientarealer har skabt bedre forhold ikke kun for patienterne, men også for personalet på afdelingen. Yderligere råder afdelingen over en 4,7 Tesla eksperimentel skanner, der netop er blevet opgraderet, hvilket har haft positiv betydning for alle studier, der køres på denne.

På det organisatoriske plan er der også sket markante ændringer. I efteråret 2010 overtog Professor Hartwig R. Siebner ledelsen af afdelingen efter Olaf B. Paulson. En ny forskningsgruppestruktur har ligeledes set dagens lys, hvor de 11 forskningsgrupper fordeler sig i to kategorier: Metodologisk forskning og Anvendt forskning. Hver gruppe har en eller flere forskningsgruppeleder(e), som har hovedansvaret for at gruppens forskning er med til at styrke afdelingens kerneforskningsområder. Ligeledes har det været en pointe med den nye struktur at gøre forskningsgruppernes profil endnu skarpere. Grupperne samt deres forskningsaktiviteter er beskrevet her i rapporten.

2009-2010 har ligeledes vist en markant stigning i publikationer på mere end 70% i forhold til (2007-2008), samtidig har centrets forskere deltaget og bidraget til flere internationale konferencer end foregående år.

Opnåelsen af ekstern finansiering nåede ligeledes usete højder, da Forsknings- og Innovationsstyrelsen (40%) og John & Birthe Meyer Fonden (60%) tilsammen donerede 66 millioner kr. til et nationalt 7 Tesla forskningscenter på afdelingen. Installationen af den nye 7 Tesla skanner forventes at ske i 2012. Derudover har Hartwig R. Siebner modtaget Lundbeckfondens *Grant of Excellence* i 2010 til et projekt, der vedrører hjernens kontrol af handlinger.

Afdelingen forventer meget af disse store projekter og ser frem til spændende forskningsaktiviteter og -resultater i de kommende år, hvilket vil være med til at sikre afdelingen som et af de førende kliniske og forsknings MR-centre i denne del af Europa.



The organizational structure of DRCMR with a clinical and a research section and a number of research groups.

Flashback on the last 15 years at DRCMR

Now that I have decided to step down as chairman of the department, but to continue as active scientist, it is worthwhile to give a flashback over the last 15 years during which I chaired the department. The department was established in 1985 and the first chairman of the department was Ole Henriksen, who successfully developed the department to an international level with international co-operation and funding. Unfortunately, Ole became suddenly disabled in 1995 at a much too young age and could not continue with his professional activities. The department suddenly lacked leadership which was problematic for its many ongoing research activities. Then in the beginning of August 1995, Erik Juhl, the chairman of the Copenhagen hospital co-operation called and asked me to take over the chairmanship of DRCMR (simultaneous to my duties as professor of neurology at Rigshospitalet). I couldn't resist and started the following day. The department that I took over after Ole was in very good shape, equipped with 3 scanners for clinical studies – two of them being only one year old as well as one scanner for small animal studies.

For the first year the task seemed rather easy, just to guide and continue the research in Ole's spirit. But, as time passed new activities had to be initiated and new hardware became necessary for keeping the departments research on the cutting edge.

Hardware has also been renewed. The first 3 Tesla MR scanner in Denmark was installed at DRCMR in 2002 (Simon Spies Foundation). In 2008, national funding was obtained to replace the department's two older scanners (dating back to 1994) with two new scanners. Also in 2008, funding (Simon Spies Foundation) was obtained to establish hyperpolarised carbon-13 research; an initiative taken by Per Åkeson. The department's scanner for small animal studies has continuously been updated but a major and complete update took place in 2009 and the scanner is now a brand new scanner just with the exception of the well functioning magnet, which dates back to 1989. The newest major funding obtained during my leadership of the department was in 2009 and 2010 for a 7 Tesla scanner for human studies (The Danish Agency for Science, Technology and Innovation and the John and Birthe Meyer foundation). This is the first funding for the 7 Tesla scanner in the Nordic countries. It is worthwhile to mention that the establishment for the 7 Tesla centre was a national initiative, and especially Århus from the western of Denmark and Rigshospitalet in Copenhagen were, in a very early stage, key players in this initiative.

The research kept growing steadily during the years and many talented young people came to write their PhD theses. Many of them were so talented that it became possible to get funding in order to keep them in the department as Post-Docs or senior researchers securing the long term research of the department. Six of them are now among the 12 research principals in the department and of these four have finished their PhD theses within the last four years. Other research principals have been headhunted either from the Niels Bohr Institute, USA, Sweden, or Germany.

Olaf B. Paulson

In 2006 a new clinical team was established and Per Åkeson was appointed as leader of the clinical section. New initiatives were now taken in clinical MR.

With strengthening of the senior research leadership in 2009 and 2010 with the appointment of Hartwig R. Siebner it became possible to expand the existing broad collaboration with other institutes and new collaborators have been added.

The future is challenging with major responsibilities for Hvidovre Hospital and the commitment to secure a true national strategy and use of the 7 Tesla facilities.

In conclusion I would say that I am proud of what has been achieved during these 15 years in co-operation with many good co-workers at Hvidovre Hospital and not to forget with many good co-workers in other Danish institutions. They have supported the concept that joining forces leads to the best result as reflected in the present annual report. When I became chairman of the Department of Neurology at Rigshospitalet 3 decades ago I promised myself that when I stepped down as chairman of a department it should be at a top level and preferentially still on an upwards slope. I feel that I have fulfilled this promise at DRCMR.

Olaf B. Paulson

Ultra-high field MRI

As mentioned earlier funding for a 7 Tesla scanner for human use has been obtained by the hospital during the last 2 years, The Danish Agency for Science, Technology and Innovation funded 40% of the project in December 2009 and The John and Birthe Meyer Foundation funded the remaining 60% in June 2010. This is the first funding in the Nordic countries for a 7 Tesla MR-scanner for human use.

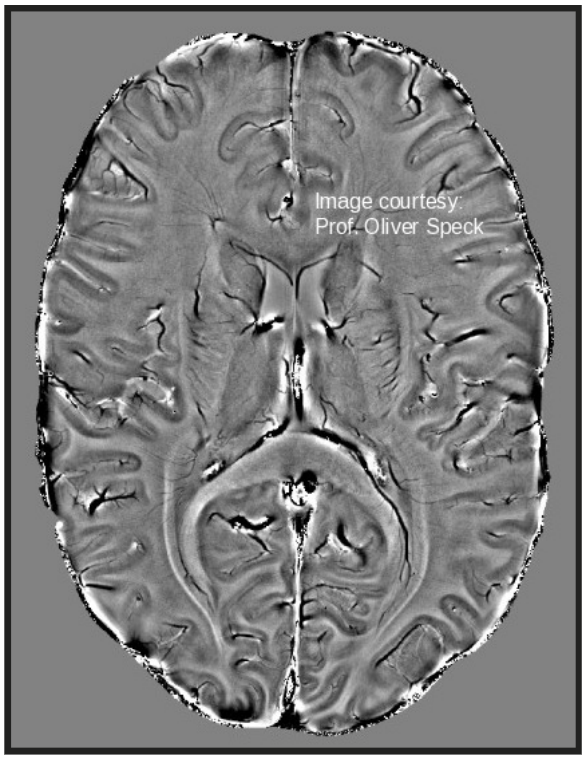
The initiative to the 7 Tesla project was taken up by Olaf B. Paulson who gathered Danish neuroscience researchers from both eastern and western Denmark in a national effort. Olaf B. Paulson has been instrumental throughout this process both by coordinating the efforts to obtain funding and leading the 7 Tesla project. According to the national frame of the project, the scientific work will be guided by a Steering group representing a broad range of institutions that have participated in the application and that will be involved in the coming research.

The timing seems excellent as a new generation of 7 Tesla scanners has been developed recently by all major vendors. Most importantly these scanners are now actively shielded comparable to ordinary MR scanners in clinical settings. This allows more flexible installation of a 7 Tesla scanner within a hospital environment without shielding with 300-400 tons of steel.

After the summer 2010 evaluation, the specification of requirements and possibilities for installation took its start. A tender call will be ready in the spring 2011, and following site visit to major international centres a decision and contract negotiation is expected to take place in the fall 2011. The installation is expected in the beginning of 2013 and research activities are expected to start in summer 2013.

International 7 Tesla meeting in Copenhagen

An international workshop on Applications of Human Ultra-High Field MRI held at the Helene Elsass Centre in May 2010, just after the annual meeting of The International Society for Magnetic Resonance in Medicine in Stockholm. The meeting was organized by Olaf B. Paulson with Lars G. Hanson (program chair), Hartwig R. Siebner, Freddy Ståhlberg, Carsten Thomsen, Leif Østergaard, and Per Åkeson as co-organizers.



Thanks to generous donations the DRCMR can soon acquire extremely detailed images of the brain using ultra-high field technology. (Image courtesy of Prof. Oliver Speck)

The meeting took place after the first part of the funding for the Danish 7 Tesla MRI centre had been obtained. The scientific programme included a wide range of lectures given by 11 highly profiled invited speakers. The speakers provided an impressive update of the ongoing research at the frontiers of ultra-high field MRI. The meeting attracted a great deal of interest with more than 80 national and international participants. It also strengthened the Danish desire to establish a 7 Tesla MRI centre.

Six weeks later we obtained the final funding. A milestone was reached in Danish MR research.

STAFF AT DRCMR

Daily life in the clinical section at DRCMR

Staff - Clinical Section

In 2009-2010 the clinical section of DRCMR included the following staff members:

Senior staff:
Marianne Dalsgaard, Head Technologist
Stefán Kristjánsson, MD, Senior Physician
Erland Magnussen, MD, Senior Physician
Per Åkeson, MD, DMSc, Senior Physician and Head of Clinical MRI

Junior medical staff:
Bodil Damgaard, MD
Camilla Gøbel Madsen, MD

Technologists:
Ravanbakhsh Ahmadnija, Radiographer
Yalda Ansari, Radiographer
Marion Berge, Radiographer
Siri Eggum, Radiographer
Jane Næsby, Radiographer
Pia Olsen, Radiographer
Ann-Sofi Sjöqvist, Radiographer

Secretarial and Administrative staff:
Lena Bech, Clinical Secretary
Kia Iben Hjølund, Clinical Secretary Trainee
Joan Husted, Clinical Secretary
Hanne Isgaard, Clinical Secretary
Tina Oppermann, Clinical Secretary
Nana Siggard-Andersen, Senior Clinical Secretary
Ruth Kielstrup, Hospital Assistant

DRCMR staff at the DHL relay race 2010

Staff - Research Section

In 2009-2010 the research section of DRCMR included the following staff members:

Senior Staff
William Baaré, PhD, Psychologist
Daniela Balslev, PhD, MD
Mark Schram Christensen*, PhD, Engineer
Tim B. Dyrby, PhD, Engineer
Bjørn H. Ebdrup*, PhD, MD
Ellen Garde, PhD, MD
Lars G. Hanson*, PhD, Physicist
Susanne Henningsson, PhD, Engineer
Pernille Iversen, PhD, Biophysicist
Terry L. Jernigan*, Professor, PhD, Psychologist
Julian Macoveanu, PhD, Engineer
Kristoffer H. Madsen*, PhD, Engineer
Peter Magnusson, PhD, Physicist
Olaf B. Paulson*, Professor
Maurice Ptito*, Guest Professor, PhD, DMSc
Thomas Z. Ramsøy*, PhD, Psychologist
Poul Ring, MSc, Engineer
Karam Sidaros*, PhD, Engineer
Hartwig R. Siebner, Professor & Head of Department
Arnold Skimminge, PhD, Physicist
Lise Vejby Søgaard, PhD, Physicist
Xingchen Wu, PhD, MD

Technologists
Sascha Gude. Laboratory Technician
Sussi Larsen, Research Technician
Hanne Schmidt, Radiographer

Secretarial and Administrative Staff
Elsebeth Nielsen, Hospital Assistant
Ina Tech Andersen, Research Secretary
Susanne Steffensen, BSc, Research Secretary
Torkil Svensgaard, Information Technologist

Junior Staff
PhD students
Christian T. Brandt*, MD
Brian V. Broberg*, MSc, Pharmacologist
Sadia Asghar Butt, MSc, Biochemist
Anne-Marie Dogonowski, MD
Torsten Dorniok, MSc, Physicist
Kristian S. Frederiksen*, MD
Morten Friis-Olivarius*, MSc, Biologist
Sofie V. Gelskov*, MSc, Biologist
Mette H. Lauritzen, MSc, Human Biologist
Trine Bjørg Hammer*, MD
Frederik Hengstenberg*, MD
Damian Herz, MD
Jens Hjortkjær*, MA, Music Psychologist
Bettina Hornbøll, MSc, Biologist
Betina V. Jensen*, MSc
Kasper W. Jørgensen*, MSc
Tanja Kassuba*, Msc, Psychologist
Helle R. Laursen, MSc, Psychologist
Christoffer Laustsen*, MSc
Matthew G. Liptrot, MSc, Engineer
Astrid R. Lou*, MD
Henrik Lund, MSc, Human Biologist
Henrik Lundell*, MSc, Engineer
Mark Lyksborg*, MSc, Engineer
Kathrine Skak Madsen, MSc, Biologist
David Meder, MSc, Psychologist
Ayna Baladi Nejad*, MSc, Psychologist
Robin de Nijs, MSc, PDEng, Medical Physicist
Nina L. Reislev, MSc, Engineer
Charlotte Ryberg*, MSc, Biologist
Annette Sidaros*, MD
Anders A. Skjolding*, MD
Martin Skov*, MA, Nordic Languages and Literature
Joyce van der Vegt*, MD
Martin Vestergaard, MSc, Psychologist
Jon Wegener*, MSc, Life Sciences and Chemistry

Junior Researchers
Vibe Nordahn Bredsdorff, MSc Student
Eline Bruun Ofei, MSc Psychology Student
Sajjad Ahmad Chughtai, Student Assistant
Emil Enemærke, MSc Physics Student
Julie Hagstrøm, MSc Psychology Student
Louise B. Johansen, MSc Engineer Student
Brith Klarborg, MSc, Psychologist
Martin Kristensson, MSc Engineer Student
Yngve Munck-Lindblom, MSc Physics Student

Conscientious Objectors
Theis Groth

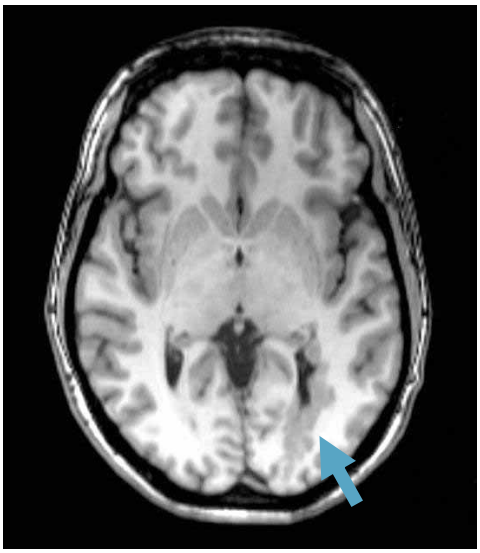
* DRCMR staff with dual affiliations – see more details in the text describing research activities.



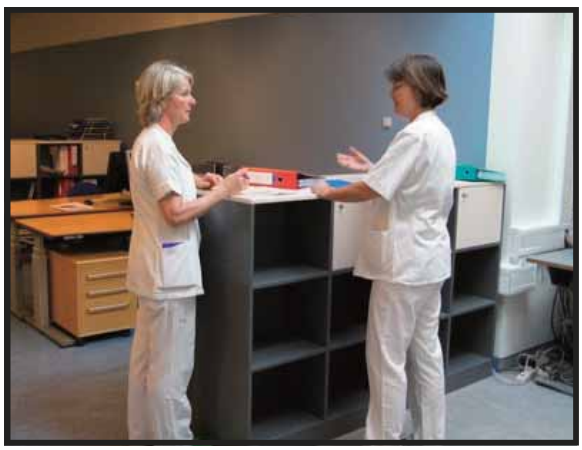
CLINICAL WORK AT DRCMR

During the last couple of years the organisation has undergone some changes as two radiologists have moved on to greater challenges. One resident has moved to a consultant position at Aalborg Hospital and one consultant has become Head of Radiology at Herlev Hospital. This, together with the fact that the clinical section has described all orthopaedic MRI cases from the Department of Radiology at Copenhagen University Hospital Hvidovre (HH), has led to a lack of radiologists hampering the production during 2009. However, it was possible to maintain the patient throughput at around 3500 examinations in 2009. In September 2009, two new radiologists were employed, one resident and one consultant. The consultant was an experienced radiologist with a Swedish specialty in neuroradiology. He was unfortunately (for us) recruited to a position as a consultant at a hospital in Jeddah, Saudi Arabia and left in June 2010. However, during 2010 he also managed to work as a part-time consultant for DRCMR holding a 20% position describing scans from home.

Two new MR-scanners, a 3 Tesla and a 1.5 Tesla scanner, ordered during 2008 were planned to be installed during 2009. This was not achieved as the building plans were changed and the rebuild became larger, but also better, allowing for a more effective patient flow. The rebuilding started in 2010 and this implied that there was only one MR scanner available during daytime. In addition, the MR-scanner at the Department of Radiology (HH) was used during evenings and on some weekends to cope with the clinical workload. After a long period of working in a building site, the new department was finally (almost) ready on June 14, 2010. Both of the new scanners were started and the first patients were scanned during the afternoon. The leap in image quality was huge. The workflow was also very much improved with cabins for the patients to change clothes in, and a more patient friendly waiting room. In the autumn the Department of Radiology's scanner was also integrated in the MR-department's organisation and the department now runs two 3 Tesla and two 1.5 Tesla MR-scanners. Due to the increased speed of the new scanners the number of patients that could be scanned per day was also increased.



Patient with epileptic seizures and heterotopia. The arrow is pointing towards the grey matter, located in the wrong part of the brain.

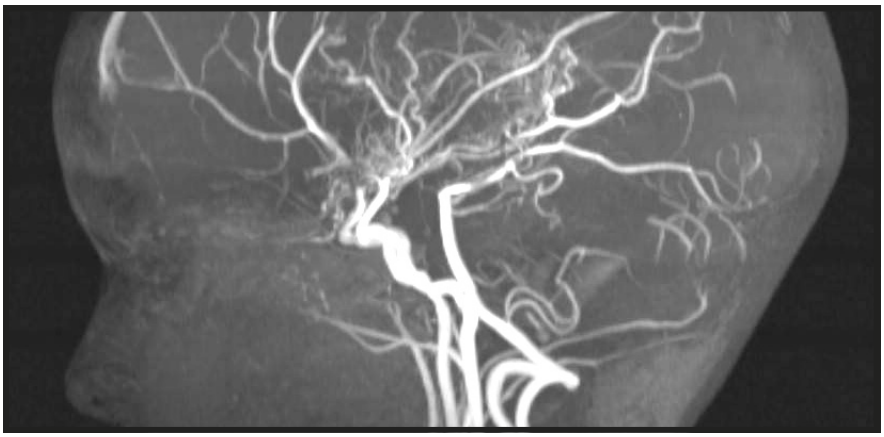


Discussion at the clinic

The majority of the examinations are referrals from HH, although about half of these 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 still dominate the panorama of examinations together with spinal examinations. Diffusion tensor imaging is now developing more into a clinical tool although still not used extensively. The same situation is true for functional MRI, although both methods are increasingly used to aid neurosurgeons.

The clinical section is represented in the 'EPI-KIR' group, a group responsible for national epilepsy patient management as well as postoperative patient management, thus selecting patients suitable for surgical intervention. Consequently, many patients with epilepsy have been imaged for the presence of structural brain abnormalities causing seizures. Patients are received from all over Denmark for these examinations. An image of a patient with epileptic seizures starting with optical sensations is shown on the previous page.

Patient with Moya-Moya Syndrome, i.e. inflammatory changes in the Intracranial arteries.



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 3 Tesla scanner for these examinations has further improved the results due to the very high resolution that can be achieved and has become routine. Above to the right is a picture of a patient with inflammatory changes in the intracranial arteries, so-called Moya-Moya syndrome.

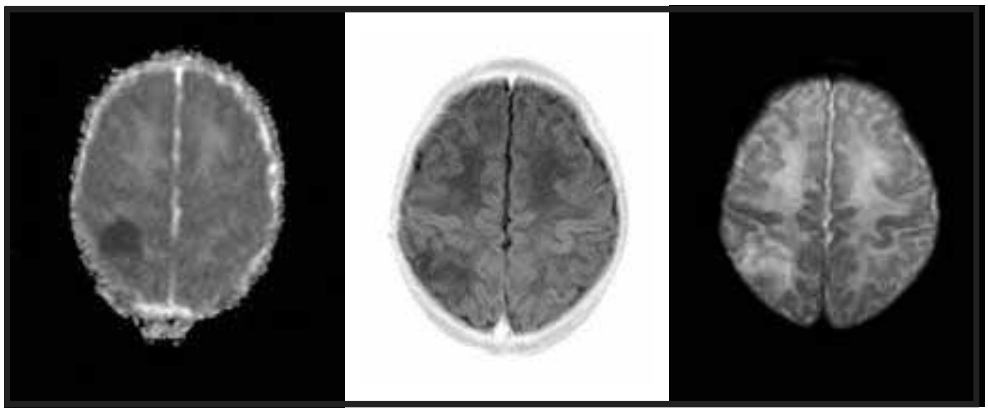
Infectious diseases like encephalitis of different origins, isolated affections of one cranial nerve or central nervous system tuberculosis and different other more or less seldom infections have also continued to increase in numbers.

Paediatric radiology, especially paediatric neuroradiology is still increasing both in neonates and older children with different neurological diseases such as hypoxic complications occurring around delivery and seizures in the postnatal period. The pictures below show diffusion imaging as well as anatomical imaging of a four-day-old infant, which has suffered an infarction, a stroke, at birth. For the investigation of diseases such as congenital malformations, cerebral and spinal as well as metabolic diseases, MRI is the method of choice readily visualizing most diseases. DRCMR is an active member of the Copenhagen network meeting regularly to evaluate difficult cases of neurological malformations and diseases.

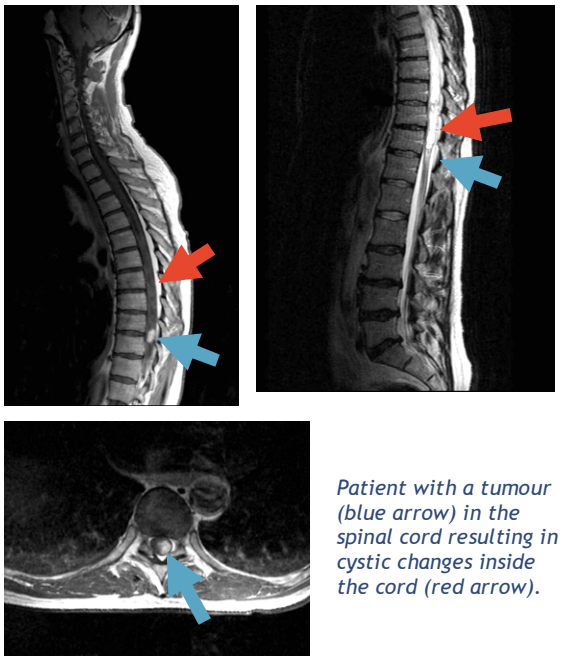
Many examinations of children in particular are performed in general anaesthesia and the department is now with the help of the Department of Anaesthesiology (HH) performing MR-scanning under general anaesthesia two days per week.

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. Below are pictures of a patient with a tumour of the spinal cord.

Investigations of musculoskeletal cases, e.g. intraarticular diseases such as meniscal tears, osteoarthritis or infections, extraarticular diseases



Diffusion (left) and anatomical imaging (middle and right) of 4-day old infant who suffered an infarction at birth

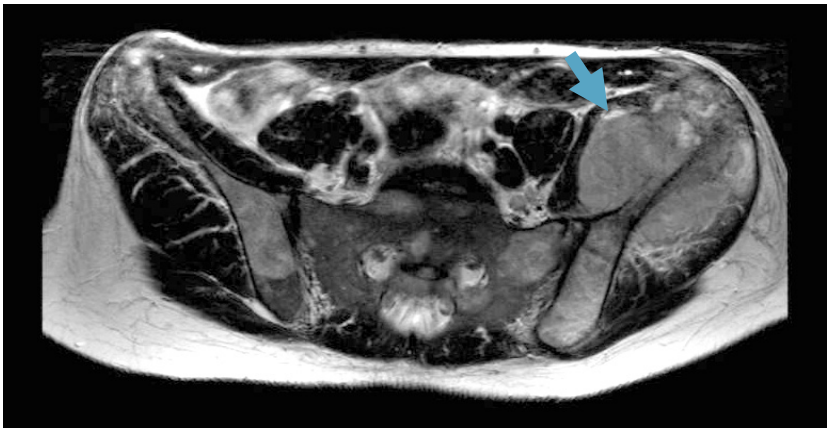


Patient with a tumour (blue arrow) in the spinal cord resulting in cystic changes inside the cord (red arrow).

such as tendinitis and soft tissue diseases as well as soft tissue tumours have continued to increase in numbers. The clinical section at DRCMR has also described the orthopaedic MRI-scans from the Department of Radiology (HH) since June 2009. The clinical section has also continued to help this department during vacation and illness concerning abdominal cases. Three-dimensional imaging has become routine and is showing much promise. MRI is used extensively in the evaluation of meniscal lesions, lesions in the cruciate ligaments, collateral ligaments and damage to the cartilage in the knees. 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 as well as humps. MR-arthrography of hip joints has improved the diagnostic results especially concerning labral lesions. Other areas where MRI is used are tendon tears around the ankle, different diseases in the foot and inflammatory diseases in the spine and the sacro-iliac joints. Infection and sift tissue tumours are another area where MRI is useful both for diagnosis and treatment planning. The number of studies with these indications has increased substantially during 2009. The figure below shows a patient with a tumour in the left side of the pelvis, which turned out to be a lymphoma, a tumour originating from lymphocytes in blood.

Due to the inclusion of the Department of Radiology's MR-scanner into the organisation in the end of 2010, the scope of examinations has widened and a variety of abdominal MR-examinations are now performed including rectal cancer examinations, small bowel examinations, MRCPs etc. These are described in co-operation with the Department of Radiology.

The new scanners have also allowed for good quality cardiac scanning and this has been implemented during 2010 together with cardiologists from the Department of Cardiology and Pulmonology at HH.



Patient with a tumour in the pelvis, that originated from lymphocytes in the blood, i.e. lymphoma.

RESEARCH AT DRCMR

A unique strength of the DRCMR is the multidisciplinary nature of its research activities. The centre has for many years had a vigorous basic research programme alongside both clinical and preclinical research programmes. The centre's research activities thus range from the development of new hardware, software and analyses methods through research that leads to a better biological understanding of the healthy human body all the way to clinical research that provides unique insight into the progression of disease.

The DRCMR has thus implicitly had a large number of research groups throughout the years. During 2009, the previous research coordinating group was transformed into more structured research groups each headed by a research group leader. The motivation for this new research structure was to sharpen the profile of these research groups and to ensure that the focus on the centre's core research areas is maintained.

Each group is headed by one or multiple research group leaders. The new structure helps give the senior researchers at DRCMR a sharper profile and clarifies the role and expectations of being a research group leader. The responsibilities of the group leaders include developing a strategy and infrastructure within their research areas as well as project management and fundraising. The groups have a wide range of collaborators, both nationally and internationally, and the research group leaders constitute the centre's points of contact with these collaborators.

Initially, twelve research groups were defined, five covering methodological research areas and seven covering applied and clinical research areas, an overview of these is provided below. Across different research areas, we have become increasingly successful in combining multiple imaging modalities and computational methods to address neuroscientific questions. At DRCMR, postdoc Arnold Skimminge is leading the work on exploiting the complementarities between different modalities, in order to emphasise each modality's qualities. Furthermore, work is focused on selecting the appropriate modality to the specific purpose as well as developing computational methods that integrate MRI and non-MRI methodologies to construct synergic value.

Apart from these research groups, DRCMR also participates in major collaborative projects, as a part of a multicentre effort, e.g. in the Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS). In the following, these research groups and the research they conduct, will be presented.

Senior Researcher William Baaré at work

Methodological research areas

- MR Physics & Acquisition research group (led by Lars G. Hanson)
- Computational Analysis & Modelling research group (led by Kristoffer H. Madsen)
- Diffusion Imaging research group (led by Tim B. Dyrby)
- Preclinical research group (led by Lise Vejby Søgaard)
- Hyperpolarized MRI research group (led by Peter Magnusson, Lise Vejby Søgaard and Per Åkeson)

Applied research areas

- Aging & Dementia research group (led by Ellen Garde)
- Brain Maturation research group (led by William Baaré and Terry L. Jernigan)
- Decision Neuroscience research group (led by Thomas Z. Ramsøy and Hartwig R. Siebner)
- Multiple Sclerosis research group (led by Hartwig R. Siebner)
- Plasticity in the Visual System research group (led by Maurice Ptito, Olaf B. Paulson and Hartwig R. Siebner)
- Sensorimotor Integration research group (led by Mark Schram Christensen and Hartwig R. Siebner)
- Cimbi (led by Terry L. Jernigan and Hartwig Siebner)

MR Physics & Acquisition

The 'MR physics and acquisition methodology group' at the DRCMR conducts research and development aimed at improving MR scanning, e.g. with respect to speed, sensitivity or specificity. The developed methods are used in a range of projects.

DRCMR members

Lars G. Hanson (group leader), Lise Vejby Søgaard, Peter Magnusson, Kristoffer H. Madsen, Arnold Skimminge, Karam Sidaros, Henrik Lundell, Torsten Dorniok, Emil Enemærke, Yngve Munck-Lindblom, Robin de Nijs and Martin Kristensson.

External collaborators

- Associate Professor Luke Haseler and Professor Bengt Saltin, Griffith University, Australia, and Copenhagen Muscle Research Centre, University of Copenhagen, Denmark
- Professor Lars Kai Hansen, Professor Jens E. Wilhjelm and PhD student Jonas Duun-Henriksen, Technical University of Denmark, Denmark
- Dr Christine i Dali, Copenhagen University Hospital Rigshospitalet, Denmark
- Dr Norman Barton, Shire Plc, Jersey, USA
- Dr Jessica Schulz and Professor Robert Turner, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Research projects

- Real-time motion correction.
- Evaluation of treatment efficacy by spectroscopic and diffusion techniques.
- Visualisation of Magnetic Resonance techniques.
- Rapid transmit field mapping.

Research methods

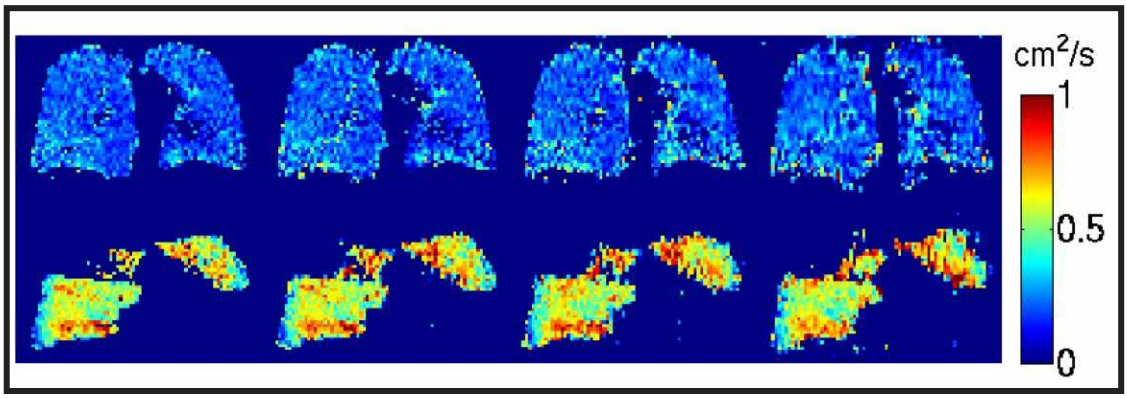
Research Group Leader: Lars G. Hanson

The group members have technical backgrounds, e.g. in physics, mathematics and engineering. The employed methods range from fundamental physics to advanced data processing techniques needed to extract important physiological parameters from the measurements. Targets of the development include imaging, spectroscopy, and acquisition combined with other non-MR techniques.

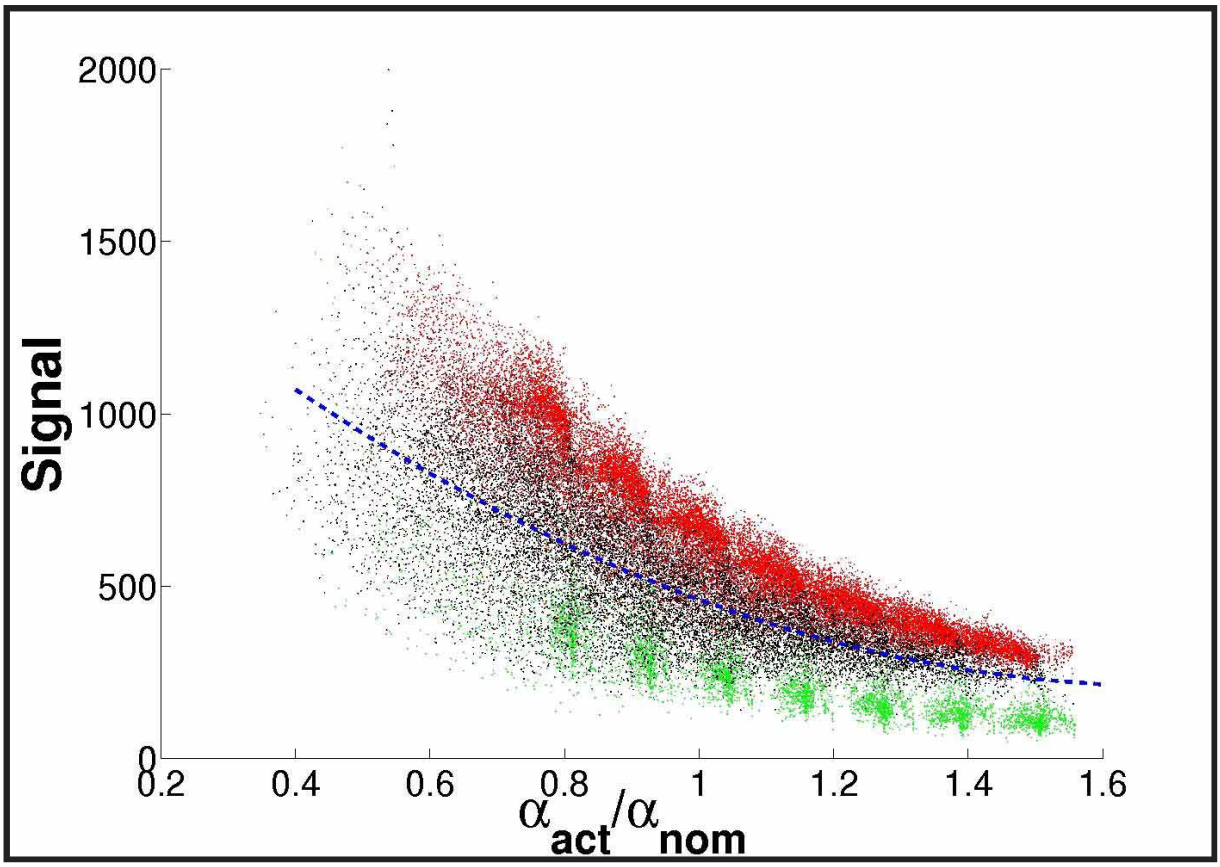
The group also provides education in MRI physics and techniques at the DRCMR, the Technical University of Denmark (DTU) and elsewhere. Educational material and software developed for this is made freely available, and is used internationally. Group activities are now being directed towards techniques of particular relevance for high field, e.g. multi-channel techniques, motion correction and field inhomogeneity handling.

Research activities

A major achievement in 2009 was the appointment of Lars G. Hanson as an Associate Professor in the Biomedical Engineering group at the Biomedical Engineering / Medicine & Technology at the Department of Electrical Engineering, DTU. Independently, Lars stayed in his former position as Senior Researcher and group leader at the DRCMR. It has been a mutual wish to strengthen the MR research and education at the DTU, in particular for the Medicine & Technology programme that is a collaboration between the DTU and the Faculty of



Accelerated lung imaging by 'compressed sensing' for healthy volunteer (top) and patient with Chronic Obstructive Pulmonary Disease (bottom). The images here show diffusion coefficients (ADCs) of magnetized ^{3}He gas in the lungs. Only a fraction of the data normally required to calculate images were used (left to right: 100%, 60%, 39%, 19%). Good image quality is found even for significant acceleration factors (Søgaard et al. 2009).



Only local contrast variation is attributed any significance in 'raw' MR images. One reason is evident in this graph showing how the image intensity varies with sensitivity of the coil (antenna) used for rotating the body magnetization. There is pronounced signal variation even within each particular type of tissue (Each voxel appears as a colored dot. Red: white matter. Black: grey matter. Green: cerebrospinal fluid). Methods were developed to remove this variation when multi-channel coils are used. (Graph from the master's project of Emil Enemærke)

Medicine at the University of Copenhagen. Similarly, technical expertise at DTU now benefits patients and research via improved contacts to MRI sites. The double appointment was an important step in that direction.

Some of the group activities described briefly here cover topics that are implemented in other groups' research activities. Peter Magnusson and Lise Vejby Søgaard continued their work to optimise fast and efficient data acquisition methods that are crucial for hyperpolarisation studies. Lise presented results on the use of compressed sensing for hyperpolarised ^{3}He lung imaging at the international MR conference ISMRM. Torsten Dorniok intensified his work in non-linear image registration of hyperpolarised ^{3}He lung MRI data and the computation of ventilation maps.

Physics students Emil Enemærke and Yngve Munck-Lindblom from the University of Copenhagen conducted Master's degree projects at the DRCMR on radio wave field mapping methods for quantitative imaging and on hippocampal spectroscopy. Martin Kristensson from DTU initiated his Masters project on rapid field mapping.

Physicist Robin de Nijs finished his PhD thesis, financed by The Danish Medical Research Council, and published a paper on motion correction methods for MR-spectroscopy.

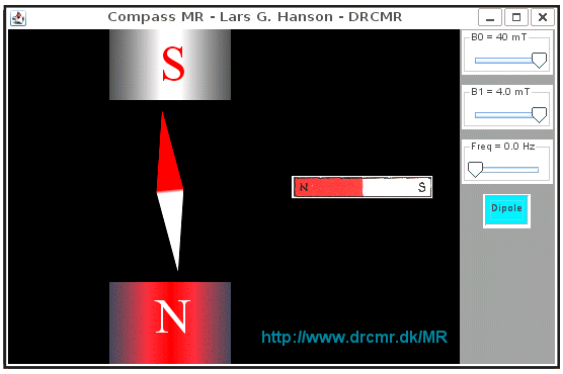
Lars G. Hanson continued analysis of data from metabolic and diffusion measurements in a major study of a rare genetic disease, metachromatic leukodystrophy. Remarkable correlations between function and metabolite measures were found. Also analysis of phosphorous muscle spectroscopy data was conducted. These data acquired in collaboration with the Copenhagen Muscle Research Center and Griffith University, Australia, fits earlier remarkable findings of increased muscle efficiency

when the blood supply is blocked pharmacologically. Several teams of DTU students conducted projects on EEG-fMRI, polarisation measurements, magnetisation transfer MRI and more.

Much effort was devoted to educational activities, and it paid off in terms of international recognition. Educational software by Lars G. Hanson for simulating MRI physics was awarded the 'InfoRESO award' for best use of information technology by the European Society for Magnetic Resonance in Medicine and Biology (ESMRMB). Following a donation from 'Tips and Lotto Midlerne', the developed 'Bloch Simulator' was later ported to run directly in a browser. Widely used Danish notes on MR, written for a broad audience, were revised and also translated to English in collaboration with Theis Groth under the name 'Introduction to Magnetic Resonance Imaging Techniques'. This text and other DRCMR educational material has since been referenced internationally in blogs and on numerous websites.

A new 'java applet' for illustrating basic magnetic resonance was published via the DRCMR homepage. Other educational software was developed in collaboration with Jonas Duun-Henriksen and Jens E. Wilhjelm at the DTU, and is used in the DTU course 'Introduction to Medical Imaging'.

In addition, Lars G. Hansen offered a well-attended course on MR imaging in collaboration with radiological departments at Copenhagen University Hospitals as a consequence of his DTU appointment. This newly established course was awarded for obtaining the best student evaluations at the Department of Electrical Engineering, DTU, spring 2010. Locally, the annual open and free DRCMR courses on MRI techniques coordinated by Arnold Skimminge and Lars G. Hanson attracted many external participants in addition to local students.



A simple 'java applet' for demonstrating basic magnetic resonance was made available at the DRCMR web page. The applet allows users to interactively experiment with the basic ingredients of MR. Most will discover the resonance phenomenon by themselves while doing so.

Selected publications

i Dali C; Hanson LG; Barton NW; Fogh J; Nair N; Lund AM: Brain N-acetylaspartate levels correlate with motor function in metachromatic leukodystrophy. *Neurology*. 2010;75(21):1896-1903.

de Nijs R; Miranda MJ; Hansen LK; Hanson LG: Motion correction of single-voxel spectroscopy by independent component analysis applied to spectra from nonanesthetized pediatric subjects. *Magn Reson Med*. 2009;62(5):1147-1154.

de Nijs R: Corrections in clinical Magnetic Resonance Spectroscopy and SPECT. *PhD thesis*, Informatics and Mathematical Modeling, Technical University of Denmark, 2010.

Hanson LG: MR-skanning ved 7 tesla feltstyrke etableres i Danmark. *Medicinsk Teknologi og Informatik*. 2010;7(4):20-22.

Sardanelli F; Fausto A; Di Leo G; de Nijs R; Vorbuchner M and Podo F: In vivo proton MR spectroscopy of the breast using the total choline peak integral as a marker of malignancy. *AJR Am J Roentgenol*. 2009; 192(6):1608-1617.

Computational Analysis & Modelling

The computational analysis group at DRCMR is engaged in research, development and application of advanced computational data analysis techniques for the analysis of brain imaging data. The efforts within this group strive to improve sensitivity and interpretability of the vast amounts of data that are acquired using modern neuroimaging techniques.

Members

The computational analysis group is headed by Kristoffer H. Madsen. In addition, the group consists of PhD students Kasper W. Jørgensen and Toke J. Hansen enrolled at the cognitive systems section at Informatics and Mathematical Modelling (IMM) at the Technical university of Denmark (DTU).
The computational analysis group at DRCMR maintains a particular strong collaboration with the cognitive systems group at DTU headed by professor Lars Kai Hansen and is actively involved in collaboration and supervision of several MSc and PhD projects at DTU.

External collaborators

- Assistant professor Morten Mørup, Cognitive systems, Informatics and Mathematical Modelling, DTU
- Professor Lars Kai Hansen, Cognitive systems, Informatics and Mathematical Modelling, DTU
- PhD student Peter M. Rasmussen, Cognitive systems, Informatics and Mathematical Modelling, DTU
- Associate professor Torben E. Lund, Center of Functionally Integrative Neuroscience, Aarhus University
- Associate professor Bharat Biswal, Department of Radiology, University of Medicine and Dentistry New Jersey
- Professor Stephen Strother, Rotman Research Institute, Department of Medical Biophysics, University of Toronto

Research activities

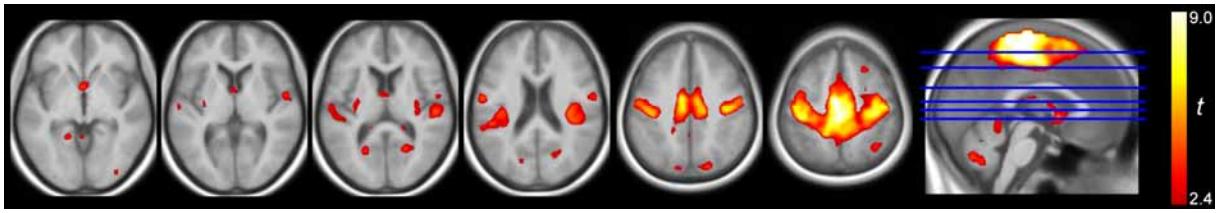
In addition to providing infrastructure, education and support related to data analysis for the other DRCMR groups, the computational analysis group at DRCMR is involved in research and development of novel data analysis techniques useful in the analysis of neuroimaging data. These efforts are mainly focused on multivariate modelling and predictive models (brain state decoding).

Research Group Leader: Kristoffer H. Madsen

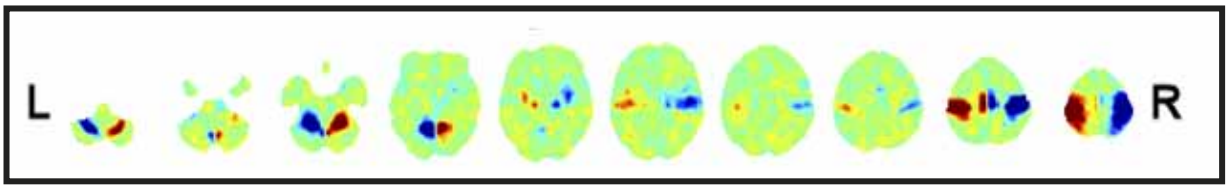
Traditionally, analysis of neuroimaging data has relied on two very important assumptions; independence and linearity. The independence assumption is at the crux of the well established mass-univariate modelling methods often applied in brain mapping studies (activation localisation) where all locations in the brain (voxels) are essentially assumed independent.
In contrast to these univariate approaches multivariate methods such as factor analysis, independent component analysis and extensions to multilinear decomposition methods are able to capture spatiotemporal patterns in the data. Such methodology was applied in the analysis of resting state scans collected from a large group of MS patients. The analysis revealed increased sub-cortical expression of the motor-network compared with a group of matched controls.

Univariate approaches are essentially limited because they only consider individual voxels. Therefore, these methods are inappropriate to capture distributed changes in multiple voxels mediated by the connections and interactions between areas. Non-linear multivariate models can be employed in order to capture complex relations between several brain regions. However, these models are typically much more computationally demanding and can cause severe overfitting in cases where the model is too flexible or where the control parameters of the model have inappropriate values. In addition, multivariate and in particular non-linear models are often much harder to interpret and visualise due to the complex interactions they are able to capture. To help circumvent these shortcomings the computational analysis group is involved in efforts aiming to visualise and investigate the reproducibility of these methods together with PhD student Peter M. Rasmussen from DTU.

In 2009 the group also initiated a project aimed at real-time analysis of functional MRI (fMRI) data, in this setting imaging data is analysed as it is acquired at the scanner. This project has many inter-



The motor network as indentified using independent component analysis.



Visualisation of classification model using sensitivity map. The sensitivity map shows which areas are important for classification by quantifying each voxel's contribution to the cost function. The sensitivity map is calculated based on a linear support vector machine classification between left and right hand in a simple finger tapping experiment. The figure displays axial brain slices with red colours indicating areas that are more expressed for right than for left finger tapping whereas blue indicate the opposite.

esting applications including using the analysed data for biofeedback and quality control of functional brain scans. Related to this topic PhD student Toke Jansen Hansen initiated his master project entitled "Real-time analysis of brain imaging data" after a successful defence he now continues the work in a PhD project granted by the Technical University of Denmark. During his master project Toke developed a high-performance real-time pipeline for the processing and analysis of real-time fMRI data. This pipeline enables running in the order of several hundreds of state-of-the-art classification models on real-time fMRI data and open possibilities of constructing classifiers that dynamically adapt to changes in the subjects strategy. The project already shows promising results using biofeedback in a simple fMRI motor task.

MSc students Nina L. Reislev and Louise B. Johansen (IMM, DTU) performed a study on methodology related to follow-up analyses of retinotopic mapping fMRI data. Retinotopic mapping is used to determine the mapping of visual input to the visual cortex. In their master project Nina and Louise investigated how this mapping is affected by acute changes in visual acuity.

Communication between different areas in the brain can be represented as functional interactions in a complex network. Functional connectivity as measured by fMRI enables us to peak into how communication is distributed in the brain and create a graph with links (connections) between nodes (spatial locations). However, graphs based on these techniques are usually very noisy, this together with the large size of the networks makes it extremely difficult to grasp the information that is contained in such graphs. Together with assistant professor Morten Mørup (IMM, DTU) the computational analysis group is developing techniques that enable complex network dynamics to be captured and represented in more accessible ways.

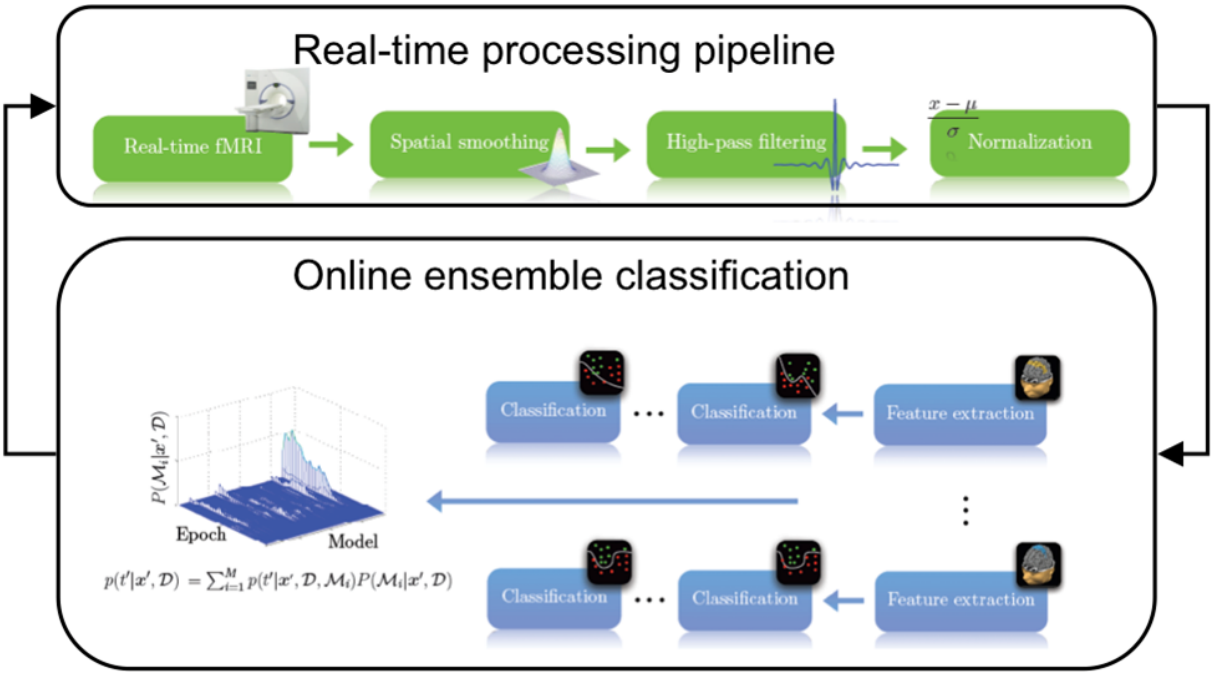
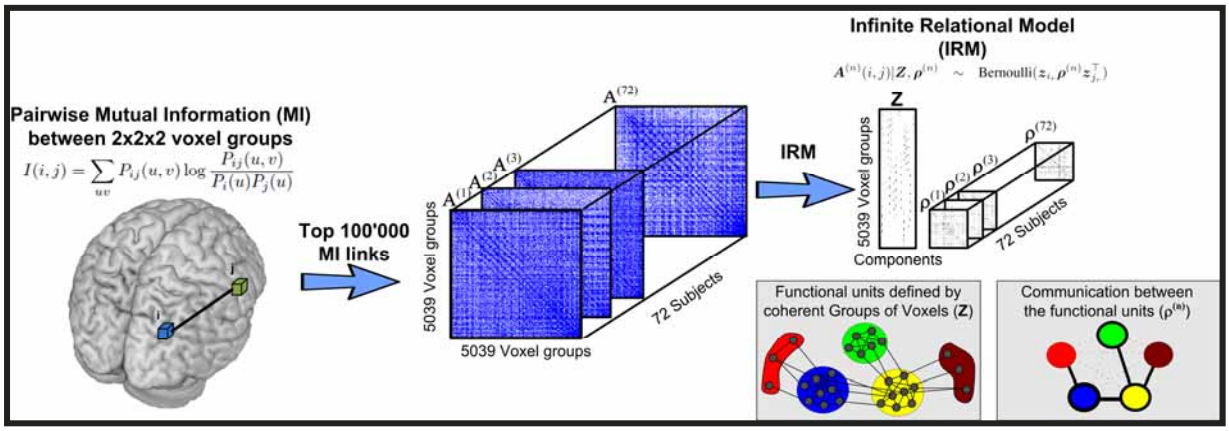


Illustration of the fMRI realtime processing pipeline.



The figure illustrates how the infinite relational model can be used to capture interactions between functional units in the brain. First the mutual information between nodes (2x2x2 voxel groups) are used to form a graphs for each subject, then the IRM establishes functional units (shared between all subjects) which communicate in a consistent way with the remaining units. The relations between the functional units are encoded in the subject specific \rho, containing an estimate of the connectivity between the functional units in that specific subject.

The infinite relational model used on fMRI is an example of such a model. The model identifies functional units (groups of nodes) that interact with the rest of the network in a consistent way. Such methodology directly takes advantages of interactions in the network whereas must other methods (such as independent component analysis and graph cut techniques) attempt to divide the network into maximally disconnected regions.

In 2009 the group was involved in a large multicenter study of resting-state fMRI data (the 1000 functional connectomes project). The study combined more than 1000 resting state fMRI scans from multiple centers around the world and showed how knowledge on the human connectome can be assessed using resting-state fMRI data. The work resulted in a joint publication in the prestigious journal PNAS.

Publications

M. Mørup, K. H. Madsen, A. M. Dogonowski, H. Siebner, L. K. Hansen,
Infinite Relational Modeling of Functional Connectivity in Resting
State fMRI, Neural Information Processing Systems 2010, 2010

R Kupers, DR Chebat, KH Madsen, OB Paulson, M Ptito; Neural correlates of virtual route recognition in congenital blindness, Proceedings of the National Academy of Sciences USA. Volume 107, 2010, number 28, pages 4734-4739

BB Biswal, et. al.; Toward discovery science of human brain function. Proceedings of the National Academy of Sciences USA, volume 107, 2010, number 10, pages 4734-4739.

Toke J. Hansen; "Real-time Analysis of Brain Imaging Data : A High-performance Distributed Pipeline for Multivariate Spatio-temporal Brain State Classification" M.Sc. Thesis, DTU Informatics, 2010

Nina L. Reislev and Louise B. Johansen; Analysis of functional Magnetic Resonance Imaging: Activation Changes Related to Cataract Surgery, DTU Informatics, 2010

Diffusion Imaging

The Diffusion Imaging Group (DIG) was founded at the DRCMR with the dual roles of maintaining a high international level of expertise in this rapidly expanding research field, where the demand for method verification and validation continues, and also to lead basic research into new ways in which diffusion MRI can be tuned to reflect specific features of tissue microstructure, such as cell size and density, and even its organisation.

DRCMR members

The DIG includes: Tim B. Dyrby (group leader), Lise Vejby Søgaard, Henrik Lundell, Matthew G. Liptrot, Nina L. Reislev, Mark Lyksborg and Kristian S. Frederiksen.

External members

External members of the DIG group are: Professor Maurice Ptito (Montreal University, Montreal, Canada) and Assistant Professor Mark Burk (Howard University, Washington DC, USA).

External collaborators

- Professor Daniel C. Alexander, University College London, United Kingdom
- Professor Geoff G. Parker, University of Manchester, United kingdom
- Dr Penny Hubbard, University of Manchester, United Kingdom
- Professor Bente Pakkenberg, Copenhagen University Hospital Bispebjerg, Denmark
- Dr Thomas Knöesche, Max Planck Institute for Human Cognitive and Brain Science, Germany
- Associate Professor Yaniv Assaf, Tel-Aviv University, Israel
- Dr Ron Kupers, University of Copenhagen, Denmark
- Professor Rasmus Larsen, The Technical University of Denmark, Denmark
- Professor Jens Bo Nielsen, University of Copenhagen, Denmark

What is Diffusion MRI?

Diffusion MRI uses special scanner sequences to generate images that are sensitive to the molecular diffusion of water within each imaged voxel. Such diffusion occurs at a microscopic scale, but if the tissue microstructure such as the axons (diameter range: ½ - 20 µm) within a voxel is homogenous, then the diffusion signal acquired will be too. Luckily, this situation occurs frequently, especially within the brain's white matter where the fibre-bundles, comprised of thousands of parallel axons, traverse the brain connecting the processing centres to each other. Consequently, diffusion imaging is able to generate maps where each voxel contains information about the preferred water diffusion direction(s).

Research Group Leader: Tim B. Dyrby

Research activities

Tim B. Dyrby MSc, Phd, is head of DIG and co-supervisor for Henrik Lundell, Matthew G. Liptrot, Nina L. Reislev, Mark Lyksborg and Kristian S. Frederiksen. Tim B. Dyrby has his main interest in mapping and in understanding the underlying microstructrual changes in brain plasticity (especially maturation) by combining diffusion MRI, tractography and mathematical models of tissue microstructure. High-quality data sets are crucial for the verification and method validation.

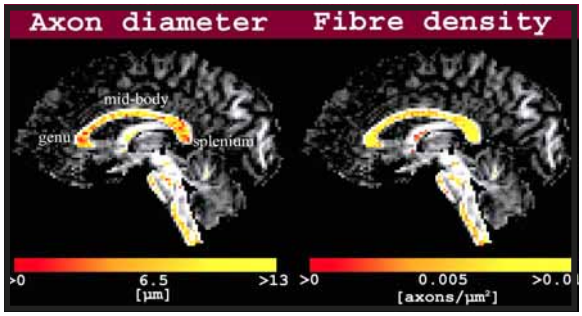
Along these lines, Tim B. Dyrby, Lise Vejby Søgaard and colleagues have over the past four years developed an ex vivo imaging pipeline on DRCMR's 4.7 Tesla preclinical MR scanner to meet this demand and have successfully employed it on post mortem pig brains and monkey brains. The Lundbeck Foundation supported Olaf B. Paulson, Tim B. Dyrby and collaborators in collecting a high-quality ex vivo monkey dataset to study brain maturation (see section on preclinical research).

What is Tractography?

Tractography is the processing of the diffusion imaging data, using the directional information within each voxel to reconstruct a 'road-map' of the white matter fibre-bundles from which the data actually originated. The voxel data is first processed in order to generate a model of the fibre-direction(s) within it. Next, these direction 'sign-posts' are chained together to produce estimates of the fibre pathways. A layer of statistics and maths is then applied to help ascertain the validity of the pathways thus found.

In December 2009 Europe's leading diffusion MRI researchers, including DRCMR's Tim B. Dyrby as a partner, joined forces in the 'CONNECT' consortium (Consortium for the Non-Invasive Exploration of Connectivity and Tracts) in a multi-disciplinary team from 12 laboratories across Europe with financial support of the Future and Emerging Technologies (FET) within the European Commission (FP7) under FET-Open. DRCMR's contribution to CONNECT will be in verification and validation of

microstructural imaging techniques towards defining the optimal white matter imaging protocol to include diffusion MRI microstructure measurements. In the CONNECT consortium, Tim B. Dyrby is Work Package leader of the Validation part.



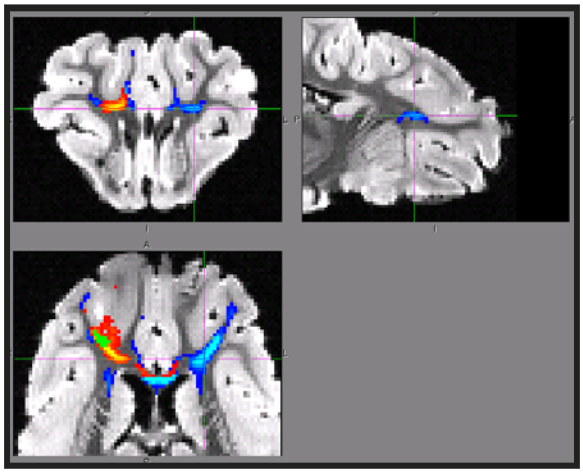
Mapping tissue microstructures in the living human brain tissue using diffusion MRI. Data from which indices of axon diameter (right) and fibre density (left) can be mapped were acquired on a clinical MR scanner in less than one hour. The optimised imaging protocols facilitate mapping of tissue microstructure independent upon the orientation of the fibre bundles. We can therefore, as shown, map microstructure in both the corpus callosum with in-plane fibre orientation, and the corticospinal tract with up-down fibre direction. Axon indices follow the histology literature with a low-higher-lower trend starting from genu, and the opposite for fibre-density.

At an international conference in 2009, Tim B. Dyrby, Professor Daniel Alexander, Professor Geoff Parker, Dr Penny Hubbard and Professor Maurice Ptito presented the first microstructrual imaging results of a live human brain, acquired in less than an hour on a clinical MR scanner (see figure above). The in vivo results were supported by microstructrual imaging of an ex vivo, fixated monkey brain. The results included indices of axon diameter and fibre density estimated from very few measurements. Optimised imaging protocols were generated using the *active imaging* approach introduced in 2008 by Professor Daniel Alexander. Ongoing research on the power-full experimental 4.7 Tesla Varian MR scanner focused upon understanding how axon diameter index is influenced by constrains such as maximal gradient strength and sequence used. The first results were presented at an international conference in 2010. This work is a part of CONNECT.

In a more clinical aspect, Tim B. Dyrby has, together with DRCMR's Per Åkeson initiated investigations into the future potential of using diffusion MRI (together with tractography) in pre-surgical planning for e.g. tumour patients (see previous section on Clinical Work at DRCMR) and a PhD project is planned initiated in the spring 2011.

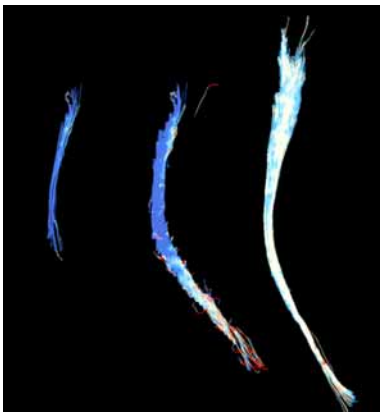
Over the past year, *Matthew G. Liptrot* has been developing a methodological improvement to the conventional, yet increasingly popular, tractographic analysis approach used to assess brain connectivity. These conventional processing techniques are far from perfect, and their accuracy is often compromised by artefacts, which can give a false representation of the true connections. However, with a new approach, named ICE-T (Iterative Confidence Enhancement for Tractography), the DIG have succeeded in drastically reducing these artefacts, enabling tractography to produce more accurate connection maps of the brain (illustrated below). The work has been collected in a thesis with several conference papers, and journal articles are under preparation. In October 2010, Matthew defended his PhD at Imperial College, University of London, United Kingdom.

Henrik Lundell, PhD student at DRCMR and Department of Exercise and Sport Sciences, University of Copenhagen, is working on DWI of the spinal cord. Two main branches are developed in his work. Firstly, human *in vivo* DWI of healthy controls and patients with spinal cord injury and secondly, *post mortem* DWI on excised spinal cord tissue.



An example of the improvement in the tractography results achieved by Matthew G. Liptrot's ICE-T Framework. The three slices show the brain sliced along the 3 orthogonal axes. The lower left image shows the axial (top-down) view with the seed region (the start of the tractography path-finding routine) in green. Conventional tractography manages to find the red fibre-tracts, whilst the new ICE-T method finds many more (shown in blue), all the way to the contra-lateral side, in agreement with a previous invasive tracer validation study on the same data. Note how ICE-T successfully traverses a problematic region in the mid-brain which was too difficult for conventional tractography to penetrate through.

In vivo DWI of the spinal cord is complicated due to physiological motion and image distortions due to field variations around the lungs and the vertebras. Henrik has investigated distortion-mapping techniques for the spinal cord, giving better geometrical consistency - something which is crucial for tractography (see figure below).



Uncorrected data is too distorted to be used for tractography in the spinal cord (left). By applying corrections we are able to follow the path of white matter in the full length of the cervical spinal cord (right).

By adopting methods developed at DRCMR for imaging and analysing brain data *post mortem* to the spinal cord it is possible to create golden standards for *in vivo* imaging (see figure below to the right). Henrik Lundell has submitted his PhD thesis and the defence will be held in the spring 2011. The PhD project has kindly been funded by the Elsass Foundation.

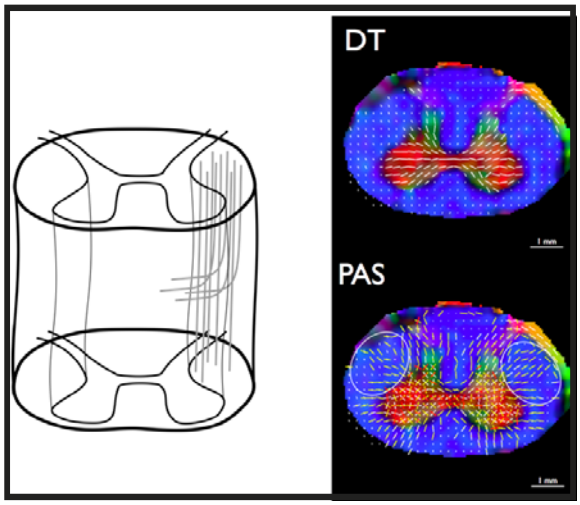
After finishing her MSc project on analysis of functional MRI from the department of Medicine and Technology at the Technical University of Denmark and University of Copenhagen, *Nina L. Reislev* joined DIG as a Research Assistant in the summer 2010. Nina has been working on initiating a new project investigating the structural connectivity of the brain of blind people using diffusion MRI and fMRI. The overall aim of the project is to gain insights into the plasticity of the brain, thereby being able to map the reorganisation of the brain following vital sensory deprivations. The project is in close collaboration with experts within the field of visual neuroscience namely Dr Ron Kupers and Professor Maurice Ptito. The project has kindly been supported by FSS and the Lundbeck foundation.

Mark Lyksborg started his PhD project in the spring 2010 and has an Engineering background with a MSc in mathematical modelling from the Technical University of Denmark. The aim of his PhD project is to investigate and develop mathematical models applied to multimodal MRI as potential biomarkers in patients with Multiple Sclerosis (MS). The focus of the project is to identify regional changes in structural brain connectivity in the major fibre tracts in MS patients using diffusion MRI and link these to specific functional impairments. The project is conducted in collaboration with Finn Sellebjerg at the Multiple Sclerosis Clinic at Rigshospitalet, and Professor Rasmus Larsen, Technical University of Denmark.

Kristian S. Frederiksen is an MD and will in his PhD project examine the effects of cortical deposits of beta-amyloid on white matter structure in AD patients by combining diffusion MRI and PET imaging. For more details see the section on Aging and Dementia.

Selected publications

Alexander DC; Hubbard PL; Hall MG; Moore EA; Ptito M; Parker GJ; Dyrby TB: Orientationally invariant indices of axon diameter and density from diffusion MRI. *Neuroimage*. 2010;52(4):1374-89.



Left: A schematic illustration of the decending fibers in the lateral column of the spinal cord. Right: Axial DWI of the monkey spinal cord with the fiber direction in each voxel determined with two different techniques; the diffusion tensor (DT) and Persistent Angular Structures (PAS). By using multi fiber reconstruction techniques, like PAS in this case, we are able to detect the small compartment of fibers bending into the grey matter in the core of the spinal cord.

Preclinical Research

The preclinical research group aims for better understanding and characterisation of healthy and diseased tissue. Models of common major diseases are used for longitudinal investigations, including effects of treatment.

The group represents a multidisciplinary team with members of various backgrounds from engineering, biochemistry, human biology, pharmacology and medicine.

DRCMR members

The group includes: Lise Vejby Søgaard (group leader), Sadia Asghar Butt, Mette H. Lauritzen, Tim B. Dyrby, Henrik Lundell, Peter Magnusson, Brian V. Broberg, Anders D. Skjolding, Ellen Garde and Sascha Gude.

External Collaborators

- Dr Niels Plath, H. Lundbeck A/S, Denmark
- Dr Börje Bjelke, Geriatric Clinic, Blekingesjukhuset, Sweden
- Professor Marianne Juhler, Department of Neurosurgery, Copenhagen University Hospital Rigshospitalet, Denmark
- Dr Lars Engelholm, Finsen Laboratory, Copenhagen University Hospital Rigshospitalet, Denmark

Research content and infrastructure

A 4.7 Tesla Varian MR scanner designed for small animal imaging and spectroscopy research is used for the preclinical group's studies. Focus areas in 2009-2010 have been in vivo studies of cell metabolism using hyperpolarised ^{13}C enriched substances in mammary cancer, ischemic heart disease and normal brain, and ex vivo studies of brain and spinal cord tissue microstructure and connectivity using diffusion imaging. In addition, pharmacologically induced brain activation in a schizophrenia model has been investigated to provide basis for development of new drugs for this disabling disorder.

In 2009 the 4.7 Tesla scanner was upgraded with a new gradient coil as well as a new console, resulting in a greatly improved system with high performance. The new gradient coil can provide a gradient strength of 400mT/m – a considerable improvement compared to the old gradient coil (140 mT/m). A high gradient strength is particularly important for the group's diffusion studies where gradients are used to reveal the diffusion properties of the water molecules in the tissue of interest, and the upgrade was made possible thanks to a grant from the Lundbeck Foundation based on an application focused on ex vivo diffusion MRI on fixed tissue. The new gradient coil also has a considerable higher duty cycle, in simple terms meaning that 'it can run faster without getting hot'. This has had the important implication for the ex vivo studies that they can now be performed within a weekend instead of lasting ten days. In general, all studies on the Varian scanner have benefitted from the upgrade as the faster and stronger gradients allow for a faster generation of MR images.

Research Group Leader: Lise Vejby Søgaard

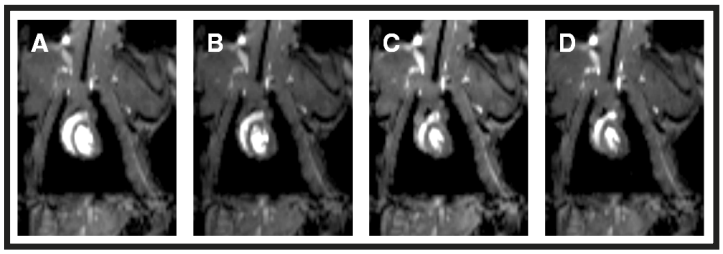
Thanks to a donation from Simon Fougner Hartmanns Familiefond the scanner was further upgraded in 2010, now to include four receive channels instead of one. This allows for the use of array coils and accelerated data acquisition using parallel imaging. A four channel ^{13}C heart array is now used for the hyperpolarised ^{13}C heart studies providing a better coverage of the heart.

Next to the scanner room the preclinical group has a laboratory, which is used for preparing the animals for scanning. This laboratory was rebuilt during 2009 and a new LAF bench was installed. The resulting laboratory provides a nice working environment for laboratory technician Sascha Gude and other members of the group.

Research activities

Sadia Asghar Butt was responsible for a large study aiming at characterising the disease progression in a mammary cancer mouse model. The transgenic mouse model of breast cancer, expressing the oncoprotein polyoma middle T antigen (PymT) in the mammary epithelium, resembles human breast cancers in many ways. The PymT mice form spontaneous tumours and are well-suited to study cancer progression and treatment and for characterisation of metabolism by MR based methods. The conversion rate of hyperpolarised pyruvate to lactate catalysed by the enzyme lactate dehydogenase (LDH) was measured at different stages of the disease (different ages) and was correlated to 1) tumour volume based on delineation of tumour regions on 3D MR images, 2) LDH activity based on biochemical analysis, 3) cellular expression pattern of LDH based on immunohistochemistry 4) disease stage based on histology. Another study followed the progression of the disease longitudinally with multiple scans for each mouse to study the effect of treatment.

Mette H. Lauritzen pursued a study using hyperpolarised pyruvate to evaluate heart ischemia where the pyruvate metabolism is known to be altered. The hypothesis is that the technique can be used as a tool to determine the degree of tissue damage after ischemia by characterising the metabolic



Anatomical coronal CINE images of a rat heart. The frames show different phases of the cardiac cycle from diastole (A) to systole (C). In order to obtain conclusive images of the heart, and avoid motion artefacts, the image acquisition is synchronised (gated) to both the respiration and the cardiac cycle. A new and improved gating technology was introduced in the preclinical research group in 2009, and has made it possible to perform more advanced heart research in small animals.

changes regionally in the heart muscle. Transient ischemia is induced in the rat heart by ligating the left descending coronary artery by a suture resulting in either a minor ischemic lesion or a more severe infarct depending on the ligation time. Chemical shift images show changed metabolism in the area of ischemia and were correlated to proton anatomical images, see figure above.
More details on the hyperpolarisation studies can be found in the section on hyperpolarisation.

Brian V. Broberg finished his work investigating brain activity in a putative rat disease model of schizophrenia in 2009 in a collaborative study involving DRCMR, University of Copenhagen and H. Lundbeck A/S. A method for evaluating neuronal brain activity in rats was set up. The method utilises cerebral blood volume (CBV) as a marker for neuronal activity and evaluates regional changes in brain activity following pharmacological stimulation. Specifically, the effect of acute stimulation with the drug phencyclidine (PCP), which induces psychotic symptoms in humans, was evaluated in a large study comparing responses between 'schizophrenic' and healthy rats. The aim was to further validate the disease model by evaluation of the results against findings in humans. Brian V. Broberg defended his PhD on the subject in July 2010. The PhD was co-financed by the University of Copenhagen, The Danish Medical Research Council and H. Lundbeck A/S.

Tim B. Dyrby optimised the diffusion measurement procedures to study brain maturation, taking advantage of the improved performance of the new gradient coil. A protocol to probe the microstructure in more detail by providing a measure of axonal diameters was also implemented. These studies were carried out ex vivo on perfusion fixed brains from pigs and Vervet monkeys. Ex vivo imaging benefits over in vivo, due to the absence of physiological noise such as head motion, respiration and cardiac cycle. Additionally, scanning time is unlimited (in principle) and we can therefore go for higher image resolution and higher signal-to-noise (SNR). (See figure below).

Henrik Lundell also used diffusion imaging to study the axonal structure in the spinal cord ex vivo. Similar techniques as used for the brain were implemented and the acquisition set-up was optimised for spinal cord. More details on the diffusion studies can be found in the diffusion section of this report.

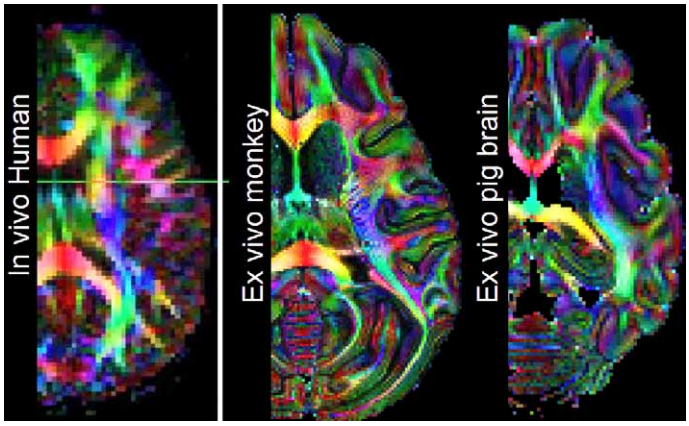
The scanner upgrade mentioned previously also made it possible to obtain good quality EPI images. This was used in a collaborative study with a group from University College London to acquire in vivo diffusion weighted EPI images for detailed microstructure modelling.

In 2010 Anders D. Skjolding began optimising the protocol for studies of hydrocephalic rats. The studies, which will investigate treatment of hydrocephalus using vasopressin delivered using an osmotic pump, are a continuation of the hydrocephalus studies carried out in 2007, and financed by the University of Copenhagen.

Selected publications

Dyrby TB; Baare WFC; Alexander DC; Jelsing J; Garde E; Søgaard LV: An ex vivo imaging pipeline for producing high-quality and high-resolution diffusion-weighted imaging datasets. *Human Brain Mapping* (in press).

Broberg B: Animal disease models of schizophrenia. *PhD Thesis*, Faculty of Health Sciences and Faculty of Life Sciences, University of Copenhagen, 2010.



Diffusion MRI of fixed brain tissue benefits from the absence of physiological noise as well as unlimited scanning time, higher image resolution and SNR. The three images show colour-coded diffusion tensor imaging (DTI) calculated from diffusion MRI of the major fibre direction in each voxel where green is frontal-posterior, blue up-down and red right-left direction. Comparing DTI reconstructed from in vivo diffusion MRI of a human brain (left) with that of ex vivo monkey brain (middle) or pig brain (right), the image quality of ex vivo is much higher.

Hyperpolarised MRI

The hyperpolarisation research group aims for a better understanding and diagnosis of major chronic diseases by means of hyperpolarisation techniques. The group branches into two hyperpolarisation modalities:

- The use of hyperpolarised ^{3}He-gas techniques (HP-^{3}He) for studying chronic obstructive pulmonary disease (COPD)
- The use of hyperpolarised ^{13}C based MR techniques (HP-^{13}C) for studying cell metabolism characteristics of chronic diseases.

DRCMR members

Per Åkeson (group leader), Peter Magnusson (group leader), Lise Vejby Søgaard (group leader), Sadia Asghar Butt, Mette H. Lauritzen, Sascha Gude, Torsten Dorniok, Frederik Hengstenberg and Ann-Sofi Sjökvist.

External members

External members are Engineer and Principal Scientist Jan Henrik Ardenkjær-Larsen, PhD (GE Healthcare) and Professor Jørgen Vestbo, MD, PhD (Department of Cardiology and Respiratory Medicine, Copenhagen University Hospital Hvidovre).

External collaborators

- Principal Scientist, Lars Engelholm, PhD, Finsen Laboratory, Copenhagen University Hospital Rigshospitalet, Denmark
- Sergei Karpuk, PhD, and Zahir Salhi, PhD, Physics Department at Johannes Gutenberg-University in Mainz, Germany
- Professor Rahim Rizi, Department of Radiology, University of Pennsylvania, Philadelphia, USA
- Ingrid Casselbrant, PhD and Sandra Diaz, PhD, Departments of Respiratory Medicine and Radiology, University Hospital Skåne, Malmö, Sweden

Research content

In the HP-^{3}He research the HP-^{3}He technique is evaluated in the clinical context of studying e.g. the progression of emphysema over time for patients with COPD. The HP-^{13}C research focuses on preclinical in vivo studies of altered cell metabolism in disease models with the HP-^{13}C technique.

Research methods

The hyperpolarisation research group has at its disposal for the HP-^{3}He research, multi-nuclear 1.5 Tesla and 3 Tesla Siemens clinical MR scanners with ^{3}He-coils, ^{3}He-gas inhalation systems, gas recycling system and had until the end of 2009 delivery of gas from Mainz University, Germany. The data has been collected under two projects with HP-^{3}He-scanning of COPD-patients and healthy subjects. One conducted in collaboration with the Department of Cardiology and Respiratory Medicine, Copenhagen University Hospital Hvidovre (ECLIPSE). Another conducted in collaboration with the Department of Radiology, University of Pennsylvania and the Department of Pulmonology, University Hospital Skåne. The MR protocol includes ^{3}He gas diffusion imaging, which measures the Apparent Diffusion Coefficient (ADC) that correlates with the size of the lung alveoli. ADC is measured both at the inspiratory and expiratory state by using a 3D sequence to provide full lung coverage at high resolution.

For HP-^{13}C research exciting new possibilities opened in 2008 with the installation of a HyperSense DNP polariser (Oxford Instruments). Using this instrument it is possible to hyperpolarise substances labelled with ^{13}C (and other nuclei such as ^{15}N) thus increasing their MR signal more than 10.000 times. By injecting such hyperpolarised substances intravenously it is possible to follow their conversion in metabolic processes non-invasively and in real time by MR spectroscopy.

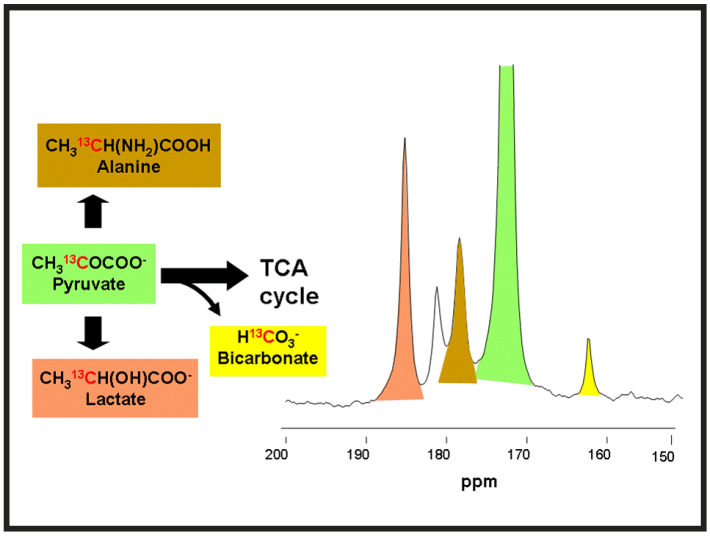
Research Group Leader: Per Åkeson

Research Group Leader: Lise Vejby Søgaard

Research Group Leader: Peter Magnusson

The first substance that has been used at DRCMR is pyruvate, which is of particular interest because it is converted to acetyl-CoA, which enters the Krebs cycle and is one of the main fuels for energy production from the mitochondria in our cells. The conversion of pyruvate to acetyl-CoA gives the by-product carbon dioxide, which is in rapid equilibrium with bicarbonate. Other products of the normal pyruvate metabolism are the amino acid alanine and the carboxylic acid lactate.

All the metabolic products appear at different chemical shifts in the carbon MR spectra, and by acquiring spectra as a function of time it is possible to model the rate constants for the individual metabolic conversions. Chemical shift imaging can be used to map the spatial distribution of the different metabolites and thereby spatially locate differences in activity such as low activity in infarcts or high activity in cancer cells (see figure on the following page).

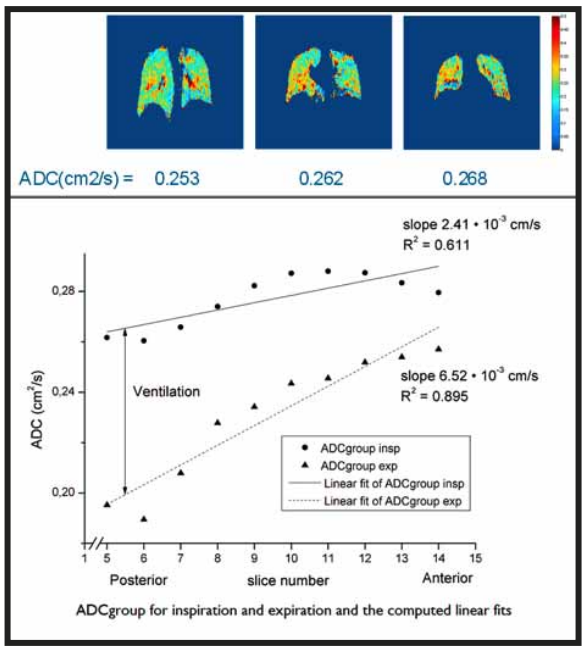


Pyruvate metabolism in the cell can be monitored in vivo after injection of hyperpolarised ^{13}C pyruvate. The MR signal follows the hyperpolarised ^{13}C label and signals from the metabolites alanine, lactate and bicarbonate are observed in addition to the pyruvate signal. The ^{13}C MR spectrum shows the corresponding peaks of the metabolites which appear at different chemical shifts. The white peak (at 180 ppm) corresponds to pyruvate hydrate at physiological pH.

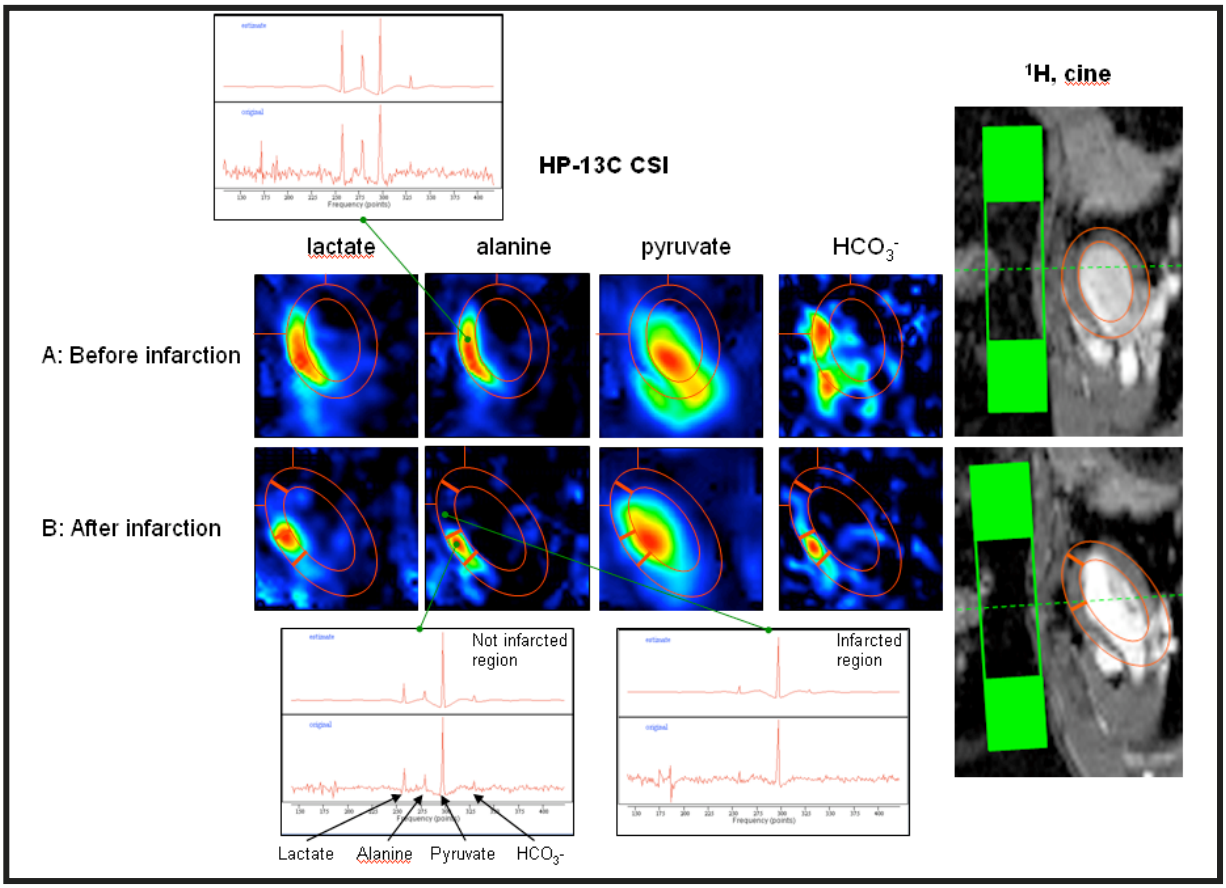
Using the DRCMR's multi-nuclear 4.7 Tesla Varian preclinical MR scanner with ^{13}C-coils, physiological monitoring equipment and animal experimental facilities, the focus of the group in 2009-2010 has been on studies of altered *in vivo* cell metabolism in disease models of breast cancer and cardiac ischemia and on preparations for *in vivo* studies of cerebral metabolism.

Research activities

HP-^{3}He: An analysis of paired inspiratory and expiratory HP-^{3}He ADC measurements was performed in 2009 (Hengstenberg et al. 2009). The results suggest that the difference in inspiratory and expiratory ADC-values (ΔADC) could be used as a biomarker for hyperinflation caused by small airway disease and consequently for differentiating between patients with small airway disease and patients with emphysema. The progression of emphysema over a one year period was further studied in 2010 in terms of changes in ADC (Hengstenberg et al. 2010). A significant annual increase in ADC could be detected in a well-defined subgroup of COPD patients with CT diagnosed emphysema and the results suggest that the HP-^{3}He ADC measurement might be used for monitoring the progression of emphysema. The HP-^{3}He data was further analysed with respect to the possibility of measuring regional lung ventilation on a slice-by-slice basis using ΔADC (Dorniok et al. 2009). The ADC values were averaged over each imaging slice, for inspiration and expiration, respectively, and the slice averages for each slice position were averaged over a subject group. The ΔADC values were found to agree with expected ventilation patterns and suggest that ΔADC can be used to measure regional ventilation (see figure below). Furthermore, Lise Vejby Søgaard and Torsten Dorniok were invited to lecture at the PHeLINet workshop in Krakow, Poland in May 2010 to speak about the current efforts in HP-^{3}He imaging at the DRCMR. Due to the limited global availability of ^{3}He-gas and the increased purchase price, the HP-^{3}He scanning was discontinued in late 2009. The HP-^{3}He research was made possible through funding from GlaxoSmithKline plc, the National Institutes of Health, USA, and through



ADC-maps measured with the HP-^{3}He-technique for a posterior, mid and anterior slice of a lung, respectively (top), showing an increased ADC in the anterior direction. Mean slice ADC measured with HP^{3}He-technique averaged over 9 subjects for each slice position at inspiration and at expiration (bottom). The greater ADC-difference between inspiration and expiration (ΔADC) for posterior slices than for anterior slices suggests that ΔADC is sensitive to changes in regional ventilation.



Metabolite maps of lactate, alanine, pyruvate and bicarbonate measured using the HP-^{13}C-technique over the anterior wall of the left ventricle of a rat heart before (A) and after (B) an induced infarction. After infarction, the metabolism was absent in the infarcted region whereas in the not infarcted region the metabolism was preserved.

the EU-granted Marie Curie Research and Training Network - PHeLINet.

HP-^{13}C: For the breast cancer model, Sadia Asghar Butt headed a project to detect tamoxifen treatment response by monitoring tumour volume and cell metabolism kinetics during MMTV-PymT mammary tumour progression *in vivo* (Butt et al. 2010). The apparent metabolic rate constant (k_{pl}) for the Pyruvate to Lactate conversion was measured with time-resolved HP-^{13}C spectroscopy at different time points during *in vivo* mammary tumour growth for a tamoxifen treated and an untreated group of animals. Pyruvate that is produced from glycolysis becomes converted to Lactate by Lactate dehydrogenase (LDH), a major enzyme involved in glycolysis regulation when oxygen resources are reduced. The volume of tamoxifen treated tumours was found significantly lower compared to the untreated tumour volume. The *in vivo* flux of ^{13}C-label from [1-^{13}C]Pyruvate to [1-^{13}C]Lactate (k_{pl}) was also found significantly reduced by tamoxifen administration. These findings were also supported by *in vitro* analysis and show that HP-^{13}C spectroscopy has the potential to be a valuable tool for detecting *in vivo* response to tamoxifen and other targeted therapies that directly or indirectly inhibit LDH. Sadia's PhD was kindly co-financed by The University of Copenhagen, The Danish Agency for Science, Technology and Innovation and Savværksejer Jeppe Juhls og hustru Ovita Juhls Mindelegat.

In her PhD project, Mette Hauge Lauritzen evaluated the HP-^{13}C technique as a tool for measuring regional tissue damage in terms of regionally changed metabolism in the rat myocardium after severe ischemia (Lauritzen et al. 2010). The experimental rat heart ischemia model involves occlusion of the left anterior descending artery (LAD) with following reperfusion. The results from HP-^{13}C spectroscopic imaging before and after the ischemic insult showed that regional changes in

metabolism after severe ischemia of the rat heart can be detected with the HP-^{13}C technique (see figure above). The severity of the damage is dependent on the duration of the occlusion. In order to determine if the HP-^{13}C metabolism measurement could be used to differentiate between degrees of rat heart ischemia, new methods were implemented in 2010 to verify the results from the HP-^{13}C measurement. It was shown that a specific cardiac marker of tissue damage (Troponin I) was sensitive enough to verify the HP-^{13}C-technique at different degrees of ischemia. An MR-method (Late Enhancement) was further evaluated as a technique to verify conditions of severe ischemia on a regional basis and was found consistent with the regional metabolism changes detected with HP-^{13}C spectroscopic imaging. The PhD project was co-financed by Copenhagen University Hospital Hvidovre, The Danish Heart Foundation and The University of Copenhagen. Mette Hauge Lauritzen received a prize (3rd place) at the Joint Annual Meeting ISMRM-ESMRMB in 2010 for her poster on this work.

Sadia Asghar Butt working with the HyperSense DNP polariser.

A new series of hyperpolarised ^{13}C studies of rat brain metabolism were initiated in 2010. Initially the focus has been to investigate the characteristics of normal brain tissue with the prospect of extending the studies to disease models later.

The HP-^{13}C research was made possible through grants from the Lundbeck Foundation, Danish Heart Foundation, Copenhagen University Hospital Hvidovre, The Spies Foundation and Simon Fougner Hartmanns Familiefond.

Selected publications

Dorniok T; Hengstenberg F; Søgaard LV; Karpuk S; Vestbo J; Magnusson P; Åkeson P: Ventilation measurement with hyperpolarized ^{3}He MRI using ADC. *Proc Annu Meet Eur Soc Magn Reson Med Biol*. 2009.

Hengstenberg F; Dorniok T; Åkeson P; Karpuk S; Vestbo J; Magnusson P; Søgaard LV: Paired inspiratory and expiratory hyperpolarized ^{3}He 3D ADC measurements in chronic obstructive pulmonary disease (COPD). *Proc Annu Meet Eur Soc Magn Reson Med Biol*. 2009.

Butt SA; Søgaard LV; Lauritzen MH; Ardenkjær-Larsen J; Engelholm L; Holck S; Magnusson P; Åkeson P: Time Resolved Metabolic ^{13}C MRS using Hyperpolarised [1-13C]pyruvate in a Transgenic Mammary Cancer Model. *Proc Joint Annual Meeting ISMRM-ESMRMB*. 2010.

Hengstenberg F; Dorniok T; Karpuk S; Vestbo J; Rizi R; Åkeson P; Magnusson P; Søgaard LV: Evaluation of Emphysema Progression in Chronic Obstructive Pulmonary Disease (COPD); ^{3}HE 3D ADC Measurements Compared with CT and Lung Function Test, Preliminary Results. *Proc Joint Annual Meeting ISMRM-ESMRMB*. 2010.

Lauritzen MH; Magnusson P; Butt SA; Ardenkjær-Larsen J; Søgaard LV; Åkeson P: Visualizing Regional Changes in Metabolism in a Rat Model of Acute Myocardial Infarction Using Hyperpolarized ^{13}C MR. *Joint Annual Meeting ISMRM-ESMRMB*. 2010.

Aging & Dementia

In the Aging and Dementia group our substantive research interests include structural as well as vascular changes in ageing populations and individuals at risk of cognitive impairment and degenerative diseases.

DRCMR members

The group includes the following members: Ellen Garde (group leader), Kristian S. Frederiksen, Charlotte Ryberg, Hanne Schmidt, Sussi Larsen, Tim B. Dyrby and Arnold Skimminge.

External collaborators

- Professor Gunhild Waldemar, Memory Disorders Research Group, Department of Neurology, Copenhagen University Hospital Rigshospitalet
- Professor Rasmus Larsen, Informatics and Mathematical Modelling, Technical University of Denmark
- Associate Professor Erik Lykke Mortensen and Professor Kirsten Avlund, Department of Public Health, University of Copenhagen
- Dr Jo Barnes, Dementia Research Centre, National Hospital for Neurology and Neurosurgery, University College London, United Kingdom
- Egill Rostrup, Functional Imaging Unit, Copenhagen University Hospital, Glostrup

Research content

The Aging and Dementia group focuses on the impact of white matter changes on brain structure and functional connectivity in ageing populations.
In addition to working closely with the clinical MR expertise at the clinical section of DRCMR, the group participates in the implementation of advanced data processing techniques developed by colleagues at the DRCMR and collaborators at the Technical University of Denmark (DTU). Data analysis approaches such as MR brain segmentation, tractography and shape analysis are used to characterise and link complex MR data with functional and biological measures to identify MR markers for early screening as well as identification of associated risk and protective factors.

Research projects

One of the focus areas in 2009-2010 has been on the impact of white matter lesions and corpus callosum atrophy on structural and functional connectivity in the brain and the relation to cognitive function and mobility in aging and dementia.

Since 2000, the group has been participating in a broader multi-site investigation by European Union collaborators entitled 'LeukoAraiosis and DISability in the Elderly' (LADIS). The LADIS study is a multicentre, multinational longitudinal study involving more than 600 subjects, recruited from 11 European centres. The Danish coordinator is Prof. Gunhild Waldemar at Rigshospitalet. The objective of the study is to assess the impact of age-related white matter changes on transition to disability.

Research Group Leader: Ellen Garde

A large volume of clinical data has been collected, as well as data from MRI scans, which have been conducted at baseline and three year follow-up. This has allowed for over 35 publications in peer-reviewed journals, eight in 2009 alone, several with major contributions from the DRCMR, especially regarding development of MRI techniques, such as shape analysis and automatic quantification of white matter hyper-intensities as well as clinical correlates of MRI based markers of pathology.

PhD student Charlotte Ryberg has continued her studies on the baseline data from the LADIS study focusing on the relationship between the corpus callosum and age-related white matter changes. Further analysis on follow-up clinical data and corpus callosum measures, generated by use of an automated method to recognise and quantify the volume of corpus callosum, has been submitted. In September 2010 Charlotte successfully defended her thesis 'Morphological Correlates and Functional Significance of Corpus Callosum Atrophy in Elderly Subjects'.

In 2009 the group welcomed Kristian S. Frederiksen to the group. As part of his PhD project Kristian continued the analysis of data from the LADIS study in collaboration with Professor Gunhild Waldemar at Rigshospitalet. A manuscript based on baseline and three year follow-up MRIs, exploring the role of the corpus callosum, a major white matter tract, on development of motor and global cognitive decline and dementia, has recently been submitted.

The close collaboration with Professor Rasmus Larsen's group at the DTU continued and resulted in yet another very promising method being tested on the LADIS data. This time Sune Darkner developed a method based on large scale hypothesis testing for selecting an appropriate threshold for given data. By estimating the prominent distribution the segment of interest can be characterised as a set of outliers of the distribution itself. Thus, a probability based on the estimated densities of outliers actually being outliers could be calculated using the false discovery rate (FDR). The paper was accepted for oral presentation at the VISAPP 2010.

Our international collaborations have also been strengthened during 2010 in particular with Dr Jo Barnes, University College London, assessing the predictive role of white matter changes in MCI.

New research projects

As part of Kristian's PhD project a new study combining MRI and PET imaging has been initiated. The ligand Pittsburgh compound-B that has affinity to beta-amyloid, a protein believed to be central in the pathological processes leading to Alzheimer's Disease (AD), is being used in the PET scans, led by Prof. Gunhild Waldemar at Rigshospitalet. We will also examine the effects of cortical deposits of beta-amyloid on white matter structure combining diffusion weighted imaging (DWI) and advanced data processing techniques developed by the Diffusion Imaging Group, led by Dr. Tim B. Dyrby (more details on the diffusion studies can be found in the section on Diffusion Imaging in this report). In a related study, 8 patients participated in a pilot study prior to a nationwide intervention study, which will examine the effects of physical activity in patients with AD. Both participants in the pilot study and a subgroup of patients in the intervention study will undergo MRI and PET. The primary focus related to imaging will be to explore whether beta-amyloid can be reduced following physical exercise and whether MRI changes may be correlated to functional changes.

Research activities

In October 2010 Ellen Garde represented the group at the International Alliances of Research Universities (IARU) Congress to exchange data and ideas on Molecular Aging, Neuro- and Muscle Degeneration, Life Course and Aging, Aging Populations, Aging and Evolution with researchers from the IARU Ageing, Longevity and Health network.

Several other international collaborations were strengthened. Visiting colleagues included Dr Jo Barnes, University College London, sharing her experiences with 'Manual and automated hippocampal measures' and Professor Kaarin Anstey, director of the Ageing Research Unit, Australia National University, presenting recent data in her talk 'The PATH Through Life project - overview and MR findings'.

Another fruitful collaboration between the Diffusion Imaging Group and the Aging and Dementia group lead to the DRCMR featuring prominently in 'DR2 Temalørdag' a full-evening television documentary about dementia, which was broadcast on national television in March 2010 (see figure on the previous page).

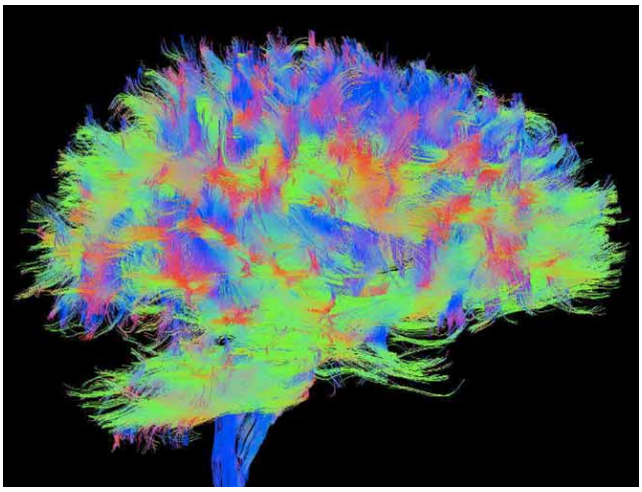
Selected publications

Barnes J; Mitchell LA; Kennedy J; Bastos-Leite AJ; Barker S; Lehmann M; Nordstrom RC; Frost C; Smith JR; Garde E; Rossor MN; Fox NC: Does registration of serial MRI improve diagnosis of dementia? *Neuroradiology*. 2010;52(11):987-95

And collaboration articles:
Verdelho A; Madureira S; Moleiro C; Ferro JM; Santos CO; Erkinjuntti T; Pantoni L; Fazekas F; Visser M; Waldemar G; Wallin A; Hennerici M; Inzitari D (LADIS Study): White matter changes and diabetes predict cognitive decline in the elderly: the LADIS study. *Neurology*. 2010;75(2):160-7.

Madureira S; Verdelho A; Moleiro C; Ferro JM; Erkinjuntti T; Jokinen H; Pantoni L; Fazekas F; Van der Flier W; Visser M; Waldemar G; Wallin A; Hennerici M; Inzitari D: Neuropsychological predictors of dementia in a three-year follow-up period: data from the LADIS study. *Dement Geriatr Cogn Disord*. 2010;29(4):325-34.

Inzitari D; Pracucci G; Poggesi A; Carlucci G; Barkhof F; Chabriat H; Erkinjuntti T; Fazekas F; Ferro JM; Hennerici M; Langhorne P; O'Brien J; Scheltens P; Visser MC; Wahlund LO; Waldemar G; Wallin A; Pantoni L (LADIS Study Group): Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *BMJ*. 2009;339:b2477.



Combining diffusion imaging data and tractography Henrik Lundell from the Diffusion Imaging Group generated this model of white matter fibre-bundles which was featured in the DR2 Temalørdag, a full-evening television documentary about dementia. In Kristian Frederiksen's study diffusion tensor imaging will examine the effects of physical activity in in patients with Alzheimer's Disease.

Brain Maturation

The focus of the research group is on brain and behavioural development during childhood and adolescence in health and disease, and on the impact of genetic, biological and environmental factors. Structural and functional brain maturation is assessed with magnetic resonance imaging (MRI) techniques. Measurements, such as brain structure volumes, cortical thickness and area, measures of tissue microstructure (fractional anisotropy and diffusivity), fibre tract characteristics, and brain activation during the performance of specific psychological tasks, are used to relate brain structure and function to clinical, behavioural, biochemical and genetic variables. Individual projects acquire longitudinal data to allow investigating individual maturational trajectories.

DRCMR members

The group includes: William Baaré (group leader), Terry L. Jernigan (DRCMR and UCSD, San Diego), Kathrine Skak Madsen, Martin Vestergaard, Hartwig R. Siebner, Olaf B. Paulson, Pernille Iversen, Arnold Skimminge, Julian Macoveanu, Sussi Larsen, Vibe Nordahn Bredsdorff, Julie Hagstrøm, Eline Bruun Ofei and Brith Klarborg.

External collaborators

National collaborators include:

- Professor Peter Udall, Senior Consultant, PhD Peter Born, and PhD student Sara Krøis, Pediatric Clinic, Copenhagen University Hospital Rigshospitalet, Denmark
- Professor Gitte Moos Knudsen, Center for Integrated Molecular Brain Imaging (CIMBI), and Neurobiology Research Unit (NRU), Copenhagen University Hospital Rigshospitalet, Denmark
- Professor Lars Kai Hansen and Professor Rasmus Larsen, Informatics and Mathematical Modeling, the Technical University of Denmark, Denmark
- Associate Professor Erik Lykke Mortensen, Department of Public Health, University of Copenhagen, Denmark
- Associate Professor Christian Gerlach, PhD Lisser Rye Ejersbo and Associate Professor Bo Steffensen, Danish School of Education, Aarhus University, Denmark
- Senior Consultant, PhD Katrine Pagsberg, Department of Child and Adolescent Psychiatry, Copenhagen University Hospital Bispebjerg, Denmark
- MSc psych., Thomas Sørensen and Professor Claus Bundesen, Center for Visual Cognition, University of Copenhagen, Denmark.

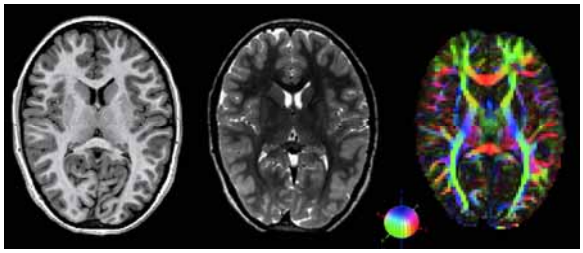
International collaborators include:

- PhD Cinnamon S. Bloss, Neuropsychology & Clinical Genomics, Scripps Genomic Medicine & Scripps Translational Science Institute (STSI), Scripps Health & The Scripps Research Institute, La Jolla, California, USA
- Professor Anders Dale, Multimodal Imaging Laboratory, the Departments of Neurosciences and Radiology, University of California, San Diego, USA
- Dr Alexander Leemans, Image Sciences Institute, University Medical Center Utrecht, The Netherlands.

Research Group Leader: William Baaré

Research methods

Generally, high-resolution 3D T1-weighted and T2-weighted whole brain scans are used to measure brain structure volume, cortical thickness and brain surface area. Diffusion-weighted imaging (DWI) is used to investigate brain tissue microstructure and the structural connections between brain regions (i.e. fiber tracts) (see figure below). Functional MRI is used to measure participants' brain activity while at rest or during the performance of specific tasks.

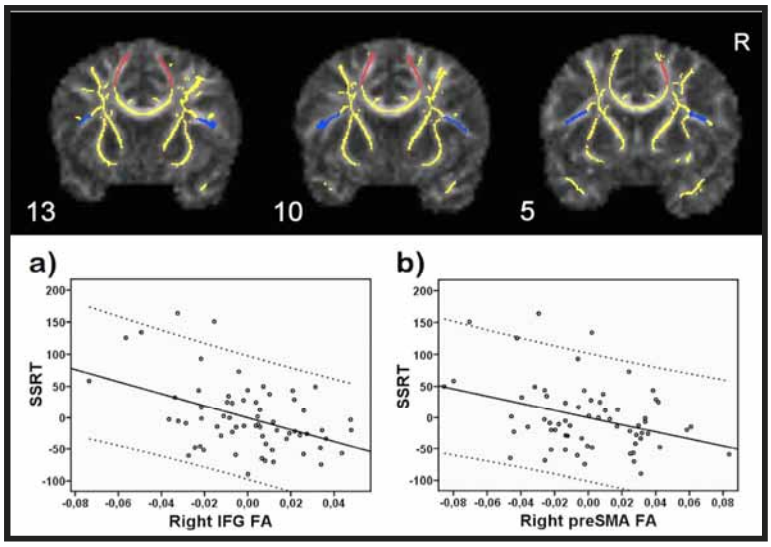


The structural MR protocol includes high-resolution 3D T1-weighted (left) and T2-weighted (middle) scan. Diffusion-weighted imaging allows investigating the microstructure of white and grey matter. At the right side of the figure a color-coded fractional anisotropy image (a measure of the directional diffusivity of water) is depicted. Diffusion directions: Green: anterior-posterior; Blue: inferior-superior; Red: left-right.

Research projects

HUBU ('Hjernens Udvikling hos Børn og Unge'/ Brain maturation in children and adolescents)

The major aims of the project are to define the degree of variability in the maturational trajectories observed for individual children, and to link these to evolving cognitive abilities and social-emotional behaviour. Additionally, the work addresses critical questions regarding the factors that place young people at risk for developing emotional problems and substance abuse, as well as related questions regarding the consequences of early stress and exposure to alcohol and drugs on continuing biological development of the brain.

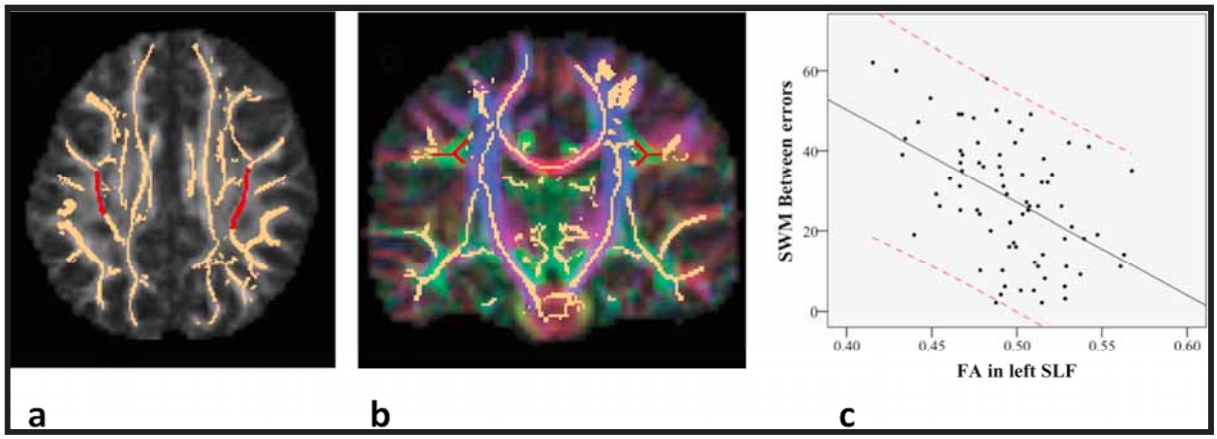


As hypothesised, faster response inhibition was significantly associated with higher fractional anisotropy (FA) and lower perpendicular diffusivity in both the right inferior frontal gyrus, pars opercularis (IFG) and the right presupplementary motor area (preSMA), possibly reflecting faster speed of neural conduction within more densely packed or better myelinated fibre tracts. Moreover, both of these effects remained significant after controlling for age and whole brain estimates of these DTI parameters. Interestingly, right IFG and preSMA FA contributed additively to the prediction of performance variability. Top: Coronal slices of the mean TBSS skeleton (yellow) are overlaid on the target FA image. The blue segments are the IFG ROIs and the red segments are the preSMA ROIs. Bottom: Partial regression plots of the stop-signal reaction time (SSRT) as a function of a) right IFG FA, adjusted for age and b) right preSMA FA, adjusted for age.

The HUBU project was initiated by Terry L. Jernigan in 2007. PhD student Kathrine Skak Madsen is the project coordinator for the HUBU project. Ninety-four typically-developing children, aged 7 to 13 years, and their families were recruited to a longitudinal study of brain and behavioural development. Longitudinal assessments are conducted at six month intervals and for, respectively, the second and third longitudinal assessments, 92 and 89 of these children were retained. Since then, a stable number of around 75 participants have been retained for the later assessments (fourth to seventh). At the end of 2010, the children's ages and genders were distributed as follows: 11/12 years: 16 girls, 11 boys; 13/14 years: 17 girls, 9 boys; 15/16 years: 13 girls, 8 boys. Julie Hagstrøm is currently responsible for the booking and testing of participants. This task has been performed earlier by respectively Martin Vestergaard and Vibe Nordahn Bredsdorff. Sussi Larsen is the MR-technician performing all MRI scans.

Besides MR scanning, the research protocol includes neuropsychological tests, questionnaires assessing among other things personality traits, stressful life events, and alcohol use (from age 12), and collection of saliva samples (measurement of stress markers, sex hormones and genetic polymorphisms).

Many resources went towards the assessment of the participants' data in 2009 and 2010. The seventh assessment was completed in November 2010.



Independent of age higher FA in the left superior longitudinal fasciculus (SLF) was associated with better spatial working memory (SWM) performance e.g. less between errors (c). The red dotted lines correspond to the 95% confidence interval for the individual data points. The association remained significant when global FA or right SLF FA were included in the model. (a) and (b) depict the SLF in red overlaid on the mean TBSS skeleton (yellow) on respectively an axial and coronal slice. The coronal slice is color-coded with fractional anisotropy values representing diffusion directionality: Green: anterior-posterior; Blue: inferior-superior; Red: left-right. The images are displayed according to neurological convention (left is left).

The eighth assessment started shortly thereafter and will be finished in June 2011.

Analyses of the baseline DWI data confirmed our a priori hypotheses that indices of fiber tract microstructure known to show age-related alterations during childhood and adolescence would significantly predict individual performance differences on behavioural control (1) (see top figure on the previous page), working memory (2) (see bottom figure on the previous page) and visuospatial 5-choice reaction time (3) (see figure to the right), and that these associations would remain after controlling for age. Observed associations may be related to variation in phase of maturation, to activity-dependent alterations in the networks subserving response inhibition, spatial working memory, or 5-choice reaction time, or to stable individual differences in underlying neural system connectivity.

Master's student Brith Klarborg sucessfully defended here master's thesis on October 15th 2010. In her thesis she investigated the relationship between sustained attention and white matter microstructure using a rapid visual information processing paradigm. The two behavioural measures of interest were the sensitivity index d' and the coefficient of variance in reaction times (RT_{CV}). Independently of age and gender FA of the right superior longitudinal fasciculus (SLF) and the superior part of the right PC were significantly associated with d', while RT_{CV} was significantly associated with right superior PC FA, but not with right SLF FA. Master's student Eline Bruun Ofei investigates the microstructural underpinnings of planning abilities as assessed with the Stockings of Cambridge task. The master's students are supervised by Kathrine Skak Madsen and Wiliam Baaré.

An emotional face recognition task was developed and implemented in the seventh assessment. Procedures for taking saliva samples were implemented in the sixth assessment. Also starting from the sixth assessment functional MRI was included focusing on resting state fMRI to map functionally connected brain networks.

To assess stressful life events on a lifetime basis, questionnaires were developed/adapted and implemented. Additional questionnaires assess physical activity and sleep for the last 12 months.

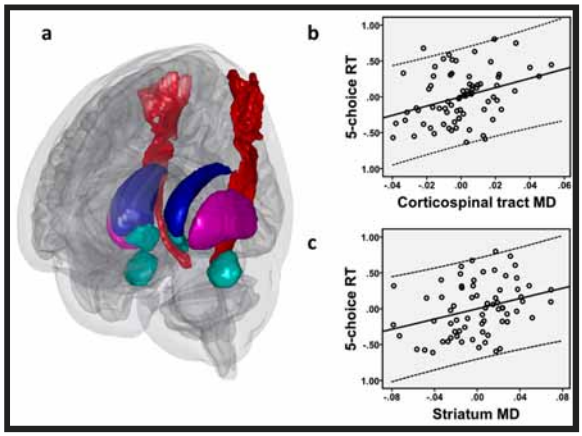
Processing pipelines have been developed for examining brain maturational changes in brain structure volume using a tensor based morphometry approach. Additionally, a DWI pipeline for extracting microstructural information from grey matter structures was developed.

Collaboration has been established with the Multimodal Imaging Laboratory (MIL), the Departments of Neurosciences and Radiology, University of California, San Diego, USA (Professor Anders Dale) to measure cortical thickness and cortical surface area in all acquired structural scans. Structural MR scans up to the sixth assessment have been transferred to the MIL for processing.

Collaboration was established with Dr Alexander Leemans, University Medical Center Utrecht with respect to longitudinal analyses of white matter fiber tracts using tractography.

In 2009, funding was obtained from the Lundbeck Foundation (2 mill. DDK, grant to Terry L. Jernigan). A collaborative PhD grant (1.5 mill. DDK) was obtained from the Danish Agency for Science, Technology and Innovation and the Faculty of Health Sciences of the University of Copenhagen.

Brain maturational effects of glucocorticoids
The focus of this project is on the relationship between the human stress hormone cortisol (glucocorticoid) and brain maturation in school-aged children between 7 and 14 years.



As predicted, faster 5-choice reaction times (RT) were associated with lower mean diffusivity (MD) in the corticospinal tracts, putamen, and caudate. MD effects on RT were bilateral in the corticospinal tracts and putamen, while right caudate MD was more strongly related to performance than was left caudate MD. (a) 3D illustrations of regions-of-interest in the corticospinal tracts (red), and neostriatum (putamen (magenta), and caudate nucleus (dark blue)). Partial regression plots of visuospatial 5-choice RT as a function of (b) corticospinal tract MD or (c) striatum MD, adjusted for age, gender and handedness. Dotted lines correspond to the 95% confidence interval.

Specifically, the project will examine potential long-term effects of glucocorticoid treatment in early life on brain development and associations between cortisol secretion in typically-developing children and brain structure and function measured with MRI. The project is carried out in close collaboration with the Pediatric Clinic at Copenhagen University Hospital Rigshospitalet, and is locally headed by PhD student Martin Vestergaard.

To examine the long-term effects of glucocorticoids two clinical groups including 30 subjects diagnosed with rheumatic or nephritic disorder are enrolled in the study alongside a control group of 40 children matched on gender and age. The two clinical groups have been treated with high doses of exogenous glucocorticoid (prednisone) in preschool years. All participants undergo structural MRI and DWI. Furthermore, two fMRI paradigms designed to engage brain regions enriched with glucocorticoid receptors have been developed and implemented. On a separate day before scanning, all children undergo clinical and psychological evaluations including assessment of cognitive and emotional information processing (please see the figure below for example). Salivary cortisol samples are collected during scanning to study state-like changes in cortisol levels in connection with the fMRI paradigms, as well as at home on two consecutive normal weekdays to study trait-like differences in circadian cortisol patterns.

A follow-up assessment is planned one year after the baseline assessment to explore for variability in individual developmental trajectories, glucocorticoid treatment and cortisol response.

Achievements in 2009 and 2010
Work in 2009 and 2010 focused on designing, planning and organising the project. Two new and original fMRI paradigms were developed to match the children's capabilities. The paradigms were designed to engage frontolimbic brain regions thought to be implicated in the regulation of cortisol secretion. Further, a behavioural '*emotional face recognition task*' was developed to examine participants baseline emotional information processing.

A pilot project was completed in the fall of 2010 and the recruitment of patients and the control group was initiated. The baseline assessment of subjects started in the winter 2010 and is expected to be completed in the fall of 2011.

Funding was obtained from the Danish Medical Research Council (2.1 mill. DDK, grant to Peter Uldall).

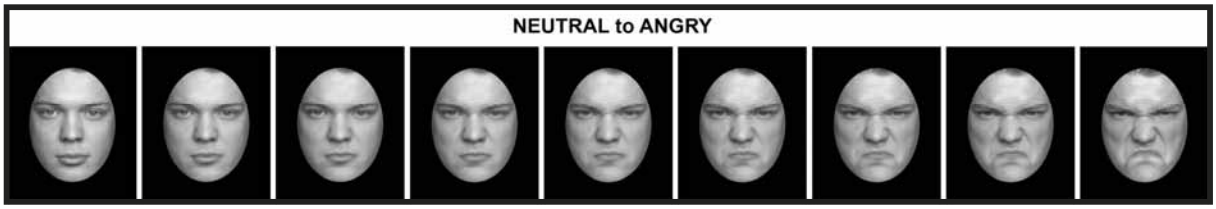
Selected publications

Madsen KS; Baare WF; Vestergaard M; Skimminge A; Ejersbo LR; Ramsoy TZ; Gerlach C; Akeson P; Paulson OB; Jernigan TL: Response inhibition is associated with white matter microstructure in children. *Neuropsychologia*. 2010;48(4):854-62.

Vestergaard M; Madsen KS; Baare WF; Skimminge A; Ejersbo LR; Ramsoy TZ; Gerlach C; Akeson P; Paulson OB; Jernigan TL: White Matter Microstructure in Superior Longitudinal Fasciculus Associated with Spatial Working Memory Performance in Children. *J Cogn Neurosci*. 2010, e-pub ahead of print.

Madsen KS; Baare WF; Skimminge A; Vestergaard M; Siebner, HR; Jernigan TL: Brain microstructural correlates of visuospatial choice reaction time in children. Submitted.

Damsted SK, Born AP, Paulson OB, Uldall P. Exogenous glucocorticoids and adverse cerebral effects in children. Eur J Paediatr Neurol. Submitted



Example display of a morphed sequence between a neutral and angry face. In the 'emotional face recognition task' the participant is instructed to decide whether different graduated facial expressions belongs to one of the six following categories; angry, fearful, happy, sad, disgusted or neutral.

Decision Neuroscience

The Decision Neuroscience Research Group (DNRG) is a recently established research group that employs a multidisciplinary study of value-based decision making. By value-based decisions the group refers to decisions that are taken on the basis of either emotional information or a valuation of different options, and that this process can take place both overtly and covertly. The DNRG, working through combining economic, psychological and cognitive neuroscience models of decision making, was formed in 2008 at the initiative of late Professor Flemming Hansen (Copenhagen Business School, CBS), Professor Olaf B. Paulson and Thomas Z. Ramsøy.

The group consists of researchers with diverse backgrounds, including economics, marketing, psychology, biology, engineering and linguistics. Consequently, the projects run in this group employ a multi-faceted approach by both studying many aspects of behavioural and neurobiological features of decision behaviours in a variety of contexts.

After co-heading the group with Thomas Z. Ramsøy Professor Flemming Hansen unfortunately and unexpectedly passed away in 2010. His contribution within behavioural economics, consumer behaviour and marketing theory was a large part of the initial DNRG structure, and his scholarly and personal contributions still influence the group today.

DRCMR members

Thomas Z. Ramsøy (group leader, DRCMR and CBS), Hartwig R. Siebner (group leader), Olaf B. Paulson, Susanne Henningsson, Julian Macoveanu, Martin Skov, Morten Friis-Olivarius, Sofie V. Gelskov, David Meder, Helle R. Laursen and Kristoffer H. Madsen.

External members

Assistant Professor Jesper Clement, Associate Professor Bo Christensen, Professor Tore Kristensen, Professor Judith Zaichkowsky and Professor Torsten Ringberg (Department of Marketing, Copenhagen Business School), Post.doc. Daniel Barratt (Department of International Culture and Communication Studies, Copenhagen Business School) and Junior Research Fellow Jon O. Lauring.

External collaborators

- Professor Antoine Bechara, University of Southern California, USA
- Assistant Professor Hilke Plassmann, INSEAD, France
- Professor Baba Shiv, Stanford Graduate School of Business, USA
- Senior Fellow Bernard J. Baars, Neuroscience Institute, USA
- Dr Oshin Vartanian, University of York, Canada
- Associate Professor Anjan Chaterjee, University of Pennsylvania, USA
- Professor Helmut Leder, University of Vienna, Austria
- Associate Professor Marcos Nadal, University of the Balearic Islands, Spain
- Senior Researcher Sid Kouider, Ecole Normale Supèrieure, France
- Associate Professor Michael Bang Pedersen, Aarhus University, Denmark
- Professor Lars Kai Hansen, Department of Informatics and Mathematical Modelling, Technical University of Denmark, Denmark
- Associate Professor Per Møller, LIFE, University of Copenhagen, Denmark
- Associate Professor Morten Overgaard, Hammel Neurocenter, Denmark
- PhD student Toke Fosgaard, LIFE, University of Copenhagen, Denmark

Research Group Leader: Thomas Z. Ramsøy

Research Group Leader: Hartwig R. Siebner

Research content

The DNRG works on triangulating three disciplines in the study of value-based decisions; psychology, economics and cognitive neuroscience. Through this, projects seek first to establish a basic understanding of the behavioural phenomenon at stake through experimental procedures, and to attempt a formalised model of such behaviours. The crucial step is to employ a neurobiological account of the behaviour, and through this to determine the causal mechanisms.

The DNRG also orients its work through the decision hierarchy; the representation of needs, valuation of options, action selection, outcome evaluation, and the effects of learning throughout these steps. Thus, projects are oriented towards different aspects of the decision making procedure.

Four basic research themes are part of DNRG's portfolio:
Expectation bias and framing effects: How can information change our expectation and evaluation of an outcome, what are the mechanisms underlying branding effects, and to what extent can we use this knowledge to improve our decisions.

Disorders of decision making: A major project concerns the neurobiological mechanisms in pathologi-

cal gambling, but related topics are also studied, including the mechanisms in other impulse control disorders or behavioural addictions such as 'shopaholism', and unhealthy behaviours such as smoking and obesity.

Aesthetics and liking: Projects in this category seek to study the neural mechanisms of aesthetics, also referred to as 'neuroaesthetics', but in particular to expand this knowledge into the effects of these processes on the decision making process. The role of different motivational systems not necessarily reflected in overt liking responses are also key in these projects.

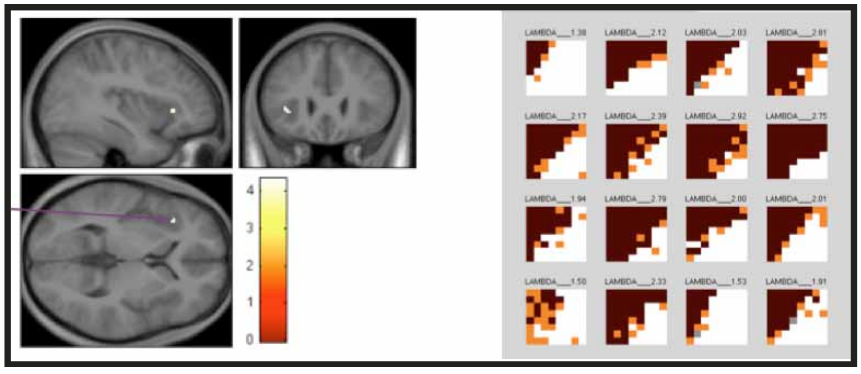
Consciousness vs. unconsciousness: As opposed to personal belief, folk psychology and even formalised models in economics and psychology, many decisions have significant components that occur under the limen of our awareness. To what extent do such processes shape and influence our behaviour, and at what stages do they occur and can they be induced?

Research projects

The group runs a large project on the neural mechanisms in pathological gambling funded by The Danish Agency for Science, Technology and Innovation. This project is headed by Thomas Z. Ramsøy and includes Sofie V. Gelskov, Hartwig R. Siebner, Susanne Henningsson, Julian Macoveanu and Kristoffer H. Madsen. The project seeks to improve our understanding of the role of loss aversion (or lack thereof) in pathological gambling. Most research on this condition has focused on the role of risk taking and reward seeking. While it follows naturally from this that subjects should also display reduced risk- and loss-aversion, few studies have explored this. To date no studies have focused on this explicitly with neuroimaging measures such as fMRI. In 2010, the group presented their first fMRI results at the Annual Meeting for the Society for Neuroscience, providing evidence that reject beliefs that aversion areas of the brain are not involved in gambling behaviours and loss aversion.
As part of the gambling project, Thomas Z. Ramsøy and Martin Skov published a key article on the neurophysiology and genetic mechanisms that may be involved in value-based decisions. Here, by first describing the core components of the decision making apparatus, Ramsøy and Skov reviewed the evidence from pathological states, psychopharmacological interventions, and genetic differences, and provide a novel view that seeks to explain and understand individual differences in decision behaviours as the function of specific biological processes.

In 2010, Helle R. Laursen joined the team as a PhD student to run examine the role of recreational drug use that affects serotonin levels (ecstasy and hallucinogens) and related behaviours. The project is carried out under the auspices of the Center for Integrated Molecular Brain Imaging (CIMBI). In particular, the project employs fMRI to study the effects of these recreational drugs on changes in brain activation related to emotional responses and behaviour. The project will make a substantial contribution to a better understanding of the neural mechanisms underlying emotions and their impact on risky behaviours.

A second main project is on the neural bases of consumer decisions, referred to as consumer neuroscience, and more popularly going under the heading 'neuromarketing'. Here, several different approaches are taken. In one study, Ramsøy and Skov found that complex emotional responses, as those found to acquired cultural objects such as brands, can operate under the limen of awareness, informing a long lasting controversy about the level of complexity that unconscious emotions can have. This study was presented at the 2010 NeuroPsychoEconomics/ConNEcs conference and received



Conjoint activation of the anterior insula during a gambling task. Left: Conjunction analysis for increasing activation to potential gains and decreasing activation to potential loss. Yields activity in left anterior insula. Uncorrected threshold at p>0.001. Right: Individual acceptance data and λ (lambda), an individual measure of loss aversiveness.

awards for both Best Session Paper and Best Conference Paper.

The DNRG has also a strong interest in the neurobiology of preference formation, and how pleasure expectation and experience can be influenced by relatively simple semantic manipulations. Earlier, the group has published studies that have demonstrated how semantic context and expertise separately influence the perceptual processing and preference formation of culture-specific items such as abstract art and architecture. In 2010, this work has focused on understanding the specific neural mechanisms at stake, but also on demonstrating the effects across domains such as fashion.

Research methods

- functional Magnetic Resonance Imaging (fMRI)
- Eye-tracking and pupil dilation
- Physiology, including skin conductance, respiration and pulse
- Behavioural assessment, including intelligence and personality assessment
- Experimental behavioural research, including response latencies
- Manipulation of behavioural antecedents through framing and anchoring effects

Research activities

In 2010 the DNRG hosted two major events. On May 31-June 1, the DNRG planned and hosted the international annual Conference on Neuroeconomics (ConNEcs) in Copenhagen, supported by The Danish Agency for Science, Technology and Innovation and Copenhagen Business School. This year, the conference was joined together with the annual NeuroPsychoEconomics conference, under the heading 'What Economics, Management, Marketing, and Finance Can Learn from Cognitive Neuroscience and Psychophysiology'. The conference was successfully completed with several attendants from an international audience.

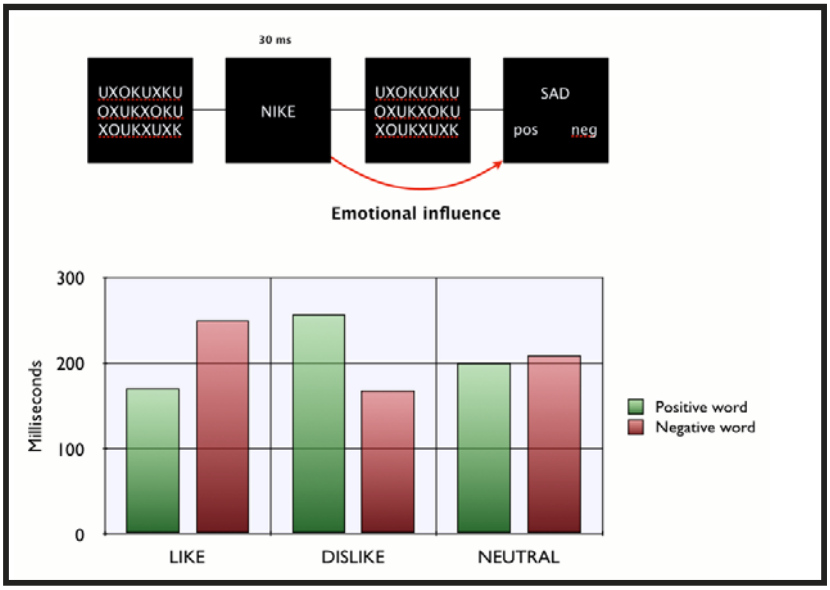
In mid-August 2010, DNRG also hosted a symposium on 'The neural bases of value-based decision making in social contexts' at the bi-annual Nordic Meeting in Neuropsychology in Aalborg, Denmark. Here, Ramsøy, Skov, Siebner, Gelskov and Henningsson presented different aspects on decision making in social contexts to an international audience of neuropsychologists and scholars in cognitive neuroscience.

Selected publications

Ramsøy TZ; Skov M: How genes make up your mind: Individual biological differences and value-based decisions. *Journal of Economic Psychology*. 2010;31:818-831.

Gelskov SV; Madsen KH; Skimminge A; Henningsson S; Siebner HR; Ramsøy TZ: Anterior insula evaluates magnitudes of potential losses. *Society for Neuroscience*, San Diego, USA, 2010.

Ramsøy TZ; Skov M: The Insentience of Brand Equity: Two Studies Of Consciousness And Brands. *NeuroPsychoEconomics/ConNEcs. Proceedings*, 2010, Best Session Paper Award and Best Conference Paper Award.



The effect of subliminally caused complex emotions on task performance on a word valence task. Top: Schematic of assumed effect of complex emotion (brand name presented for 30 milliseconds) on a subsequent task of classifying emotion words. Bottom: Individual level of preference for brand (x-axis) was associated with significant changes in response latencies for positive and negative words.

Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease leading to widespread and diffuse damage of the neural tissue of the brain and spinal cord. MS is the leading cause of nontraumatic neurological disability among young adults. In the last decades, MRI has firmly established itself as an essential technique in the diagnosis, management and research of MS. The implementation of MR-based criteria allow for earlier and more accurate diagnosis of MS.

In clinical practice, proton density, T1/T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences and the contrast agent gadolinium (Gd)-DTPA are routinely used to detect active lesions and assess treatment efficacy. Especially contrast-enhanced MRI has been shown to be very sensitive in detecting acute, new lesions. MRI can also be used to make predictions about the clinical prognosis in patients with clinically isolated syndrome.

In addition, MRI measures of disease related changes in brain and spinal cord have become key supportive outcome measures to test the efficacy of experimental treatments in randomized, controlled trials.

DRCMR members

The Multiple Sclerosis Research group at DRCMR includes: Hartwig R. Siebner (group leader), Olaf B. Paulson, Ellen Garde, Tim B. Dyrby, Xingchen Wu, Kristoffer H. Madsen, Henrik Lund, Anne-Marie Dogonowski and Mark Lyksborg.

External collaborators

Professor Per Soelberg Sørensen, Dr Morten Blinkenberg, Associate Professor Finn Sellebjerg, Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital Rigshospitalet, Denmark

Associate Professor Bharat Biswal, Department of Radiology, University of Medicine and Dentistry of New Jersey, USA

Professor Lars Kai Hansen, PhD student Peter M. Rasmussen, Cognitive systems, Department of Informatics and Mathematical Modelling, Technical University of Denmark, Denmark

Professor Rasmus Larsen, Medical Image Analysis, Department of Informatics and Mathematical Modelling, Technical University of Denmark, Denmark

Associate Professor Torben E. Lund, Center of Functionally Integrative Neuroscience, Aarhus University

Research activities

At DRCMR, repeated MRI of the brain are performed in clinical trials to monitor the therapeutic efficacy of new immunomodulatory agents in close collaboration with the Danish Multiple Sclerosis Center at the Department of Neurology at Rigshospitalet. The use of MRI in therapeutical MS trials constitutes the core activity of the *Reader Centre* at DRCMR (see section on the *Reader Centre* for further details).

Research Group Leader: Hartwig R. Siebner

From a research perspective, advanced quantitative measures derived from proton MR spectroscopy, diffusion MRI, magnetization transfer imaging (MTI), and functional MRI (fMRI) have shed important light into the pathophysiological mechanisms causing brain injury, repair and functional adaptation in patients affected by MS. The Multiple Sclerosis Research group at DRCMR uses these advanced MRI techniques to reveal how multiple sclerosis affects the structural and functional integrity of the brain. This includes the development of innovative data analytic methods and the refinement of MR protocols. For instance, quantitative T1-measurements have been performed to map disease-related tissue changes in the so-called 'normal appearing white matter' (Henrik Lund, Arnold Skimminge and Associate Professor Lars G. Hanson). Another project focussed on the use of Proton-MR-Spectrocopy to characterize disease related tissue damage (Xingchen Wu and Associate Professor Lars G. Hanson). The research involves a long-standing collaboration with the Danish Multiple Sclerosis Center and the Department of Informatics and Mathematical Modelling (IMM) at the Technical University of Denmark.

One line of research is concerned with the *integration of several MRI modalities* and the use of trained neural networks for optimized classification and segmentation of brain tissue in MS (e.g. brain white matter, brain grey matter and MS lesions). This is a 'continuation' of the artificial neural network approach that was developed at the DRCMR by Tim Dyrby and colleagues for multi-centre studies of white matter lesions in conjunction with the LADIS study group. Furthermore, clinical and neuropsychological measures are related to the disease-related tissue changes to clarify which MRI findings reflect best disease severity. This project is supported by the Danish Multiple Sclerosis Society (Grant to Olaf B. Paulson).

MS leads to widespread and diffuse damage of white matter tissue of the brain and spinal cord. This impairs functional integration within and between brain networks which might underlie the various clinically neurological symptoms. Therefore, a major aim of the ongoing research is to

characterize how MS affects functional and structural brain connectivity.

Here *diffusion MRI* of the brain is used in MS patients to identify regional changes in structural brain connectivity in the major fibre tracts and link this to specific functional impairments (PhD project by Mark Lyksborg supervised by Post.doc Tim B. Dyrby, Professor Hartwig R. Siebner and Professor Rasmus Larsen (IMM). This project is supported by the Danish Multiple Sclerosis Society (Grant to Tim B. Dyrby) and the Danish Council for Strategic Research (awarded to Finn Sellebjerg).

Another line of research uses *resting-state functional MRI to identify MS-related changes in functional connectivity* in distinct brain networks and to link these changes to functional impairment. In recent years, resting-state functional magnetic resonance imaging (rs-fMRI) has emerged as a powerful method to study functional connectivity in the human brain. rs-fMRI measures spontaneously occurring, slow-frequency (< 0.1Hz) fluctuations in the blood oxygen level dependent (BOLD) signal in awake subjects who are lying in the MRI scanner without performing a task ('resting state'). It has been shown that the correlating BOLD signal oscillations at rest reflect concurrent changes in regional neuronal activity within connected brain areas. Anne-Marie Dogonowski conducted a first rs-fMRI study, which focused on resting-state connectivity in the sensori-motor resting-state network in 42 clinically stable patients with relapsing-remitting or secondary progressive MS and 30 age- and sex-matched controls (PhD project supervised by Post.doc Kristoffer H. Madsen, Professor Olaf B. Paulson and Professor Hartwig R. Siebner). Subcortical nuclei, namely the middle putamen and adjacent globus pallidum, thalamus and nucleus subthalamicus, were more strongly integrated into the sensori-motor resting-state network in MS relative to controls.

These results suggest an impaired capacity to funnel neural processing in the cortico-basal ganglia-thalamo-cortical loops in MS. The data were presented at the 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis in Gothenburg, Sweden (October 13–16th 2010). This project is supported by the Danish Multiple Sclerosis Society (Grant to Hartwig R. Siebner).

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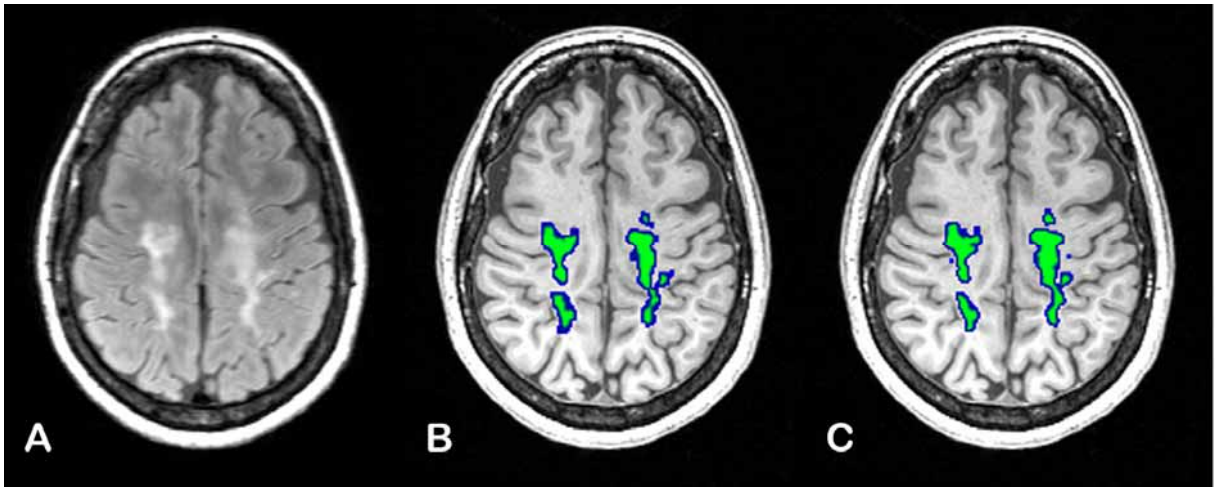
Sorensen PS; Mellgren SI; Svenningsson A; Elovaara I; Frederiksen JL; Beiske AG; Myhr KM; Sogaard LV; Olsen IC; Sandberg-Wollheim M: NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): a randomised, placebo-controlled trial. *Lancet Neurol*. 2009;8 (6):519-529.

Ravnborg M; Sorensen PS; Andersson M; Celius EG; Jongen PJ; Elovaara I; Bartholome E; Constantinescu CS; Beer K; Garde E; Sperling B: Methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN study): a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial. *Lancet Neurol*. 2010;9(7):672-680.



A) Axial FLAIR image with bright areas indicating tissue damage of white matter (lesions). B) Axial slice from a T1-weighted image with the white matter lesion (green) positioned on top of the image. The lesion was delineated manually by a trained radiographer. C) Same as B), but where the lesion was delineated by an automated segmentation method developed at the department.

Multisensory Integration & Cross-modal Plasticity in Sensory Systems

The DRCMR has a strong tradition for investigating the plasticity of the visual system.

DRCMR members

The Sensory Systems Research group at DRCMR includes: Maurice Ptito (DRCMR/Université de Montréal), Hartwig R. Siebner and Olaf B. Paulson (group leaders), Tim B. Dyrby, Louise B. Johansen, Astrid R. Lou, Kristoffer H. Madsen, Nina L. Reislev and Tanja Kassuba.

External collaborators

- Associate Professor Ron Kupers, Professor Albert Gjedde, Institute of Neuroscience and Pharmacology, Panum Institute, University of Copenhagen, Denmark
- Professor Troels Kjær, Department of Neurophysiology, Copenhagen University Hospital Rigshospitalet, Denmark
- Professor Brigitte Röder, Department of Psychology, University of Hamburg, Germany
- Dr Marc Tittgemeyer, Max Planck Institute for Neurological Research, Cologne, Germany.

Research activities

Plasticity in the visual cortex

A PhD project has been conducted by Astrid R. Lou and involved two experiments designed in order to investigate how the brain reacts to acute changes in visual input. The first experiment used monocular visual deprivation as an intervention to induce plasticity in the adult visual cortex. Adopting a multimodal approach, short-term reorganisation within the visual system was examined with transcranial magnetic stimulation (TMS) as well as structural and functional MRI. TMS was applied over the occipital cortex to elicit phosphenes. The sequential TMS measurements revealed a decrease in visual cortex excitability during monocular deprivation (MD) which was rapidly reversible when the eye patch was taken off after two days (Lou et al., in press). The functional MRI part of that study revealed that MD induced an increase in the BOLD response of several higher order visual regions to checkerboard stimulation including the dorsal visuospatial network.

In a second study, Astrid R. Lou used structural and functional MRI to prospectively assess the plasticity in elderly adults who undergo cataract surgery. The fMRI part of this project was analysed by two DTU students in a Masters project (Louise B. Johansen and Nina L. Reislev). These experiments yielded converging evidence that the visual system maintains its potential for anatomical and functional adaptability throughout the entire human adult life-span.

Object recognition within and across sensory modalities

The focus of a second PhD-project is to map structural and functional connectivity in brain systems contributing to higher order perception such as object recognition within and across sensory modalities (visual, auditory, and tactile modality). This PhD project is pursued by Tanja Kassuba, a PhD student at the University of Hamburg, Germany. The project involves mainly functional MRI (fMRI) and TMS but also diffusion tensor imaging (DTI). In a first fMRI study, she showed that visual, auditory, and haptic processing of manipulable objects converges in the left fusiform gyrus, a brain area known to be involved in storing conceptual object knowledge (Kassuba et al., in press). In a second fMRI study, she showed that a region in the left posterior superior temporal gyrus is relevant for both, auditory and haptic object recognition but shows a clear preference for auditory input when it comes to more complex processes (Kassuba et al., submitted).

Research Group Leader: Maurice Ptito

Research Group Leader: Hartwig R. Siebner

Research Group Leader: Olaf B. Paulson

Another part of her project entails the shaping of neuronal activity with TMS and then measuring the compensatory functional reorganization with fMRI. In a combined rTMS-fMRI study, she first stimulated the left lateral occipital complex, a region that is known for integrating visual and haptic object information, and then mapped the functional effects on visuo-haptic object recognition with fMRI. The results showed that visual and haptic processes are differently affected by the TMS stimulation, indicating that vision and touch entail different shares in the multisensory integration process. In addition, she also collected DTI data in order to describe anatomical connections between relevant multisensory brain areas. In a collaboration with Marc Tittgemeyer from the Max Planck Institute in Cologne, she works on a parcellation of the fusiform gyrus by clustering the anatomical connections (measured with DTI) from this region to other brain regions.

Plasticity in the blind

Visiting Professor Maurice Ptito is heading a research program on congenital blindness supported

by the Danish Medical Research Council and the Harland Sanders Foundation in Canada. The research involves functional investigations of plasticity in congenital blindness using several different types of sensory stimulation including stimulation of the tongue by the so-called tongue display unit. The tongue display unit is able to project 'images' on the tongue by pulsed electrical stimulation thereby enabling the possibility of delivering tactile information about visual scenes to blind subjects (see figure below, left side).

In the past year, the group has been involved in a series of experiments investigating sensory substitution and cross-modal plasticity in the visually deprived brain through other senses such as touch and olfaction.

In the tactile experiments, we have mapped brain activity while the tongue display unit converted visual stimuli into electro-tactile pulses and applied these 'images' to the tongue via a grid made out of 144 electrodes. Our previous results showed that following a one-week training with the TDU, congenitally blind (but not sighted control) subjects activate their visual cortex when solving an orientation discrimination task using the TDU. This prompted a series of brain imaging studies investigating the integrity of the two visual streams, the so-called 'ventral' (the WHAT pathway dealing with object recognition, faces and colour) and 'dorsal' (the WHERE pathway dealing with motion, navigation…) stream, in congenitally blind subjects.

In a motion paradigm whereby participants were asked to discriminate the direction of moving dots using the TDU, congenitally blind subjects showed a strong bilateral activation of the visual motion area hMT+ and of the occipital cortex. In contrast, blindfolded sighted controls showed only a small activation of left hMT+ and no activation of their occipital cortex (Ptito et al., 2009; Matteau et al, 2010). In a shape detection paradigm whereby subjects were asked to discriminate between various geometric shapes presented through the TDU, blind subjects strongly recruited the inferotemporal cortex and more widespread areas within the ventral visual stream (Matteau et al., submitted). In contrast, blindfolded counterparts only activated the inferotemporal cortex. Together, these studies indicate that both 'visual' streams are still functional in the congenitally blind.

The group also investigated the navigational skills of blind and blindfolded individuals in a life-size obstacle course and in a virtual navigation task during an fMRI experiment. Data show that blind subjects outperform their blindfolded seeing counterparts in the detection and avoidance of obstacles (Chebat et al., in press). In the virtual navigation task, blind subjects activated brain regions that are normally recruited when sighted individuals perform a visual navigation task, namely the right parahippocampus and the visual cortex (Kupers et al., 2010) (see figure below, right side). Blindfolded sighted controls did not activate these brain areas but recruited more frontal regions. Interestingly, when tested in a tactile finger maze where allocentric navigational cues were strongly reduced, blind subjects performed worse that the blindfolded seeing controls (Gagnon et al., 2010).

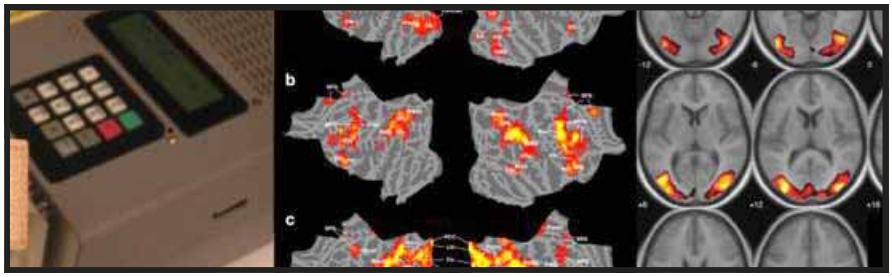
In the past year, the group has also tested the sense of smell in the absence of vision. Behaviourally, we measured odour detection threshold, odour discrimination and odour identification. In addition, we used the Odour Awareness Scale (OAS) to assess consciousness of olfactory sensations. We showed that blind subjects had a lower odour detection threshold compared to the sighted. Interestingly, the OAS revealed that blind participants scored higher for odour awareness. The largest group differences were found for items of the OAS that measure responses to body odours and fragrances (Beaulieu-Lefebvre et al., 2010).

Selected publications

Gagnon L; Kupers R; Schneider FC; Ptito M: Tactile maze solving in congenitally blind individuals. Neuroreport. 2010;21(15):989-92.

Kupers R; Chebat DR; Madsen KH; Paulson OB; Ptito M: Neural correlates of virtual route recognition in congenital blindness. *Proc Natl Acad Sci U S A*. 2010;107(28):12716-21.

Ptito M; Matteau I; Gjedde A; Kupers R: Recruitment of the middle temporal area by tactile motion in congenital blindness. *Neuroreport*. 2009; 20 (6):543-7.



Left: Tongue Display Unit. Right: Brain activation in blind subjects in virtual navigation task.

Sensorimotor Integration in Health & Disease

The Sensorimotor Integration research group at DRCMR has expertise within the fields of basic motor control, sensation, perception, motor learning and plasticity, sensorimotor integration, cognitive motor control, rehabilitation, and movement disorders.

DRCMR members

The motor control group includes: Mark Schram Christensen (group leader, DRCMR/University of Copenhagen), Hartwig R. Siebner (group leader), Olaf B. Paulson, Anne-Marie Dogonowski, Henrik Lundell, Daniela Balslev and Damian Herz.

External members

External members are: Professor Jens Bo Nielsen, Post.doc. Jesper Lundbye-Jensen, Visiting Researcher Michael J. Grey, PhD student Tue Hvass Petersen and PhD student Anina Rosenbaum (Copenhagen Neural Control of Movement group, Department of Exercise and Sport Science, University of Copenhagen).

External collaborators

Furthermore the group collaborates with:

- Abraham T Zuur and Thomas Sinkjær, Center for Sensory-Motor interaction, University of Aalborg, Denmark
- Henrik Ehrsson, Department of Neuroscience, Brain, Body and Self Laboratory, Karolinska Institutet, Stockholm, Sweden
- Emma Gowen, Faculty of Life Sciences, University of Manchester, United Kingdom
- Hans Otto Karnath, Section of Neuropsychology, University of Tübingen, Germany
- John Rothwell and Nick Ward, Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, United Kingdom
- Christine Klein and Norbert Brüggemann, Department of Neurology, Section for Neurogenetics of movement disorders, Lübeck University, Germany
- Bastian Bloem, Department of Neurology, Universitair Medisch, Centrum St. Radboud Nijmegen, The Netherlands.
- Professor Chris Miall, **Behavioural Brain Sciences Centre**, University of Birmingham, United Kingdom.

Research content

The group aim at understanding the complex mechanisms that make humans able to perform and refine movements using incoming sensory information and integrate these with motor commands in order to efficiently improve movements through learning. Ongoing projects focus on how to improve methods for neuro-rehabilitation and studies of motor learning in relation to sport science. The group has a strong interest in examining the reorganisation of motor control systems after spinal cord injury, stroke as well as in patients with movement disorders. Humans rely on visual inputs in order to control certain movements. Here it is studied how sensory stimuli are integrated with motor commands in order to obtain goal directed behaviour and how that can be accomplished both at a conscious and unconscious level. Finally, the complex integration of motor commands and ongoing evaluation of sensory feedback that gives rise to a feeling of ownership of movements and underlies the conscious experience of movements is studied.

Research Group Leader: Mark Schram Christensen

Research Group Leader: Hartwig R. Siebner

Research methods

The Sensorimotor Integration Group aims at combing imaging techniques with electrophysiological measures. The group has access to neurophysiological test facilities both at DRCMR and at Copenhagen Neural Control of Movement group, which includes numerous transcranial magnetic stimulators, EEG equipment, amplifiers, fMRI compatible writing tablet, forcetransducers, joysticks for detailed studies of motor control and neuronavigation systems.

Selected research projects

Daniela Balslev followed up on the discovery of a proprioceptive position signal from the extraocular eye muscles in the human brain (Balslev et al. 2008) by mapping its projection using fMRI (with Postdoctoral Scholar Neil B. Albert, University of Chicago, and Professor Chris Miall, University of Birmingham) and by demonstrating a functional connection between eye proprioception and visual attention (with Dr Emma Gowen, University of Manchester and Professor Chris Miall). They found that the somatosensory homunculus has the extraocular muscles from both eyes represented in each hemisphere, unlike the hand, where the eye proprioceptive projection is only in the contralateral brain. By applying transcranial magnetic stimulation over this somatosensory area it is possible to alter the cortical signal of eye position and thus dissociate the real direction of gaze from the perceived direction of gaze. Using this method, Daniela and her colleagues found that among two images presented at equal retinal eccentricity, the one located further from the perceived direction of

gaze is perceived less accurately. They suggest that we attend in the direction where we look not only voluntarily, but also involuntarily, compelled by the eye proprioceptive system (Balslev et al. in press). Daniela Balslev received a grant from the Danish Medical Research Council and a Marie Curie intra-European fellowship for career development under the EU 7th Framework.

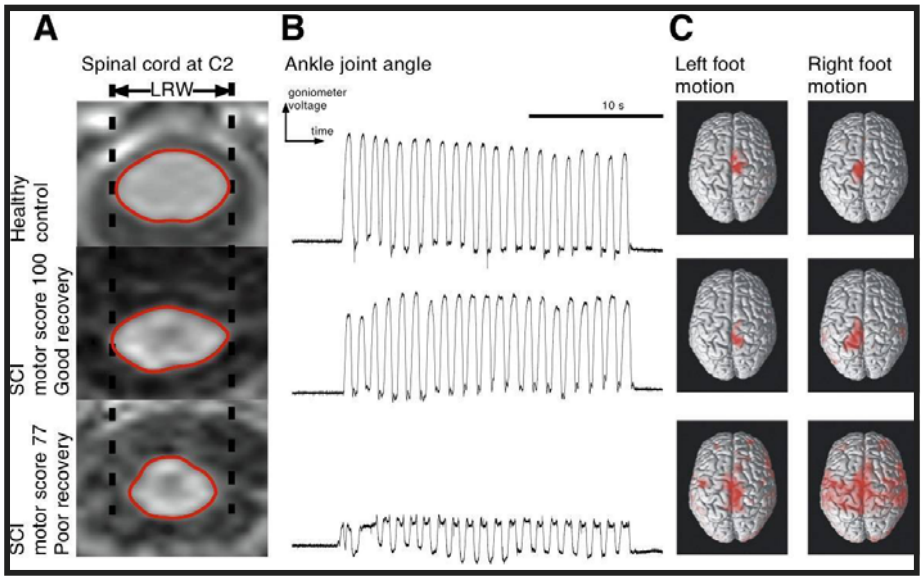
The Sensorimotor integration group is also interested in the question of how distinct genetic phenotypes impact on brain function and structure. While genetically informed neuroimaging has been widely used in other brain systems (Siebner et al. 2009), relatively little work has been carried out to understand the genetic underpinnings of brain function and structure in the motor system. The potential applications of genetically informed imaging for motor neuroscience have been summarised in a joint review paper together with colleagues in London (United Kingdom) and Kiel (Germany) (Cheeran et al. 2009).

Genetically informed imaging bears a great potential for studying the pathophysiology of movement disorders. In an international collaboration with researchers in Germany (Lübeck and Kiel) and the Netherlands (Nijmegen), functional and structural MRI was used to gain a better understanding of the pre-symptomatic period of Parkinson's disease (PD) (van Nuenen et al 2009a and 2009b, van der Vegt et al 2009, Reetz et al. 2009). Mutations in the Parkin (PARK2) and PINK1 gene (PARK 6) can cause recessively inherited PD. The presence of a single Parkin or PINK1 mutation is associated with a dopaminergic nigrostriatal dysfunction and conveys an increased risk to develop PD throughout life. Therefore neuroimaging of non-manifesting individuals with a mutant Parkin or PINK1 allele opens up a window for the investigation of preclinical and very early phases of PD in vivo.

Another disease in which MRI of mutation carriers provides important insights into the pathophysiology in the preclinical period is Huntington's disease. Huntington's disease is an autosomal dominant inherited neurodegenerative disorder caused by an expansion of CAG repeats in the gene encoding huntingtin. Affected patients show progressive motor and cognitive dysfunction with psychiatric problems. Functional MRI of pre-symptomatic carriers with a CAG repeat expansion provided a valuable means of studying compensatory mechanisms that underlie the phenomenon of retained motor function in the presence of degenerative change (Kloppel et al. 2009). The results show that preclinical compensation goes beyond a simple shift of activity from premotor to parietal regions involving multiple compensatory mechanisms in executive and cognitive motor areas.

One of the advantages of the motor system is that electrophysiological measures can be correlated with functions. Using the flexible technique of transcranial magnetic stimulation (TMS) PhD student Abraham Zuur from the Department of Exercise and Sport Sciences, University of Copenhagen and Center for Sensory-Motor Interaction, University of Aalborg together with Mark Schram Christensen, Thomas Sinkjær, Michael J. Grey, and Jens Bo Nielsen published a study of the stretch reflex in man during walking and during sitting position in *Journal of Physiology*. Here they showed that the long latency component of the stretch reflex is suppressed up to 25 min after rTMS.

In 2010, Henrik Lundell handed in his PhD thesis on the topic structural, functional and diffusion MR imaging of the spinal cord. One of the studies



The first column shows the area of the spinal cord at cervical level in a healthy subject, a spinal cord injured patient showing good recovery and a spinal cord injuried patient with poor recovery. The second column are traces of the ankle joint movement performed during functional MRI, and the third column show the associated activations. Notice the extended areas of activation in the SCI patient with poor recovery.

showed that the area of the spinal cord in spinal cord injured patients correlates with their functional deficits. In particular it was possible to relate left-right width and anterior-posterior width of the spinal cord at cervical level with functional scores for motor and sensory disability respectively. This study was published in the *journal Spinal Cord*. Furthermore, in another study Henrik Lundell et al. (in press) showed that the cortical activation in ipsilateral primary motor cortex and bilateral dorsal premotor cortex measured with BOLD fMRI correlated negatively with functional abilities in a population of 19 spinal cord injured patients (see figure to the left). This study will be published in the *Journal Neuro-Image* in 2011.

In collaboration with the Departments of Anaesthesia at Bispebjerg and Herlev Hospital and the Copenhagen Neural Control of Movement group, Mark Schram Christensen conducted a study in which he used 500 ms bursts of repetitive TMS at 20 Hz to elicit an illusory sensation of movement. TMS was applied over different sensory and motor regions of the brain (see figure to the right). During normal conditions TMS over primary motor regions induces muscle twitches, which are perceived as small movements of the corresponding limb. Two populations of subjects were either exposed to anaesthesia of the hand using an ischemia nerve block or anaesthesia of the lower limbs using spinal anaesthesia. Thereby the TMS did not evoke any movements and subjects could not feel any sensory feedback from the anaesthetised limb, but the sensation of movement that was evoked by TMS when applied over dorsal premotor cortex was not affected by the anaesthesia. However, the sensation of movement evoked when primary motor cortex was stimulated, was reduced. This suggests that other mechanisms than sensory feedback can contribute to the sensation of movement. The study was published in the open access journal *PLoS ONE*.

Hartwig R. Siebner from the DRCMR as last author was involved in a study, where it was demonstrated that the primary brain area involved in hand movement (M1hand) decreases in size after a four-weak period of hand immobilisation, and that the size recovers after subsequent training. Thus, even short periods of changed muscle and brain activity can cause brain shape changes in either direction. The findings suggest, for example, that if writing is stopped during school holidays, it may lead to temporary changes in brain structure. The study will be published in the journal *NeuroImage* (Granert et al 2011).

In a study published in *Journal of Neuroscience*, Hartwig R. Siebner from the DRCMR, and co-workers demonstrated that left-handed people

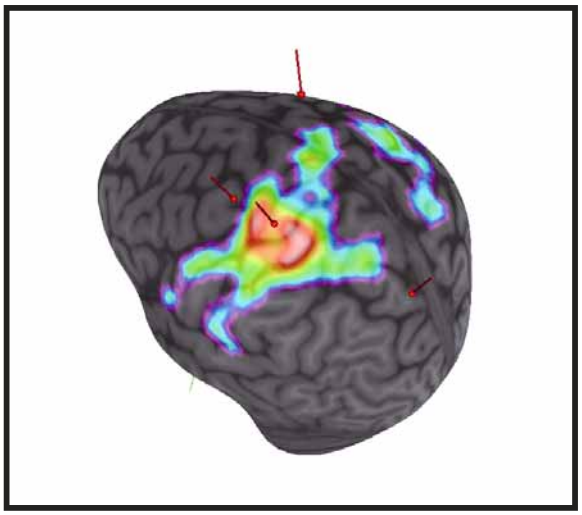


Image shows a brain with overlayed functional activations from a finger movement paradigm. The red pointers indicate areas that have been targeted with TMS. Using the information from the fMRI activations and the anatomical MRIs, it is possible to directly target whether the activated region is necessary for a specific functional task. This combined technique of using fMRI for accurate TMS coil positioning is beginning to be widely used at DRCMR with the newly established electrophysiological laboratory.

being forced to use their right hand acquire structural brain changes. The results are in accordance with a more general recent finding: The brain changes shape depending on its use.

Hartwig R. Siebner and co-workers from London, Kiel and Lausanne showed that rTMS applied to the premotor cortex can have a lasting positive influence on task performance, i.e. give less errors. This shows that the performance of a person solving a task can be improved by specific brain lesions. More specifically, in this case when the lesion suppresses an impulse that would normally make it difficult to solve the task. This was the focus of a study that has just been published in *Journal of Neuroscience*.

The motor control group at DRCMR played an active role in the Brain Awareness Week 2009, which focused on the brain and movements. Jens Bo Nielsen was responsible for the book 'Hjernen i Bevægelse', which was published in connection with the Brain Awareness Week and contained chapters by Jens Bo Nielsen, Tue Hvass Petersen, Jesper Lundbye-Jensen, Anne-Marie Dogonowski, Theis Groth, Hartwig R. Siebner, Michael J. Grey and Mark Schram Christensen, all connected to DRCMR's Sensorimotor Integration Group.

The Sensorimotor Integration Group obtained grants from the Danish Medical Research Council, the Danish Multiple Sclerosis Society and Fondsbørsvekselerer Henry Hansen og hustru Karla Hansen, f. Westergaards legat with Hartwig R. Siebner as the principal investigator on all grants.

In late 2010, Hartwig R. Siebner received a generous donation (3 mill. Euro) for a five year project from the Lundbeck Foundation in order to establish a research group on Control of Actions (ContAct). In 2011 ContAct will take over the research areas covered by the Sensorimotor Integration group.

Selected publications

Bergmann TO; Groppa S; Seeger M; Molle M; Marshall L; Siebner HR: Acute changes in motor cortical excitability during slow oscillatory and constant anodal transcranial direct current stimulation. *J Neurophysiol*. 2009;102(4):2303-2311.

Christensen MS; Lundbye-Jensen J; Grey MJ; Vejlby AD; Belhage B; Nielsen JB: Illusory sensation of movement induced by repetitive transcranial magnetic stimulation. *PLoS One*. 2010;5(10): e13301.

Kloppel S; Mangin JF; Vongerichten A; Frackowiak RS; Siebner HR: Nurture versus nature: Long-term impact of forced right-handedness on structure of pericentral cortex and basal ganglia. *J Neurosci*. 2010; 30(9):3271-5.

Lundell H; Barthelemy D; Skimminge A; Dyrby TB; Biering-Sorensen F; Nielsen JB: Independent spinal cord atrophy measures correlate to motor and sensory deficits in individuals with spinal cord injury. *Spinal Cord*. 2010, e-pub ahead of print.

Ward NS; Bestmann S; Hartwigsen G; Weiss MM; Christensen LO; Frackowiak RS; Rothwell JC; Siebner HR: Low-frequency transcranial magnetic stimulation over left dorsal premotor cortex improves the dynamic control of visuospatially cued actions. *Journal of Neuroscience*. 2010;30(27): 9216-23.

Cimbi

Center for integrated molecular brain imaging

Center for integrated molecular brain imaging (Cimbi), funded by the Lundbeck Foundation, is based on a close collaboration between various partner institutions. The core group includes Neurobiology Research Unit (NRU), Copenhagen University Hospital Rigshospitalet, Danish Research Centre for Magnetic Resonance, (DRCMR), Copenhagen University Hospital Hvidovre, Informatics and Mathematical Modelling (IMM), The Technical University of Denmark and Department of Medicinal Chemistry (DMC), Faculty of Pharmaceutical Sciences, University of Copenhagen. Additionally, several national and international institutions are collaborators in various projects contributing to this interdisciplinary centre.

The center is headed by Professor Gitte Moos Knudsen at Rigshospitalet and has been running since 2006. From DRCMR, Terry L. Jernigan and Hartwig R. Siebner are part of the steering committee for Cimbi as well as principal investigators heading the DRCMR activities in Cimbi. Hartwig R. Siebner replaced Olaf B. Paulson in the steering committee in April 2009.

The following staff members from DRCMR are also involved in projects at Cimbi: Karam Sidaros, William Baaré, Pernille Iversen, Julian Macoveanu, Thomas Z. Ramsøy, Bettina Hornbøll, Sussi Larsen, Jon Wegener, Helle R. Laursen, Kathrine Skak Madsen and Arnold Skimminge.

Research projects

The main focus for the research executed within Cimbi is on the neural bases of personality dimensions that predispose individuals to affective and substance use disorders, with special emphasis on the serotonergic neurotransmitter system. This system is involved in a large variety of psychophysiological functions, including feeding, mood, aggression, and pain. Serotonin is also a critical neurotransmitter in brain development and in the generation and regulation of emotional behaviour. Finally, it plays a prominent role in the inhibition of impulses.

Overall, the research at Cimbi can be divided into six main projects:

1. Molecular brain imaging of the serotonergic system
2. Genetic and biochemical determinants of the serotonergic transmitter system
3. Relation between personality, biochemistry, and brain structure.
4. Functional brain imaging under serotonergic challenges
5. Development of a PET agonist tracer to probe endogenous serotonin release
6. A meta-analytic approach to knowledge discovery in molecular brain imaging

Cimbi project 3: Relation between personality, biochemistry, and brain structure

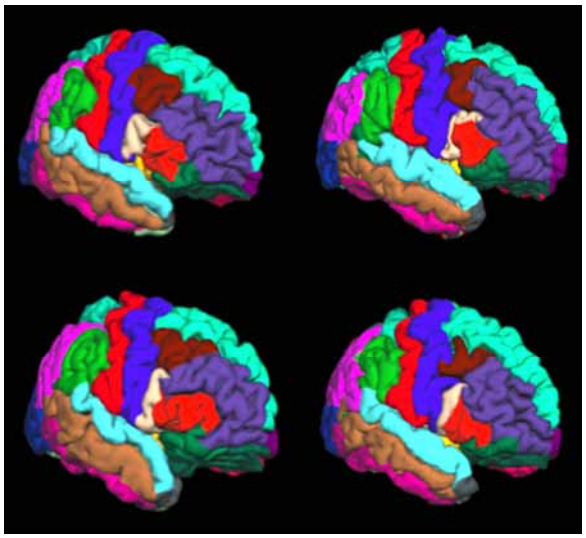
The major aim of the Cimbi 3 project is to apply structural neuroimaging approaches to the participants in Cimbi, so that differences in anatomy can be linked to genetic variability on the one hand, and to personality traits, cognitive functions, and other functional parameters on the other. Thus, it may be possible to determine to what extent genetic influences on the brain's serotonin system and anatomical structure may mediate behaviour.

Apart from improvements of the integration with other Cimbi projects and image analysis procedures at the Cimbi computing cluster at the Technical University of Denmark, 2009-2010 saw significant progress in testing 'Freesurfer', a software program that allows cortical thickness and surface measurements (see figure on the previous page). Furthermore, the project continued to con-

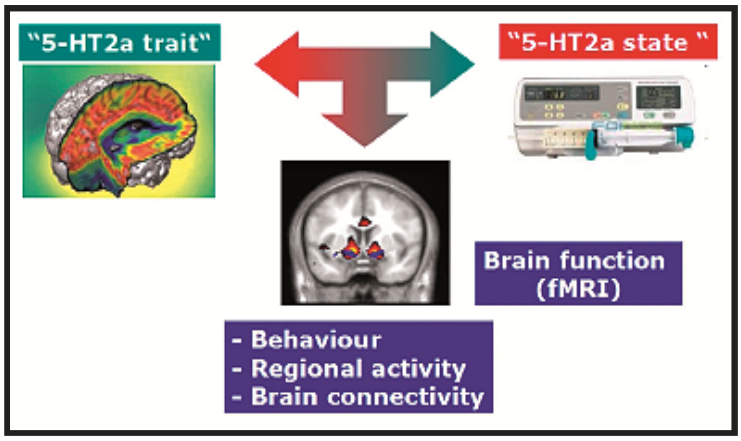
Research Group Leader: Terry L. Jernigan

Research Group Leader: Hartwig R. Siebner

Research Group Leader: Olaf B. Paulson



CIMBI project 3 - Freesurfer provides automated tools to reconstruct the cortical surface of the brain and to segment the cortex in anatomical meaningful areas. Measurements of cortical thickness and surface area can be extracted. Here the right hemispheres of four individual brains are shown.



The multimodal brain mapping approach integrates PET-related 'trait' measures of serotonin-related neurotransmission (e.g., mapping the regional binding of a PET ligand to 5-HT2a receptors in the brain), and pharmacological 'state' manipulations of serotonergic function (e.g., blockade of 5HT2a receptors with ketanserin). The effects of the pharmacological challenges are assessed with functional magnetic resonance imaging (fMRI) during experimental tasks. The experimental tasks probe emotional and cognitive domains related to serotonin.

tribute actively to the efforts to design and implement a centralized database for Cimbi observations, which is an important initiative as investigators at Cimbi begin to perform the cross-project analyses that will take advantage of synergy within the center.

A manuscript describing observations that healthy individuals, who have a twin afflicted with major depression (i.e. high risk subjects), had reduced hippocampal volumes, has been published. This 'marker' of depression may either be associated with the genetic predisposition for depression, or to environmental factors that are shared by affected and healthy twins growing up in the same environment, but it is unlikely to be entirely due to the depressive illness itself or to the treatments for depression, neither of which afflicted these healthy co-twins of depressed individuals.

In 2010, two studies were completed in which diffusion weighted imaging data was analysed to assess white and grey matter microstructure. Findings from the first study suggest that the balance between left- and right-sided limbic circuits may bear an important relationship to HPA-axis reactivity, and to the tendency to experience negative emotions. Results from the second study suggest that the balance between left and right hippocampus microstructure bears a specific relationship to HPA-axis tonus. The findings of the two studies together raise important questions about how the architecture of limbic system fibre tracts and limbic microstructure are related to negative emotionality and neuroendocrine functions.

Finally, integration between the Cimbi 3 project and the HUBU project has been intensified (for more information see the section on Brain Maturation). HUBU can provide unambiguous results with respect to whether observed differences are either markers of predisposing vulnerability or consequences of these conditions because of our existing data on preadolescent brain and behavioural attributes of the study cohort.

Cimbi project 4: Functional brain imaging under serotonergic challenges

In Cimbi functional Magnetic Resonance Imaging (fMRI) has mainly been used to map the functional brain response to pharmacological interventions that induce acute changes in the serotonergic system. In other words researchers can map regional brain activity when individuals perform a task by using fMRI.

Test subjects were asked to perform tasks where the serotonergic system is known to be involved. All individuals were scanned with fMRI in three different 'brain states' with normal, increased or reduced serotonergic tone. The regional brain activations measured with fMRI at a 'low', 'normal' or 'high' serotonin level are to be compared to detect differences in task related activity, see figure to the left. This will enable us to identify those brain regions where neuronal activity depends on the availability of serotonin.

In 2010, fMRI measurements in Cimbi were extended to volunteers, who did not participate in pharmacological challenges. The extension of the fMRI research program to a larger group of subjects will render it possible to relate inter-individual variations in personality (e.g. impulsivity) or genotype (e.g. SNPs) with interindividual variations in resting-state connectivity and functional brain response to face emotions, reward or punishment.

Selected publications

Hornbøll B; Wegener J; Paulson OB; Rowe JB; Knudsen GM; Siebner HR; Macoveanu J: Acute blockade of 5HT2a receptors reduces orbitofrontal cortex response to angry and fearful faces. *Proceedings of the Nordic Meeting in Neuropsychology*. 2010.

Collaborative Research Projects - Schizophrenia

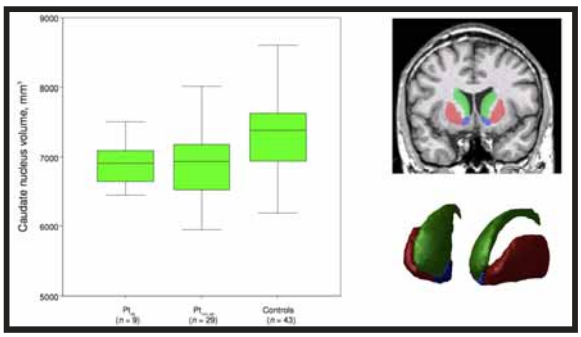
Schizophrenia is a severe psychiatric illness affecting approximately 1% of the general population. Although the aetiology of schizophrenia is largely unknown, genetic factors as well as environmental factors are involved. Heritability estimates of schizophrenia are around 80%. *In vivo* imaging studies have been pivotal for our understanding of schizophrenia as a brain disease.

Members of the group

The MR research is done in close collaboration with the Center for Neuropsychiatric Schizophrenia Research (CNSR) and the Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Psychiatric Center Glostrup, both headed by Professor Birte Glenthøj. Furthermore, collaboration is established with the Child and Adolescent Psychiatric Center Bispebjerg.

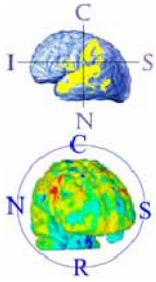
Internal researchers from DRCMR include: Hartwig R. Siebner, William Baaré, Arnold Skimminge and Per Åkeson. Ayna Baladi Nejad is affiliated to both the DRCMR and CNSR/CINS. Olaf B. Paulson is member of the CINS steering group.

Main researchers involved from CNSR/CINS are: Professor Birte Glenthøj, Dr Bjørn H. Ebdrup and PhD student Trine Bjørg Hammer. Katrine Pagsberg, MD, represents the Department of Child and Adolescent Psychiatry.



Left: Boxplot of caudate nucleus volumes in schizophrenia patients with any lifetime substance abuse (Pt_{ab}), patients with no lifetime substance abuse ($Pt_{non.ab}$) and matched healthy controls. Volumes are corrected for age, sex and intracranial volume. In the box-and-whisker plot, the central box represents the values from the lower to upper quartile. The transverse line in the box represents the median corrected volume. The vertical line extends from the minimum to the maxi- mum value, excluding outside values. Outside values are defined as values smaller or larger than the lower quartile minus 1.5 times the interquartile range and if present are displayed as separate points (o). No outliers were identified. Right: Regions of interest. Green: Caudate nucleus; Red: Putamen; Blue: Nucleus accumbens.

Research content



The schizophrenia MR projects at the DRCMR mainly focus on very early stages of the disease. Investigation of (early onset) first-episode (drug-naïve) schizophrenia patients is important as they control, to a large extent, for effects of factors such as long-term hospitalisation, medication treatment and disease chronicity.

The main project is entitled: 'Structural and functional brain changes in drug-naïve first-episode schizophrenia patients: relation to cognitive function and antipsychotic medication'. In February 2010, Bjørn H. Ebdrup successfully defended his thesis 'Structural Brain Changes in Antipsychotic-Naïve First-Episode Schizophrenia Patients Before and After Six Months of Antipsychotic Monotherapy'. PhD student Ayna Nejad investigates the differences in brain activity patterns in schizophrenia patients and healthy controls using functional MRI during a verbal working memory task.

Other projects include 'Schizophrenia: clinical, psychophysiological and neurobiological manifestations', a 5-year follow-up study of a previous cohort of drug naïve first episode schizophrenia patients performed by PhD student Trine Bjørg Hammer and 'First episode psychotic children and adolescents: a 5 year follow-up study of brain structure and function', performed by Dr Katrine Pagsberg.

Selected publications

Ebdrup BH; Glenthoj B; Rasmussen H; Aggernaes B; Langkilde AR; Paulson OB; Lublin H; Skimminge A; Baare W: Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia. *J Psychiatry Neurosci*. 2010;35(2):95-104.

Ebdrup BH; Skimminge A; Rasmussen H; Aggernaes B; Oranje B; Lublin H; Baare; Glenthoj B: Progressive striatal and hippocampal volume loss in initially antipsychotic-naive, first-episode schizophrenia patients treated with quetiapine: relationship to dose and symptoms. *Int J Neuropsychopharmacol*. 2011;14(1):69-82.

Ebdrup BH; Lublin H; Akeson P; Glenthoj BY: Patients with first-episode psychosis should not be scanned as a routine procedure. *Ugeskr Laeger*. 2011;173(7):484-9.

Nejad AB; Ebdrup BH; Siebner HR; Rasmussen H; Aggernæs B; Glenthøj BY; Baaré WFC: Impaired temporoparietal deactivation with working memory load in antipsychotic-naïve patients with first-episode schizophrenia. *World Journal of Biological Psychiatry*. Epub 2011.

READER CENTRE

MRI is used increasingly in clinical trials. During the last decade the DRCMR Reader Centre has been involved in image analysis for a number of ongoing clinical trials as well as international and national investigator driven projects. In addition, the centre collaborates with research groups on white matter lesion assessment.

Centre team

Head of the DRCMR Reader Centre is Ellen Garde. Other members include Hanne Schmidt, Sascha Gude, Arnold Skimminge, Henrik Lund, Torkil Svensgaard, Mark Lyksborg, Lise Vejby Søgaard, Xingchen Wu and Olaf B. Paulson. In addition, the centre benefits from a close collaboration with the academic research groups at DRCMR and radiologists at the clinical DRCMR section.

External collaborators

- Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital Rigshospitalet, Denmark
- Steno Diabetes Center, Gentofte, Denmark
- NMR Research Unit, Department of Neuroinflammation, University College London, United Kingdom
- Professor Rasmus Larsen, Department of Informatics and Mathematical Modelling, Technical University of Denmark, Denmark

Services

In addition to providing centralised image analysis of MRI data obtained in trials of potential new disease modifying agents in Multiple Sclerosis, the centre offers expertise on white matter lesion detection and assessment. Due to its academic and clinical embedding, the centre holds highly advanced knowledge on data quality and computational methods and algorithms to analyze and quantify MR data. The centre's experienced readers provide expert support to help trial sites optimize the image management in order to obtain high quality and accurate results for analysis. Quantitative measures such as lesion volume, differential brain volumes, and brain parenchymal fraction are used as endpoints in cross-sectional as well as longitudinal studies.

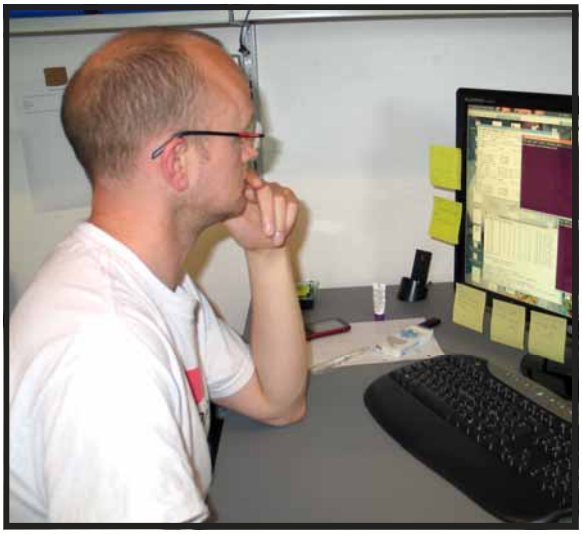
In recent years, the DRCMR Reader Centre has further worked with refinement of its sensitive and reproducible algorithms to render the evaluation of lesions and lesion size more automatic and less dependent on subjective assessment. Image analysis technology developed by the DRCMR academic research groups is being integrated into a workflow system for rapid configuration to trial specific requirements.

Trials as well as clinical research demand ever more specific and robust MRI techniques and the DRCMR Reader Centre is currently in the process of incorporating advanced MR measures such as diffusion tensor imaging (a technique that reveals aspects of tissue structure not visible using standard structural MRI scans), magnetisation transfer imaging (which indirectly helps us to measure the myelin content of tissues), iron deposition quantification, and resting-state fMRI.

Activities

Clinical trials

In 2009-10 three multi-centre double-blind randomized placebo-controlled trials were completed and the – highly interesting - results published in collaboration with the Danish Multiple Sclerosis Center and collaborating centres in Europe. Four



Torkil Svensgaard provides the crucial technical support at DRCMR

Sascha Gude and Hanne Schmidt are evaluating images

investigator-driven studies are currently executed and several other studies planned.

Research projects
The centre also contributed to a number of research projects including a study focusing on the pathophysiological mechanisms underlying changes in cerebral activation in MS patients (see the section on the Multiple Sclerosis elsewhere in this report).

In 2009, a promising collaboration with the Steno Diabetes Center was established with a prospective observational study on the prognostic value of cardio- and cerebrovascular risk factors in patients with diabetes. A pilot study assessing plasma NT-proBNP and white matter hyperintensities in type 2 diabetic patients, with or without asymptomatic coronary artery disease, has been completed.

One of the highlights in 2010 was an inspiring talk by visiting colleague Kelvin Hunter, University College London, sharing his experiences with imaging data management in clinical trials.

Selected publications

Sorensen PS; Mellgren SI; Svenningsson A; Elovaara I; Frederiksen JL; Beiske AG; Myhr KM; Sogaard LV; Olsen IC; Sandberg-Wollheim M: NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): a randomised, placebo-controlled trial. *Lancet Neurol*. 2009;8 (6):519-529.

Ravnborg M; Sorensen PS; Andersson M; Celius EG; Jongen PJ; Elovaara I; Bartholome E; Constantinescu CS; Beer K; Garde E; Sperling B: Methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN study): a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial. *Lancet Neurol*. 2010;9(7):672-680.

Hanne Schmidt in front of a poster about the Reader Centre

COLLABORATION

National and international collaboration is highly emphasised by the DRCMR, a listing of the academic as well as industry partners is provided below.

National Collaborations

Aalborg University
- *Center for Sensory-Motor Interaction*

Aarhus University
- *Center of Functionally Integrative Neuroscience*
- *Danish School of Education*

Copenhagen Business School
- *Decision Neuroscience Research Group, Department of Marketing*
- *Department of International Culture and Communication Studies*

H. Lundbeck A/S
Hammel Neurocenter
Learning Lab Denmark
Magventure A/S
PhaseOne Trials A/S
Steno Diabetes Center, Gentofte, Denmark
Technical University of Denmark
- *Department of Electrical Engineering*
- *Department of Informatics and Mathematical Modelling*

University of Copenhagen
- *Center for Visual Cognition*
- *Copenhagen Biocentre*
- *Copenhagen Muscle Research Centre, CMRC*
- *Department of Exercise and Sport Sciences*
- *Department of Neuroscience and Pharmacology*
- *Department of Psychology*
- *Faculty of Life Sciences*
- *Department of Public Health, Department of Health Psychology*
- *Neural Control of Movements*
- *The Niels Bohr Institute*

University of Southern Denmark

Copenhagen University Hospitals

Departments at Hvidovre Hospital
- *Department of Anaesthesiology*
- *Department of Neurorehabilitation*
- *Department of Orthopedic Surgery*
- *Department of Paediatrics*
- *Department of Radiology*
- *Department of Cardiology and Respiratory Medicine*

Departments at Rigshospitalet
- *Center for Integrated Molecular Brain Imaging*
- *Clinic for Spinal Cord Injuries*
- *Danish Multiple Sclerosis Center*
- *Department of Clinical Genetics*
- *Department of Clinical Physiology and Nuclear Medicine*
- *Department of Infectious Diseases*
- *Department of Neurophysiology*
- *Department of Neurosurgery*
- *Department of Ophthalmology*
- *Department of Psychiatry*
- *Department of Radiology*
- *Diagnostic Centre*
- *Finsen Laboratory*
- *The Bartholin Institute, XPU*
- *The Memory Disorders Research Unit*
- *The Neurobiology Research Unit*
- *The Pediatric Clinic*

Departments at other Copenhagen University Hospitals
- *Department of Anesthesiology, Bispebjerg Hospital*
- *Department of Anesthesiology, Herlev Hospital*
- *Research Laboratory for Stereology and Neuroscience, Bispebjerg Hospital*

Psychiatric centres in the Capital Region
- *Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Glostrup*
- *Center for Neuropsychiatric Schizophrenia Research, Glostrup*
- *Psychiatric Centre Glostrup*
- *Child and Adolescent Psychiatric Centre Bispebjerg*

International Collaborations

Blekingesjukhuset, Geriatric Clinic, Sweden
Brookhaven Lab's Medical Department, New York, USA
Centre Hospitalier Universitaire Pitié-Salpetrière, Paris, France
Ecole Normale Supèrieure, Paris, France
- *Laboratoire de Sciences Cognitives et Psycholinguistique*

Emsense, USA
GE Healthcare, International
Göteborg University, Göteborg, Sweden
- *Department of Neurology, Sahlgrenska University Hospital*

Griffith University, Queensland, Australia
- *School of Physiotherapy and Exercise Science*

Howard University, Washington DC, USA
INSEAD, Paris, France
Johannes Gutenberg-University Medical School, Mainz, Germany
- *Department of Interventional and Diagnostic Radiology*
- *Department of Physics*

Karolinska Institutet, Stockholm, Sweden
- *Department of Neuroscience, Brain, Body and Self Laboratory*

London Business School
Lund University, Lund, Sweden
- *Department of Medical Radiation Physics*
- *Department of Radiology*

Lund University Hospital, Sweden
- *Department of Radiation Physics*

A new scanner arrives at the hospital

Lübeck University, Germany
Department of Neurology, Section for Neurogenetics of movement disorders
Max-Planck-Institute, Germany
Biological Cybernetics, Tübingen
Human Cognitive and Brain Sciences, Leipzig
Neurological Research, Cologne
Medical Imaging Research Institute GmbH, Heidelberg, Germany
Millward Brown, London, United Kingdom
NeurImageNord Imaging Center, Universities of Hamburg, Kiel and Lübeck, Germany
Neuroscience Institute, San Diego, USA
New York State University, Buffalo, USA
Buffalo Neuroimaging Analysis Center (part of the Jacobs Neurological Institute)
Scripps Genomic Medicine & Scripps Translational Science Institute (STSI), Scripps Health & The Scripps Research Institute, La Jolla, California, USA
Stanford Graduate School of Business, Stanford University, California, USA
Tel-Aviv University, Israel
Universitair Medisch, Centrum St. Radboud Nijmegen, The Netherlands
Department of Neurology
University College London, United Kingdom
Dementia Research Centre, National Hospital for Neurology and Neurosurgery
NMR Research Unit, Department of Neuroinflammation
Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology
Wellcome Trust Centre for Neuroimaging, Institute of Neurology
University Hospital of Freiburg, Germany
The MR development and application center
University Hospital Skåne, Malmö, Sweden
Department of Pulmonology
University Medical Center Utrecht, Utrecht, The Netherlands
Image Sciences Institute
University of the Balearic Islands, Spain
Department of Psychology
University of Birmingham, United Kingdom
School of Psychology
University of California, San Diego, USA
Center for Human Development
Department of Neurosciences
Department of Radiology and Biomedical Imaging
Laboratory of Cognitive Imaging
MultiModal Imaging Laboratory
University of Cambrige, United Kingdom
Behavioural and Clinical Neuroscience Institute, MRC Cognition and Brain Sciences Unit and Neurology Unit
Department of Clinical Neurosciences
Medical Research Council, Cognition and Brain Sciences Unit
University of Chicago
University of Hamburg, Germany
University of Liverpool, United Kingdom
Division of Orthoptics
University of Manchester
Department of Neuroscience
Department of Psychiatry
Faculty of Life Sciences
School of Medicine, Image Science & Biomedical Engineering
University of Medicine and Dentistry of New Jersey
Department of Radiology, Newark, USA
University of Messina, Italy
Department of Neurosciences, Psychiatric and Anaesthesiological Sciences
University of Montreal, Canada
Department of Physiology
University of Pennsylvania, Philadelphia, USA
Department of Neurology
Department of Radiology, MMRRCC B1 Stellar-Chance Laboratories
University of Sheffield, Sheffield, United Kingdom
Academic Unit of Radiology
University of Southern California, USA
USC Neuroscience
University of Toronto, Canada
Rotman Research Institute, Department of Medical Biophysics
University of Tübingen, Germany
Section of Neuropsychology, Center for Neurology
University of Vienna, Austria
Department of Psychological Basic Research
University of York, Canada
Zeppelin University, Germany

International Multi-Centre Research Collaborations

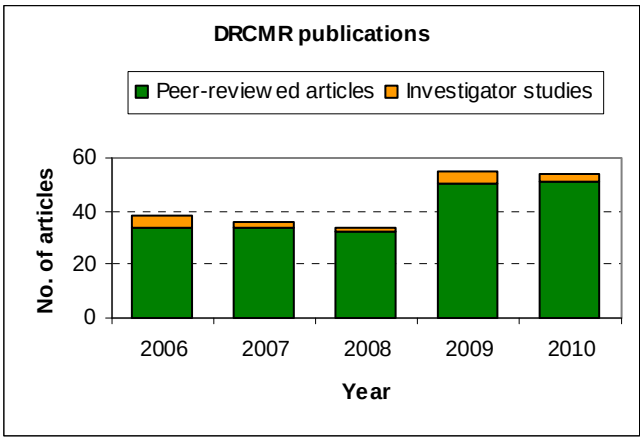
Consortium of Neuroimagers for the Non-invasive Exploration of Brain Connectivity and Tractography (CONNECT). EU 7th Framework Programme
Diagnostic Molecular Imaging: The DiMI Project: An international network of excellence for the advancement of diagnostic molecular imaging (DiMI). EU 6th Framework Programme
Leukoaraiosis and Disability in the elderly (LADIS). EU 5th Framework Programme
Polarized Helium Lung Imaging Network (PHeLINet). EU 7th Framework Programme: Research and Training Network (RTN).
The 1000 functional connectomes project

Clinical Trials

Collaborators in Clinical Trials include: AC-Immune SA, Biogen Idec Ltd, BioMS Technology Corp, Bristol-Myers Squipp, F. Danish Multiple Sclerosis Center, Hoffmann-La Roche Ltd, GE Healthcare Ltd, GenMab A/S, Genzyme Europe, GeoMab A/S, GlaxoSmithKline, Merck Serono International, Shire Ltd and Zymenex A/S.

Taking a break at the DRCMR retreat 2010

PUBLICATIONS



Peer-reviewed articles and investigator studies 2006—2010. As can be seen, 2009 and 2010 saw a significant increase in the number of peer-reviewed journal articles reflecting the high level of activity during this period.

2009

PhD and Doctoral Theses 2009

Brandt CT
Experimental studies of pneumococcal meningitis.
Statens Serum Institut, November 27, 2009.

Sidaros A
MRI in severe traumatic brain injury - Micro- and Macrostructural changes.
Faculty of Health Sciences, University of Copenhagen, March 31, 2009.

Peer Reviewed Journal Articles 2009

1. Bandholm T; Magnusson P; Jensen BR; Sonne-Holm S: Dorsiflexor muscle-group thickness in children with cerebral palsy: Relation to cross-sectional area. *NeuroRehabilitation*. 2009;24 (4):299-306.
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Social activities at DRCMR 2010

Akeson P: Progression of emphysema in a 12-month hyperpolarized 3He-MRI study: lacunarity analysis provided a more sensitive measure than standard ADC analysis. *Acad Radiol*. 2009; 16 (6):700-707.

9. Diaz S; Casselbrant I; Piitulainen E; Magnusson P; Peterson B; Wollmer P; Leander P; Ekberg O; Akeson P: Validity of apparent diffusion coefficient hyperpolarized 3He-MRI using MSCT and pulmonary function tests as references. *Eur J Radiol*. 2009;71(2):257-263.
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11. Djarmati A; Hagenah J; Reetz K; Winkler S; Behrens MI; Pawlack H; Lohmann K; Ramirez A; Tadic V; Bruggemann N; Berg D; Siebner HR; Lang AE; Pramstaller PP; Binkofski F; Kostic VS; Volkmann J; Gasser T; Klein C: ATP13A2 variants in early-onset Parkinson's disease patients and controls. *Mov Disord*. 2009;24(14):2104-2111.
12. Erritzoe D; Frokjaer VG; Haugbol S; Marner L; Svarer C; Holst K; Baare WF; Rasmussen PM; Madsen J; Paulson OB; Knudsen GM: Brain serotonin 2A receptor binding: relations to body mass index, tobacco and alcohol use. *Neuroimage*. 2009;46(1):23-30.
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Investigator studies 2009

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Conference Proceedings 2009

In 2009 the researchers from DRCMR were represented at 57 meetings and conferences, presenting a total of 112 abstracts.

2010

PhD and Doctoral Theses 2010

Broberg BV
Animal disease models of schizophrenia. Phenotypical characterization of two treatment paradigms involving phencyclidine – sub-chronic and early postnatal treatment.
Faculty of Health Sciences and Faculty of Life Sciences, University of Copenhagen, July 9, 2010.

Ebdrup B.H.
Structural Brain Changes in Antipsychotic-Naïve First-Episode Schizophrenia Patients Before and After Six Months of Antipsychotic Monotherapy.
Faculty of Health Sciences, University of Copenhagen, February 26, 2010.

de Nijs R
Corrections in clinical Magnetic Resonance Spectroscopy and SPECT: Motion correction in MR spectroscopy Downscatter correction in SPECT.
Informatics and Mathematical Modelling, Technical University of Denmark, March 2, 2010.

Ryberg C
Morphological Correlates and Functional Significance of Corpus Callosum Atrophy in Elderly Subjects.
Faculty of Health Sciences, Memory Disorders Research Group, University of Copenhagen, September 29, 2010.

Skimminge A
Longitudinal MRI studies of brain morphometry.
Informatics and Mathematical Modelling, Technical University of Denmark, November 23, 2010.

Peer Reviewed Journal Articles 2010

1. Aggernaes B; Glenthoj BY; Ebdrup BH; Rasmussen H; Lublin H; Oranje B: Sensorimotor gating and habituation in antipsychotic-naive, first-episode schizophrenia patients before and after 6 months' treatment with quetiapine. *Int J Neuropsychopharmacol*. 2010;13(10):1383-1395
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Daily life in the research section at DRCMR

Madden DJ; Madsen KH; Margulies DS; Mayberg HS; McMahon K; Monk CS; Mostofsky SH; Nagel BJ; Pekar JJ; Peltier SJ; Petersen SE; Riedl V; Rombouts SA; Rypma B; Schlaggar BL; Schmidt S; Seidler RD; Siegle GJ; Sorg C; Teng GJ; Veijola J; Villringer A; Walter M; Wang L; Weng XC; Whitfield-Gabrieli S; Williamson P; Windischberger C; Zang YF; Zhang HY; Castellanos FX; Milham MP: Toward discovery science of human brain function. *Proc Natl Acad Sci U S A*. 2010;107(10):4734-4739.

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Investigator studies 2010

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2. Schmidt R; Ropele S; Ferro J; Madureira S; Verdelho A; Petrovic K; Gouw A; van der Flier WM; Enzinger C; Pantoni L; Inzitari D; Erkinjuntti T; Scheltens P; Wahlund LO; Waldemar G; Rostrup E; Wallin A; Barkhof F; Fazekas F: Diffusion-weighted imaging and cognition in the leukoariosis and disability in the elderly study. *Stroke*. 2010;41(5):e402-e408.
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Conference Proceedings 2010

In 2010 the researchers from DRCMR were represented at 31 meetings and conferences, presenting a total of 63 conference contributions. (10 oral presentations, 16 invited talks and 37 abstracts/ posters)

Peer-reviewed e-pub journal articles 2010

During 2010 12 articles were published online as 'e-publications ahead of print' prior to the print publication in the following year.

Spin gymnastics at the 2010 DRCMR Christmas Symposium.

ACKNOWLEDGEMENTS

The DRCMR would like to thank the following institutions for their financial support in 2009-2010

Copenhagen University Hospital Hvidovre
EU 6th Framework Programme
EU 7th Framework Programme
Federation of European Neuroscience Societies
Fondsbørsvekseler Henry Hansen og Hustru Karla Hansen f. Westergaards Legat
GE Healthcare
Gerda and Aage Haensch's Foundation
GlaxoSmithKline plc
Ludvig and Sara Elsass Foundation
Neuroscience School, University of Copenhagen
Philips Healthcare
Savværkejer Jeppe Juhl og Hustru Ovital Juhl's Mindelegat
Siemens Healthcare
Simon Fougner Hartmanns Familiefond
Simon Spies Foundation
The Capital Region of Denmark
The Danish Agency for Science, Technology and Innovation
The Danish Council for Strategic Research
The Danish Heart Foundation
The Danish Medical Research Council
The Danish Multiple Sclerosis Society
The Danish Social Science Research Council
The Harland Sanders Foundation
The International Society for Magnetic Resonance in Medicine
The John and Birthe Meyer Foundation
The Lundbeck Foundation
The National Institute of Health (NIH)
The Research Committee at Rigshospitalet
The Swedish Research Council
The Technical University of Denmark
Tips- og Lottomidler
University of Copenhagen, Faculty of Health Sciences
William Demants og Hustru Ida Emilies Fond / The Oticon Foundation

NOTES

DRCMR retreat 2010

This report is published by:

Danish Research Centre for Magnetic Resonance
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