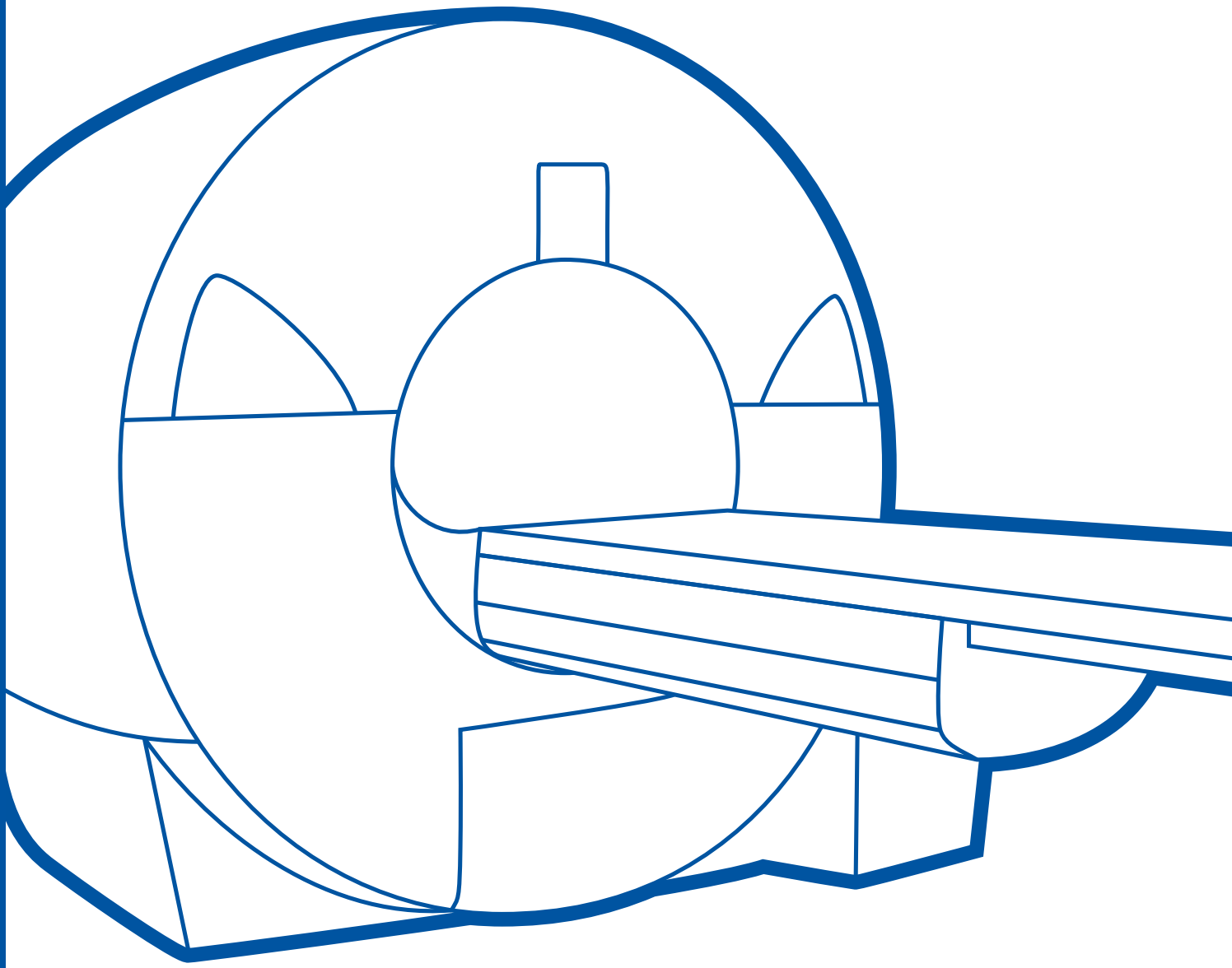
DRCMR

DANISH RESEARCH CENTRE FOR MAGNETIC RESONANCE

BIENNIAL REPORT 2011 – 2012



REGION H Hvidovre Hospital

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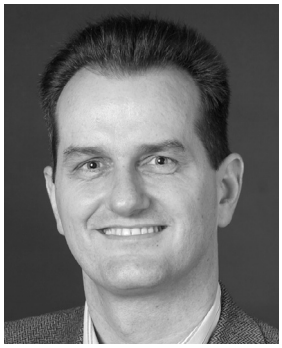


THE DANISH RESEARCH CENTRE FOR MAGNETIC RESONANCE IN 2011 & 2012

We are pleased to present to you the Biennial Report of the Danish Research Centre for Magnetic Resonance (DRCMR). This year we have decided to slightly change the format of our report. We wish to bring a few research programs into focus, which we consider to be of high strategic relevance. Additionally, in order to shift the focus from research infrastructure to individual researchers we decided to link "faces" to "facts" by presenting some of our researchers who push the boundaries of magnetic resonance imaging and imaging neuroscience. Following the tradition of previous reports, we also want to present the broad range of scientific activities at the DRCMR by briefly describing the various research programs in dedicated sections. Together these programs resulted in a steady increase in scientific productivity with an increase in the average number of annual publications from 36 peer-reviewed publications in the period from 2006 to 2009 to 52 peer-reviewed publications in the period from 2009 to 2012. At the same time the number of externally funded research personal markedly increased. More than 20 researchers joined the DRCMR in 2011 and 2012, increasing the ratio between intramurally and extramurally funded staff from 1:2 in 2009 to 1:6 in 2012.

THANK YOU!

Our research program strongly relies on the many collaborative ties with research groups in our hospital and the Capital Region of Denmark as well as with other national and international research centers. A warm "Thank you" goes to all our partners for their continued support and for the enthusiastic and inspiring interaction. We are looking forward to conducting many more projects in the future.
I would also like to express our gratitude towards the public funding agencies and private foundations whose generous financial support has enabled the Danish Research Centre for Magnetic Resonance to tackle key questions in MR research and neuroimaging of the human brain.
My special thanks go to the Board of Directors, Amager and Hvidovre Hospitals, especially to chief director Torben Ø. Pedersen and vice-director Torben Steen Mogensen who have been very supportive. I also wish to thank chief consultant Claus Leth Petersen for valuable advice and the positive collaboration as "tandem leadership" of the Centre for Functional and Diagnostic Imaging and Research.
Finally, I would like to convey my most sincere "thank you" to all researchers and staff members for an excellent job done in 2011 and 2012. It is your commitment and engagement that creates the enthusiastic, open-minded, and inspiring atmosphere that makes excellent research happen and fosters collaboration, innovation and creativity.

All the best wishes

Hartwig Roman Siebner

HIGHLIGHTS & MILESTONES 2011 – 2012

The mission of the DRCMR is to advance the biomedical use of magnetic resonance imaging (MRI) and to use MRI to conduct groundbreaking neuroscience. Researchers at DRCMR strive to deliver the best research and education in basic and applied MR-research. The years 2011 and 2012 brought a series of exciting new developments that added significant momentum to the science conduced at DRCMR and that opens up exciting possibilities for the future.

A NEW DEPARTMENTAL ORGANIZATION

During the summer of 2011, the Centre for Functional and Diagnostic Imaging and Research (Funktions og Billeddiagnostisk Enhed = FBE) was established across Amager and Hvidovre Hospitals. The FBE led by Claus Leth Petersen (Chief consultant) and Professor Hartwig Roman Siebner (Research leader) includes the former departments of Radiology, Clinical Physiology and Nuclear Medicine, and Magnetic Resonance (DRCMR). The foundation of the FBE marked a major change in the organizational structure of the DRCMR, which previously had been an independent department joining the clinical and research branch. Fortunately, the more explicit separation of clinical and research-related MR activities strengthened both the research activities and the long-standing partnership between clinicians and researchers. Here I wish to express my gratitude to all staff members of the clinical MR section for their continuous support and fruitful collaboration with the various research teams.

The new organizational structure facilitated the possibilities for multimodal imaging and scientific collaboration with other research groups in the FBE and Amager-Hvidovre Hospital. An important milestone was reached when the Cardiovascular Imaging Unit (CIU) was established in late 2012 as cooperation between the FBE and the Department of Cardiology with Associate Professor Jens D. Hove as research coordinator. The intention is to develop a strong clinical and scientific cardiac imaging program, which entails cardiac MRI, computed tomography and advanced echocardiography. The cardiac imaging group involves collaboration with Professor Andreas Kjær (Department of Clinical Physiology, Nuclear Medicine & PET, Copenhagen University Hospital Rigshospitalet and Department for Endocrinological Research, Panum Institute, Faculty of Health, Copenhagen University) and the group has already initiated several research projects using cardiac MRI.

COUNT DOWN FOR THE NATIONAL 7T MR PROJECT ...

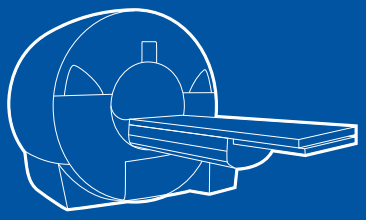
We are very proud that the DRCMR hosts the national 7T MR project which is another key element that will shape the future research at DRCMR offering ample opportunities for national and international cooperation and pushing the boundaries of biomedical brain imaging. Although the installation of the 7-tesla MR scanner is not expected until 2014, the national 7T MR project has already gained momentum. A more detailed update on the status of the project is provided in a specific section.

ADVANCES IN IMAGING NEUROSCIENCE

The DRCMR hosts an excellent MR-research infrastructure and a strong multi-national team of highly motivated researchers, making the DRCMR a highly dynamic research centre. The majority of research projects at DRCMR develops or applies advanced MR methods to unravel the function and structure of the human brain in health and disease. In 2011 and 2012, the neuroscience program at DRCMR experienced a major boost since significant advancements in diffusion MRI, multimodal image integration and computational modeling were paralleled by an increase in ambitious neuroscientific projects on brain maturation and plasticity, decision making, multiple sclerosis, movement disorders, and psychiatric imaging. Two major developments deserve a few comments:

THE CONTROL-OF-ACTION (CONTACT) GROUP FUNDED BY THE LUNDBECK FOUNDATION

The ContAct group is led by Professor Hartwig R. Siebner and funded by a "grant of excellence" (2011-2015) from the Lundbeck Foundation. The central research question is how the human brain flexibly integrates relevant contextual dimensions into appropriate actions. ContAct researchers integrate advanced brain mapping techniques, transcranial magnetic stimulation (TMS), pattern



classification and advanced modeling to identify neural interactions that determine predictive, inhibitory and intentional aspects of action control. The central question is how the human brain integrates relevant contextual dimensions with internal goals, expectations, and experience. An important line of research will combine advanced magnetic resonance imaging (MRI) with brain transcranial stimulation techniques to study causal interactions within motor brain systems and to trace sensorimotor plasticity.
The "ContAct" project also received generous support from the management of Amager and Hvidovre Hospitals who secured additional laboratory space for ContAct and in the summer 2011, the ContAct laboratories were established, including a laboratory for transcranial magnetic stimulation (TMS) and high-resolution electroencephalography (EEG). These laboratories are open to other groups at DRCMR who wish to pursue integrative neuroimaging projects that combine MRI with TMS or EEG.

RECRUITMENT OF TALENTED ENGINEERS AND NEUROSCIENTISTS

The DRCMR houses a highly dynamic international research community with a critical mass of well-trained, talented scientists and engineers who can advance the use of MRI in neuroscience. Over the last five years the number of researchers conducting research at DRCMR nearly doubled. 24 of the 65 researchers who are working at DRCMR are coming from abroad. Six post-doctoral researchers from Austria, France, Germany, the United Kingdom, and Sweden / USA joined the DRCMR in 2011 and 2012. Seven visiting scientists from Germany, Japan, Italy, and the Netherlands decided to conduct neuroscientific MR projects at DRCMR. These "new arrivals" have greatly inspired the research at DRCMR and make the DRCMR a very international and cosmopolitan place characterized by respect, openness, and collaboration.

DEVELOPING MR RELATED METHODS AND TECHNOLOGY

The quality of applied MR research critically depends on cutting-edge MR methodology. Therefore, we are very pleased that research at DRCMR has also contributed to push the border of magnetic resonance imaging and its biomedical applications.

DIFFUSION MRI

The diffusion imaging group led by Senior Researcher Tim Dyrby made substantial progress developing new types of diffusion MRI sequences that are sensitive to axonal diameters and cellular density providing unprecedented insights into the microstructure of the brain, its plastic dynamics and structural connectivity. Tim B. Dyrby, DRCMR was a key member of an EU consortium of 12 research groups where novel microstructure imaging techniques was developend that have the potential to change the face of neuroscience and medicine over the coming decade. The work relied on groundbreaking diffusion MRI technology and was funded by the future and emerging technologies program (FET/ICT) of the EU with a grant of 2.4 million Euros. The participants of the project, called CONNECT, were drawn from leading research centers in countries across Europe including.

HYPERPOLARIZED ^{13}C MR TECHNIQUES

While the main focus has traditionally been on brain research, other lines of MR research have been developed in recent years. This includes pre-clinical research into hyperpolarized ^{13}C MR techniques. Jan Henrik Ardenkjær-Larsen, who is an adjunct Professor at the Department of Electrical Engineering (DTU) and employed by General Electric (GE), took over the scientific leadership in the start of 2012 from consultant Per Åkeson. We are very pleased that this interesting line of research continuous to flourish at DRCMR and see great potential for translational scientific projects as evidenced by the recent collaboration with Professor Andreas Kjær, Chief Physician at Rigshospitalet, Copenhagen University Hospital, Dept. of Clinical Physiology, Nuclear Medicine and PET).

MULTIMODAL INTEGRATION

Another important area of research that has emerged in 2011 and 2012 is multimodal integration of various MR techniques with other neuroimaging modalities such as TMS, EEG, and PET. It is with great pleasure that we were able to welcome Axel Thielscher from the Max Planck Institute of Biological Cybernetics in Tübingen, Germany as research group leader. Axel Thielscher is also employed as Associate Professor at the Department of Electrical Engi-

neering, Technical University of Denmark (50%). We are confident that multimodal integration will be central to the research at DRCMR and foster the already very enthusiastic and productive collaboration with the Technical University of Denmark.

NEW FACILITIES AND HARDWARE

More office space

The rapid growth in number of employees over the last years caused a notorious shortage of desk space with a workstation to process their MR data. We were very pleased that part of the funding we obtained for the national 7T MR facility was earmarked to the construction of new offices for research staff. Around 400 m^2 of office space and meeting rooms became available in the newly constructed "pavilion 7" next to the existing DRCMR building by the end of 2012. This was an important improvement that was greatly appreciated by all employees and will benefit the scientific collaboration between centres in the national 7T project.

Expanded scanning capacity

The increasing number of researchers at DRCMR also produced increasing "pressure" on the MR scanners. The distribution of scanning time became more and more a problem. In the end of 2012, a 3 tesla Philips Achieva system with a 32-channel head coil and other state-of art MR equipment was installed in the MR research section. Since this research-only scanner will be dedicated to scientific projects, more MR scanning time will be available – matching the demands from an increasing number of researchers and projects.

New computing facilities

In 2012, DRCMR purchased a state-of-the-art scalable server infrastructure platform to address the continuously increasing demand for computational capacity in our hunt for detecting even finer dynamic changes of the brain and its network. The new computing facility is currently equipped with 22 high-end dual processor server nodes where each node comprises a total of 200 processing cores and 640 Gb of physical memory. Increasing activities at the DRCMR produce enormous amount of data and therefore our new servers have been supplemented with an upgraded storage facility, with a total of 200 Tb raw storage.

DRCMR retreat at the Helene Elsass Center in Charlottenlund

NATIONAL AND INTERNATIONAL COLLABORATIONS

Collaboration is the key to successful research. Therefore, we are very pleased that DRCMR researchers have established strong collaborative links to major research groups in Denmark and abroad. The DRCMR is partner in two Lundbeck Foundation centers

The Lundbeck Foundation Center for Integrated Molecular Brain Imaging (CIMBI), headed by Professor Gitte Moos Knudsen (Neurobiological Research Unit, Department of Neurology, Copenhagen University Hospital Rigshospitalet), addresses basic questions regarding interindividual differences in behavior and personality in healthy people that are related to interindividual variations in the serotonergic neurotransmitter system (www.cimbi.dk).

The Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia (CINS) is headed by Professor Birthe Glenthøj (Mental Health Centre Copenhagen, Copenhagen University Hospital Glostrup, Capital Region of Denmark). The primary aim of CINS is to optimize and individualize the treatment of patients with schizophrenia by providing a scientific basis for new treatment and preventive strategies directed at the pathogenetic and pathophysiological disturbances in individual patients with schizophrenia (http://www.psykiatri-regionh.dk/CINSR).

Beyond these pre-existing collaborations, DRCMR joined forces with other research centers kicking of a number of new collaborative research projects in 2011 and 2012:

The "Arv, Miljø og Funktion", ("Inheritance, Environment and Function") project employs a translational approach to understand the link between genetic and environmental factors and psychiatric disorders. The DRCMR is concerned with phenotyping of brain structure and function in individuals who carry a 22q11 microdeletion which confers a considerable risk for psychiatric disorders. This research is conducted in collaboration with Professor Thomas Werge who is heading the Research Institute for Biological Psychiatry at the Mental Health Centre Sanct Hans, Capital Region of Denmark and Dr. Michael Didriksen, Associate Director - Synaptic transmission. H. Lundbeck A/S – Denmark. The neuroimaging program is conducted in collaboration with a EU-funded training network, the Psychiatric Diagnostic and Prevention Consortium (psych-dpc).

Tackling the "cocktail party problem". In 2012, the DRCMR also has become neuroimaging partner of the Oticon Centre of Excellence for Hearing and Speech Sciences (CHeSS). CHeSS has been founded under the leadership of Professor Torsten Dau, DTU-Electro and has a special focus on cross-disciplinary basic research in the audiological disciplines (http://www.hea.elektro.dtu.dk/about_us/Presentation). The different disciplines will investigate the codes of the human auditory system, and the results are expected to open up a deeper understanding of how speech and music are represented in the brain. One important goal of research in CHeSS is to tackle the so-called 'cocktail party problem' which refers to hearing in noisy situations where people with a hearing impairment are especially challenged.

Grammer in the brain. In 2012 the interdisciplinary research group on Information PROminence and GRAMmar (PROGRAM) was selected as one of 18 projects that were funded by the **University of Copenhagen Excellence Program for Interdisciplinary Research** (UCPH 2016). The PROGRAM group is headed by Associate Professor Kasper Boye, Department of Scandinavian Studies and Linguistics at Copenhagen University (http://program.ku.dk/). The PROGRAM group strives toward unraveling how grammar contributes to the prominence of information in language.

Migraine and brain structure. The Women with Migraine with Aura Neuroimaging (WOMAN) study is a collaborate effort led by Professor David Gaist from Odense University Hospital. In the WOMAN study, the Department of Neurology, Odense University Hospital & Institute of Clinical Medicine, Faculty of Health Sciences, University of Southern Denmark, the Danish Headache Center, Department of Neurology, Glostrup Hospital, University of Copenhagen, the Danish Twin Registry, University of Southern Denmark and the DRCMR joined forces to assess whether migraine with aura is associated with structural lesions and morphology changes of the brain evaluated by MRI. The WOMAN study is carried out among female Danish twins and is supported by Lundbeck and Novo Nordisk Foundation & Fabrikant Wilhelm Pedersens og hustrus mindelegat.

FEATURED PROJECTS

ALCOHOL VS. YOUNG DANISH BRAINS

by Morten Andersen

Using a unique study design, DRCMR and its partners have an unprecedented opportunity to provide new insights into how high alcohol consumption during adolescence may impact the brain.

Adolescence is the transition from childhood to adulthood and is behaviorally characterized by increased peer-directed social interactions, reward- and novelty-seeking, and risk-taking behaviors. The cognitive and behavioral changes observed in adolescence are paralleled by significant regional specific anatomical and functional changes in the underlying brain systems. Adolescence is also a period in which individuals start exploring the use of alcohol and other drugs and in which several psychiatric illnesses, such as anxiety and mood disorders, psychosis, and substance use disorders emerge.

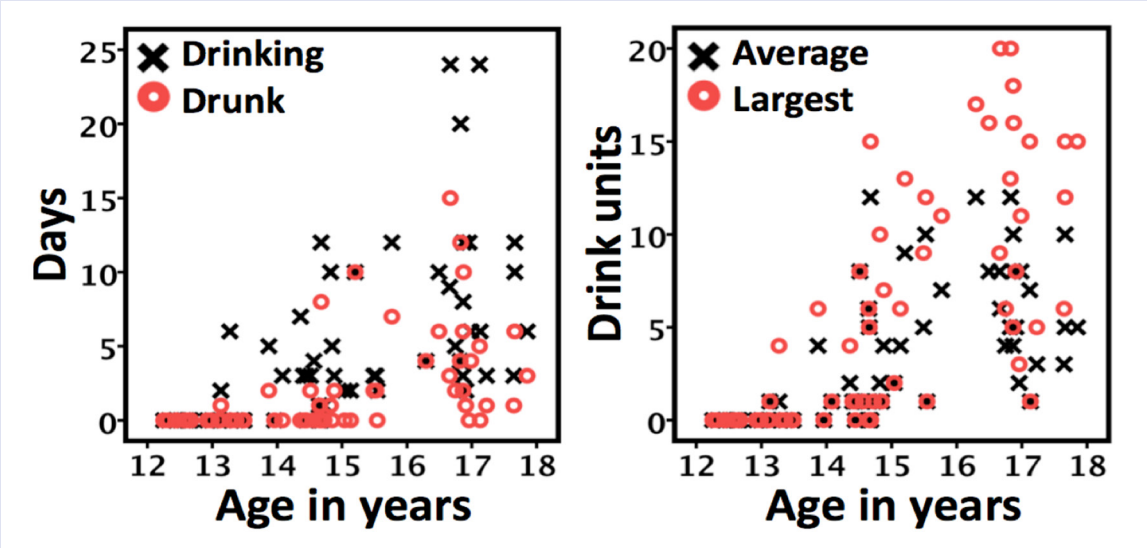
For several years now Danish teenagers have topped statistics on alcohol consumption. The phenomenon does seem deeply rooted in Danish culture, in which social drinking is not only widely accepted but also expected. Based on unique research, DRCMR and its scientific partners will be able to investigate how the developing brain may be affected. Further, any observed structural and functional brain changes can be linked behavior, and social and cognitive functions.

The expected advance in our understanding on how alcohol may affect the developing brain is made possible by an ongoing longitudinal study in healthy children, the HUBU ("Hjernens Udvikling hos Børn og Unge", i.e. Danish for Brain Maturation in Children and Adolescents) project, which started in 2007.

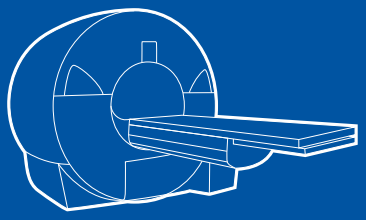
The major aims of HUBU are to define the degree of variability in maturational trajectories of different brain circuits among healthy children, and to link these to evolving cognitive abilities and social-emotional behavior, however, the impact of environmental factors such as alcohol are also investigated.

Overcoming the "hen-egg" problem

Importantly in relation to studying the effect of alcohol, the 92 healthy children recruited at study start were between 7 and 13 years of age, meaning that they at the time had not entered into the pattern of alcohol consumption, which characterizes the vast majority of Danish adolescents.



Scatter plots showing the alcohol consumption of 65 participants across age within the last 6 months before the 10th visit. The left plot shows the number of days, the participants drank alcohol or were drunk. The right plot shows the average and the largest number of drink units drunk in one day. Uniquely, MRI and psychological data have been acquired before the participants started to drink alcohol.



"Since we were able to map brain structure and function prior to exposure to alcohol, we can begin to detect changes when they start to drink alcohol. This is a world's first," says DRCMR post doc Kathrine Skak Madsen, heading the alcohol-related research in HUBU.

Other studies have focused on participants who had already begun drinking alcohol, making it difficult to document the specific changes due to the so-called "hen-egg" dilemma. Studies may show that young adult binge drinkers perform worse in a number of cognitive tests. However, it is possible that they at least to some extent performed worse on these tasks even before they started drinking – and this could indeed have been a part of the reason they started drinking in the first place.

"The way HUBU is set up, we will be able to document the changes associated with alcohol use. It is our hypothesis, that the effect of alcohol will be more severe in brain regions, which are maturing the most during that particular part of life. For instance, the regions linked with working memory, and social and emotional interactions are known to develop rapidly during adolescence," Kathrine Skak Madsen explains.

Closing in on markers for high alcohol use

Excessive use of alcohol in adolescence has been linked to impaired social and cognitive functions, such as loss of executive function, memory and attention. These effects can also be linked to structural and functional changes in the brain. For instance, a prospective fMRI study in 38 young adolescents with very limited alcohol use at baseline found that less activity on a response inhibition task in several brain regions, including fronto-parieto-striatal network regions, predicted heavy alcohol use 4 years later.

The HUBU Study

The HUBU project ("Hjernens Udvikling hos Børn og Unge", i.e. Danish for Brain Maturation in Children and Adolescents) began in 2007. The project recruited 92 healthy children aged from 7 to 13 years for a longitudinal study of brain and behavioral development.

The major aims of HUBU are to define the degree of variability in maturational trajectories of different brain circuits among healthy children, and to link these to evolving cognitive abilities and social-emotional behavior. The impact of environmental and genetic factors is also investigated.

The participants are being assessed at 6-month intervals. The key assessments methods are structural MRI scanning of the brain, including diffusion-weighted imaging (DWI), enabling in vivo studies of microstructural maturation of gray and white matter and functional MRI scanning, allowing to probe brain activity during rest and while performing a task in the scanner. Besides the MRI scanning, which takes 45 to 60 minutes, participants undergo a 2-hour psychological and clinical assessment during each visit. This assessment covers e.g. response inhibition, emotional control, decision-making and risk behavior, attention, working memory, visual and verbal memory, executive function, language processing, verbal fluency, emotional face recognition, psychomotor speed, and visio-constructional ability. Also a number of risk factors are addressed through questionnaires: personality traits, alcohol, tobacco and drug use, stressful events, and family history of psychiatric disorders. Further, patterns of sleep, physical activity, social and emotional function and other relevant factors are monitored. Last but not least genotyping has been performed. The study is unique both in its duration, the high frequency of assessments (every 6 months) and in the variety and quality of assessment tools.

The HUBU study is sponsored by Amager and Hvidovre Hospital, the Lundbeck Foundation, the Danish Council for Independent Research / Medical Sciences, the Danish Agency for Science, Technology and Innovation, and the Faculty of Health Sciences of the University of Copenhagen (SUND). Besides DRCMR the project involves the University of California, San Diego, USA; Danish School of Education; National Center for Reading; Psychology department, University of Southern Denmark and Center for Integrated Molecular Brain Imaging.

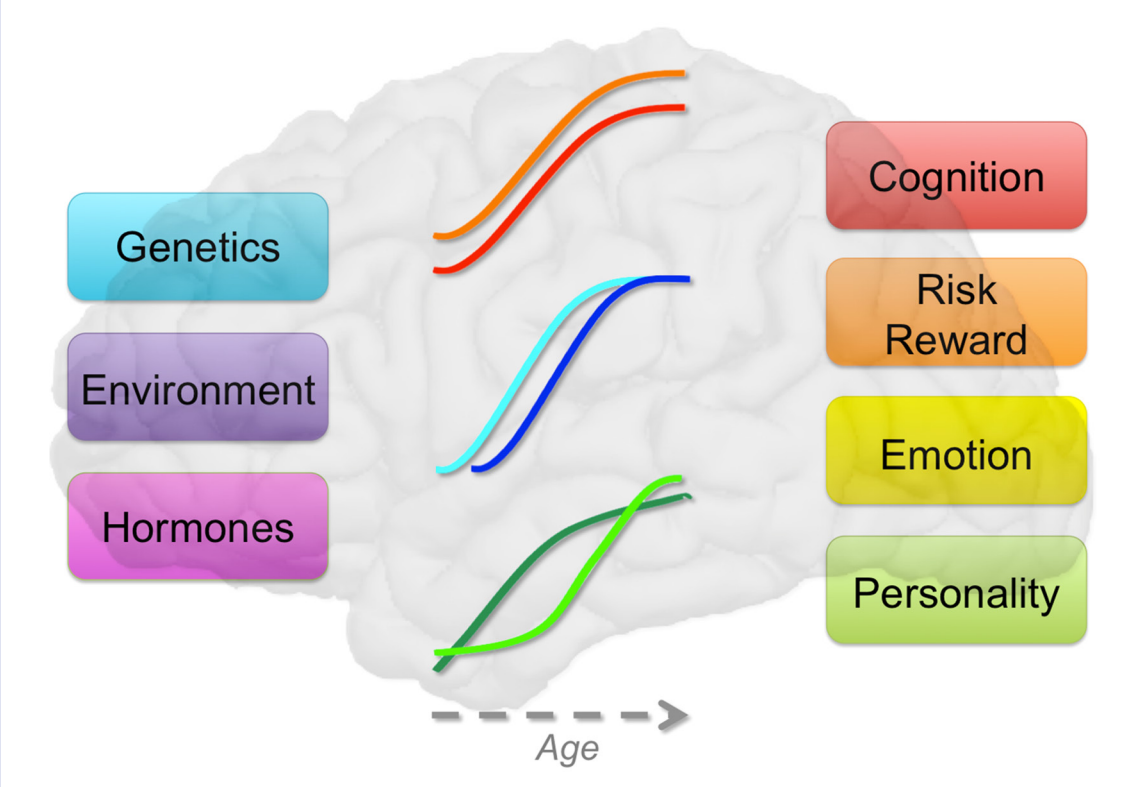
Recently, a DWI (diffusion-weighted imaging) study found that lower baseline fractional anisotropy (FA – thought to reflect axonal density, diameter and myelination) in the fornix and superior corona radiata predicted the number of days with substance use the following 18 months in 16-19 year olds, who were already using substances at baseline. These studies raise the possibility that there might be functional and structural markers in the brain that are associated with a predisposition for heavy alcohol use. *"In other words: differences in certain regions, if present prior to the onset of drinking, may trigger a disposition for heavier consumption. However, this hypothesis has been especially difficult to establish in other studies. Characteristic deviations in heavy drinkers have been seen, but again it has been impossible to know whether these changes have been caused by alcohol or vice versa. In HUBU we will be able to tell,"* Kathrine Skak Madsen comments.

A pattern of binge drinking

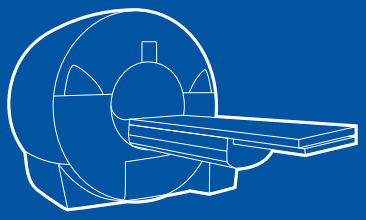
The HUBU participants follow the drinking pattern, which has become characteristic for Danish adolescents. Questionnaires filled out by the participants show a steep increase in the frequency of binge drinking (five or more drink units) in a subset of the older participants.

"While studies in other countries have sought out subjects with high alcohol consumption, we sadly do not need to do that. The general consumption in Denmark is just very high," Kathrine Skak Madsen notes.

According to senior scientist William Baaré, group leader for brain maturation research at DRCMR: *"The pattern of Danish adolescent binge drinking has developed over some decades and*



The HUBU project acquires a wealth of longitudinal data in several domains (boxes). The line plots in the figure´s center represent different theoretical individual differences in the maturational trajectories of two fictive children, represented in light/dark blue, red/ orange and light/dark green. Orange/red depicts variable asymptotes (stable individual differences), blue depicts differences in the phase of maturation, and green depicts variable shapes of maturational trajectories. Variability in maturational trajectories may be caused by different factors, such as genetic, environmental (e.g. alcohol and drug use, stressful events, physical activity) and hormonal variability.



has various underlying reasons, most of which are presumably cultural. For the individual adolescent it may be difficult to break free from this pattern. A typical remark you'd hear when trying to find common ground on the drinking habits of kids, would be something like "Let them have some fun. It's not like we didn't have a good time ourselves at that age, and we've done all right, haven't we". However, while it is well known that excessive use of alcohol impacts the brain negatively, it has been difficult to document how much damage may be done to the developing brain with the high level of alcohol intake seen in Danish youngsters."

This scene is about to change.

"HUBU will provide unique insights regarding the effects of alcohol in adolescent brains. Further, it is likely that we can show how some of these alterations will cause a disposition for even heavier drinking in some individuals, creating a vicious circle. If this is true, an indifferent attitude toward adolescent drinking will become increasingly hard to defend," William Baaré concludes.

THE GAME OF MINDREADING

by Morten Andersen

Do you mind me reading your brain and predicting your actions? Patients with Parkinson's disease, stroke, and hand dystonia are some of the patients likely to benefit from new insight into the processes involved in controlling our actions.

You'd be foolish to face Hartwig Siebner in a game of poker. That is, at least if the brain scientist and head of DRCMR is permitted to place you in an MRI scanner during the game.

"Mind reading really interests me. And I can say with confidence, that we are quite good at it here," he opens.

Before dwelling into the details of how it's done, it should be noted that this type of mind reading is much more than entertainment or a possible con scheme for gamblers. For instance, the treatment of several neurological diseases such as Parkinson's disease, stroke, and hand dystonia, is likely to benefit from the knowledge obtained in the "ContAct" project led by Hartwig Siebner.

With the formal title of "Mapping, Modulating and Modeling the Control of Actions" the project focuses on brain processes involved in the regulation of actions. This is a coin with two sides. Just as important as the processes leading to a certain action, are the processes which exclude alternatives. Hartwig Siebner illustrates his point by grabbing the cup of coffee in front of him:

"In principle I would be able to lift this cup in multiple different ways, but my brain has selected a favorite method, which I will automatically apply. By selecting just one option for a routine action and excluding others, the brain rationalizes its work."

When the brain is challenged

The brains' control of a routine action can be challenged.

"If, for instance, I am about to lift an empty cup, but in fact somebody had filled it without my knowledge, my brain will need to do a very quick readjustment of the planned movement. This process is really interesting. Here we are at the very core of the brains' functionality. It is highly imaginable that we may be able to help patients with various brain defects by stimulating the regions which are responsible for this type of adjustment. Quite often these patients experience difficulties in performing certain everyday life actions, and it would be a tremendous help if their brains could be stimulated into creating new routes to control actions instead of the original routes which are malfunctioning."

Being a pioneer in neuro-navigated trans-cranial magnetic stimulation (TMS), Hartwig Siebner does have special hopes for this non-invasive method. TMS enables the painless activation of certain brain regions. At the DRCMR laboratories, TMS can be applied while brain activity is mapped in an MRI scanner. The simultaneous use of TMS and MRI neuroimaging is only possible in very few laboratories worldwide. The combination allows for accurate monitoring of the TMS effects on the brain.

"We have shown that we are able to stimulate a relevant region and shape its function positively, and under the circumstances the effect may last from a few seconds to an hour. So, while the effect is by no means permanent, it could well be that it may assist in giving just the push needed for a given patient to refocus a crucial brain process."

Activating pathways in the brain

An example is patients with Parkinson's disease. Beside visible symptoms such as trembling the disease is often characterized by a lack of vigor. Seemingly, changes in the brain deprive the patient of the signals which normally lead to spontaneous initiative. Instead of having a relative or a health care worker prompting activity, it would obviously be highly beneficial if the patients' own brain could do the job through a "strengthened" pathway.

Similarly, the research is relevant to patients recovering from a stroke. Several training regimes exist, but not all patients benefit to the same degree. At DRCMR the patient can be mapped prior to the initiation of training and after for instance one week. If no effect is seen, one might consider changing the format of the training.

Another group likely to benefit is patients with special forms of dystonia, for instance a violinist experiencing un-voluntary finger cramps while playing the instrument.

"It is not uncommon that people are forced to give up their profession on account of severe finger cramps. Again, it would increase their quality of life tremendously if it was possible to find new routes for the brain-muscle interaction, so they could continue their activity," Hartwig Siebner states.

Keen to investigate clinical implications

Despite the promising perspectives for treatment of various groups of patients, Siebner emphasizes that ContAct so far has focused on the basic rules of action control, studying mainly healthy individuals.

"We are keen to investigate clinical implications, but that would be in the next round of projects. Right now it is all about knowing what goes on in the brain."

The group is highly multidisciplinary involving researchers with both clinical and basic science background covering diverse fields such as behavioral studies, brain mapping, trans-cranial stimulation of the brain, neuroimaging, engineering, pattern classification, network modeling, and others.

Besides TMS, a suite of other research tools are utilized including EEG, diffusion sensitive and functional MRI. The group has developed several devices which can be used during an MRI scan. The experiments all focus on understanding the brain processes involved in certain types of decisions, and how they can be manipulated.

An excellent take-off – An Interview with Sissel Vorstrup

by Morten Andersen

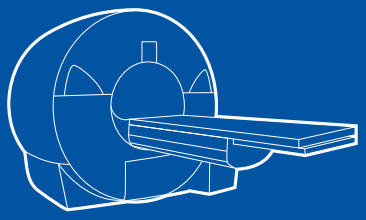
"Within a few years, DRCMR has positioned itself as a highly productive research center with many publications and an extensive international network. The fact that the center has managed to maintain its focus while growing considerably is impressive."

"The main focus area is brain processes controlling motor actions. This is crucial for instance to hand dystonia, a huge problem for musicians and other groups. The condition involves finger cramps which may ultimately stop the individual from continuing within his profession."

"In addition, it is a quality that the DRCMR is open to various clinical applications. The center maintains a broad focus, mainly concentrating on methodological issues. The center may have to focus its activities more in the future, but so far we can only be satisfied with the outcome of the support, we have given. DRCMR has had an excellent take-off, establishing laboratories and hiring international staff from around the world, while at the same time maintaining a high output of scientific publications."

Sissel Vorstrup, Associate Director of Research, Lundbeckfonden.

Lundbeckfonden has supported the establishment of 15 research centers within medicine and natural sciences, including the DRCMR. In addition, the foundation supports a number of research projects at the DRCMR. The main purpose of Lundbeckfonden is to secure and develop companies related to the foundation – Lundbeck, Alk-Abello, and Falck – and to support high quality scientific research.



A cautious species

In one of the studies the subject is playing a virtual dice game. A number from 2-6 will give him a bonus accordingly plus the right to continue. But should "1" come up, he will lose the accumulated sum.

"A computer would know exactly when to stop, as the optimal moment for exiting the game with maximal probability of gain can be put on mathematical formula. However, as humans we tend to stop sooner than the optimal moment, because we are afraid of losing," Hartwig Siebner notes.

"This is interesting in itself, as it shows that we as a species are quite risk averse. Even more interesting though, is the fact that some individuals tend to play on for much longer. Not only is the variability high between individuals, it is also dependent on a number of factors such as mood, motivation etc. We are confident that these differences are reflected in the physical composition of each individual's brain."

The individual differences in behavior can be picked up in various ways.

"We have built in tiny mechanical sensors inside the computer mouse operated by the participant. Thus we are able to measure how much the force of pressing a button to continue the game becomes weaker, the more the participant approaches his "decision boundary". The boundary marks the point in the game, where the probability to continue or stop is equal. The dice game is a good example of an experiment, where we want to extract the brain activity pattern that predicts whether the subject will stop or continue gambling in the next trial. You can imagine that I would like to play a game against this person. We really are close to actual mind reading here."

We are far from being robots

It is possible to manipulate the decisions in various ways.

"In the outset the subjects press a button if they wish for the computer to throw the next virtual dice. Alternatively, we can set the computer in an automatic repetition mode in which it continues until the subject commands it to stop by pressing a button. We predict that the average participant will play on for longer if the physical effort is higher to stop the dice game than the effort to continue the game - even though the math and the probabilities involved are exactly the same as before."

Another way of manipulating results is by changing the individual's motivation.

"For instance we have been able to improve the results of certain cognitive tests by subjecting the participants to TMS. But interestingly, the improvement was only found, when they were motivated by a real, economic reward," says Hartwig Siebner, summing up:

"This again emphasizes how control of action is a complex matter. We cannot look at the human as a robot to which a change or stimulation of the brain will automatically prompt a certain response. We need to keep track of a variety of disciplines involved, and to be open to combinations of techniques, especially as we approach clinical implications within the coming years."

MRI HAS LIFTED TREATMENT OF SCLEROSIS

by Morten Andersen

The availability of MRI has moved the treatment of multiple sclerosis to a new level. This is according to Associate Professor Finn Sellebjerg, Danish Multiple Sclerosis Center, Copenhagen University Hospital Rigshospitalet.

"In particular, significant progress has been made in treating the most common form of sclerosis where patients experience attacks alternating with calm periods. With MRI we are able to detect, whether the patient is benefitting from the treatment or not, which has been crucial to this success. Further, we may predict from the images whether a given patient is likely to benefit from a suggested form of treatment," says Finn Sellebjerg.

Still, there is a need for new or more efficient treatment.

"One example is patients with a different subtype of the disease where the first attack occurrs later in life but progress without calmer periods of recovery. Typically, patients with this so called progressive type of sclerosis do not benefit from the currently available treatment regimes."

A joint Rigshospitalet/DRCMR project has addressed this.

"Based on the project we are confident that we will be able to provide an efficient treatment for patients with progressive MS within a reasonable time period. The drug has shown positive effects in other types of MS but was not expected to benefit progressive MS. So it was a surprise to many that the research project did indeed documented an effect," Finn Sellebjerg notes.

In the project, the group at Rigshospitalet has investigated the efficiency of treatment through biochemical analysis of blood and spinal fluid, while DRCMR has carried out MRI scans. The project was funded by Skleroseforeningen and by the Danish National Council for Strategic Research.

Finn Sellebjerg is keen to continue the cooperation with DRCMR:

"While a treatment for progressive MS patients has been found, we still would like to better understand this subtype of the disease. Presently a standard MRI scan does not allow us to distinguish between the various subtypes, which would be highly desirable. Firstly, this would allow for suggesting the proper treatment regime for the given patient and secondly, it would help us in understanding the cause of this aggressive subtype. Once we understand the mechanism better, we stand a better chance of developing a more specific treatment regime."

Finally, Finn Sellebjerg and his colleagues at the Danish Multiple Sclerosis Center look forward to further progress in MRI:

"Current conventional imaging techniques are not able to reveal in details how severely the brain of a given patient is affected. We do have high hopes for the continuing collaboration with DRCMR in this regard, especially since the center will soon host even more powerful scanners (i.e. the national 7T project, Ed.). Also ever more specialized methods for the currently available scanners are developed."

Multiple Sclerosis (MS)

The number of patients living with multiple sclerosis continues to rise in Denmark. This is partly caused by a rise in newly diagnosed cases, especially among women. However, the rise also reflects a progress in efficienct treatment of multiple sclerosis , leading to a significantly longer average life after receiving the diagnosis. Danish Multiple Sclerosis Center has cooperated with DRCMR for several years.

HYPERPOLARIZED MRI GOES CLINICAL

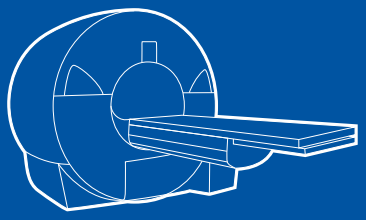
by Morten Andersen

As a consequence of a scientific cooperation with DRCMR, both Rigshospitalet and Skejby Hospital have invested in hyperpolarized MRI. The technique provides new diagnostic possibilities for several groups of patients, for instance patients with prostate cancer.

Based on a pioneering effort by the Hyperpolarized MRI Research Group at DRCMR a novel imaging technique will soon become available to patients at Copenhagen University Hospital Rigshospitalet, and Skejby University Hospital, Aarhus. After some years of scientific cooperation with the group at DRCMR, both hospitals have decided to invest in the technology for clinical research. They thereby join an exclusive circle of internationally leading hospitals using hyperpolarized MRI.

One group that is likely to benefit from this collaboration is patients with prostate cancer . It is well known that this type of cancer is highly variable – being aggressive in some patients while in others the development is very slow. Ideally, the treatment approach should be customized according to type, but at present the non-invasive diagnostic tools cannot distinguish between various subtypes.

PET-CT scans may provide this type of insight, but due to the ionizing radiation involved in this technique it is not suited for frequent follow-up scans to monitor the progression of disease or response to treatment. As for MRI, the technique has traditionally been dismissed due to lack of sensitivity. MRI normally images the water in the body, but cannot image the low concentration of cellular metabolites. This situation has changed with the development of hyperpolarized MRI.



Early notice on cancer therapy efficiency

Besides being non-invasive and free of ionizing radiation, the method shows promising results as a method to monitor the efficiency of therapy in early stage of the disease.

"With other methods one has to wait to see the volume of the tumor change to know if the treatment works. This is a rather crude measure. With hyperpolarized MRI it is possible to detect biochemical changes in the cells, and you do not need to wait for the volume of the tumor to change," says Jan Henrik Ardenkjær-Larsen, Professor at DTU and one of two group leaders for the Hyperpolarized MRI Research Group at DRCMR.

"Since the equipment here at DRCMR is not qualified for clinical use, we have not been able to scan patients. But based on MRI scans of animal models done in cooperation with groups at the two hospitals and at Copenhagen University and Aarhus University we can say that the method is promising," notes Senior Researcher Lise V. Søgaard, preclinical research group leader at DRCMR.

Worldwide about 30 groups have put the novel technique to use.

"Only six of these groups will soon have clinical equipment. The groups in Copenhagen and Aarhus will now be joining them," says Jan Henrik Ardenkjær-Larsen.

The "magic" of hyperpolarization

Traditionally, MRI will require a fairly large sample of molecules in order to get good images. Thus, in a biological context the technique is normally reserved for imaging substances like water, which is abundant in the body. Following the fate of a substance occurring in small quantities such as an injected tracer or cellular metabolites related to a given type of cancer cell would not be possible.

However, hyperpolarization is capable of enhancing MRI sensitivity by as much as a factor of 100,000.

The first enhancement is achieved by doing the polarization under cryogenic conditions at around 1 K. By dampening the thermal energy, the signals of interest are increased by a factor of 300.

The remaining enhancement is achieved through the "magic" of hyperpolarization. By a technique known as Dynamic Nuclear Polarization (DNP), it is possible to align the nuclear spins in a biological molecule. The alignment "ear-marks" the probe atoms, which in turn makes it possible to follow their fate once injected into the body. As the nuclei in the surrounding biological matter have random spins, the ear-marked spins will stand out by a factor of 100,000 against the background level.

Highly suited for studying metabolism

The studies aim at a better understanding of major chronic diseases. Due to the urgent need for better diagnostic tools for prostate cancer, this disease is in focus. However, several other groups of patients are likely to benefit. For instance, DRCMR is engaged in projects related to diabetes and cardiac ischemia. The studies are done on animal models created by groups at Copenhagen University and Aarhus University.

"Collaboration with experts from different research areas is necessary for these types of studies. The two universities have the expertise for creating these advanced animal models, while we are the experts on the MRI and hyperpolarizing techniques. We also have experience with creating simple animal models and facilities to keep small animals here," explains Lise V. Søgaard.

The group at DRCMR has experience with various hyperpolarized molecules. For many applications molecules containing ^{13}C are well suited since carbon, normally in the form of ^{12}C, is present in high quantities in all biological matter.

"The method is highly suited for biological research, as it is possible to follow the compound when it engages in biochemical reactions and is transformed to other substances. This makes the technique well suited for studying cell metabolism. We can even tell, from which substance the signal comes," explains Jan Henrik Ardenkjær-Larsen. Along with his positions with DTU and DRCMR he is a consultant at GE Healthcare. The company manufactures the machine utilized for preparing the molecules under the trade name Polarizer.

The fact that DNP uses ^{13}C is also a limitation as the isotope has low natural abundance. On the other hand, this limitation also means that the hyperpolarization technique has high specificity, since other substances in the body do not produce a signal.

No time to relax

There is no time to relax once the tracer has been prepared. As the polarization is rapidly lost, you have no more than a few minutes to get your images. Thus it is paramount that the sample preparation is situated right next to the MRI scanner. For clinical use the equipment will need to be in vicinity of the patients, as will be the case at Rigshospitalet and Skejby Hospital. After due qualification procedures both hospitals expect to be fully operational in 12-18 months' time.

This will by no means make the hyperpolarization activities at DRCMR redundant, Lise V. Søgaard emphasizes:

"We hope to be able to continue our fruitful cooperation with the university groups. Through scans on animal models we hope to pave the way for new diagnostic possibilities to a wide range of patients."

Also, development of alternative tracers will be an important activity, according to Jan Henrik Ardenkjær-Larsen:

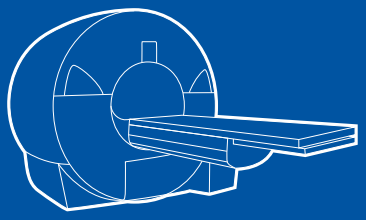
"Besides cell metabolism, which is a well-known marker for cancer cell activity, it is likely that monitoring other factors such as acidity or redox-potential may improve diagnostic procedures. Our current tracers are not ideal for those purposes, but we do have several ideas which we are keen to develop."

THE FIRST MICRO-STRUCTURE ATLAS OF THE HUMAN BRAIN HAS BEEN COMPLETED – THE CONNECT PROJECT

Senior researcher Tim B. Dyrby, DRCMR was a key member of an EU consortium of 12 research groups, who have built the first atlas of white-matter microstructure in the human brain. The project's final results have the potential to change the face of neuroscience and medicine over the coming decade. The work relied on groundbreaking MRI technology and was funded by the future and emerging technologies program (FET/ICT) of the EU with a grant of 2.4 million Euros. The participants of the project, called CONNECT, were drawn from leading research centers in countries across Europe including: Israel, United Kingdom, Germany, France, Denmark, Switzerland and Italy. On Friday, October 19th 2012 after 3 years of research, the project investigators meet in Paris to announce the conclusion of the project in celebratory mood.

Up to now, biomedical research teams around the world studying brain science rely on a brain atlas that was produced by painstaking and destructive histological methods on the brains of a few individuals who donated their bodies to science. The new atlas uses MRI exams of over 100 subjects. MRI produces three-dimensional pictures of each brain, which are then combined to form the atlas. CONNECT developed new advanced MRI methods providing unprecedented detail and accuracy in the new atlas. The atlas is similar to what we might obtain by examining every mm2 of brain tissue (around 100 million per brain) in each brain with a microscope: the new MRI methods automate that impossibly painstaking process and, moreover, leave the brain intact.

The key novelty in the atlas is the mapping of microscopic features (such as average cell size and packing density) within the white matter, which contains the neuronal fibers that transmit information around the living brain. The breakthrough in this project was made possible by new MRI technology that produces new kinds of images of the human brain non-invasively. In addition, the atlas combines and averages information from more than 100 healthy subjects aged 25-35 years. The results of the project, obtained through advanced image processing techniques, provide new depth and accuracy in our understanding of the human brain in health and disease. The new atlas describes brain's microstructure in standardized space, which enables non-expert users, such as physicians or medical researchers, to exploit the wealth of knowledge it contains. The atlas contains a variety of new



images that represent different microscopic tissue characteristics, such as the fiber diameter and fiber density across the brain, all estimated using MRI. These images will serve as the reference standard of future brain studies in both medicine and basic neuroscience.
The project will dramatically facilitate and promote future research into white matter structure and function. Historically in neuroscience, the vast majority of research effort has been invested in understanding and studying gray matter and neurons, while white matter has received relatively little attention. This owes largely to the lack of effective research tools to study white matter, even though it comprises about half the volume of the brain. The new MRI methods that were developed in CONNECT allow researchers, for the first time, to visualize the micro-structure of the living brain over the whole brain. This opens new realms in our understanding of our most complex organ. In the future, the project members intend to use the technology they have developed to study the dynamics and time dependence of the micro-structure in white matter. For example they will search for a finger print or a trace that a cognitive task imprints on white matter microstructure encoding new experiences in the wiring of the brain. Another future direction is to characterize and understand micro-structural changes caused by different neurodegenerative diseases, such as Alzheimer's or schizophrenia, in order to develop better diagnostic procedures for these and other devastating conditions.

ANOSMIA

The history of how a Faroese family, without any sense of smell, was first recognized is a remarkable one. In the 60's a Greek doctor was practicing in the Faroe Islands. A young woman had been cleaning his kitchen and happy with a good days work she sat down to light a ciga-

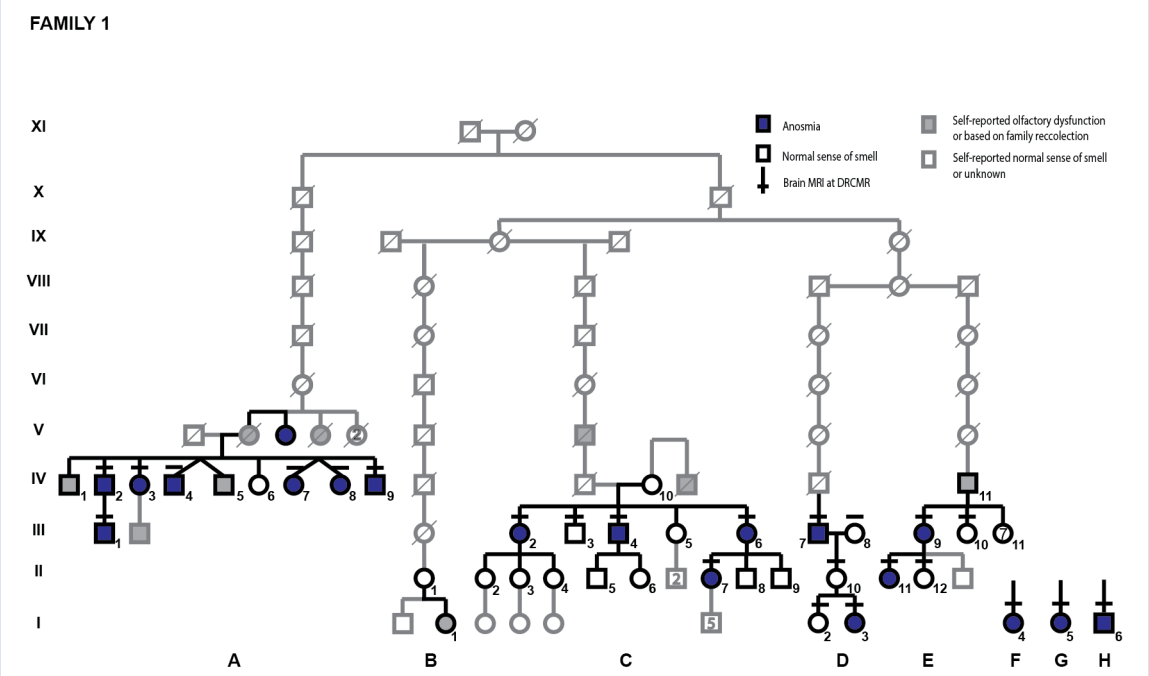


Figure 1: Faroese pedigree of the seemingly dominant inherited isolated congenital anosmia (ICA) with incomplete penetrance. A shared common ancestor is found in the 7th generation. Males and females are represented by squares and circles, respectively. Individuals with ICA are shown in blue, self-reported ICA is shown in grey, and individuals with normal sense of smell are shown in white. Individuals tested at DRCMR are marked by a black bar.

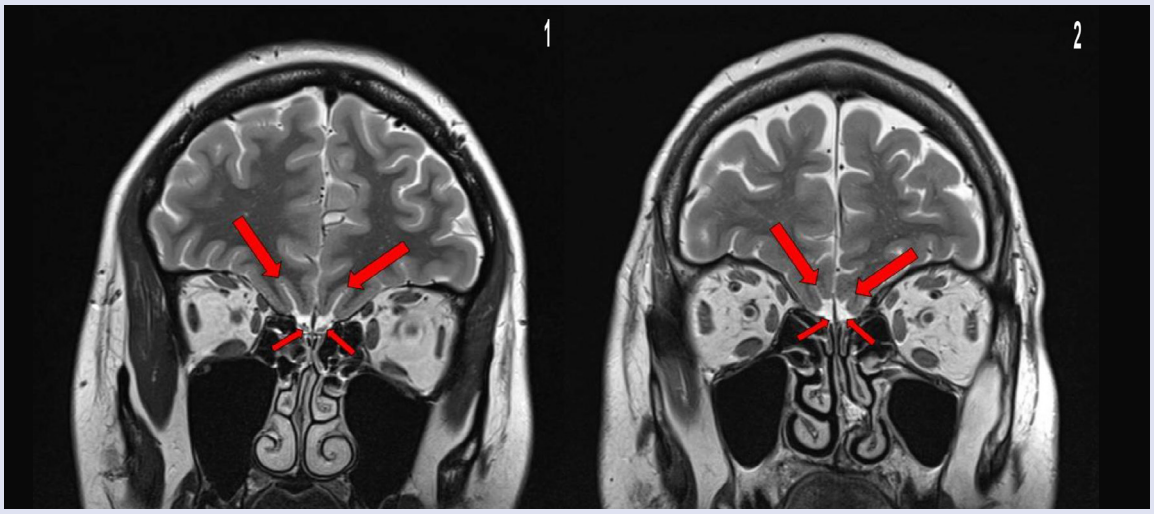


Figure 2: Coronal T2-weighted images. Picture 1 shows a normal olfactory bulb (small arrows) and olfactory sulcus (large arrows) on both sides. Picture 2 depicts aplasia of the olfactory bulb and diminished olfactory sulcus depth.

rette. During her work the gas-pipe behind the oven had fallen off and since she was unable to smell she was not aware that the room was filled with gas.

Our ability to detect odorous molecules through the air is a remarkable sense which has been essential for life throughout the history of evolution. For animals the sense of smell is essential for detection of danger, location of food, reproduction and parent-offspring relations and even fungi and bacteria are capable of detecting odorants. Nevertheless, the sense of smell in humans is probably the less recognized of our senses and often we first really acknowledge it in its absence e.g. during a cold or when suffering from permanent loss of smell (anosmia). Approximately, 5% of the population are anosmic. Typically, it is an acquired condition resulting from shearing of the olfactory nerve due to head trauma, infections in the nose, drug use or inhalation of chemical agents. In addition, anosmia has been reported as a pre-clinical sign in Parkinson´s and Alzheimer´s disease. A small minority of the anosmic population is born without a sense of smell and is classified as having isolated congenital anosmia (ICA). Even though ICA has a clear genetic component, no genes in humans have been described to date.

Fortunately for the young Faroese girl, the cigarette was never lid as the doctor returned just in time. It turned out that several family members of the young woman were also born without a sense of smell and the family was first published in 1969 (Hereditas, 1969;61 (3):413-6). At the Wilhelm Johannsen Centre for Functional Genome Research the family (Fig. 1) had gone through thorough genetic testing, but we were eager to learn more about the structural morphology of the brain of these patients and with this in focus a collaboration with DRCMR was initiated.

At DRCMR individuals with ICA and healthy controls from the Faroe Islands were scanned for structural differences in their brains. Behaviourally we tested odour threshold, discrimination and detection as well as taste, vision, hearing and touch. Furthermore, three fMRI paradigms were set up to test brain-activation during smell vs. non-smell, gustatory stimuli vs. water and viewing of smelling objects vs. non-smelling objects. This project is the first to comprehensively describe a large genetically heterogeneous cohort with ICA. The structural brain MRI demonstrated that patients with anosmia had absent or diminished olfactory bulb and olfactory sulcus depth, which confirmed our initial diagnosis (Fig. 2). In addition, we are able to visualize and describe the olfactory bulb and sulcus in this exclusive patient cohort in great detail, which provides us with new knowledge to the interesting field of olfaction.

THE NATIONAL 7T MR PROJECT

For years, it had been an important strategic goal to establish a national ultra-high field MR facility at DRCMR. It was Professor Olaf B. Paulson who gathered researchers from eastern and western Denmark in a national effort to secure Danish scientists access to this unique research instrument and to strengthen the Danish position in international MR-related research. This effort was eventually rewarded: In December 2009, the Danish Agency for Science, Technology and Innovation granted Hvidovre Hospital (3.6 million €). This was followed by a generous donation of 5.2 million € from the John and Birthe Meyer Foundation in June 2010. Hereby, sufficient funding was secured to finance the establishment of an ultra-high field MR facility for human use at DRCMR.

After a thorough evaluation process which involved site visits to major 7 tesla MR centers in the US, a decision was made. An actively shielded 7 tesla MR system operating at a magnetic field strength of 7 tesla was ordered from Philips in January 2012. This research-only MR system will provide unprecedented possibilities for *in vivo* mapping the human brain. Brain images acquired at ultra-high magnetic fields, for example, can be extremely detailed and the contrast differs significantly from those acquired at conventional field strengths. Functional MRI used to map brain activity and spectroscopic measurements of regional metabolite concentrations are among the techniques that will benefit most from the new scanner.

According to the national frame of the 7 tesla MR project, a National Steering group was established to guide the scientific work. The steering group represents a broad range of institutions that have participated in the 7T MR application.

A National success: sharing resources – an Interview with Prof. Leif Østergaard

by Morten Andersen

Over the last 8 years, an increasing number of brain researchers have travelled back and forth between Aarhus and Hvidovre. This tendency will only get stronger, according to Professor Leif Østergaard, Director of CFIN (Center of Functionally Integrative Neuroscience), Institute of Clinical Medicine, Aarhus University.

"The national 7T project will take our already extensive cooperation to an even higher level. Both technically and scientifically this new equipment will involve a number of CFIN staff."

Situated at Aarhus University Hospital, CFIN joins brain researchers from numerous departments, institutes and faculties within University of Aarhus and The Royal Academy of Music, in an effort to understand the human brain.

"Since we, just like the DRCMR, depend on highly advanced, expensive equipment it makes sense to cooperate closely especially around major new purchases of equipment," says Leif Østergaard.

"For instance, whereas the 7T scanner will provide extremely high spatial resolution, the existing MEG scanner here in Aarhus provides extremely high resolution in time. For some purposes, the 7T instrument will be better, while the MEG is superior for other tasks. Thus it is very valuable to be able to choose the best instrument for a given project without being restricted by the physical location."

"Also, we co-organize a number of workshops and similar events, in which scientists from both centers can exchange ideas. I find this very fruitful," says Leif Østergaard, pointing out diffusion-weighted imaging (DWI) as a field of strong mutual interest.

Further, the cooperation has spurred a joint initiative abroad, namely at the Sino-Danish Center for Education and Research in Beijing, China. The center, set up by the Danish Ministry for Science, Technology and Innovation in 2008, offers dual Masters' degrees at universities in both countries.

"By cooperating, CFIN and DRCMR are able to contribute to a Masters' degree with a strong profile in MR-imaging in the Sino-Danish center. This is just an example of the added value of cooperating, which has been truly beneficial for a number of years both on a personal and a professional level."

THE NATIONAL 7T MR PROJECT

The National 7T Project is a Unique Opportunity – an Interview with Torben Mogensen

by Morten Andersen

"As part of our strategy, Amager and Hvidovre Hospital have committed ourselves to be a front-runner in research. Seen in this context, DRCMR in general, and the 7T project specifically, provides a unique opportunity for strengthening research within several fields related to the understanding of brain functionality. The 7T scanner provides images of significantly higher resolution compared to conventional scanners making it possible to image structures such as individual nerve cells."

"At the same time I want to stress the fact, that 7T is a national project. As the scanner will be the only one of its kind in Denmark, vast opportunities for cooperation between the various Danish groups within brain research are opening up."

"Actually very few scanners of this capacity exist in the world. Thus the 7T project will pave the way for an even higher level of international collaborations than today. Current IT technology allows for easy exchange of research data between countries and between the Danish regions. My expectation is that many groups will be keen to visit. They can have their scans executed here, and then go back to conduct the data processing and analysis at their home base."

Torben Mogensen, Deputy Director, Amager and Hvidovre Hospital, Region H.

We are very grateful that Professor Jørgen Frøkjær (Department of Clinical Medicine, Nuclear Medicine and PET Imaging, Århus University) has generously agreed to act as chairperson of the national Steering group despite of his many other obligations and duties. We would like to convey our most sincere thanks to him for an excellent job done so far and all steering group members for their continuous commitment to the project.

The 7T project has already led to substantial improvements of the research environment at DRCMR. Since apart of the funding for the national 7T MR facility was earmarked to the establishment of new office space. 15 new offices and meeting rooms became available mainly in the newly constructed "pavilion 7" next to the existing DRCMR building by the end of 2012. The increase in office space will provide sufficient space for local and visiting researchers who wish to work on 7T related projects at DRCMR. At the same time, a 3 tesla Philips Achieva system was installed in the MR research section which is only dedicated for research. This system enables researchers at DRCMR to gain experience with the Philips MR platform and will enable future research projects which compare scans obtained at 3 and 7T or which take advantage of using different magnetic field strength.

The delivery of the 7T MR scanner was scheduled in 2013, but unfortunately there will be a significant delay. The 7T MR scanner is now expected to be installed in 2014. Nevertheless, the national 7T MR project has already gained momentum through enthusiastic collaborations with other 7T MR sites in Europe, especially the Dutch 7T MR centers in Utrecht and Leiden. This will enable us to start the 7T MR research program immediately after hand-over of the 7T MR scanner.

Advances in ultra-high field MR methodology are taking place at an astonishing pace. Therefore, it is a major strategic goal to recruit a high-profiled senior researcher within the field of ultra-high field MR and to establish a 7T MR hardware laboratory at DRCMR in close collaboration with the Department of Electrical Engineering at DTU. This will be critical to be able to fully exploit the potential of the first human 7T MR scanner which will be installed as a national research facility at Hvidovre Hospital.

Philips Country Manager Christian Hornstrup and Hospital Director Torben Ø. Pedersen signing the purchase agreement for the 7T scanner in January 2012.

RESEARCH AT DRCMR

A unique strength of the DRCMR is the multi-disciplinary 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 research at DRCMR has since 2009 been structured into a number of research. Each group is headed by one or multiple research group leaders. This 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 on the following pages. Across different research areas, we have become increasingly successful in combining multiple imaging modalities and computational methods to address neuroscientific questions. 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). These research groups and the research they conduct are also presented.

NEW COMPUTING FACILITIES

DRCMR purchased a state-of-the-art scalable server infrastructure platform to address the departments ever increasing demand for computational capacity. The Fujitsu PRIMERGY CX1000 is a special rack with centralized power and front-to-top cooling which provides the basic infrastructure for up to 38 server nodes, and is currently equipped with 22 dual processor server nodes. The server nodes themselves use the latest Intel® Xeon® Processor 5600 series delivering excellent performance, and comprises a total of 200 processing cores and 640 Gb of physical memory. The remaining 16 rack slots can be filled when the need arises, at greatly reduced cost compared to similar systems without centralized power and cooling.

The new servers are supplemented with an upgraded storage facility, with a total of 200 Tb raw storage. The storage servers make use of the latest advancements within storage technologies, such as Solid State Disks for caching of active data and the advanced file system ZFS for data redundancy, file duplication and live snapshots for backup and improved safety. The storage servers are now connected to the new server infrastructure with 10-gigabit network allowing greatly improved data throughput and lower latencies.

This computing facility runs a virtual desktop infrastructure, which allows lengthy computational analysis to run uninterrupted on the system. Furthermore, a queuing system distributes load across the entire system to allow maximum usage and fair sharing between users. The entire infrastructure is powered with an uninterruptible power supply, which potentially allows any analysis to run for eternity.

MR PHYSICS & ACQUISITION GROUP

MR imaging and spectroscopy makes use of the magnetic properties of certain atomic nuclei, e.g., the nucleus of hydrogen present in all body tissues. Using varying magnetic fields, the atomic nuclei are prepared so they emit radio waves reflecting physiologically relevant properties of the body tissues. Work performed in the DRCMR Physics&Acquisition group focuses on making optimal MR measurements (sequences and protocols) that improve the performance with respect to speed, sensitivity or specificity. Another focus of the group is education in MR physics and methodology needed for designing and interpreting MR studies, and to advance MR methodology.

DRCMR members

Lars G. Hanson (group leader, also associate Professor in the Biomedical Engineering group at DTU Elektro), Lise Vejby Søgaard, Peter Magnusson, Kristoffer H. Madsen, Arnold Skimminge, Davud Ahmadi, Daniel Tamir Nilsson, Mads Andersen, Mark B. Vestergaard, Jeppe Andreasen.

External collaborators

- **Dr. Gunther Helms**, University of Göttingen, Germany, and Drs. Antoine Lutti, Nikolaus Weiskopf, University College London, England,
- **Dr. Katarina Steding and Professor Bengt Saltin**, Rigshospitalet, Denmark, and Dr. Luke Haseler, Griffith University, Australia
- **Dr. Jessica Schulz and Professor Robert Turner**, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
- **Drs. Vitaliy Zhurbenko and Johan Mohr**, Department of Electrical Engineering, Technical University of Denmark
- **MSc. Signe Refsgaard Bech og Dr. Nikolai Nordsborg**, Department of Exercise and Sport Sciences, University of Copenhagen, Denmark.
- **Profs. Gitte Moos Knudsen**, Tom Bolwig, Olaf B. Paulson, Anders Fink-Jensen and Martin Balslev Jørgensen, Rigshospitalet, Denmark; Prof. Helene Benveniste and Dr. Hedok Lee, Stony Brook University, New York, USA.

MR PHYSICS & ACQUISITION GROUP ACTIVITIES

The 'MR physics and acquisition group' at the DRCMR conducts research and development aimed at improving MR scanning methodology. The group members have technical backgrounds, e.g. in physics, mathematics and engineering. Many group member activities are not performed in the context of the group, and are described in other sections of this annual report.

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 ultra-high field, e.g. multi-channel techniques, motion correction and compensation of field inhomogeneity.

Research activities

In 2011, Mark B. Vestergaard conducted a project to finalize his education in biomedical engineering at the Technical University of Denmark. In collaboration with scientists at the Max Planck Institute in Leipzig and Lars G. Hanson, a novel method for motion tracking during MRI was developed, tested, presented at the ESMRMB conference and later refined. The method relies on an effect well known from EEG recording performed during MR scanning: When electrodes are placed in the MR scanner, severe scanner-induced noise appears in the recordings. The noise depends on the position of the electrodes. Using advanced signal processing techniques and a simple calibration procedure, independent measures of the head position were made with sub-millimetre spatial resolution during MRI (Figure 1). Patient motion is a severe confounding factor for MR scanning, and the method has considerable potential for further improvement.

A related idea for compensating other magnetic fields during motion is pursued in a PhD study conducted by Mads Andersen from late 2012 in collaboration with the Biomedical Engineering group at the EE department

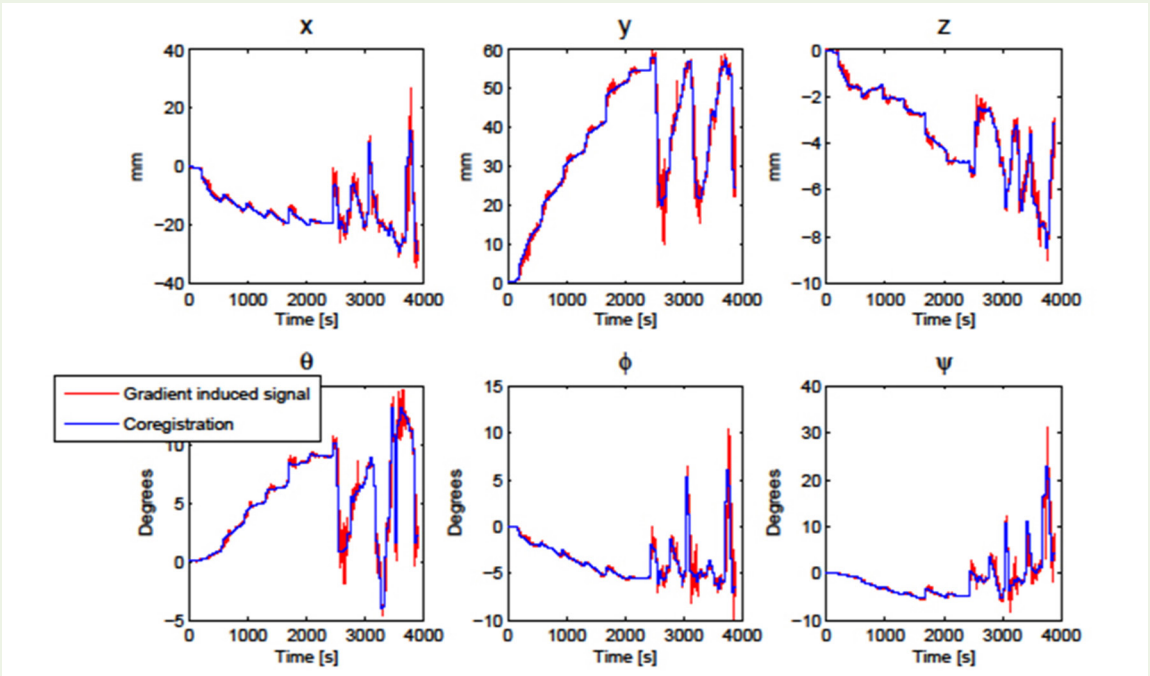


Figure 1: In the MSc project by Mark B. Vestergaard it was shown that patient motion can be tracked during MRI using EEG equipment. The method was subsequently improved regarding accuracy and temporal resolution. The curves show the evolution of parameters characterizing person motion during a 4000 second scan. Using inflatable pillows, the head is moved in a semi-controlled way during the first half of the scan, and is moved freely by the scanned person thereafter. Parameters extracted from the EEG (red) correlate well with parameters extracted from MRI (blue) but the prior can be acquired more rapidly, and be used to improve MRI. When the high frequency noise apparent in the EEG data is filtered, motion tracking with sub-millimeter precision results.

at the Technical University of Denmark (financial support from Radiometer Medical and the national research councils). Kristoffer Madsen is the DRCMR supervisor. Before Mads started his PhD study, he conducted his MSc study on validation of simultaneous EEG and MRI recording using novel electronic phantoms (Figure 2). The work was supported by a Novo Scholarship stipend and was presented at the ESMRMB conference in 2012.

A study of muscle metabolism was initiated with researchers at Rigshospitalet, Department of Exercise and Sports Sciences, University of Copenhagen, and Griffith University, Australia. Some of the same measures have been applied before but with the new wide-bore 3T scanner, methods and procedures needed adaption. Considerable improvements in ergometry were implemented. Trained elderly persons and heart patients were studied by Katarina Ehrenborg, Luke Haseler, Bengt Saltin and Lars G. Hanson. A new collaboration was initiated between

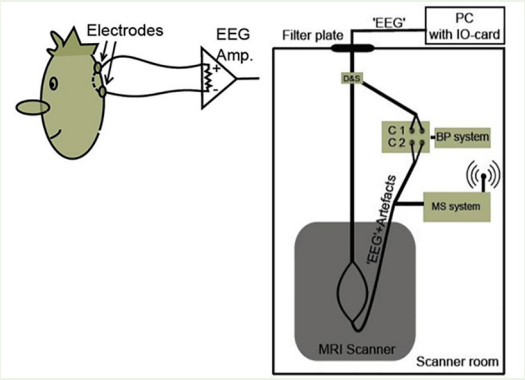


Figure 2: The EEG-fMRI validation setup developed for Mads Andersen's MSc project. A normal pre-recorded EEG synthesized by a PC is sent through the scanner and mixed with scanner-induced noise. Both the noisy and the noise-free signals are sampled in a traditional MR-compatible EEG system ("BP system"). For comparison, the signals were also measured with a home-built EEG system ("MS system"). The systems were compared, and algorithms for removing scanner noise validated by comparing noise-free and noise-corrected signals.

Signe Refsgaard Bech, Nikolai Nordsborg, Lise Vejby Søgaard, Jeppe Andreasen and Lars G. Hanson regarding the effect of beta-alanine food supplement for elite kayak rowers. Muscle metabolism is characterized using ergometry and phosphorous/proton spectroscopy.
Methods for analysis of data acquired in a study of severely depressed patients subject to electroconvulsive treatment were established by Peter Magnusson and Arnold Skimminge. The project also involves Lars G. Hanson, collaborators at Rigshospitalet, and Stony Brook University in New York. It is conducted with financial support from the Lundbeck Foundation.
Lise Vejby Søgaard and Peter Magnusson supervised MSc student Daniel Tamir Nilsson on a coil development project for the preclinical scanner. The main supervisors at DTU were Vitaliy Zhurbenko and Johan Mohr. MSc student Davud Ahmadi, Arnold Skimminge and Peter Magnusson established methods for measurement of body lipids for studies of metabolism in collaboration with the Departments of Endocrinology and of Pediatrics, Hvidovre Hospital. Lars G. Hanson got involved in Anders Filsøe Pedersen's master student project on MRI at ultra-low electromagnetic field initiated by the Department of Physics at the Technical University of Denmark in collaboration with University of California, Berkeley.
A new collaboration was established with Drs. Gunther Helms, Antoine Lutti and Nikolaus Weiskopf regarding implementation of quantitative MRI in research studies (see Reader Centre for example).

Other activities

The group makes significant contributions to higher education, e.g. the Medicine & Technology program in a collaboration between the DTU and the Faculty of Medicine at the University of Copenhagen. The group also contributes to a new neuroscience education offered in China by the Sino-Danish Center for Education and Research. The collaboration with DTU regarding education is mediated mainly by Lars G. Hanson who is appointed both at the DRCMR and at the Department of Electrical Engineering, DTU, but several others contribute significantly, e.g., by providing teaching and supervision. At the DRCMR, the free annual courses on MRI techniques given by Arnold Skimminge and Lars G. Hanson attracts around 20 internal and external participants.
Other educational activities were aimed at the International Society for Magnetic Resonance in Medicine and Biology where 2 submissions were accepted for the annual meeting's new educational category. During the sessions five short videos on basic MRI physics were recorded and published at YouTube which by the end of 2012, had been viewed more than 40.000 times. As a result of the educational focus, Lars G. Hanson was invited speaker at the NMR conference "Magnetic Moments in Central Europe" and the "European Association of Nuclear Medicine Annual Congress", and a conference paper on the use of software for MRI education was published.
The planning of the national ultra-high field MRI facility required substantial work in 2011-2012. Efforts involving also the Danish Society for Magnetic Resonance in Medicine (DSMMR) and the Danish Radiological Society (DRS) were made to prevent detrimental effects of the upcoming EU directive regarding work in electromagnetic fields. Aspects of this work was presented in a conference paper and an invited talk prepared for the ISMRM Safety Workshop 2012.

SELECTED PUBLICATIONS

- **M. B. Vestergaard, J. Schulz, R. Turner and L. G. Hanson.** "Motion tracking from gradient induced signals in electrode recordings", Proc. of the ESMRMB 28th Annual Meeting, 368, 2011.
- **L. G. Hanson.** "A visual, interactive introduction to basic and advanced magnetic resonance techniques" and "What is Magnetic Resonance?", Proc. of the ISMRM 19th Annual Meeting, 4686, 2011.
- **M. Andersen and L. G. Hanson.** "A phantom based validation framework for EEG-fMRI acquisition methods", Proc. of the ESMRMB 29th Annual Meeting, 626, 2012.
- **L. G. Hanson.** "The EU directive on work in electromagnetic fields – practical and clinical aspects", Proc. of the ISMRM safety workshop, 2012.

COMPUTATIONAL MODELLING & ANALYSIS

The computational modelling and analysis group at DRCMR is engaged in research, development and application of advanced computational data analysis techniques that are suited for 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

Kristoffer H. Madsen, Arnold Skimminge and PhD students Kasper W. Jørgensen, Toke J. Hansen and Bettina Vase Jensen enrolled at the DTU Compute. Through these PhD students as well as several colaborative projects the group maintains a particular strong collaboration with the cognitive systems section as well as the section for image analysis at DTU Compute. The group is also actively involved in the supervision of several BSc MSc and PhD projects at DTU Compute.

External collaborators

- **Assistant Professor Morten Mørup**, Cognitive systems, DTU Compute
- **Professor Lars Kai Hansen**, Cognitive systems, DTU Compute
- **Professor Rasmus Larsen**, Image Analysis and Computer Graphics, DTU Compute
- **Associate Professor Torben E. Lund**, Center of Functionally Integrative Neuroscience, Aarhus University
- **Professor Carsten Thomsen**, Centre of Diagnostic Investigation, Rigshospitalet
- **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

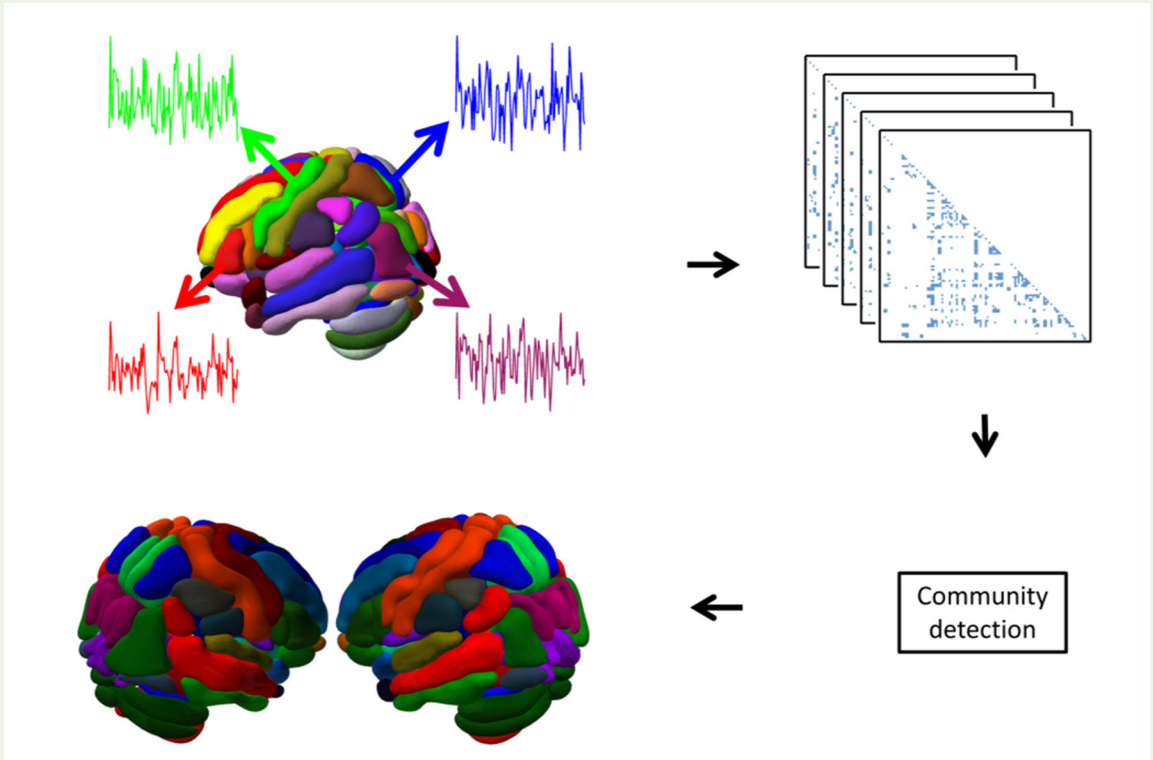


Figure 1: Complex network analysis based on the infinite relational model. The functional MRI time series data from different regions in the brain is extracted and used to form an adjacency matrix of connections between the regions. The infinite relational model is then used to form communities of regions (regions with a particular connectivity structure).

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 methods and predictive models.

Traditionally, analysis of functional MRI (fMRI) 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. However, there is now an increasing interest in analysing interactions and relationships between brain regions both under task conditions but also while the brain is at rest. By regarding the brain as a network consisting of nodes (brain regions) and edges (connections) methods that are useful for analysis of complex network data can be used to investigate communication in the brain. In the computational analysis group we are working together with the cognitive systems group at DTU Compute on development of novel complex network models for identifying grouping structure in fMRI data. The models, which are variants of the so-called Infinite Relational Model (IRM), group brain regions into communities, which are groups of brain regions with similar functional characteristics, that is, they share the same linking structure both internally in the community but also to other communities. Some of the advantages of this model compared to other complex network methods are that it provides a natural mean of integrating data from multiple subjects, which is often needed because of the relative low signal-to-noise ratio in fMRI. Another advantage is that it provides a direct measure of the relations between brain communities, as such it can provide information not only about how the structure of the brain communities but also about the relations between communities. By allowing subject specific community relations this method can provide insights into how the brain communication is changed due to neurological and psychological diseases.

Resting-state fMRI is concerned with analysis of fMRI data in the absence of any task. In such data functional connectivity (statistical dependencies) between certain brain areas, often termed resting-state networks, are observed. These networks are often identified by use of unsupervised decomposition techniques such as independent component analysis. Multivariate techniques are capable of extrating spatiotempotal patterns in the data and have been used in several projects at DRCMR. Other approaches for the analysis of resting-state MRI data include analysis of local homogeniety. In this settting the homogeniety of the signal in each voxel is determined by comparing the voxel time series to time series of neighbooring voxels using non-parametric correlation measures. As standard normality assumptions does not hold for these measures cluster based random permutation tests are used to assess the signifance of effects. The computational analysis group is involved in applying this methodology in several projects including a cross sectional study of multiple sclerosis patients.

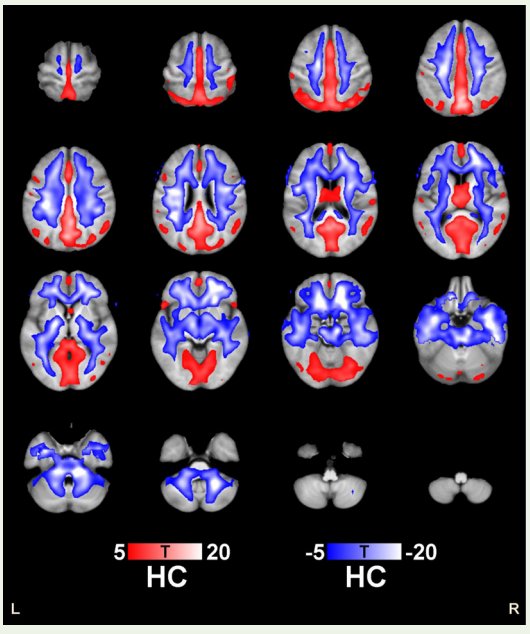


Figure 2: Local homogeneity analysis. The figure shows the local homogeneity in healthy control (HC) subjects as measured using Kendall's coefficient of concordance (KCC), which is a rank, based correlation measures. The KCC values were converted to z-scores for each subject and a random effects one sample t-test over the scans from 31 HCs is used for visualisation purposes.

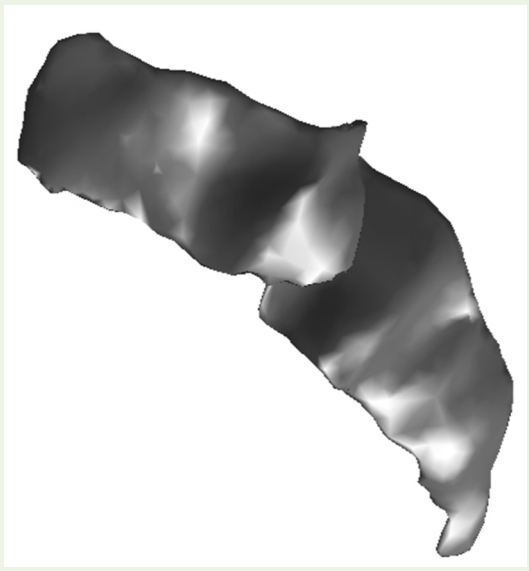
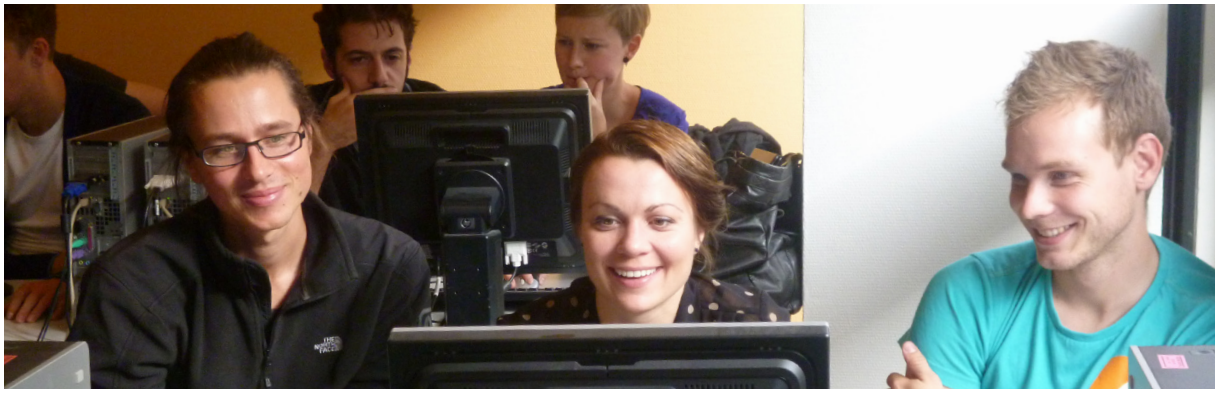


Figure 3: The extracted shape of the central sulcus.

Analysis of changes in brain anatomy as measured by MRI is often assessed using voxel based morphometry methods. However, the univariate structure of this methodology may limit this sensitivity in the identification of morphological changes. In these cases a multivariate analyses of shape may help to improve sensitivity. PhD student Bettina Vase Jensen is using statistical shape analysis to assess handedness related changes in the shape of the central sulcus. This project includes extraction of central sulcus in 3D, pre-processing, feature selection and statistical analysis. This project is important because the central sulcus is one of the most stable and prominent folds of the human brain, since it marks the functional separation between motor and somatosensory areas. Although the central sulcus is one of the simplest cortical folds its size and shape vary substantially across individuals and between hemispheres.
Left handers differ from right handers in the size of certain cortical folds. It has been found that the central sulcus is deeper or longer in the dominant right hemisphere of left handers and vice versa for right handers. However, the impact of handedness on the shape of the central sulcus is unexplored.

PUBLICATIONS

- **P. M. Rasmussen,** "Mathematical modeling and visualization of functional neuroimages" PhD thesis, DTU Informatics, April 2012
- **P. M. Rasmussen, T. J. Abrahamsen, K. H. Madsen, and L.K. Hansen,** "Nonlinear denoising and analysis of neuroimages with kernel principal component analysis and pre-image estimation" NeuroImage 60, 1807–18 (2012).
- **P. M. Rasmussen, L. K. Hansen, K. H. Madsen, N. W. Churchill, and S. C. Strother,** "Model sparsity and brain pattern interpretation of classification models in neuroimaging" Pattern Recognition (2011)
- **P. M. Rasmussen, K. H. Madsen, T. E. Lund, and L. K. Hansen,** "Visualization of nonlinear kernel models in neuroimaging by sensitivity maps," NeuroImage 55(3), 1120 –1131 (2011).
- **K. W. Andersen, K. H. Madsen, H. Siebner, L. K. Hansen, and M. Mørup,** "Identification of Functional Clusters in the Striatum Using Infinite Relational Modeling," in Machine Learning and Interpretation in Neuroimaging, G. Langs, I. Rish, M. Grosse-Wentrup, and B. Murphy, Eds. Springer Berlin Heidelberg, 2012, 226–233.
- **K. W. Andersen, M. Mørup, H. Siebner, K. H. Madsen, and L. K. Hansen,** "Identifying modular relations in complex brain networks," in Machine Learning for Signal Processing (MLSP), 2012 IEEE International Workshop on, 2012, pp. 1–6



Exercises at the 2012 SPM PhD course held at DRCMR

DIFFUSION IMAGING GROUP

The Diffusion Imaging Group (DIG) (http://dig.drcmr.dk) aims at understanding the brain on several levels, including isolated tissue compartments (cellular spaces, sizes of neurons, exchange over cell membranes) and via tractography visualization and statistical analysis of whole brain connectivity networks. This knowledge is subsequently applied in pre-clinical, clinical and cognitive research projects and eventually clinical settings. Joining pre-clinical knowledge with clinical experience our research provide an unique translational profile.

DRCMR members

The DIG includes: Tim B. Dyrby (group leader), Lise Vejby Søgaard, Henrik Lundell, Matthew G. Liptrot, Helle Sickmann, Nina L. Reislev, Mark Lyksborg, Kristian S. Frederiksen, Kasper W. Andersen and Casper K. Sønderby. (For personnel details see our DIG homepage)

External members

- **Professor Maurice Ptito**, Montreal University, Montreal, Canada and University of Copenhagen, Denmark
- **Assistant Professor Mark Burk**, Howard University, Washington DC, USA

External collaborators

- **Professor Daniel C. Alexander**, University College London, United Kingdom
- **Professor Geoff JM. Parker**, 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
- **Professor Ron Kupers**, University of Copenhagen, Denmark
- **Professor Rasmus Larsen**, Technical University of Denmark, Denmark
- **Assistant Professor Julien Cohen-Adad**, Polytechnique Montréal, Montreal, Canada

RESEARCH ACTIVITIES

In 2009 a multi-disciplinary team of Europe's leading diffusion MRI researchers from 12 laboratories, including DRCMR's Tim B. Dyrby, joined forces in the 'CONNECT' consortium (Consortium for the Non-Invasive Exploration of Connectivity and Tracts) with support from the Future and Emerging Technologies (FET) within the European Commission (FP7) under FET-Open. Our contributions to CONNECT have been related to research in new sequence design, methodological validation against e.g. tracers, histology, electron microscopy and phantoms (see Project Highlights). Data has been collected using our pre-clinical ex vivo imaging pipeline to ensure high-quality and high-resolution diffusion MRI datasets (Dyrby et al 2011). In the DIG we have chosen a policy for sharing a wide selection of our published ex vivo diffusion MRI datasets now available on our DIG download central (http://dig.drcmr.dk).

In 2011/2012 our sequence design research shifted toward new types of diffusion MRI sequences namely oscillating gradients (OGSE) and double (d)PGSE also known as double wave-vectors. As part of the CONNECT project *Tim B. Dyrby* and *Professor Daniel C. Alexander* suggested that the conventional PGSE sequence although being sensitive to the smallest axon diameter distributions (ADD) it cannot accurately differentiate these smaller sizes axons due to limited gradient strength (Dyrby et al 2012). As part of his post.doc *Henrik Lundell* has implemented and simulated different configurations of OSGE sequences and in fixed monkey brain showed how OGSE provides a unique contrast in tissue regions with high cellular density (see Preclinical Research Figure 2 on Page 36). Also, the double PGSE sequences provide new contrasts for e.g. **cell-membrane permeability of water molecules**. *Casper Sønderby* did his B.Sc. project in DIG and showed how cell-membrane permeability in tissue due to a mixture of the neurites (axons and dendrites) and cells, modelled as tubes and spheres, depends on the geometrical orientation of these. We showed how water exchange is linked to anisotropic diffusion (Figure 1).

Stress, and especially prenatal exposure to stressors significantly potentiate susceptibility to mood disorders. Limited knowledge about the structural and functional impact of pre-

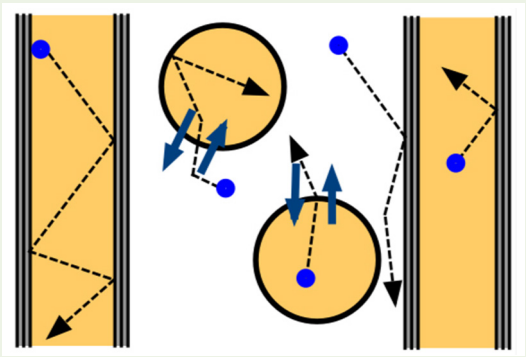


Figure 1: Schematic view of water exchange across the cell membranes of permeable gliacells and impermeable nerve fibers. Water exchange across the cell membrane is an important regulatory mechanism and alterations of the cell membrane permeability are associated with diseases such as cancer and Parkinson's disease. The DIG group is actively developing and implementing novel methods to provide clinically feasible in vivo measurements of the membrane permeability using non-invasive MR technology.

natal stress (PS) on the stress-mediating brain circuitries exist. Moreover, there are currently no diagnostic tools that afford identification of prodromal stages of depression vulnerability after prenatal stress. This project will address these gaps by examining changes in functional brain neurotransmission between limbic regions (hippocampus, amygdala and paraventricular hypothalamius) following PS in a preclinical model. EEG recordings will be used to evaluate sleep changes following PS and the brains will subsequently be examined ex vivo by diffusion MRI with techniques beyond DTI and histology to correlate functional and structural changes. This four-year post.doc project carried out by *Helle Sickmann*, in a collaboration between Copenhagen University, Tim B. Dyrby at DRCMR and Lundbeck Pharma A/S) is supported by The Advanced Technology Foundation and the Lundbeck Foundation.

Brain connectivity. Structural connectivity between brain regions can be estimated from tractography while functional MR can estimate brain activity from BOLD activity. As part of his PhD *Kasper W. Andersen* (2011–2014) is working on new complex network methods combining these two modalities in order to provide better insight into brain communication. The model cluster brain regions into groups or so-called communities, which are groups of brain regions with a higher internal structural and functional connectivity. The project is a collaboration between the Technical University Denmark and DRCMR and has been partly supported by The Lundbeck Foundation and Technical University Denmark.

Tractography is an in vivo non-invasive tracking technique for visualising and analysing how the brain is structurally connected via its white matter fibre tracts formed by bundles of axons. As part of *Nina Reislev's* Ph.D. project (2011–2014) and in collaboration with *Professor Ron Kupers* and *Professor Maurice Ptito*, we use tractography to gain insights into the plasticity of the blind brain (Figure 1). The aim this project supported by the Lundbeck Foundation and FSS is to map the reorganisation of the brain following sensory deprivations. Furthermore we have in collaboration with *Thomas Knöesche* from the Max Planck Institut, validated many of the widely used tractography methods and with our ICE-T method shown that path-length dependency in tractography is clearly reduced. The ICE-T project was a part of *Matthew G. Liptrot's* Ph.D.-project and in 2011 he received his degree. The projects were part of CONNECT.

Whole-brain tractography is a new way of generating an anatomical connectivity map (ACM) of the brain that is tract non-specific but describes the connectedness of a voxel in relation to the rest of the brain. In the Ph.D. project of *Mark Lyksborg* (2010–2013) we investigate mathematical models of diffusion MRI as potential biomarkers in patients with Multiple Sclerosis (MS). When applied to a cohort of MS patients the ACM technique was superior to the traditionally used DTI indices for monitoring MS severity and the ACM technique is now being implemented in other research projects. Additionally, Mark Lyksborg visited assistant Professor Gary Zhang, University Collage London for six months and here he work on a method for performing tract-orented statistics group-wise based on the shape of WM tracts. See example Figure 2. The project is a collaboration with Finn Sellebjerg at the Multiple Sclerosis Clinic, Rigshospitalet, and *Professor Rasmus Larsen*, Technical University of Denmark and has been supported by FSS and Sclerose Foreningen.

The effects of cortical deposits of beta-amyloid on white matter microstructure structure in Alzheimer Disease patients is examined in

Kristian S. Frederiksen's (MD) Ph.D.-project by combining clinical diffusion MRI and PET imaging (see Aging and Dementia group).

SELECTED PUBLICATIONS

- **Dyrby TB, Søgaard LV, Hall MG, Ptito M, Alexander DC,** Contrast and stability of the axon diameter index from microstructure imaging with diffusion MRI, Magnetic Resonance in Medicine, Sep 8. doi: 10.1002/mrm.24501, 2012
- **Lundell H, Nilsen JB, Ptito M, Dyrby TB,** Distribution of collateral fibers in the monkey cervical spinal cord detected with diffusion weighted magnetic resonance imaging, Neuroimage, 2011, 1;56(3):923-9.
- **Dyrby TB, Baaré WF, Alexander DC, Jelsing J, Garde E, Søgaard LV,** An ex vivo imaging pipeline for producing high-quality and high-resolution diffusion weighted imaging datasets, Hum Brain Mapp. 2011;32(4):544-63

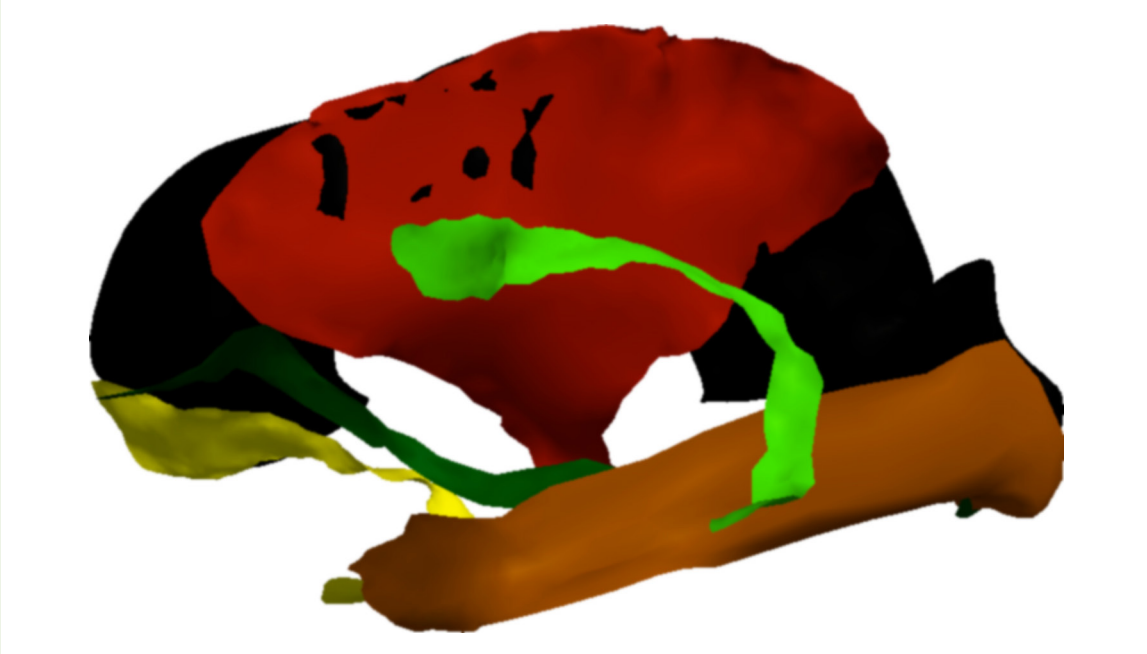


Figure 2: Shows six sheet-like models of specific WM tracts for group analysis in the human brain; Sagittal view (frontal cortex to the left) with sheet models of major white matter are: the corpus callosum (black), the corticospinal tract (red), the inferior fronto-occipital fasciculus (dark green), the acuate fasiclulus (light green), the inferior longitudinal fasciculus (brown) and the uncinate fasciculus (yellow). These models have the benefit of simplifying statistical analysis of MRI studies and aid in visualizing the outcome of the analysis.

INTEGRATIVE NEUROSTIMULATION AND NEUROIMAGING

The Integrative Neurostimulation and Neuroimaging Group (INN) was newly established in 2012 when Axel Thielscher (http://www.drcmr.dk/Thielscher) took up his positions as Senior Researcher at the DRCMR and Associate Professor at the Biomedical Engineering Section of the Technical University of Denmark (DTU BME). Its mission is the advancement of neurostimulation methods to improve their utility in basic and clinical neuroscientific research. A particular focus lies on the integration of neurostimulation with neuroimaging methods. The research activities range from technical developments (e.g., setup for combined TMS-fMRI) to biophysical models to predict the electric current flow caused by neurostimulation in the head and further on to assessing the physiological impact of stimulation using brain imaging modalities such as fMRI and EEG. In close collaboration with the ContAct group headed by Hartwig Siebner, the novel developments are applied in studies mostly on sensorimotor integration and motor control, which constitute the neuroscientific focus of the group. In the next years, a recent grant provided by the Lundbeck Fonden will allow developing the mission of the INN group further.

Members

Axel Thielscher (group leader), Hartwig Siebner, Tahnée Engelen, Sofie Nilsson and Lars Ewald.

External collaborators

- **Prof. Klaus Scheffler**, Dr. Andreas Bungert and Dr. Andre Antunes, MPI for Biological Cybernetics, Tübingen, Germany
- **Dr. Brain Corneil**, University of Western Ontario, Canada
- **Dr. Marc Himmelbach**, University of Tübingen, Germany
- **Dr. Thomas Knösche**, MPI for Human Cognitive and Brain Sciences, Leipzig, Germany
- **Dr. Astrid van Lier and Dr. Nico van den Berg**, UMC Utrecht, The Netherlands
- **Prof. Uta Noppeney**, University of Birmingham, UK
- **Prof. Walter Paulus**, University Clinics of Göttingen, Germany
- **Dr. A. Peer**, Technical University of Munich, Germany
- **Dr. Masashi Hamada and Prof. John Rothwell**, University College London, United Kingdom
- **ANT Neuro**, Enschede, The Netherlands
- **MagVenture A/S**, Farum, Denmark

RESEARCH ACTIVITIES

The following gives an overview over the research activities that have been started in the INN group since mid 2012. The three main foci are methods developments for brain stimulation and its integration with neuroimaging, biophysics of brain stimulation and mapping of brain connectivity using interleaved TMS-fMRI (Figure 1).

Methodological developments for neurostimulation: To the largest extent, TMS still relies on the technical solutions developed during its initial period in the 1980s. However, electronics has made dramatic changes in the meantime. We contribute to the further technical development of TMS and its better integration with neuroimaging mehthods. A long-standing collaboration between *Axel Thielscher* and **MagVenture (Farum, Denmark)** exists on the development of setups for the online combination of Transcranial Magnetic Stimulation (TMS) with fMRI. For example, an MR compatible device for coil positioning designed by Axel and colleagues during his time at the MPI for Biological Cybernetics (Germany) is now offered as commercial product by MagVenture (Fig. 3 Top). In a similar vein, Axel has been involved in the development and testing of the MR-compatible TMS coils provided by MagVenture. Before coming to the DRCMR, *Lars Ewald* gained several years of experience in technical R&D for TMS at **MagVenture (Farum, Denmark)** and worked on a prototype power supply for a novel generation of TMS stimulators (Flex Mag, TU Munich) during his BSc thesis in 2012. He will continue this topic at DRCMR, ultimately leading to a novel stimulator with unprecedented flexibility for the selection of stimulation pulse shapes and protocols.

Biophysics of non-invasive neurostimulation: TMS can be used to non-invasively assess a

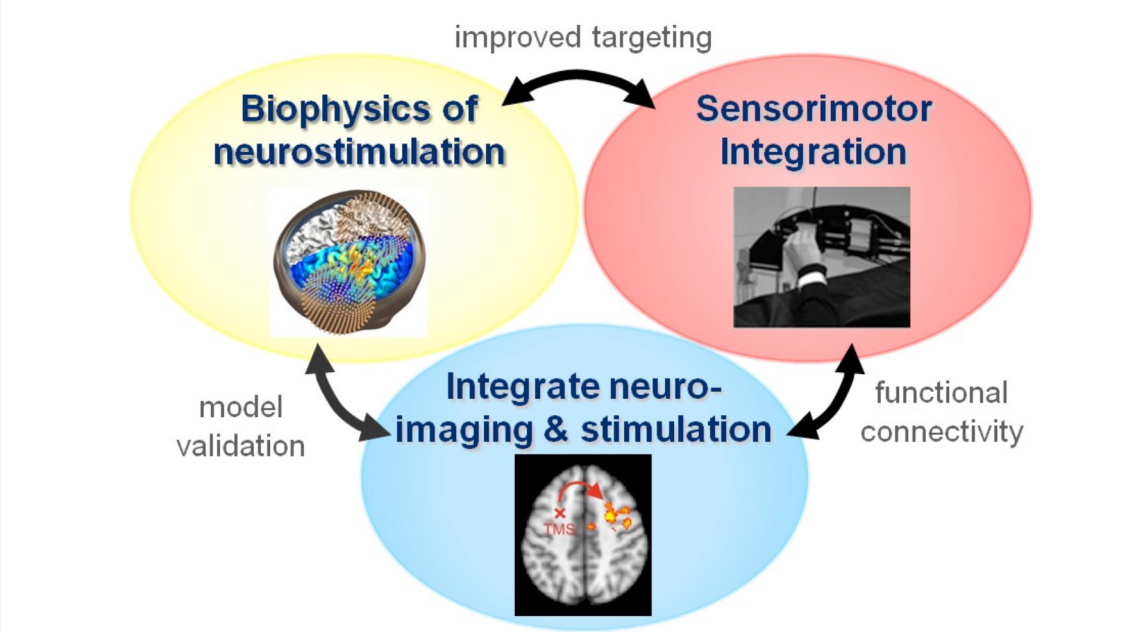


Figure 1: Overview of the research topics in the INN group

range of physiological parameters in-vivo in healthy subjects and disease populations. However, its diagnostic value is still strongly limited by a strong interindividual variability of the stimulation effects, in particular by the fact that the causes of the variations are still largely unclear. We have therefore started to explore the question of how the physiological TMS effects link to the brain structure, both on the micro-and macroscopic level. Electric field calculations play a key role in this endeavour because they allow us to better localize the stimulated target structures and to improve the spatial resolution of stimulation (Fig. 2). We employ finite element methods and individual head models derived from structural and diffusion-weighted MRI. Numerical techniques such as the Finite Element Method (FEM) are methodologically demanding so that they have been rarely used in brain stimulation up to now. We developed an optimized processing pipeline allowing for the automatic generation of individualized high-quality head models from magnetic resonance images. This pipeline is published as open-source (www.simnibs.de) and represents an important first step towards a more frequent and easier application of accurate field calculations. Part of this work is done in close collaboration with colleagues from the the the Department for High-field Magnetic Resonance of the Max-Planck Institute for Biological Cybernetics (Tübingen, Germany). It is supported by two grants which Axel Thielscher received from the German Research Foundation and the

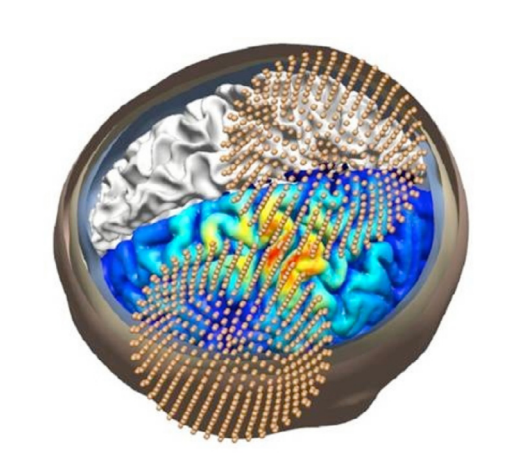


Figure 2: Electric field calculated at very high spatial resolution for stimulation of the motor cortex

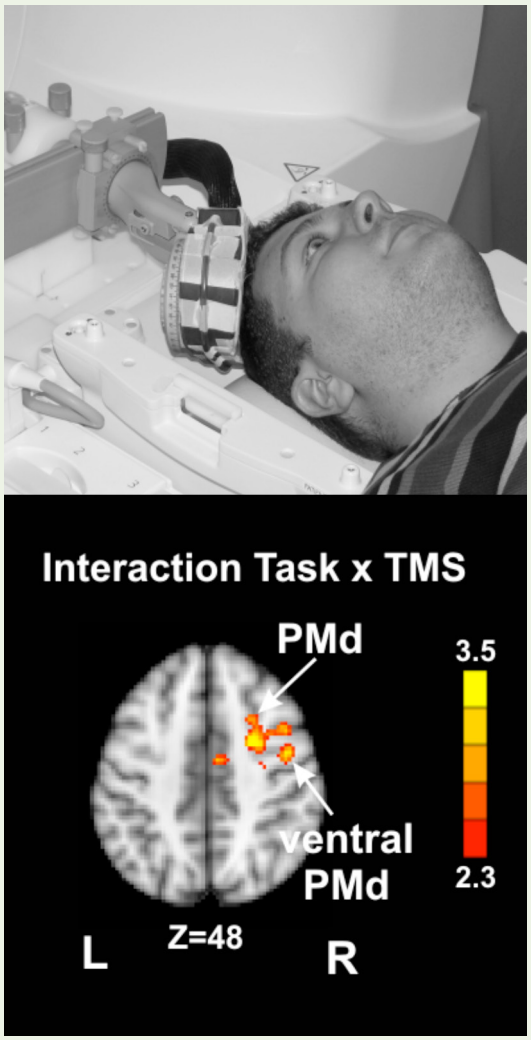


Figure 3: Top: Setup for interleaved TMS-fMRI. Bottom: The interaction between task and TMS effects demonstrates that the remote effects of left PMd stimulation depend on the behavioral task

German Fedral Minitry of Economics and Technology before moving to Denmark. At the dawn of 7T MR imaging at the DRCMR, this strong link to will proof highly advantages in the next years.

Interleaved (or concurrent) TMS-fMRI: It is stunning to see that the physiological and behavioural effects of TMS strongly depend on the actual brain state. That is, the identical TMS protocol given to the same brain area can have very different outcomes depending on the context in which is applied. This has important implications for the potential therapeutic use of TMS, but also opens up interesting possibilities for basic neuroscience. We use the online combination of TMS with fMRI to directly assess the effects of stimulation on the blood-oxygen-level dependent signal (BOLD) measured by fMRI. By this, we can, e.g. look at the changes in effective connectivity between brain areas that accompany changes in the behavioral task or in sensory stimulation. We compared the effects of left PMd stimulation on the activation patterns of two motor tasks, one relying on learned sensorimotor associations while the second allowed free response selections. Critically, both tasks evoked very similar activation patterns in a "standard" fronto-parietal motor network. That is, fMRI alone failed to demonstrate differences between the brain activations evoked by the two tasks. However, TMS applied to the left PMd exerted specific network effects only for the task relying on sensorimotor associations. Therefore, the TMS perturbation yielded causal evidence that the left PMd is implicated in mapping external cues onto the appropriate movement in humans. This confirms the results of prior primate studies. Based on these findings, *Tahnée Engelen* and *Sofie Nilsson* are currently working on a follow-up study in which they look at the involvement of the PMd and related motor regions in response selection when the information content of the visual cues is varying.

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PRECLINICAL RESEARCH

With a 4.7 tesla MR scanner designed for small animal imaging and spectroscopy as a major player the preclinical research group aims for better understanding and characterisation of healthy and diseased tissue. Models of several major diseases are used for longitudinal investigations, including effects of treatment.
The group represents a multidisciplinary team with experts from engineering, biochemistry, human biology, physics and medicine.

DRCMR members

The group includes: Lise Vejby Søgaard (group leader), Sadia Asghar Butt, Mette H. Lauritzen, Christoffer Laustsen, Anders D. Skjolding, Tim B. Dyrby, Henrik Lundell, Peter Magnusson, Charlotte Viemose Larsen and Sascha Gude.

External members/Collaborators

- **Professor Marianne Juhler**, Department of Neurosurgery, Copenhagen University Hospital Rigshospitalet, Denmark
- **Professor Niels Christian Nielsen and Dr Mads Sloth Vinding**, Center for Insoluble Protein Structures (inSPIN), Interdisciplinary Nanoscience Center (iNANO) and Department of Chemistry, Aarhus University, Denmark
- **Professor Daniel C. Alexander**, University College London, United Kingdom

RESEARCH ACTIVITIES

Focus areas in 2011 have been *in vivo* animal studies of brain structure in hydrocephalus, cell metabolism in the heart, kidney, brain, muscle and tumours using hyperpolarised ^{13}C enriched substances, as well as *ex vivo* studies of brain and spinal cord tissue microstructure and connectivity using diffusion imaging.
Next to the scanner room the preclinical group has a laboratory, which is used for housing and preparing the animals for scanning. The laboratory had to be closed down during the last quarter of 2011 due to renovation of the ventilation system in the building. As a nice side effect the result of this renovation was an even better working environment for laboratory technician Sascha Gude and other members of the group.
As a continuation of the hydrocephalus studies carried out in 2007 Anders D. Skjolding performed pilot studies to optimise the protocol for pharmacological intervention in hydrocephalic rats. Direct brain delivery was obtained by using an osmotic pump. To evaluate the performance of the osmotic pumps, they were filled with a Gd-containing MR contrast agent and imaged both *ex vivo* embedded in a gel and *in vivo* implanted in normal rats (Fig. 1). These studies confirmed the MRI-compatibility and general efficiency of the pumps. Hydrocephalus was induced by kaolin induction in a separate group of animals. The rats were baseline scanned after one week and osmotic pumps with either vasopressin agonist, antagonist or vehicle were implanted. After one week of treatment the rats were scanned again to evaluate the possible effects of treatment. In addition brains were removed and processed for tissue analysis. Anders continued these studies at the University of Utah during his half year stay there in 2012.
A number of technical projects were conducted in 2011-12. Mads Sloth Vinding and Christoffer Laustsen optimised and implemented 2D spatial selective optimal control RF pulses. The method uses cleverly designed RF pulses that are applied together with modulated gradient waveforms to excite the magnetization only within a certain spatial area leaving uninterresting outer regions untouched. In order for the method to work it is important to know the exact performance of the gradients, in this case a spiral trajectory. Methods to map the gradients were implemented, and as a demonstration of the performance of the method experiments were conducted showing that it was possible to excite a spatial area corresponding to the shape of the three letters "dnp" in a phantom of hyperpolarized pyruvate.
Charlotte Viemose Larsen conducted a Master project with the goal of suppressing signal from the blood. In studies using hyperpolarized carbon-13, the interesting signal from the tissue is often hidden behind a large signal from the blood. By adding flow-encoding gradients

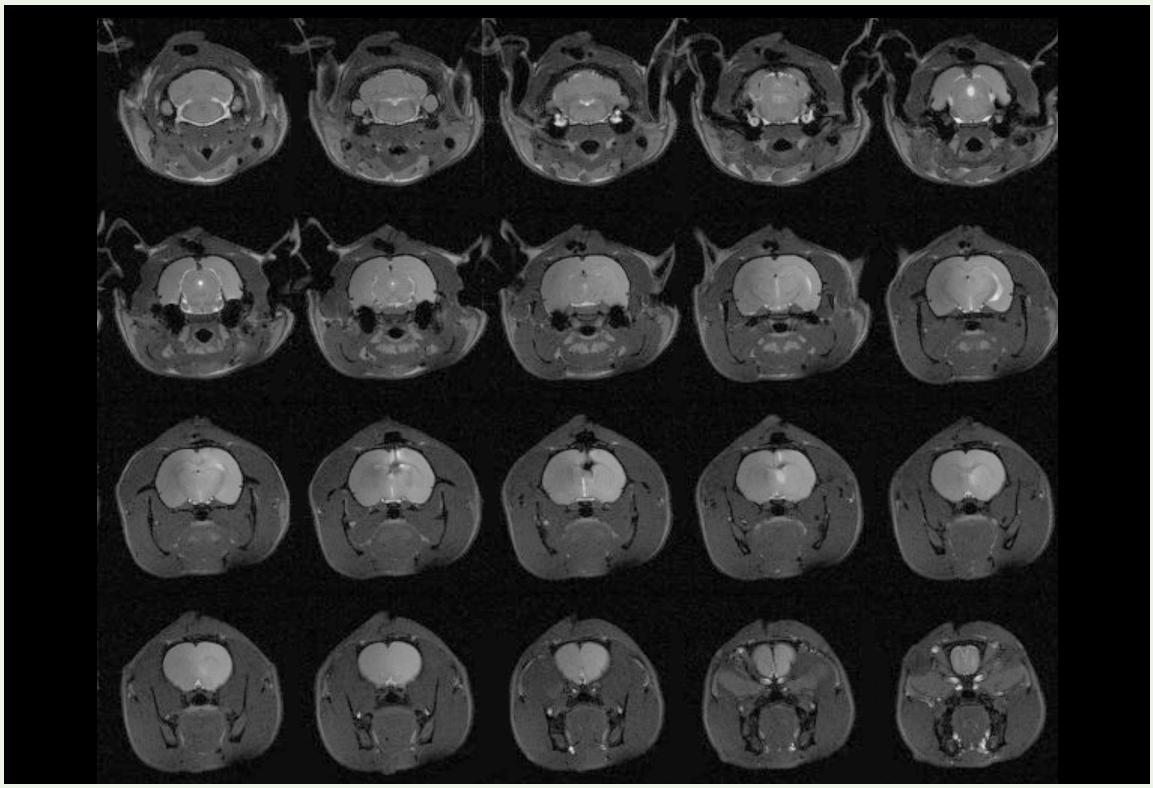

Figure 1: T1-weighted imaging one day post implantation of osmotic micropump catheter in right hemisphere of a normal rat brain. In vivo imaging after 24h of Gadolinium infusion revealed contrast enhancement in the ipsilateral part of the ventricular system including third ventricle. In addition contrast enhancement was seen in whole of the ipsilateral hemisphere. This confirmed the used of the osmotic micropumps for intracerebroventricular drug administration.

during the RF excitation it was the aim only to excite stationary spins (see Hyperpolarised MRI). Henrik Lundell has worked on imaging methods to capture diffusion processes on shorter time scales than normally captured by conventional diffusion weighted imaging methods, e.g. diffusion tensor imaging (DTI). Providing insight into smaller microenvironments than conventional could be of interest when increased specificity is required as in pathology studies. A new oscillating gradient spin echo (OGSE) sequences were developed and studies on ex vivo tissue performed (Fig. 2) (see Diffusion Imaging Group). Tim B. Dyrby continued his work on the ActiveAx technique in close collaboration with Professor Daniel C. Alexander. The ActiveAx technique

WHAT IS PRECLINICAL RESEARCH?

As indicated by the name, preclinical research concerns research preceding clinical studies. The preclinical research group at DRCMR strives to improve our understanding of normal biology, structure, micro-structure, function and biochemistry by using a variety of MR techniques in both *in vivo* and *ex vivo* studies. One of the great advantages of MRI is that it is non-invasive and therefore allows for longitudinal studies in the same animal providing a unique possibility to understand mechanisms for disease and disease progression. The MR scanner used for the preclinical studies is equipped with high-performance gradients which allows us to use new techniques which at present are impossible to implement at clinical systems due to hardware constraints.

uses a simple geometrical model of white matter axons called minimal model of with matter diffusion (MMWMD) to model diffusion MRI data acquired using optimised imaging protocols to provide indices of axon diameter and fibre density. They investigated imaging protocols using the pulsed-gradient-spin-echo sequence with different maximal available gradient strengths (G_{max}) and showed that a higher Gmax improves contrast between anatomical details. Further, it was investigated how ActiveAx could be used with the stimulated echo sequence (STEAM) to obtain longer diffusion times (> 80ms). Gradients like the slice selective and crusher gradients in the STEAM sequence can introduce a significant unwanted diffusion weighting along specific directions which bias axon diameter indices. The problem was overcome by adding compensating gradients to the unwanted diffusion weighting. The diffusion studies were carried out by the diffusion imaging group.

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- **Dyrby TB, Baaré WF, Alexander DC, Jelsing J, Garde E, Søgaard LV.** An ex vivo imaging pipeline for producing high-quality and high-resolution diffusion-weighted imaging datasets. Hum Brain Mapp 2011, Apr;32(4):544-63.
- **Dyrby TB, Søgaard LV, Hall MG, Ptito M, Alexander DC.** Contrast and stability of the axon diameter index from microstructure imaging with diffusion MRI. Magn Reson Med 2013, 70(3):711-21.

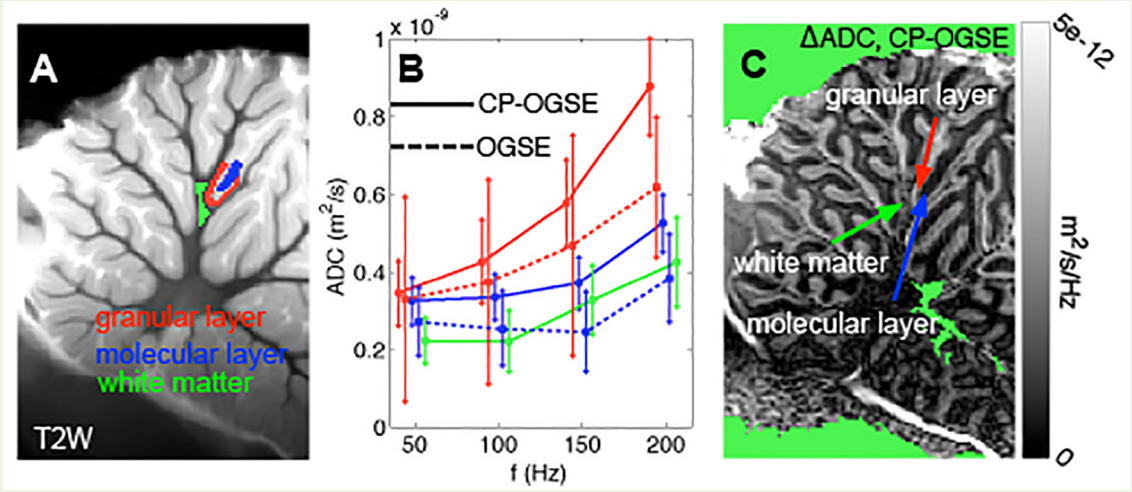

Figure 2: Oscillating gradient spin echo (OGSE) can capture diffusion processes on much shorter times scales than conventional diffusion weighted imaging and provides a new contrast to tissue microstructure. A) shows a T2-weighted image of the monkey cerebellum with three regions of interest covering different tissue types. The granular and molecular layers are not distinguishable in conventional modalities, but the tissues are well separated at high OGSE frequencies (red and purple solid lines in B). This contrast mechanism can be used to create new maps corresponding to cellular density as shown in figure C).

HYPERPOLARISED MRI

The group uses hyperpolarised (HP) ^{13}C based MR techniques for studying characteristics of cell metabolism in chronic diseases.

DRCMR members

Jan Henrik Ardenkjær-Larsen (group leader), Per Åkeson (group leader until end 2011), Lise Vejby Søgaard, Peter Magnusson, Sadia Asghar Butt, Mette Hauge Lauritzen, Christoffer Laustsen, Charlotte Viemose Larsen and Sascha Gude

External members/Collaborators

- **Prof Andreas Kjær and Carsten Haagen Nielsen (PhD student)**, Cluster for Molecular Imaging, Department of Biomedical Sciences, University of Copenhagen and Department of Clinical Physiology, Nuclear Medicine and PET, Copenhagen University Hospital Rigshospitalet, Denmark
- **Dr Sean Bowen and Hans Kasper Lipsø (PhD student)**, Technical University of Denmark, Denmark
- **Prof Michael Petersen and Dr Steffen Ringgaard**, Aarhus University, Skejby Hospital, Denmark
- **Prof Niels Christian Nielsen and Dr. Mads Vinding**, Aarhus University, Denmark
- **Prof Allan Flyvbjerg**, Aarhus University, Denmark
- **Franz Schilling (PhD student) and Dr Marion Menzel**, Technical University Munich, Germany
- **Prof. Lucio Frydman and Rita Schmidt (PhD student)**, Weizmann Institute, Israel
- **Prof. Malcolm Levitt and Dr Giuseppe Pileio**, University of Southampton, UK

RESEARCH ACTIVITIES

The focus of the group in 2011–12 has been on *in vivo* studies of cerebral and muscle metabolism and cell metabolism in disease models of diabetes, cardiac ischemia and cancer.

Sadia Asghar Butt continued a series of studies on cerebral metabolism using HP-^{13}C substances. . Hyperpolarized ketoisocaproate (KIC) was used to assess the *in vivo* activity of branched-chain amino transferases (BCAT), a

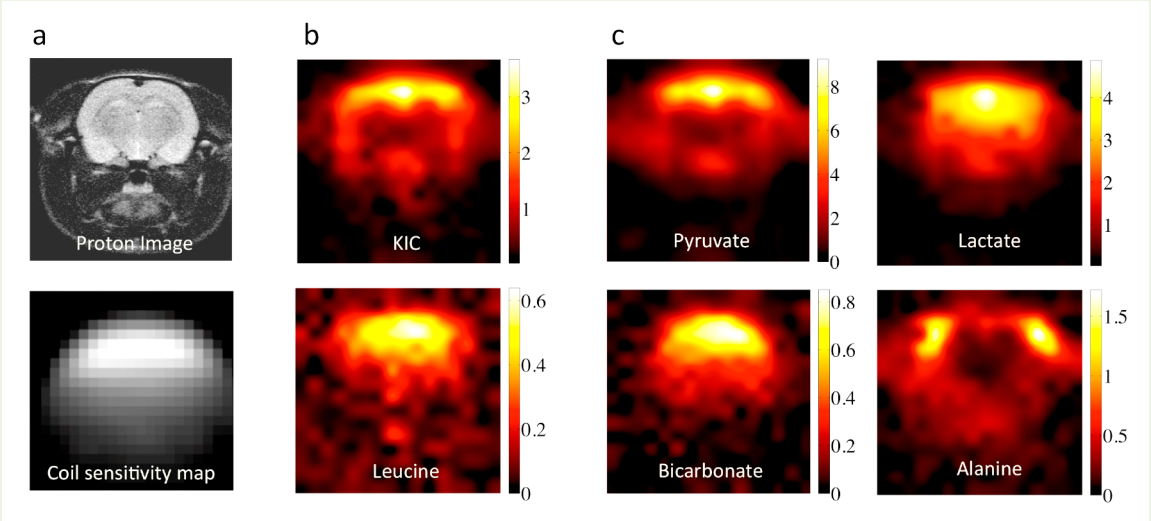

Figure 1: Chemical shift imaging of rat brain BCAT activity in vivo. a) Anatomical proton image and the surface coil sensitivity profile are shown. b) Metabolic maps of [1-13C]KIC and [1-13C]leucine (sum of 6) recorded 20 s after end of hyperpolarized [1-13C]KIC injection. Hyperpolarized [1-13C]leucine is specifically observed inside the brain. c) Hyperpolarized [1-13C]pyruvate was used as a reference substrate and its metabolic map is shown together with [1-13C]lactate, [1-13C]bicarbonate and [1-13C]alanine (sum of 6). Absolute color scale is shown for each metabolite image (a.u).

metabolic enzyme that plays an important role in regulation of the brain activity and glutamate homeostasis in the normal rat brain (Fig. 1). Catalyzed by BCAT, KIC is converted to the branched chain amino acid, leucine. Pyruvate was used as a reference substrate and the metabolic maps from pyruvate and KIC were compared. The results showed significantly higher KIC metabolism in hippocampal regions compared to the muscle tissue.

In her PhD project, Mette Hauge Lauritzen evaluates the HP-^{13}C technique as a tool for measuring regional changes in metabolism in the myocardium of rats after severe ischemia. Since the project aims to detect subtle regional changes in the heart metabolism it is of utmost importance that the initial metabolic conditions are well-controlled. In 2011 Mette developed a method for stabilizing the glucose metabolism in rats. Infusion of a mixture of glucose, insulin and potassium were found to upregulate the glucose metabolism in the heart improving the utility the HP-^{13}C technique for studying myocardial ischemia and other cardiac diseases that affect cardiac metabolism.

It is well-known that the kidneys are affected in the late stages of diabetes and the aim of Christoffer Laustsen Phd project was to evaluate whether HP-^{13}C methods can help identify kidney changes in early stages of the diabetic nephropaty. We have shown that the lactate signal increases in the diabetic kidney compared to the healthy kidney yielding a biomarker for diabetic nephropatic development (Fig. 2). The project is carried out in collaboration with Prof Allan Flyvbjerg's group at Aarhus University.

In collaboration with Prof. Andreas Kjær and Carsten Haagen Nielsen a combined hyperpolarized ^{13}C-MR and PET/CT tumor study was initiated in 2012, The aim of the study is to compare the sensitivity of two techniques when assessing changes in tumor metabolism after treatment in a xenograft mouse model.

By combining the spectroscopic data acquisition with diffusion weighting it is possible to acquire more specific information on the compartmentalization of the hyperpolarized metabolites. Lise Vejby Søgaard and Franz Schilling implemented a pulse sequence to measure the apparent diffusion coefficient of hyperpolarized metabolites and conducted a series of in vivo measurements in muscle tissue.

In an effort to increase the spatial resolution of the metabolite map and decrease the acquisition time beyond what is currently used on a routine basis at DRCMR, Peter Magnusson implemented a new MR pulse sequence which was tested on phantoms and *in vivo* on rat brain. The sequence is based on a spectrally sparse sampling multi-echo (FSEME) version of the Fast Spin-Echo sequence. Promising results were achieved with this technique in terms of single time-frame (acquisition time=1s) high spatial resolution *in vivo* images of rat brain metabolism.

Hyperpolarized water could be a safe and efficacious contrast agent for morphological imaging applications. Jan Henrik Ardenkjær-Larsen, Christoffer Laustsen and Sean Bowen succeeded in hyperpolarizing water to the equivalent of a 500 T MRI scanner and utilizing this overwhelming signal in vivo as an angiographic contrast agent in rats.

Hyperpolarized MRI/MRS is a compromise between spatial, spectral and temporal resolution. In a collaboration with Lucio Frydman and Rita Schmidt (Weizmann Institute) we are seeking to overcome some of these compromises, by merging the spectral and spatial acquisition, with the novel SPEN method developed in the

WHAT IS HYPERPOLARISATION?

The signal in MR is proportional to the spin polarisation which is only a few parts per million at normal magnetic field strenghs. By advanced techniques it is possible to hyperpolarise MR-sensitive nuclei outside the scanner thus increasing their MR signal more than 10.000 times. In this way it is possible to hyperpolarise ^{13}C-enriched substances and by chemical shift sensitive MR methods follow their metabolic conversion in cells *in vivo* after intravenous injection. Also noble gas nuclei such as ^{3}He can be hyperpolarised and imaged after inhalation into the lungs. A major advantage of the hyperpolarisation techniques is that the resulting MR signal can be detected without any disturbing background signal.

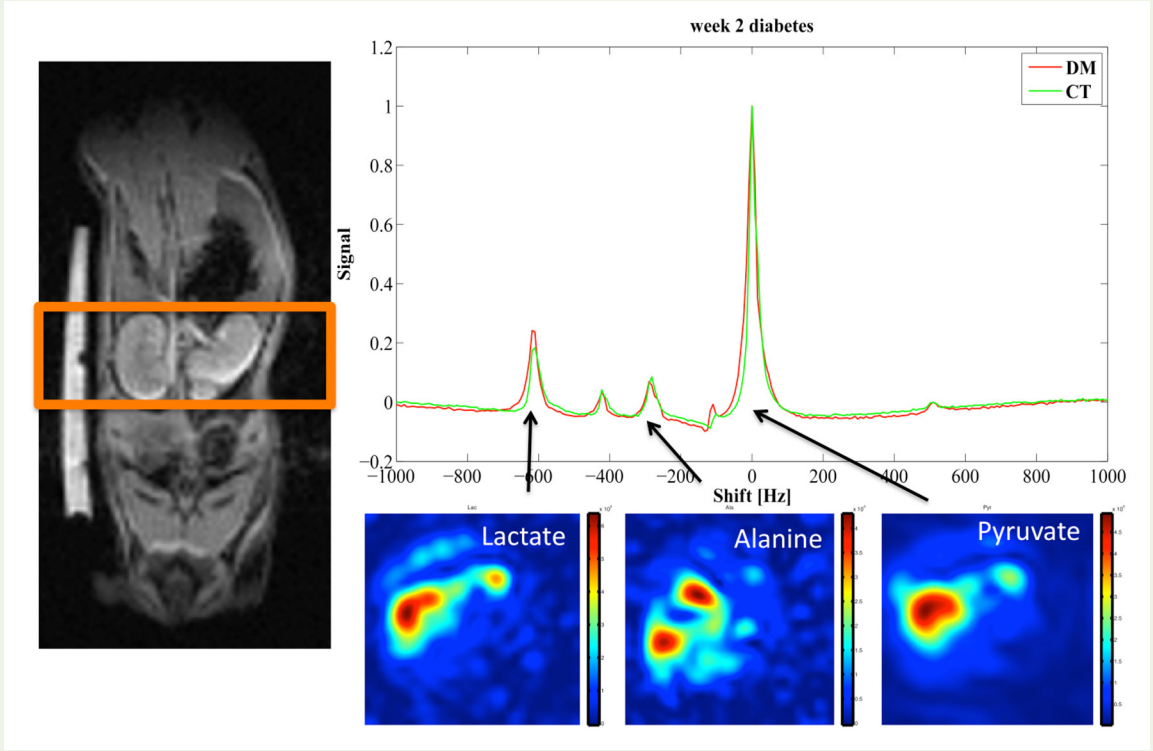

Figure 2: Kidney metabolism of intravenously injected hyperpolarized [1-^{13}C]pyruvate. Axial metabolite maps (lower right) of lactate, alanine and pyruvate from a healthy rat are shown together with averaged spectra (upper right) corresponding to the sum of all kidney pixels for a group of diabetic rats (red curve) and a group of control animals (green curve). The position of the axial slice is indicated on the proton image (left).

Frydmann lab. Christoffer Laustsen, Rita Schmidt and Jan Henrik Ardenkjær-Larsen implemented the sequence and acquired the first hyperpolarized in vivo images with the SPEN method, showing equal or better signal to noise ratio compared to the golden standard CSI, with a ultra fast truly singlet shot MRS method, with high spectral resolution.

Hyperpolarized substrates are limited by the longitudinal relaxation times, reducing the time window for investigations. Christoffer Laustsen and Jan Henrik Ardenkjær-Larsen have in collaboration with the group of Malcolm Levitt shown that it is possible to extend the lifetime of hyperpolarized substanses by several orders of magnitude even with pre-clinical and clinical MRI systems. This is achieved by utilizing singlet states, which in principle have no net spin and therefore are less affected by several dominant relaxation mechanisms.

The hyperpolarization 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.

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- **Laustsen C, Ostergaard JA, Lauritzen MH, Nørregaard R, Bowen S, Søgaard LV, Flyvbjerg A, Pedersen M, Ardenkjaer-Larsen JH.** Assessment of early diabetic renal changes with hyperpolarised [1-(13) C]pyruvate. Diabetes Metab Res Rev 2013, 29(2):125-9.
- **Laustsen C, Pileio G, Tayler MC, Brown LJ, Brown RC, Levitt MH, Ardenkjaer-Larsen JH.** Hyperpolarized singlet NMR on a small animal imaging system. Magn Reson Med. 2012 Oct;68(4):1262-5.

AGING & DEMENTIA

Research into the structure and function of the aging nervous system is key to understanding functional decline as well as functional well-being in ageing populations. Both advancing age and cognitive impairment are associated with increased prevalence of various brain diseases such as Alzheimer's disease (AD) and cerebrovascular disease (CVD). Abnormalities of cerebral white matter commonly seen on a magnetic resonance image (MRI) as white matter hyperintensities (WMH) increases with age, CVD, and as a possible consequence of AD. In the Aging and Dementia group we study the impact of white matter changes, particularly WMH, on cognition with aging and in the setting of cognitive impairment syndromes such as mild cognitive impairment (MCI) and AD. The main research areas of the Aging and Dementia group relate to the investigation of structural, functional as well as vascular changes in MR in ageing populations and individuals with neurodegenerative diseases.

DRCMR members

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

External collaborators

- **Professor Gunhild Waldemar**, Memory Disorders Research Group, Department of Neurology, Copenhagen University Hospital Rigshospitalet
- **Associate Professor Steen G. Hasselbalch**, Memory Disorders Research Group, Department of Neurology and Neurobiology Research Unit, Copenhagen University Hospital Rigshospitalet
- **Professor Rasmus Larsen**, Informatics and Mathematical Modelling, Technical University of Denmark
- **Associate Professor Koen van Leemput**, Technical University of Denmark and the Martinos Centre, Boston, Massachusetts, USA
- **Professor Erik Lykke Mortensen and Professor Kirsten Avlund**, Department of Public Health, University of Copenhagen
- **Professor Kaarin Anstey**, Aging Research Unit, Australian National University.

RESEARCH ACTIVITIES

Recent research in our group has focused on the impact of white matter lesions and corpus callosum atrophy on white matter integrity and the relation to cognitive function and mobility in aging and dementia.

The LADIS study

For more then a decade the group has been contributing to a multi-site investigation by European Union collaborators entitled 'LeukoAraiosis and DISability in the Elderly' (LADIS). The LADIS study is a multi-centre, 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 White Matter Hyperintensities (WMH) on transition to disability (Fig. 1).
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 more then 40 publications in peer-reviewed journals, six in 2011 alone, several with major contributions from the DRCMR, especially regarding development of MRI techniques for the automated assessment of brain structures.

ALZHEIMER'S DISEASE CHANGES THE BRAIN

In Alzheimer's disease abnormal clusters of protein fragments (plaques) build up between nerve cells leading to nerve cell death throughout the brain in a predictable pattern. Plaques form when protein pieces called beta-amyloid clump together which can be visualised with amyloid PET imaging (PIB-PET). Over time, the brain shrinks dramatically, affecting nearly all its functions. MRI can highlight these changes in the brain even before symptoms appear.

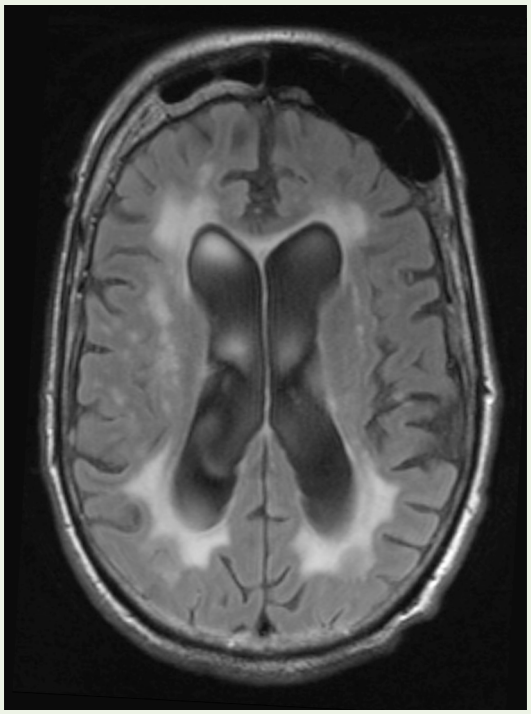

Figure 1: White matter hyperintensities are seen as diffuse bright areas on this axial fluid attenuated inversion recovery (FLAIR) image. In addition, marked atrophy is noted. As nerve cells die, they are replaced with fluid, which appears dark on some MRI scans. Both atrophy and white matter hyperintensities are typical findings in patients with AD..

Kristian S. Frederiksen, Phd student at the Danish Dementia Research Center, Rigshospitalet, continued the analysis of data from the Leukoaraiosis And DISability study. 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 published.
As part of Kristian's PhD project a new study in collaboration with Steen G. Hasselbalch, Rigshospitalet, combining MRI and PET imaging, was initiated. The ligand Pittsburgh compound-B that has affinity to beta-amyloid, a protein believed to be central in the pathological processes leading to AD, is being used in the PET scans. The aim of the project is to explore the effects of cortical deposition of beta-amyloid on white matter tracts and employs 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 Group). An abstract has recently been submitted to Alzheimer´s Association International Conference 2013.

The ADEX MR-study

As an add-on to this project, a small study was initiated to explore the feasibility and safety of aerobic exercise in patients with AD. The study serves as a pilot study to a nationwide intervention study initiated by Professor Gunhild Waldemar and supported by the Strategical Research Counsil. The overall scope of the "Preserving quality of life, physical health and functional ability in Alzheimer's disease: The effect of physical exercise" (ADEX) study is to explore whether aerobic exercise may be an adjunct to pharmacological treatment in AD. Moreover, in a substudy potential biological mechanisms and predictors of the effect of physical exercise in patients with AD will be investigated. By combining structural, resting state-fMRI and DTI data with PiB-PET the link between local damage, long-range disconnection, and more widespread physiological and clinical implications will be asessed.
In 2011 the group welcomed Christian Thode Larsen from Technical University of Denmark. In close collaboration with Associate Professor Koen van Leemput from the Martinos Centre, Boston, Massachusetts, USA. Christian's

BRIGHT AREAS IN THE AGING BRAIN

From the beginning of the fifth decade of life, healthy adults show significant shrinkage of the brain with expansion of CSF-filled cavities, and a pattern of differential regional shrinkage. At the same time White Matter Hyperintensities appear as bright areas on MRI images. While these changes may be present in healthy older adults, they are not entirely benign. As they predict an increased risk of stroke, dementia, and death their presence should prompt detailed screening for risk factors such as hypertension, diabetes, and atrial fibrillation.

PhD-project is centered around computational analysis of longitudinal MR images of the brain. A specific focus of this project is the development of methods for automatic correction of intensity inhomogeneity imaging artefacts also known as bias field or B1-field inhomogeneity correction. This is highly relevant especially for the analysis of repeated structural and functional MRI scans as it ensures more accurate segmentation of brain tissue and structures. One such longitudinal study is the ADEX-study. Participants of the study exercise one hour, three times a week for a period of three months. The participants are scanned at baseline and again after 3 months of structured and supervised exercise. We hypothesise that exercise will correlate with hippocampal volume and cognitive memory function, and a relative increase in grey matter volume. To test this data will be assessed using the widely used brain segmentation tool Freesurfer (Fig. 2), developed at the Martinos Centre. It is a long-term goal of the Phd-project to explore the possibility of including Christian's work on bias-field correction in the Freesurfer pipeline.

The middle-aged brain

In 2012 Ellen visited the Aging Research Unit, Australian National University in Canberra, strengthening our collaboration with Professor Kaarin Anstey on the PAHT Trough Life Project. Based on data from this longitudinal study of Adults from 20 to 75 years our current focus is on identifying risk factors that moderate the trajectory of cognitive development and decline and the impact of cognitive ageing on brain changes in normal aging.

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- Corpus Callosum Tissue Loss and Development of Motor and Global Cognitive Impairment: The LADIS Study. **Frederiksen KS, Garde E, Skimminge A, Barkhof F, Scheltens P, van Straaten E, Fazekas F, Baezner H, Verdelho A, Ferro JM, Erkinjuntti T, Jokinen H, Wahlund L-O, O'Brien J, Basile AM, Pantoni L, Inzitari D, Waldemar G** on behalf of the LADIS study group. Dement Geriatr Cogn Disord, 2011;32(4):279-86
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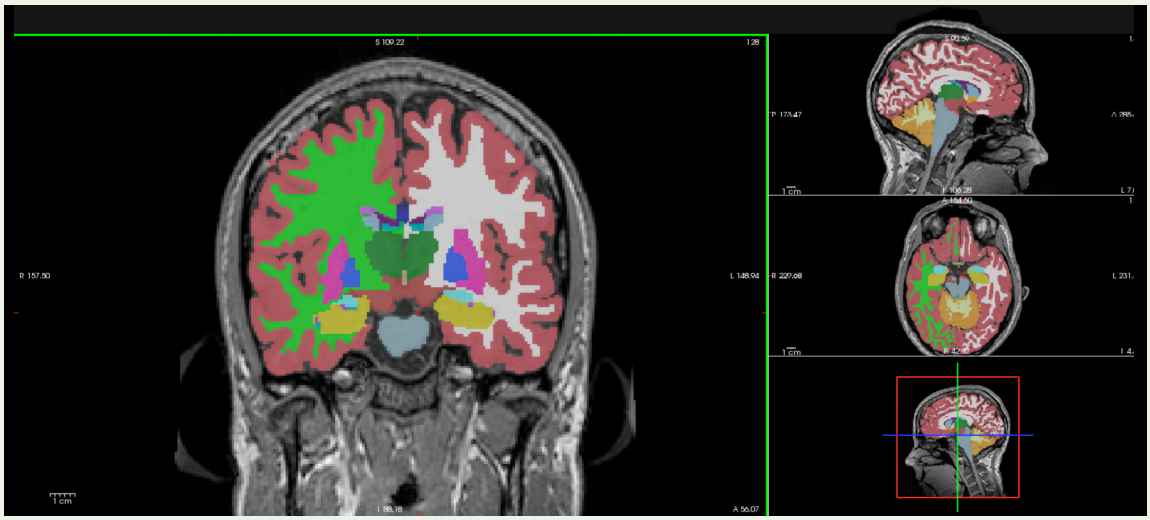
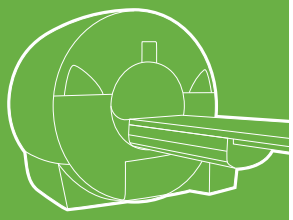


Figure 2: A T1-weighted scan of a (healthy) brain analysed with Freesurfer. The segmentation has been displayed with the Freesurfer tool 'Freeview'. The segmented brain structures are displayed in different colors. The yellow areas on the coronal image mark the hippocampus, an area of the brain known to be associated with memory. Atrophy of the hippocampus is a typical finding in AD.



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  Ryberg C, Rostrup E, Paulson OB, Barkhof F, Scheltens P, van Straaten EC, van der Flier WM, Fazekas F, Schmidt R, Ferro JM, Baezner H, Erkinjuntti T, Jokinen H, Wahlund LO, Poggesi A, Pantoni L, Inzitari D, Waldemar G; LADIS study group.
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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, indices of tissue microstructure and fibre tract characteristics, as well as brain activation during rest or while performing specific psychological tasks, are used to relate brain structure and function to clinical, behavioural, biochemical and genetic variables.

DRCMR members

William Baaré (group leader), Kathrine Skak Madsen, Hartwig R. Siebner, Louise Baruël Johansen, Martin Vestergaard, Sara Krøis (DRCMR & Pediatric Clinic, Rigshospitalet), Olaf B. Paulson, Arnold Skimminge, Eline Bruun Ofei, Julie Hagstrøm, Troels Lukassen, Jonathan Holm-Skjold.

External members

Peter Udall and Peter Born, Pediatric Clinic, Rigshospitalet, Denmark, and Terry L. Jernigan (DRCMR & UCSD)

External collaborators

We have close collaborations with several national and international research groups (http://www.drcmr.dk/Maturation).

RESEARCH ACTIVITIES

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

The major aims of this longitudinal project are to define the degree of variability in the maturational trajectories of different brain circuits among healthy children and to link these to evolving cognitive abilities and social-emotional behaviour. Moreoveover, the impact of environmental (e.g. stress, physical activity, and alcohol and drug use), genetic (e.g. common polymorphisms in genes related to the dopamine, serotonin system and the brain-derived neurotrophic factor gene) and biological (cortisol, sex hormones) factors are investigated.

The HUBU project was initiated by Terry L. Jernigan in 2007 and has been coordinated and extended by Kathrine Skak Madsen. Participants were enrolled in either 1st, 3rd or 5th grade and are assessed with 6 months intervals. We retained 92 and 89 children in the 2nd and 3rd assessment. From the 4th to 9th assessment around 70–75 children were retained in each round. The 10th assessment finished in August 2012 and included 65 participants.

Structural MRI scans in HUBU include high resolution T_1 and T_2 weighted images and diffusion weighted images. Starting from the 6th assessment, a 10-minute resting-state fMRI scan has been obtained at each visit, to allow for mapping of functional connected brain networks. In the 10th assessment, an emotional face gender discrimination fMRI task was implemented similar to that used in adult healthy CIMBI volunteers, in which participants were required to carry out a gender discrimination task of angry, neutral and happy faces (face emotion was irrelevant to the task).

Besides structural and functional MR scanning (Fig. 1), the research protocol includes neuropsychological tests (e.g. response inhibition, working memory, attention, reaction time, verbal fluency, emotional face Go/No Go, the Cimbi affective memory task behavior), questionnaires assessing e.g. 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).

The research efforts focusing on emotional processing and stress have been embedded in the Center for Integrated Molecular Brain Imaging (CIMBI, see Page 60).

During 2011 and 2012, three assessments were performed. In 2011, Louise Baruël Johansen joined the group as PhD student funded by the "the Danish Agency for Science, Technology and Innovation and the Faculty of Health Sciences of the University of Copenhagen". Louise focuses on resting-state and task-based (emotional face gender discrimination task) fMRI studies, examining the link between functional connectivity within the limbic system and developing personality, emotional processing and HPA-axis

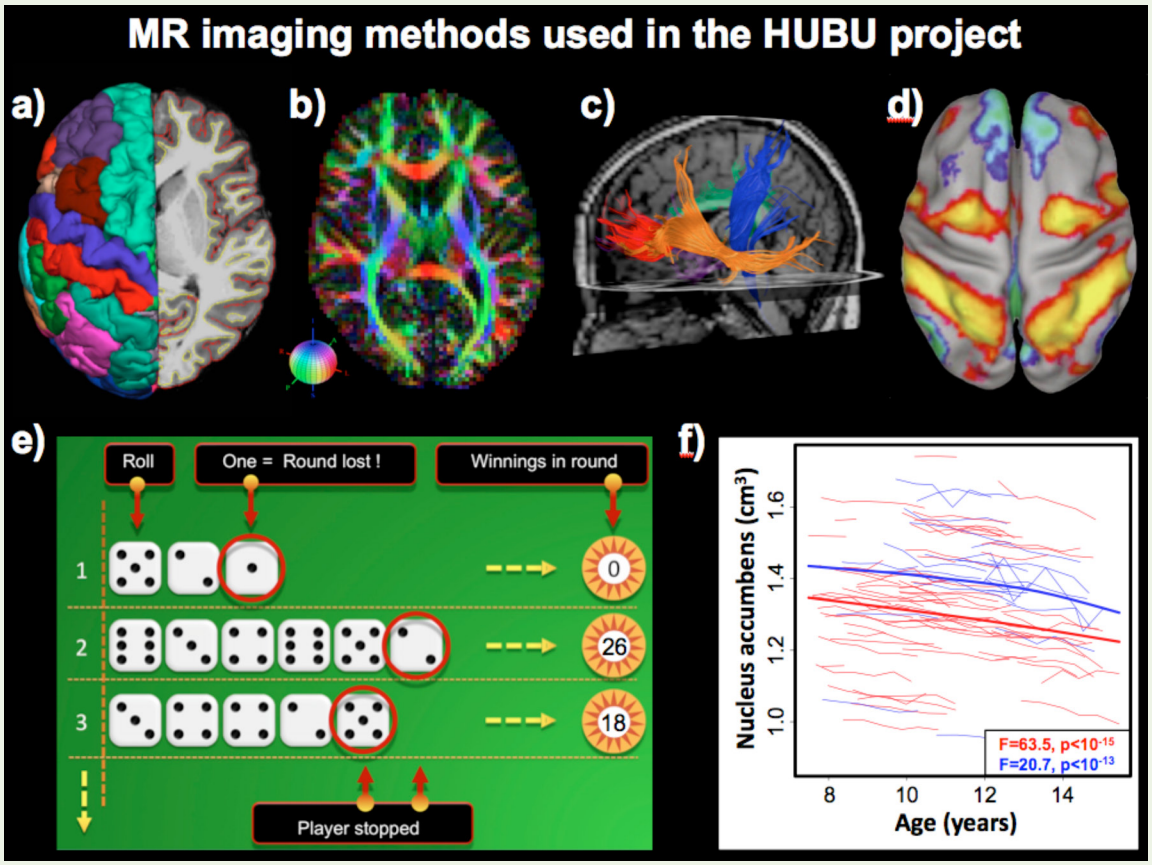


Figure 1: a) High-resolution T1 weighted images allow extraction of e.g. surface area and thickness of cortical regions (FreeSurfer). b) Colour-coded FA map representing the diffusion directionality of water within a voxel. The primary direction is colored as: green = anterior/ posterior, red = right/ left, blue = inferior/superior. c) Diffusion tractography allows extraction of specific white matter fibre tracts. d) (Resting state) fMRI allows investigation of functional connectivity in neural networks of interest. e) Risk behavior related brain activity will be assessed while subjects perform a dice game. f) Individual changes over time in nucleus accumbens volume over the first 6 HUBU assessments.

functioning. Processing streams for functional connectivity analyses were developed and optimized. Additional funding was obtained for a research year (scholar stipendium) for medical student Troels Lukassen. Troels started a research year in July 2012 and will extract white matter fibre tracts of interest on all longitudinal diffusion-weighted data as well as investigate the effects of physical activity on brain maturation. Longitudinal diffusion-weighted images have been processed and protocols for the extraction of specific white matter fibre tracts have been established. Psychology student Jonathan Skold-Holm did a 3-month internship at the end of 2012 focussing on risk behaviour as assessed with the locally developed Dice Game. Eline Bruun Ofie completed her Master thesis in 2011. Kathrine Skak Madsen successfully defended her PhD thesis "Brain microstructural correlates of behavioural and neuroendocrinological phenotypes" on April, 29th 2011 and received a post doc grant from the "Det Frie Forskningsråd | Sundhed og Sygdom".

Analyses of the baseline DWI data confirmed our a priori hypotheses that indices of fibre tract microstructure known to show age-related alterations during childhood and adolescence would significantly predict individual differences in performance on working memory (1), visuospatial 5-choice reaction time (2) and sustained attention (3) and that these associations would remain after controlling for age. Observed associations may be related to variation in individual phase of maturation, to activity-dependent alterations in

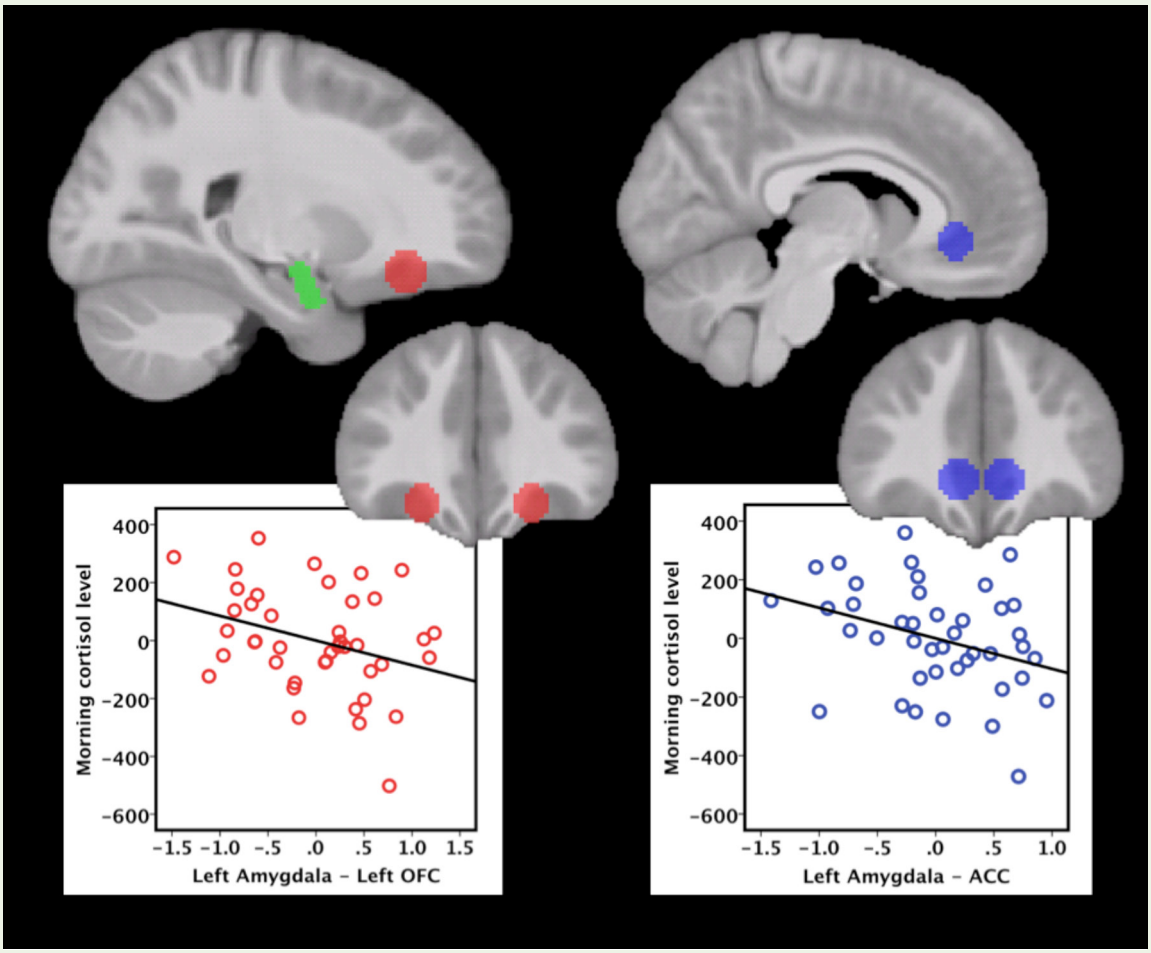


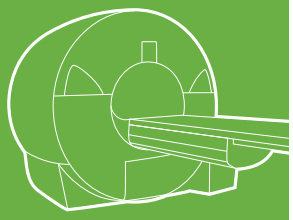
Figure 2: Top: Functional connectivity analyses based on identified central-lateral amygdala parcel (in green) and regions in orbitofrontal cortex (OFC) in red and the anterior cingulate cortex (ACC) shown in blue. Partial regression plots showing that higher morning cortisol levels were significantly associated with lower functional connectivity between the left central-lateral amygdala parcel and the left OFC (left) and ACC (right) cluster regions (adjusted for gender, age, and the interaction between age and amygdala functional connectivity.

the networks subserving these functions, or to individual differences in the underlying neural system connectivity that emerge earlier during brain development and remain stable in spite of superimposed biological changes associated with maturation. Recently, we showed that higher morning cortisol levels were associated with lower functional connectivity between a left central-lateral amygdala subregion and regions in the left anterior cingulate and left orbitofrontal cortex (Figure 2). Finally, higher neuroticism was associated with higher fractional anisotropy (FA) in the right relative to left cingulum in boys, whereas in girls it was associated with higher left relative to right cingulum FA.

Brain maturational effects of glucocorticoids

This project focuses on the relationship between the stress hormone cortisol (glucocorticoid) and brain maturation in school-aged children between 7 and 14 years.

The project examines the 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 coordinated by PhD students Sara Krøis and Martin Vestergaard.



The data acquisition was completed mid 2012. In total 24 subjects diagnosed with rheumatic and 14 subjects with nephritic disorder were enrolled in the study alongside a control group of 42 children matched for gender, age and demographics. One publication is in preparation on group analyses of behavioural and biological markers between patients and controls. Structural and functional data analyses are ongoing with publications being planned for DTI and fMRI in 2013/2014.

SELECTED PUBLICATIONS

- **Damsted SK, Born AP, Paulson OB, Uldall P.** Exogenous glucocorticoids and adverse cerebral effects in children. Eur J Paediatr Neurol. 2011;15(6):465-77.
- **Klarborg B, Skak Madsen K, Vestergaard M, Skimminge A, Jernigan TL, Baare WFC.** Sustained attention is associated with right superior longitudinal fasciculus and superior parietal white matter microstructure in children. Hum Brain Mapp. Jul 17 2012.
- **Jernigan TL, Baare WF, Stiles J, Madsen KS.** Postnatal brain development: structural imaging of dynamic neurodevelopmental processes. Prog Brain Res. 2011;189:77-92.
- **Madsen KS, Baare WF, Skimminge A, Vestergaard M, Siebner HR, Jernigan TL.** Brain microstructural correlates of visuospatial choice reaction time in children. Neuroimage. 2011; 58(4):1090-100.
- **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. 2011; 23(9):2135-46.

CARDIOVASCULAR IMAGING UNIT

The Cardiovascular Imaging Unit (CIU) was established at the DRCMR in late 2012 as a co-operation between the Centre for Functional and Diagnostic Imaging (Director Claus Leth Petersen and Director Hartwig Siebner) and the Cardiovascular Section (Director Walter B Nielsen).
The daily manager of CIU is Jens D Hove. The strategy of clinical involvement as well as the strategy of research is defined by a "CIU-nucleus" comprising Claus Leth Petersen (chair), Jens Hove and Andreas Kjær. Our intention is to develop a strong clinical cardiac MRI unit based on a profound research development program. In recent years, cardiac MRI has been well established as a unique imaging modality in several areas:

- To characterize and distinguish known hypertrophic and/or dilated cardiomyopathies
- To distinguish viable from fibrotic myocardium in ischaemic cardiomyopathy
- For non-invasive examination of regional myocardial blood perfusion
- For examination of patients with complicated valve- and myocardial diseases including patients with valve regurgitation

The CIU also entails a comprehensive list of other imaging modalities such as cardiac CT, advanced echocardiography (3-dimensional echo and speckle-tracking analysis) and cardiac Positron Emission Tomography (PET). Specialists in radiology, nuclear medicine as well as cardiologists are involved in the multimodal cardiac imaging approach.
The clinical cardiac MR imaging is supervised by a SCMRI level III accredited cardiologist, the clinical cardiac CT imaging is supervised by a SCCT level III accredited cardiologist and the echocardiography program is supervised by an ESC accredited cardiologist.

DRCMR members

Jens D Hove (group leader), Claus Leth Petersen, Walter Bjørn Nielsen, Hartwig Siebner, Per Lav Madsen.

External collaborators

- **Professor Søren Møller**, MD, D.M.Sc. Department of Clinical Physiology and Nuclear Medicine, Copenhagen University Hospital Hvidovre, Denmark
- **Professor Flemming Bendtsen**, MD, D.M.Sc, Department of Gastroenterology Copenhagen University Hospital Hvidovre, Denmark
- **Professor Steen Madsbad**, MD, D.M.Sc, Department of Endocrinology Copenhagen University Hospital Hvidovre, Denmark

RESEARCH ACTIVITIES

Various metabolic diseases are associated with cardiovascular disease often through direct influence on cardiac metabolism with associated influence on cardiac systolic and diastolic function, and such interaction will be a cornerstone in the research at Hvidovre. Among others, we plan to follow a cohort of patients with cirrhosis and to study the influence of obesity and diabetes mellitus and the effect of treatment with novel anti-diabetic drugs. We have also planed a study on patients diagnosed and treated for carcinoid tumours. We have a strong objective towards the development of novel CMR analysis tools and collaborate closely with several other DRCMR groups to achieve this goal. Perfusion studies and studies of myocardial fibrosis, tractography and regional wall motion using strain imaging are under development.

CONTROL OF ACTION (ContAct) GROUP

THE BRAIN TAKING ACTION ...

In an ever-changing world, we need to flexibly adjust our actions to the challenges imposed by the environment. Even an apparently simple activity such as writing an email requires the integration of multiple internal and external factors: Internal aspects like whether and when we write the email and what we write therein reflect our intentions, preferences and skills. External factors, for instance the spatial arrangement of the keys on the keyboard or the display of a mobile phone determine how we perform the act itself. The social context (e.g. official or personal mails) also frames the act of typing.

This example shows that the human brain is very skilled to flexibly integrate relevant contextual dimensions into appropriate actions. However, this ability is often severely affected in neurological and psychiatric disorders such as stroke, Parkinson disease, or schizophrenia. The research program of the Control of Action (ContAct) group led by Prof. Hartwig Roman Siebner is designed to gain a better understanding of the neural mechanisms mediating the flexible control of actions. A core hypothesis of ContAct research is that the brain achieves the flexible control of voluntary actions by dynamically adjusting the functional interactions within and across specialized motor brain networks. To identify and understand these temporo-spatial brain dynamics of motor control, the Contact group integrates multimodal brain mapping, non-invasive brain stimulation, and computational modelling.

The ContAct group offers an attractive platform for talented young neuroscientists and has already established strong collaborative links with highly profiled national and international neuroscientists who share a common interest in human motor control. The ContAct group is funded by a large "Grant of Excellence" awarded by the Lundbeck Foundation to Hartwig R. Siebner (25 Mill DKK, 2011-2015)

DRCMR members

The Control of Action (ContAct) group includes: Professor Hartwig R. Siebner (group leader), Anke Karabanov, Axel Thielscher, Estelle Raffin, Kristoffer H. Madsen, Olliver Hulme, Tim B. Dyrby, Brian Haagensen, Conrad Stanek, Damian Herz, David Mehder, Giovanni Pellegrino, Jonathan Kornholt, Alessandro Calamuneri, Joyce van der Vegt, Kasper Winther Andersen, Keiichiro Shindo, Lars Ewald, Norbert Brüggemann, Sofie Johanna Nillson, Steffen Angstmann, Yuko Shindo, Tina Haren

External collaborators

- **Associate Professor Annemette Løkkegaard**, Department of Neurology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark
- **Professor Christine Klein**, Institute for Neurogenetics, University of Lübeck, Germany.
- **Professor Jens Bo Nielsen**, Department of Exercise and Sport Sciences and Department of Neuroscience and Pharmacology, Panum Insitute, University of Copenhagen
- **Professor Kerstin von Plessen**, Centre for Child and Adolescent Psychiatry Bispebjerg, Capital Region Psychiatry, Denmark.
- **Professor Lars Kai Hansen**, Associate Professor Morten Morup, PostDoc Carsten Stahlhut Cognitive systems, DTU-Compute, Technical University of Denmark, Denmark
- **Professor Vincenzo DiLazzaro**, Department of Neurology, Campus Biomedico University, Rome, Italy.

RESEARCH ACTIVITIES

The ContAct research program consists of three methodologically oriented lines of research and three work packages centered around important themes of human motor control.

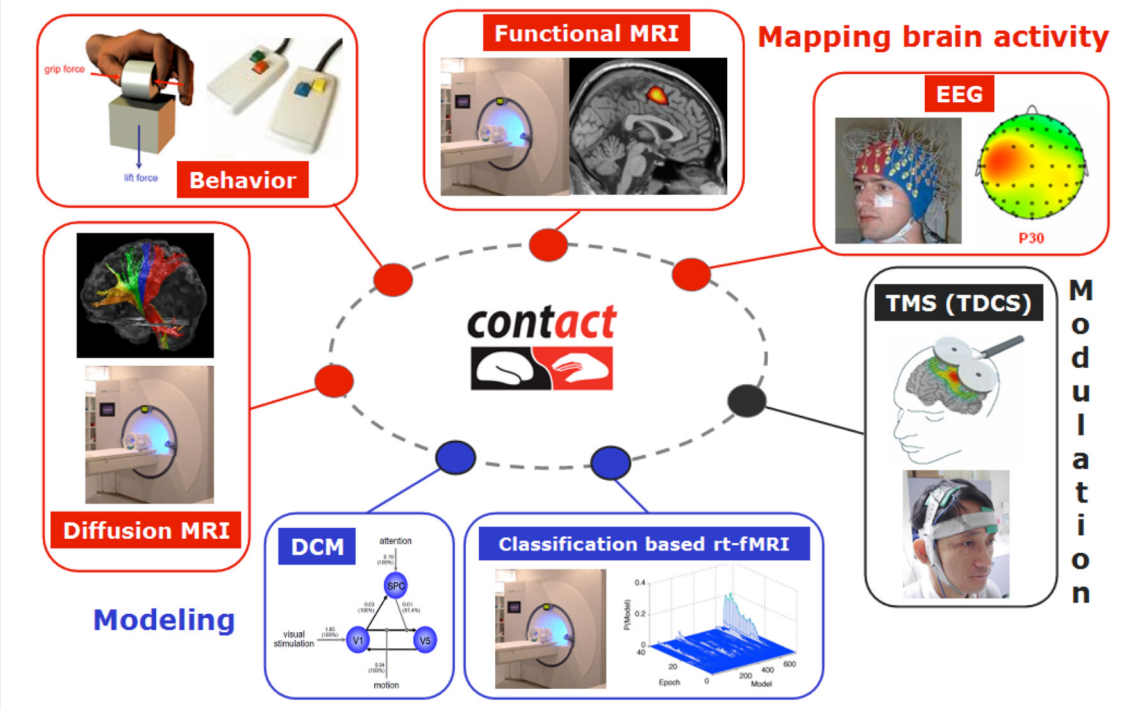
METHODS IN ACTION (Work packages 1–3)

The three methodological work packages are concerned with mutimodal integration of brain mapping techniques, interventional neuromodulation, and tracing structural correlates of brain connectivity.

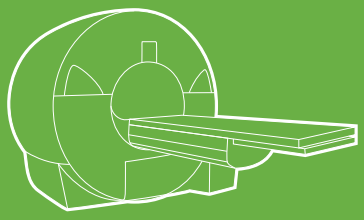
1. Dynamic Multimodal Motor Mapping

Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have been successfully applied to map the functional activation of brain regions controlling our actions. EEG and fMRI are complementary brain mapping techniques: While fMRI has an excellent spatial resolution, EEG offers a high temporal resolution. Therefore, the combination of EEG and fMRI will not only allow to map functional interactions within and across systems involved in action control at high spatial and temporal resolution but also to trace state-dependent changes in the expression of these temporo-spatial interactions.

The ContAct group implements so-called "real-time" fMRI to trace changes in distributed brain activity patterns in real time, while individuals are carrying out a motor task. One application will be to use real-time fMRI to trace activation patterns that reflect our will to act (for example the will to carry out a particular action and to refrain from an alternative action). In other words, we wish to decode emerging states of the mind and study how these emerging brain states are related to the control of action. These "real-time" information about the state of the brain can be used as bio-feedback for training subjects – helping them to establish or maintain a specific state of mind using a brain-computer interface (BCI) approach. Furthermore, advanced modelling of the measured brain activity at rest as well as during motor tasks will yield causal models of the connectivity changes underlying action control. This line of research is coordinated by Senior Researcher Kristoffer H. Madsen and involves a close collaboration with the *Computational Modelling & Analysis group*.



The ContAct research program – Mapping, modelling and modulating brain activity involved in human motor control.

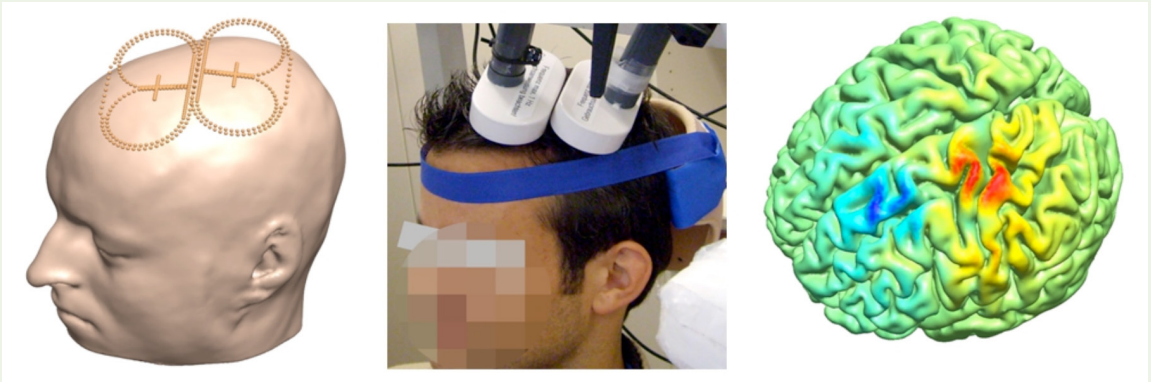


2. Shaping the Motor Brain

A core aspect of ContAct research is the use of non-invasive brain stimulation such as such as transcranial magnetic stimulation (TMS) and transcranial current stimulation (tDCS) to actively shape the function of motor brain networks. An inherent limitation of fMRI and EEG is that these techniques can only be used to correlate changes in brain activity with motor behaviour. This correlative nature of fMRI and EEG makes it difficult to draw causal inferences about the underlying neural network architecture. In addition, the vast majority of studies have exclusively focused on regional changes in activity rather than on distributed changes in activity and connectivity within brain networks. To overcome these limitations, the ContAct group combines advanced brain mapping and modelling techniques with non-invasive brain stimulation techniques such as TMS and low-intensity transcranial current stimulation using direct or alternating electrical currents. TMS uses a rapidly changing magnetic field to induce weak electric currents in the cortex of the human brain. This current causes neural activity in the stimulated parts of the brain with only minimal discomfort, allowing the functioning and interconnections of the brain to be studied. By actively shaping ongoing neuronal activity in the stimulated cortex, it is possible to selectively manipulate specific functional units within the human motor system. We also use dual-site TMS to interfere with neural activity in two brain regions in a coordinated fashion. The TMS technique in combination with other brain mapping methods opens up exciting possibilities to characterise the causal interactions in functional brain systems controlling our actions. This work is carried out in close collaboration with associate Professor Axel Thielscher who is heading the *Integrative Neurostimulation and Neuroimaging Group*.

3. Tracing Motor Connectivity

While fMRI and EEG can characterize how brain regions functionally interact (referred to as functional connectivity), these methods provide no information about the anatomical connections among brain regions (referred to as structural connectivity). To find out which parts of the brain are structurally connected with each other, we use diffusion MRI, an MR technique, which is sensitive to the diffusion of water in the body. In white matter tracts, water diffusion occurs preferentially along the direction of the neural axons. The directional preference of water diffusion can be imaged with diffusion MRI, and this information can be used to reconstruct the white matter tracts (i.e. tractography). Tractography based on diffusion MRI will provide detailed knowledge about the strength of anatomical connections in individual brains. This knowledge about the "strength" of specific connections between motor brain areas will inform our functional MRI analyses and thus, greatly help to unravel the functional integration within the motor system during action control. This work is carried out in close collaboration with senior researcher Tim Dyrby who is leading the *Diffusion Imaging group* at DRCMR.



Bifocal transcranial magnetic stimulation with two coils: *Painless non-invasive stimulation targets the dorsal premotor cortex and the primary motor cortex of the left hemisphere in a healthy volunteer. The right panel shows the map of the induced electrical field in the cortex.*

THE BRAIN IN ACTION (work packages 4–6)

The three thematic work packages are centred on the question how the human brain predicts, selects and implements intentions into actions.

1. THE PREDICTIVE BRAIN

An important feature of motor control is prediction. When we grasp and lift a cup, the motor system implements predictive knowledge about the weight and the shape of the cup. These predictions are essential for the optimal use of the cup. These "internal models" in the brain make us very proficient in predicting the perceptual, social and emotional outcome of our actions. This is because our brain has established strong predictive associations between our actions and the outcome of our actions. Predictive motor control is essential for making optimal decisions, gaining a sense of agency, and establishing motor routines. One line of ContAct research focuses on predictive motor control. Here the methods developed in the methodogical work packages are applied to better understand the neural mechanisms involved in updating internal representations of action-outcome contingencies.

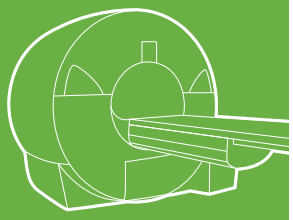
2. THE COMPETING BRAIN

When we go shopping or go to work, we continuously deal with multiple options for action. This gives us flexibility, but we also have to continuously make up our mind which option to act out. In other words, action control is very often a high-dimensional process offering a multitude of possible choices. One important neural process in this context is the ability to effectively suppress the activation of automatic but inappropriate tendencies to act. For instance a green traffic light will trigger an automatic response to cross the street, but this action needs to be suppressed when an emergency vehicle is driving by at high speed and with the siren wailing. The work is expected to provide major new insights into how the human brain resolves the conflict between routine (but inappropriate) and non-routine (but appropriate) reactions.

3. THE INTENTIONAL BRAIN

Our intentions motivate whether we act, when we act and what kind of actions we perform. For instance, when we consider to visit a friend, we ask ourselves whether we really want to do this (Shall I really visit my friend or better stay at home and relax?), when we want to visit (Shall I visit my friend today or tomorrow?) and what we do on order to realize our plan (Shall I take the bike or better call a cab?). These intentional decisions are motivated by our internal goals and depend on our personal preferences but also on our present bodily state such as being hungry or tired.

The ContAct research group in May 2012



A major focus of the ContAct research program is to study functional brain activity related to our intentions and the transformation of intentions into actions. The aim is to delineate patterns of brain activity and connectivity that are specifically associated with the decision which action to execute (What?), when to execute an action (When?), or whether to execute an action or not (Whether?). This will shed new light on where in the brain and how intentional factors are implemented in the control of actions.

SELECTED PUBLICATIONS

- Herz DM, Christensen MS, Reck C, Florin E, Barbe MT, Stahlhut K, Amande K, Pauls M, Tittgemeyer M, Siebner HR, Timmermann L (2012) Task-specific modulation of effective connectivity during two simple unimanual motor tasks: a 122-channel EEG study. Neuroimage 59:3187-3193.
- Moisa M; Siebner HR, Pohmann R; Thielscher, A (2012) Uncovering context-dependent changes in functional connectivity of human dorsal premotor cortex during response selection. J Neurosci 32:7244-7252.
- van Nuenen BFL, Kuhtz-Buschbeck J, Schulz C, Bloem BR, Siebner HR (2012) Weight-specific anticipatory coding of grip force in human dorsal premotor cortex. J Neurosci 32:5272-5283.

THE DECISION & MOTIVATION GROUP

The Decision & Motivation group engages in research that asks how decisions are made, how they are motivated, and what functions they serve. We are interested in a diversity of questions, spanning decisions made in social and economic contexts, through to the decisions that help regulate the homeostatic systems of the body. To do this we triangulate between a number of techniques primarily, computational modelling, psychophysics, fMRI, endocrinology, pharmacology and genotyping.

DRCMR members

The group began under the joint leadership of Thomas Ramsøy and Hartwig Siebner. Ollie Hulme has recently taken over from TR, who now runs the Decision Neuroscience Research Group at Copenhagen Business School. Members include: David Meder (PhD cand. KU), Helle Laursen (PhD cand. KU), Tobias Morville (Msc. and Res. Ass, KU), Silas Nielsen (Res. Ass, KU), Brian Haagensen (PhD cand. KU), Tina Haren (PhD cand. KU), Susanne Henningsson (Postdoc, CIMBI), Julian Macovenau (Postdoc, CIMBI), Morten Friis-Olivarius (PhD cand. CBS), Joyce van der Vagt (PhD cand. KU), Sofie Gelskov (PhD cand. KU), Bjorn Hallson (Res. Ass. KU).

RESEARCH ACTIVITIES

It is often said that, life is the sum of all decisions. Without claiming to study the entire space of human life, the group's research activities divides decision-making and motivation into three categories that span at least some of the key dimensions of everyday life - the homeostatic, the monetary, and the social. Here is an overview of some of the key research themes:

Tobias Morville and Ollie Hulme are investigating how decision-making is oriented toward regulating the body – how it optimises homeostatic state. The state of the body, whether it is energy, hydration, or temperature, is highly regulated for the simple reason that small deviations in these states can be fatal. Decision-making is thus highly sensitive to fluctuations in bodily state. To investigate how homeostatic state of the body can modulate reward value, they are engaging in experiments which manipulate blood glucose, and using theoretical models to make predictions for how the brain updates its motivational drive, and the reward value of satisfying those physiological needs (Fig. 1). The experiments combine computational modelling, hormonal manipulations, and fMRI, and will ultimately be tested in psychiatric populations suffering from anhedonia, a core symptom of depression.

Decisions about monetary outcomes are convenient because they are natural objects of the modern world and it is relatively easy to quantitatively manipulate gains, losses, risks and probabilities. More importantly, human test subjects tend not to fall asleep in the scanner when they are gambling for real money. Recently, Brian Haagensen, David Meder and others have focused on sequential gambling tasks, to try to delineate how decision-making dynamically evolves over time. With subjects gambling for real money in a real world dice game, they found that lateral OFC activity reflected individual differences with respect to the absolute amounts that subject were willing to put at stake. Sofie Gelskov is investigating how this effect differs in people suffering from gambling addiction. Specifically, she has focused on willingness to take monetary risks and the asymmetrical over-weighting of losses compared to gains. The latter concept, also denoted "loss aversion", has in her previous work in healthy subjects been found to involve two important emotional and value-related regions in the brain when evaluating gain-loss ratios, namely the amygdala and the ventral striatum. Finally, Julian Macoveanu has been investigating the role of serotonin in decision-making. He has performed several pharmacological fMRI studies on subjects as they play simple card gambling games, and has revealed several components of the reward processing networks that are sensitive to modulation by serotonin.

Social decisions are complex by virtue of their interactivity and strategy. Unlike simple perceptual decisions, it is often hard to determine objectively measureable dimensions that constitute the evidence for or against a given decision. Recently, Helle Laursen, Tina Haren, Silas Nielsen and others set about defining an empathy test that can measure the ability of people to decode the experience of others, in order to understand

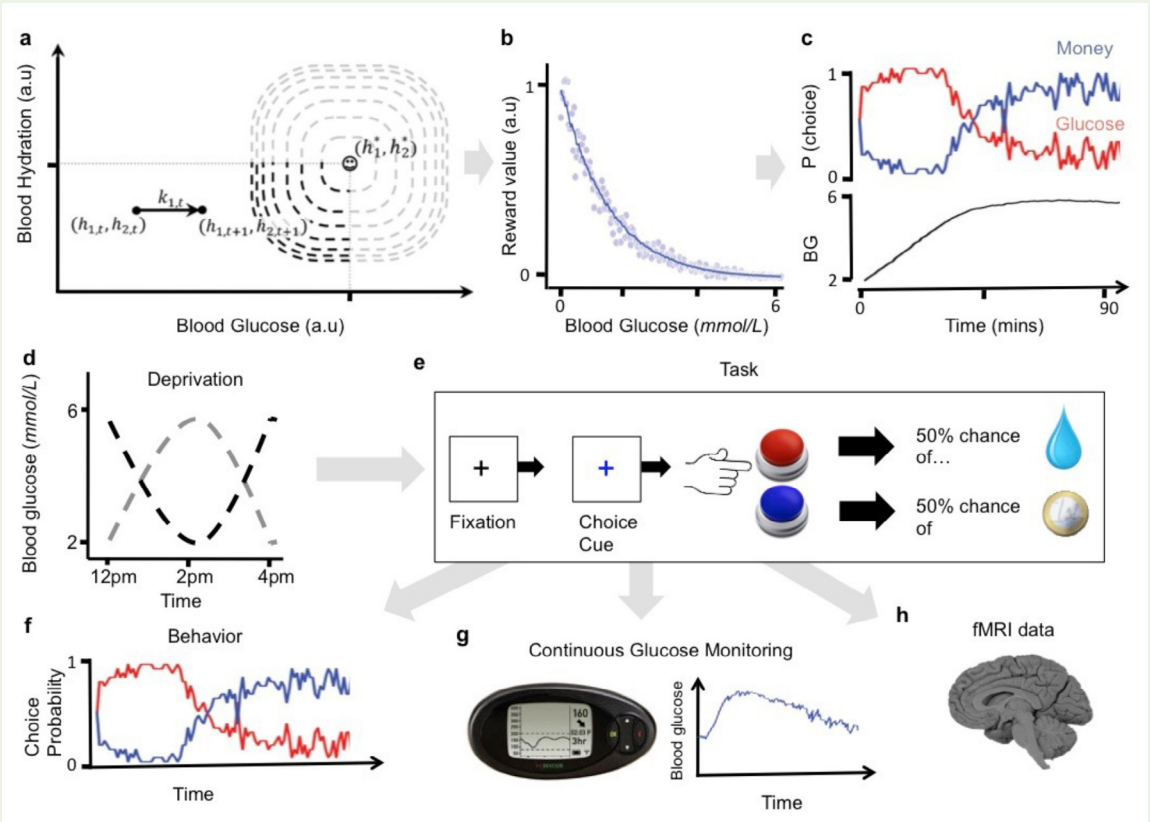


Figure 1: Shows the experimental rationale for the homeostatic decision-making experiments, where a-c represent model predictions, d-e represent the pragmatics of the paradigm, and f-h schematise the data obtained.

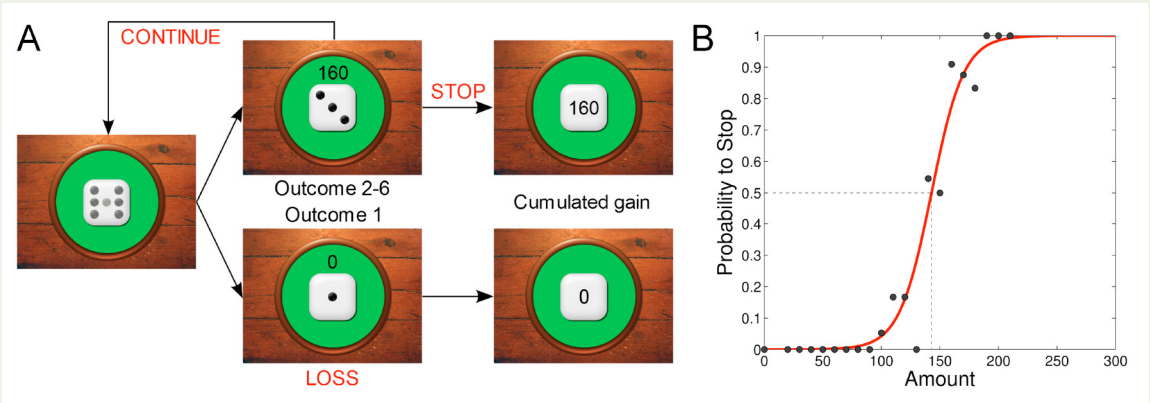


Figure 2: a) Shows the sequential dice gambling task b) Shows summary of typical gambling behaviour as the game progresses.

how this varies amongst people from different populations, and to characterise the neural networks dedicated to empathy. They videoed the faces of a group of subjects as they experienced different degrees of pain, via electric shocks to the hand. Another group of subjects were then

Figure 3: Shows the experimental setup for recording videos for the empathy experiment. The head mounted camera is used in the recording of facial expression videos as subjects receive electric shocks.

tasked with trying to infer how much pain the person had experienced, only from their facial expression. They are currently testing how these abilities vary across different genotypes linked to serotonin and oxytocin, two important neuromodulators that are thought to be involved in pain and empathy. Also of interest is how brain damage can impair empathic abilities, as they test this in populations of patients with traumatic brain injury. Susanne Henningsson and Bjørn Hallson are investigating the interplay between social and economic motivations in decision-making. Using games from economics, their participants are subjected to a series of fair and unfair monetary offers, which they can either accept, or reject in order to punish their partner at a personal monetary cost. Thus, monetary considerations and a concern for fairness are pitted against each other. Using this basic setup, combined with psychological methods to transiently lower a person's capacity for self-control, they are investigating whether participants' default response to unfair offers, is to adhere to economic or social considerations. Using fMRI, and whilst manipulating the levels of the neurotransmitters serotonin and dopamine, they will infer the neuropharmacological role of these transmitters, and the neuroanatomical distribution of their influence in the social-economic domain.

NEUROIMAGING IN MULTIPLE SCLEROSIS (NiMS)

Researchers at DRCMR have a long-standing interest in neuroimaging of multiple sclerosis (MS). MS is an inflammatory demyelinating and neurodegenerative disease of the central nervous system leading to widespread and diffuse damage of the neural tissue in the brain and spinal cord. MS is the leading cause of non-traumatic 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 Neuroimaging in Multiple Sclerosis (NiMS) group includes: Professor Hartwig R. Siebner (group leader), Ellen Garde, Professor Olaf B Paulson (until June 2012), Tim B. Dyrby, Camilla Gøbel Madsen, Kristoffer H. Madsen, Henrik Lund, Anne-Marie Dogonowski, Mark Lyksborg, Hanne Schmidt, Sascha Gude.

External collaborators

- **Professor Per Soelberg Sørensen**, Professor Finn Sellebjerg, Morten Blinkenberg and other physicians form the Danish Multiple Sclerosis Centre, Department of Neurology, Copenhagen University Hospital Rigshospitalet, Denmark
- **Associate Professor Bharat Biswal**, Department of Radiology, University of Medicine and Dentistry of New Jersey, USA
- **Associate Professor Morten Morup**, Cognitive systems, DTU-Compute, Technical University of Denmark, Denmark

RESEARCH ACTIVITIES

In 2011 and 2012 the NIMS group pursued five lines of research in close collaboration with the Danish Multiple Sclerosis Centre at Copenhagen University Hospital Rigshospitalet. The research on MS was generously supported by the Danish Multiple Sclerosis Society.

Resting-state connectivity in the motor network

The first line of research used resting-state functional MRI (rs-fMRI) to detect changes in functional connectivity within the motor system and relate these changes in functional cross-talk with motor symptoms (PhD-Project Anne-Marie Dogonowski). The project was designed to detect changes in inter-regional coupling (Dogonowski et al., 2012). We were able to identify a more widespread coupling of the basal ganglia with the motor resting-state network. This might indicate an impaired "funnelling" function of the basal ganglia in MS.

Structural connectivity and lesion features revealed with diffusion MRI.

The second line of research used diffusion MRI in the search for new structural based biomarkers for disease progression. The diffusion MRI based research projects are realised with the Diffusion Imaging Group. One succesfull project is Anatomical connectivity mapping (ACM), a new tool based on whole-brain probabilistic tractography that produces a voxel-wise map expressing how well connected one voxel is to the rest of the brain. The ACM framwork has been developed by Mark Lyksborg as part of his phd study, and he showed how ACM provide higher sensitivity to MS pheno types not possible with DTI indices.

Cognitive Impairment and Normal-Appearing Brain Tissue in MS

The third project examined retrospectively whether T2 changes in normal appearing brain tissue (NABT) could explain part of the cognitive impairment seen in fifty patients with clinically definite MS (PhD-project Hen-

rik Lund). Voxel-wise T2 estimates in normal appearing brain tissue (NABT) and total T2 lesion volume were derived from MRI and assessed whether these MR metrics correlate with the individual scores in eight cognitive domains, a general cognitive dysfunction factor (CDF), the Kurtzke Expanded Disability Status Scale (EDSS), and the Multiple Sclerosis Impairment Scale (MSIS). Distinct clusters of voxels in NABT showed a correlation between T2 estimates and CDF, mental processing speed, complex motor speed, verbal fluency, and MSIS (Lund et al., 2012). These results suggest that MRI can detect changes in the NABT which are associated with an underlying pathology and possibly contribute to the cognitive impairment in patients with MS.

Measuring MS-induced atrophy in upper cervical spinal cord.

The purpose of the fourth project was to establish a neuroimaging marker of upper spinal cord atrophy in MS derived from routine MR scans of the brain (Henrik Lundell / Ellen Garde). In multiple sclerosis spinal cord abnormalities are thought to manifest in more significant clin-

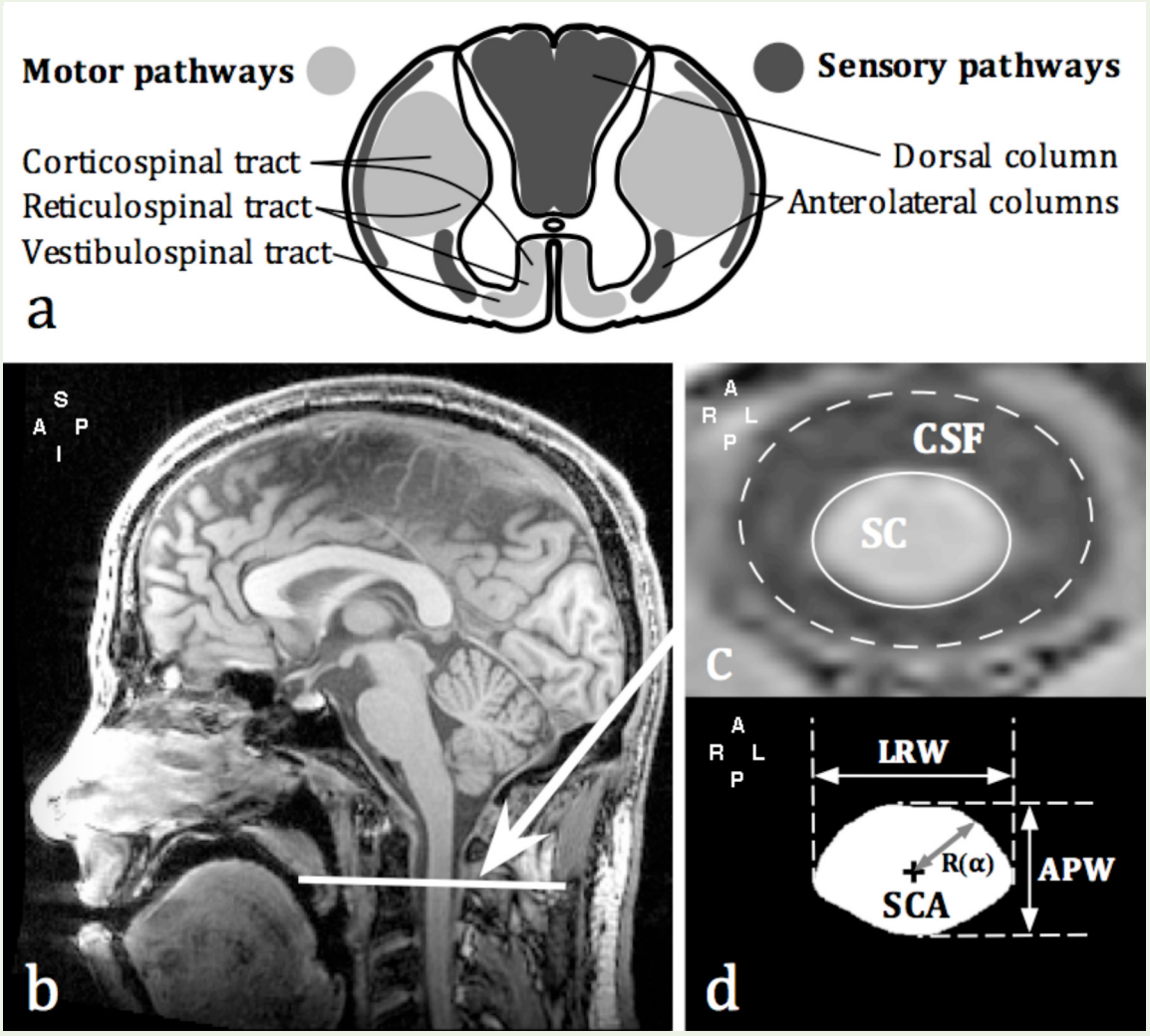
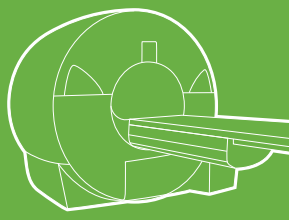


Figure: Overview of measurement of spinal cord atrophy showing the location of the main sensory and motor pathways (a), the T1-weighted image used with indication of the perpendicular plane at C1/C2 (b), projection of the plane with solid and dashed ellipses outlining the CSF and spinal cord (SC) (c), and an example of an extracted spinal cord mask (d). Left-right width (LRW), antero-posterior width (APW), spinal cord area (SCA).



ical symptoms, highlighting the importance of including assessment of the spinal cord for a more complete picture of the degree of CNS involvement. However, imaging artefacts associated with MRI of the spinal cord render detection of lesions challenging. In a recent study from our centre we have introduced a new volumetric measure of the upper part of the cervical spinal cord that can be extracted from conventional 3D T1-weighted structural images of the brain and that correlated specifically with sensorimotor deficits in patients with spinal cord injury (Lundell et al., 2011). In addition to measuring cross-sectional area (CSA), our method calculates the widths of the spinal cord in the anterior–posterior (APW) and left–right (LRW) directions (Figure). Additionally, the angular variation in spinal cord radius is extracted to capture atrophy in oblique directions. In order to assess the applicability of our new morphometric method on patients with MS we have analyzed scans from MS patients with different phenotypes. Since clinical evaluation of these patients included the Multiple Sclerosis Impairment Scale (MSIS) with detailed information on sensory and motor function we are able to detect a phenotype specific association between spinal cord atrophy in the antero-posterior direction and clinical measures. The results were presented at the ECTRIMS conference 2012 in Lyon.

No evidence that MS is caused by chronic cerebrospinal venous insufficiency (CCSVI)

The fifth project was led by Morten Blinkenberg from the Danish Multiple Sclerosis Centre at Copenhagen University Hospital Rigshospitalet. This study was prompted by the claim that multiple sclerosis (MS) is caused by chronic cerebrospinal venous insufficiency (CCSVI). This claim stirred a lot of interest in patients because endovascular treatment of CCSVI was advertised as potential treatment. The aim was to assess the prevalence of CCSVI in Danish MS patients using sonography and compare these findings with MRI measures of venous flow and morphology in 24 patients with relapsing-remitting MS. In line with many other studies, the study was essentially negative (Blinkenberg et al., 2012): The examinations did not corroborate the presence of vascular pathology in patients with MS and provided no evidence supporting the CCSVI hypothesis.

SELECTED PUBLICATIONS

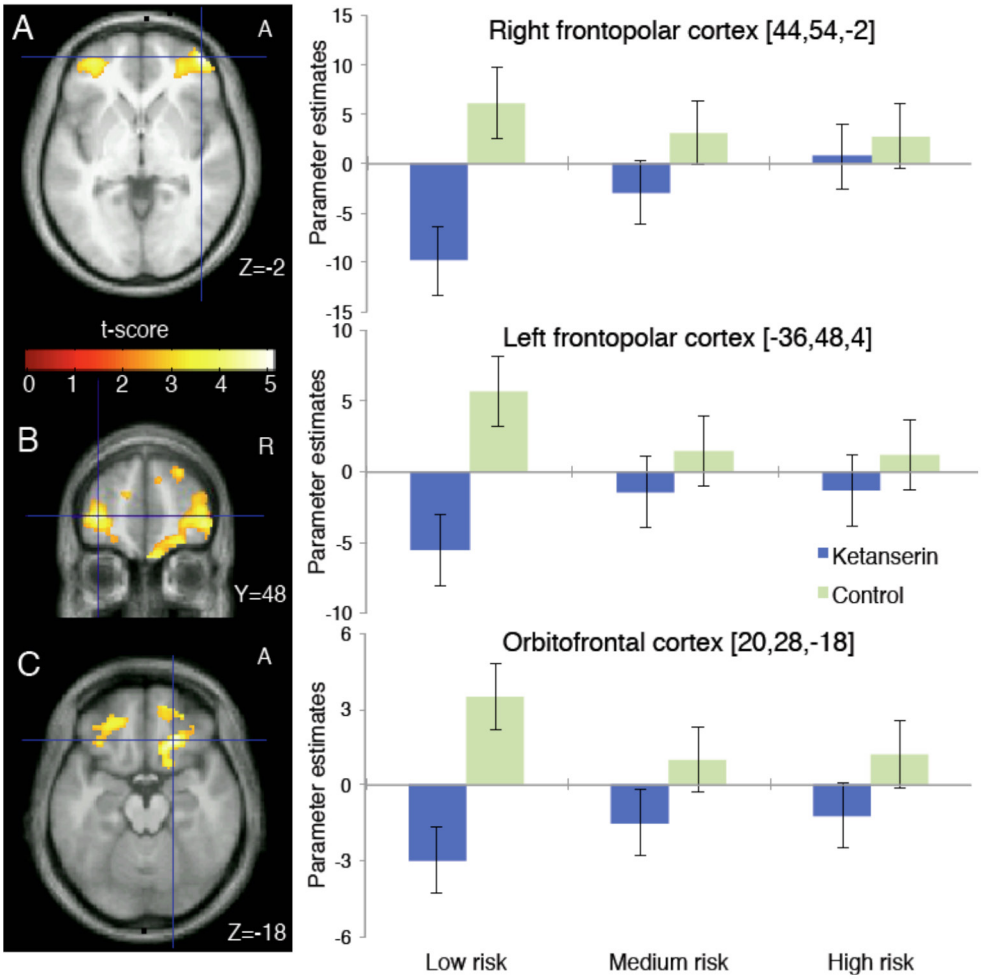
- **Blinkenberg M, Akeson P, Sillesen H, Lövgaard S, Sellebjerg F, Paulson OB, Siebner HR, Sørensen PS.** Chronic cerebrospinal venous insufficiency and venous stenoses in multiple sclerosis. Acta Neurol Scand. 2012 Dec;126(6):421-7.
- **Lundell H, Barthelemy D, Skimminge A, Dyrby TB, Biering-Sørensen F, Nielsen JB.** Independent spinal cord atrophy measures correlate to motor and sensory deficits in individuals with spinal cord injury. Spinal Cord. 2011 Jan;49(1):70-5.
- **Dogonowski AM, Siebner HR, Sørensen PS, Wu X, Biswal B, Paulson OB, Dyrby TB, Skimminge A, Blinkenberg M, Madsen KH.** Expanded functional coupling of subcortical nuclei with the motor resting-state network in multiple sclerosis. Mult Scler. Epub 2012 Sep 25.
- **Lund H, Jønsson A, Andresen J, Rostrup E, Paulson OB, Sørensen PS.** Cognitive deficits in multiple sclerosis: correlations with T2 changes in normal appearing brain tissue. Acta Neurol Scand. 2012 May;125(5):338-44.

COLLABORATIVE RESEARCH PROJECTS

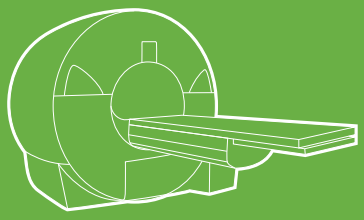
CENTER FOR INTEGRATED MOLECULAR BRAIN IMAGING (CIMBI)

Cimbi THE LUNDBECK FOUNDATION
Center for integrated molecular brain imaging

We are very happy to be partner in the Center for Integrated Molecular Brain Imaging (CIMBI) funded by the Lundbeck Foundation since 2006. The reseach in CIMBI covers neurobiology, physiology, and pathophysiology, molecular imaging and neuroreceptor ligands with focus on the serotonergic system.



Pharmacological 5-HT2A receptor blockade in healthy individuals led to a reduced response to losses in frontopolar and orbitofrontal cortex. The highest effect is observed to losses that are caused by a low-risk choice when the participants missed out on a high monetary reward. Behaviorally, this reduction in cortical activity was paralleled by an increased tendency to choose low risk choices.
Reprinted from NeuroImage 83 (2013) 35-44, Macoveanu et al., "Serotonin 2A receptors contribute to the regulation of risk-averse decisions", Copyright (2013), with permission from Elsevier



CIMBI includes various partner institutions:

- **Neurobiology Research Unit**, Copenhagen University Hospital Rigshospitalet
- **Danish Research Centre for Magnetic Resonance**, Copenhagen University Hospital Hvidovre
- **Cognitive Systems Group**, DTU-Compute, Technical University of Denmark, and
- **Department of Medicinal Chemistry**, Faculty of Pharmaceutical Sciences, University of Copenhagen.

Professor Gitte Moos Knudsen, Chair of the Neurobiology Research Unit at Copenhagen University Hospital Rigshopitalet is the director of CIMBI. From DRCMR, Terry L. Jernigan and Hartwig R. Siebner are part of the steering committee for Cimbi. Kathrine Skak Madsen, Susanne Henningsen, and William Baaré are members of the Council of Investigators in CIMBI. In addition, the following staff members from DRCMR are involved in projects at Cimbi: Arnold Skimminge, Bettina Hornbøll, David Meder, Helle Ruff Laursen, Julian Macoveanu, Pernille Iversen, Sussi Larsen.

SELECTED PUBLICATIONS

- **Macoveanu J, Rowe JB, Hornboll B, Elliott R, Paulson OB, Knudsen GM, Siebner HR.** Playing it safe but losing anyway-Serotonergic signaling of negative outcomes in dorsomedial prefrontal cortex in the context of risk-aversion. Eur Neuropsychopharmacol. 2012 Oct 7. [Epub ahead of print]
- **Madsen KS, Jernigan TL, Iversen P, Frokjaer VG, Knudsen GM, Siebner HR, Baaré WF.** Hypothalamic-pituitary-adrenal axis tonus is associated with hippocampal microstructural asymmetry. Neuroimage. 2012 Oct 15;63(1):95-103.
- **Madsen KS, Jernigan TL, Iversen P, Frokjaer VG, Mortensen EL, Knudsen GM, Baaré WF.** Cortisol awakening response and negative emotionality linked to asymmetry in major limbic fibre bundle architecture. Psychiatry Res. 2012 Jan 30;201(1):63-72.

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. 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.

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'. 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, who succesfully defended her PhD thesis November 10th, 2011, 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; 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.
- **Hammer TB, Oranje B, Skimminge A, Aggernaes B, Ebdrup BH, Glenthoj B, Baare W.** Structural brain correlates of sensorimotor gating in antipsychotic-naive men with first-episode schizophrenia. J Psychiatry Neurosci. 2012;37(4):110148.
- **Nejad AB, Madsen KH, Ebdrup BH, et al.** Neural markers of negative symptom outcomes in distributed working memory brain activity of antipsychotic-naïve schizophrenia patients. International Journal of Neuropsychopharmacology. 2012; Nov 20:1-10 (Epub)
- **Nejad AB, Ebdrup BH, Siebner HR, et al.** Impaired temporoparietal deactivation with working memory load in antipsychotic-naive patients with first-episode schizophrenia. World J Biol Psychiatry. Jun 2011;12(4):271-281.

22Q11 DELETION SYNDROM

The project aims to identify (intermediate) phenotypes of copy number variants (CNVs) that are associated with an increased risk of developing severe psychiatric illness. The project will initially investigate subjects with 22q11 deletions which are associated with the highest genetic risk of developing psychiatric illness, and later expand to other know pathogenic CNVs.
The project is designed as a classical case-control study and compares carriers and non-carriers of CNVs associated with severe psychiatric illness whom are matched on age and gender. The study will examine specific behavioral characteristics and cognitive abilities across different research methodologies including psychiatric interviews, neurocognitive tests, EEG and structural and functional magnetic resonance imaging (MRI) imaging. Importantly, we will incorporate tests/paradigms that are translational into animal models of investigated CNVs.

MEMBERS OF THE GROUP

The MR and EEG research is done in close collaboration with the Psychiatric Center "Sct. Hans", Roskilde, Denmark, headed by Professor, Ph.D. Thomas Werge , project initiator and PI, and Michael Didriksen, M.Sc. Ph.D, Associate Director, Synaptic Transmission 2, H. Lundbeck.
Internal researchers from DRCMR include: Hartwig R. Siebner, William Baaré, Oliver Hulme, Elvira Fischer, Mellissa Kit Larsen and Giovanni Pellegrino.
Main researchers involved from the Psychiatric Center "Sct. Hans" and Lundbeck: Thomas Werge, Line Olsen, Anders Vangkilde, Henriette Smock, Michael Didriksen and Michelle Rosgaard Birknow.

RESEARCH CONTENT

The investigations will include both structural (T1, T2 and diffusion weighted) as well as functional MRI (resting state and a mismatch negativity (MMN) task fMRI, and perfusion) scans and EEG (resting state, clasical and roving MMN, gamma band oscillations). Specifically, the MMN paradigms used during fMRI and EEG are exactly the same, and allow translation to results of MMN examinations that will be performed in mice with 22q11 deletions.
The mismatch negativity paradigm taps on the early stages of sensory information processing. It is a negative-going deflection in the evoked reponse potential that occurs when a sequence of repetitive "standard" stimuli is occasionally interrupted by infrequent "deviant" stimuli that differ in some stimulus characteristic such as duration or pitch. MMN is thought to reflect a predominantly automatic, pre-conscious process of detecting a "mismatch" between the deviant stimulus and a sensory–memory trace.

Inclusion of participants is expected to start in February 2013.

READER CENTRE

With its academic and clinical embedding, the centre holds highly advanced knowledge on data quality, computational methods, and algorithms to analyze and quantify MR data including quantitative measures such as lesion volume and differential brain volumes.

Centre team

Head of the DRCMR Reader Centre is Ellen Garde working closely together with Arnold Skimminge, Hanne Schmidt, Henrik Lund, Henrik Lundell, Pernille Iversen, and Sascha Gude. The centre benefits from a close collaboration with the DRCMR academic research groups and radiologists at the clinical DRCMR section.

External Collaborators

- **Professor Per Soelberg Sørensen**, Danish Multiple Sclerosis Research Center, Rigshospitalet.
- **Professor Peter Rossing and Henrik Reinhardt**, Steno Diabetes Center, Copenhagen
- **Professor Poul Videbech**, Centre for Psychiatric Research, Aarhus University Hospital.
- **Ass. Prof David Gaist**, Dept. of Neurology, Odense University Hospital.
- **Ass. Prof Messoud Ashina**, Dept. of Neurology and Danish Headache Center, Glostrup Hospital

ACTIVITIES

Image analysis

Lesion assessment is one of the focus areas of the centre. In addition to years of experience with analysis of lesions related to multiple sclerosis the centre benefits from expertise with determining pathophysiological changes in the brain associated with small vessel disease such as white Matter Hyperintensities (WMH). Drawing on the combined skills of the group in recent years the reader center has further refined its sensitive and reproducible algorithms to render the evaluation of lesions and lesion size more automatic and less dependent on subjective assessment. The image analysis technology developed by the DRCMR academic research groups has been integrated into a workflow system for rapid configuration to project specific requirements.

Trials as well as clinical research demand ever more specific and robust MRI techniques and at the DRCMR reader centre we are 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 (see DIG for details), magnetization transfer imaging (MTR) which indirectly helps us to measure the myelin content of tissues, iron deposition quantification, and resting-state fMRI.

Quality assurance is inherent in the reader center workflow and is a focus area, which is continuously refined. The quality assessment is conducted at several levels in the work processes from the images are generated at the scanner including image quality assessment, evaluation of software outcome measures, statistical evaluation and inter-rater validation. In addition, 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.

Investigator driven studies

In 2011 a multi-center double-blind randomized placebo-controlled trial was completed in collaboration with the Danish Multiple Sclerosis Center at Rigshospitalet, Copenhagen and collaborating centers in Europe.

In 2012 a wide range of investigator driven clinical studies were initiated, which continues well into 2013.

Teaching activities

The centre hosts a range of teaching activities in 2012 an introductory course in MR and MS. Thesis work on multiple sclerosis was conducted by a medical student from University of Copenhagen focusing on quantitative MR measures in MS including a comparison of software methods for tissue segmentation and parcellation. The centre also collaborated with Roskilde Katedralskole on student's SRP project (3rd year project)

focusing on multiple sclerosis, MRI physics and how MR is applied in relation to multiple sclerosis.

RESEARCH PROJECTS

Multiple Sclerosis

The centre contributed to a number of research projects at the DRCMR including a study focusing on the pathophysiological mechanisms underlying changes in cerebral activation in MS patients as well as spinal cord atrophy in MS *(see the MS section for details)*.

Diabetes in the heart and brain

Elevated plasma N-terminal (NT)-proBNP from the heart as well as WMH in the brain predict cardiovascular mortality in the general population. However, the cause of poor prognosis associated with elevated P-NT-proBNP is not known. In collaboration with the Steno Diabetes Center a prospective observational study on the prognostic value of cardio-and cerebrovascular risk factors in patients with diabetes was performed. In a pilot-study we assessed whether P-NT-proBNP is associated with WMH or brain atrophy in asymptomatic high risk cardiovascular type 2 diabetic patients with microalbuminuria. We found that WMH varied considerably (Fig. 1) and demonstrated for the first time that plasma NT-proBNP was independently associated with WMH, suggesting a linkage between heart and brain disease.

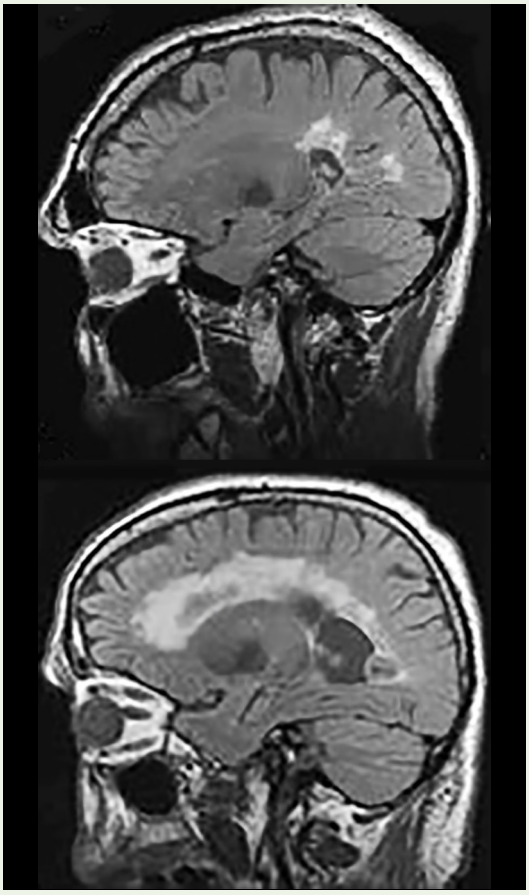


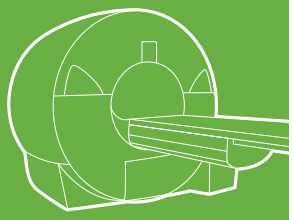
Figure 1: A sagittal FLAIR image of 2 patients with type 2 diabetes, coronary artery disease, and microalbuminuria illustrating a patient with moderate (upper) and severe (lower) WMH. Levels of plasma N-terminal (NT)-proBNP from the heart was associated with WMH volume in the brain.

Late-onset major depression in the brain and heart

In another study linking the brain and the heart we collaborate with Centre for Psychiatric Research, Aarhus University Hospital. The pathophysiology of major depression is complex with cardiovascular diseases, such as carotid atherosclerosis and coronary artery disease as potentially important factors. In 29 patients with late-onset major depression and 27 non-depressed controls the relationship between late-onset depression, WMH, and carotid and coronary atherosclerosis was evaluated. Data has been analysed and will be submitted shortly.

Twins with migraine

Migraine affects up to 20% of women but has so far been considered a neurological disorder that causes no permanent brain damage. However, recent population-based studies report an increased risk of subclinical brain infarcts in patients with migraine. Especially, patients with aura (MA) were found to be at risk with infarcts as well as increased burden of WMH which have been linked to an increased risk of dementia, stroke and overall morbidity. In order to assess whether MA is a progressive disorder associated with infarcts, WMH, and other structural changes of the brain a collaboration with the DRCMR was initiated by ass. professor Messoud Ashina, the Danish Headache Center at Glostrup Hospital and ass. professor David Gaist, Odense University Hospital. In this population-based cross-sectional study women with MA are recruited from The Danish Twin Registry, the oldest national twin-register in the world. In addition to twins with MA co-twins as well as



twins with no history of headache are invited to participate. Coupling this unique sample with state of the art imaging techniques makes it ideal for testing whether migraine is associated with structural and functional changes in the brain. At the end of 2012 more then a hundred participants had been scanned and we expect the study to continue through 2013.

SELECTED PUBLICATIONS

- Plasma NT-proBNP and white matter hyperintensities in type 2 diabetic patients.
  Reinhard H, Garde E, Skimminge A, Akeson P, Ramsøy T, Winther K, Parving HH, Rossing P, Jacobsen PK. Cardiovasc Diabetol. 2012 Oct 3;11(1):119.

DISSEMINATIONS

ASTRID ROSENSTAND LOU

Title of phd project
Plasticity of the visual system throughout life – lesson from changes in monocular vision.

Summary
The purpose of the study has been to characterize structural and functional changes in visual regions in acute change of monocular vision. The study investigated the effect of acute monocular deprivation (MD) in the visual system using transcranial magnetic stimulation (TMS) and functional magnetic resonance (fMRI). The TMS study showed a decreased cortical excitability in V1 following 48h of MD. In the fMRI study, the MD-group showed an increased BOLD response bilaterally in secondary visual regions, which normally are facilitated by a stereoscopic vision. The final study investigated the effect of acute monocular visual improvement following cataract surgery using voxel based morphometry (VBM). The study showed that the grey matter in V2 grew significantly and independent of age (49-85 year) during the postoperatively period of 6 week. All three experimental studies revealed an impressive plasticity of the adult brain, even in old age up to 85 years.

Supervisors
- Troels Wesenberg Kjær, MD, PhD
- Olaf B. Paulson, MD, DMSc
- Kristoffer H. Madsen, MSc, PhD
- Hanne Olsen Julian, MD, PhD
- Jan Ulrik Prause, MD, DMSc
- Hartwig R. Siebner, MD, DMSc

The university
Faculty of Health and Medical Sciences, University of Copenhagen

Date of defence
14th of October 2011

Today working
Department of Ophthalmology. Copenhagen University Hospital, Glostrup Hospital.

SADIA BUTT

Title of phd project
Metabolic Imaging of Breast Cancer and the Normal Brain Application of Hyperpolarized 13C Magnetic Resonance Spectroscopy

Summary
The PhD thesis is based on experimental studies on the cellular metabolism using MRS in two biological systems – breast cancer and normal brain. Breast cancer metabolism was longitudinally monitored in a mouse model using MRS of hyperpolarized pyruvate. The results demonstrated that we could monitor the changes in metabolism with increasing disease severity. The normal cerebral metabolism of hyperpolarized ketoisocaproate (KIC) was studied in the rat brain. The findings showed that hyperpolarized KIC is a promising substrate for in vivo evaluation of specific enzymatic activity.

Supervisors
- Professor Olaf Paulson (MD, D.M.Sc), DRCMR, NRU
- Per Åkeson (MD, PhD), DRCMR
- Senior Researcher, Peter Magnusson (PhD), DRCMR
- Senior Researcher, Lise Vejby Søgaard (PhD), DRCMR

The university
Faculty of Health Sciences, University of Copenhagen, Denmark

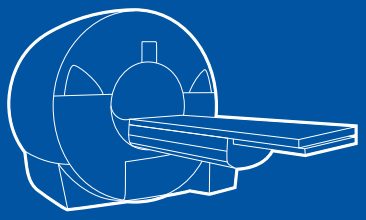
Date of defence
30th of May 2012

Today working
Philips Healthcare

HENRIK LUNDELL

Title of phd project
Methods for mapping spinal cord connectivity using diffusion, functional and conventional MRI

Summary
In his project, Henrik developed new methods for characterizing the integrity of the spinal cord in the healthy and injured. His methods are now



adopted by multiple sclerosis projects at DRCMR as well as at other groups abroad.

Supervisors
- Professor Jens Bo Nielsen, the Department of Exercise and Sport Sciences and the Department for Neuroscience and Pharmacology, University of Copenhagen
- Senior Researcher Tim B Dyrby, DRCMR
- Associate Professor Lars G Hanson, DRCMR and DTU

The university
Faculty of Health Sciences, University of Copenhagen, Denmark

Date of defence
18th of March 2011

Today working
Postdoc in the Diffusion Imaging Group at DRCMR

MATTHEW G. LIPTROT

Title of phd project
Image Processing in Diffusion MRI Tractography

Summary
Over the past decade, MRI has provided the ability to measure in-vivo displacement of water molecules. This Diffusion Weighted Imaging takes measurements along many different angular directions per voxel, and by their combination enables a mapping of restrictions or hindrances to the diffusion process. Hence water molecules can be employed as probes to gauge tissue microstructure. In highly organised regions (e.g. white-matter tracts within the brain) such hindrances are highly structured, leading to overall anisotropy in the reconstructed diffusion profile within each voxel. Probabilistic tractography is a recent attempt to meaningfully conjoin these anisotropic profiles by sending thousands of streamlines out from each voxel of a seed region in order to produce a connection confidence map, thus attempting to provide a measure of connectivity-likelihood across the brain. However, one of its limitations is path-length dependency, where the values thus produced are modulated by a gradual decline in the likelihood of successful propagation as the distance from the seed region increases. In so favouring short- vs long-range connections, the method's ability to perform fibre-tracking to distal regions is compromised. Surprisingly little focus has been directed towards the path-length dependency problem, which not only hampers the estimate of connectivity with a single subject, but also prevents inter-subject comparison. This thesis addressed the issue with a novel tractography framework, Iterative Confidence Enhancement for Tractography (ICE-T), inspired by the region-growing techniques utilised within image-processing. Substantial improvement over conventional methods was demonstrated.

Supervisor
- Professor Richard Kitney OBE, FREng, DSc (Eng), FCGI, Imperial College London

Co-supervisor
- Senior Researcher Tim B. Dyrby, DRCMR

The University
Imperial College, London

Date of defence
1st of October 2010, Awarded: 31st March 2011

Today working
Post Doc in the Image Group, Department of Computer Science (DIKU), Copenhagen University.

KATHRINE SKAK MADSEN

Title of phd project
Brain microstructural correlates of behavioural and neuroendocrinological phenotypes

Summary
The PhD project examined brain microstructural correlates of individual differences in behavioural and neuroendocrinological phenotypes by employing diffusion-weighted imaging in two different cohorts. In typically-developing children aged 7 to 13 years, better response inhibition performance on the stop-signal task was associated with higher fractional anisotropy (FA) in the white matter underlying the right inferior frontal gyrus and right presupplementary motor

area. Faster 5-choice reaction time on a visuospatial motor task was linked to lower mean diffusivity in the corticospinal tract and neostriatum. The observed associations may be related to individual variations in the phase of maturation, to activity-dependent alterations in the networks subserving these functions, or to more stable individual differences in underlying neural system architecture. In healthy adults, individual differences in trait neuroticism and circadian cortisol patterns were associated with left-right microstructural asymmetry of the limbic system. Specifically, higher neuroticism scores and cortisol awakening response were associated with left-right microstructural asymmetry of the cingulum bundle and uncinate fasciculus. Higher daytime cortisol level was associated with microstructural asymmetry of the hippocampus. The findings suggest that the balance between left- and right-sided limbic circuits may bear an important relationship to HPA-axis activity, and to the tendency to experience negative emotions.

Supervisors
- Professor Terry L. Jernigan, UC San Diego, CA; Director, UCSD Center for Human Development; Honorary Professor in Neuroimaging, Department of Neurology, Psychiatry, and Sensory Sciences, University of Copenhagen
- Senior Researcher, William F.C. Baaré, DRCMR

The university
Faculty of Health Sciences, University of Copenhagen, Denmark

Date of defence
April 29, 2011

Today working
Post doc at DRCMR and Cimbi

ANNE-MARIE DOGNOWSKI

Title of phd project
Resting-state Functional Connectivity of the Motor System in Multiple Sclerosis Short

Summary
This PhD-project studied inter-regional and intra-regional (local) resting-state functional connectivity in patiens with multiple sclerosis (MS) with focus on the motor system. Patients with MS showed a spatial expansion of motor resting-state connectivity in deep subcortical nuclei. Also, patients with MS showed an increase in coupling between the left dorsal pre-motor cortex and the motor resting-state network with increasing clinical disability. Last, MS patients showed impaired local cerebellar connectivity that reflected clinical disability

Supervisors
- Olaf B. Paulson, MD, DMSc
- Hartwig R. Siebner, MD, DMSc
- Kristoffer H. Madsen, MSc, PhD
- Xingchen Wu, MD, PhD
- Morten B. Blinkenberg, MD, PhD

The university
Faculty of Health and Medical Sciences, University of Copenhagen

Date of defence
19th of November 2012

Today working
Radiologisk afdeling X, Herlev Hospital

TRINE BJØRG HAMMER

Title of phd project
Sensorimotor Gating in Schizophrenia: Long term outcome and structural brain correlates in (initially) antipsychotic-naïve first-episode patients

Short summary
The PhD project investigated disturbances in information processing, presumed to be core symptoms of schizophrenia, with psychophysiological and MRI methods. Habituation and prepulse inhibition (PPI) of the startle reflex paradigm were used as operational measures of automatic, preconscious information processing. In a 6 years follow-up study, we studied the stability of habituation and PPI in antipsychotic-naive first-episode schizophrenia patients and healthy matched controls. While significantly lower at baseline, PPI significantly increased in patients and significantly decreased in controls over time. This improvement in patients may be caused by the disease or treatment related fac-

tors. The structural brain correlates of PPI in schizophrenia are unclear. Using voxel based morphometry we observed significant positive associations between PPI and gray matter volume in right superior parietal cortex and positive associations with three areas in the frontal cortex independent of group. Associations with the pre-supplementary motor areas and the rostral portion of the dorsal premotor cortex, were driven predominantly by the controls. While the superior parietal cortex may be involved in the regulation of PPI in both antipsychotic-naïve first-episode schizophrenia patients and controls, our data suggest a possible link between dysfunctions within the frontal premotor areas and PPI deficits in schizophrenia.

Supervisors

- Professor Birte Glenthøj, Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS) Psychiatric Center Glostrup, Copenhagen University Hospital, Glostrup, Denmark
- Bob Oranje, Accociate Professor, CNSR and CINS, Psychiatric Center Glostrup, Copenhagen University Hospital, Glostrup, Denmark
- Senior Researcher William F.C. Baaré, DRCMR

The university

Faculty of Health Sciences, University of Copenhagen, Denmark

Date of defence

November 10, 2011

Today working

Working as a physician at the Department of Clinical Genetics at Kennedy Centre, Rigshospitalet, Denmark.

DRCMR Summer Party 2011

COMING TO DRCMR

AXEL THIELSCHER COMING FROM GERMANY

Associate Professor Dr. Axel Thielscher studied electrical engineering at the University of Ulm (Germany) where he subsequently conducted PhD theses in Biomedical Sciences and Electrical Engineering, graduating in both topics with highest distinction. During that time he became deeply interested in systems neuroscience, neuroimaging and non-invasive neurostimulation. After a post-doctoral stay at Brown University (RI, USA; 2004-2005) he joined the Max-Planck-Institute for Biological Cybernetics (Germany) in 2005 where he was promoted to a project group leader in 2008. In 2012, Axel Thielscher started in Denmark on a joint position as Senior Researcher at the DRCMR and Associate Professor at the Bio medical Engineering Section of the Technical University of Denmark (DTU BME).

His methodological research foci are on the on the integration of brain stimulation and brain imaging and the biophysics of brain stimulation. He pioneered the direct combination of transcranial magnetic stimulation (TMS) and functional MRI (fMRI) at 3 tesla to characterize the TMS effects on the network activity in the brain. Further, he employed finite-element simulations of unprecedented spatial resolution to characterize the electric field induced by neurostimulation in detail, resulting in an improved spatial accuracy of stimulation. He applies these methods in his neuroscientific research that focuses on identifying the functional roles of parietal and frontal areas in sensorimotor integration and motor control.

His overarching aim for the next years will be on closely integrating the three research topics described above (Figure 1). Specifically, the goal is to markedly improve the knowledge on brain stimulation to allow for the development of optimized and clinically efficient stimulation

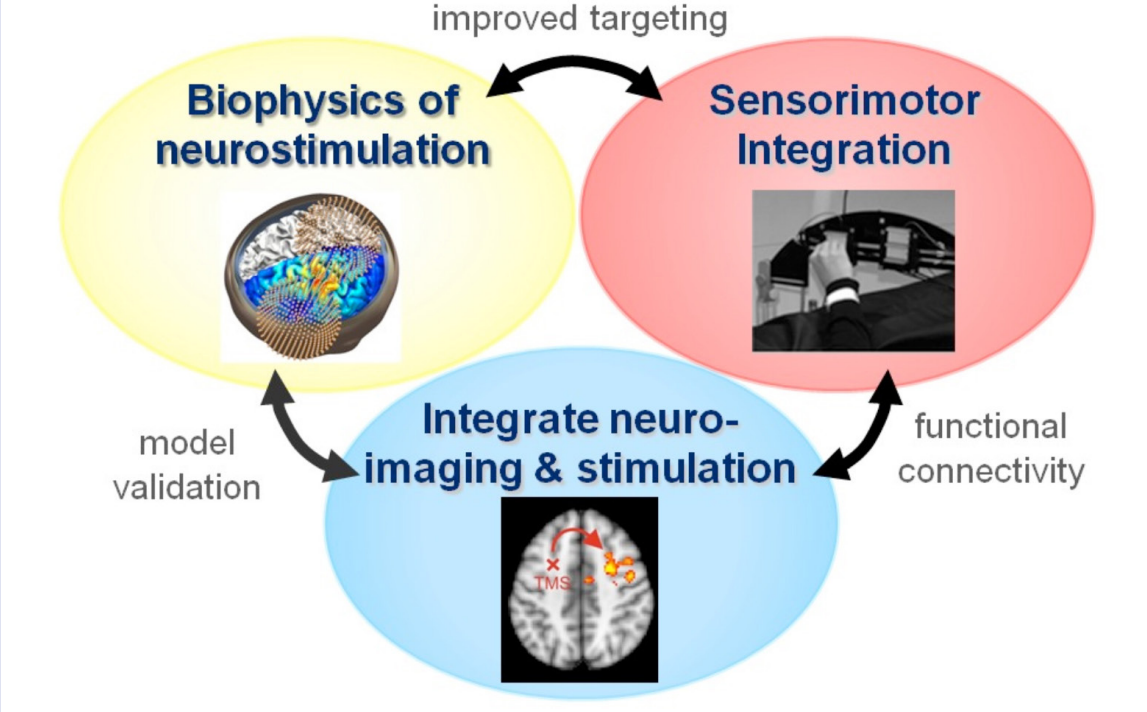


Figure 1: Research outline

protocols. These activities nicely complement the ongoing activities and interests in the contact research group and extend them by methodological research in conjunction with DTU BME.

Project description

Within the contact research group, Axel Thielscher successfully started up a combined TMS-fMRI study to test the role of human premotor areas in modulating the activitiy in the primary motor cortex during movement planning. In particular, the aim is to assess how this role depends on the available (informative vs. non-informative) visual cues. He further established a collaborative project together with Dr. Masashi Hamada and Prof. John Rothwell (UCL, London, UK) that aims at deciphering the cause of the large interindividual differences in the outcome of repetitive TMS stimulation. This is a key problem that still hampers the development of more stable and clinically efficient stimulation protocols. Axel Thielscher received a grant from the Lundbeck Foundation that will allow him to improve and rigorously validate the biophysical models for brain stimulation that he has been developing up to now. This project will start soon and will be carried out jointly at the DRCMR and DTU BME.

ANKE KARABANOVA COMING FROM UNITED STATES

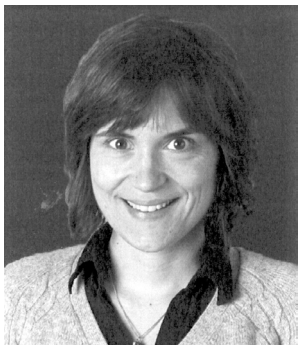
Anke Karabanov is a postdoctoral researcher at the DRCMR since October 2011. Her research focuses on the interaction between basic motor control and higher cognitive processes, especially on the influence of motor control on self-consciousness and perception.

Dr. Karabanov/Anke Karabanov came to Denmark after having studied both in the United States and several European countries: She received a bachelor degree in Cognitive Science from her home country Germany (University of Osnabrueck) and a PhD in Medical Sciences in collaboration between the Karolinska Institute (Sweden) and the National Institutes of Health (NIH) (USA).

When wanting to return to Europe and after having spent several years in the United States the DRCMR was an excellent place to start a postdoctoral research career. The research focus of on cognitive motor control, the strong emphasis of integrating different advanced brain mapping and stimulation techniques as well as the excellent network of neuroscientists at the DRCMR ideally complemented Dr. Karabanov's/Anke Karabanov training and research interests. This ideal combination was also recognized by the Swedish National Research Council, which is currently funding Dr. Karabanov's research at the DRCMR.

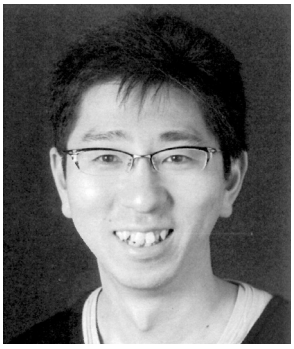
The stimulating research environment at DRCMR at the many possibilities of the greater Copenhagen area made it easy for both Anke Karabanov and her family to feel professionally and personally at home in Denmark.

ESTELLE RAFFIN COMING FROM FRANCE



I have conducted my PhD (2008-2011) under the supervision of Professor P. Giraux and Dr K. Reilly in Lyon in France. I conducted behavioural and neuroimagery (fMRI) studies in normal subjects and in patients with brain damage (stroke patients) or peripheral injury (amputees, brachial plexus) in order to understand the functions of different brain regions in motor planning or visuomotor adaptations in the context of motor rehabilitation. I also used functional brain imaging to study sensorimotor plasticity after limb amputation. Immediately after my defence I applied for a postdoc position in the ContAct research group, headed by Prof. Hartwig R. Siebner. The ContAct group at DRCMR pursues integrative research on human cognitive aspects of motor control. The institute provides the necessary infrastructures and a very strong background in electrophysiological and neuroimaging methods, in link with my postdoc project. I wish to investigate the neurobiological underpinnings of motor skill learning. My choice of host institution is also strongly motivated by the rich intellectual environment offered at the DRCMR (Symposium, Courses, Lectures ...).

YUKO KASASHIMA SHINDO AND KEIICHIRO SHINDO COMING FROM JAPAN

We are medical doctors at Department of Rehabilitation Medicine at Keio University School of Medicine in Japan. We have been engaged in the researches about electromyography (EMG)-triggered electrical stimulation and Brain computer interfaces (BCI) for stroke patients.

Our main interests are to investigate the mechanism of neuroplasticity, especially using noninvasive brain stimulation and creative activities such as music and art, with functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), and electroencephalogram (EEG).

There were several reasons why we came to DRCMR from Japan. First of all, our main purpose was to study MRI and get the opportunity to research brain with it. DRCMR has a great environment for research of MRI, TMS and EEG. There are a lot of specialists and the latest equipment. Second, DRCMR is international. We found that the people in DRCMR are very friendly as well as enthusiastic in reserch, when we visited there in 2011. Third, Keiichiro's first project, repetitive TMS for dystonia, was referred to Prof. Harwig's article in Stroke journal. Furthermore, Prof. Hartwig was used to be a colleague of our senior researcher in London. Additionally, Denmark is famous as the happiest county in the world, which has a good welfare system. We were also interested in living there. Therefore, we decided to come there.

We have been studying as guest researchers in DRCMR since September in 2012.

Now, we are happy and enjoy our lives as researchers. We believe we will learn many things, which will be contributed to our future. We appreciate our opportunities to study at DRCMR and strongly recommend people from foreign countries to come there.

OLLIE HULME COMING FROM UNITED KINGDOM

I came to DRCMR from British Columbia, Canada in September 2011. I had originally left the UK for Canada a couple of years earlier, where I was travelling and snowboarding, and after a year I began working as a lecturer at the university of British Columbia teaching neurobiology and statistics. When it was time to leave, my girlfriend received a job offer in Copenhagen, and so I wrote to Thomas Ramsøy and Hartwig Siebner who were closest to my research interests, and realised there was an opportunity to begin working with their research groups, and that there were excellent facilities to do this. Since then I have secured more long-term funding from the Danish Government, for what is a relatively new research direction for me – looking at homeostatic processes of the body and their interaction with the motivation of action. I find that the work-life at DRCMR suits me very well; it is relaxed but productive, well organised but not oppressive, and has a steady flow of international researchers with different expertise and interests. I have found it very easy to move to Copenhagen, and I feel very at home here. I look forward to building the next phase of my scientific career at DRCMR.

COLLABORATION

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

NATIONAL COLLABORATIONS

Aarhus University, Aarhus, Denmark

- Center of Functionally Integrative Neuroscience (Ass. Prof. Torben Lund, Ass. Prof. Sune Jespersen, Simon Eskildsen)
- Center for Insoluble Protein Structures (inSPIN) (Prof. Niels Christian Nielsen)
- Centre for Psychiatric Research (Prof. Poul Videbech)
- Danish School of Education (Ass. Prof. Lisser Rye Ejersbo)
- Department of Chemistry (Prof. Niels Christian Nielsen)
- Department of Endocrinology and Internal Medicine
- Interdisciplinary Nanoscience Center (iNANO)
- MR Research Centre, Department of Clinical Medicine

Copenhagen Business School, Frederiksberg, Denmark

- Department of Innovation and Organizational Economics
- Department of Law
- Department of Marketing, Decision Neuroscience Research Group (Ass. Prof. Thomas Ramsoy, Martin Skov)
- Department of Strategic Management & Globalization

Gubra Aps, Hørsholm, Denmark

- Dr. Jacob Jelsing, CSO

H. Lundbeck A/S, Valby, Denmark

- Dr. Nils Plath, Head of Department Synaptic Transmission I
- Dr. Michael Didriksen, Head of Department Synaptic transmission II

National Center of Reading, Copenhagen, Denmark

- Ass. Prof. Bo Steffensen

Odense University Hospital, Odense, Denmark

- Department of Neurology (Prof. David Gaist)

Steno Diabetes Center, Copenhagen

- Professor Peter Rossing

Technical University of Denmark, Lyngby, Denmark

- Department of Electrical Engineering (Ass. Profs. Sadasivan Puthusserypady, Helge B. Sørensen, Vitaliy Zhurbenko, Johan Mohr, Profs. Torsten Dau, Jens E. Wilhjelm)
- Department of Informatics and Mathematical Modelling (Prof. Lars Kai Hansen, Prof. Rasmus Larsen, Ass. Prof. Morten Mørup)
- Department of Physics (Ass. Profs. Claus Schelde Jacobsen, Jørn Bindslev Hansen)

University of Copenhagen, Copenhagen, Denmark

- FACULTY OF HEALTH AND MEDICAL SCIENCES
  - Cluster for Molecular Imaging, Department of Biomedical Sciences
  - Department of Biostatistics (Ass. Prof. Klaus Kähler Holst)
  - Department of Neuroscience and Pharmacology (Prof. Jens Bo Nielsen, Prof. Maurice Ptito, Prof. Ron Kupers)
  - Department of Nutrition, Exercise and Sport Sciences (Prof. Jens Bo Nielsen, Ass. Prof. Nikolai Nordsborg)
  - Institute of Public Health, Department of Health Psychology (Prof. Erik Lykke Mortensen)
  - Wilhelm Johannsen Centre for Functional Genome Research, Department of Cellular and Molecular Medicine (Prof Niels Tommerup)
- FACULTY OF HUMANTITIES
  - Department of Economics
  - Department of Scandinavian Studies and Linguistics (Ass Prof. Kasper Boye)
- FACULTY OF SOCIAL SCIENCES
  - The Unit for Cognitive Neuroscience, Department of Psychology (Prof. Jesper Mogensen)

University of Southern Denmark, Odense, Denmark

- Department of Psychology (Ass. Prof. Christian Gerlach)
- Institute of Clinical Medicine (Prof. David Gaist)

COPENHAGEN UNIVERSITY HOSPITALS

Copenhagen University Hospital Bispebjerg, Bispebjerg, Denmark

- Department of Neurology (Annemette Løkkegaard, Ass. Prof. Hanne Christensen)
- Department of Radiology (Senior Consultant Anders Christensen)
- Research Laboratory for Stereology and Neuroscience (Prof. Bente Pakkenberg)

Copenhagen University Hospital Glostrup, Glostrup, Denmark

- Department of Neurology (Ass. Prof. Messoud Ashina)
- Department of Rheumatology (Prof. Mikkel Østergaard)
- Functional Imaging Unit (Prof. Henrik B. W. Larsson)

Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

- Department of Paediatrics (Prof. Ole Axel Pryds)
- Gastrounit (Chief Consultant Svend Schulze, External clinical lector Thue Bissgård)

Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

- Center for Integrated Molecular Brain Imaging (Prof. Gitte Moos Knudsen, Prof. Olaf B. Paulson, Dr. Vibe Frøkjær, Dr. Patrick Fisher)

- Danish Multiple Sclerosis Center (Prof. Finn Selleberg, Per Soelberg, Dr. Morten Blinkenberg)
- Department of Clinical Physiology and Nuclear Medicine and PET (Prof. Andreas Kjær)
- Department of Neurosurgery
- Department of Radiology (Prof. Carsten Thomsen)
- Department of Paediatrics and Adolescent Medicine (Prof. Peter Uldall, PhD Peter Born)

Psychiatric Centres in the Capital Region

- Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Glostrup (Prof. Birte Glenthoj, PhD Bjørn Ebdrup)
- Child and Adolescent Psychiatric Centre Bispebjerg (Prof. Kerstin von Plessen, Senior Consultant PhD Katrine Pagsberg)
- Psychiatric Center Nordsealand Hillerød (Prof. Per Beck)
- Psychiatric Center Rigshospitalet (Prof. Lars Kessing, PhD Kamilla Miskowiak, Ass. Prof. Martin Balslev Jørgensen, Prof. Tom Bolwig)
- Research Institute of Biological Psychiatry, Psychiatric Center Sct. Hans Hospital, Roskilde (Prof. Thomas Werge)

INTERNATIONAL COLLABORATIONS

Australia National University, Canberra, Australia

- Centre for Research on Ageing (Prof. Kaarin Anstey)

Brookhaven Labaratory, New York, USA

- Medical Department (Prof. Helene Benveniste)

Cambridge University, Cambridge, United Kingdom

- Department of Clinical Neurosciences (Dr. James B Rowe, Dr. Jiaxiang Zhang)
- Medical Research Council Cognition and Brain Sciences Unit

Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Paris, France

- Charlotte Rosso

Christian-Albrechts-University, Kiel, Germany

- Department of Neurology (Dr. Sergiu Groppa, Oliver Granert)
- Institute for Physiology (Prof. Johann Kuhtz-Buschbeck)
- Institute for Sexual Medicine (Dr. Jorge Posenti)
- Neuropediatric Department, Pediatric Hospital (Prof. Michael Siniatchkin)

Eberhard Karls Universität Tuebingen, Germany

- Department for Neurology (Prof. Ulf Ziemann)

Ecole Normale Supèrieure, Paris, France,

- Group for Neural Theory

Forschungszentrum Jülich, Institute of Neuroscience and Medicine

- Dr. Kaveh Vahedipour, Prof. Simon Eickhoff

GE Healthcare, International

German Center for Neurodegenerative Diseases, Bonn

- Dr. Tony Stöcker

Griffith University, Queensland, Australia

- School of Physiotherapy and Exercise Science (Ass. Prof. Luke Haseler)

Howard University, Washington DC, USA

- Department of Physiology and Biophysics (Ass. Prof. Mark Burke)

Istituto di Scienze e Tecnologie della Cognizione- Consiglio Nazionale delle Ricerche, Isola Tiberina, Rome, Italy

Karolinska Institutet, Stockholm, Sweden

- Department of Neuroscience, Brain, Body and Self Laboratory (Prof. Giorgio Innocenti)

Lund University Hospital, Lund, Sweden

- Department of Medical Radiation Physics (Prof. Freddy Ståhlberg)
- Department of Radiology

Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts, USA

- A. Martinos Center for Biomedical Imaging (Ass. Prof. Koen van Leemput)

Max-Planck-Institutes, Germany

- Biological Cybernetics, Tübingen
- Human Cognitive and Brain Sciences, Leipzig (Dr. Thomas Knösche, Prof. Robert Turner)
- Neurological Research, Cologne (Dr. Marc Tittgemeyer)

Munich University of Technology, Munich, Germany

- Department of Neuropediatrics (Prof. Volker Mall)

Neurospin, Gif sur Yvette, France

- Laboratoire de Neuroimagerie Assistée par Ordinateur (Prof. Jean-François Mangin)

Oxford University, Oxford, United Kingdom

- Department of Physiology, Anatomy and Genetics (Dr. Kristine Krug)

Radboud University Nijmegen, Njmegen, The Netherlands

- Department of Neurology (Prof. Bastian Bloom)
- Donders Institute for Brain, Cognition and Behaviour, (Dr. Til Ole Bergmann)

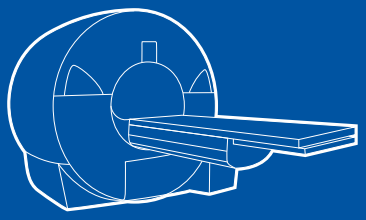
Scripps Translational Science Institute (STSI), San Diego, California, USA

- Cinnamon S. Bloss, Neuropsychology & Clinical Genomics

Sino-Danish Center for Education and Research (Ass. Prof. Kim Ryun Drasbek)

Tel-Aviv University, Israel

- Department of Neurobiology (Prof. Yaniv Assaf)



Università Campus Bio-Medico, Rome, Italy
- Prof. Vincenco DiLazzaro, Dr. Giovanni Pellegrino

University College London, Londaon, United Kingdom
- Department of Computer Science (Prof. Daniel Alexander, Ass. Prof. Hui Zhang, Dr. Ivana Dropnjak)
- Sobell Department of Motor Neuroscience and Movement Disorders (Prof. John Rothwell, Dr. Sven Bestmann, Dr. Nick Ward)
- Wellcome Trust Centre for Neuroimaging (Prof. Cathy Price)

University Medical Center Hamburg-Eppendorf, Hamburg, Germany,
- Department of Neurology (Priv. Doz Götz Thomalla, Prof. Alexander Muenchau)

University Medical Center Utrecht, Utrecht, The Netherlands
- Image Sciences Institute (Ass Prof. Alexander Leemans)

University of Birmingham, United Kingdom
- College of Life and Environmental Sciences
- School of Sport and Exercise Sciences

University of California, San Diego, USA
- Center for Human Development (Prof. Terry Jernigan)
- Department of Neurosciences
- Department of Psychiatry (Ass Prof. in Residence Wesley Thompson)
- Department of Radiology and Biomedical Imaging
- Laboratory of Cognitive Imaging
- MultiModal Imaging Laboratory (Prof. Anders Dale)

University of Cologne, Cologne, Germany
- Department of Neurology (Prof. Lars Timmermann)

University of Hamburg, Hamburg, Germany
- Biological Psychology and Neuropsychology (Prof. Brigitte Röder)

University of Leipzig, Leipzig, Germany
- Department of Neurology, Language & Aphasia Lab (Dr. Gesa Hartwigsen, Priv. Doz Dorothee Saur)

University of Lübeck, Lübeck, Germany
- Department of Neuroendocrinology (Prof. Jan Born, Professor Lisa Marshall, Dr. Matthias Mölle)
- Institute of Neurogenetics (Prof. Christine Klein, Prof. Alexander Muenchau, Priv. Doz Norbert Brüggemann)

University of Manchester, Manchester, United Kingdom
- Biomedical Imaging Institute (Prof. Geoff Parker, Dr. Penny Hubbard)

University of Medicine and Dentistry of New Jersey, USA
- Department of Biomedical Engineering and Department of Radiology (Prof. Bharat Biswal)

University of Messina, Messina, Italy
- Department of Neurosciences, Psychiatry and Anaesthesiological Sciences (Prof. Angelo Quartarone)

University of Montreal, Canada
- School of Optometry (Prof. Maurice Ptito)

University of Oslo, Oslo, Norway
- Center for the Study of Human Cognition (Prof. Kristine Walhovd, Prof. Anders Fjell)

University of Queensland, Brisbane St Lucia, Australia
- Queensland Brain Institute

University of Southampton, Southampton, United Kingdom

Universtity of Zurich, Zurich, Germany
- Department of economics

University Politecnica of Madrid, Madrid, Spain
- Centre for biomedical technology
- The laboratory for clinical neuroscience

Weizmann Institute of Science, Rehovot, Israel

INTERNATIONAL MULTI-CENTRE RESEARCH COLLABORATIONS

- Arterial spin labelling Initiative in Dementia, European cooperation in science and technology (COST) framework.
- Consortium of Neuroimagers for the Non-invasive Exploration of Brain Connectivity and Tractography (CONNECT). EU 7th Framework Programme (www.brain-connect.eu)
- Neuroprotective autologous mesenchymal stem cells for multiple sclerosis – A randomised, placebo controlled, blinded phase II trial (MESEMS): Danish Multiple Sclerosis Research Center, Department of Clinical Immunology Rigshospitalet, University of Genoa – Department of Neurosciences, Ottawa Hospital Research Institute – MS Research Clinic, University Hospital Basel – MIAC, Queen Square – Queen Square MS Centre
- Polarized Helium Lung Imaging Network (PHeLINet). EU 7th Framework Programme: Research and Training Network (RTN).

CLINICAL TRIALS

- Collaborators in Clinical Trials include: AC-Immune SA, Biogen Idec Ltd, Bristol-Myers Squibb, Danish Dementia Research Center, Danish Multiple Sclerosis Center, Hoffmann-La Roche Ltd, Genzyme Europe, GlaxoSmith-Kline, Novartis.

PUBLICATIONS

PH.D. THESES

2011

1. Hammer TB. Sensorimotor Gating in Schizophrenia: Long term outcome and structural brain correlates in (initially) antipsychotic-naïve first-episode patients. Faculty of Health Sciences, University of Copenhagen, 2011.
2. Liptrot MG. Image Processing in Diffusion MRI Tractography. Department of Bioengineering, Imperial College, University of London, 2011.
3. Lou AR. Plasticity of the visual system throughout life - lessons from changes in monocular vision. Faculty of Health Sciences, University of Copenhagen, 2011.
4. Lundell H. Methods for mapping spinal cord connectivity using diffusion, functional and conventional MRI. Faculty of Science, University of Copenhagen, 2011.
5. Madsen KS. Brain microstructural correlates of behavioural and neuroendocrinological phenotypes. Faculty of Health Sciences, University of Copenhagen, 2011.

2012

1. **Asghar Butt, S.** Metabolic Imaging of Breast Cancer and the Normal Brain: Application of Hyperpolarized 13C Magnetic Resonance Spectroscopy. Faculty of Health and Medical Sciences, University of Copenhagen. 84 p., 2012.
2. **Dogonowski, A-M.** Resting-state Functional Connectivity of the Motor System in Multiple Sclerosis. Faculty of Health and Medical Sciences, University of Copenhagen. 2012.
3. **Kassuba, T.** Object recognition - Convergence of vision, audition, and touch. German University Libraries. 140 p., 2012.
4. **Rasmussen, P. M.** Mathematical Modeling and Visualization of Functional Neuroimages. Technical University of Denmark, Informatics and Mathematical Modelling. 2012.

BOOK CHAPTERS

2011

1. **Klarborg B; Siebner HR.** At sove er at lære - søvn og plasticitet. Nielsen JB;Gade A, Hjerneforum, Copenhagen, 2011.
2. **Kupers R; Ptito M; Gjedde A.** Sansernes foranderlighed. Nielsen JB;Gade A, Hjerneforum, Copenhagen, 2011.

2012

1. **Angstmann, p. & Siebner, H. R.** Effects of Cortical Stimulation on Cortical Functional Connectivity: Imaging Studies. Cortical Connectivity: Brain Stimulation for Assessing and Modulating Cortical Connectivity and Function. Chen, R. & Rothwell, J. (ed.). Springer, Chap. 4, p. 71-91. 21 p. 2012.
2. **Hansen, T. J. , Hansen, L. K. & Madsen, K. H.** Decoding Complex Cognitive States Online by Manifold Regularization in Real-Time fMRI. Machine Learning and Interpretation in Neuroimaging: International Workshop, MLINI 2011, Held at NIPS 2011, Sierra Nevada, Spain, December 16-17, 2011, Revised Selected and Invited Contributions. Langs, G., Rish, I., Grosse-Wentrup, M. & Murphy, B. (ed.). Springer Berlin Heidelberg, p. 76-83. 8 p. 2012.
3. **Hasselbalch, p. & Paulson, O. B.** The Coupling of Cerebral Metabolic Rate of Glucose and Cerebral Blood Flow In Vivo. Neural Metabolism In Vivo. Choi, I-Y. & Gruetter, R. (ed.). Springer Publishing Company, Vol. 4, Chap. 14, p. 417-432. 16 p. (Advances in Neurobiology). 2012.
4. **Henningsson, p. , Laursen, H. R. & Siebner, H. R.** Serotonin og social kognition. Den sociale hjerne. Gade, A. (ed.). 2012 udg. København: Hjerneforum, Vol. 1, Chap. 8, p. 79-88. 10 p. 2012.
5. **Ramsøy, T. & Fosgaard, T.** Hvordan andre påvirker hjernens valg. Den sociale hjerne. Gade, A. (ed.). Hjerneforum, Chap. 7, p. 66-78. 13 p. 2012.
6. **Siebner, H. R. & Ritter, C.** Kortikale Schmerzmodulation mit Motorkortexstimualtion, transkranieller Gleichstrom- und Magnetstimulation. Interventionelle Neurophysiologie: Grundlagen und therapeutische Anwendungen. Classen, J. & Schnitzler, A. (ed.). Thieme, Georg, Verlag KG, Chap. 4.8, p. 182-190. 9 p. 2012.
7. **Siebner, H. R. & Ziemann, U.** Transkranielle Magnetstimulation. Leitlinien Klinische Neurophysiologie und funktionelle Bildgebung. Bischoff, C. & Straube, A. (ed.). W. Kohlhammer GmbH, Chap. 1.7 2012.
8. **Ziemann, U. & Siebner, H. R.** Zervikale Myelopathie. Leitlinien Klinische Neurophysiologie und funktionelle Bildgebung. W. Kohlhammer GmbH, Chap. 2.6.2 2012.

PAPERS IN PEER-REVIEWED JOURNALS

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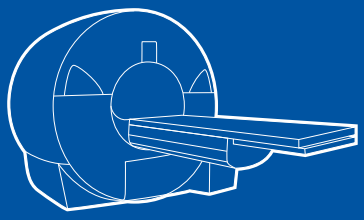

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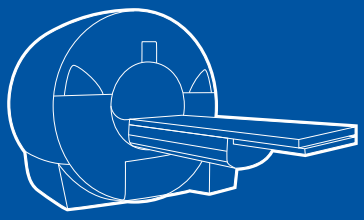

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DRCMR staff at the annual DHL race in Copenhagen in 2011

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