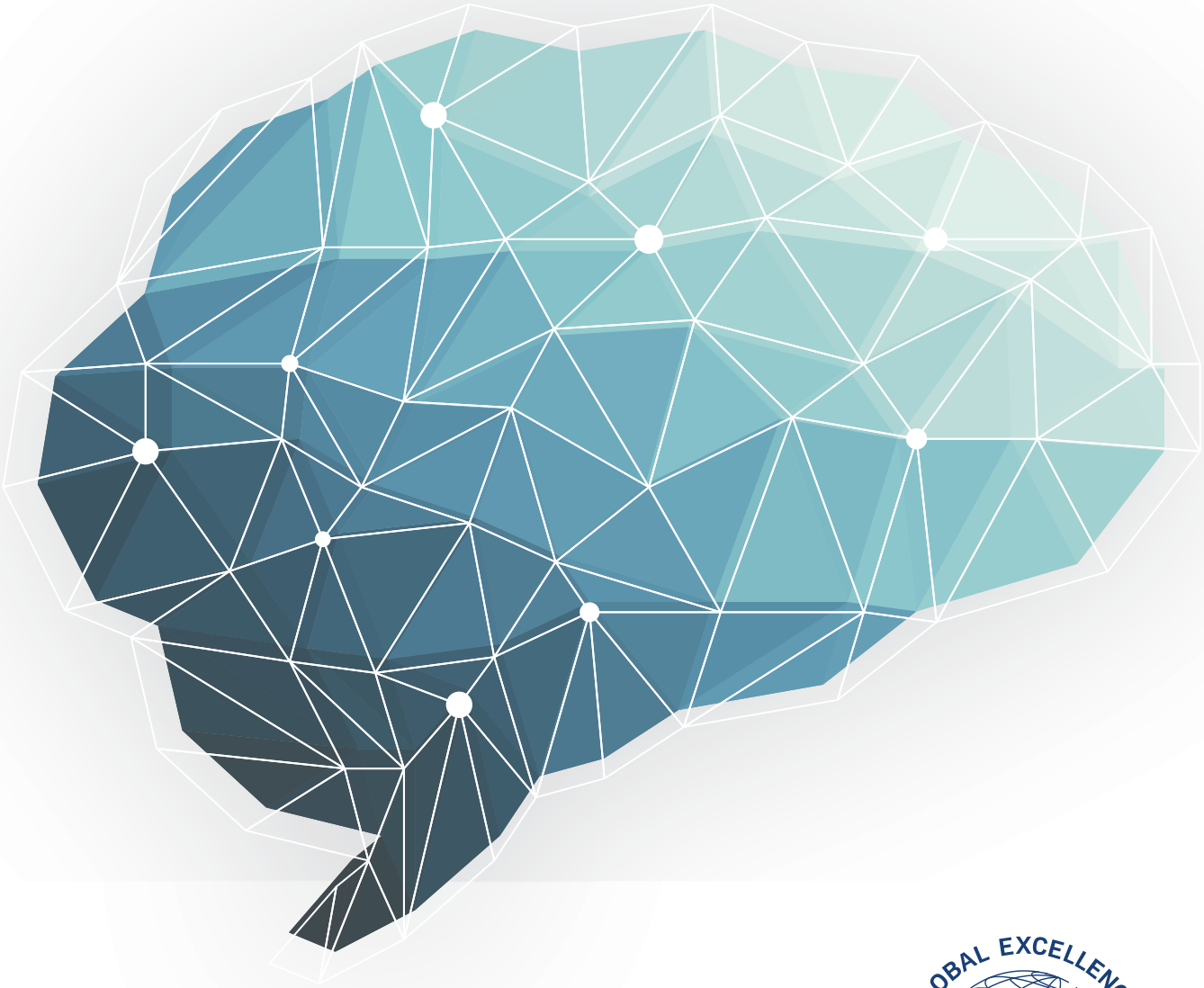
DRCMR

DANISH RESEARCH CENTRE FOR MAGNETIC RESONANCE

BIENNIAL REPORT 2013 – 2014



REGION Hvidovre Hospital

DRC MR

GLOBAL EXCELLENCE IN HEALTH

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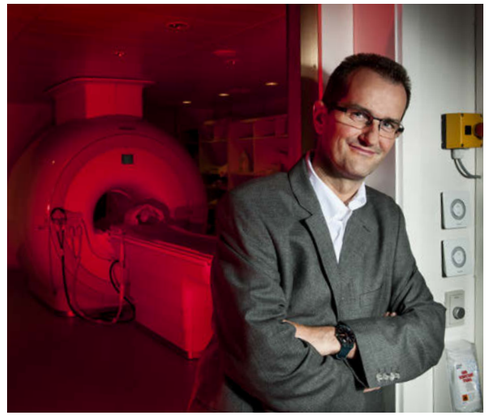


Hartwig Siebner, Head of research at DRCMR, Photo: Joachim Rohde.

THE DANISH RESEARCH CENTRE FOR MAGNETIC RESONANCE IN 2013 & 2014

2013 & 2014 have been great years for science at DRCMR. As you can read in our biennial report, the past two years reflect a continuation of our "discovery journey" which started with the foundation of DRCMR back in 1985. We are steadily growing – both in terms of our scientific activities and in terms of our research infrastructure. New talented researchers joined the DRCMR in 2013 & 2014. Currently, a multi-disciplinary team of approximately 75 researchers is carrying out MR research at DRCMR. More than 20 countries are represented at the research centre, making the DRCMR a very international research environment. Furthermore, we have a large number of collaborators both nationally and internationally with whom we interact on a daily basis.

In this biennial report, we wish to share with you the lines of research that are pursued at DRCMR. It gives you a glimpse of what we are doing and how we do it. We follow the format of the last biennial report. The first part of the report is dedicated to research highlights and featured projects. The second part is a description of our main research areas and research groups, followed by a short introduction to our major external collaborations. And finally we have a list of disseminations and a presentation of new faces.

I would like to express my gratitude towards the foundations and institutions as well as the collaborators who have made it possible for the Danish Research Centre for Magnetic Resonance to enable and secure our frontline position in MR research. And hopefully our collaboration will continue for many years to come.

All the best wishes

H Siebner

Hartwig Siebner

HIGHLIGHTS & MILESTONES 2013 – 2014

Over the last decades, Magnetic resonance imaging (MRI) has emerged as a powerful non-invasive technique to study the human body. This is particularly true when it comes to brain imaging. Here MRI offers unprecedented opportunities to unravel the secrets of the human brain. The mission of the Danish Research Centre for Magnetic Resonance (DRCMR) is twofold. The main goal of the methodological line of research is to advance the biomedical use of MRI. Our applied line of research is geared to conduct ground-breaking basic and clinical neuroscience.
The brain is an enormously complex organ and we benefit tremendously from working in partnership with colleagues from a large variety of scientific disciplines. The DRCMR houses a multi-disciplinary and multi-national research team with expertise in MR physics, data processing, pre-clinical research, motor control, cognitive neuroscience, interventional neurophysiology, multimodal integration, neurology and psychiatry. Researchers at DRCMR strive to deliver the best research and education. Being part of a large university hospital, our research is oriented towards understanding how brain disorders affect brain structure, function, and metabolism. This knowledge will promote early diagnosis and monitoring, but also yield novel insights into disease mechanisms and how the brain is able to cope with damage.
The years 2013 and 2014 brought a series of exciting new developments that added significant momentum to the science conduced at DRCMR and opened up exciting possibilities for the future.

TOWARDS ULTRA-HIGH FIELD MRI IN HUMANS – THE NATIONAL 7T MR PROJECT

The preparations for the National 7T MR project gained speed in 2013 and 2014. A team of architects, engineers, and researchers orchestrated the rebuilding activities which were necessary for housing the 7T MR facility in the hospital. One challenge was to reinforce the building in order to accommodate the over 40 tons heavy magnet. The magnet was finally lifted in on March 1st 2014. Two of the largest mobile cranes in Europe were needed to lift this heavy-weight magnet into its final position centrally in the Radiology Section. Philips completed the on-site installation of the rest of the scanner in November 2014 and the magnet was ramped up to full field in January 2015. This event was marked with an official inauguration of the national 7T Mr facility on February 24th 2015.

Photo 1: *An early morning at DRCMR.*

In parallel to the efforts related to systems implementation, we looked out for a scientist to lead the ultra-high field research program. Among a highly competitive field of international applicants, Esben Thade Petersen from the University Medical Center Utrecht was recruited in fall 2014 as leader of the 7T physics group. Esben has several years of experience working with ultra-high field MR and will be an important asset to the DRCMR. His recruitment was a critical step to secure the success of the national 7T project.

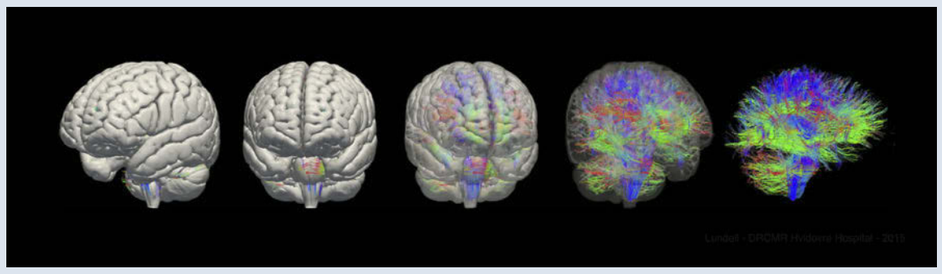


Figure 1: *White-matter pathways reconstructed with tractography from diffusion MRI. The animation reveals the structural connections between different parts of the brain (animation by Henrik Lundell).*

Photo 2: *The 7T magnet arrives at Hvidovre Hospital.*

EXPANDING THE RESEARCH INFRASTRUCTURE

New office space: The rapid growth in number of researchers over the last years caused a notorious shortage of desk space at DRCMR. 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 and DRCMR researchers moved into the new pavilion in January 2013. This was greatly appreciated by the more than 70 researchers carrying out MR-based research at DRCMR and will benefit the scientific collaboration between centres in the national 7T project.

Photo 3: *The new office space buliding to the left and the old office space building to the right.*

A new research-only 3T MR scanner: The installation of a research-only Philips Achieva 3T MR scanner was completed early 2013. It took only a few months until this scanner was fully booked, making the Achieva 3T MR system with a 32-channel head coil and other state-of art MR equipment an important "workhorse" for our research. In particular, the availability of a research-only MR scanner boosted MRI research that involves scanning of large cohorts or requires a lot of technical assistance.

Photo 4: *The new 3T research only scanner.*

EDUCATION IS KEY

Teaching is given high priority at DRCMR and is an integrated part of our daily activities. The DRMCR therefore hosts an annual PhD course in collaboration with the Faculty of Health Sciences at the University of Copenhagen. In 2013, the course was entitled "Multimodal brain imaging: interfacing neuroimaging and computational methods to map human brain structure", while the topic of the 2014 course was "Linking magnetic resonance imaging (MRI) to the neuroanatomy of the human brain". Both courses incorporated international as well as national experts as speakers.
Young researchers at DRCMR come from different backgrounds with different needs for scientific training. In order to ensure an optimal training, we established a curriculum for first year students to teach them the essential skills necessary for their

Photo 5: *Postdoc Anke Karabanov teaching.*

research. This has evolved into a rich and varied educational program that spans from philosophy of science, statistics, math, and matlab, to the specific applications of MR physics and neuroimaging data analysis. The programme is headed by Oliver Hulme and Kristoffer Madsen, but involves several other researchers at DRCMR as well.

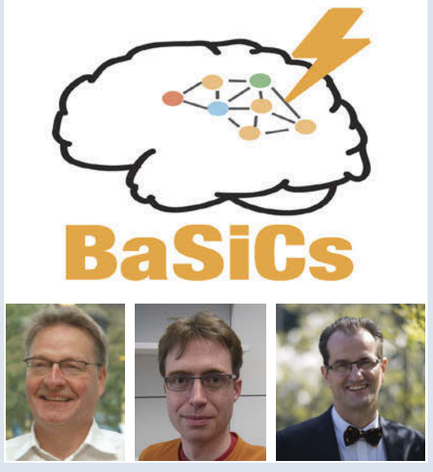


Figure 2: *The BaSICs-logo and the three PIs: Lars Kai Hansen, Axel Thielscher and Hartwig Siebner.*

BASICS SYNERGY GRANT

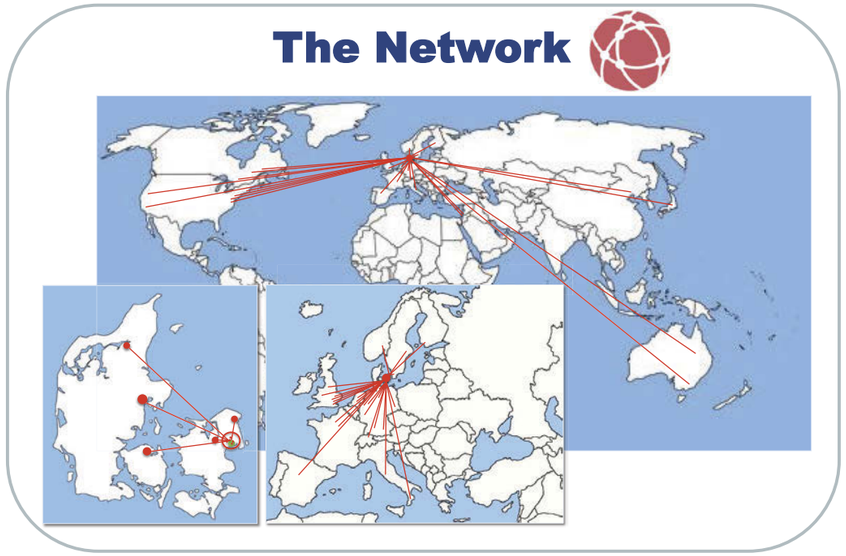
The combination of transcranial brain stimulation and human brain mapping has long been a research focus at DRCMR. This line of research received a major boost at the end of 2014: Together with co-applicants Lars Kai Hansen (DTU-Compute) and Axel Thielscher (DTU-Electro), principal investigator Hartwig Siebner received a 15 millions DKK synergy grant from the Novo Nordisk Foundation for a 3-year project entitled "Biophysically adjusted State-informed Cortex stimulation" (BaSiCs). This highly ambitious project aims to integrate advanced modelling of the electrical fields induced with non-invasive transcranial brain stimulation, with real-time recording of brain states using EEG and functional MRI in order to dynamically adapt the spatiotemporal properties of non-invasive transcranial brain stimulation to the intrinsically expressed brain states. We expect that this research will yield important discoveries regarding the neural underpinnings of human brain function and dysfunction. Our ambition is to push the frontiers of non-invasive transcranial brain stimulation making it an efficient interventional tool to optimize the function of human brain networks.

GLOBAL EXCELLENCE AWARD

In 2014, the DRCMR received the "Global Excellence in Health" award on the basis of evaluations by a specialist review committee of national as well as international experts. The Global Excellence programme is sponsored by the Capital Region of Denmark and recognises the extent and quality of our research and development as well as our efforts in teaching, innovation and dissemination of new knowledge at DRCMR. The Global Excellence distinction is valid for a period of five years and includes a grant of app. EUR 200,000, which will be used to strengthen the international profile and network of DRCMR. We feel very honoured and grateful for this recognition which is highly motivating to further increase our efforts to perform cutting-edge neuroimaging research for the benefit of the patients and society.

DRCMR AND THE WORLD

DRCMR INTERACTING WITH THE WORLD ...



... AND THE WORLD COMING TO DRCMR

THE NATIONAL 7 TESLA MR PROJECT

The Danish National 7 Tesla MR Project was initiated more than ten years ago by Professor Olaf B. Paulson and it was finally materialized in 2014. On March 1st the 44 tons heavy magnet was lifted into the premises of the Danish Research Centre for Magnetic Resonance, located at Hvidovre Hospital. Throughout the summer and autumn the installation work was ongoing and the system is expected to be fully operational in 2015.

The realization of the national ultra-high field MR facility at DRCMR is an important strategic achievement. It will gather researchers from both eastern and western Denmark. Currently, the hospitals in the capital region, the universities in Aarhus and Copenhagen, Copenhagen Business School and the Technical University of Denmark are represented in the Danish National 7 Tesla MR Project. A national steering committee, chaired by Professor Jørgen Frøkiær from Aarhus University, secures the scientific quality and ensures equal access to the system resources.

Scientists will soon have access to this unique instrument, which will strengthen the Danish position in MR-related research. This very ambitious project is only possible due to the generous funding from The John and Birthe Meyer Foundation and the Danish Agency for Science and Innovation. A dedicated 7 Tesla MR user group at the DRCMR will ensure the daily operation of the Ultra High Field MRI system.

Photo 2: *Philips engineer Klaus Rye installing the highly complex system. 5000 liter of liquid helium is used to keep the superconducting magnet at its working temperature of 4 Kelvin (-269 degrees Celsius).*

Photo 1: *The big lift! The magnet was lifted and rolled to its current location on 1st of March 2014. Two of the strongest mobile cranes available in Denmark participated in this tandem lift of the 44000 kg heavy magnet.*

The scanner, which is only approved for research, gives a much more detailed insight into human physiology and diseases than clinical MR scanners. Examples include imaging of brain structure and activation as well as studies of metabolism. Several studies have already been planned on the scanner, which is a national instrument available to MR researchers nationwide.

Senior researcher Esben Thade Petersen was recruited from the University Medical Center Utrecht in the autumn of 2014 as leader of the 7T MR research group at DRCMR, which will actively participate in local and national collaborations to ease project planning and execution. At the same time, the group will have its own research profile in particular within functional and metabolic imaging of the brain. Since the 7T MR research group will develop hardware for ultra-high field scanning, a fully equipped hardware lab will soon be established in connection with the 7 Tesla MR project, making it possible to develop, test and repair own coils and other equipment. This will benefit research at the high-field MR system. Particularly for imaging outside the brain, there is often a need to design dedicated coils for the organ of interest. In addition, the system is prepared for multi-nuclear imaging and spectroscopy (other nuclei than protons, e.g. phosphorous, sodium or carbon) which benefit much from higher field strength. Coil design projects that have multi-transmit capability have already been initiated in collaboration with Vitaliy Zhurbenko from DTU.

In summary, an important strategic research infrastructure has been put in place and we are very much looking forward to taking advantage of its potentials in the years to come. The setup is ideal concerning available hardware, the planned adjacent hardware lab and the existing research infrastructure at DRCMR. This unique setting will offer very exciting research synergies not only locally at DRCMR but also nationwide, something we really look forward to in the years to come!

Photo 3: *The national steering committee of the Danish national 7 Tesla MR project.*

EDUCATING PHD-STUDENTS AT DRCMR: A HOLISTIC APPROACH

As in most neuroimaging centres, the education of PhD students is challenging at DRCMR, because students come from a wide range of disciplines. Students need to learn new methods and develop new skills within fields quite far from traditional master programmes – and as such, there is no coherent path from novice to ninja. Previously, the DRCMR ran several courses for students training them in basic methods. However, the approach was patchy and lacked alignment between the courses. Students rather needed a clear overview of the foundations that they were expected to acquire in order to ease the students' introduction to a highly interdisciplinary research field. To meet this need a curriculum with mandatory courses was set up in order to give our students a foundational training for doing neuroimaging research and to provide them with basic competences that enable them to acquire project-specific advanced skills. Establishing the curriculum prompted senior researchers at DRCMR to think more holistically about the type of education they wish to provide at DRCMR. The holistic approach has evolved into a rich and varied educational programme, spanning from philosophy of science, neurobiology, neuroanatomy, statistics, maths and programming in matlab, to the specific applications of MR physics, analysis of imaging data, but also including more practical elements such as scanner training, programming, and presentation skills.
In addition to the internal curriculum, the DRCMR also arranges one PhD course every year as part of the Neuroscience PhD Graduate Programme of the Faculty of Health and Medical Sciences at the University of Copenhagen. Topics for these courses have changed throughout the years. In 2013, the theme of the course was MULTIMODAL BRAIN IMAGING. Students attending the course learned how neuroimaging and computational methods can be integrated to map human brain structure and function. The PhD course in 2014 focussed on NEUROANATOMY. In key note lectures and group exercises, the students learned how magnetic resonance imaging can be used to study the neuroanatomy of the human brain in health and disease.

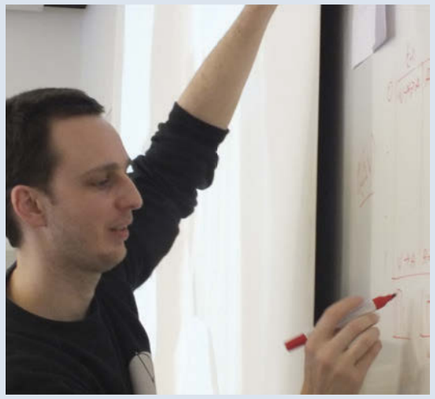


Photo 1: *Senior Researcher Ollie Hume teaching the PhD students.*

"I really like the changes in internal teaching that have been implemented at DCMR over the last year. When I first started as a master student, internal teaching was fragmented or non-existing. It has therefore been great to see and experience at first-hand how researchers from different fields came together to develop a structured and manageable curriculum for students at the department.
Because everyone starting at the DRCMR has a specific educational background, it is hard to know everything. Having a master in psychology, it was challenging for me to cope with many technical aspects of MRI, EEG, and programming, I am not saying that the course will make me a world-class programmer, or make our engineers experts in developmental psychology, but the course does go a long way to ensure that everyone has a fundamental understanding of the many fields that play a role in imaging neuroscience and becomes familiar with all methodological research tools."
Jonathan Holm-Skjold, PhD student (MA in Psychology)

GLOBAL EXCELLENCE IN HEALTH 2014

The Danish Research Centre for Magnetic Resonance was in August 2014 granted the Global Excellence in Health Award by the Capital Region of Denmark. The award is given to acknowledge and highlight world class research and therapy environments in the field of healthcare at hospitals and universities in the Capital Region of Denmark. The aim of the award is to recognize and increase visibility of research, education, innovation and healthcare provisioning living up to the highest international standards. Through this initiative the Region seeks to encourage internationalization with a view to attracting international partners, researchers, talents and both private-sector and public funding for research. The award is only given if applicants excel in their performance in the research, development and implementation of innovative knowledge and technologies as well as in new courses of treatment aimed at healthcare services in Denmark.

When awarding the DRCMR the nomination committee put special emphasis on outstanding contributions to research and disease management regarding neurological diseases, such as multiple sclerosis and Parkinsonism. Insight into the treatment of these is obtained using an interdisciplinary approach combining MRI and other techniques. The nomination committee was also impressed by DRCMR's ability to attract international prominent researchers and ensure extended regional and global collaboration with the best researchers within the field. Last but not least, the committee mentioned the extremely impressive research infrastructure at DRCMR, including the 7T MRI-scanner.

Photo 1: *Hartwig Siebner, Head of research at DRCMR, receiving the Global Excellence in Health award.*

The Global Excellence program

The program was established in 2010 by the Capital Region of Denmark in close cooperation with the University of Copenhagen and the Technical University of Denmark (DTU). It comprises the awarding of one or two prizes each year, followed up with focused support in the form of consultancy, tools, website development, conferences, etc. The selected Global Excellence environments have been chosen by the executive committee of the Capital Region of Denmark on the basis of evaluations by a specialist review committee of national as well as international experts. The Global Excellence distinction is valid for a period of five years.

FEATURED PROJECTS

A FOCUS ON MENTAL HEALTH IN CHILDREN AND ADOLESCENTS

A Collaboration between the Child and Adolescent Mental Health Centre – Capital Region of Demark and Danish Research Centre for Magnetic Resonance (DRCMR)

Many children experience some form of mental problems from infancy through their adolescent years. This may result in negative emotions such as anxiety, depression, problematic behaviour such as hyperactivity, or eating disorders. These feelings and behaviours of affected individuals may cause severe problems in their lives and the lives of those around them and often require medical treatment.

Neuropsychiatric disorders in children and adolescents are closely related with ongoing brain development. This explains why brain development is a central research theme in Child and Adolescent Psychiatry. Neuroimaging research into mental well-being and neuropsychiatric disorders during infancy and adolescence can establish important links to brain maturation. This knowledge can be used to promote mental health of children and adolescents in Europe and to inform future therapeutic interventions.

"The Child and Adolescent Mental Health Centre, Capital Region of Denmark, has a strong collaboration with the scientists at DRCMR. Our joint research is focused on finding relevant outcome measures for children with tics, hyperactivity or attention deficits. Apart from taking science one step further and making new evidence-based and objective measures for the treatment of children and adolescents with psychiatric disorders, the international environment at DRCMR also has an important influence on our PhD-students."
Professor Kerstin Jessica Plessen

While the focus has traditionally been on developmental psychopathology and its phenotypic expression, factors that promote mental health have come more and more into the focus in recent years. We aim to map the genetic and neurobiological constraints underlying psychological dimensions and psychiatric symptoms in children and adolescents in the quest of finding the right keys for effective treatment approaches. The collaboration between clinicians at Child and Adolescent Mental Health Centre (BUC) and neuroimaging experts at the DRCMR offers unique avenues to map developmental processes in healthy children, children who are at risk, children with manifest disorders, and lastly – as shown in this first project – in young people that have overcome a disorder.

Anorexia Nervosa, Performance Monitoring and Perfectionism

PhD student psychologist Tine Pedersen; supervisors: Professor Kerstin Plessen, Professor Hartwig Siebner

In spite of a rather homogenous presentation of anorexia, which has the highest rates of mortality in a psychiatric disorder, its neurobiological basis and factors contributing to the maintenance of abnormal eating behavior are not well known. A fairly large subgroup of patients does not respond optimally to treatment, and clinical observations suggest that personal traits such as perfectionism may be predictors of reduced treatment effect.

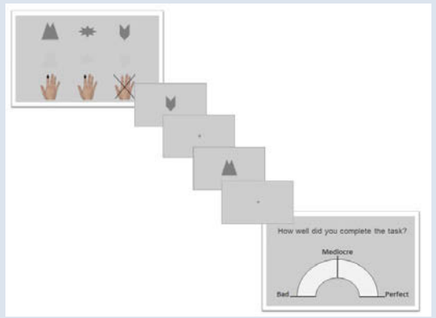
We know that perfectionism as a personal trait is frequently present in adolescents with this disorder, but we do not know if these traits correlate to different patterns of brain activation during performance monitoring and if this might affect prognosis.

Previous studies on anorexia have faced two major challenges. First, the anorexia patient group weighs significantly less than the control group, which can affect brain structure and function separately. Secondly, the anorexia patients exert increased inhibitory control making it difficult to study adaptations to errors. We do not know whether previous findings are merely a consequence of the patients' bodily state, reflect trait features that characterize vulnerability for the disorder, or constitute factors involved in the maintenance of the illness. Therefore, well-controlled studies in recovered patients will contribute to a deeper understanding of the link between overly perfectionism and excessive cognitive control on one hand, and the problems to control the invading thoughts concerning thinness on the other hand. In the Anorexia Study we investigate adolescents' monitoring of their own performance during a task that requires cognitive control, due to changing circumstances. We use functional MRI to map task-related brain activity while participants perform a "Go-NoGo task", in which arbitrary symbols instruct participants to either perform a movement ("Go") or to suppress such a movement (NoGo). We study three separate groups: (a) recovered adolescents with a previous diagnosis of anorexia, who are at a healthy body weight, b) adolescents who currently receive treatment for anorexia, and c) healthy control subjects. We expect to find increased activation of prefrontal brain regions after erroneous responses (i.e., unsuccessful "no go" stimuli = errors of commission) in recovered and in currently ill adolescents with anorexia compared to the control group.

At the end of every block, participants evaluate their performance by placing a slider on a continuum from bad to perfect. It will be very interesting to see, whether the BOLD activations will reflect the differences in self-evaluation that we see behaviorally. At the behavioral level adolescents with anorexia show more negative self-evaluation than the healthy group, while the recovered group lies in between the other two groups. The MRi data analysis is still ongoing.

Overview of one task block during functional MRI

An instruction screen initiates a block and is followed by three symbols shown eighteen times in randomized order. The block ends with a self-evaluation screen. Duration ~1 minute.



Motivation on Self-Regulatory Control in Children with Tourette syndrome

PhD student MD Katrine Maigaard; supervisors: Professor Kerstin Plessen, Professor Hartwig Siebner; in collaboration with Associate professor, dr. med. Liselotte Skov

Tourette syndrome is a neuropsychiatric disorder starting in childhood and is characterized by multiple motor and vocal tics. A large proportion of children with Tourette syndrome also suffer from additional disorders such as Attention-Deficit/Hyperactivity Disorder (ADHD) or Obsessive Compulsive Disorder (OCD). It is becoming increasingly apparent that co-morbidities may affect the child's performance and well-being in everyday life, but little is known of how these co-morbidities affect a child's response with respect to motivation and cognitive control, which both play a central role in non-pharmacologic treatment approaches. We will compare children with isolated Tourette syndrome (TS), children with TS and co-morbid ADHD, and typically developing children without TS or ADHD. This novel trans-diagnostic approach has given rise to a fruitful collaboration between the Department of Paediatrics, Herlev Hospital, the Child and Adolescent Mental Health Centre – Capital Region, and the Danish Research Centre for Magnetic Resonance (DRCMR).

After a thorough clinical evaluation, including a state-of-the-art diagnostic test battery and extensive measurements of different phenotypic aspects of cognitive control, working memory, attention, impulsivity and risk taking behavior, we investigate whether children can mobilise an inhibitory reserve when motivated extrinsically. Mobilisation of an inhibitory reserve may lead to more efficacious non-pharmacological interventions for children with TS that aim to increase the amount of self-regulation and to change existing dopaminergic circuits of reward.

Using functional MRI, we examine the activity of executive brain networks which are dealing with conflicting response tendencies. We also

modulate the level of motivation by introducing a prospect of reward in some of the trials. We map task-related brain activation as well as task performance in children with TS alone, with ADHD alone, or with TS and ADHD and compare our findings with the data obtained in a healthy age- and gender-matched control group.
Improving our knowledge of motivational processes in fronto-striatal circuits in TS children, with and without co-morbid ADHD, will allow us to better understand how disturbances in the development of those circuits contribute to difficulties associated with childhood neuropsychiatric disorders. The findings of this study will inform treatment options, especially those involving active changes in habit formation.

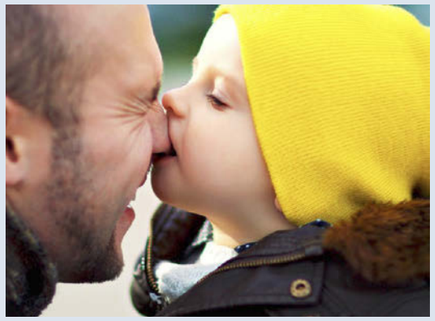


Photo 1: *Self-Control: as a child matures, it learns to take more control of its actions and impulses.*

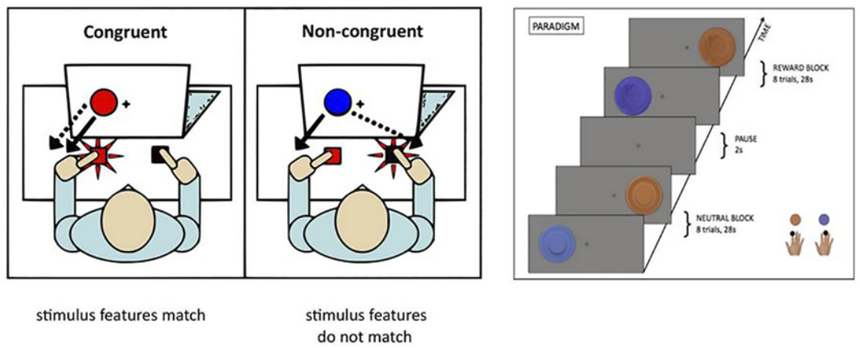


Figure 1: *Modified Simon task used during fonctional MRI.*

LINKING GENOMIC VARIATION TO BRAIN FUNCTION AND STRUCTURE: THE 22Q11.2 DELETION SYNDROME

The DRCMR is part of the National Danish 22q11 research initiative, initiated and lead by the Institute for biological Psychiatry at Sankt Hans Hospital, Roskilde, headed by Professor Thomas Werge.

The challenge

Early therapeutic intervention of debilitating complex neurodevelopmental brain disorders with heterogeneous etiologies such as schizophrenia, autism and attention deficit hyperactivity disorder (ADHD) is hampered by our inability to identify individuals at high risk prior to disease onset. We need to understand how biological, subclinical and cognitive endo- or intermediate phenotypes are linked to observable behavioral and clinical phenotypes to improve our understanding of the neurobiological pathogenesis of these disorders to enable development of more targeted treatment options with improved efficacy.

"We have been collaborating with DRCMR for several years on projects that have been challenging both scientifically, logically and economically. This has however compromised neither the joy nor the benefits of the teamwork. During the process both parties have learned from each other, in particular how to boost the efficiency of our future cooperation. We are looking much forward to initiating these cross-disciplinary projects, linking genomic variation to functional changes of the brain.
Professor Thomas Werge, Institute for biological Psychiatry at Sankt Hans Hospital

Insights into the pre-morbid disease dynamics and the underlying biological disease mechanisms may come from studies of subjects with homogenous etiologies. The National Danish 22q11.2 research initiative performs comprehensive studies in unaffected individuals with the 22q11.2 deletion syndrome who have a high risk of developing neurodevelopmental brain disorders, with the risk of developing schizophrenia being up to 30 to 40 %. Given that 22q11.2 carriers carry the same high impact risk factor and therefore have a more homogeneous underlying etiology, the chance of identifying neuropathophysiological risk markers should be high.
Participating individuals with the 22q11.2 deletion syndrome and age and sex matched healthy volunteers undergo a comprehensive research program to gather a large amount of detailed biological, clinical, behavioral, cognitive, epidemiological, and structural and functional brain data. Moreover, the initiative includes translational investigations in 22q11.2 deletion and wild type mice that allow mapping deficits across multiple levels from altered behavior, anatomical and physiological changes to molecular disturbances. Hence, the initiative brings together a strong team of researchers and clinicians from different disciplines including genetics, biology, physiology, psychology, neurosciences, medicine, psychiatry, bioengineering, computer sciences and mathematics.

Research aim

The overall aim of this initiative is to identify multi-dimensional markers, spanning cognitive, neuroanatomical, and neurophysiological domains as well as environmental exposures and family disposition, predictive of the pathology underlying autism, attention deficits and schizophrenia.
By studying unaffected individuals with a 22q11.2 deletion, we have a unique opportunity to identify neuropathophysiological risk markers before the actual onset of the mental disease. The latter is important as this means that our findings will not be contaminated by for example disease severity, chronicity, or psychoactive medication use. Equipped with these markers we will then be in an excellent position to detect individuals with an increased risk for autism, ADHD, or schizophrenia and psychosis independent of their genetic disposition. Importantly, studying 22q11.2 deletion carriers who do not develop a neurodevelopmental brain disorder may help us to identify "protective factors" that enhance resilience. Finally, it will ultimately enable the development of more tailored treatment options with improved efficacy.

Epidemiological studies

The initiative incorporates epidemiological studies, utilizing information obtained from the National

Danish Health Registries including the Danish Civil Registration System, the Danish National Patient Registry, the Danish Psychiatric Central Register and the Danish cytogenetic central register, and functional studies in a case–control sample. For the epidemiological studies the Institute for biological Psychiatry was able to identify a representative sample of 244 Danish citizens (125 males and 119 females) who are recorded in Danish Cytogenetic Central Register as 22q11.2 deletion carriers.

Functional studies

For the functional case-control studies that are performed at the DRCMR, 22q11.2 carriers, above the age of 12, were recruited primarily from the department of Pediatrics, Aarhus University Hospital, the department of Clinical Genetics, Copenhagen University Hospital, and through postings at family meetings held by the Danish National 22q11DS Association. In total, 44 carriers and age and sex matched healthy volunteers consented to participate in the functional studies. Researchers of the Institute for biological Psychiatry perform detailed genetic, clinical and cognitive assessments, while DRCMR researchers perform in vivo measurements of brain function and structure using Electroencephalography (EEG) and magnetic resonance imaging (MRI).

Functional brain mapping

The focus of the studies performed at DRCMR is to elucidate neurophysiological risk markers. We employ a mismatch negativity (MMN) paradigm, which probes the brain response to a sudden change in the auditory input. Previous studies have shown that the MMN response is significantly reduced in patients suffering from schizophrenia, suggesting a disruption of feedback from higher cortical areas to lower cortical areas predicting irregularities. By applying a MMN paradigm during functional brain mapping, consisting of separate EEG and fMRI measurements, we can capture specific brain responses to distinct auditory changes on a high temporal and spatial scale. The auditory MMN paradigm consists of a streak of equal tones that is disrupted by a so-called oddball, a tone of a different pitch (frequency) or duration. Such irregularities give rise to the so-called mismatch negativity response as measured by EEG and specific to the detection of unexpected events. We use two types of auditory roving MMN paradigms in order to study the underlying neural network of 22q11.2 deletion carriers compared to control subjects.

The 22q11.2 deletion Syndrome

The syndrome covers several disorders, including DiGeorge and Velocardiofacial syndrome, which encompass multiple somatic conditions, such as congenital heart disease, velopharyngeal insufficiency, immune deficiency and intellectual disability. Over the past decades it has become increasingly clear that the 22q11.2 deletion also confers very high risk of neurodevelopmental disorders, including autism, ADHD and schizophrenia.
The 22q11.2 deletion refers to the deletion that occurs near the middle of chromosome 22 at a location called q11.2, with an estimated prevalence of approximately 1:2000 to 1:4000 live births. Most 22q11.2 deletion carriers miss a sequence of about 3 million DNA building blocks (base pairs), containing 30 to 40 genes, while a small percentage of affected individuals have shorter deletions of 1,5 million base pairs in the same region. The function of many of these genes is not yet well characterized. The 22q11.2 deletion occurs most often as a random event during the formation of reproductive cells (eggs or sperm) or in early fetal development and is only inherited from a parent in approximately 10 % of the cases.

Besides the Institute for biological Psychiatry and DRCMR partners include:
Lundbeck, DTU Compute, Department of Applied Mathematics and Computer Science, Technical University of Denmark, the Center for Child- and Adolescent Psychiatry Bispebjerg, the Child and Adolescent Mental Health Center, Mental Health Services, Capital Region of Denmark, the Department of Pediatrics, Aarhus University Hospital and the Department of Clinical Genetics, Copenhagen University Hospital, Rigshospitalet.

Advanced modeling strategies such as so-called dynamic causal modeling will be employed to establish the dynamics of the functional brain networks that subserve MMN processing and identify how these dynamics may differ between 22q11.2 carriers and healthy controls.
In addition, the EEG protocol includes an auditory steady-state gamma entrainment paradigm to study cortical integration of information. This paradigm allows to test whether 22q11.2 deletion carriers show a reduced entrainment of gamma band activity, similar to patients with schizophrenia.

A translational perspective

The functional paradigms have been developed in close collaboration with researchers at Lundbeck. Here EEG is measured in 22q11 deletion and wild type mice during similar paradigms. Studies in mice allow for more detailed and interventional studies than possible in humans, and are paramount for identifying molecular targets for new treatments.

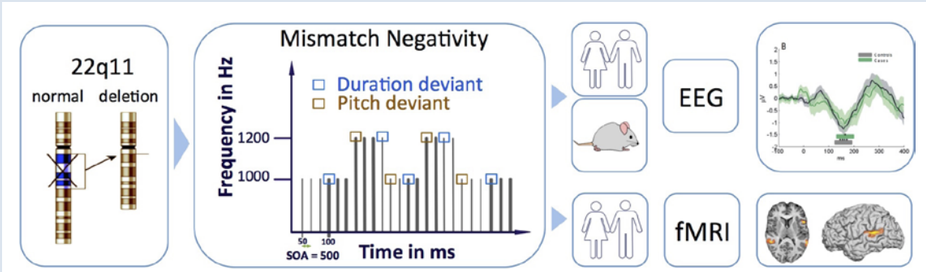


Figure 1: *The 22q11.2 project employs electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) to investigate neurophysiological signatures that have been related to schizophrenia, such as the mismatch negativity. Human carriers of a 22q11 deletion and healthy controls without a deletion are assessed with EEG and fMRI at the DRCMR, while 22q11 deletion mice and their controls are assessed with EEG at Lundbeck. The mice studies allow detailed mapping of deficits across multiple levels from altered behavior, anatomical and physiological changes to molecular disturbances and thus can inform human study results.*

PHD STUDENT WORKING ON PARKINSONISM RECEIVES PRESTIGIOUS PRIZE

PhD student Damian Herz received the Parkinson prize for young promising scientists for his research in 2013. The prize is sponsored by the Danish Parkinson Association every year to honour a young scientist who has made an outstanding scientific contribution in the field of Parkinson research. In his PhD project, Damian investigated the neural mechanisms underlying motor impairment in patients with Parkinson's disease (PD) who develop involuntary movements (dyskinesia) during long-term dopamine replacement therapy. The project was performed as collaboration between the Movement Disorders group at the Department of Neurology, Bispebjerg Hospital, University of Copenhagen and DRCMR.

"It has been a great pleasure to be part of this excellent collaborative research project conducted at the DRCMR and the Movement Disorders Clinic, Bispebjerg Hospital, University of Copenhagen with Damian Herz as an outstanding PhD student. In this project we investigated the neural mechanisms underlying the detrimental effects of dopamine replacement therapy in Parkinson's disease. This important and innovative project increased the knowledge on the debilitating involuntary movements that the majority of Parkinson patients develop because of dopaminergic treatment, and for which treatment options are scarce. The project generated new possibilities for future research, and the development of improved treatments, and provided an exemplary basis for the further collaboration between DRCMR and the movement disorders group at Bispebjerg Hospital, University of Copenhagen."
Associate professor Annemette Løkkegård, Copenhagen University Hospital Bispebjerg

Project: Functional MRI discloses the network dynamics of levo-dopa induced dyskinesia

PhD student MD Damian Herz; supervisors: Professor Hartwig Siebner, Associate professor Annemette Løkkegård, Senior researcher: Mark Schram Christensen, Kristoffer H. Madsen, in collaboration with Professor James B. Rowe, Cambridge

Levodopa-induced dyskinesia is hyperkinetic involuntary movements that result from chronic pharmacological treatment of Parkinson's disease and are triggered by the intake of levo-dopa. More than half of PD patients display levodopa-induced dyskinesia after 5–10 years of levo-dopa treatment and the percentage of affected patients, as well as the severity of dyskinesia steadily increase with disease duration. Levo-dopa induced dyskinesia most commonly occurs at the time of peak levo-dopa plasma concentrations. Treatment of dyskinesia is challenging and dyskinesia has very negative impact on the patient's quality of life. While recent years have made substantial progress in studying the molecular and cellular pathogenesis of levodopa-induced dyskinesia, studying its pathophysiology in humans remains a challenge because the dyskinesias cause substantial movement artifacts during brain imaging.

Damian Herz overcame this problem by adopting a novel neuroimaging strategy. Rather than scanning patients while they had dyskinesia, he performed neuroimaging in the time between levo-dopa intake and the actual manifestation of dyskinesia, thus in a time window where dyskinetic brain activity gradually built up in the motor networks but without being strong enough to produce involuntary movements. To investigate the neural mechanisms leading to the emergence of dyskinesia in PD, Damian mapped brain activity with functional MRI in PD patients with and without dyskinesia. Patients performed a task in which they had to perform or refrain from a button press depending on cues that were shown on a screen. Task-related brain activity was continuously recorded with functional MRI both after withdrawal of medication and immediately after intake of dopaminergic medication until dyskinesia emerged. The results showed an abnormal dopamine-induced increase in activity of the preSMA and bilateral putamen when a motor response had to be withheld preceding dyskinesia. These neural responses to dopamine predicted whether a patient would develop dyskinesia and how severe these would be even before dyskinesia emerged (Herz et al, 2014, Annals of Neurology). Furthermore, analysis of neural connectivity indicated that this neural response was mediated by an abnormal feedback signal from the putamen to preSMA (Herz et al, 2015, Brain).

Together, these results show that the putamen and the preSMA are centrally involved in the pathophysiology underlying PD. The function of these areas can be improved by dopamine replacement therapy. However, during progression of the disease these areas develop an abnormal response to dopamine, which results in the emergence of involuntary dyskinesia movements. In addition to improving our understanding of the mechanisms underlying PD and dyskinesias, the studies demonstrated putative neural targets for therapeutic approaches using non-invasive brain stimulation in PD.

Damian is currently a Marie Sklodowska-Curie fellow at the University of Oxford, where he is working on developing adaptive deep brain stimulation, a novel technique for the treatment of Parkinson's disease.

Photo 1: *Protector Countess Alexandra handing over the Parkinson prize for young promising scientists to Damian Herz. Photo kindly provided by The Danish Parkinson Association who sponsored the prize and photographer Nicola Fasano.*

THE LISTENING BRAIN – A NEUROIMAGING COLLABORATION BETWEEN DTU-ELECTRO AND DRCMR

Post-doctoral researcher Jens Hjortkjær, Professor Hartwig Siebner, Professor Thorsten Dau

The WHO estimates that more than 100 million individuals in the EU will be suffering from hearing impairment by the year 2020. Denmark holds a unique position in the global market for hearing aids with world leading companies in the field. The development of hearing aids and hearing rehabilitation strategies relies on an accurate characterization of auditory processing in the ear, but also on knowledge about how the brain adapts to the loss and restoration of sound perception. Ideally, a hearing aid works like eye-glasses that instantly restore vision, but this is often not the case. Many hearing-aid users complain that they are unable to follow conversations in noisy environments with many speakers. Simple amplification of sounds by a hearing aid does not necessarily help the listener to segregate sound sources from the background. This involves cognitive mechanisms that rely on brain processes that are still only poorly understood.

Oticon Centre of Excellence for Hearing and Speech Sciences (CHeSS) was established at DTU-Electro in 2013 and supported by the OTICON foundation. The centre is led by Professor Thorsten Dau and represents a collaboration between DTU Hearing Systems and DRCMR to furnish fundamental research in auditory neuroscience in Denmark. The collaboration combines research in psychoacoustics, computational modeling of the auditory system and neuroimaging.

"The collaboration with DRCMR has been central for CHeSS and particularly productive and successful" says Torsten Dau. "It has been exciting to develop ideas and new stimulation paradigms together to study the representation of complex sounds in the human brain – using the world leading imaging facilities available at DRCMR. The interaction with DRCMR indeed offers a number of new opportunities to test hypotheses about the mechanisms involved in the processing and perception of speech and music. I am enthusiastic about the perspectives of this collaboration – also beyond CHeSS".

Torsten Dau, professor at the Department of Electrical Engineering at the Technical University of Denmark, head of the Hearing Systems group, head of the Oticon Centre of Excellence for Hearing and Speech Sciences (CHeSS) and head of the Centre for Applied Hearing Research (CAHR).

A number of CHeSS projects have been launched to investigate auditory cognition and basic aspects of cortical sound processing. As part of the centre, new laboratory facilities have been established that allow the simulation of complex real-life acoustic scenarios inside the laboratory where controlled behavioral and neurophysiological measurements can be made.

One branch of research within CHeSS focuses on understanding how speech perception may be experienced as more or less effortful. Audiology traditionally measures speech perception in terms of the noise level where speech becomes unintelligible. But even in situations where all words of a spoken sentence are well recognized, the ability to recognize speech may require considerable mental effort. High levels of effort may over time result in fatigue, especially for hearing impaired individuals. Since different hearing impaired individuals may experience the same acoustic input as being more or less effortful, hearing aid settings can be adjusted based on how effortful an individual user experiences the sound. Combining neurophysiology and pupillometry, CHeSS researchers have investigated objective physiological correlates of listening effort in different acoustic conditions and under different kinds of cognitive load. Experimental findings indicate that increases in pupil size as well as changes in low-frequency neural oscillations correlate with mental processing load, suggesting that these measures may eventually be useful in clinical audiology.

Another focus has been to investigate training-dependent changes in the auditory system. While sound processing in the inner ear and the early auditory system eventually determines the maximal resolution of sound perception, it is known that extensive auditory training, such as musical training, leads to improved perception of speech in noise. One CHeSS research project uses fMRI and pupillometry to investigate how musicians may have superior cortical coding of pitch and how auditory receptive fields may undergo training-related plasticity.

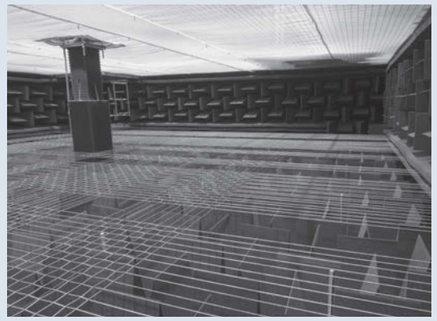


Photo 1: *Picture from the CHeSS audio-visual immersion laboratory at DTU-Electro. The lab offers unique possibilities for simulating real-world acoustic scenarios.*

An important area of CHeSS research focuses on auditory attention and the ways in which attention to a particular sound source affects the neural representation of that sound. With fMRI we investigate cortical responses to sounds from natural objects presented under different attentional contexts. Brain responses are obtained to the same sound but asking listeners to focus on different aspects of the sound, e.g. what action was performed or what material the sounding object is made of. Using advanced machine learning tools we analyze patterns of cortical activity that reveal how the brain selectively represents a given sound based on the attention of the listener. Using EEG recorded in sound environments where two or more speakers are talking simultaneously, we are also developing tools to analyze which talker a listener is attending to. These methods may eventually be used to control a hearing aid, so that the hearing aid selectively amplifies the signal from the talker that the user attends to.

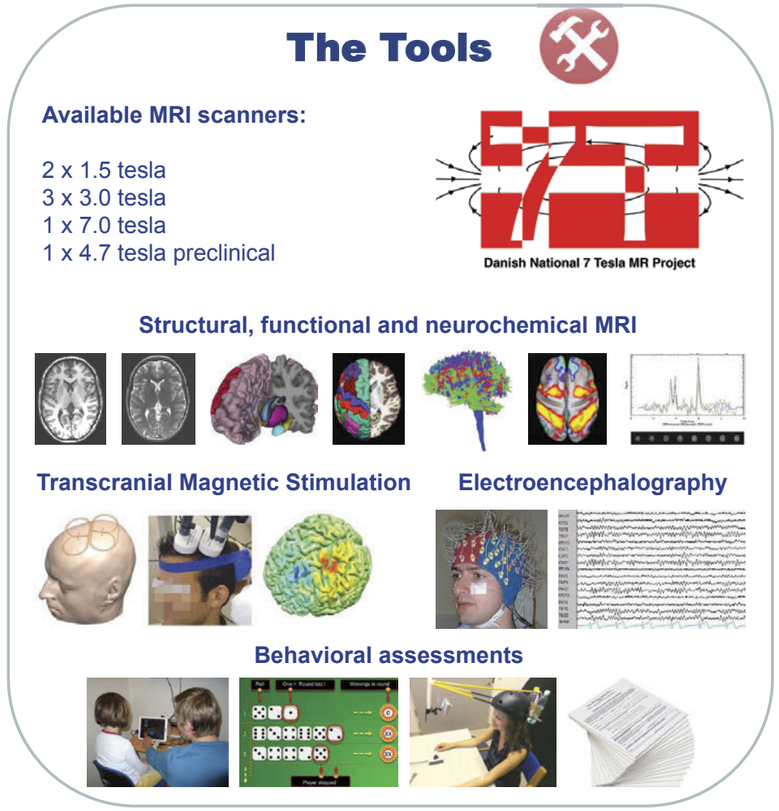
Photo 2: *Hartwig Siebner and Jens Hjortkjær with the new 3T research only scanner.*

An exciting and novel branch of research in CHeSS investigates the basic acoustic features that the brain uses in order to encode natural sounds. Unlike visual stimuli, sounds from many sources and locations typically arrive at the ears simultaneously. A natural sound signal like speech is characterized by fine-grained variations that must be represented by the brain with millisecond precision in order to decode the signal. Other sounds are complex 'textures' with many simultaneous sound sources, such as cocktail parties, traffic noise, birds chirping, or water flowing. Investigations of such texture sounds reveal statistical regularities that remain relatively constant over time. We find that we can create naturalistic sound textures based on these statistics suggesting that the brain may use this statistical information to encode complex sound textures in a highly compact and efficient way. Using fMRI, we investigate how such statistical properties of sounds are encoded by the brain. We show how the auditory cortex responds to particular statistical properties by directly manipulating these statistics in natural sounds.

CHeSS
Oticon Centre of Excellence for Hearing and Speech Sciences

RESEARCH AT DRCMR

DRCMR has for many years had a vigorous basic research program on MR methodology alongside both clinical and preclinical research programs. The centre's research activities thus range from the development of new hardware, software, and analises methods through research that leads to a better biological understanding of the healthy human body all the way to clinical research.
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.
The research at DRCMR has since 2009 been structured into a number of research groups. One or multiple research group leaders head each group. 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.
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) and the Center for Integrated Molecular Brain Imaging (CIMBI). These research groups and the research they conduct are also presented.



REWARD AND HOMEOSTASIS

The reward and homeostasis group is a new group formed in late 2013. We aim to address some apparently simple, but surprisingly difficult problems; why is it that only some things feel good? And why do they feel good only some of the time? How are reward values computed by the brain? And what function does this ultimately serve? The framework we work from makes one key assumption: The principal role of primary rewards is to shape behavior toward optimizing homeostatic states of the body, which in turn optimizes survival.
The work we do is thus partly theoretical and partly empirical. We seek to derive theories of reward that are grounded on fundamental principles of homeostatic dynamics and their evolution. We draw on concepts, tools, and results from a diversity of fields, including economics, ecology, physiology, and computational biology. We use these to build computational models of reward and homeostasis. From these models we derive falsifiable predictions for behavioral, physiological, and neural responses. In human subjects, we triangulate between computational modeling, fMRI, physiological monitoring, and economic behavior. And through ongoing collaborations with the Crick Institute, we are testing parallel predictions in animal models using opto- and pharmaco-genetics.
Experimentally, we focus primarily on variables such as glucose, hydration, and temperature. We take the strategy of manipulating central homeostatic states, to probe how these states are sensed, and how such states modulate reward computation. As such we are principally interested in homeostatic-reward interfaces in the brain, in particular the interface between the hypothalamus and the midbrain. Future work aims to test for reward-homeostasis dysfunctions in psychiatric and metabolic disorders.

Current group members

Senior researcher Oliver Hulme (group leader), PhD student Tobias Morville, Master student Magnus Koudahl.

RESEARCH ACTIVITIES

We are engaged in several ongoing theoretical projects. The first addresses how biological agents behaviorally optimise their own body temperature using reinforcement learning algorithms operating on homeostatic drive functions derived from physiological ecology data. The second formulates a general homeostatic theory of reward that conjectures how fundamental features of economic behavior can be unified into a single explanatory framework. The third attempts to formulate a generalized model of homeostatic dynamics, and to derive reward functions from first principles of fitness maximization.
In parallel we are pursuing several empirical projects that follow from this theoretical framework. First, we are currently acquiring functional imaging data of reward responses to the oral consumption of glucose and the modulation of these responses by blood glucose. Second, we are collaborating on parallel experiments in animal models that will test the same experimental protocol using calcium imaging, opto- and pharmaco-genetics in hypothalamic-midbrain networks. Third, following explicit predictions from homeostatic theory that contradict economic theory, we are testing risk preferences for costs, and their covariance with structural and connectivity brain data. Finally, we are testing reward responses to foods as a function of homeostatic state and metabolic interventions in gastric bypass patients.
Finally with the physics group at DRCMR we are implementing and developing selective excitation imaging sequences to probe the hypothalamic-midbrain regions that implement the interface between homeostasis and reward.

BRAIN MATURATION GROUP

Childhood and adolescence are critical developmental periods in human life shaping body, brain, and behavior and in which several psychiatric disorders have their debut. The research group focuses 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. The main projects are the HUBU (Hjernens Udvikling hos Børn og Unge) and the Cortisol project. The HUBU project longitudinally follows typically-developing children, while the Cortisol project investigates possible long-term effects of previous glucocorticoid treatment in children diagnosed with rheumatic or nephrotic disorder.
Homepage: http://drcmr.dk/Maturation

Group members

Senior Researcher William Baaré (Group leader), Postdoc Kathrine Skak Madsen (HUBU project leader), Professor Hartwig Siebner (Cortisol project project leader at DRCMR), PhD student Louise Baruël Johansen, PhD student Martin Vestergaard, PhD student Sara Krøis (DRCMR & Pediatric Clinic, Rigshospitalet), Professor Olaf B. Paulson (Neurobiology Research Unit, Rigshospitalet), Postdoc Arnold Skimminge, Master student Jonathan Holm-Skjold, Student Troels Lukassen, Professor Peter Uldall (Principal Investigator of the Cortisol project) and Senior Consultant Peter Born (Pediatric Clinic, Rigshospitalet).

External collaborators

Center for Integrated Molecular Brain Imaging (CIMBI), Copenhagen, Denmark (Prof. Gitte Moos Knudsen). Institute of Public Health, Department of Health Psychology, University of Copenhagen (Associate Prof. Erik Lykke Mortensen). DTU compute, Denmark (Dr. Mark Lyksborg). Center for Human Development, Department of psychiatry, and the Multimodal Imaging Laboratory, University of California, San Diego, La Jolla, California, USA (Prof. Terry Jernigan, Dr. Wesley Thompson, and Prof. Anders Dale). Oregon Health & Science University, Washington, USA (Damian Fair). Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands (Dr. Alexander Leemans).

RESEARCH ACTIVITIES

At its initiation in 2007 HUBU included 94 typical-developing children between 7 and 13 years of age. Participants were assessed 10 times with 6 months intervals. In December 2013, we completed the biannual 11th assessment (see Figure 2). Postdoc Kathrine Skak Madsen investigates the maturational patterns predictive of cognitive control, emotional regulation and hypothalamic-pituitary-adrenal (HPA) axis function. The PhD project of Louise Baruël Johansen concerns the relationship between the trait neuroticism and baseline and longitudinal graph theoretical measures of resting-state functional MRI networks. Medical student Troels Lukassen successfully finished his research year in July 2013 in which he investigated the relationship between physical activity and diffusion-weighted imaging measures of white matter fibre tracts of interest. Troels observed that in subjects carrying a met allele of the brain derived neurotrophic factor (BDNF) val66met (rs6265) polymorphism higher physical activity was associated with lower white matter mean diffusivity, while no significant effects were observed in the val/val homozygous children. Psychology student Jonathan Holm-Skjold successfully finished his master thesis on the link between white matter microstructure and outcome measures of the emotional Go/Nogo task, using data acquired in the 6th assessment. Jonathan found that better discrimination between negative and neutral face stimuli was linked to higher left relative to right fractional anisotropy (FA) in ventromedial prefrontal cortex (PFC) white matter. PhD students Martin Vestergaard and Sara Krøis finalised the data acquisition in the Cortisol project. Martin's thesis concerns neural and endocrinological correlates of previous glucocorticoid treatment with a focus on white matter tract microstructure and functional MRI during performance on a delayed matching-to-sample task using threat-associated stimuli. Sara's focus in her thesis is on the clinical, cognitive and behavioral as well as cortical and subcortical anatomical correlates of previous glucocorticoid treatment. Finally, in collaboration with Dr. Alexander Leemans we developed a robust method for extracting fibre tracts from longitudinally acquired diffusion weighted imaging data (see Figure 1).

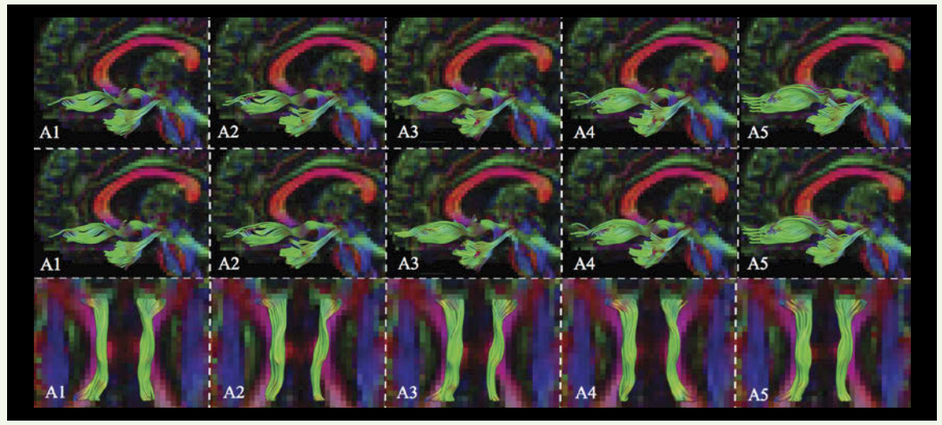


Figure 1: *Automated extraction of the forceps minor (top row), uncinate fasciculus (middle row) and body of the cingulum bundle (bottom row) using Automated longitudinal intra-subject analysis (ALISA) for diffusion MRI tractography for one subject at 5 time points.*

SELECTED PUBLICATIONS

- **Aarnink SH, Vos SB, Leemans A, Jernigan TL, Madsen KS, Baare WF.** Automated longitudinal intra-subject analysis (ALISA) for diffusion MRI tractography. Neuroimage. 2014;86:404-416.
- **Klarborg B, Skak Madsen K, Vestergaard M, Skimminge A, Jernigan TL, Baare WF.** Sustained attention is associated with right superior longitudinal fasciculus and superior parietal white matter microstructure in children. Hum Brain Mapp. 2013;34(12):3216-3232.

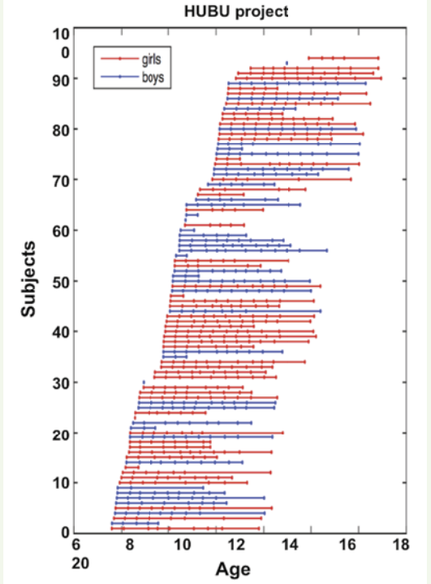


Figure 2: *HUBU sample composition and number of scans per subject. Each line represents a participant (N=94) and the circles on the lines represent a MR-scan (N=735). The ages of the participants are given on the x-axis.*

AGEING AND DEMENTIA

Advancing age is associated with increased risk of diseases such as Alzheimer's disease (AD) and cerebrovascular disease (CVD) but as recent research has shown even an ageing brain has a potential for preservation and plasticity. In the Ageing and Dementia Group we use MRI to characterize the richness in structural and functional reorganization occurring in the ageing brain in order to understand functional decline as well as functional well-being in ageing populations. For more than a decade the group has contributed to knowledge on structural as well as vascular changes on MRI with a particular interest in the impact of abnormalities in the cerebral white matter such as White Matter Hyperintensities (WMH) in ageing populations. Recent studies also include intervention studies on patients with Alzheimer's disease as well as large population-based cohorts. The group benefits from a close collaboration with the DRCMR Reader Center for the refinement and development of new methods for assessment of brain structures but also for optimization of procedures for MR-scanning of large cohorts.

Group members

Senior researcher Ellen Garde (group leader), Postdoc Nina L. Reislev, PhD student Christian Thode Larsen, Manager of Reader Center Pernille Iversen, Research technologist Sussi Larsen, Research radiographer Hanne Schmidt.

External collaborators

Professor Gunhild Waldemar, Memory Disorders Research Group, Department of Neurology, Copenhagen University Hospital Rigshospitalet, 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 Michael Kjær, Department of Clinical Medicine, Bispebjerg Hospital, University of Copenhagen, Professor Kaarin Anstey, Aging Research Unit, Australian National University, Associate professor Claudine Gauthier, Concordia University Montreal, Canada.

RESEARCH ACTIVITIES

Vascular brain aging

In 2013, Ellen Garde 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 a study identifying factors that moderate the trajectory of cognitive development and decline and the impact of cognitive ageing on brain changes in normal ageing was published.

A new and productive collaboration with Concordia University in Montreal investigated the impact of vascular degradation on brain structure and function in healthy younger and older adults. The results suggest that preservation of vessel elasticity may be one of the key mechanisms by which physical exercise helps to alleviate cognitive aging. Grant applications have been submitted to strengthen future collaborations.

As a continuation of the group's contribution to the LADIS ('LeukoAraiosis and DISability in the Elderly') study, a multi-centre, multinational longitudinal study involving more than 600 subjects, 2 further papers were published. Lead by the Research Centre for the Neurosciences of Ageing, Australia National University, the results support that in patients with WMH, caudate atrophy plays an important part of the frontostriatal circuit.

Physical activity in Alzheimer's Disease

In a nationwide intervention study assessing the effects of physical activity in patients with AD **(the ADEX study)**, the potential biological mechanisms and predictors for the effect of physical exercise in patients with AD were investigated. To comprehensively explore the restorative effects of physical training on brain structure and function MRI was performed in a subset of patients with AD. Data collection was finished in 2014 and in a collaboration with the Memory Disorders Research Group Rigshospitalet, the Technical University of Denmark, and the Martinos Centre, Boston, Massachusetts, Christian Thode Larsen completed the analysis of the 71 subjects using the segmentation tool FreeSurfer (Fig. 1) and results for regional brain volumes are currently tested in relation to clinical outcome measures. During a 7 months visit to the Martinos Centre, Christian developed a method for automatic correction of intensity inhomogeneity imaging artefacts also known as bias field or B_1-field inhomogeneity correction to be implemented in the FreeSurfer package.

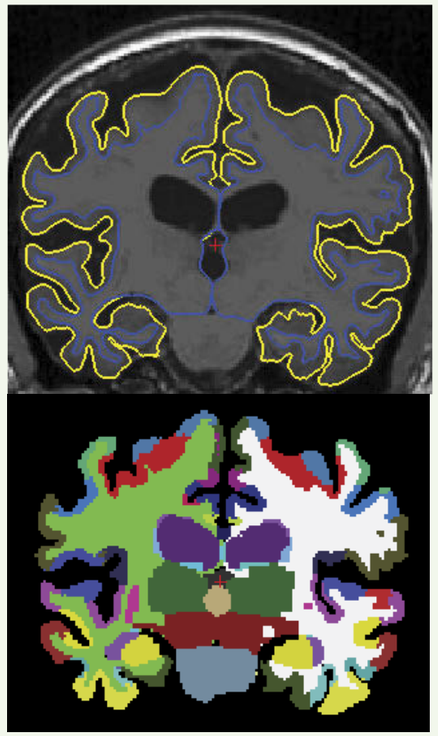


Figure 1: *T1-weighted MR-scan (coronal view) from the ADEX-study illustrating deliniation of grey matter (a) and segmentation (b) using FreeSurfer.*

Physical activity in healthy aging

In 2014, the collaboration with Centre for Healthy Ageing, and Bispebjerg Hospital, University of Copenhagen was initiated with a large cohort study, the **Live active healthy ageing (LISA) study**. In addition to physical and cognitive assessments performed at Bispebjerg Hospital, 2 MRI scans of the brain and thighs are performed at the DRCMR in order to analyze the effect of over one year moderate and high intensity physical training. MR-scanning of 450 community-dwelling healthy individuals aged 62–70 years began May 2014. Scanning is expected to be finished end of 2016.

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- **Anstey KJ, Sargent-Cox K, Garde E, Cherbuin N, Butterworth P.** Cognitive Development Over 8 Years in Midlife and Its Association With Cardiovascular Risk Factors. Neuropsychology. 2014 Jul;28(4):653-65
- **Gauthier CJ, Lefort M, Mekary S, Desjardins-Crépeau L, Skimminge A, Iversen P, Madjar C, Desjardins M, Lesage F, Garde E, Frouin F, Bherer L, Hoge RD.** Hearts and minds: linking vascular rigidity and aerobic fitness with cognitive aging. Neurobiol Aging. 2014 Aug 20.
- **Simonsen AH, Mattila J, Hejl AM, Garde E, van Gils M, Thomsen C, Lötjönen J, Soininen H, Waldemar G.** Application of the PredictAD Decision Support Tool to a Danish Cohort of Patients with Alzheimer's Disease and Other Dementias.Dement Geriatr Cogn Disord. 2013.Oct 26;37(3-4):207-213.
- **Habekost T, Vogel A, Rostrup E, Bundesen C, Kyllingsbaek S, Garde E, Ryberg C, Waldemar G Visual processing speed in old age.**Scand J Psychol. 2013, 54(2):89-94.
- **Macfarlane MD, Looi JC, Walterfang M, Spulber G, Velakoulis D, Crisby M, Orndahl E, Erkinjuntti T, Garde E, Waldemar G, Wallin A, Wahlund LO; LADIS Study Group.** Executive dysfunction correlates with caudate nucleus atrophy in patients with white matter changes on MRI: A subset of LADIS. Psychiatry Res. 2013 30;214(1):16-23

NEUROIMAGING IN MULTIPLE SCLEROSIS (NIMS)

Researchers at DRCMR have a long-standing interest in neuroimaging of multiple sclerosis. Multiple sclerosis (MS) is an inflammatory, demyelinating and neuro-degenerative disease causing widespread and diffuse tissue damage in the brain and spinal cord. This disease 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 allows for earlier and more accurate diagnosis of MS. However, there is generally a weak correlation between conventional MRI-based measures of MS lesion burden and clinical disability. To address this problem, the NEUROIMAGING in MULTIPLE SCLEROSIS (NiMS) group at DRCMR employs advanced MRI techniques with improved specificity and sensitivity to characterize the diffuse tissue damage and uncover the pathophysiological mechanisms of MS.
The group adopts a multimodal neuroimaging approach which comprises functional MRI, magnetic resonance spectroscopy (MRS), and diffusion weighted imaging (DWI), but also electrophysiological methods such as electroencephalography (EEG) and transcranial magnetic stimulation (TMS). The main goal is to develop more sophisticated imaging techniques and analyses to improve the sensitivity for detecting subtle disease related brain damage using new functional and structural MR measures.

Group members

Professor Hartwig Siebner (group leader).

Senior researchers and Postdocs: Kasper W. Andersen, Kristoffer H. Madsen, Ellen Garde, Pernille Iversen, Tim B. Dyrby, Henrik Lundell, Consultants Anne-Mette Leffers, Camilla Gøbel Madsen.

PhD students: Anne-Marie Dogonowski, Christian Bauer, Mark Lyksborg, Olivia Svolgaard.

Others: Hanne Schmidt, Sascha Gude, Sussi Larsen.

External collaborators

Professor Per Soelberg Sørensen, Professor Finn Sellebjerg, Morten Blinkenberg and other physicians from the Danish Multiple Sclerosis Centre, Department of Neurology, Copenhagen University Hospital Rigshospitalet, Flemming Roland Therkildsen. Faculty of Health and Technology, Metropolitan University College, Associate Professor Morten Mørup, Cognitive systems, DTU-Compute, Technical University of Denmark, Professor Christian Dettmers, Kliniken Schmieder, Konstanz, Germany.

RESEARCH ACTIVITIES

The NiMS group pursued several lines of neuroimaging research in MS, including studies on the blood-brain barrier dysfunction in normal appearing white matter (PhD project Henrik Lund) and the atrophy pattern of the upper cervical spinal cord (Ellen Grade and Henrik Lundell). A main focus was on examining how MS alters functional and structural brain connectivity and how such MS-related connectivity changes are related to clinical disability. Another very important part of the research in the NIMS group was the participation in several clinical therapeutic trials and the initiation of a comprehensive multi-modal brain mapping study, in which we aim at delineating abnormalities in brain function and structure that lead to fatigue in patients with MS (PhD project Olivia Svolgaard and Christian Bauer).

Finally, a highlight in 2014, was Postdoc Henrik Lundell receiving a "Sapere Aude" award by the Danish Council for Independent Research for a research project in which he will combine magnetic resonance spectroscopy with diffusion MRI to shed new light on the microstructural brain alterations caused by MS. This research will be conducted on the first ultra-high field (7T) MR scanner in Denmark, located at DRCMR.

Using resting-state functional MRI (rs-fMRI)

The NiMS group was able to identify distinct changes in functional connectivity in the motor resting-state network in a group of patients with relapsing-remitting or secondary progressive MS (PhD project Anne-Marie Dogonowski). We found that MS impairs regional functional connectivity in the cerebellum. At the brain network level, patients with MS showed a more widespread coupling of the basal ganglia with the motor resting-state network, indicating an impaired "funnelling" function of the basal ganglia in MS. Moreover, resting-state connectivity of pre-motor cortex reflected the degree of disability on the Expanded Disability Status Scale (EDSS). Using a novel neuroimaging approach called anatomical connectivity mapping we showed that these changes in functional connectivity were paralleled by a decrease in whole-brain anatomical connectivity in distinct white-matter regions related to the motor system.

Clinical trials in multiple sclerosis

In 2013 and 2014, the DRCMR acted as neuroimaging centre in a series of investigator-driven therapeutic trials, which tested the efficacy of new therapies in multiple sclerosis. All trials were initiated and conducted by the Danish Multiple Sclerosis Research Centre (DMSC), Rigshospitalet. The clinical trials are run under Reader Centre management (see the Reader Centre page 50).

MESEMS (Mesenchymal stem cells for multiple sclerosis) trial

We participate in a large international therapeutic trial on stem cell treatment in multiple sclerosis, called the MESEMS study. The local principal investigator is Roberto S. Oliveri at the stem cell section at the Dept. for Clinical Immunology Rigshospitalet and the sponsor is Professor Per Soelberg Sorensen (DMSC). The study is on-going and the DMSC is the site that included most patients so far. All participating patients are examined with MRI at DRCMR.

EPO study

In cooperation with the DSMC, we also performed a double blind, placebo-controlled study which was designed to assess the effects of high-dose

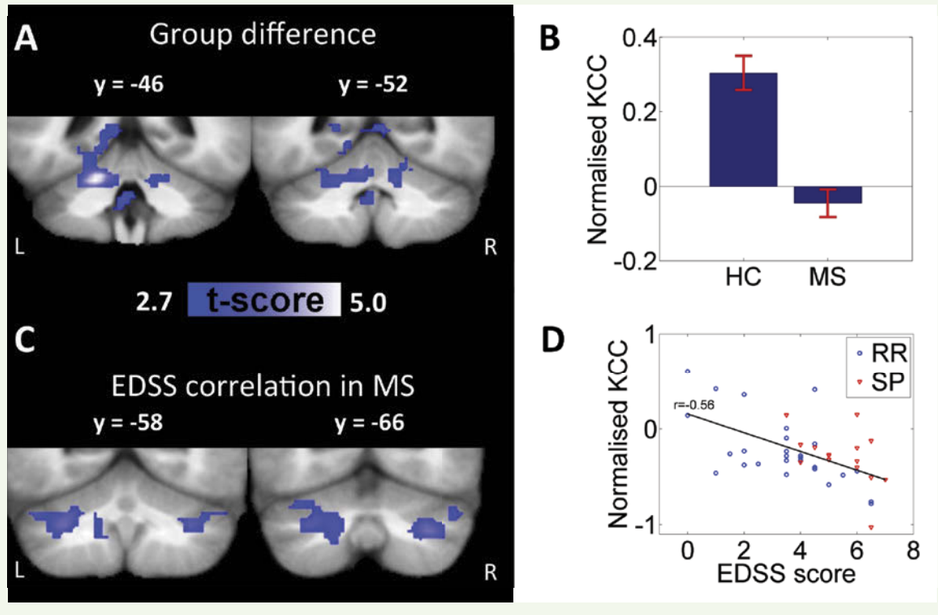


Figure 1: *A) Coronal slices showing areas in cerebellum where multiple sclerosis (MS) patients have reduced local functional connectivity, measured with Kendall's Coefficient of Concordance (KCC), compared with healthy controls (HC). B) Bar-plot showing mean and standard error of mean of the normalized KCC values in the cluster in left cerebellum, which survives correction for multiple comparisons (FWE<0.05). A similar cluster in right cerebellum reaches trendwise difference between HC and MS. C) Coronal slices showing areas where local functional connectivity correlates negatively with disease progression measured with the Expanded Disability Status Scale (EDSS). D) Scatterplot of EDSS score vs. normalized KCC in a cluster in left cerebellum showing significant correlation (FWE corrected). Similarly, a cluster in right cerebellum shows correlation at the trend level. (Plot adapted from Dogonowski et al, 2014).*

Erythropoietin (EPO) treatment on clinical disability and MRI detectable brain pathology in patients with progressive multiple sclerosis. EPO has previously been found to have neuroprotective effects in the brain and a variety of animal models have shown that EPO promotes axonal repair and birth of neurons. Based on this knowledge, it is hypothesized that EPO produces a therapeutic benefit in patients with progressive MS.

COMTiMS (Cyclic Oral Methylprednisolone trial in Multiple Sclerosis)

The COMTiMS study evaluates the efficacy and safety of treatment with cyclic oral methylprednisolone in MS. The EPO and the COMTiMS studies have been analysed and the results have been submitted for publication.

SIRPMS (Systemisk Inflammation hos Raske og Progressive MS patienter) study:

Several studies have previously linked smoking to an increased risk of debuting with progressive MS and to decrease the time to transition to the progressive phase in MS patients. In 2014 we became collaborators on the SIRPMS study, which investigates the effects of smoking on systemic inflammation and disease progression in progressive MS patients. This study is still ongoing.

Tackling motor fatigue

Fatigue is one of the most common symptoms in MS which has a tremendously negative impact on the patient's quality of life. The pathophysiology of the symptom is still largely unknown despite numerous studies exploring the immunological, metabolic, pharmacological, neurostructural and neurofunctional aspects of the symptom. To advance the understanding of fatigue and develop an objective way of measuring fatigue in MS, PhD students Olivia Svolgaard and Christian Bauer are conducting a multimodal imaging study using structural MRI, combined EMG, EEG and fMRI, gait analysis and dual-site TMS.

SELECTED PUBLICATIONS

- **Lund H, Krakauer M, Skimminge A, Sellebjerg F, Garde E, Siebner HR, Paulson OB, Hesse D, Hanson LG.** Blood-Brain Barrier Permeability of Normal Appearing White Matter in Relapsing-Remitting Multiple Sclerosis. Plos One 8. 2013;e56375.
- **Dogonowski AM*, Andersen KW*, Madsen KH, Soelberg Sørensen P, Paulson OB, Blinkenberg M, Siebner HR.** Multiple sclerosis impairs regional functional connectivity in the cerebellum. Neuroimage Clinical. 2103; 4:130-108. (* shared first authorship)
- **Dogonowski AM, Siebner HR, Soelberg Sørensen P, 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. 2013b; 19:559-566.
- **Dogonowski AM, Siebner HR, Soelberg Sørensen P, Paulson OB, Dyrby TB, Blinkenberg M, Madsen KH.** Resting-state connectivity of pre-motor cortex reflects disability in multiple sclerosis. Acta Neurol Scand 2013 Nov;128(5):328-35.

CARDIOVASCULAR IMAGING UNIT

The Cardiovascular Imaging Unit was established at the DRCMR in late 2012 as a co-operation between the Centre for Functional and Diagnostic Imaging and Research (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 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 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.

Group members

Consultant Jens D Hove (group leader), Chief consultant Claus Leth Petersen, Consultant Walter Bjørn Nielsen, Professor Hartwig Siebner, Senior Researcher Tim B Dyrby.

External member

Professor Andreas Kjær.

External collaborators

Professor Søren Møller, Professor Flemming Bendtsen, Professor Steen Madsbad, Consultant Klaus F. Kofoed, Consultant Niels Vejlstrup, Consultant John Greenwood, Leeds University Hospital, UK.

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 follow a cohort of patients with cirrosis and we plan to study the influence of obesity and diabetes mellitus and the effect of treatment with novel anti-diabetic drugs. Also, we have a study on patients diagnosed and treated for carcinoid tumours. We have a strong objective towards the development of novel cardiovacular magnetic resonance imaging (CMR) analysis tools and collaborate closely with several other DRCMR groups to achieve this goal. Perfusion studies and studies of myocardial fibrosis, and regional wall motion using strain imaging are under development.

NEUROIMAGING OF MOVEMENT DISORDERS

The Neuroimaging of Movement Disorders (NiMoDis) group is a joint research group of the Department of Neurology at Bispebjerg Hospital and the DRCMR at Hvidovre Hospital. The mission of the NiMoDis group is to use advanced brain mapping techniques to investigate how movement disorders alter brain function and structure in motor, cognitive and limbic brain systems. We are not only interested in studying primary dysfunction directly caused by the movement disorder but also secondary dysfunctions of brain networks that are associated with therapy. The research primarily focuses on Parkinson´s disease and dystonia.

Group members

Professor Hartwig Siebner (group leader) Consultants Annemette Løkkegaard, PhD student Brian Haagensen, PhD student Damian Herz, Research assistant Anne Kathrine Lorentzen, Student Silas Nielsen.

External collaborators

Professor Alexander Münchau, Head of Paediatric and Adult Movement Disorders and Neuropsychiatry Group; Institute of Neurogenetics, University of Lübeck, Professor Angelo Quartarone, Dept. of Neurosciences, Psychiatry and Anaesthesiological Sciences, University of Messina; Professor Bastiaan R. Bloem, Parkinson Centre Nijmegen, Department of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen Medical Centre, Nijmegen; Professor James Rowe, Behavioural and Clinical Neuroscience Institute, MRC Cognition and Brain Sciences Unit and Neurology Unit, Dept. of Clinical Neurosciences, University of Cambridge.

RESEARCH ACTIVITIES

Parkinson's disease results from a progressive neurodegeneration affecting multiple brain systems, manifesting as a spectrum of motor, cognitive and affective deficits. Degeneration of dopaminergic neurons in the substantia nigra causes the classical motor symptoms. We conducted a meta-analysis of functional neuroimaging studies which included fMRI or PET activation studies to study motor control in Parkinson´s disease. This meta-analysis yielded an interesting result, showing that the most consistent abnormality across studies was a blood oxygen level-dependent signal change in the posterior putamen. This finding has not been previously emphasized because the focus was on alteration in task-related cortical activation. Yet, our meta-analysis result makes a lot of sense because the posterior putamen is the key input structure for the cortico-basal ganglia motor loop and most severely affected by nigrostriatal neurodegeneration in Parkinson´s disease.

Is the reward system compromised in early Parkinson disease?

A commonly held notion is that the function of the reward system is relatively preserved at the clinical onset of the disease because nigrostriatal degeneration of dopaminergic neurons is less prominent in the ventral limbic territory of the striatum relative to the dorsal motor territory. PhD student Joyce van der Vegt used fMRI in newly diagnosed patients with Parkinson´s disease to test how much the reward system is already impaired at clinical disease onset. During fMRI, patients performed a simple two-choice gambling task. In patients with Parkinson's disease, the neural response to reward outcome as reflected by the blood oxygen level-dependent signal was profoundly attenuated in the entire reward system. This study provided clear evidence that the core regions of the meso-cortico-limbic dopaminergic system are already significantly compromised in the early stages of the disease. Since fMRI was performed before the start of dopamine replacement therapy, these deficits cannot be attributed to the contaminating effect of dopaminergic treatment.

Tracing the emergence of dyskinesia

In a collaborative research project conducted at the DRCMR and Movement Disorders Clinic, Bispebjerg Hospital, PhD student Damian Herz investigated the neural mechanisms underlying detrimental effects of dopamine replacement therapy in Parkinson's disease. The project focused on dopamine-induced dyskinesia, involuntary movements which the vast majority of Parkinson patients develop as a side-effect to dopaminergic treatment. The neural correlates of this side effect were largely unknown, because the involuntary movements heavily impair data quality during functional neuroimaging. To bypass this problem we developed a novel pharmacodynamic neuroimaging approach: We continuously acquired functional magnetic resonance imaging in Parkinson patients with and without dyskinesias directly after dopamine intake and before the emergence of dyskinesia movement, i.e. no dyskinesia were present during the scan. We then analysed the dynamic change in neural activity and connectivity preceding dyskinesia. We found that an area deep inside the brain (putamen) and an area at the surface of the brain (pre-supplementary motor area), two areas which are centrally involved in motor control, showed an aberrant response to dopamine in patients who later developed dyskinesia. Importantly, measuring these brain signals in the time period preceding dyskinesia allowed us to precisely predict whether an individual patient would develop dyskinesia or not and how severe these would be. The results have been published in Annals of Neurology. PhD student Damian Herz was awarded the Young Researcher Prize 2013 by the Danish Parkinson Association for his research. The study will be followed up by a new research project where we will investigate whether non-invasive brain stimulation of the pre-supplementary motor area can alleviate dyskinesia in patients suffering from Parkinson's disease.

SELECTED PUBLICATIONS

- **Herz DM, Eickhoff SB, Løkkegaard A, Siebner HR.** Functional neuroimaging of motor control in Parkinson's disease: A meta-analysis. Hum Brain Mapp. 2014; 35:3227-3237.
- **Herz DM, Haagensen BN,Christensen MS, Madsen KH, Rowe J, Løkkegaard A, Siebner HR.** The acute brain response to levodopa heralds dyskinesias in Parkinson's disease. Ann Neurol. 2014 Jun; 75(6):829-36. 2014
- **Van der Vegt JPM, Hulme OJ, Zittel S, Madsen KH, Weiss MM, Buhmann C, Bloem BR, Münchau A, Siebner HR.** Attenuated neural response to gamble outcomes in drug-naive patients with Parkinson's disease. Brain. 2013; 136:1192-1203.

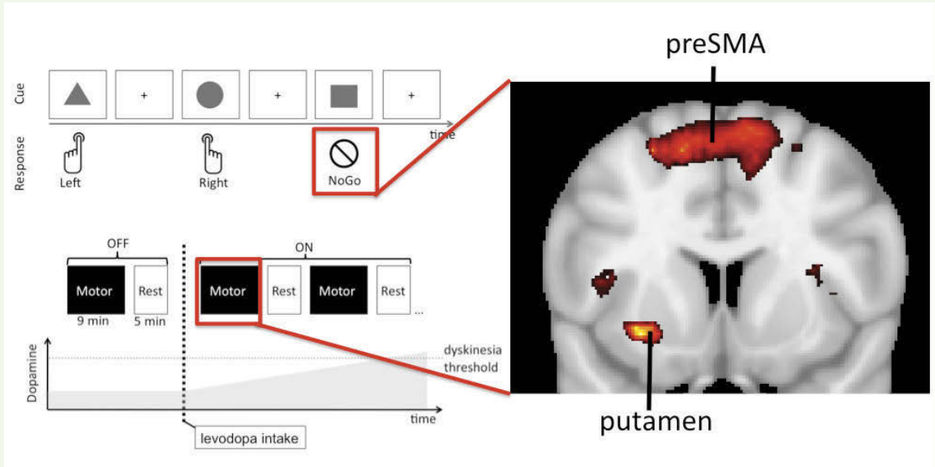


Figure 1: *Patients had to press a button on a computer mouse (Right or Left) or refrain from a response (NoGo) after dopamine withdrawal (OFF) and immediately after levodopa intake (ON), whilst fMRI was simultaneously acquired. Analysis of brain activity in the time period directly after levodopa intake and before the emergence of dyskinesias, showed overactivity of the preSMA and putamen in patients who later developed dyskinesias. This difference in brain activity was only observed when patients had to withhold a movement (NoGo). Furthermore, the extent of the abnormal brain response to levodopa predicted whether or not a patient would develop dyskinesias and how severe these would be.*

TRAUMATIC BRAIN INJURY

The Alterations in the Brain's Connectome after severe Traumatic Brain Injury ("ABC in TBI") project is carried out by an interdisciplinary group of researchers from the DRCMR and the Research Unit on Brain Injury Rehabilitation Copenhagen (RUBRIC). RUBRIC is administratively part of Rigshospitalet but placed at Hvidovre Hospital. The main aim of the project is to disentangle the brain structural and functional mechanisms that underlie the recovery of consciousness after a severe TBI. Using a multimodal brain mapping approach, we wish to identify predictive markers of recovery by prospectively comparing patients who recover and patients who do not recover from a TBI-derived disorder of consciousness. The "ABC in TBI" project is funded by three independent Danish funding agencies, namely the Danish Council for Independent Research, Lundbeck Foundation, and the research fund of the Capital Region of Denmark.

Group members

Professor Hartwig Siebner (principal investigator), Associate professor Lars P. Kammersgaard (principal investigator), Postdoc Ingrid Poulsen (group leader), Postdoc Tue H. Petersen, Postdoc Virginia Conde, MD, Senior clinical nurse Karen B. Larsen, Senior researcher Kristoffer H. Madsen, Senior researcher Tim B. Dyrby, MD Karina Madsen, PhD student Sara H. Andreasen.

External collaborators

Marcello Massimini, University of Milan, Jesper Mogensen, Copenhagen University, Lars Kai Hansen, Technical University of Denmark.

RESEARCH ACTIVITIES

TBI is considered one of the **most relevant causes of disability** in individuals under the age of 45 with an incidence of approximately 500/100.000 in Europe. The main aim of the *"ABC in TBI"* project is to shed light upon this major clinical problem by the use of **advanced neuroimaging and brain stimulation techniques**. During the last 15 years, functional brain mapping techniques have greatly expanded our knowledge of residual brain function after severe TBI and attracted considerable interest as a diagnostic and prognostic tool in TBI patients with disorders of consciousness (DOC). Two influential theories of consciousness, the Information Integration theory by Tononi et al., and the Global Neuronal Workspace theory of consciousness by Dehaene and Changeux, propose that consciousness **emerges from the integrated behavior of widespread cortical networks**.

Motivated by these theories, the *"ABC in TBI"* group studies how such widespread cortical networks rearrange and dynamically change during recovery from TBI with concomitant DOC. Using a cutting-edge multimodal mapping approach, the dynamics of cortical network changes during recovery are prospectively explored with **high-resolution structural, functional, and diffusion Magnetic Resonance Imaging (MRI)**. The goal is to trace macro- and micro-structural connectivity within and across cortical regions, as well as functional connections between relevant cortical regions such as the frontal and parietal cortices, believed to be part of an essential network for consciousness. Moreover, the property of the brain to transfer information across cortical regions has been suggested indispensable for the maintenance of high levels of consciousness and has been shown to be disrupted in patients with chronic TBI. Patients with TBI with lower levels of consciousness show a breakdown of directed connectivity, which is partially restored in patients with a higher level of consciousness.

The *"ABC in TBI"* group has recently implemented a novel multimodal technique which combines **Transcranial Magnetic Stimulation (TMS) with Electroencephalography (EEG)**, and which has been used by our external collaborator Marcello Massimini to assess information transfer and integration in patients with chronic TBI. TMS is capable of depolarizing neurons within a target cortical site, and such activation has been shown to transfer to distant cortical regions within few milliseconds, which can in turn be assessed with high-density EEG. Together with these modalities, different clinical assessment scales are used to measure level of consciousness and function. In contrast to prior studies, **patients are included in the "ABC in TBI" study during the sub-acute phase while their recovery is ongoing**. They are assessed at three time points during their in-patient stay at the TBI unit, with an additional assessment one year after their TBI incident. Under the main hypothesis of the dependence of consciousness recovery upon brain functional and neuroanatomical changes in patients with TBI, **this novel combination of neuroimaging techniques will dramatically improve the overall picture of the underlying mechanisms that subserve recovery from DOC**. Moreover, it will give a much finer and more precise perspective of potential markers predicting the outcome in DOC derived from the combination of multidimensional functional and anatomical consciousness correlates. The *"ABC in TBI"* group will moreover use this rich multimodal data set to significantly extend previously established brain connectivity metrics that are associated with the re-emergence of consciousness employing multivariate statistical analysis.

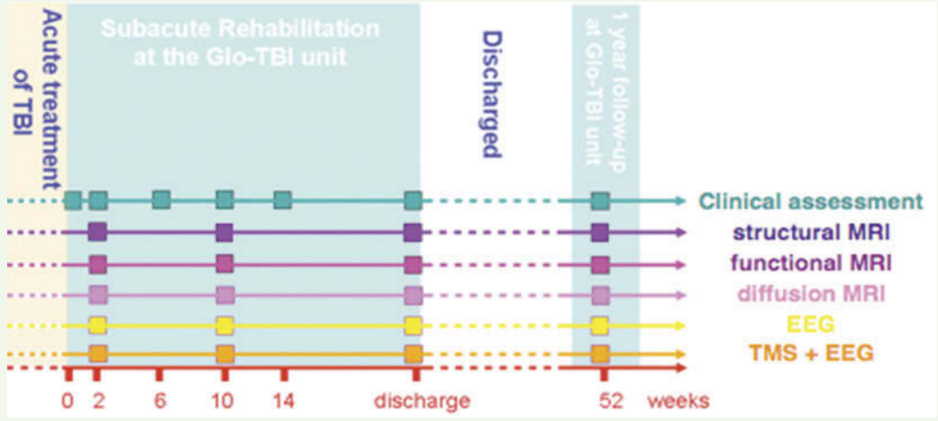


Figure 1: *Schematic representation of the longitudinal experimental time-line.*

THE PRECLINICAL RESEARCH GROUP

The Preclinical Research Group is a local core facility used mainly by the members of the Diffusion Imaging Group (DIG) and the Hyperpolarization Research Group (HRG) at DRCMR. We have student projects on MR physics as well as research collaborations with companies and other academic institutions. The overall aim is for better understanding and characterisation of healthy and diseased tissue, treatment effects and with advanced imaging technologies in focus.

Group members

Lise Vejby Søgaard (group leader)

It is with great regret that our dear group-leader Lise passed away in March 2014 due to sudden illness. All our thoughts are going to her husband and two children.

Senior researcher Tim B. Dyrby (group leader), Senior Researcher Peter Magnusson (HRG), Postdoc Henrik Lundell (DIG), Research Technologist Sascha Gude, Postdoc Helle M. Sickmann (DIG), Guest researcher Samo Lasic (DIG), PhD student Casper Sønderby (DIG), PhD student Mette H. Lauritzen (HRG), PhD student Abubakr Eldirdiri (HRG), PhD student Andreas Clemmensen (HRG), PhD student Kasper Lipsø (HRG).

External collaborators

Professor Jan Henrik Ardenkjær-Larsen, DTU; Professor Hans Stødkilde-Jørgensen, Aarhus University, Skejby Hospital; Dr. Mathilde Lerche, Albeda Research Aps; Dr. Niels Plath, H. Lundbeck A/S.

RESEARCH ACTIVITIES

Mette Hauge Lauritzen defended her PhD thesis entitled *"Imaging Cardiac Metabolism using Hyperpolarized [1-^{13}C]pyruvate MRS"*. She continued as a Postdoc on an industrial collaboration project where she used her expertise on heart imaging and hyperpolarised ^{13}C.

Two PhD-student projects have been initiated as part of the Hyperpolarization research group investigating new hyperpolarized substances, sequences and their application in e.g. cancer. Further, for the detection of cancer in ex vivo lymph nodes, a cross-disciplinary project for developing new hyperpolarized substances and imaging technologies, has been supported by the Advanced Technology Foundation (today: Innovation Fund Denmark).

For further information on research using hyperpolarization techniques, see HPG section.

In the Microstructural imaging projects using diffusion weighted imaging (DWI) Helle Sickmann has set up a prenatal stress animal model and used combined Diffusion Tensor Imaging (DTI) and the new advanced Neurite Orientated Dispersion and Density Imaging (NODDI) to understand how brain structure and network is impaired in stress-induced depression. Preliminary results show that FA is increased in the amygdala (involved in fear and anxiety) after exposure to prenatal stress. An average FA map of all ex vivo rat brains is shown in Figure 1. Marked with yellow is the basolateral part of the amygdala. The project was supported by The Advanced Technology Foundation and The Lundbeck Foundation.

Double diffusion encoding (DDE) is a novel DWI technique explored in DIG in collaboration with Sune Jespersen, CFIN, University of Aarhus, Denmark. DDE can be used to un-couple macroscopic effects i.e. non-straight axons that otherwise bias our microscopic estimates in DTI indices e.g. as known problematic in Fractional Anisotropy (FA). This new unbiased microstructural anisotropy measure is named Fractional Eccentricity (FE) or also micro-FA (μFA) (Jespersen et al 2013). DDE has also been used to estimate water exchange between different microscopic compartments. Casper Sønderby explored the implications of tissue complexity of this technique when applied to real neuronal tissue (Sønderby et al 2013). Samo Lasic, from the Swedish startup company CR Development, joined DIG in 2013 within the frames of a Marie Curie funded project and is exploring the perspectives for translation of these experimental novel techniques from preclinic to human in vivo applications.

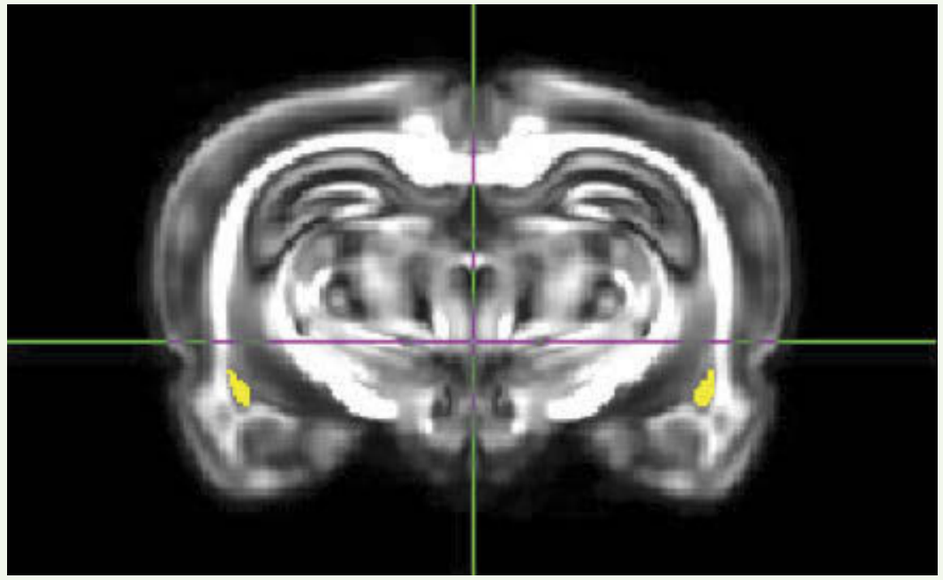


Figure 1: *Average FA map constructed from the 32 high-quality, high-resolution and multi-shell ex vivo diffusion MRI data sets of normal and prenatal stress rat brains. Marked with yellow is the basolateral part of the amygdala.*

SELECTED PUBLICATIONS

- **Jespersen SN, Lundell H, Sønderby KS, Dyrby TB.** "Rotationally invariant sampling of double pulsed field gradient diffusion: estimating apparent compartment eccentricity", NMR in biomedicine, 2013;26(12):1647-62
- **Lauritzen MH, Sogaard LV, Madsen PL, Ardenkjaer-Larsen JH.** "Hyperpolarized Metabolic MR in the Study of Cardiac Function and Disease", Curr Pharm Des. 2014 (ahead of print)

HYPERPOLARIZED MRI

With the aim of improved diagnosis and understanding of disease processes, the hyperpolarisation research group uses hyperpolarisation MR techniques for studying cell metabolism characteristics of disease.

Group members

Professor Jan Henrik Ardenkjær-Larsen (group leader), Senior Researcher Lise Vejby Søgaard, Associate professor Lars P.G. Hanson, Senior Researcher Peter O. Magnusson, Postdoc Mette H. Lauritzen, PhD student Abubakr Eldirdiri, PhD student Andreas Clemensen, PhD student Kasper Lipsø, Research Bio analyst Sascha Gude.

External collaborators

Dr Mathilde Lerche, Albeda Research Aps, Dr Pernille Rose Jenssen, Albeda Research Aps, Dr Magnus Karlsson, Albeda Research Aps.

RESEARCH ACTIVITIES

The focus of the group is on in vivo studies of cell metabolism of the heart in relation to diabetes, cancer, and on measurements of metabolism in ex vivo tissue samples.

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

All the metabolic products appear at different chemical shifts in the carbon MR spectra, and by acquiring spectra as a function of time it is possible to model the rate constants for the individual metabolic conversions. Chemical shift imaging can be used to map the spatial distribution of the different metabolites and thereby spatially locate differences in metabolic activity.

After defending her PhD thesis, Mette Hauge Lauritzen continued as a Postdoc on an industrial collaboration project with Novo Nordisk A/S where she used her expertise on heart imaging and hyperpolarised ^{13}C to study the effect on cardiac and kidney metabolism from treatment of type-2 diabetes with Liraglutide. Example results from hyperpolarized metabolic imaging of the rat heart are shown in Figure 1.

Histology of sentinel lymph node ex vivo tissue samples is used in clinical routine for diagnosis of breast cancer metastasis. This histological procedure requires time consuming sample analysis. 3D Magnetic Resonance Spectroscopic Imaging of a hyperpolarized compound can potentially speed up the diagnosis. In 2014, a collaboration with Albeda Research Aps company was initiated, where a MR method was developed by Peter Magnusson for an application that uses spectral under-sampling and that efficiently utilizes the hyperpolarized magnetization. The company Albeda Research Aps develops the substances. In a later stage, the project will be transferred to Skejby Hospital, Århus for the application to human samples.

Kasper Lipsø was comparing intra-arterial injection and intravenous injection of a hyperpolarized agent for cerebral angiography, where the performance of two standard angiographic pulse sequences; the gradient echo and the balanced steady-state free precession, were also studied.

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 strengths. 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.

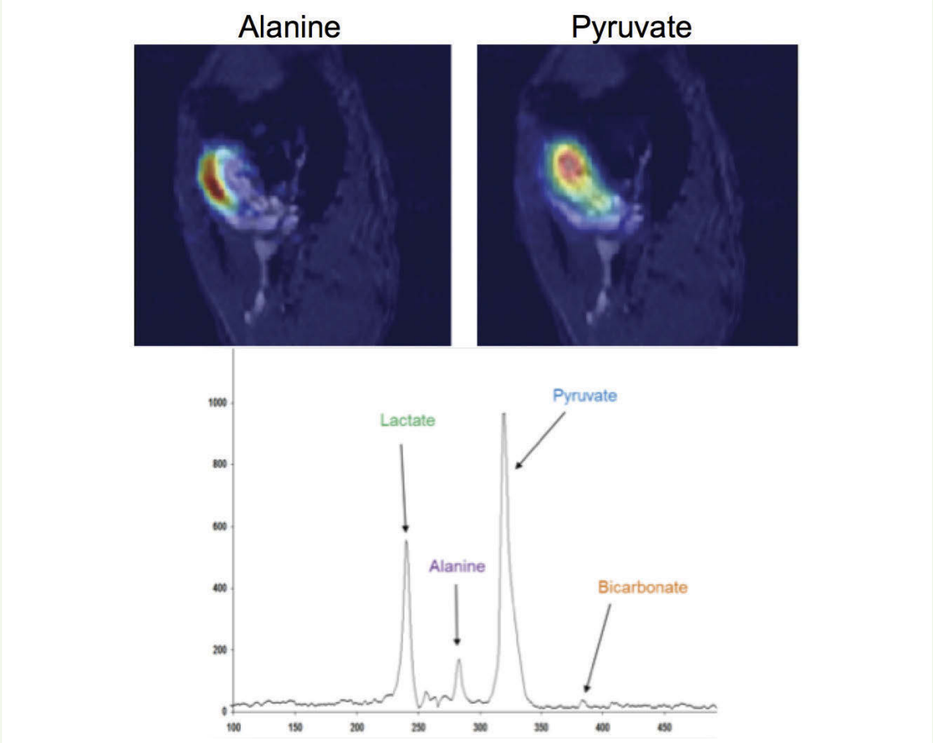


Figure 1: *Hyperpolarized ^{13}C metabolic imaging of the rat heart (top) and corresponding spectra of metabolites (bottom). Metabolite maps of Alanine and Pyruvate are displayed as overlay on corresponding structural images, demonstrating the myocardium specific Alanine metabolite signal (top left) and ventricle Pyruvate signal (top right).*

Andreas Clemmensen and Abubakr Eldirdiri have investigated the use of hyperpolarized pyruvate as a marker for detecting early treatment response in cancer. The results were compared to the current gold standard, FDG PET imaging, as well as other PET tracers, at Cluster for Molecular Imaging, Department of Biomedical Sciences, University of Copenhagen. A model of human lung cancer in mouse xenografts was used and the imaging results were validated using histological staining and molecular biology assays.

The hyperpolarization MR research was made possible through grants from the Lundbeck Foundation, Danish Heart Foundation, Hospital Hvidovre, The Spies Foundation, and Simon Fougner Hartmanns Familiefond.

SELECTED PUBLICATIONS

- **Asghar Butt S, Søgaard LV, Ardenkjaer-Larsen JH, Lauritzen MH, Engelholm LH, Paulson OB, Mirza O, Holck S, Magnusson P, Akeson P.** Monitoring mammary tumor progression and effect of tamoxifen treatment in MMTV-PymT using MRI and magnetic resonance spectroscopy with hyperpolarized [1-13 C]pyruvate, Magnetic Resonance in Medicine, 2015; 73(1):51-58
- **Lauritzen MH, Laustsen C, Butt SA, Magnusson P, Søgaard LV, Ardenkjær-Larsen JH, Åkeson P.** Enhancing the [^{13}C] bicarbonate signal in cardiac hyperpolarized [1-^{13}C] pyruvate MRS studies by infusion of glucose, insulin and potassium, NMR in Biomedicine, 2013; 26(11): 1496-1500

MR PHYSICS

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 performance with respect to robustness, speed, sensitivity or specificity. Another focus of the group is education in MR physics and methodology needed for designing and interpreting MR studies.
Homepage: http://drcmr.dk/acquisition

Group members

Associate professor Lars G. Hanson (group leader), Senior researcher Lise Vejby Søgaard, Senior researcher Peter Magnusson, Senior Researcher Kristoffer H. Madsen, PhD student Mads Andersen, PhD student Jan Ole Pedersen, Student Jeppe Andreasen, Student Søren Bohøj.

RESEARCH ACTIVITIES

The 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. Some group member activities are described in other sections of this report, for example concerning multiple sclerosis and hyperpolarization.
Mads Andersen conducts a PhD project on motion induced field changes in collaboration with the Biomedical Engineering group at DTU Elektro at the Technical University of Denmark. The project is supported financially from Radiometer Medical and The Danish Council for Technology and Innovation. Breathing induced dynamic field perturbations in the head cause problems for high field MR, e.g. line broadening in spectroscopy as well as signal dropout, ghosting, displacement artifacts and blurring when imaging other modalities. It has previously been proposed to continuously stabilize the magnetic field by real-time updating of the shim fields based on synchronous field measurements with external probes, but there is a need for a thorough analysis of how accurate such field measurements at few positions outside the head can reflect the spatially varying dynamic fields in the brain. A study was conducted by Mads Andersen, Kristoffer Madsen and Lars Hanson together with researchers from Leiden University Medical Center and University Medical Center Utrecht. Scanner-acquired field maps of the head and corresponding field probe measurements were compared during inhalation and exhalation (see figure 1). In addition, the field probe measurements were used to perform real-time updating of the linear shim-settings. The study was conducted in connection with Mads' half year stay in Leiden, and showed that there are significant gains of probe-based field stabilization during breathing.
Mads was also involved in a successful MSc project by Søren Bohøj establishing scanner updating to compensate motion.
Peter Magnusson finished the morphometric and spectroscopic analysis in a study funded by the Lundbeck Foundation concerning the effects of electroconvulsive therapy and conducted in collaboration with clinicians and researchers at Rigshospitalet and Stony Brook Medicine, New York. Clear effects were found, and publication is pending.
A number of student projects were conducted in collaboration with Biomedical Engineering at DTU Elektro, for example, addressing quantitative MRI, scanner power consumption, non-equidistant sampling, motion tracking/correction, and establishing and using phosphorous and proton muscle spectroscopy. The latter included a study of kayak rowers conducted by Lise Vejby Søgaard, Jeppe Andreasen and Lars Hanson in collaboration with Department of Nutrition, Exercise and Sports at the University of Copenhagen.
The first ESMRMB course on MRI Simulation was arranged in Bonn 2013, with Tony Stöcker and Lars Hanson as main organizers. MR simulations based on the Bloch equations developed by Lars Hanson

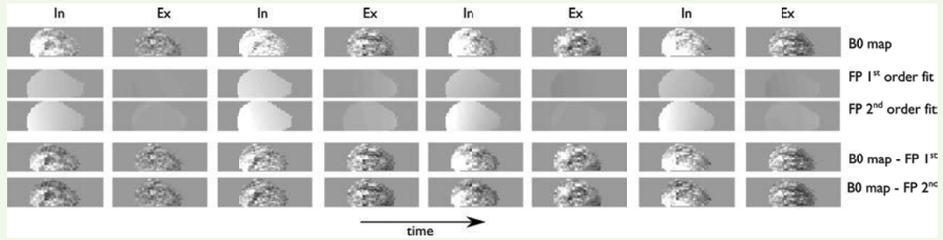


Figure 1: *The figure shows the dynamic field changes in a sagittal slice of a volunteer. Field probe fits, field maps measured by the scanner, and corrected field maps are shown for the case of fitting fields up to first and second order.*

are of high educational value, and further serve as essential tools in basic MR method development, sequence design and protocol optimization. 40 participants attended and the course was well received, so a repeat was planned in Copenhagen, 2015. Lars was also the main organizer of the technical part of the MR Basics course for the Danish Society for Medical Magnetic Resonance, DSMMR, 2014. Two days of lectures were organised with Birgitte Kjølby, Aarhus University Hospital, and Janus Damm, Bispebjerg Hospital. Lectures were organised with a number of courses in the Medicine and Technology education line at DTU, and in Beijing for the Advanced MRI course in the neuroscience education offered by the Sino-Danish Center, SDC. The latter university collaboration led to the initiation of a PhD study by Jan Ole Pedersen late 2014, supervised by Lars Hanson together with Professor Rong Xue at the Chinese Academy of Sciences, and Associate professor Vitaliy Zhurbenko, DTU Elektro. The study is sponsored by the SDC and DTU Elektro.
Considerable efforts went into establishing the national 7T facility at the DRCMR. Group activities are now being directed towards techniques of particular relevance for ultra-high field, e.g. motion correction and compensation of inevitable field imperfections.

SELECTED PUBLICATIONS

- **Andersen M, Madsen KH, Hanson LG, Boer V, van der Velden T, Wezel J, von Osch M, Versluis M.** Mapping and correcting respiration-induced field changes in the brain using fluorine field probes. Proceedings of the Joint Annual Meeting ISMRM-ESMRMB, 2014, 1391.

DIFFUSION IMAGING GROUP

The Diffusion Imaging Group (DIG) has become internationally acknowledged for developing novel MRI sequence designs for diffusion weighted imaging (DWI) technologies and for their translational novel experimental approaches for getting insight into and the application of tractography technologies for non-invasively mapping of the brain network. The DWI imaging technique detects the random motion of water molecules as probes for mapping microstructural features in tissue, today only visible with histology. Such features could be cell density and geometrical properties like cell sizes e.g. axons, the spatial organization and direction of neuritis as well as cell membrane permeability. We seek to merge the microstructural features onto brain connectomics in a translational approach for getting new detailed insight into brain plasticity in the healthy and diseased brain.
Homepage: http://dig.drcmr.dk

Group members

Senior researcher Tim B. Dyrby (group leader), Postdoc Henrik Lundell, Postdoc Nina L. Reislev, Guest researcher Samo Lasic, Postdoc Kasper W. Andersen, Postdoc Helle Sickman, PhD student Karen S. Ambrosen, PhD student Christian Bauer, PhD student Christian Skoven.

RESEARCH ACTIVITIES

From DIG two PhD theses have been defended in 2013-2014: Nina L. Reislev used tractography in her PhD project to investigate microstructural plastic alterations to brain connections in the congenitally blind, the late blind, and the healthy human brain. Kasper W. Andersen combined functional imaging techniques with tractography in his PhD project to explore the relation between functional brain communities and structural connections in the human brain.
We continuously improve our unique ex vivo imaging setup of postmortem brain tissue for obtaining very high image resolution and quality dataset, which today is the backbone of our basic research projects of novel diffusion weighting experiments (Dyrby et al., 2011). An example is "non-invasive histological MRI" where a type of sequence design named oscillating gradient spin echo (OGSE) enable a direct cell type and cell density contrast in our raw MRI data. Henrik Lundell extended this sequence design and introduced the circularly polarized OGSE (CP-OGSE), which enhances the sensitivity and gives this technique better potential for human clinical applications (Lundell et al., 2015).
We have investigated whether interpolation of the raw diffusion MRI data to higher image resolution improves the anatomical details in DTI as if data were acquired in higher image resolution (Dyrby et al. 2014.). The interpolation method used does have an impact on the finer anatomical details visible in DTI. Interpolation does reveal anatomical features, with the effect mostly seen in the details, and pitfalls do exist. Interestingly, we found that interpolating the diffusion tensor improves over the interpolation of raw data.
Probabilistic tractography is used in the generation of brain connectomics to non-invasively visualize the brain network. However, there is an increasingly burning question whether the tractography method used introduce a bias dependent on the length of individual connections i.e. path-length dependency (PLD). Tim B. Dyrby and Matthew G. Liptrot demonstrated and quantified the existence of such unwanted PLD effect and showed that it is a non-linear effect. The ICE-T framework is presented as a wrapper around existing tractography methods to reduce the PLD effect (Liptrot et al., 2014).
The new human 7T facility at DRCMR brings new potential for exploring tissue microstructure. In 2014, Henrik Lundell started his Postdoc project on diffusion weighted spectroscopy (DWS) of healthy individuals and patients with multiple sclerosis. DWS combines the cell specificity of magnetic resonance spectroscopy with the sensitivity to geometrical changes of diffusion weighting. This project is a collaboration with professor Itamar Ronen at Leiden University Medical Center, The Netherlands, and has been awarded a Sapere Aude award from the Danish Research Council for Independent Research.

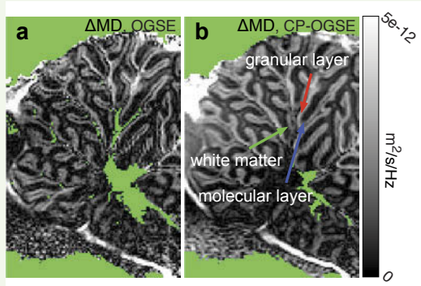


Figure 1: *When using standard Oscillating gradient Spine Echo (OGSE) (a) compared with the introduction of our novel Circular-Polarized OGSE (CP-OGSE) sequence (b). The novelty of CP-OGSE is that two independent diffusion weighting gradients are applied at the same time and thereby enable a stronger diffusion weighting for a given diffusion time than compared with standard OGSE. It is therefore possible to obtain higher quality images with finer anatomical details e.g. the molecular layers. Figure from Lundell et al. 2015.*

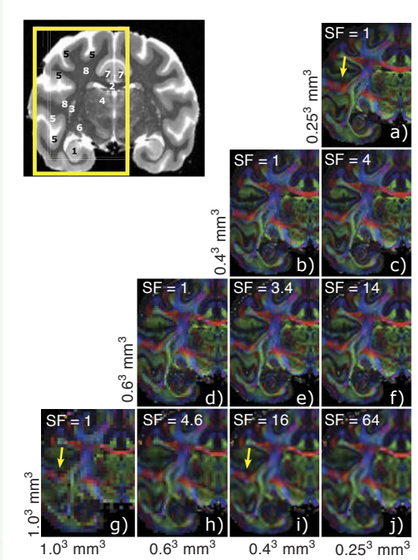


Figure 2: *Investigation of the effect of interpolating the raw diffusion MRI dataset before reconstruction. Interpolation of the raw diffusion weighted MRI with sampling factors (SF) where SF of 1 is the same as keeping the original image resolution. Data set in different image resolutions (SF=1) has been acquired as shown for each column. The data set is collected on postmortem monkey brains obtained from the Montreal brain bank. The colors show color-coded fractional anisotropy (FA) maps where red: right-left; green: in-plan and blue: up-down fibre direction. Figure from Dyrby et al 2014.*

SELECTED PUBLICATIONS

- **Assaf Y, Alexander DC, Jones DK, Bizzi A, Behrens TE, Clark CA, Cohen Y, Dyrby TB, Huppi PS, Knoesche TR, Lebihan D, Parker GJ Poupon C and CONNECT consortium.** "The CONNECT project: Combining macro- and micro-structure.", Neuroimage, 2013;80:273-82
- **Lundell H, Sønderby CK, Dyrby TB.** "Diffusion weighted imaging with circularly polarized oscillating gradients", Magnetic Resonance in Medicine, 2015;73(3):1171-6
- **Dyrby TB, Lundell H, Burke MW, Reislev NL, Paulson OB, Ptito M, Siebner HR.** "Interpolation of diffusion weighted imaging datasets", Neuroimage, 2014;103:202-13
- **Liptrot MG, Sidaros K, Dyrby TB.** "Addressing The Path-Length-Dependency Confound In White Matter Tract Segmentation", PlosOne, 2014; 9 (5), e96247

COMPUTATIONAL MODELLING AND ANALYSIS GROUP

The computational modelling and analysis group at DRCMR is engaged in research, development and application of advanced modelling and data analysis techniques suited for neuroimaging data. The efforts within this group strive to improve sensitivity and interpretability of the vast amounts of data that are acquired with neuroimaging techniques.
Homepage: http://www.drcmr.dk/modelling

Group members

Senior researcher Kristoffer H. Madsen,
Postdoc Kasper W. Andersen, PhD student
Brian Numelin Haagesen

RESEARCH ACTIVITIES

The computational modelling and analysis group provides infrastructure, education and engages in data modelling and analysis tasks, which are important for many projects at DRCMR. Furthermore, the group is involved in the development of novel data modelling and analysis techniques with applications in neuroimaging. These efforts are mainly focussed on multivariate modelling techniques for assessment of functional brain connectivity.

Traditional analysis of functional magnetic resonance imaging (fMRI) data involves inferring brain activity for each volume element (voxel) individually using a so-called mass univariate approach. However, since the brain is one gigantic neuronal network, there's an increasing interest in modelling how brain regions interact, both during task conditions and at rest. We are collaborating with the cognitive systems group at DTU Compute in developing new models, which build upon graph theoretical approaches and machine learning.

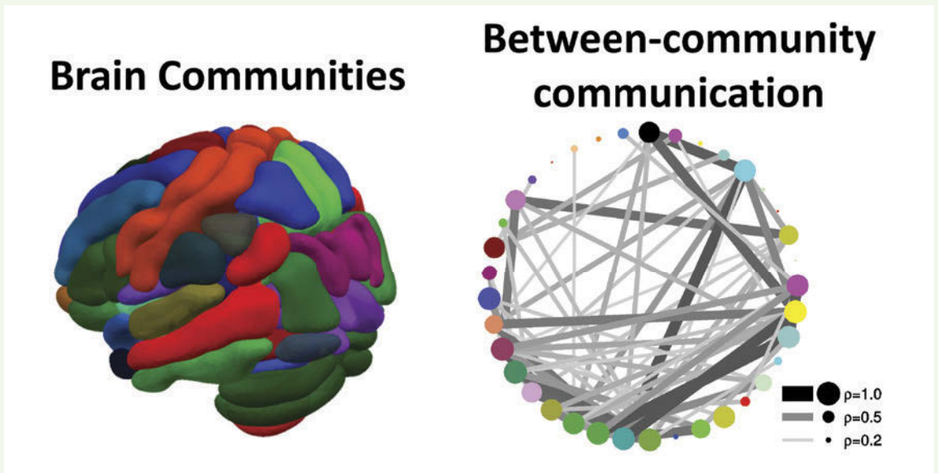


Figure 1: *The left figure illustrates how brain regions can be functionally clustered according to a community model based on fMRI data recorded at rest. The right figure shows the estimated connectivity between and within each of the communities.*

Here, the brain is considered as a network where each brain region interacts with other brain regions according to the functional connectivity between the brain regions. We investigate different models for grouping brain regions into clusters according to the connectivity to other brain regions. Here we found that resting state brain networks are best captured with models, which adhere to the definition of community structure. Meaning that connections within clusters are more common than connections between clusters of brain regions.

We also found that it is important to consider separate connection strengths between clusters, as compared to having fixed connectivity strength shared between all clusters, as this increases both reproducibility and predictability of the models.

In addition to modelling functional connectivity alone we also developed a novel methodology aiming at jointly modelling both functional and structural connections. In this framework structural connections between brain regions are estimated based on diffusion weighted imaging. So far the results from this modelling approach indicate that the expression of networks derived from the two modalities are too different to directly benefit from shared modelling. We attribute these differences mainly to dissimilar methodical limitations of the imaging techniques respectively.

Dynamic causal modelling (DCM) is an example of a model of effective brain connectivity that can be applied to fMRI data. Due to the computational complexity DCM is mainly useful for investigating connectivity between a few key brain regions. For example Brian Numelin Haagesen applied DCM investigating how inhibitory connections are graded when subjects are engaged in making decisions at varying risk-levels. It was found that the subthalamic nucleus increases its connectivity with prefrontal cortex with rising risk. In addition, the coupling between the subthalamic nucleus and the pre-supplementary motor area (pre-SMA) was stronger in more risk-averse individuals.

SELECTED PUBLICATIONS

- **Andersen KW, Madsen KH, Siebner HR, Schmidt MN, Mørup M, Hansen LK.** Non-parametric Bayesian graph models reveal community structure in resting state fMRI. NeuroImage, 2014;100:301–315.
- **Dogonowski A-M, Andersen KW, Madsen KH, Sørensen PS, Paulson OB, Blinkenberg M, Siebner HR.** Multiple sclerosis impairs regional functional connectivity in the cerebellum. Neuroimage clinical, 2013;4.
- **Nejad AB, Madsen KH, Ebdrup BH, Siebner HR, Rasmussen H, Aggernæs B, Glenthøj BY, Baaré WFC.** Neural markers of negative symptom outcomes in distributed working memory brain activity of antipsychotic-naive schizophrenia patients. Int J Neuropsychopharmacology 2013;16:1195–204.

INTEGRATIVE NEUROSTIMULATION AND NEUROIMAGING

The Integrative Neurostimulation and Neuroimaging (INN) group has a *neuroscientific* focus on sensorimotor integration and motor control. We are interested in the patterns of functional brain connectivity that evolve during the performance of sensorimotor tasks. To this end, we employ the online combination of transcranial magnetic stimulation (TMS) with functional MRI (fMRI) as a cutting-edge tool to causally test brain connectivity. This is complemented by a strong and internationally leading methodological research focus on the biophysics of non-invasive brain stimulation (NIBS). The goal is to make NIBS spatially more specific and to shed light on its neural mechanisms. This will help to make the effects of NIBS better predictable and stable both in neuroscientific research and clinical applications.

Group members

Senior researcher Axel Thielscher (group leader), Postdoc Johannes Stelzer, PhD student Cihan Göksu, PhD student Sofie Johanna Nilsson, Student Tahnée Engelen, Student Sena Minjoli, Intern Guilherme Bicalho Saturnino.

RESEARCH ACTIVITIES

Building on prior research of Axel Thielscher (Moisa et al., 2012), **Sofie Johanna Nilsson** and **Tahnée Engelen** conducted the first study at DRCMR based on the online combination of TMS with fMRI (Fig. 1A). The study was performed in collaboration with Hartwig Siebner and the ContAct research group. We were interested to see how the motor network adapts when the probabilities change that a movement has to be initiated versus inhibited. A Go/NoGo paradigm was used in which a pre-cue signaled the likelihood of a subsequent Go. Preliminary results indicate that changing likelihoods for a movement are reflected in the connection strengths between the premotor areas involved in preparing the response and areas of the "inhibition network".

We employ a comprehensive approach to characterize the biophysics of NIBS, built upon realistic field calculations and MRI-based head models (Fig. 1B). In order to further increase the accuracy of the estimated fields, **Johannes Stelzer** worked on an improved modeling of the skull based on low-dose computer tomography. **Guilherme B. Saturnino** contributed largely to an improved version of our open-source software for NIBS with enhanced functionality and usability (www.simnibs.org; Thielscher et al., 2015). In addition, he characterized the field distributions generated by weak direct current stimulation (Saturnino et al., 2015). His findings helped to rectify some of the conclusions drawn from prior simplified modeling approaches. We further expect the findings to have a clear influence on how tDCS is performed in practical experiments (Fig. 1D). **Sena Minjoli** characterized the field distributions of NIBS in stroke patients and demonstrated substantial differences to those in healthy participants (Fig. 1C). This suggests that NIBS may require substantial modifications before it will be effective in stroke populations. Ensuring the accuracy of the employed field calculations is a major challenge to validate the predictions derived from the biophysical models. **Cihan Göksu** started to implement novel methods for phase-sensitive MRI to allow for highly sensitive non-invasive measurements of the current flow patterns. This work is done in collaboration with Lars G. Hanson (MR physics). Along similar lines, a new method to get accurate field characterizations for TMS stimulation coils was developed together with Kristoffer H. Madsen (computational analysis and modelling).

EXTERNAL COLLABORATIONS

In a collaboration with Uta Noppeney, University of Birmingham, UK, we employed combined TMS-fMRI to explore the brain networks underlying multisensory integration (Leitão* et al., 2013). The INN group had intense interactions with Andre Antunes and Andreas Bungert, Max-Planck-Institute for Biological Cybernetics, Germany, Anders Korshøj and Jens Hedemann Sørensen, Aarhus University, as well as Alexander Opitz (Nathan Kline Institute for Psychiatric Research, USA; Opitz et al., 2015) on the development, application and validation of our NIBS modeling pipeline.

FUNDING

The INN group received funding by a project grant from the Lundbeck Foundation. End of 2014 we received major funding in form of an interdisciplinary synergy grant "BASICS" (biophysically adjusted state-informed cortex stimulation) from the Novo Nordisk Foundation together with Hartwig Siebner (Main PI) and Lars Kai Hansen, DTU Compute. We are excited about the possibilities opened up by BASICS.

SELECTED PUBLICATIONS

- **Leitão* J, Thielscher* A, Werner S, Pohmann R, Noppeney U.** Concurrent TMS-FMRI provides a multisensory perspective on TMS effects on unisensory processing at the primary cortical level. Cerebral Cortex. 2013; 23, 873-884. *equal contribution
- **Moisa M, Siebner HR, Pohmann R, Thielscher A.** Uncovering a context-specific connectional fingerprint of human dorsal premotor cortex. J Neurosci. 2012; 32, 7244-7252.
- **Opitz A, Paulus W, Will S, Antunes A, Thielscher A.** Determinants of the electric field during transcranial direct current stimulation. Neuroimage. 2015; 109, 140-150
- **Saturnino GB, Antunes A, Thielscher A.** On the importance of electrode parameters for shaping electric field patterns generated by tDCS. Neuroimage accepted. 2015
- **Thielscher A, Antunes A, Saturnino GB.** Field modeling for transcranial magnetic stimulation: a useful tool to understand the physiological effects of TMS? Annual International Conference of the IEEE Engineering in Medicine and Biology Society 2015, Milan, Italy.

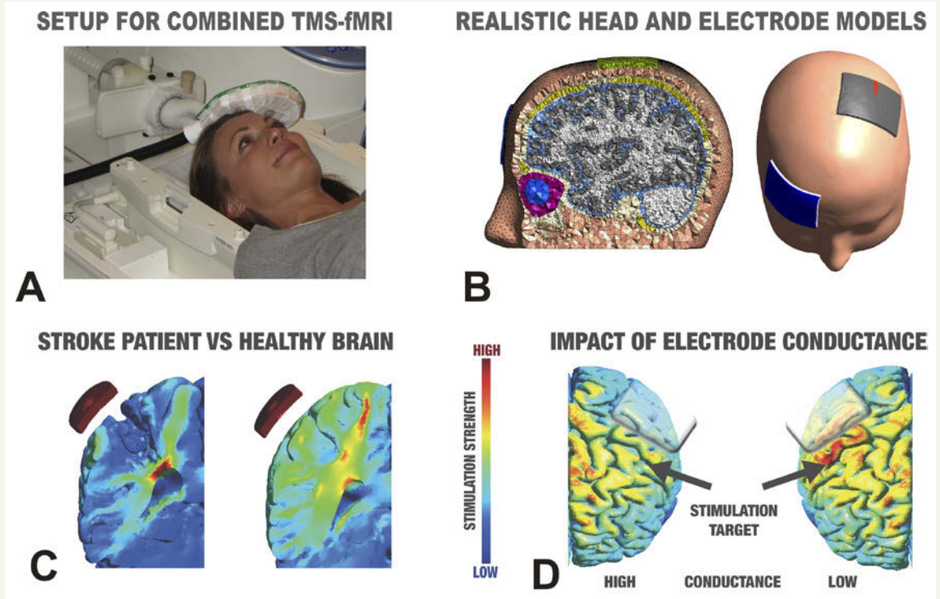


Figure 1: *A. Setup for combined fMRI-TMS. B. Example head model. C. Chronic cortical stroke can strongly reduce the field strength during TDCS/TACS in large parts of the brain, rendering standard treatments ineffective (Minjoli et al, in preparation). D. Electrode properties such as its electrical conductivity affect the electric field in the brain and determine whether the region under the electrode is the most strongly stimulated part or is mostly spared (Saturnino et al., 2015).*

EEG GROUP

The Electroencephalography group (EEGg) has been formed in 2014. The aim of the group is to make DRCMR one of the leading centres in investigating cortical states and connectivity, also during non-invasive transcranial stimulation.
In the neuroscience community there is a growing interest in EEG because it can be easily combined with other techniques for multimodal investigations and it can provide real-time information about the state of the brain. In fact, EEG is able to acquire brain dynamics with high temporal resolution and is able to detect brain rhythms that can explain brain state and connectivity.
One of the main goals of the EEG group is to take advantage of the EEG properties and develop new methodologies that will detect in real time the brain state. This information can then be used to inform non-invasive brain stimulation procedures. The closed-loop setup, where the brain is itself triggering the stimulation devices, is the most promising procedure for developing individually-adjusted stimulation protocols for both the investigation of the brain features in healthy subjects and as potential new tools for treatments in various neurological diseases.

Group members

Senior researcher Leo Tomasevic (group leader), Postdoc Mitsuaki Takemi, Postdoc Anke Karabanov, Postdoc Virginia Conde, Postdoc Violaine Michel Lange, Postdoc Jens Hjortkjær, PhD student Janine van Bellen, PhD student Melissa Larsen, PhD student Konrad Stanek, PhD student Sofie Nilsson.

RESEARCH ACTIVITIES

Multiple ongoing projects involve EEGg members and cover a large spectrum of investigations.

- Neurological disorders: Schizophrenia, Multiple Sclerosis, Traumatic Brain Injury;
- Cognitive and systemic studies: Language processing, Free will, signatures of body ownership, hearing processing, motivation and action;
- Multimodal: EEG/EMG, TMS/EEG, EEG/fMRI;
- Methods: data analysis, experimental design, development of new stimulation protocols to be applied in combination with EEG.

Regarding the last point, the group will work on innovative procedures for the removal of artefacts, which originate from different sources, but mostly from the brain stimulation devices. There are still no methods that can provide a reliable way for data retrieval during direct magnetic or electric stimulation.
The list of projects shows not only the richness of different backgrounds and expertise of the members of the group, but also that the facilities present at DRCMR permits this wide range of studies. The research performed in the EEG group is at the core of the BASICS project funded by the Novo Nordisk Foundation (see page 6).

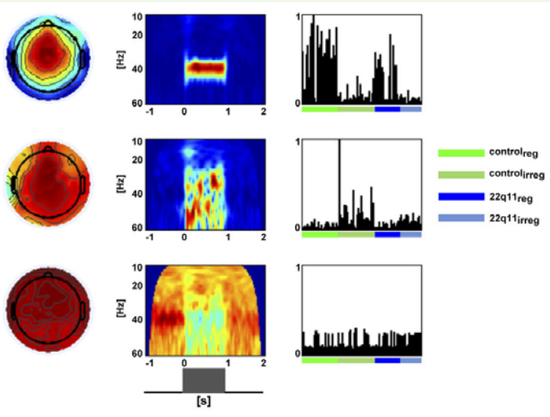


Figure 1: *Developing EEG screening methods for identifying individuals at risk for developing schizophrenia.*

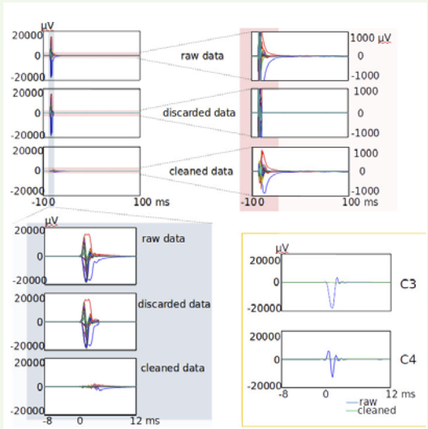


Figure 2: *A method for removal of magnetic pulse artefact induced by transcranial magnetic stimulation from EEG data.*

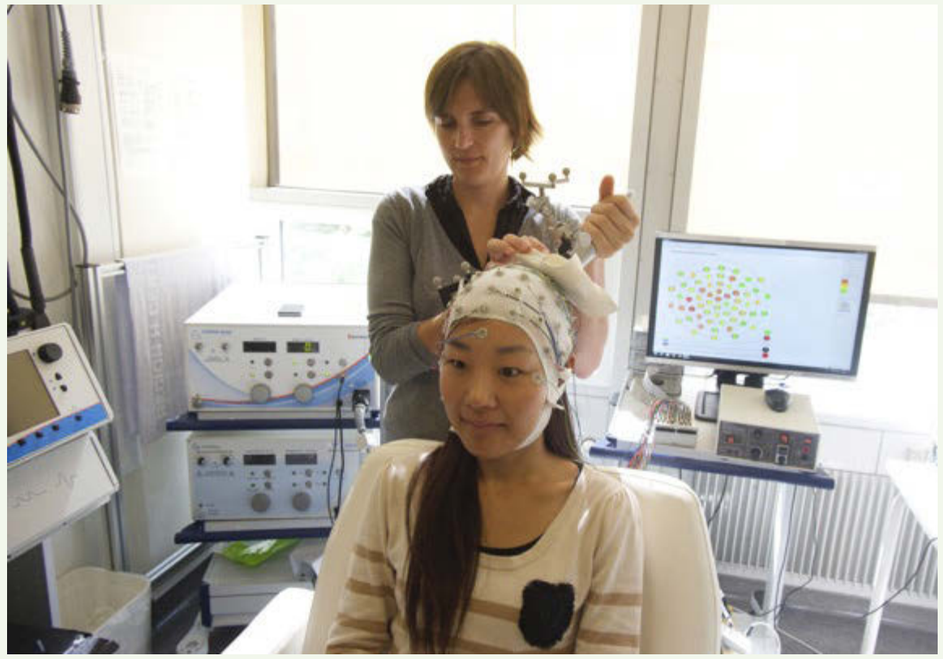


Photo 1: *An MRI guided neuronavigation system allows for accurate positioning of the TMS coil on the head for stimulation and the simultaneous EEG recording measures the response.*

READER CENTRE

The Reader Centre offers highly advanced knowledge on quality assurance of MR data, computational methods, and algorithms to analyse and quantify MR data such as lesion volume and regional brain volumes. We continuously work to extend our method repertoire while always ensuring high data quality.
Lesion assessment is one of the core areas of expertise in the Reader centre. We have years of experience with analysis of lesions related to Multiple Sclerosis (MS) and extensive expertise in quantifying changes related to small vessel disease such as White Matter Hyperintensities (WMH). Quality assurance is a major focus area, which is thoroughly and continuously integrated in all work processes in order to obtain high quality results and deliverables to our collaborators. In addition, our experienced staff provides expert support to our partners within the areas of study coordination, logistics and data management.
Homepage: www.drcmr.dk/readercentre

Group members

Pernille Iversen (manager as of April 2013), Senior researcher Ellen Garde (clinical manager), Senior researcher Arnold Skimminge (until July 2014), Research radiographer Hanne Schmidt, Research bioanalyst Sascha Gude, Research bioanalyst Sussi Larsen.

External collaborators

Danish Multiple Sclerosis Center, Rigshospitalet. Center for Healthy Aging, University of Copenhagen.

RESEARCH ACTIVITIES

Longitudinal clinical studies: The Reader Centre is a partner in several investigator driven clinical studies, specifically within MS where we have a strong collaboration with the Danish Multiple Sclerosis Center. In these studies the patients are scanned multiple times at our facility and scanning sequences and image processing procedures are adapted accordingly. For instance, in 2013 we have concluded data collection and evaluation in two studies on patients with progressive MS, a total of 242 scans and in 2014 we are collaborators in a 3 year follow up study (see the Multiple Sclerosis group for further information).
Cohort studies: In recent years the Reader Center has become engaged in large cohort studies where several hundred patients are scanned, and our collaborators benefit from our close collaboration with the Ageing & Dementia group and expertise with study coordination, logistics and big data handling.
In the Collaborative project Women with Migraine Aura Neuroimaging Study (WOMAN) the Reader Centre collaborate with the nationwide Danish Twin Registry, David Gaist, Odense University Hospital and Messoud Ashina, Rigshospitalet Glostrup. Since an increased risk of WMH and lacunar infarcts have been reported in women with migraine with aura this study was initiated to determine whether structural and functional brain changes could be detected in women with migraine as compared to women without. Data from more than 380 twins have been collected, including state of the art MRI-scans (structural, functional and quantitative MRI), blood samples, physical assessment, and various questionnaires. Based on our extensive experience with lesion assessment a detailed analysis of vascular changes including WMH rating and quantification has been performed.
In May 2014 the LISA (Live actIve – Successful Ageing) study was initiated as a collaboration between the Aging & Dementia group (page 26), Bispebjerg Hospital and the Centre for Healthy Ageing at the University of Copenhagen. This community-based cohort-study investigates the effect on brain and thigh muscle mass of one year moderate and high intensity physical training in 450 healthy individuals aged 62 to 70 years. With more than 900 MR-sessions the Reader Center plays a crucial role in coordination, rigorous quality assurance as well as data-handling and -analysis. In addition to MRI of the brain this study also requires MRI of thigh muscle mass. Welcoming a new challenge, the Reader Center collaborates with the MR Physics & Acquisition group on sequence development and data analysis. Data collection will continue well into 2017 (see the Ageing and Dementia group for further information).
Expanding method portefolio: Establishment of new methods in the Reader Center is done in collaboration with relevant experts in order to offer state of the art methods. In 2014 we included FreeSurfer, Fazeka rating and Schelten's semi-quantitative visual scoring to our catalogue of expertise. In addition, we have set up a novel procedure for visual assessment and quality assurance of MR scans of thighs.

SELECTED PUBLICATIONS

- **Gaultier CJ, Lefort M, Mekary S, Desjardins-Crépeau L, Skimminge A, Iversen P, Madjar C, Desjardins M, Lesage F, Garde E, Frouin F, Bherer L, Hoge RD.** Hearts and Minds: linking vascular rigidity and aerobic fitness with cognitive aging, Neurobiology of Aging, 2015;36(1):304-14
- **Romme Christensen J, Ratzer R, Börnsen L, Lyksborg M, Garde E, Dyrby TB, Siebner HR, Sorensen PS, Sellebjerg F.** Natalizumab in progressive MS: results of an open-label phase 2A, proof-of-concept trial, Neurology, 2014;82(17):1499-507
- **Lyksborg M, Siebner HR, Sørensen PS, Blinkenberg M, Parker GJ, Dogonowski AM, Garde E, Larsen R, Dyrby TB.** Secondary progressive and relapsing remitting multiple sclerosis leads to motor-related decreased anatomical connectivity. PLoS One. 2014 Apr 18;9(4):e95540

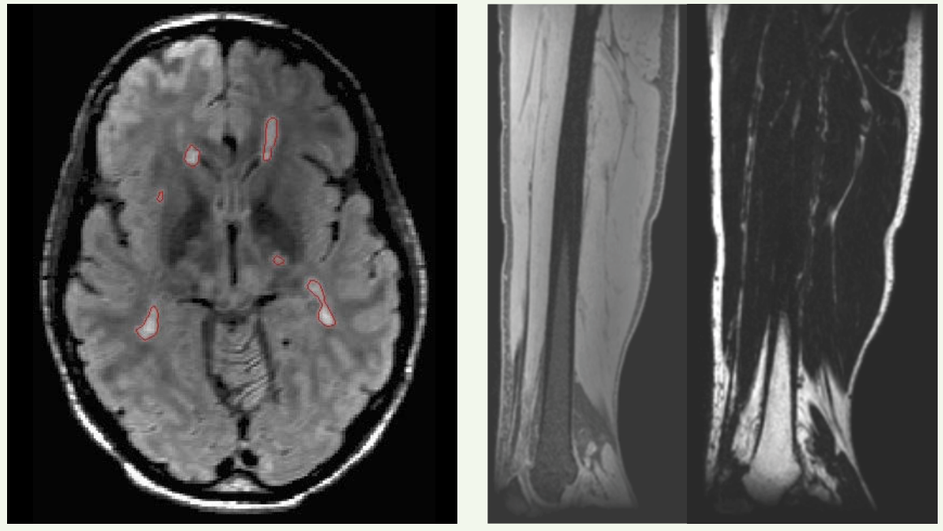
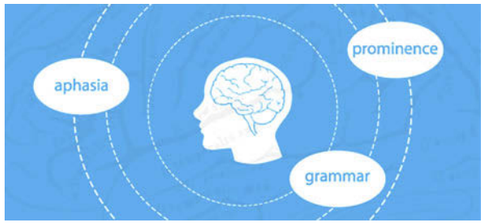


Figure 1: *A: MRI brain scan from an MS patient where the lesions have been delineated and are ready for quantitative evaluation. B: MRI thigh scans weighted for water (left) and fat (right).*

COLLABORATIVE RESEARCH PROJECTS

PROGRAM – INFORMATION PROMINENCE AND GRAMMAR IN MIND AND BRAIN



ProGram is an interdisciplinary research and educational centre for neurolinguistics at the University of Copenhagen. The aim of the ProGram project is to advance the current knowledge about the neuro-cognitive basis of grammar to facilitate diagnosis and treatment of agrammatic aphasia as well as grammar teaching.
More specifically the scientific goal of the project is to find the "back door" to grammar – a link between grammar and non-linguistic background information. The success of the project will have a significant impact on society:
Agrammatic aphasia may be diagnosed by the ability to deal with non-linguistic background information; and individuals learning grammar (whether native or foreign language learners), as well as individuals with agrammatic aphasia, may benefit from exercises, that stimulate this ability.
The project is one of 18 Excellence Programs at the University of Copenhagen. The excellence programs support interdisciplinary strengths and through their research address major challenges facing society today.
The project brings together researchers and students from three faculties (Humanities, Health and Medical Sciences, and Social Sciences) to test this hypothesis in a number of behavioural and neurological experiments, and subsequently translate the results into diagnostic, therapeutic and didactic advances.
Homepage: http://program.ku.dk/english/

Group members

Kasper Boye (PI), Hartwig Siebner (co-PI), Jesper Mogensen (co-PI), Peter Harder, Lise Randrup Jensen, Line Burholt Kristensen, Violaine Michel Lange, Nicoline Munck Vinther, Byurakn Ishkhanyan.

PROGRAM is one of 18 projects funded by the University of Copenhagen's Excellence Programme for Interdisciplinary Research (2013 – 2016)

RESEARCH ACTIVITIES

The theoretical basis of the project is a combination of two novel breakthrough theories: 1) a linguistic theory of what it means to be a grammatical expression, developed by PI Kasper Boye and team member Peter Harder (e.g. Boye & Harder 2012), and 2) a neuropsychological theory of the relation between cognitive functions and their neural underpinnings, developed by co-PI Jesper Mogensen (e.g. Mogensen 2011, 2012). Based on these theories, our central hypothesis is that: processing of grammatical expressions shows patterns of behaviour and involves neural patterns associated with the processing of background information.
Using electro-encephalography (EEG), functional Magnetic Resonance Imaging (fMRI) and corpus-based analyses of aphasic speech, the project will investigate spatio-temporal differences between the processing of grammatical and lexical elements.
Differences in the processing of grammatical vs. lexical elements might be too subtle to detect with a behavioural task e.g. with reaction times measurements, but the use of electrophysiological measures and neuroimaging may detect such subtle differences.
Postdoc Violaine Michel Lange and PhD student Nicoline Munck Vinter are currently investigating the time course of grammar processing using EEG in speech production and perception paradigms. The main purpose is to establish a clear time course and signature of grammatical element processing and retrieval in speech production and perception. Postdoc Line Burholt Kristensen is using fMRI to examine whether processes involved in lexical retrieval of grammatical vs. lexical elements activate different brain areas.
PhD student Byurakn Ishkhanyan is currently looking at lexical and grammatical pronouns in French agrammatic speech. Additionally, she is working on an experiment to test the REF-model.

Photo 1: *Researchers from the Faculty of Humanities (HUM), the Faculty of Social Sciences (SAMF) and the Faculty of Health and Medical Sciences (SUND) at the University of Copenhagen are involved with the project.*

SELECTED PUBLICATIONS

- **Boye, K & Harder, P 2012.** "A usage-based theory of grammatical status and grammaticalization". Language. 88. 1-44.
- **Brink, ET, Boye, K & Jensen, LR 2015.** Når grammatikken går i stykker. Om agrammatisme. Mål og Mæle. 37. 9-13.
- **Michel Lange, V, Perret, C, Laganaro, M.** Comparison of single-word and adjective-noun phrase production using event-related brain potentials. Cortex. 2015; 67, 15-29. doi:10.1016/j.cortex.2015.02.017
- **Mogensen, J.** "Reorganization of Elementary Functions (REF) after brain injury: Implications for the therapeutic interventions and prognosis of brain injured patients suffering cognitive impairments". Schäfer, A.J. & J. Müller (eds.). Brain damage: Causes, management and prognosis. Hauppauge, NY: Nova Science Publishers, Inc. 2012; 1-40.
- **Vinther, NM, Boye, K & Kristensen, LB.** Grammatik i baggrunden. Opmærksomhed under læsning. Nydanske Sprogstudier. 2014; 47. 99-139.

CHeSS

The Oticon Centre of Excellence for Hearing and Speech Sciences (CHeSS) was recently established with support from the Oticon Foundation. CHeSS combines auditory cognitive neuroscience and audiological research with the aim of deepening our understanding of auditory perception and hearing impairment. The research focuses on computational modeling of processing at peripheral and central stages of the auditory system in order to understand the mechanisms that allow normal hearing listeners to extract relevant sound signals in complex acoustic scenes and how this becomes more challenging for hearing impaired listeners.
Homepage: www.hea.elektro.dtu.dk/about_us/About-Hearing-Systems/CHESS

Group members

Torsten Dau (PI at DTU Electro), Hartwig Siebner (Co-PI at DRCMR), Jens Hjortkjær, Federica Bianchi, Richard McWalter, Sébastien Santurette

External collaborators

DTU, Université Paris Descartes, University of California Berkeley

RESEARCH ACTIVITIES

One branch of investigation focuses on cortical encoding of natural sound statistics. Unlike temporally complex signals like speech, natural sound 'textures', like birds chirping or water flowing, can be characterized by statistical regularities over time. We use fMRI and natural sounds synthesized via their statistics to investigate how auditory cortex may use these statistics as an efficient way of coding complex sounds.
Another focus is to investigate training-dependent changes in the auditory system. Specifically, we investigate how musicians may have superior cortical pitch processing to learn how training may alter the neural processing of simple auditory features. We use fMRI to characterize pitch coding mechanisms and training-related plasticity of auditory receptive fields.
Using EEG and pupillometric measurements, we also investigate objective physiological correlates of 'listening effort'. Hearing impaired listeners often experience considerable difficulty in understanding speech in noisy environments, which can result in fatigue even when using advanced hearing aids. Fitting of hearing instruments is still largely based on pure-tone audiometry that is not informed about any cognitive effects and the development of more stable cognitive measures are needed for individualized diagnosis and better hearing aid fitting.

SELECTED PUBLICATIONS

- **McWalter, R, Dau, T.** Analysis of the Auditory System via Sound Texture Synthesis. Proceedings of the International Conference on Acoustics 2013: 1114-1117
- **Bianchi, F, Santurette, S, Wendt, D, Dau, T.** "Objective correlates of pitch salience using pupillometry". Proceedings of Forum Acusticum, 2014

22Q11.2 DELETION SYNDROME

The 22q11.2 deletion syndrome project was initiated by Professor Thomas Werge from the Institute for Biological Psychiatry (IBP), Skt. Hans, in Roskilde and is part of the iPsych initiative. Patients with 22q11.2 deletion syndrome are at very high risk of neurodevelopmental disorders, including autism, ADHD and schizophrenia. The chance of developing schizophrenia is estimated to be approximately 30%. The 22q11.2 deletion research at DRCMR aims to investigate whether changes in effective brain connectivity represent a functional marker in individuals prone to schizophrenia and psychosis. Specifically, EEG and fMRI are used to investigate subject's ability to detect stimulus changes in the auditory domain on a high temporal and spatial scale. This ability is significantly diminished in schizophrenia patients. Results of this project will contribute significantly to detecting neural connectivity changes associated with schizophrenia and psychosis and will broaden our understanding of psychiatric disorders.
Homepage: http://ipsych.au.dk/about-ipsych/research-groups/thomas-werge-group/

DRCMR group members

Professor Hartwig Siebner and Senior researcher William Baaré (group leaders), Postdoc Elvira Fischer, PhD student Melissa Larsen, Senior researcher Ollie Hume, Radiographer Christian Bauer.

External Collaborators

Professor Thomas Werge, PhD Line Olsen, MD and PhD student Henriette Schmock, MD and PhD student Anders Vangkilde (Institute for Biological Psychiatry), PhD Michael Didriksen (Director), PhD student Michelle Rosgaard Birknow (Therapeutic Biology Lead for schizophrenia and psychosis, H. Lundbeck A/S), Associate professor Morten Mørup (DTU COMPUTE, Department of Applied Mathematics and Computer Science).

RESEARCH ACTIVITIES

The case-control study started in March 2013 in order to investigate the clinical, cognitive, functional and structural brain changes in 22q11.2 deletion carriers in a recruited sample of Danish individuals. Structural and functional brain mapping was conducted at the DRCMR. Melissa Larsen and Elvira Fischer used identical mismatch negativity (MMN) paradigms in respectively EEG and MR. After a sequence of repeated standards, an oddball was randomly introduced and became the new standard, referred to as "rowing" MMN paradigm. In addition, the EEG session contained a further gamma-entrainment paradigm to test whether 22q11.2 deletion individuals show a reduced entrainment of gamma band activity, similar to patients with schizophrenia. Obtained structural MR scans will be used to elucidate any kind of structural differences between healthy controls and 22q11.2 deletion cases. Data collection was accomplished in close collaboration with the Institute for biological Psychiatry, Skt. Hans. Further, Michelle Birknow at Lundbeck conducted animal studies in 22q11.2 mice. The latter provides a translational approach that allows more insight on the neurophysiology underlying 22q11.2 deletion and consequently schizophrenia. Importantly, the translational results between the human EEG and the recordings in mice will lead to a better understanding of the neural mechanisms underlying the development of schizophrenia and psychosis.

AFFECTIVE DISORDERS

The DRCMR has a longstanding collaboration with the Psychiatric Center Copenhagen, Rigshospitalet, concerning neuroimaging of affective disorders. Three collaborative projects have been pursued together in 2013 – 2014.

Group members

The NEAD study: PhD-student Iselin Meluken, PhD-student Ninja Meinhard, Professor Hartwig Siebner (DRCMR), Professor Catherine Harmer (University of Oxford), Dr Martina Di Simplicio and Professor Emily Holmes (University of Cambridge), Professor K Luan Phan (University of Chicago), Dr Henry Chase and Professor Mary Phillips (University of Pittsburgh), Professor Lars Vedel Kessing and Dr Maj Vinberg (Psychiatric Centre Copenhagen, Rigshospitalet), Dr Julian Macoveanu and Dr Kamilla Miskowiak (Psychiatric Centre Copenhagen, Rigshospitalet, and DRCMR) (Internal PIs: Hartwig Siebner, Kamilla Miskowiak; External PIs: Kamilla Miskowiak, Maj Vinberg).

The EPO study: Dr Kamilla Miskowiak (PI), Psychiatric Centre Copenhagen, Rigshospitalet and DRCMR, Professor Hartwig Siebner, DR Julian Macoveanu and Postdoc Arnold Skimminge, DRCMR, Professor Gitte Moos Knudsen and Professor Olaf Paulson, Neurobiology Research Unit, Professor Catherine Harmer, University of Oxford, Professor Hannelore Ehrenreich, Max-Planck Institute, Göttingen, Dr Maj Vinberg and Professor Lars Vedel Kessing, Psychiatric Centre Copenhagen, Rigshospitalet.

The ECT study: Dr Kamilla Miskowiak (PI), Psychiatric Centre Copenhagen, Rigshospitalet, and DRCMR, Professor Hartwig Siebner, DRCMR, Dr Julian Macoveanu, DRCMR, Professor Olaf Paulson, Neurobiology Research Unit, Professor Per Bech, Psychiatric Centre Hillerød, Professor Catherine Harmer, University of Oxford, Professor Lars Vedel Kessing and Professor Martin Balslev Jørgensen, Psychiatric Centre Copenhagen, Rigshospitalet.

Neuromappping of Endophenotypes for Affective Disorders

A twin study of neurocognitive, neuroimaging, cellular and epigenetic markers (the NEAD study): Unipolar disorder (UD) and bipolar disorder (BD) are among the ten leading causes of disability worldwide. These affective disorders are heterogeneous and characterized by a high rate of misdiagnosis; 70 – 93 % of BD patients are misdiagnosed most commonly as having UD and more than one third remain misdiagnosed for over 10 years. This results in delay or absence of appropriate treatment and thus a high rate of disability, recurrence and unemployment. This highlights a need for identification of illness biomarkers (endophenotypes) to improve diagnostic accuracy. Monozygotic twins are nearly always genetically identical and therefore provide a particularly strong methodology for endophenotype research. The NEAD study consequently investigates neuroimaging, cognitive, cellular and epigenetic endophenotypes in monozygotic twin-pairs discordant or concordant for affective disorder.

The effects of erythropoietin in biomarker models of cognitive function in patients with treatment resistant depression or bipolar disorder in remission (the EPO study)

Cognitive dysfunction is a core symptom of UD and BD that contributes to impaired workforce capacity. However, there is a lack of treatment options that would lead to solid and lasting cognitive improvement. The multi-functional growth factor erythropoietin (EPO) is a promising candidate treatment for cognitive dysfunction in mood disorders. We recently demonstrated that 8 weeks EPO treatment has beneficial effects on cognitive function in UD and BD. Using prospective MRI of these patients, we demonstrated that EPO treatment reversed volume loss in the left hippocampal cornu ammonis 1-3 and subiculum, which correlated with patients' memory improvement. At a functional level, improved cognitive performance in EPO vs. placebo-treated patients was accompanied by enhanced neural activity in a fronto-parietal network during working memory and episodic encoding. Together, these findings suggest that structural increase in the left hippocampus and enhanced task-relevant fronto-parietal activity may be key neurobiological mechanisms of the EPO-associated cognitive improvement.

Effects of electroconvulsive therapy (ECT) on neural and cognitive processing of emotional information in major depression (the ECT study)

Patients with depression show increased attention to and memory for negative compared with positive information. This negative bias is associated with greater depression severity, illness duration and risk of relapse. Antidepressant medication normalizes these negative biases before changes in mood and symptoms. This is thought to be a key neuropsychological mechanism of drug action that contributes to mood improvement when the patient learns to respond to the new and more positive environment. The ECT study investigates whether ECT influences neural and cognitive processing of emotional information in a similar way to antidepressant medication. This would highlight modulation of neural and cognitive processing of emotional information as a common mechanism across distinct treatments for depression.

SELECTED PUBLICATIONS

- **Miskowiak KW, Macoveanu J, Vinberg M, Assentoft E, Randers L, Harmer CJ, Ehrenreich E, Paulson OB, Knudsen GM, Siebner HR, Kessing LV.** Erythropoietin induced memory improvement in mood disorder associated with neural activity changes: a randomized trial (in review)

WOMEN WITH MIGRAINE WITH AURA NEUROIMAGING – (WOMAN) STUDY

The overall objective is to assess whether migraine with aura is associated with structural lesions and morphology changes of the brain evaluated by MRI. An increased risk of WMH and lacunar infarcts have been reported in women with migraine with aura and therefore it is relevant to determine whether structural and functional brain changes could be detected in women with migraine as compared to women without. Data from more than 380 twins have been collected, including state of the art MRI-scans (structural, functional and quantitative MRI), blood samples, physical assessment, and various questionnaires. Based on our extensive experience with lesion assessment a detailed analysis of vascular changes including WMH rating and quantification has been performed. The WOMAN study has received funding from Lundbeck and Novo Nordisk Foundation & Fabrikant Wilhelm Pedersens og hustrus mindelegat.

The WOMAN study is a collaborate effort of various partner institutions:

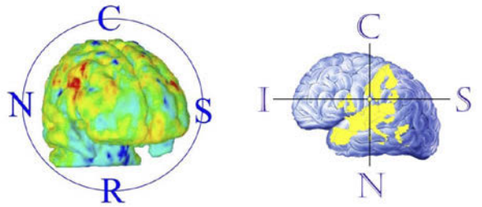
- Department of Neurology, Odense University Hospital & Institute of Clinical Medicine, Faculty of Health Sciences, University of Southern Denmark
- Danish Headache Center, Department of Neurology, Glostrup Hospital, University of Copenhagen
- Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital, Hvidovre
- Danish Twin Registry, University of Southern Denmark

Group members

Professor David Gaist (Principal investigator), Professor Hartwig Siebner, Professor Kirsten Kyvik, Associate Professor Messoud Ashina, Senior Researcher Ellen Garde, Consultant Camilla Gøbel Madsen, Research Bioanalyst Sussi Larsen, Senior Researcher Kristoffer Madsen, Senior Researcher Tim Dyrby and Associate Professor Lars Hansson.

Photo 1: *The WOMAN group members.*

CLINICAL INTERVENTION AND NEUROPSYCHIATRIC SCHIZOPHRENIA RESEARCH (CINS)



Schizophrenia is a severe mental disorder that not only negatively impacts the affected individual but also their families and society as a whole. Neuroscientific research and in vivo brain imaging are pivotal in understanding schizophrenia as a brain disease and in generating explanatory and predictive biological models. The schizophrenia MR research at DRCMR is done in 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 Dr. Kathrine Pagsberg of the Child and Adolescent Psychiatric Center Bispebjerg.
Homepage: https://www.psykiatri-regionh.dk/CNSR-english/Pages/default.aspx

DRCMR Group members

Hartwig Siebner William Baaré, Ayna Baladi Nejad, Kristoffer Madsen and Louise Baruël Johansen.

External collaborators

Main researchers involved from CNSR/CINS are Professor Birte Glenthøj, Dr Bjørn H. Ebdrup. Katrine Pagsberg, Dr. Lone Baandrup, and PhD student Lea Klærke. Katrine Pagsberg, MD, represents the Department of Child and Adolescent Psychiatry.

RESEARCH ACTIVITIES

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 hospitalization, medication treatment and disease chronicity. In the beginning of 2013 Ayna Nejad successfully defended her PhD thesis "Longitudinal MRI study of functional brain connectivity during a working memory task in antipsychotic-naïve, first-episode schizophrenia patients". Among other things, Ayna showed that functional connectivity of frontoparietal working memory networks differentiated patients who improved in negative symptoms at follow-up from those who did not. This finding is promising for the stratification of schizophrenia patients and the possible personalization of their treatment. In 2014 a unique longitudinal study was initiated by CNRS/CINS to follow-up on 75 initially first-episode (drug-naïve) schizophrenia patients who were first seen 10 and 15 years ago.

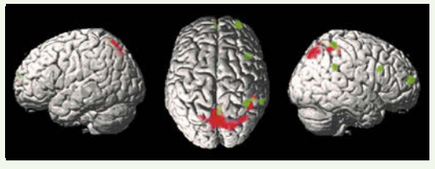


Figure 1: *3D brain showing the two frontoparietal working memory components which were most informative for the prediction of whether patients would later improve in negative symptoms with antipsychotic medication.*

SELECTED PUBLICATIONS

- **Nejad AB, Madsen KH, Ebdrup BH, Siebner HR, Rasmussen H, Aggernaes B, Glenthoj BY, Baare WF.** Neural markers of negative symptom outcomes in distributed working memory brain activity of antipsychotic-naive schizophrenia patients. Int J Neuropsychopharmacol. 2013;16(6):1195-1204.
- **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. 2013;38(1):34-42.

CENTER FOR INTEGRATED MOLECULAR BRAIN IMAGING (CIMBI)

The DRCMR is one of four partners in the Center for Integrated Molecular Brain Imaging (CIMBI) funded by the Lundbeck Foundation since 2006. CIMBI is headed by professor Gitte Moos Knudsen, Chair of the Neurobiology Research Unit, Copenhagen University Hospital Rigshopitalet. The research in CIMBI covers neurobiology, physiology, and pathophysiology, molecular imaging and neuroreceptor ligands with focus on the serotonergic system. DRCMR researchers within CIMBI address basic questions regarding inter-individual differences in cognitive and emotional behavior, and personality that are related to inter-individual variations in the serotonergic neurotransmitter in healthy population.
Homepage: http://www.cimbi.dk

Cimbi
Center for integrated molecular brain imaging

DRCMR Group members

Professor Hartwig Siebner (CIMBI steering committee Member), Postdoc Kathrine Skak Madsen, Postdoc Julian Macoveanu and Senior researcher William Baaré (Members of the Council of Investigators in CIMBI). PhD student Louise Baruël Johansen, PhD student Jonathan Holm-Skjold. Other involved DRCMR personnel: Arnold Skimminge, Bettina Hornbøll, David Meder, Helle Ruff Laursen, and Pernille Iversen.

RESEARCH ACTIVITIES

Julian Macoveanu showed that healthy volunteer adults, after three weeks of treatment with a selective serotonin reuptake inhibition drug, showed reduced activations to risky decisions during a functional MRI gambling task in the orbitofrontal cortex, a brain region critical for the integration of cognitive and emotional information. The SSRI treated group also showed reduced response in raphe, the main serotonin producing brain region. Kathrine Skak Madsen showed, as earlier observed in adults, that higher neuroticism was associated with higher right relative to left cingulum fractional anisotropy in boys. Intriguingly, the asymmetry effect on neuroticism was opposite in girls.

See the CIMBI annual report www.cimbi.dk for further information.

SELECTED PUBLICATIONS

- **Macoveanu J, Fisher PM, Haahr ME, Frokjaer VG, Knudsen GM, Siebner HR.** Effects of selective serotonin reuptake inhibition on neural activity related to risky decisions and monetary rewards in healthy males. Neuroimage 2014;99:434–42
- **Hornboll B, Macoveanu J, Rowe J, Elliott R, Paulson OB, Siebner HR, Knudsen GM.** Acute serotonin 2A receptor blocking alters the processing of fearful faces in the orbitofrontal cortex and amygdala. J Psychopharmacol. 2013;27(10):903-914.

IN MEMORIAM – LISE VEJBY SØGAARD

In February 2014 our very dear friend and colleague Lise Vejby Søgaard passed away unexpectedly due to sudden and acute illness during her winter holidays in Norway. It came as a complete shock to everyone. Lise was exceptionally thoughtful, helpful and always prioritized higher goals over own benefit. Subtle humor, excellent collaboration skills, and a clear mind made her both popular and busy. She was very considerate, and many enjoyed her warmth and kind friendship.
At a professional level, Lise was the senior scientist heading the preclinical group. She made important contributions to countless projects over the years, e.g. working with hyperpolarisation and diffusion MR imaging.
Lise will live on in our memories. Our warmest thoughts go to her family who suffers the greatest loss of all.

DISSEMINATIONS 2013

KRISTIAN FREDERIKSEN

Title of project
Corpus callosum in aging and dementia

Summary
The thesis included three papers on changes in the corpus callosum in a large cohort of elderly subject, who underwent MRI and clinical assessment at baseline and 3 years later. Tissue loss was found to be associated with motor impairment, and the size of the corpus callosum differed considerably between patients with Alzheimer´s disease and elderly controls.

Supervisors
- Main supervisor: Professor Gunhild Waldemar, Copenhagen University Hospital, Rigshospitalet
- Professor Steen Hasselbalch, Copenhagen University Hospital Rigshospitalet
- Senior researcher Ellen Garde, DRCMR

The University
University of Copenhagen

Date of defence
August 28th, 2013

Working today
Danish Dementia Research Centre

HENRIK LUND

Title of project
MR Study of Normal-Appearing Brain Tissue in MS – Cognitive Correlations and Blood-Brain Barrier Permeability

Summary
Conventional MR measures of the disease load of patients diagnosed with multiple sclerosis (MS) are based on the number of lesions or their combined volume. This approach bears the risk that tissue destruction flies under the radar even if it has profound influence on the clinical outcome. We therefore investigated structural brain changes in the normal appearing brain tissue of MS and studied how these changes may contribute to an understanding of the underlying disease mechanisms. After the injection of contrast agent, we found an increased variation of T1 values in the normal appearing white matter, a finding that points to an increased regional inhomogeneity of the blood-brain barrier function in MS.
Additionally, we found distinct clusters of voxels where T2 estimates correlated with several cognitive measures. These T2 changes presumably reflect inflammation, edema, demyelination, Wallerian degeneration or axonal loss.
Our results suggest that even within the normal appearing brain tissue, MRI can be used to detect changes in the brain structure, which are likely to be associated with an underlying pathology and which possibly contribute to the impairment of MS patients.

Supervisor
Professor Hartwig Siebner, DRCMR and Copenhagen University Hospital Hvidovre

University
University of Copenhagen

Date of defence
October 1st, 2013

Working today
LEO Pharma

MARK LYKSBORG

Title of project
Determination of magnetic resonance imaging biomarkers for multiple sclerosis treatment effects

Summary
Thesis work mainly consisted of methods developed for the assessment of white matter pathology in multiple sclerosis patients.

Supervisors
- Main supervisor: Professor Rasmus Larsen, DTU Compute
- Professor Hartwig Siebner, DRCMR and Copenhagen University Hospital Hvidovre
- Senior Scientist Tim Dyrby, DRCMR

University
Technical University of Denmark

Date of defence
June 2013

Working today
Technical University of Denmark

AYNA BALADI NEJAD

Title of project
Longitudinal MRI study of functional brain connectivity during a working memory task in antipsychotic-naive, first-episode schizophrenia patients

Summary
The thesis study used functional MRI to investigate working memory dysfunction in antipsychotic-naïve patients with first-episode schizophrenia before and after 6-month antipsychotic (quetiapine) drug treatment. First, the study investigated the primary working memory deficits that were present before patients received medication and found that patients were not able to decrease brain acitivity in the temporoparietal cortex during an increase in working memory load. I speculated that this abnormal attenuation of brain activity could be reflective of an inability to shift from a verbal to a visuospatial strategy as the task became harder to perform. Lastly, using multivariate pattern analysis, I also found that pre-treatment functional networks were successful in differentiating patients who later improved in negative symptoms from those who did not. This work demonstrated the potential importance of examining whole-brain networks in the search for predictive relationships between brain activity and treatment response in psychiatry.

Supervisors
- Main supervisor: Professor Hartwig Siebner, DRCMR and Copenhagen University Hospital, Hvidovre
- Senior researcher William F.C. Baaré, DRCMR
- Professor Birte Y. Glenthøj, Center for Neuropsychiatric Schizophrenia Research & Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Copenhagen University Hospital, Psychiatric Center Glostrup

University
Department of Neuroscience and Pharmacology, Faculty of Health and Medical Sciences, Copenhagen University

Date of defence
January 25th, 2013

Working today

After completing her PhD Ayna went on as a Postdoc at the Brain and Spine Institute (ICM), l'Hopital de Pitié-Salpêtriere, followed by a Research Fellowship at the Department of Psychiatry, Harvard Medical School. Currently she is back at DRCMR, studying brain activity patterns associated with the development, course, and treatment response of psychiatric symptoms.

KASPER WINTHER ANDERSEN

Title of project
Brain Network Modelling

Summary
Nonparametric Bayesian models are used to model brain networks derived from resting state fMRI and diffusion weighted imaging. Resting state networks were shown to be community structured and to have complex between community connectivity. Also, a new method for jointly modeling of functional and structural networks was presented, which revealed only limited similarity in community structure between structural and functional networks. In addition, the local connectivity was investigated in a cohort of multiple sclerosis (MS) patients, where we observed decreased local functional connectivity in cerebellum in MS. Finally, a principled way of selecting the parameters for kernel principal component analysis denoising was presented. This was a machine learning technique for removing noise from data which can lie on non-linear manifolds.

Supervisors
- Main supervisor: Professor Lars Kai Hansen, Department of Applied Mathematics and Computer Science, Technical University of Denmark
- Professor Hartwig Siebner, DRCMR
- Senior researchers Kristoffer H. Madsen and Tim B. Dyrby, DRCMR

University
Technical University of Denmark

Date of defence
April 24th, 2014

Working today
Postdoc at DRCMR

SOFIE GELSKOV

Title of project
The Neural Mechanisms of Loss Aversion during Decision-Making

Summary
The major aim of this PhD thesis was to study the neural mechanisms underlying decision-making in healthy subjects and pathological gamblers. Loss aversion reflects a well-known behavioural bias in which people, when presented with risky gambles with equal chances of winning and losing, demand on average twice the amount of potential gains compared to losses in order to accept the gambles. To investigate loss aversion in healthy and pathological gambling decisions, I employed a novel setup, which quantified behavioural measures of loss aversion and mapped task-related functional magnetic resonance imaging (fMRI). The thesis contains two fMRI studies. The first study mapped choice-related regional activity of the amygdala in relation to the individual "decision space" with respect to varying gain-loss ratios in a healthy group of male subjects (N=16). The fMRI results are in agreement with the notion that the amygdala reinforces the individual bias towards loss aversion by signalling subjective appetitiveness or aversiveness of gain-loss ratios during risky decisions. In a second part of this thesis, I contrast healthy and pathological decision-making, employing pathological gambling as a faulty decision-making model. Pathological gamblers (N=14) but not control subjects (N=15) displayed a u-shaped hypersensitivity to increasingly appetitive and aversive gain-loss ratios in caudate nuclei and dorso-lateral prefrontal cortex. These novel results indicate a specific role for the associative cortico-striatal network in aberrant decision-making.

Supervisors
- Main supervisor: Professor Hartwig Siebner, DRCMR and Copenhagen University Hospital Hvidovre
- Ass. Professor Thomas Z. Ramsøy, CBS

University
Faculty of Health and Medical Sciences, University of Copenhagen

Date of defence
May 5th, 2014

Working today
Postdoc at Department of Cognitive Studies, École Normale Supérieure, Paris, France funded by a grant from the Carlsberg Foundation.

DAMIAN HERZ

Title of project
Neural mechanisms underlying motor impairment in Parkinson's disease

Summary
In my PhD, I aimed to investigate the neural mechanisms underlying motor impairment in patients with Parkinson's disease (PD), in particular patients who develop involuntary movements (dyskinesia) during dopaminergic treatment. The work was subdivided into four studies.
In a first study, we quantitatively summarized previous neuroimaging studies of PD patients in a meta-analysis (Herz et al., 2014, Human Brain Mapping). In study 2 and 3, we investigated the neural mechanisms leading to the emergence of dyskinesia in PD using functional magnetic resonance imaging (fMRI). We found an abnormal levodopa-induced increase in activity of the pre-supplementary motor area (preSMA) and bilateral putamen as well as an abnormal modulation of connectivity from putamen to preSMA and primary motor cortex preceding dyskinesia (Herz et al., 2014, Annals of Neurology and Herz et al., 2015, Brain). In study 4, we used a combined offline transcranial magnetic stimulation (TMS) - fMRI approach in healthy young participants to better understand the role of the preSMA in motor control. The results suggest that the preSMA is part of a cortico-subcortical network, which is centrally involved in the control of automatic response tendencies. This network is strongly modulated by contextual modulations and perturbing preSMA function by TMS can result in improved motor control (Herz et al. ,2014, Journal of Neuroscience).

Supervisors
- Main supervisor: Professor Hartwig Siebner, DRCMR and Copenhagen University Hospital Hvidovre
- Associate Professor Annemette Løkkegaard, Department of Neurology, Bispebjerg Hospital

University
University of Copenhagen

Date of defence
June 13th, 2014

Working today
Postdoc, University of Oxford funded by a Marie Curie early training Fellowship.

METTE HAUGE LAURITZEN

Title of project
Imaging Cardiac Meta-bolism using hyperpolarized [1-^{13}C] pyruvate

Summary
Hyperpolarized ^{13}C magnetic resonance imaging (MRI) is an emerging new imaging technique, which is able to image important biological reactions in living tissue. In the present PhD thesis, hyperpolarized ^{13}C MRI was used to study the rat heart under different metabolic conditions. First the technique was used to image changes in cardiac metabolism in a rat model of acute myocardial infarction in vivo. In the second study, i.v. infusion of glucose, insulin and potassium was used to increase the glucose metabolism in the rat heart and thereby increase the signal from hyperpolarized [^{13}C]bicarbonate. Besides evaluating the application of hyperpolarized ^{13}C MRI in rats, the PhD thesis also discusses the potential of the technique to advance basic knowledge and improve diagnosis of cardiac diseases in humans.

Supervisors
- Main supervisor: Professor Olaf B. Paulson
- Consultant Per Åkeson, Senior researcher Lise Vejby Søgaard, Senior researcher Peter Magnusson, Professor Jan Henrik Ardenkjær Larsen, DTU

University
University of Copenhagen

Date of defence
March 26th, 2014

Working today
Postdoc Medical Faculty, Institute of Experimental Medical Science, Lund University, Sweden.

HELLE RUFF LAURSEN

Title of project
On empathic accuracy and emotional face processing and associations with variation in the oxytocin receptor and serotonin transporter genes and long-term ecstasy use.

Summary
The PhD thesis concerns processes related to empathic accuracy and emotional face perception and their associations with functional variations in the oxytocin receptor and serotonin transporter genes and long-term ecstasy use.

Supervisors
- Main supervisor: Professor Hartwig Siebner, DRCMR and Copenhagen University Hospital Hvidovre
- Ass. Professor Thomas Z. Ramsøy, CBS
- Postdoc Susanne Henningsson, DRCMR

University
University of Copenhagen

Date of defence
June 23rd 2014

Working today
Psychologist at Søstjerneskolen (autism specific school)

NINA LINDE REISLEV

Title of project
The Wiring of the Blind Brain

Summary
Blindness results in the recruitment of the "visual" cortex during auditory and tactile sensory input. This thesis investigated structural aspects of brain plasticity in congenitally and late blind individuals. We used diffusion-weighted MRI to assess the local microstructure and connectivity of the brain. We hypothesised that especially congenital blindness will lead to the generation of new connections, or unmasking and strengthening of existing pathways. We did not find evidence to support formation of new pathways, but found significant differences in tissue microstructure and connectivity in the congenitally blind, and that such structural alterations depend on the onset of blindness.

Supervisors
- Main supervisor: Professor Hartwig Siebner, DRCMR and Copenhagen University Hospital Hvidovre
- Senior researcher Tim B. Dyrby, DRCMR
- Professor Maurice Ptito, University of Copenhagen
- Associate Professor Ron Kupers, University of Copenhagen

University
University of Copenhagen, Faculty of Health and Medical Sciences

Date of defence
October 28th, 2014

Working today
Postdoc at DRCMR and Center for Healthy Aging (CEHA), University of Copenhagen.

COMING TO DRCMR

ELVIRA FISCHER

My background is in psychobiology with a Bachelor's degree from the University of California Los Angeles, UCLA and in cognitive neuroscience with a Masters and PhD in Behavioural and Cognitive Neuroscience from the University of Tübingen and the Max Planck Institute for Biological Cybernetics. My PhD and my work before joining the DRCMR in spring 2013 was mainly focusing on how the brain disentangles objective motion from self-motion using eye-movements as investigated by fMRI and psychophysics.
At the DRCMR I expanded my field of interest and started on a collaborative project with the Institute for biological Psychiatry Sankt Hans, Roskilde and "The Initiative for Integrative Psychiatric Research"- iPSYCH, studying the underlying neural correlates for schizophrenia by investigating children with 22q11 syndrome, the greatest genetic factor associated with schizophrenia. Individuals suffering from this genetic disorder have a 30 – 40 fold risk of developing schizophrenia and psychosis, next to other physiological and psychiatric disorders. Here we used fMRI and an oddball paradigm called mismatch negativity to reveal cortical areas and their connectivity which could play a major role in schizophrenia. Since 2014 I am funded by the Lundbeck Foundation to follow my own project which is concerned with the audio-visual integration of unexpected events and how the brain establishes a probabilistic map of expected events and consequently processes unexpected events in both modalities.
I am really happy to be a part of this thriving environment at the DRCMR and I truly appreciate the open work culture, the collaborative energy and my colleagues, who are always happy to help whenever needed.

ESBEN THADE PEDERSEN

I came to DRCMR from University Medical Center Utrecht, The Netherlands in December 2014. I obtained my degree in electronic engineering at the University of Aarhus in Denmark and subsequently I worked at the European Organization for Nuclear Research (CERN) in Switzerland. Later I finished my master's degree and PhD in biomedical engineering, also at the University of Aarhus in Denmark. I did my PhD as a collaboration between the Center of Functionally Integrative Neuroscience (CFIN) in Aarhus and National Neuroscience Institute in Singapore. After the PhD I worked at the Clinical Imaging Research Centre (CIRC) under the Agency for Science, Technology and Research (A*STAR), also in Singapore. In 2011, seven years later, I moved to Utrecht Medical Centre in the Netherlands where I worked across the department of oncology, radiology and the Ultra-High-Field MRI group. My main interest area is methodological MRI developments for imaging of blood flow and metabolism, particularly in the brain. When the opportunity of building up a 7 Tesla research group came up at DRCMR, my family and I had no doubts that we were moving to Denmark. My wife is doing metabolic research and thanks to the very stimulating and vibrant research environment Copenhagen offers, she soon got a job at The Novo Nordisk Foundation Center for Basic Metabolic Research at Copenhagen University. It has therefore been easy for my family to feel at home in Denmark and I am very happy to be back after more than 10 years abroad!

LEO TOMASEVIC

I am an Electronic Engineer with a PhD on EEG brain features for the development of brain-computer interface systems. Before coming to DRCMR, I was at the Italian National Research Council (CNR) working on new approaches to evaluate brain activity in the sensorimotor area and new methods to process the EEG data. I applied for a Post-doc position at DRCMR to continue my research in one of the best environments to develop my interests and ideas into complete projects. This is possible because of the high level of both the technology of the facilities and the extensive expertise in various fields of research. Now, I have the opportunity to continue my studies with new inputs. Together with my new colleagues I have established the EEG group at DRCMR to create a forum where scientists with interest in EEG can learn from each other. I am also involved in the project on real time EEG evaluation to close the loop between the brain state and the non-invasive brain stimulation techniques. This is a really cutting edge study and I was lucky to arrive at DRCMR just before the study started. From the personal point of view, the international milieu in DRCMR makes me feel as part of a group without borders.

SAMO LASIC

Since 2009 I am employed as a researcher at CR Development, AB, Lund, Sweden. Thanks to the Vinnova (Marie Curie) grant, I am also joining the Diffusion imaging group (DIG) at DRCMR in the period 2014 – 2016. My research involves development of novel diffusion weighted NMR/MRI pulse sequences to study properties of tissue microstructure. Within DIG I am focusing on NMR/MRI methods to probe molecular exchange between different tissue microenvironments and study tissue anisotropy on sub-voxel length scales. The new methods are first tested on a preclinical scanner and then applied on multiple sclerosis patients in a clinical study. I obtained my PhD in Physics at the Faculty of Mathematics and Physics, Ljubljana, Slovenia in 2006 with the title "Translational dynamics of granular matter studied by NMR". Between 2007 – 2009 I conducted post-doctoral research at the Division of Physical Chemistry, Lund University, Sweden.

VIRGINIA CONDE

I came to work as a post-doctoral researcher at the DRCMR in August 2013 after having finished my PhD studies in Biomedicine at the Neurology Department of the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany. Before moving to Germany, I finished my studies in Psychology at the University of Seville, Spain. My main motivation to come to the DRCMR was the unique possibility to explore human neuro physiology in a multimodal fashion, as well as the long-standing expertise of Professor Hartwig Siebner in human neuroplasticity as studied with non-invasive brain stimulation. During my PhD I focused on the study of neuroplasticity mechanisms occurring at the systems level of the human brain by the use of non-invasive brain stimulation and structural magnetic resonance imaging, so coming to the DRCMR has given me the chance to expand on my prior research by acquiring new multimodal technical skills and by being in contact with an interdisciplinary group of international researchers.

COLLABORATIONS

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 (Assoc. Professor Torben Lund, Assoc. Professor Sune Jespersen, Simon Eskildsen)
- Center for Insoluble Protein Structures (inSPIN) (Professor Niels Christian Nielsen)
- Centre for Psychiatric Research (Professor Poul Videbech)
- Danish School of Education (Assoc. Professor Lisser Rye Ejersbo)
- Department of Chemistry (Professor Niels Christian Nielsen)
- Interdisciplinary Nanoscience Center (iNANO) (Professor Niels Christian Nielsen)
- MR Research Centre, Department of Clinical Medicine (Professor Hans Stødkilde Jørgensen)

Albeda Research Aps (Drs. Mathilde Lerche, Pernille Rose Jensen, Magnus Karlsson)

Copenhagen Business School, Frederiksberg, Denmark

- Department of Marketing, Decision Neuroscience Research Group (Martin Skov)

Gubra Aps, Hørsholm, Denmark (Dr. Jacob Jelsing, CSO)

H. Lundbeck A/S, Lundbeck Research, Valby, Denmark (Senior Director, Synaptic Transmission I, Nils Plath, Dr.Michael Didriksen, Head of Department - Synaptic transmission II)

Metropolitan University College, Radiography (Anne-Mette Briand de Crevecoeur)

National Center of Reading, Copenhagen, Denmark (Assoc. Professor Bo Steffensen)

Odense University Hospital, Odense, Denmark

- Department of Neurology (Professor David Gaist)

Steno Diabetes Center, Copenhagen (Professor Peter Rossing)

Technical University of Denmark, Lyngby, Denmark

- Department of Applied Mathematics and Computer Science (Assoc. Professor Koen van Leemput)
- Department of Electrical Engineering (Assoc. Professor Sadasivan Puthusserypady, Helge B. Sørensen, Vitaliy Zhurbenko, Professor Torsten Dau, Jens E. Wilhjelm, Jan Henrik Ardenkjær-Larsen)
- Department of Informatics and Mathematical Modelling (Professor Lars Kai Hansen, Professor Rasmus Larsen, Assoc. Professor Morten Mørup)
- Department of Physics (Professor Ulrik Lund Andersen, 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 (Assoc. Professor Klaus Kähler Holst)
  - Department of Food and Resource Economics (Assoc. Professor Toke Reinholt Fosgaard)
  - Department of Neuroscience and Pharmacology (Professor Jens Bo Nielsen, Professor Maurice Ptito, Professor Ron Kupers)
  - Department of Nutrition, Exercise and Sport Sciences (Professor Jens Bo Nielsen, Assoc. Professor Nikolai Nordsborg)
  - Institute of Public Health, Department of Health Psychology (Professor Erik Lykke Mortensen)
  - Wilhelm Johannsen Centre for Functional Genome Research, Department of Cellular and Molecular Medicine (Professor Niels Tommerup)
  - Center for Healthy Aging (Professor Lene J. Rasmussen)
- FACULTY OF HUMANTITIES
  - Department of Economics (Assoc. Professor Alexander Sebald)
  - Department of Scandinavian Studies and Linguistics (Assoc. Professor Kasper Boye)
- FACULTY OF SOCIAL SCIENCES
  - The Unit for Cognitive Neuroscience, Department of Psychology (Professor Jesper Mogensen)

University of Southern Denmark, Odense, Denmark

- Department of Psychology (Assoc. Professor Christian Gerlach)
- Institute of Clinical Medicine (Professor David Gaist)

COPENHAGEN UNIVERSITY HOSPITALS

Copenhagen University Hospital Bispebjerg, Bispebjerg, Denmark

- Department of Neurology (Assoc. Professor Annemette Løkkegaard, Assoc. Professor Hanne Christensen)
- Department of Radiology (Senior Consultant Anders Christensen)
- Research Laboratory for Stereology and Neuroscience (Professor Bente Pakkenberg)
- Department of Clinical Medicine (Professor Michael Kjær)

Copenhagen University Hospital Glostrup, Glostrup, Denmark

- Department of Neurology (Assoc. Professor Messoud Ashina)
- Department of Rheumatology (Professor Mikkel Østergaard)
- Functional Imaging Unit (Assoc. Professor Egill Rostrup)

Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

- Department of Paediatrics (Professor Ole Axel Pryds)

- Gastro Unit Surgical Division
  (Chief Consultant Svend Schulze, Professor Thue Bissgård)
- Department of Clinical Medicine
  (Professor Sten Madsbad)
- Clinical Research Center
  (Assoc. Professor Thomas Brabdholm)

Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

- Centre for Integrated Molecular Brain Imaging, Neurocenter (Professor Gitte Moos Knudsen, Professor Olaf B. Paulson, Dr. Vibe Frøkjær, Dr. Patrick Fisher)
- Danish Multiple Sclerosis Centre, Neurocenter (Professor Finn Selleberg, Professor Per Soelberg, med. Consultant Morten Blinkenberg)
- Danish Dementia Research Centre, Neurocenter (Professor Gunhild Waldemar)
- Department of Clinical Physiology, Nuclear Medicine and PET (Professor Andreas Kjær)
- Department of Radiology (Professor Carsten Thomsen)
- Department of Paediatrics and Adolescent Medicine (Professor Peter Uldall, Peter Born PhD)

Psychiatric Centres in the Capital Region

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

INTERNATIONAL COLLABORATIONS

Australia National University, Canberra, Australia

- Centre for Research on Ageing (Professor Kaarin Anstey)
- Research Centre for the Neurosciences of Ageing, Academic Unit of Psychiatry and Addiction Medicine (Assoc. Professor Jeffrey Looi)

Brookhaven Labaratory, New York, USA

- Medical Department (Professor Helene Benveniste)

Cambridge University, Cambridge, United Kingdom

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

Centre de Recherche de l'Institut du Cerveau et de la Moelle épinière, Paris, France (Charlotte Rosso)

Chinese Academy of Sciences

- Institute of Biophysics (Professor Rong Xue)

Christian-Albrechts-University, Kiel, Germany

- Department of Neurology
  (Professor Thilo van Eimeren, Oliver Granert)
- Institute for Sexual Medicine (Priv.-Doz. Jorge Posenti)

Concordia University, Montreal, Canada

- PERFORM Centre/Department of Physics
  (Claudine Cauthier)

Eberhard Karls Universität Tuebingen, Germany

- Department for Neurology (Professor Ulf Ziemann)

Ecole Normale Supèrieure, Paris, France,

- Group for Neural Theory (Professor Boris Gutkin)

École polytechnique fédérale de Lausanne, Lausanne, Switzerland, Signal Processing Laboratory (Professor Jean-Philipp Thiran)

Forschungszentrum Jülich, Institute of Neuroscience and Medicine (Professor Simon Eickhoff)

GE Healthcare International (Professor Jan Henrik Ardenkjær-Larsen)

German Center for Neurodegenerative Diseases, Bonn (Prof.Tony Stöcker)

Griffith University, Queensland, Australia

- School of Physiotherapy and Exercise Science
  (Assoc. Professor Luke Haseler)

Howard University, Washington DC, USA

- Department of Physiology and Biophysics
  (Assoc. Professor Mark Burke)

Istituto di Scienze e Tecnologie della Cognizione- Consiglio Nazionale delle Ricerche, Isola Tiberina, Rome, Italy (Professor Franca Tecchio)

Karolinska Institutet, Stockholm, Sweden

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

Lund University Hospital, Lund, Sweden

- Department of Medical Radiation Physics (Professor Freddy Ståhlberg, Assoc. Professor Gunther Helms)

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

- A Martinos Center for Biomedical Imaging
  (Assoc. Professor Koen van Leemput)

Max Planck Institutes, Germany

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

Munich University of Technology, Munich, Germany

- Department of Neuropediatrics (Professor Volker Mall)

Neurospin, Gif-sur-Yvette, France

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

Oxford University, Oxford, United Kingdom

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

Radboud University Nijmegen, Nijmegen, The Netherlands

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

Sino-Danish Center for Education and Research (Assoc. Professor Kim Ryun Drasbek)

Tel Aviv University, Israel

- Department of Neurobiology (Professor Yaniv Assaf)

Università Campus Bio-Medico, Rome, Italy (Professor Vincenco DiLazzaro, Dr. Giovanni Pellegrino)

University College London, London, United Kingdom

- Department of Computer Science
  (Professor Daniel Alexander, Assoc. Professor Hui Zhang, Dr. Ivana Dropnjak)
- Sobell Department of Motor Neuroscience and Movement Disorders (Professor John Rothwell, Dr. Sven Bestmann, Dr. Nick Ward)
- Wellcome Trust Centre for Neuroimaging
  (Professor Cathy Price)

University Medical Center Hamburg-Eppendorf, Hamburg, Germany,

- Department of Neurology (Priv. Doz Götz Thomalla, Professor Alexander Muenchau)

University Medical Center Utrecht, Utrecht, The Netherlands

- Image Sciences Institute
  (Assoc. Professor Alexander Leemans)
- Department of Radiology (Professor Jeroen Hendrikse, Professor Peter Luijten, Assoc. Professor Dennis Klomp, Assoc. Professor Hans Hoogduin)
- Department of Neonatology (Professor Manon Benders)

Leiden University Medical Center, Leiden, The Netherlands

- C. J. Gorter Center for High Field MRI, Department of Radiology (Professor Andrew Webb, Assoc. Professor Matthias van Osch, Assoc. Professor Itamar Ronen)

University of California, San Diego, USA

- Center for Human Development
  (Professor Terry Jernigan)
- Department of Psychiatry
  (Assoc. Professor in Residence Wesley Thompson)
- MultiModal Imaging Laboratory (Professor Anders Dale)

University of Cologne, Cologne, Germany

- Department of Neurology (Professor Lars Timmermann)

University of Hamburg, Hamburg, Germany

- Biological Psychology and Neuropsychology
  (Professor Brigitte Röder)

University of Leipzig, Leipzig, Germany

- Department of Neurology, Language and Aphasia Lab
  (Dr. Gesa Hartwigsen, Priv. Doz Dorothee Saur)

University of Lübeck, Lübeck, Germany

- Institute of Neurogenetics
  (Professor Christine Klein, Professor Alexander Muenchau, Priv. Doz Norbert Brüggemann)

University of Manchester, Manchester, United Kingdom

- Biomedical Imaging Institute
  (Professor Geoff Parker, Dr. Penny Hubbard)

University of Medicine and Dentistry of New Jersey, USA

- Department of Biomedical Engineering and Department of Radiology (Professor Bharat Biswal)

University of Messina, Messina, Italy

- Department of Neurosciences, Psychiatry and Anaesthesiological Sciences (Professor Angelo Quartarone)

University of Montreal, Canada

- School of Optometry (Professor Maurice Ptito)

University of Oslo, Oslo, Norway

- Centre for the Study of Human Cognition
  (Professor Kristine Walhovd, Professor Anders Fjell)

University of Queensland, Brisbane St Lucia, Australia

- Queensland Brain Institute
  (Assoc. Professor Martha Garrido)

University of Zürich, Zürich, Switzerland

- Department of Economics (Dr. Justin Chumbley)

INTERNATIONAL MULTI-CENTRE RESEARCH COLLABORATIONS

- Arterial spin labelling Initiative in Dementia, European cooperation in science and technology (COST) framework.
- 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

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, GlaxoSmithKline, Novartis.

PUBLICATIONS

PH.D. THESES AND DISSERTATIONS

2013

1. **Frederiksen, K.** Corpus Callosum in Aging and Dementia.Faculty of Health and Medical Sciences, University of Copenhagen. 2013.
2. **Laustsen, C.** Non-invasive real-time metabolic kidney function in diabetic rats evaluated by hyperpolarised 13C MR, University of Aarhus. 2013.
3. **Lund, H.** MR Study of Normal-Appearing Brain Tissue: Cognitive Correlations and Blood-Brain Barrier Permeability. Faculty of Health and Medical Sciences, University of Copenhagen. 2013.
4. **Lyksborg, M.** Determination of Magnetic Resonance Imaging Biomarkers for Multiple Sclerosis Treatment Effects. Department of Applied Mathematics and Computer Science, Technical University of Denmark. 2013.
5. **Nejad, A. B.** Longitudinal MRI Study of Functional Brain Connectivity During a Working Memory Task in Antipsychotic-Naïve, First-Episode Schizophrenia Patients. Faculty of Health and Medical Sciences, University of Copenhagen. 2013.

2014

1. **Andersen, K. W.** Brain Network Modelling. Department of Applied Mathematics and Computer Science, Technical University of Denmark. 2014.
2. **Gelskov, S. A. V.** The Neural Mechanisms of Loss Aversion during Decision-Making. Faculty of Health Science, University of Copenhagen. 2014.
3. **Herz, D.** Neural Mechanisms Underlying Motor Impairment in Parkinson's Disease. Faculty of Health Science, University of Copenhagen. 2014.
4. **Lauritzen, M. H.** Imaging Cardiac Metabolism using Hyperpolarized [1-^{13}C]pyruvate MRS. Faculty of Health Science, University of Copenhagen. 2014.
5. **Laursen, H. R.** On empathic accuracy and emotional face processing and associations with variation in the oxytocin receptor and serotonin transporter genes and long-term ecstasy use. Faculty of Health Sciences, University of Copenhagen. 2014.
6. **Reislev, N. L.** The Wiring of the Blind Brain. Faculty of Health Science, University of Copenhagen. 2014.

BOOK CHAPTERS

2013

1. **Baruël Johansen, L., Siebner, H. R., Werge, T. M. & Madsen, K. S.** Hjernen – Genetik og Udvikling i Billeder. Den Genetiske Hjerne. Tommerup, N. (red.). Hjerneforum, Vol. 2013, Kap. 3, p. 23-34, 2013.
2. **Siebner, H. R. & Herz, D.** fMRI in Parkinson's Disease. fMRBasics and Clinical Applications. Ulmer, S. & Jansen, O. (red.). Second Edition udg. Springer, Kap. 18, p. 227-238, 2013.

2014

1. **Hjortkjær, J.** The musical brain. An Introduction to Neuroaesthetics: The Neuroscientific Approach to Aesthetic Experience, Artistic Creativity and Arts Appreciation. . Lauring, J. (red.). Museum Tusculanum Press/ Chicago University Press 2014.
2. **Siebner, H. R. & Ziemann, U.** Transkranielle Magnetstimulation. Leitlinien Klinische Neurophysiologie und funktionelle Bildgebung. . Bischoff, C. & Straube, A. (red.). Kohlhammer, Kap. A-7, p. 67-75, 2014.
3. **Siebner, H. R. & Ziemann, U.** Zentrale demyelinisierende Erkrankungen. Leitlinien Klinische Neurophysiologie und funktionelle Bildgebung. . Bischoff, C. & Straube, A. (red.). Kohlhammer, Kap. B-4.3, p. 256-260, 2014.
4. **Siebner, H. R. & Ziemann, U.** Zervikale Myelopathie. Leitlinien Klinische Neurophysiologie und funktionelle Bildgebung. . Bischoff, C. & Straube, A. (red.). Kohlhammer, Kap. A-4.2, p. 253-255, 2014.

JOURNAL ARTICLES

2013

1. **Agner, B. R., Åkeson, P., Linde, J., Jensen, G. B. & Dixen, U.** Assessment of Left Atrial Volume by Magnetic Resonance in Patients with Permanent Atrial Fibrillation. The Short-axis Method vs. the Single Plane Area-length Method. The Open Cardiovascular Imaging Journal. 4, p. 4-10, 2013.
2. **Assaf, Y., Alexander, D. C., Jones, D. K., Bizzi, A., Behrens, T., Clark, C. A., Cohen, Y., Dyrby, T. B., Huppi, P. S., Knoesche, T. R., Lebihan, D., Parker, G. J. M., Poupon, C., Anaby, D., Anwander, A., Bar, L., Barazany, D., Blumenfeld-Katzir, T., De-Santis, S., Duclap, D., Figini, M., Fischi, E., Guevara, P., Hubbard, P., Hofstetter, S., Jbabdi, S., Kunz, N., Lazeyras, F., Lebois, A., Liptrot, M. G., Lundell, H., Mangin, J-F., Dominguez, D. M., Morozov, D., Schreiber, J., Seunarine, K., Nava, S., Poupon, C., Riffert, T., Sasson, E., Schmitt, B., Shemesh, N., Sotiropoulos, S. N., Tavor, I., Zhang, H. G., Zhou, F-L. & CONNECT consortium.** The CONNECT project: Combining macro- and micro-structure. NeuroImage. 80, p. 273-82, 2013.
3. **Axelsen, M. B., Poggenborg, R. P., Stoltenberg, M., Kubassova, O., Boesen, M., Hørslev-Petersen, K., Bliddal, H., Hanson, L. G. & Østergaard, M.** Reliability and responsiveness of dynamic contrast-enhanced magnetic resonance imaging in rheumatoid arthritis. Scandinavian Journal of Rheumatology. 42, 2, p. 115-22, 2013.
4. **Barthélemy, D., Knudsen, H., Willerslev-Olsen, M., Lundell, H., Nielsen, J. B. & Biering-Sørensen, F.** Functional implications of corticospinal tract impairment on gait after spinal cord injury. Spinal Cord. 51, 11, p. 852-6, 2013.
5. **Baumgaertner, A., Hartwigsen, G. & Roman Siebner, H.** Right-hemispheric processing of non-linguistic word features: Implications for mapping language recovery after stroke. Human Brain Mapping. 34, 6, p. 1293-1305, 2013.
6. **Blinkenberg, M., Sellebjerg, F., Leffers, A. M., Madsen, C. G. & Sørensen, P. S.** Clinically silent PML and prolonged immune reconstitution inflammatory syndrome in a patient with multiple sclerosis treated with natalizumab. Multiple sclerosis (Houndmills, Basingstoke, England). 19, 9, p. 1226-9, 2013.
7. **Broberg, B. V., Madsen, K. H., Plath, N., Olsen, C. K., Glenthøj, B. Y., Paulson, O. B., Bjelke, B. & Søgaard, L. V.** A schizophrenia rat model induced by early postnatal phencyclidine treatment and characterized by Magnetic Resonance Imaging. Behavioural Brain Research. 250, p. 1-8, 2013.
8. **Brüggemann, N. & Siebner, H. R.** Transkranielle Magnetstimulation bei Amyotropher Lateralsklerose. Neurophysiologie – Labor. 35, 2-3, p. 109,–113 5 p., 2013.
9. **Christensen, M. S. & Grey, M. J.** Modulation of proprioceptive feedback during functional electrical stimulation: an fMRI study. The European journal of neuroscience. 37, 11, p. 1766-78, 2013.
10. **Dogonowski, A-M., Andersen, K. W., Madsen, K. H., Sørensen, P. S., Paulson, O. B., Blinkenberg, M. & Siebner, H. R.** Multiple sclerosis impairs regional functional connectivity in the cerebellum. NeuroImage: Clinical. 4, p. 130-8, 2013.
11. **Dogonowski, A-M., Siebner, H. R., Sørensen, P. S., Paulson, O. B., Dyrby, T. B., Blinkenberg, M. & Madsen, K. H.** Resting-state connectivity of pre-motor cortex reflects disability in multiple sclerosis. Acta Neurologica Scandinavica. 128, 5, p. 328,–335 2013.
12. **Dogonowski, A-M., Siebner, H. R., Sørensen, P. S., Wu, X., Biswal, B., Paulson, O. B., Dyrby, T. B., Skimminge, A., Blinkenberg, M. & Madsen, K. H.** Expanded functional coupling of subcortical nuclei with the motor resting-state network in multiple sclerosis. Multiple Sclerosis. 19, 5, p. 559-566, 2013.
13. **Dyrby, T. B., Søgaard, L. V., Hall, M. G., Ptito, M. & Alexander, D. C.** Contrast and stability of the axon diameter index from microstructure imaging with diffusion MRI. Magnetic Resonance in Medicine. 70, 3, p. 711-721, 2013.
14. **Fagerlund, B., Pinborg, L. H., Mortensen, E. L., Friberg, L., Baaré, W. F. C., Gade, A., Svarer, C. & Glenthøj, B. Y.** Relationship of frontal D2/3 binding potentials to cognition: a study of antipsychotic-naive schizophrenia patients. International Journal of Neuropsychopharmacology. 16, 1, p. 23-36, 2013.
15. **Frøkjær, V., Erritzoe, D., Holst, K. K., Jensen, P. S., Rasmussen, P. M., Fisher, P., Baaré, W. F. C., Madsen, K. S., Madsen, J., Svarer, C. & Knudsen, G. M.** Prefrontal serotonin transporter availability is positively associated with the cortisol awakening response. European Neuropsychopharmacology. 23, 4, p. 285-294, 2013.
16. **Grady, C. L., Siebner, H. R., Hornboll, B., Macoveanu, J., Paulson, O. B. & Knudsen, G. M.** Acute pharmacologically induced shifts in serotonin availability abolish emotion-selective responses to negative face emotions in distinct brain networks. European Neuropsychopharmacology. 23, 5, p. 368-378, 2013.
17. **Groppa, S., Muthuraman, M., Otto, B., Deuschl, G., Siebner, H. R. & Raethjen, J.** Subcortical substrates of TMS induced modulation of the cortico-cortical connectivity. Brain Stimulation. 6, 2, p. 138-146, 2013.
18. **Haahr, M. E., Fisher, P., Holst, K., Madsen, K., Jensen, C. G., Marner, L., Lehel, S., Baaré, W. F. C., Knudsen, G. & Hasselbalch, S.** The 5-HT(4) receptor levels in hippocampus correlates inversely with memory test performance in humans. Human Brain Mapping. 34, 11, p. 3066-3074, 2013.
19. **Habekost, T., Vogel, A., Rostrup, E., Bundesen, C., Kyllingsbaek, S., Garde, E., Ryberg, C. & Waldemar, G.** Visual processing speed in old age. Scandinavian Journal of Psychology. 54, 2, p. 89-94, 2013.
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