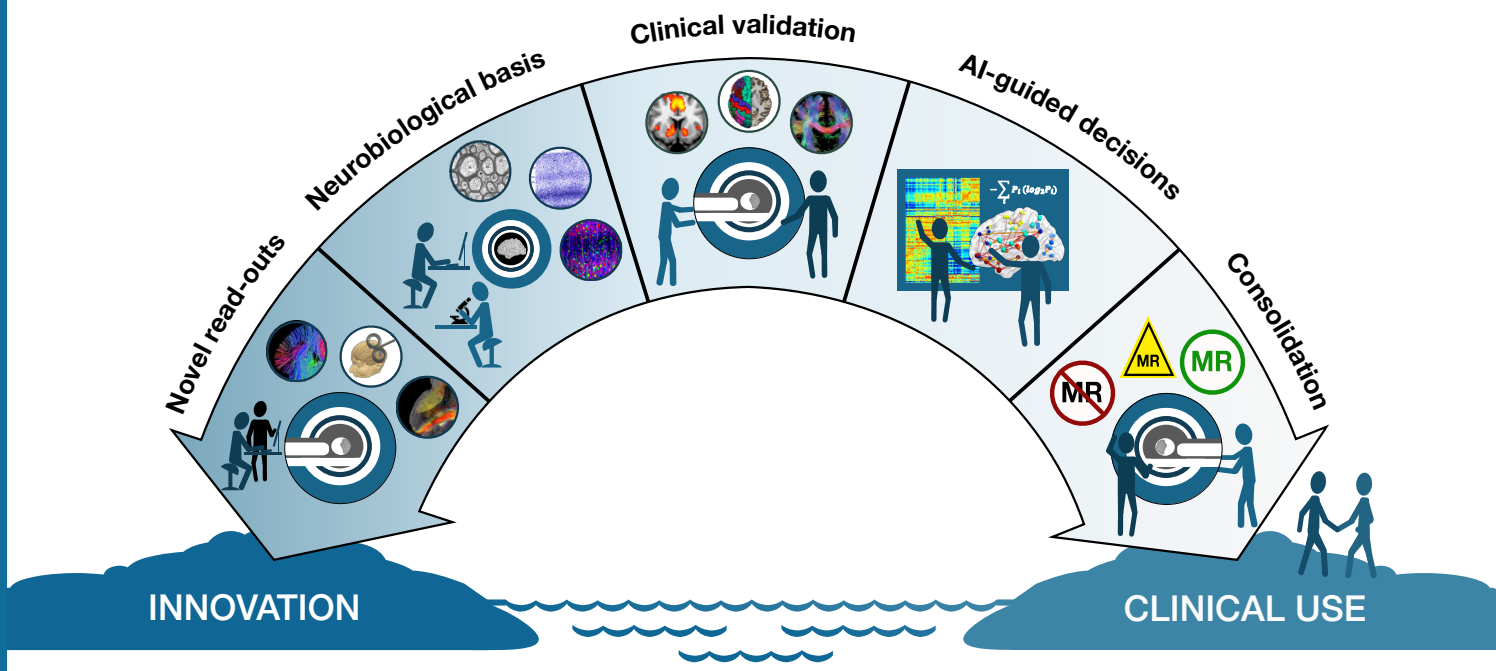
DRCMR

DANISH RESEARCH CENTRE FOR MAGNETIC RESONANCE

Triennial Report
2019 – 2021



Hvidovre Hospital

DANISH RESEARCH CENTRE FOR MAGNETIC RESONANCE

GLOBAL EXCELLENCE IN HEALTH

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PREFACE

THE DANISH RESEARCH CENTRE FOR MAGNETIC RESONANCE IN 2019, 2020 AND 2021

The last three years have been both challenging and successful. The CoVid-19 pandemic challenged our way to do research and required major ad-hoc adjustments, but it also evidenced a great deal of cohesion and resilience. We discovered new ways to interact and to take care of each other, going "virtual" rather than having in-person meetings. In spite of these challenges, our center continued to grow and we were able to strengthen our collaboration links with the Technical University of Denmark, the University of Copenhagen, and the Capital Region of Denmark.

Professor Hartwig Siebner, Head of Research at DRCMR. Photo: Joachim Rode.

DIVERSITY IS OUR DNA

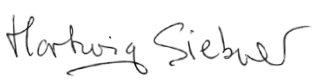
We were also able to recruit talented researchers with diverse backgrounds and competences. Currently, a multi-disciplinary team of approximately 80 researchers is pursuing front-line basic and applied biomedical MR research at DRCMR. Our diversity and unique infrastructure, united under one roof, enable us to bridge between the development of innovative mapping and stimulation methods and their neuroscientific and clinical evaluation and application. In the years to come, we will focus on the retention of our young talents, improving their long-term career perspectives in academia. We will also work on improving gender balance at the senior staff level and on increasing the proportion of clinically trained researchers at DRCMR.

SHOWCASING OUR RESEARCH: ACHIEVEMENTS AND CULTURE

In this report, we wish to share with you the scientific progress we made in 2019, 2020, and 2021. We hope that the report will give you insights into our research activities and culture. We are developing new MR coils and new data acquisition techniques. We have massively expanded our preclinical research to improve our translational research capabilities. We have built up a unique intramural educational program and a highly transparent and interactive research culture. Our research is embedded in an open matrix structure without rigid borders between groups facilitating the initiation of innovative projects and avoiding a silo mentality.

THANK YOU !

All this would not have been possible without massive financial support for our research programs, including major funding for collaborative research from the Lundbeck Foundation and Innovation Fund Denmark. Without the continued and generous support of Danish and European funding agencies, we would not be able to push the frontiers of MRI-based brain research and to educate the next generation of scientists. We would also like to thank the management of Copenhagen University Hospital Amager and Hvidovre and the Capital Region of Denmark for their continued support. And – last, but not least – we would like to thank our collaborators and our research staff for their engagement, team spirit, and hard work which make the DRCMR a fantastic place for brain imaging and neuroscience.

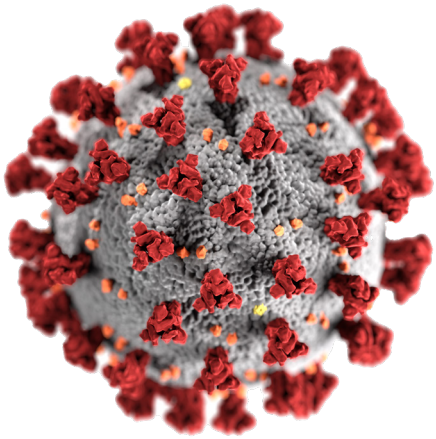


Hartwig Roman Siebner
Head of Research (DRCMR)
Clinical Professor with special focus on Precision Medicine
(Faculty of Health and Medical Sciences, University of Copenhagen)
The professorship is sponsored by the Lundbeck Foundation

HIGHLIGHTS AND MILESTONES 2019–2021

COPING WITH THE COVID-19 PANDEMIC

The first thing that comes to mind for most people when thinking about what happened in 2019-2021 is the global Covid-19 pandemic. The pandemic had massive effects on society as a whole and on our research at DRCMR as well. We witnessed society going into lockdown for prolonged periods and the health sector being turned up-side-down. Our hospital made massive efforts to ensure sufficient capacity to treat a new, unknown disease. Our research staff worked from home for prolonged periods. Online meetings became daily routine and had to be balanced with home schooling. We saw a plethora of ever-changing restrictions at the hospital and in the public as flexible adjustments to the CoVid-19 challenge, complemented by regular testing for Covid-19 and a nation-wide vaccination programme. The last years were undoubtedly a tough period, especially for our junior researchers and international staff. PhD students and post-docs had to cope with significant delays of their research projects during the first lock-down in spring 2020. Foreign researchers, who had joined us in recent years and had not yet established a large social network in Denmark, found themselves isolated at home in this period of uncertainty, being cut-off from their colleagues and far away from their families. On the positive side, we had no serious cases of Covid-19 among DRCMR staff. The forced "deceleration" during the lock-down periods offered researchers the opportunity to immerse themselves in their data or into a topic of interest. The lockdown also gave the opportunity to finish up a lot of manuscripts resulting in a record-high number of publications in 2020. These even included a couple of Covid-19 related publications where DRCMR researchers applied their statistical experience to help analyse Covid-19 data being collected elsewhere.



GLOBAL EXCELLENCE IN HEALTH

Back in 2014, our research centre received the "Global Excellence in Health" award by the Capital Region of Denmark, which was renewed in 2017 until the end of 2020. The Capital Region of Denmark decided to discontinue the Global Excellence programme after 2020. The award has been a large asset for us to facilitate scientific interactions and initiate research collaborations within and beyond the Capital Region of Denmark, boosting the DRCMR's regional, national, and global reputation. We would like to thank the Capital Region for this recognition – a recognition that fuels our efforts to pursue translational neuroimaging research at the highest quality and to further develop our center as key infrastructure for interdisciplinary and diverse brain imaging in the Capital Region.

Senior Vice President Jan Egebjerg from the Lundbeck Foundation giving the Welcome notice at the 2nd International Symposium on Advancing stimulation precision medicine of brain disorders. The symposium was held at Hvidovre Hospital on Nov 29. 2019.

PRECISION MEDICINE

The multimodal integration of complementary MRI modalities bears enormous potential of precision imaging of brain disorders. Precision MRI can characterize how the brain's structure, function, and metabolism are affected in a single patient. Likewise, advances in non-invasive brain stimulation provide unique, yet underexplored possibilities for personalized precision treatment of dysfunctional brain circuits.

Precision brain imaging and stimulation are combined by Hartwig Siebner, full professor with special focus on precision medicine at the Faculty of Health and Medical Sciences at the University of Copenhagen. This five-year professorship has been generously sponsored by the Lundbeck Foundation. In the last three years, our research into precision brain imaging and stimulation has received a major boost, thanks to two major grants. In 2019, Innovation Fund Denmark invested 14 million DKK (Grand Solutions grant) in a 5-year project to develop precision brain stimulation as a therapy for major depressive disorder. The project, Precision-BCT, is led by DRCMR and involves MagVenture A/S (Farum, Denmark), the Centre for Neuropsychiatric Depression Research of the Mental Health Centre Glostrup, DTU Health Tech, Localite GmbH (Bonn, Germany) and the Ludwig Maximilian's University (Munich, Germany) as partners.

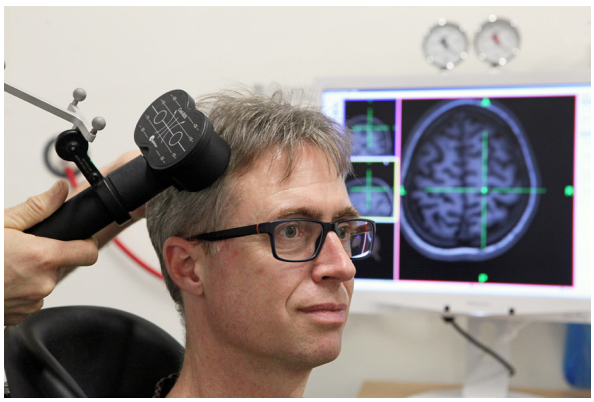
In the Precision-BCT project, we develop novel transcranial magnetic stimulation and navigation equipment that will enable simultaneous stimulation of several brain regions, precise spatial targeting and dose control, and highly flexible stimulation patterns. These new technical solutions will be integrated with structural and functional brain imaging to establish a workflow that can efficiently and selectively target the individual brain-circuit dysfunction in patients with major depressive disorder.

In 2021, the Lundbeck Foundation awarded Hartwig Siebner, Professor Andrea Kühn, Charité Universitätsmedizin in Berlin, Germany, and Professor Angela Cenci Nilsson, Lund University, Sweden, a Collaborative Projects grant (35 million DKK) to address a central question in neuroscience with enormous therapeutic implications: How can the dysfunction of brain circuits in Parkinson's disease be normalized with device-based neuromodulation? Using a multimodal and multiscale approach, the project team will investigate how the cortico-basal ganglia circuit is altered in Parkinson's disease as well as levodopa-induced dyskinesia. Based on this knowledge they aim to develop treatments with tailored non-invasive and invasive brain stimulation. The 5-year project is entitled ADAptive and Precise brain-circuit Targeting in Parkinson's disease (ADAPT-PD).

A NEW PROFESSOR

In 2021, Axel Thielscher was appointed full professor at the Technical University of Denmark (DTU), Department of Health Technology. His research focuses on testing the mechanisms of action of non-invasive brain stimulation methods and on identifying the factors that cause variability in the stimulation outcome and hamper the clinical efficacy of non-invasive brain stimulation. His vision is to transform transcranial brain stimulation into an effective medical treatment by personalizing established transcranial stimulation methods and introducing novel stimulation approaches which expand the precision and efficacy of transcranial brain stimulation. Thielscher shares his time equally between DTU and DRCMR.

Axel´s research received a substantial boost in 2019. He was awarded a Lundbeck Foundation Ascending Investigator grant (5 mill. DKK) which supports his project "Accurate Computational Dose Control for Transcranial Electric and Ultrasound Stimulation". The project is geared to substantially advance



Professor Axel Thielscher demonstrating Transcranial Magnetic Stiumation (TMS) of the brain. Photo: Amager and Hvidovre Hospital.

computational dosimetry of two powerful and complementary stimulation techniques, namely Transcranial Electric Stimulation and Transcranial Focused Ultrasound Stimulation.

EDUCATION AND RECOGNITION

We have a strong focus on thorough in-house education to provide young scientists with necessary knowledge and skills to conduct cutting-edge research, covering all aspects of neuroimaging neuroscience. The intra-mural educational activities engage all staff members, fostering an inspiring multi-disciplinary research environment and openness and respect for other disciplines. A special focus is on mentoring our researchers and assisting them in planning their career to unfold the scientific potential and secure the wellbeing of each member of staff. We are therefore always very proud when one of our researchers achieve grants, awards or when Danish media show an interest in their results.

Mads Just Madsen, a PhD-student at DRCMR, won the DAREMUS prize for his talk at the annual meeting of the Danish Society for Research in Mulitple Sclerosis in 2021. Mads was also awarded a prize from the Torben Fog and Erik Trier's Foundation.

OTHER MAJOR GRANTS

Our pool of talented young researchers at DRCMR is growing, and several emerging talents have attracted major funding. Senior Researcher Oliver Hulme has been awarded a "Novo Nordisk Foundation Exploratory Synergy" Grant (5 million DKK) with his partners at the London Mathematical Laboratory in 2021. The project aims to study ergodicity and whether the brain computes time averages.

In 2021, research fellow David Meder was awarded a "Sapere Aude Research Leader" grant from the Independent Research Fund Denmark to build up his own group at the DRCMR and do research on novel theories of the dopamine system in health and Parkinson's disease.

DRCMR reaserchers in Tokyo in Oct 2019 on a visit to Japanese collaborators. The visit was supported by an International Network Grant from The Danish Agency for Science and Higher Education.

Postdoc Oula Puonti received a sub-project grant as a co-applicant from the National Institutes of Health (NIH). The project is led by Assitant Professor Douglas Greve from Massachusetts General Hospital in Boston, USA, and aims to continue development and hardening of the neuroimaging software package FreeSurfer. Oula Puonti was also awarded a Lundbeck NIH Brain Initiative grant, as one of three researchers at Danish universities and hospitals. In collaboration with colleagues at Massachusetts General Hospital, Oula will seek to map the lateral prefrontal cortex, which is part of the brain's outer layer, the cortex.

Professor Axel Thielscher also won a grant as co-applicant from the NIH along with assistant Professor Alexander Opitz from the University of Minnesota in Minneapolis, USA. The project aims to develop an open-source software solution to integrate non-invasive brain stimulation with functional imaging data.

Our talented postdocs, Lasse Christiansen, Melissa Larsen, and Vanessa Wiggermann received postdoc grants from the

Fun and games at the 2020 DRCMR summer picnic in Valbyparken.

DRCMR staff at the 2021 DHL relay race - an annual event.

Lundbeck Foundation in 2020 and 2021. Two research Fellows, Leo Tomasevic and Nathalie Just, were awarded Lundbeck Foundation Experiment grants in 2020 and 2021, respectively, allowing them to pioneer novel lines of MRI-based neuroscientific research.

We are very proud on behalf of our researchers that they have succeeded in attracting funding for pursuing their scientific goals, and we would like to thank the supporting funding agencies for their strong support.

RECRUITMENT

Over the past three years, we have been successful in attracting new talents, both from Denmark and abroad. We have recruited 15 new researchers at a postdoctoral level or higher, and we are happy to welcome them aboard and to be able to present them here. Several international researchers who joined DRCMR at the peak of the Covid-19 pandemic had to face additional challenges due to restrictions to enter the country due to travel restrictions and difficulties to finalize the official paperwork with all public offices being closed. Despite these obstacles, they have become an integral part of the DRCMR team and have already made significant contributions.

RESEARCHERS, STUDENTS, AND SUPPORT STAFF MEMBERS

The absolute highlight of the past years is once again our staff. Researchers, students and administrative staff have once again made DRCMR an incredible place to work. Everybody is working hard to achieve the best and most innovative results, but nobody seems to forget their colleagues and the fact that collaboration is key to success. Against all odds, our staff has been able to maintain the good spirit and to overcome the challenges that had to be faced during the pandemic. We are looking back with pride at three memorable, prosperous years, and looking optimistically forward that our fantastic team will break new ground with their research, advancing our understanding of the human brain and its disorders.

VISITING PROFESSORSHIPS

RAY DOLAN – VISITING PROFESSOR AND BRAIN PRIZE WINNER

In 2017, Ray Dolan, a Professor of psychiatry at University College London, won the Brain Prize for his seminal work on understanding the reward system. At the prize conference in Denmark, he sat down with members of DRCMR for lunch, where he mentioned his interest in taking a sabbatical, and that Copenhagen seemed a nice place to consider as a destination. Fast forward two years and Ray was a visiting professor at DRCMR for a 6-month visit, funded by the Lundbeck Foundation. He split his time between his office at DRCMR, and the Black Diamond library where he was working on a writing project, amongst other things. The visit was valuable for DRCMR, particularly for those working in the cognitive and computational neurosciences. During the visit, our weekly research meeting was host to around eight talks by different members of Ray's research institute, where we heard about topics such as hippocampal replay in planning and problem-solving, computational psychiatric approaches to depression and OCD, consciousness and metacognition, and neuroaesthetics to name a few. The visit was unfortunately cut short due to the beginning of the pandemic. Fortunately, it had already helped galvanise a connection between Ray's group and DRCMR, with both Oliver Hulme and David Meder being made honorary fellows of the Max-Planck UCL centre for Computational Psychiatry and Aging. The influence of this connection is ongoing in their current and future work on the reward system, and its disorders in Parkinson's disease. The visit is arguably testament to the broader value provided by the Brain Prize for Danish neuroscience research.

Professor Ray Dolan

ABOUT THE VISITING PROFESSORSHIP

Visiting Professorship within the field: "How the brain constructs models of the world to enable planning and decision making".

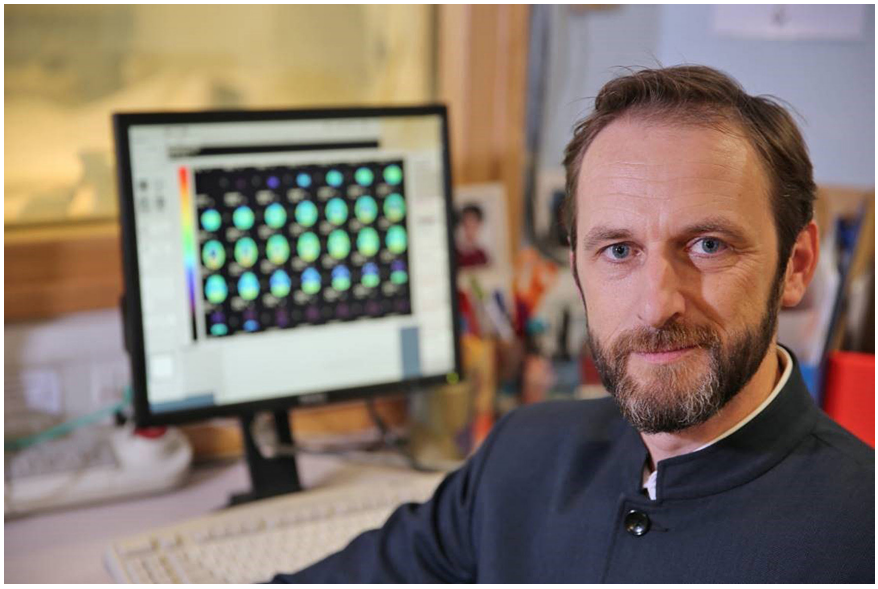
Research Area: Cognitive and Neuroscience, Reward and Homeostasis research group

University of Copenhagen and Hvidovre Hospital, Danish Research Centre for Magnetic Resonance (DRCMR)

Sponsored by a grant from the **Lundbeck Foundation**: DKK 362,636

JAMES ROWE - VISITING PROFESSOR

James Rowe is Full Professor of Cognitive Neurology at the University of Cambridge and adjunct Professor of Clinical Neuroscience at the University of Copenhagen. He has been a close collaborator of our research centre for many years. James also has close family ties to Denmark (especially Bornholm) and spent a year of his neurological training at Rigshospitalet. In 2019, this collaboration was strengthened thanks to a 5-month visiting professorship at the DRCMR, generously funded by the Lundbeck Foundation. James is a world-leading expert in frontotemporal dementia, Parkinson´s disease and other neurodegenerative diseases. In his research, he combines neuroimaging techniques including ultra-high field MR imaging, PET and MEG to study how neurodegeneration affects neural circuits and their functions. During his visit, he gave several lectures in the Copenhagen area and interacted with research groups at Rigshospitalet, Hvidovre Hospital and Bispebjerg Hospital. Beyond his participation in department-wide research meetings, it was especially the movement disorders group that benefited from his engagement with ongoing projects, helpful comments and advice. Two of his lab members from the University of Cambridge also visited DRCMR and kindly shared their expertise on the post-processing of ultra-high resolution imaging data of different brain stem nuclei such as the locus coeruleus. Even though a planned research exchange back to Cambridge was delayed indefinitely due to the pandemic, the visit stimulated continued interaction between both departments.



Professor James Rowe

ABOUT THE VISITING PROFESSORSHIP

Visiting Professorship within the field: "Advancing ultra-high field magnetic resonance imaging of the locus coeruleus".

Research Area: Clinical Precision Imaging, Cognition in Movement Disorders and Movement Disorders groups.

University of Copenhagen and Hvidovre Hospital, Danish Research Centre for Magnetic Resonance (DRCMR)

Sponsored by a grant from the **Lundbeck Foundation**: DKK 149,846

THE PANDEMIC
COVID-19 LOCKDOWN

Just like most of the public sector in Denmark, DRCMR was locked down in 2020 due to the Covid-19 pandemic. The prime minister announced the lockdown on March 11, effective March 13. This meant that all staff that was non-essential for patient treatment had to work from home. Given that DRCMR is a research-only centre, this meant that all staff, save Hartwig Siebner, had to work from home. Only on rare occasions and for specific special needs was DRCMR staff allowed to come to DRCMR.

Clinical activity at the hospital was reduced to a minimum so as to prepare for an expected surge in Covid-19 patients – the first wave. At the Centre for Functional and Diagnostic Imaging and Research, this meant that only urgent radiological procedures were performed during the lockdown. This freed up clinical staff that could assist in the departments treating Covid-19 patients.

Given that the vast majority of DRCMR staff doesn't have clinical training, the lockdown meant that researchers had to embrace new work routines and set up home-offices. Video conferences and online teaching became the norm – along with home-schooling for staff with children. New concepts, such as virtual coffee-breaks and virtual Friday-beer, were also introduced as a meagre compensation for much-missed social interactions. This was a challenging period for everyone, but especially many of our international researchers that had only recently arrived at DRCMR and didn't have a large social network in Denmark.

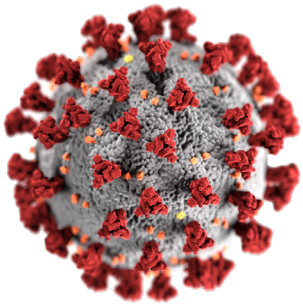
Having the whole department for himself, Hartwig Siebner started exploring the different offices and labs in the department. Using close-up pictures from the different offices, he initiated a daily quiz and newsletter with updates from the hospital – something that was very much appreciated by the staff.

Tents being erected at Hvidovre Hospital just outside DRCMR to receive Covid-19 patients in spring 2020.

Had the staff been able to come to the DRCMR, they would have witnessed a different landscape than usual. Fearing a huge surge in Covid-19 patients, the hospital set up a large array of inter-connected tents in the gardens and parking lot just outside the DRCMR buildings. Here, patients suspected of having Covid-19 could be received, tested and transported safely without having to go through the main parts of the hospital.

Thankfully, the first wave of Covid-19 wasn't as bad as originally feared. The wave peaked in April 2020 with approximately 65 Covid-19 in-patients at the hospital. So after approximately 1½ months of lockdown, the hospital and DRCMR gradually started

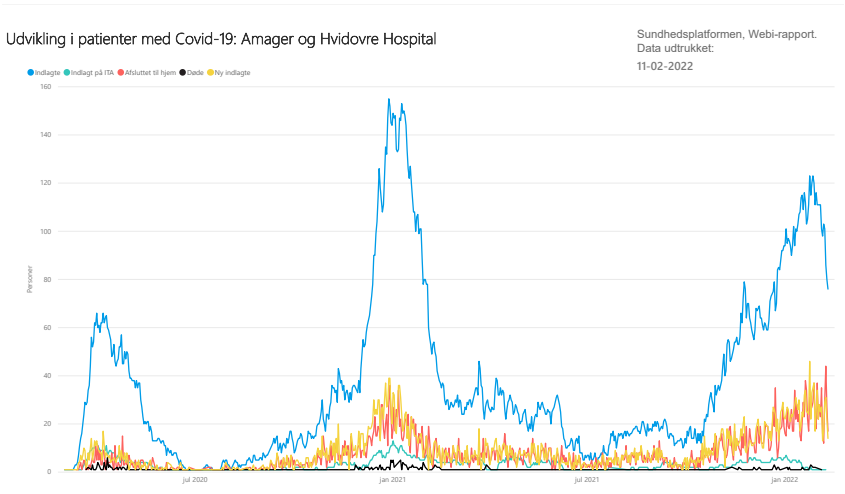
DRCMR summer picnic held in Valbyparken when restrictions are eased in June 2020.



re-opening and research staff could return to DRCMR to some extent from May 2020. This meant the introduction of a large number of restrictions and new guidelines at DRCMR to minimize the risk of infection to staff, patients and research subjects. The summer of 2020 saw a large decrease in the number of Covid-19 patients at the hospital (and in Denmark in general) and life at DRCMR started being a bit more relaxed again. However, online meetings or at least hybrid meetings were still the norm and many staff members still worked from home 2-3 days per week. Regular testing was introduced and was handled locally at the hospital. The relaxed restrictions during the summer allowed us to have a summer picnic in Valbyparken which was well-attended by staff.

The second Covid-19 wave hit towards the end of 2020 and a lot of restrictions were re-introduced. Face masks were introduced at the hospital for several months. Social interactions were again minimized, and we had to cancel our annual Christmas symposium and Christmas party. Instead we introduced an online Christmas calendar with the research groups taking turns on giving an entertaining talk or quiz during lunch.

The second wave peaked just before New Year's with approximately 155 in-patients at Hvidovre Hospital. Although this peak was much higher than in the first wave, the mortality rates had dropped significantly. The hospital didn't go into an actual lockdown again with the second wave, but clinical radiological procedures were reduced significantly in January 2021. Spring 2021 again saw a decrease in Covid-19 cases at the hospital and by summer most things were more or less back to normal. With the arrival of fall of 2021, the third wave started building up and several restrictions, e.g. face masks, were re-introduced at the hospital. However, the latest Covid-19 variant, omicron, proved to cause less serious illness although being more infectious. Also, 2021 witnessed the massive vaccination programme with the vast majority of the Danish population being vaccinated. So although infection rates throughout society sky-rocketed in January-February 2022, the no. of hospitalised patients remained lower than in the second wave. Although several DRCMR staff members were infected with Covid-19 during the pandemic, especially during the third wave, thankfully none of them experienced a serious infection that required hospitalization. The pandemic has, however, had serious consequences for many of the ongoing research projects. Many projects have been significantly delayed due to the researchers having to work from home or e.g. due to patient recruitment stopping or slowing down. Many new projects have also been delayed indirectly due to delays in e.g. the Ethics Committee evaluations. Several PhD-students had to have a virtual PhD-defence, which at first was somewhat worrying, given how many online meetings were prone to technical hiccups. Happily, all the online PhD-defences proceeded without problems and were successful, although the receptions afterwards were missed. On the positive side, the lockdown enabled many researchers to finish up writing papers on completed experiments, resulting in a record high number of publications in 2020.

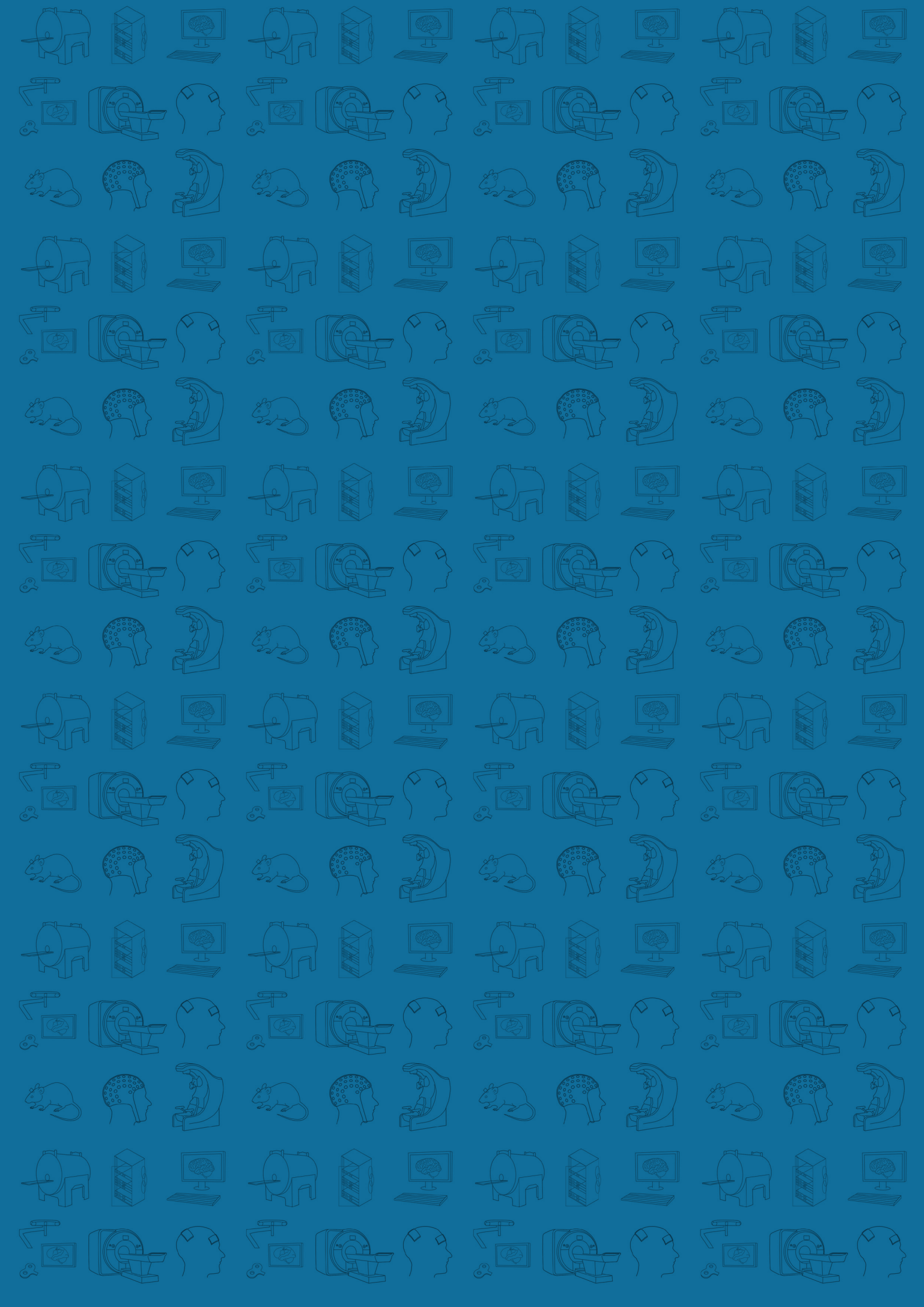


Number of Covid-19 patients at Hvidovre Hospital over time (blue curve) showing the three waves of Covid-19 infection in Denmark.

2020 and 2021 were definitely two years that have left their mark. But overall, DRCMR staff have been incredibly flexible in accommodating to a constant flow of new or changed restrictions and procedures. With the onset 2022, we hope that Covid-19 will have a much smaller impact on DRCMR and society as a whole in the years to come.

KEY PROJECTS

At DRCMR, we have a large number of interesting ongoing projects. Some projects are quite big, involving numerous researchers and are carried out in close collaboration with national or international partners while others are smaller projects involving a single PhD student and his/her supervisor. In this section, you can get a taste of some of the projects we have been working on in 2019–2021.



C-MORPH

THE MICROCOSMOS BEYOND WHAT IS VISIBLE WITH CONVENTIONAL IMAGING.

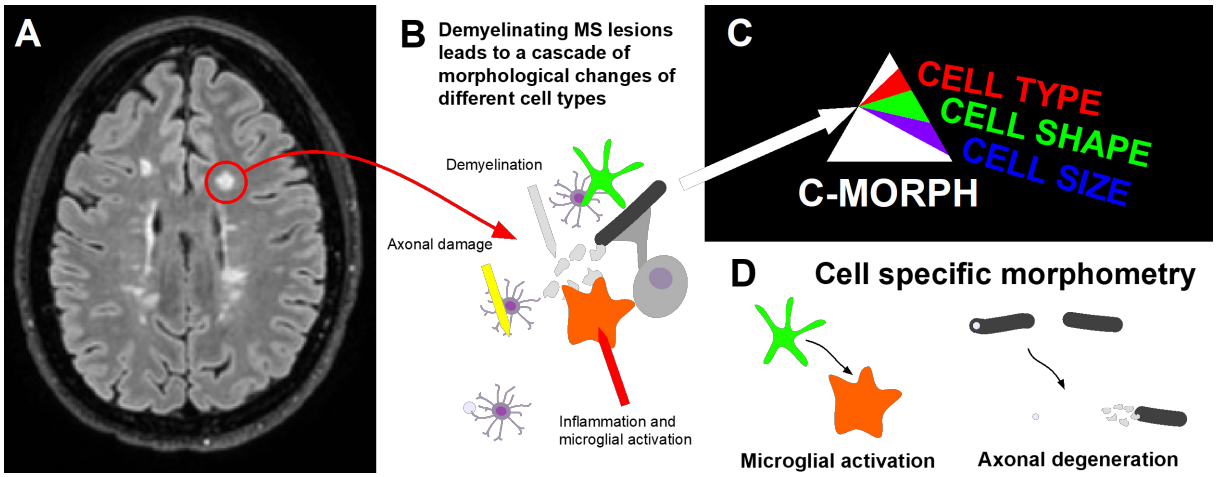
The project is funded by an ERC (European Research Council) starting grant given to Senior Researcher Henrik Lundell who is using MR imaging and spectroscopy as a tool to identify specific fingerprints of underlying disease processes and runs from 2018 to 2025. C-MORPH stands for cell type specific morphometry and has the primary goal of independently identifying neuroinflammatory and -degenerative processes with end goal applications in multiple sclerosis (MS). These processes are in a tight interplay in MS but to a different degree active in different disease stages and phenotypes. While this heterogeneity across time and individuals is known from histology, the diagnostic tools are still lacking to understand the right treatment strategy for the individual patients at a given time. The methods developed in C-MORPH could be thought of as a prism separating disease processes by identifying morphological changes to individual cell types, such as neurons and glial cells in the human brain.

To realize these goals on two independent spectroscopic MR methods developed by Henrik Lundell: The first MR method is called Powder averaged diffusion weighted spectroscopy (PADWS) and can provide an unbiased marker for cell specific structural degeneration. The second method uses Spectrally tuned gradient trajectories (STGT) which can isolate cell shape and size. In the C-MORPH project, Lundell and co-workers push these techniques further and combine them for MR-based precision medicine on state-of-the-art MR hardware.

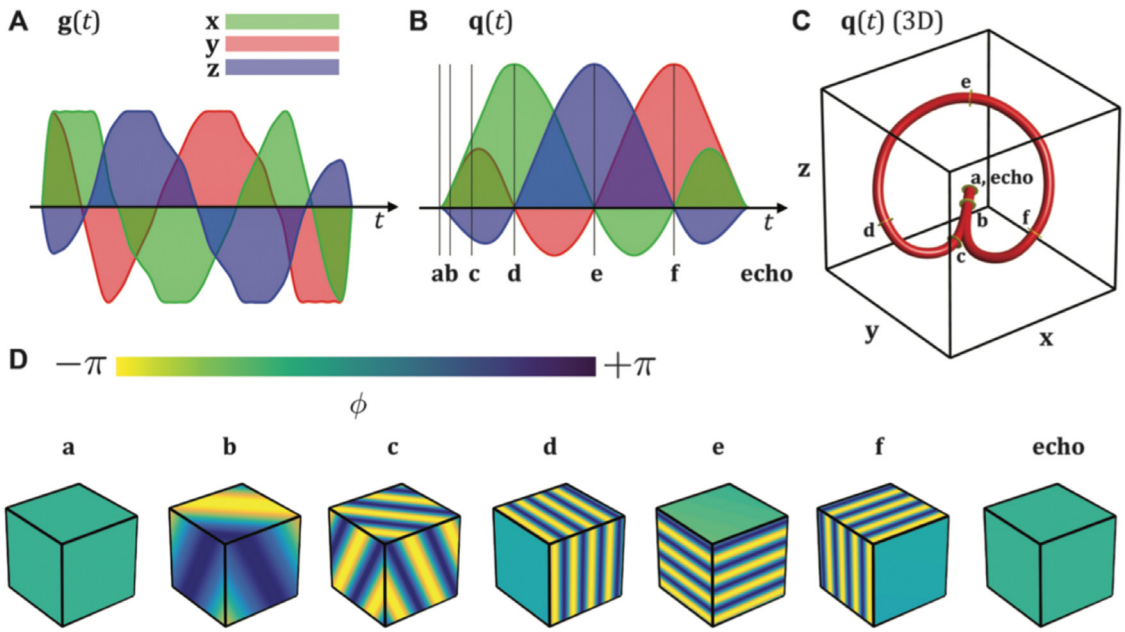
The project is divided into four work packages focusing on methods and applications. On the method side, WP1 pushes theory development, simulations and preclinical optimization of the techniques and WP3 turns these insights into robust and simplified methods feasible for human in vivo settings. These methods will be applied and tested both in rodents (WP2) and finally in humans with multiple sclerosis (WP4).

In 2019, Dr. Samo Lasic joined the C-MORPH project and this kickstarted WP1. An early outcome of this work has been a massive book chapter, covering novel diffusion encoding techniques. The chapter gave the opportunity to collect the theoretical foundation for the project, but the chapter is also looking into the future and brings in several new concepts that are currently being translated from theory to practice. In 2021, Dr. Nathalié Just came onboard the project. She has brought her expertise in preclinical MRI in general with a special focus on spectroscopy into the project. This has led to the first in vivo demonstrations in rodents leading the way towards further validation studies of the techniques.

The project also benefits from a fruitful collaboration with Ass Prof. Itamar Ronen from University of Sussex, UK (previously Leiden University Medical Centre, The Netherlands). This has focus on the human in vivo side in WP3 and in the most recent work, double diffusion encoded spectroscopy (DDES) was applied to the human brain demonstrating the feasibility of cell type specific morphometry, a central goal of the project.



MS lesions visible in FLAIR images (A) are the result of multiple inflammatory and degenerative processes (B). C-MORPH aims at distinguishing these processes by creating measurements separating cell type, shape and size (C). From observed changes in a particular cell types the underlying process will be inferred (D).

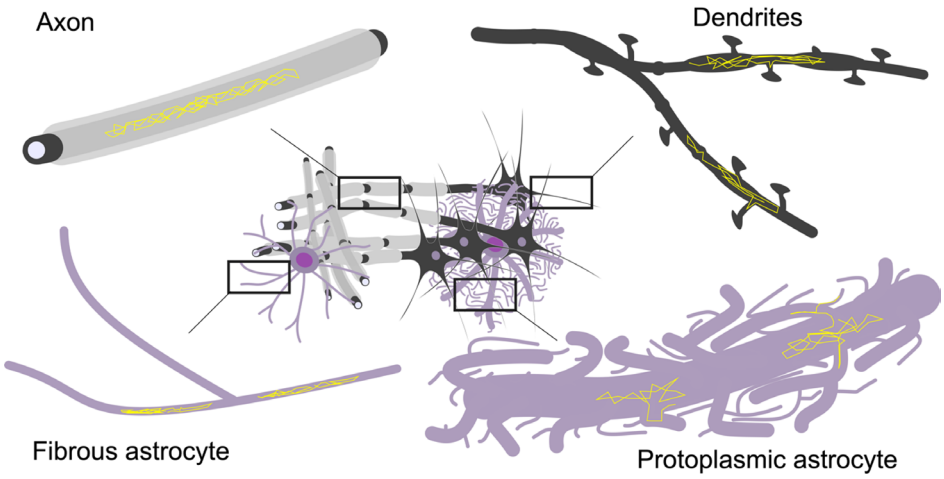


As part of WP1, a book chapter on diffusion encoding with generalized gradient waveforms is thought both as an educational background to the methodologies used in C-MORPH, but the chapter is also presenting some new concepts under development.

The direct measurements of metabolite mobility in this work provide remarkably detailed views into differences in neuronal and glial morphologies in human gray and white matter.

Knowledge attained prior to and during the C-MORPH project was also incorporated in a recent review paper with Henrik Lundell as one of the co-authors. Further, the still ongoing work in the C-MORPH project has already spun off into applications in characterization of cardiomyocytes in collaboration with Irvin Teh, University of Leeds, UK, which demonstrates the wide interest and power of these new methods. The project also benefits from a long going collaboration with the Danish Center for Multiple Sclerosis, Rigshospitalet.

The C-MORPH team will grow in the coming years with a focus shifting more from method development to applications. This will push the frontiers of MR-based personalized medicine, guiding therapeutic decisions by providing sensitive probes of cell-specific microstructural changes caused by inflammation, neurodegeneration or treatment.



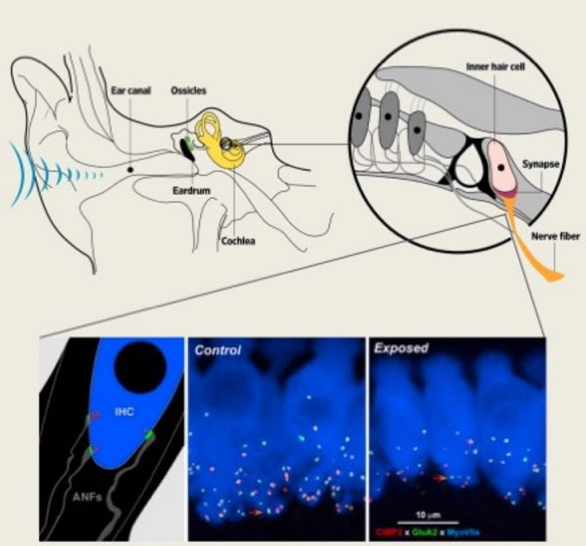
A central goal for C-MORPH has been reached: the detection of cell type specific morphology in the human brain in vivo. The figure is a graphical interpretation of how the DDES method detect very different conditions in different cell types and tissue types.

This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 804746).

UHEAL

UNCOVERING HIDDEN HEARING LOSS

Age-related hearing loss is among the most prevalent chronic health conditions in the world. In the EU alone, untreated hearing loss is estimated to cost more than 185 billion Euros each year. Untreated hearing loss in mid-life is the highest known risk factor for developing dementia later in life. The conventional view has been that the primary cause of age-related hearing loss is loss of the outer hair cells that amplify vibrations in the inner ear. Loss of these cells make soft sounds inaudible and require external amplification by a hearing aid. In 2009, seminal work from the auditory physiologist Charles Liberman and co-workers at the Massachusetts Eye and Ear Infirmary (MEEI) at Harvard Medical School challenged this conventional view. Mice exposed to noise for 2 hours showed no damage to hair cells, but instead an acute loss of synapses between the sensory cells and the auditory nerve. Despite extensive neural damage, the noise exposure did not make soft sounds inaudible. In consequence, the neural damage to the ear remained 'hidden' in standard clinical tests of hearing. The existence of such hidden hearing loss may help explain why many people experience difficulties following speech in noisy situations already in mid-life, although they may have normal hearing in standard clinical tests. Adding insult to injury, these neural damages set off a cascade of neurodegenerative processes that eventually lead to clinical hearing loss later in life. Diagnosis of this type of hidden hearing loss is critical to enable early interventions but is currently missing.



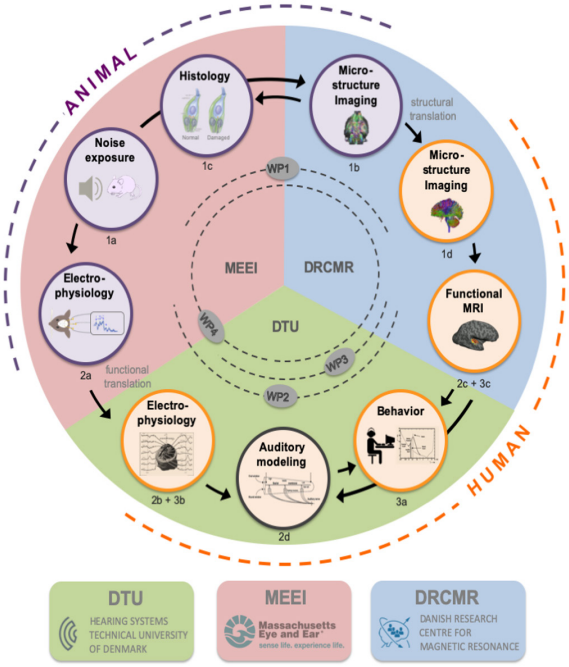
Loud sounds damage synapses and nerve fibres in the inner ear. Clinical hearing tests today do not capture this synaptopathy. Hence the term 'hidden hearing loss' (histology data from MEEI)

In the UHEAL synergy project supported by the Novo Nordisk Foundation, auditory researchers from DTU Hearing Systems (Torsten Dau, Jens Hjortkjær), and MEEI (Charles Liberman) have teamed up with the DRCMR (Hartwig Siebner, Tim Dyrby) to tackle this challenge. The project combines animal and human physiology with structural and functional MRI, computational modelling and psychophysics to investigate auditory neural degeneration and its consequences for hearing. In WP1 of the project, ears exposed to noise at MEEI are sent to DRCMR for preclinical imaging with the goal to detect microstructural changes. WP2 develops measures of neural degeneration by using functional and structural MRI at DRCMR and electrophysiology at DTU in a large cohort of human listeners. WP3 combines this evidence with behavioral listening tests and measures of central brain processing to understand what the consequences of hidden hearing loss are, for instance, in terms of listeners' ability to decode speech in noisy environments.

Collection of data in the UHEAL project is ongoing, but sub-studies and preliminary results already disclose promising results. James Breen-Norris is a postdoc working with Tim Dyrby in the UHEAL project on preclinical imaging of the cochlea. With Charles Liberman at MEEI, the DRCMR group investigates the microstructure of the inner ear of healthy and noise-exposed animals. Diffusion imaging at ultra-high field (7T) is performed at DRCMR to image the soft tissue of the ear otherwise only seen through a microscope. The group has been able to push image resolution to visualize the 3D morphology of the inner ear. Maps of fractional anisotropy, for instance, reveal the stria vascularis curling inside the spiral ligament of the cochlea, a structure that is responsible for maintaining a positive potential inside the healthy ear. This level of detail has not previously been

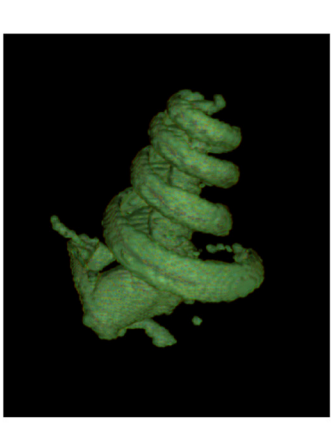
seen with MRI of the ear. Other imaging techniques, including micro-CT and synchrotron imaging, are currently being pursued in the project to push resolution even further.

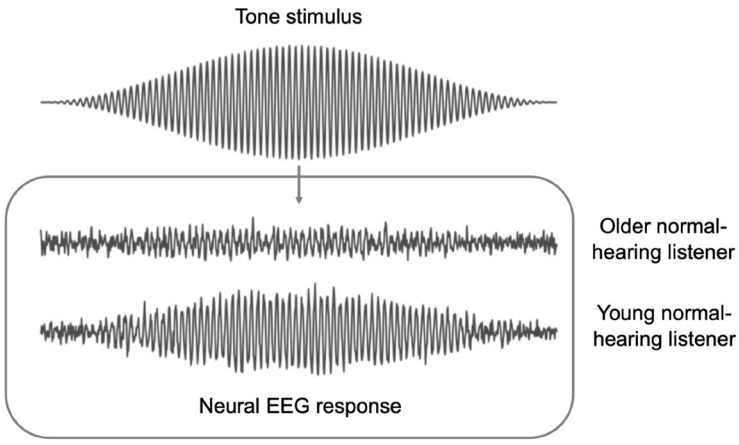
In another sub-study in the UHEAL project, PhD-student Jonatan Märcher-Rørsted combines electrophysiology and computational modelling to understand how loss of auditory nerve fibers affects the nerve's ability to transmit temporal information to the brain. By presenting tones while recording EEG signals inside the ear canal, Jonatan observes how well the brain potentials follow the frequency of the tone. In older listeners with clinically normal hearing, this ability to code fast fluctuations in sounds is reduced, despite the fact that the tones can still be heard. AT DTU, a computational model of the auditory nerve was combined with human histopathology from MEEI to show that this reduction in frequency-following neural responses is consistent with an age-related loss of auditory nerve fibers. Paradoxically, the studies also revealed that the coding of slow variations in sound signals are restored and even enhanced in the aging auditory system. This points to a compensatory brain mechanism that can help restore the detection of sounds after neural damages to the ear, but the fine temporal information needed for accurate sound perception is lost.



DRCMR collaborates with DTU and MEEI in the multidisciplinary UHEAL synergy project. The project combines imaging of the auditory system with animal and human physiology, computational modelling and clinical audiology.

Therapies to reverse auditory nerve damages are currently under development, making diagnostic markers of auditory degeneration critical. Frequency-following responses as those pursued in the UHEAL project can readily be adapted in the hearing clinic. Along with MRI biomarkers of hearing health, such measures present a considerable advance in our current tools for characterizing hearing loss and identifying signs of auditory decline at an early stage.





Left: diffusion MRI image of the inner ear showing its spiral structure and the auditory nerve within the cochlear modiolus. Right: frequency-following EEG responses to a tone in older and young normal-hearing listeners.

PRECISION-BCT

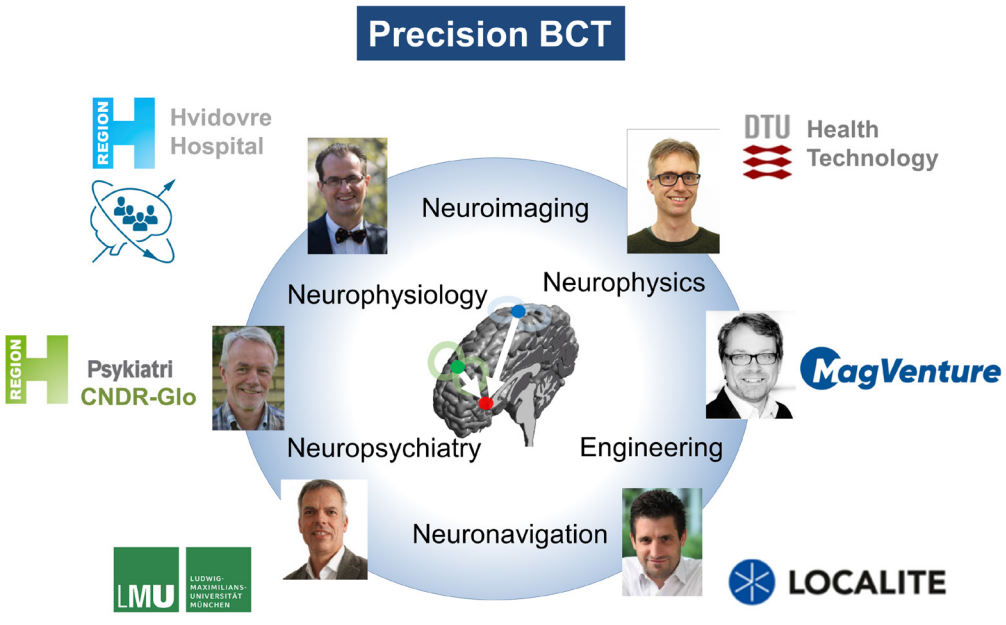
PERSONALIZED MULTI-TARGET BRAIN STIMULATION TO RESTORE BRAIN FUNCTION IN TREATMENT-RESISTANT DEPRESSION

In Precision-BCT, we combine leading clinical, technical and methodological expertise of Danish and international partners to implement a new treatment of major depressive disorder (MDD), based on personalized non-invasive transcranial magnetic stimulation (TMS). Supported by a Grand Solutions grant from Innovation Fund Denmark, it is led by DRCMR and involves MagVenture A/S (Farum, Denmark), the Centre for Neuropsychiatric Depression Research of the Mental Health Centre Glostrup, DTU Health Tech, Localite GmbH (Bonn, Germany) and the Ludwig-Maximilians-University (Munich, Germany) as partners. Our aim is to improve and innovate on all aspects of TMS-based MDD treatments to boost their clinical efficacy.

MDD is among the most frequent brain disorders and severely affects the social life and relationships of the patients. It increases their risk for lowered financial income and unemployment and can result in somatic comorbidities and a lower life expectancy. MDD also poses a huge economic burden for society as a whole. However, not all patients respond to the available treatment options, including various antidepressants and different types of psychotherapy, even when these are given in combination. New alternative treatments are therefore required, and TMS has emerged as a promising option. TMS applies strong electromagnetic field pulses to cause highly synchronized neural activity in the targeted brain area. Repetitive TMS, which consists of multiple pulses given in a short time period, is a safe, pain-free and non-invasive method to modify neural plasticity in the stimulated brain area at a high level of spatial specify.

In MDD patients, repetitive TMS (rTMS) of the prefrontal cortex can successfully restore normal activity in the dysfunctional brain networks and by that reduce the clinical symptoms of the disease. Prefrontal rTMS is approved as MDD treatment in the USA and EU, especially because it has been shown to be efficacious in many of the patients that are deemed resistant to standard therapies. However, rTMS is so far given as "one-size-fits-all" therapy that does not account for the substantial between-patient variability of the disease-related brain circuit alterations. Currently, this still limits clinical efficacy, but also opens up for the possibility to increase its clinical value further by personalizing the treatment.

Precision-BCT develops novel TMS stimulation and navigation equipment that will enable simultaneous stimulation of several brain regions, precise spatial targeting and dose control, and highly flexible stimulation patterns. These new technical solutions will be integrated with structural and functional brain imaging to establish a workflow that can efficiently and selectively target the underlying individual brain-circuit dysfunction in each MDD patient. We strive to create the clinical knowledge and the software and hardware tools that are needed for establishing an efficient and smooth clinical workflow towards a personalized acute and long-term rTMS treatment of MDD. This treatment approach will be grounded in the underlying circuit-dysfunction and will pave the way for large-scale clinical studies and later broad clinical adoption.



ACCURATE COMPUTATIONAL DOSE CONTROL FOR TRANSCRANIAL ELECTRIC AND ULTRA-SOUND STIMULATION

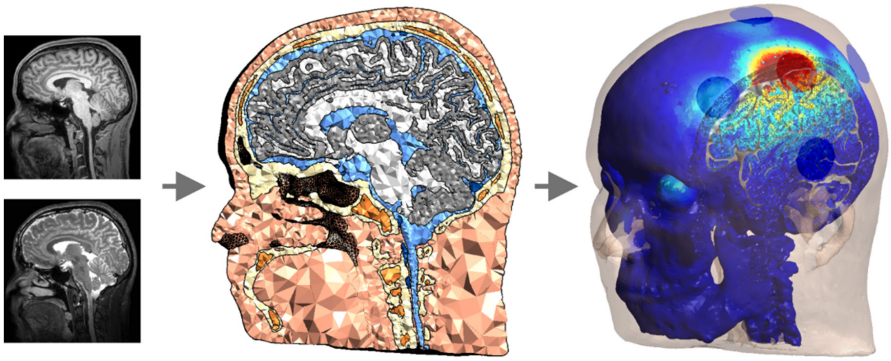
Transcranial Brain Stimulation (TBS) has great potential to treat neuropsychiatric diseases. Although the individual anatomy of the brain and head determines how transcranial brain stimulation engages the targeted brain regions, the existing approaches largely ignore anatomical differences across patients, leading to substantial variations in the therapeutic response. Computational methods can help to estimate and optimize the stimulation patterns in the individual brain in order to ensure that the stimulation is focused on the relevant brain areas and an undesired co-stimulation of other areas is minimized. The general goal of this project, which is supported by a Lundbeck Foundation Ascending Investigator grant, is to substantially advance computational dosimetry for two powerful and complementary stimulation techniques, Transcranial Electric Stimulation (TES) and Transcranial Focused Ultrasound Stimulation (TUS). The project implements three complementary lines of research to reach this goal:

First, we will derive novel methods that robustly enable personalized computational dose calculations also for clinical populations. This will include patients with structural brain alterations, such as post-stroke patients with large brain lesions, and has the aim to make computational dosimetry available as a routine tool for clinical trials on transcranial brain stimulation.

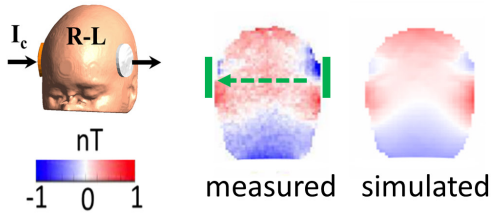
Second, we aim to increase the accuracy of the dose calculations by informing them about the individual variations in the relevant tissue properties (ohmic conductivity for TES, acoustic properties for TUS). For that, we will establish new non-invasive reference measurements that can be included as standard procedures in clinical and neuroscience trials and that can be used to calibrate the dose calculations.

Third, we will establish clinical and preclinical research on the physiological effects of TUS to expand our knowledge about effective and safe parameter ranges. TUS is still new and has a number of unique properties compared to other transcranial stimulation techniques. In particular, it has the ability to focus the stimulation selectively on deeper brain areas. Our research aims to gain the basic knowledge that is required for reliably reaching the desired physiological stimulation outcome when using TUS.

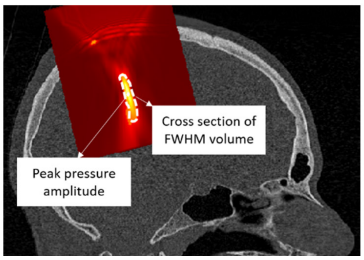
Personalized Dose Simulations: Transcranial Electric Stimulation



MR Current Density Imaging: In-vivo Dose Measurements



Personalized Dose Simulations: Transcranial Ultrasound Stimulation



7T-MS

CORTICAL LESIONS AND GREY MATTER DYSFUNCTION IN MULTIPLE SCLEROSIS

In multiple sclerosis (MS), cortical pathology contributes significantly to disability and has therefore attracted considerable interest in the last decade. However, we are yet to understand the impact of cortical damage on both the connectivity and functional integrity of the affected area and other parts of the central nervous system.

Clinical magnetic resonance imaging (MRI) at 1.5 or 3 Tesla is indispensable to the diagnosis and monitoring of MS-related brain damage. However, the greater sensitivity of 7 Tesla MRI is needed to assess cortical damage more comprehensively. 7 Tesla MRI more than doubles the number of detectable cortical lesions, and allows for high-resolution myelin mapping of the cortex. Nevertheless, cortical involvement is only partially captured, even at 7T. Furthermore, common MRI features alone are known to be insufficient predictors of disability in MS as they only partially reflect functional properties of affected brain networks.

Therefore, this project exploits both quantitative 7T MRI and transcranial magnetic stimulation (TMS). TMS complements MRI, because it allows to directly investigate cortical integrity and conduction properties of the corticospinal system. In previous studies, TMS was able to detect non-symptomatic damage in MS.

Using both MRI and TMS, this project addresses two main research questions:

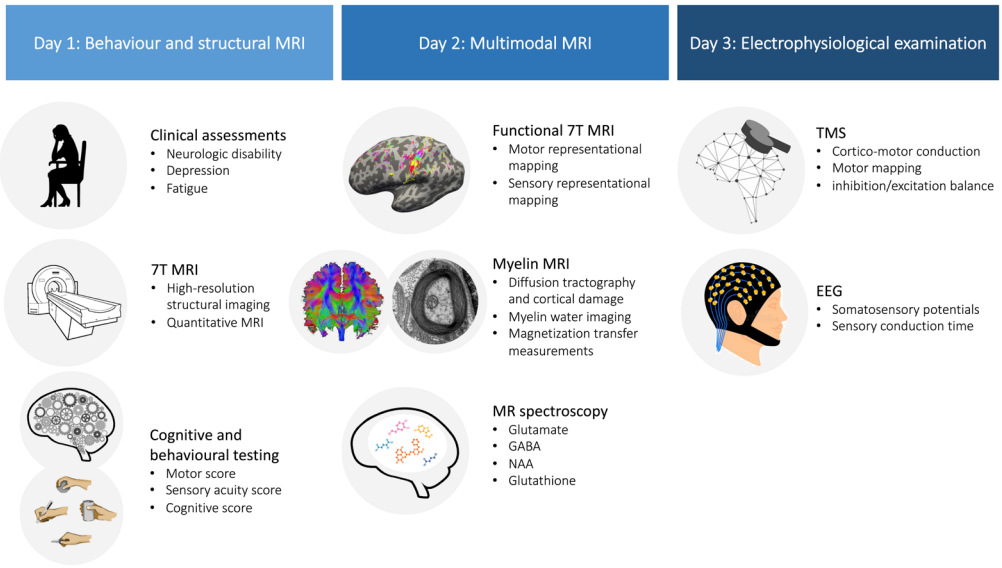
1) What is the impact of individual cortical lesions, specifically in the primary sensorimotor hand area, on hand dexterity in different subtypes of MS

2) What role do focal and diffuse cortical myelin changes play in relation to physical and cognitive function in primary progressive MS

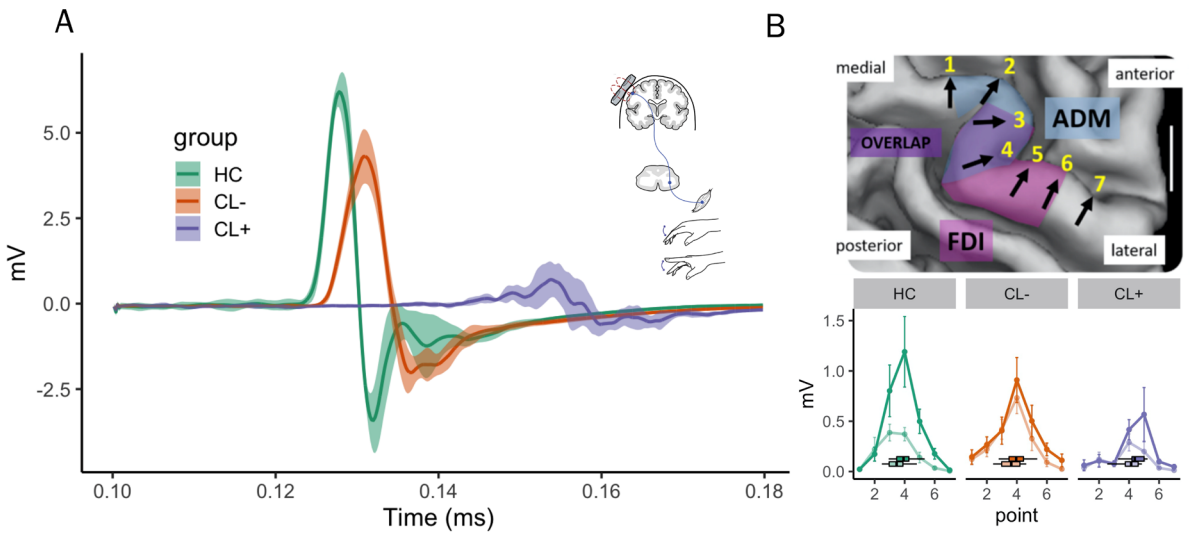
In close collaboration with the Danish Multiple Sclerosis Center at Rigshospitalet Glostrup, we are in the unique position to investigate these questions in MS patients at all stages of the disease.

Starting from 2017, we developed and optimized high-resolution MR sequences for our 7T MRI system and set up a neurophysiological experimental protocol for direct measurements of sensorimotor conduction time and cortical integration, using TMS and electroencephalography (EEG). To date, we have collected data from 38 relapsing remitting patients, 12 patients with secondary progressive MS and 28 matched, non-neurological controls.

Our preliminary results show that having a cortical lesion in the primary sensorimotor hand area is associated with a significant reduction in both manual dexterity and sensory acuity of the fingers. Additionally, our results demonstrate that TMS is sensitive to the disruption of cortical function due to cortical lesions, and that this disruption might be related to increased disability.



Overview of the experimental protocol and methodology used in the project.



(A) The three motor evoked potentials (MEP) traces show that the onset latency was longer and lower in amplitude for both relapsing remitting MS patients compared to a healthy control (HC), but much more so in the patient with cortical damage (CL+). (B) TMS motor mapping successfully separates the representation of the FDI (bold) and ADM (faded color) muscle in all three groups.

In continuation of this project, we are now combining MRI-based cortical myelin imaging at 7T with advanced neurophysiological TMS mapping of the corticomotor pathways in 30 Danish MS patients with primary progressive disease and matching control subjects. Cortical remyelination presents a viable treatment target, but myelin imaging has not yet been widely explored at 7T.

By using state-of-the art anatomical and quantitative MRI at 7T, supplemented by TMS, we can identify radiologically visible and invisible features of cortical grey matter damage that contribute to physical and cognitive impairment in MS. The ongoing project aims to 1) utilize submillimeter anatomical MRI to map the distribution of the different types of cortical lesions in primary progressive MS and compare to our data in relapsing remitting and secondary progressive MS patients; 2) characterize and compare cortical lesions, perilesional grey and white matter as well as normal appearing grey matter using quantitative myelin sensitive MRI sequences; 3) explore the relationship between MRI measures of focal and diffuse myelin injury with neurophysiological integrity of the corticospinal system and clinical disability in order to establish novel stratification tools and predictive biomarkers.

IMPACT

This project will reveal key insights into how cortical demyelination and damage, both regionally and globally, contribute to cognition and motor impairment in MS, two major disabling problems for patients. We will advance the possibilities of MRI to capture cortical involvement in Danish MS patients with the goal to improve individual stratification, monitoring of disease progression and capturing of the individual response to therapy.

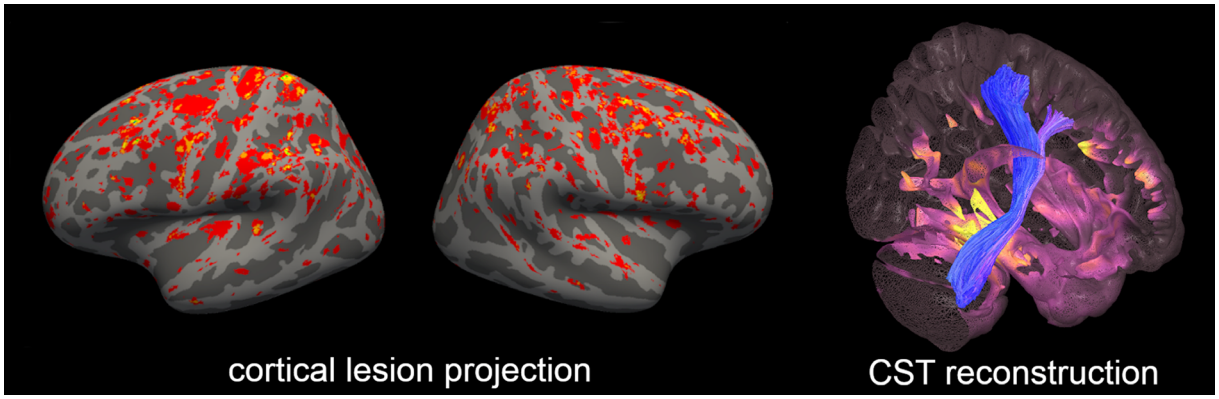
FACTS

Project period: 01.01.2017 - 01.03.2024

Principal investigators: Hartwig Siebner and Vanessa Wiggermann

Collaboration: Danish Multiple Sclerosis Center, Rigshospitalet Glostrup

Funding: Scleroseforeningen, Independent Research Fund Denmark, Hvidovre Hospital, Gangsted fonden, The Lundbeck Foundation.



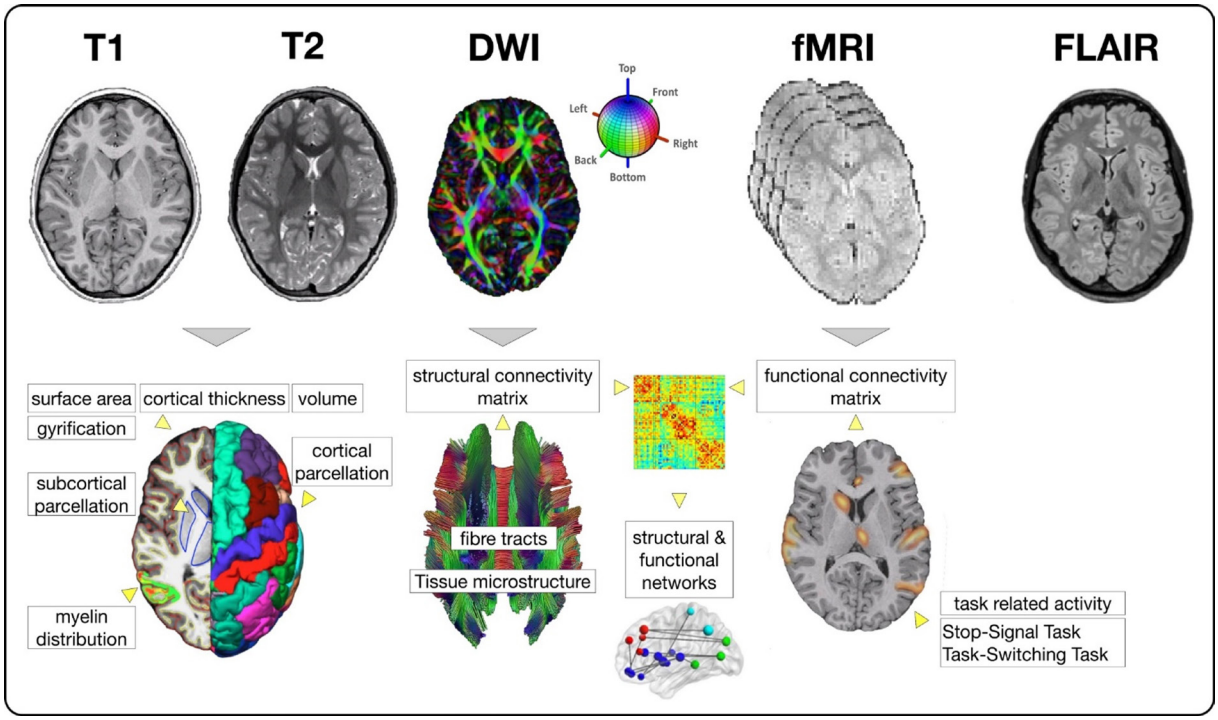
Cortical lesions identified in 50 MS patients. Large parts of the premotor, motor and somatosensory cortex are dominated by lesions, presumably causing severe physical and cognitive deficits. Individual corticospinal tracts (CST) are reconstructed from the diffusion data to determine lesion loads in functionally relevant white matter tracts.

TECTO BRAIN IMAGING

TREATMENT **E**FFECTS OF FAMILY-BASED **C**OGNITIVE **T**HERAPY IN CHILDREN AND ADOLESCENTS WITH **O**BSESSIVE COMPULSIVE DISORDER

A growing number of studies have related obsessive-compulsive disorder (OCD) symptomatology to structural and functional brain changes in specific regions of parallel dorsal and ventral cortico-striato-thalamo-cortical (CSTC) circuits. Normal functioning of these regions is known to be imperative to successful response inhibition in healthy subjects. During treatment with cognitive behavioral therapy, including exposure and response prevention (CBT-ERP), patients with OCD are purposefully exposing themselves to anxiety-provoking stimuli (e.g. by touching something dirty) whilst refraining from acting on the desire to respond (e.g. by not excessively washing hands immediately after). Although CBT-ERP is effective for some patients, about half of all children and adolescents with OCD do not or only partially benefit from the treatment, and it is largely unknown how the brain of patients that benefit from treatment differs from the brain of patients that do not.

Exploring why some benefit from treatment and others do not is an important step to improving individualized treatment. The wide use of CBT-ERP for pediatric OCD stands in contrast to the lack of knowledge about the mechanisms underlying the treatment effect. Previous studies using imaging have demonstrated abnormal response-inhibition-related activation of CSTC-circuits in patients with OCD, and changes in the activation of these regions is potentially critical to treatment outcome. However, most studies of the underlying mechanisms of CBT-ERP for OCD have focused on behavioral changes,



Multimodal brain imaging. High resolution structural T1-weighted and T2-weighted scans, diffusion-weighted imaging scans and blood-oxygenation level dependent weighted functional MR scans (fMRI) are obtained on a Philips 3 Tesla scanner. Structural and diffusion-weighted imaging scans will be used to quantify regional cortical thickness, surface area and gyrification, microstructural properties and volume of cortex, subcortical nuclei, and white-matter tracts, T1/T2 ratio-based myelin distribution as well as structural network connectivity. Response-inhibition-related brain activity will be measured with fMRI using a Stop-Signal Task (SST) and a Task-Switching (TS) paradigm. SST and TS tap different aspects of response inhibition processes. In the SST, a selected and initiated motor response must occasionally be inhibited (action cancellation), whereas in TS, the correct response to a target must be selected from a bimodal task-response set with interference from an irrelevant and incongruent response (interference control).

IMPACT

TECTO will improve understanding of the interplay of factors that predict, moderate, and mediate treatment response by combining neural, cognitive, emotional, and neuroendocrine measures. Results are crucial to improve psychotherapy and targeted interventions for pediatric OCD that can minimize medication use, prevent chronicity, and reduce the substantial socioeconomic burden of the disorder.

whereas studies documenting neurobiological changes are just emerging. One recent functional imaging study on pediatric OCD shows a potential CBT-ERP-related normalization of regions in CSTC-circuits after treatment, but this study did not use an RCT design. A direct comparison of CBT-ERP and an active control treatment is necessary in order to distinguish between brain changes that occur due to the putative effective component of the treatment (i.e., exposure and response prevention) and changes that occur due to general features of psychotherapy (e.g., psychoeducation, the therapeutic alliance or family problems being dealt with). Furthermore, a direct comparison of patients with OCD and healthy control subjects is required in order to distinguish between effects of time (e.g., normative maturation of the brain) and effects of treatment.

TECTO-BRAIN

TECTO-brain is a collaborative sub-project to TECTO that is carried out in close collaboration between the Child and Adolescent Mental Health Centre (BUC), Gentofte Hospital and the Danish Research Centre for Magnetic Resonance (DRCMR), Hvidovre Hospital.

Major aims of TECTO-brain

The overarching goal of TECTO-brain is to delineate structural and functional brain profiles of pediatric OCD and elucidate connections between neural and neurocognitive measures and treatment response. The most important aims are as follows:

1. To determine the structural and functional brain profile of pediatric OCD by comparing patients with healthy control subjects matched on age and gender.
2. To investigate changes in the neural profile of the brain in patients after treatment with CBT-ERP or psychoeducation and relaxation therapy (PRT).
3. To identify neural and neurocognitive factors that are predictive of treatment response.

The entire TECTO study includes 128 patients, age 8 through 17 years, with a primary diagnosis of OCD and 128 age- and sex-matched healthy control subjects. Patients are randomized at the allocation ratio 1:1 to receive either CBT-ERP or PRT. Both treatments comprise 14 sessions of 75 minutes each, delivered over 16 weeks by trained and supervised doctors or psychologists.

All participants of TECTO are offered participation in TECTO-brain. The brain of both patients and healthy control subjects partaking in TECTO-brain are magnetic resonance (MR)-scanned at baseline and immediately after treatment (week 16).

In TECTO-brain, we take a multimodal approach to brain imaging. TECTO-brain utilizes modern methods and technology to reduce the amount and significance of movement during scanning. All our structural scans include online motion correction as children generally have more difficulties lying still during scanning. Our pilot data show a systematic underestimation of gray matter volume from structural images when motion is present and uncorrected, and online motion correction improved image quality substantially even in the presence of significant movement. Sequences have been tailored to scan children and have been validated in a pilot study on both patients and healthy control subjects. Because comorbid anxiety disorders are common among OCD patients, we use a narrated virtual reality environment that has been developed for this project, in which the participants can experience being virtually scanned in 3D. Finally, we use a mock-scanner to train the tasks and train lying still on the first day of scanning.

Results from TECTO-brain are expected, as a minimum, to improve our understanding of pediatric OCD and of CBT-ERP as an intervention for OCD. However, we aim to also make significant contributions to the development of individually tailored interventions for pediatric OCD. TECTO-brain can realistically do so by illuminating the neural mechanisms underlying the treatment effects.

The enrollment of participants is ongoing. Currently, a total of 97 patients and 36 healthy controls have been included in TECTO-brain.

FACTS

TECTO is led by Prof. Anne Katrine Pagsberg from the Research Unit - Child and Adolescent Mental Health Centre (CAMHC), Mental Health Services, Capital Region, Denmark.

The study was initiated by Prof. Kerstin Plessen, who is now at the University of Lausanne, Switzerland.

The Copenhagen Trail Unit, led by Director Dr. Christian Gluud, oversees RCT procedures and statistical analyses.

TECTO received funding from the Mental Health Centre for Child and Adolescent Psychiatry, the Lundbeck Foundation, Capital Region Psychiatry, the Capital Region Research Fund, Gangstedfonden and Psykiatrisk Forskningsfond af 1967.

For a video presentation of the TECTO trail see: bit.ly/2OrqyZv

LIFEBRAIN

OPTIMISING THE USE OF EUROPEAN BRAIN IMAGING COHORTS – HEALTHY MINDS FOR 0-100 YEARS

Lifebrain aims to identify determinants of brain, cognitive and mental health at different stages of life and to establish foundational knowledge for understanding how brain, cognitive and mental health can be optimized through the lifespan. Lifebrain works with stakeholders and health authorities and strives to provide the evidence base for (personalised) policy strategies for prevention and intervention, improving clinical practice and public health policy for brain, cognitive and mental Health.

Lifebrain was initiated in 2017 after successfully securing EU Horizon 2020 funding and brings together top European brain research centres and a small medium-sized enterprise, VITAS, that specializes in measuring and monitoring biomarkers in dried blood spots (http://www.lifebrain.uio.no/)

Lifebrain integrates 11 longitudinal and seven cross-sectional, mostly population-based, European cohort studies from eight research centres, investigating the interrelationships between structural and functional brain changes and cognitive and mental health across the lifespan. For details on the organization, work packages and Lifebrain partners see https://www.lifebrain.uio.no/lifebrain-project/).

Lifebrain also links data from existing Lifebrain cohorts to data from other large international studies such as the UK biobank (https://www.ukbiobank.ac.uk) or the ABCD study (Adolescent Brain Cognitive Development; https://abcdstudy.org).

LIFEBRAIN ACHIEVEMENTS

The first few years

Lifebrain is characterized by a transparent, focused, smooth and productive collaboration across all partners and has made great progress in all the years of its existence and delivered on all EU project milestones.

Initially, work focused on harmonizing the very rich, multidimensional data within Lifebrain, containing of e.g., demographic, environmental, physical (health), behavioral, clinical, structural and diffusion weighted magnetic resonance brain imaging, and genetic data. Lifebrain includes longitudinal MRI and behavioral data of more than 5,000 subjects, and behavioral data of more than 10,000 subjects. This data was furthermore enriched by acquiring online multidimensional behavioral and cognitive data across several Lifebrain cohorts as well as by acquiring data on specific biomarkers of interest within Lifebrain, such as vitamin D, proinflammatory cytokines, lipids and stress hormones, using the specific Lifebrain home-kits for sampling dried blood spots developed by VITAS.

Besides, data harmonization and data enrichment, much of the early efforts went into establishing the necessary communication, data sharing and computational infrastructure, vital for smooth communication and collaboration, and robust data management, sharing, and analyses across national borders. Standardised brain image analyses pipelines and advanced novel statistical tools for analysing multidimensional longitudinal and multicentre data have been developed.

Finally, right from the very start Lifebrain has organized a number of stakeholder engagement activities, including workshops attracting e.g., patient organizations, health professionals, policy makers, researchers, and research participants as well as public lectures.

The final years

All the above groundwork has made it possible to harvest the rich Lifebrain data and deliver on Lifebrain's objectives within the official Lifebrain funding period and beyond.

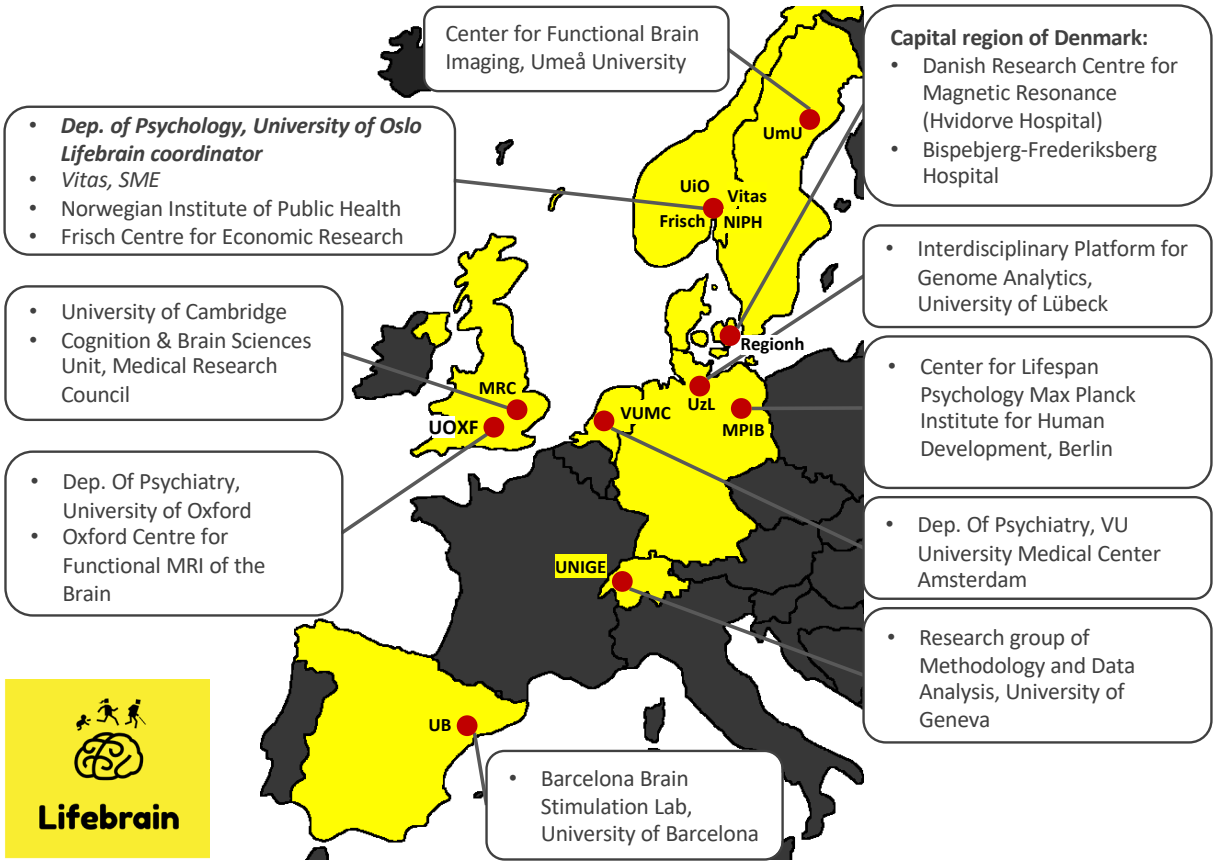
FACTS

The funding period runs from January 1st 2017 until June 30st 2022.

Lifebrain is funded by the EU Horizon 2020 framework with Euro 10 million.

Lifebrain coordinator is Prof. Kristine Walhovd, Centre for Lifespan Changes in Brain and Cognition, University of Oslo, Norway and is realized through a close collaboration between major European brain research centres and VITAS (an SME) specialized in measuring biomarkers in dried blood spots (see figure).

Lifebrain is organized in seven work packages. Senior researcher William Baaré from DRCMR is work package leader of work package 2: Data management and integration.



European Lifebrain partners and the Lifebrain logo.

In 2019, Lifebrain, in collaboration with national brain councils in Norway, Germany, and Belgium, Brain Foundations in the Netherlands and Sweden, the National University of Ostroh Academy and the Women's Brain Project, initiated a large-scale international survey (regarding the views and perceptions of healthy adults regarding Brain health. The survey was made available in 14 languages and closed August 2020. More than 27,590 people from 81 countries responded to the survey, including more than 1,000 people from Denmark. Articles disseminating results of the survey are in preparation.

A multitude of studies on the rich Lifebrain data are in progress and findings of several studies have already been published. A key study investigates the role of social economic status and cognitive abilities on structural brain measures using a meta-analytic framework. Other studies focus on e.g., memory, depression, educational attainment, personality, physical activity and health and sleep. Information about current research results, publications, events and deliverables are disseminated through e.g. the Lifebrain website (http://www.lifebrain.uio.no/), Facebook page (www.facebook.com/lifebrain.h2020/) and a monthly e-newsletter. For an overview of all publications see https://www.lifebrain.uio.no/publications/.

IMPACT

Lifebrain aims to make major conceptual, methodological and analytical contributions towards large integrative cohorts and their efficient exploitation. Moreover, Lifebrain will provide novel information on brain, cognitive and mental health maintenance as well as onset and course of brain, cognitive and mental disorders. This will pave the way for earlier diagnosis of brain disorders, aberrant development and decline of brain, cognitive and mental health, as well as future preventive and therapeutic strategies. Lifebrain will closely work with stakeholders and health authorities to promote personalised policy strategies for prevention and intervention and improving clinical practices. Finally, Lifebrain will promote public health policies for brain, cognitive and mental health.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 732592.

MAX4IMAGERS

Synchrotron imaging opens a new horizon in medical imaging because it is possible to obtain 3D tomographic scanning of anatomical structures at a much higher resolution than with any other existing imaging technology. Successful usage of synchrotron imaging is truly an interdisciplinary endeavour, and the MAX4Imagers project aimed to establish the expertise amongst the universities and capital hospitals in the region.

After four years of carrying out synchrotron research we have obtained a good practical knowhow on how to prepare for the different types of experiments that one can perform at synchrotron facilities in Europe. We obtained unique insight how to obtain good synchrotron image quality which is essential for the further data analysis. Actually, the time spent at the beamline to collect data is only a few days – whereas the data analysis takes much, much longer. We have established different image analysis tools that can be widely used by other researchers in different types of projects. Much of our practical know-how and many of our data analysis algorithms have been and will continue to be shared through workshops.

Was it worth it, then? Absolutely - every second was worth it! All samples we have synchrotron imaged have provided new insights into the finest details of anatomy that we have ever dreamed of.

FOUR DEMONSTRATION PROJECTS:

The researchers have investigated and demonstrated how to derive at the full potential of synchrotron imaging in healthcare for better disease understanding and diagnostics. This was applied in four demonstration projects that cover a wide spectrum of tissue types from the A) microstructure of the brain, B) sperm cells, pathological mechanisms in muscle contractures, and C) in tooth bone microstructure.

A. The microstructure of brain in health and disease

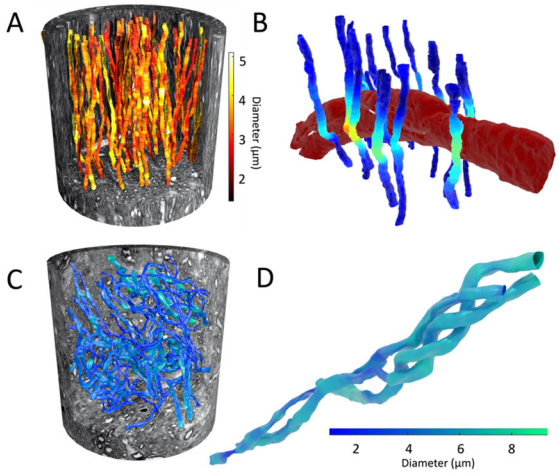
We used synchrotron imaging to investigate the 3D microstructure of healthy and diseased brain tissue, including cells, blood vessels, and axons - the nerve fibres which are responsible for communication in the brain. The morphology of important structures such as axons is related to their function, i.e. an axon with a larger diameter will relay information faster than one with a smaller diameter.

As part of the MAX4Imagers aim, we collected synchrotron data of a bundle of axons from tissue samples taken from monkey, rat and mice brains. We have established advanced image analysis algorithms in combination with hard work of manual editing to enable axon morphology analysis. We found the axon morphology to be very complex: The axon shows large variation in diameter along its trajectory. What causes this large variation in axon morphometry? It is the nearby structures such as blood vessels, cell clusters, vacuoles or even crossing axons that mechanically push the axon, so it changes shape. Having obtained the novel insight into the real axon morphometry from synchrotron imaging we can validate axon diameter estimation from diffusion MRI. Indeed, the shape changes of real axons strongly influences the axon estimation with diffusion MRI – however, using the newest axon diffusion MRI methods the impact can easily be minimized.

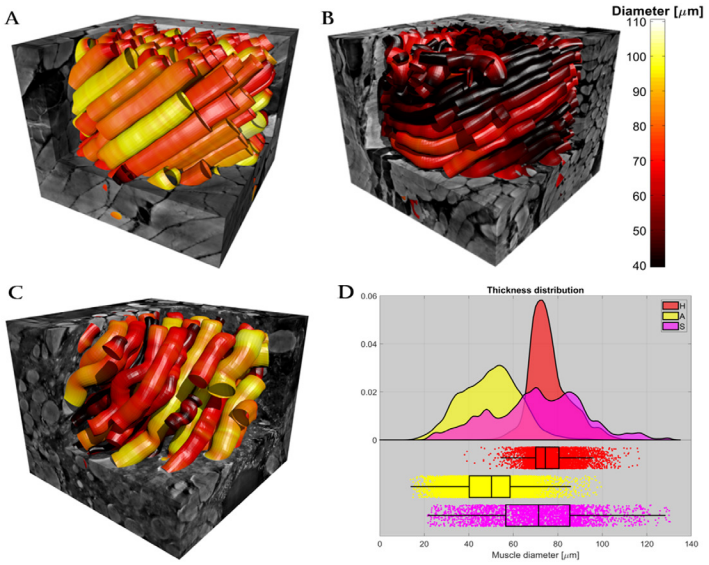
The results are published in Proceedings of the National Academy of Sciences of the United States of America (Andersson et al 2020, PNAS).

B. Pathological mechanisms in muscle contractures

Muscle contractures is a frequent complication in patients with Central Nervous System (CNS) lesions. Here we aimed to elucidate whether the composition and the amount of connective tissue is changed in muscle tissue with a contracture using synchrotron imaging. The results of this project are of crucial importance for patients with CNS lesions, since a clarification of the arising of muscle contractures can create a base for an effective preventative treatment of patients with CNS lesions.



Quantitative analysis of axonal morphology in the vervet monkey brain. A) Visualization of segmented axons in a synchrotron image volume of the vervet monkey splenium. The colour represents the local axonal diameter in accordance with the colour bar. B) Axons bend around a blood vessel (red) in the splenium region. The axonal colour represents the deviation of the axons from their average trajectories. Dark blue: small deviation, yellow: large deviation. C-D) Visualizations of segmented axons in a synchrotron image volume of a complex crossing fibre region in the vervet monkey brain. The colour represents the local axonal diameter in accordance with the colour bar. In D, axons are shown to twist around each other, and accommodate each other's trajectories.



Quantitative image analysis on muscle fibres. A, B and C) Visualization of segmented muscle fibres in synchrotron samples taken from respectively a healthy control subject (label H), a stroke patient (label A) and a SCI patient (label S). The colour indicates local muscle fibre diameter in accordance with the colour bar. D) The statistics of muscle fibre diameter results.

Muscle samples were taken from CP patients undergoing an operation for muscle elongations of contractured Gastrochnemius muscles. Furthermore, muscle biopsies were taken from the medial Gastrocnemius of spinal cord injury (SCI) patients and Stroke patients. The muscle tissue was embedded accordingly. X- ray tomography was conducted at the Paul-Scherer Institute in Switzerland.

In the MAX4Imagers project, we applied the same image analysis methods as used for axons to quantify shape, density and elongation of muscle cells. With these new analysis tools, we obtained new insights into muscle shape and elongation in disrupted muscle cells only seen with 3D imaging techniques as synchrotron imaging – not with 2D histology.

C. Sperm cell tail beating

Sperm cells are highly specialized cells responsible for the delivery of a haploid paternal genome into the egg. In order to do so, the sperm cell has shut off unnecessary functions, packed the genome tightly into the head and is equipped with a huge beating flagellum. The flagella beating frequency is fast (up to 30 Hz) but to penetrate the tight mucus layer surrounding the egg, the sperm cell needs to be hyperactivated, which entails high amplitude flagellar bending, a reduction in beat frequency, and side-to-side yawing.

Poor sperm motility and inadequate hyperactivation can lead to infertility.

FACTS

PI is Tim B. Dyrby, DRCMR, Hvidovre Hospital

Partners are Rigshospitalet, University of Copenhagen, Technical University of Denmark (DTU) and international partners at MAXIV, Lund University, Sweden.

Funded by a DKK 4.5 million grant from the Capital Region Research Fund for Healthcare

Funding period: 2017-2021

IMPACT

Our novel 3D anatomical insights from synchrotron imaging - combined with the development of algorithms to analyse the huge amounts of data produced - will lay the ground for:

Improved knowledge of the 3D microstructure in different tissues

Understanding of disease mechanisms

New imaging biomarkers for disease

Improvement of the imaging methods currently used in the clinic for diagnosis e.g. MRI

In the MAX4Imagers project, we aimed to dynamically image sperm cell tail beating – alive. It is a very complex setup to realize. First, we did establish a new image contrast by incorporating nanoparticles into the tails of the cells. Then we explored the time a cell can survive in the x-ray beam. The next step is to perform dynamic imaging.

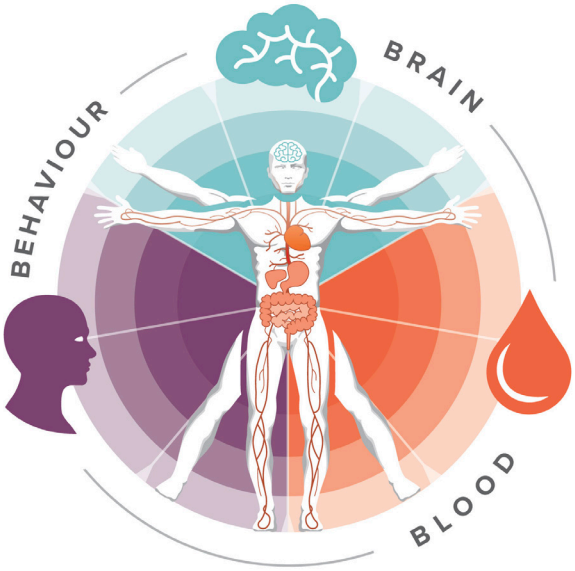
D. Bone microstructure and Evaluation of Peri-implant Hard Tissues

Bone microarchitecture is an interconnected network of plate- and rod-like structures. Tooth loss is associated with bone loss. In this project, a goat model has been used to mimic a critical sized defect used for evaluation of osseointegration and peri-implant hard tissue in the mandible after immediate vertical bone augmentation. The purpose of this study was to perform a standardized histological method to be compared with synchrotron imaging for evaluation of peri-implant bone and bone microarchitecture. Synchrotron data was collected at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France as part of a recently finished PhD project by Camilla A Neldam. The first results investigated bone in close proximity to a titanium implant surface i.e. direct bone-to-implant contact (Neldam et al, 2017, JCMFS, 45:1448-1457).

OMNISAM

THE OMNIBUS SATIETY METRIC PROJECT

The OmniSaM project was a project funded by Arla Food for Health in 2016 in response to their need to improve how satiety is measured. Designing food and drink that maximizes satiety has long been an ambition of both the food industry, as well as in public health. Foods that fill faster and for longer are desirable for weight management and for public health programs designed to prevent obesity. OmniSaM's main objective was to develop a multi-modal based metric of satiety that is predictive of future energy consumption. Our aim was to surpass the performance of existing benchmark metrics, and to demonstrate a proof-of-concept for using such metrics in industrial R&D. The strategy was to develop a multi-modal metric that targets the spectrum of processes underlying the satiety cascade comprising brain, blood, and behavioural data (BBB). In the experiments, subjects underwent a pre-load – ad libitum intake paradigm comparing milkshake-type drinks differing in their levels of calories and protein-to-carbohydrate ratio. Extracting the dynamics of the BBB data, we attempted to construct a metric for predicting next-meal intake. The results are still being interpreted and written up for publication. We expect several papers to be out in the next year on the OmniSaM data. The first paper, currently being drafted, highlights the most surprising finding of the project. To summarise, we found that of all the hormonal, subjective, and metabolic variables we measured, there was one hormone that was dominant in its ability to predict how much people would eat. This was Ghrelin, the only hormone known to stimulate hunger directly. We found that Ghrelin measurements were systematically predictive of food intake, an effect that was replicated at all timepoints preceding the meal test. Even when Ghrelin was measured over 3 hours prior to the meal test, it still strongly predicted intake. What is surprising about this is the degree to which it outperformed all other subjective and blood-based variables that we recorded. Subsequent papers will focus more in detail on the brain response to food cues and whether they are predictive of intake. Finally, we will put all data modalities together into one multi-modal metric, thus completing the original objective.



An overarching schematic that depicts our aim to combine data from brains, blood and behaviour to understand and predict satiety.

The experiment in action. The participant is lying on the bed about to go into the scanner, where they will respond to images of food. Periodically, we stop the scanner to perform questionnaires and to sample their blood.

FACTS

Funding:	DKK 5.4 million from Arla Food for Health
Period:	2016-2019
Awarded to:	Hartwig Siebner at DRCMR Sten Madsbad at Department of Endocrinology, Hvidovre Hospital, and
Project leader:	Derek V. Byrne from the group "Food, Quality Perception & Society" at Aarhus University, Department of Food Science

IMPACT

The work of the OmniSaM project is intended to have broader impact in the long term. Firstly, it offers to develop a foundational insight into how satiety works that will be vital for understanding how satiety mechanisms can go wrong in metabolic disorders that either involve over- or under-eating. Secondly, by improving satiety measurement, it is hoped that it will be possible to design food and beverages to maximise satiety, as a healthier means of helping people control their dietary intake that relies less on self-control.

CANID

CARDIOVASCULAR AUTONOMIC NEUROPATHY IN DIABETES

Diabetes affects almost half a billion individuals worldwide, a fast-growing number. It is an uncurable disease, hence the focus is to prevent comorbidity by all means. Cognitive decline progressing to clinical dementia is an established comorbidity which is receiving increased attention. The ramifications of developing dementia are often devastating for the patient and puts major strain on healthcare services as it is one of the costliest disorders of the brain.

Previous studies have shown that the diabetic state itself has several specific effects on the brain, some of which are known to feed into the pathological cascade leading to dementia. The timely and precise supply of blood to the brain parenchyma, the result of a complex interaction between neurons, glia and vessels, is of utmost importance to ensure proper function. One way diabetes may lead to dementia is by detrimentally altering this perfusion, possibly through cardiovascular autonomic neuropathy.

This current core project of the Brain-Body Interaction group aims to delineate these mechanisms underlying dementia in Diabetes. Thus, it tests the hypothesis that patients with type-2 diabetes (T2DM) and cardiovascular autonomic neuropathy loose intrinsic regulatory control over the brain's blood supply at the tissue level. To accomplish this, T2DM patients with and without cardiovascular autonomic neuropathy are compared to age-, BMI-, and sex-matched healthy controls. Participants are subjected to a wide variety of autonomic, sensory and cognitive tests as well as structural and functional MRI-scans of brain and abdomen. The latter include, among other sequences, a specially designed paradigm using CO_2-induced hypercapnic stimulation during arterial spin labeling and visual stimulation. Furthermore, a method recently developed at DRCMR is applied to investigate control of mesenterial blood flow in response to ingestion of a standardized meal. Following ingestion, phase contrast MRI is performed at regular intervals to quantify the autonomic response to distention and caloric intake, providing a more systemic understanding of autonomic neuropathy in Diabetes. This opportunity is also used to take the patient's hormonal "fingerprint" – i.e. measure hormones including GLP-1, insulin, glucagon etc.

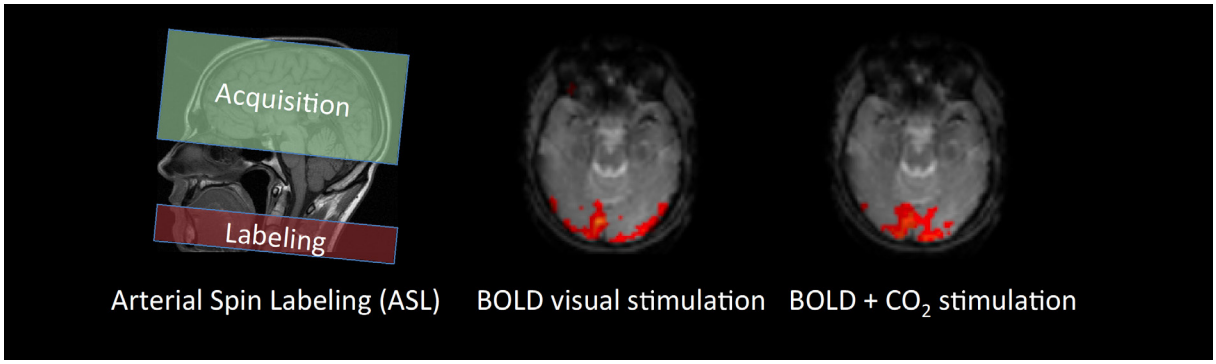
This study brings cutting-edge MRI techniques to clinically well-characterized patients in the overall research theme of investigating brain-body interaction. It is founded in well-established research environments as a collaboration between DRCMR, the Department of Endocrinology at Hvidovre Hospital and Steno Diabetes Center, Copenhagen. The project is currently underway and actively recruiting and scanning patients with a timeline of 1-2 years.

FACTS

The CANiD study, led by prof. Hartwig Siebner, is a collaboration between Steno Diabetes Center, the dept. of Endocrinology at Hvidovre Hospital and DRCMR where the imaging is nested in the Brain-Body Interaction group, headed by Mads Barløse. Involved partners include Christian Bauer (DRCMR), Esben Thade Petersen (DRCMR), Sten Madsbad (Endocrinology, Hvidovre Hospital), and Christian Stevns Hansen and Birgitte Brock (Steno).

IMPACT

CANiD is unique in its focus on both central and peripheral control of blood flow. It will provide insight into the mechanisms underlying cognitive decline and deregulation of blood supply in diabetes. The multidisciplinary approach to a patient group blazes a trail for future projects focusing on other conditions.



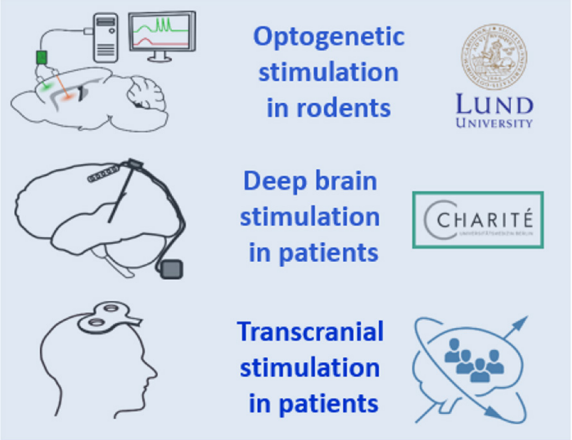
Left: Visualization of the Arterial Spin Labeling ASL technique. Middle: Brain activation based on visual stimulation. Right: Brain activation based on both visual stimulation and hypercapnic stimulation.

ADAPT-PD

ADAPTIVE AND PRECISE BRAIN-CIRCUIT TARGETING IN PARKINSON'S DISEASE

ADAPT-PD is a collaborative project that addresses a central question in neuroscience with enormous therapeutic implications: How can the dysfunction of brain circuits in Parkinson's disease be normalized with device-based neuromodulation?
Parkinson's disease (PD) is a common and disabling, multi-system neurodegenerative disease which affects motor and non-motor brain networks. The symptoms of PD are motor symptoms like bradykinesia and tremor as well as non-motor symptoms such as autonomic dysfunction and cognitive decline. As of today, the main therapeutic approach is dopaminergic replacement therapy like levodopa. Unfortunately, most patients develop adverse effects with time. One common and disabling adverse effect is levodopa-induced dyskinesia (LID) which are involuntary movements caused by the non-physiological fluctuations in dopamine concentrations and maladaptive plasticity at the cortico-striatal synapses.
The project is led by Professor Hartwig Siebner at DRCMR, who will collaborate with Professor Andrea Kühn, Charité Universitätsmedizin in Berlin, Germany, and Professor Angela Cenci Nilsson, Lund University, Sweden. Each site focuses on different aspects of PD and by combining the different levels of analysis, this project can achieve a unique understanding of the disease and how to treat it.

We will use an array of well-aligned methods to characterize how the cortex and its projections to the basal ganglia contribute to motor and non-motor disabilities in PD and LID.
Invasive recordings and optogenetic stimulation in rodent models of PD and LID will yield novel insights into critical cortico-basal ganglia circuit features that constitute candidate targets for ADAPT.



Each site focuses on a different stimulation technique.

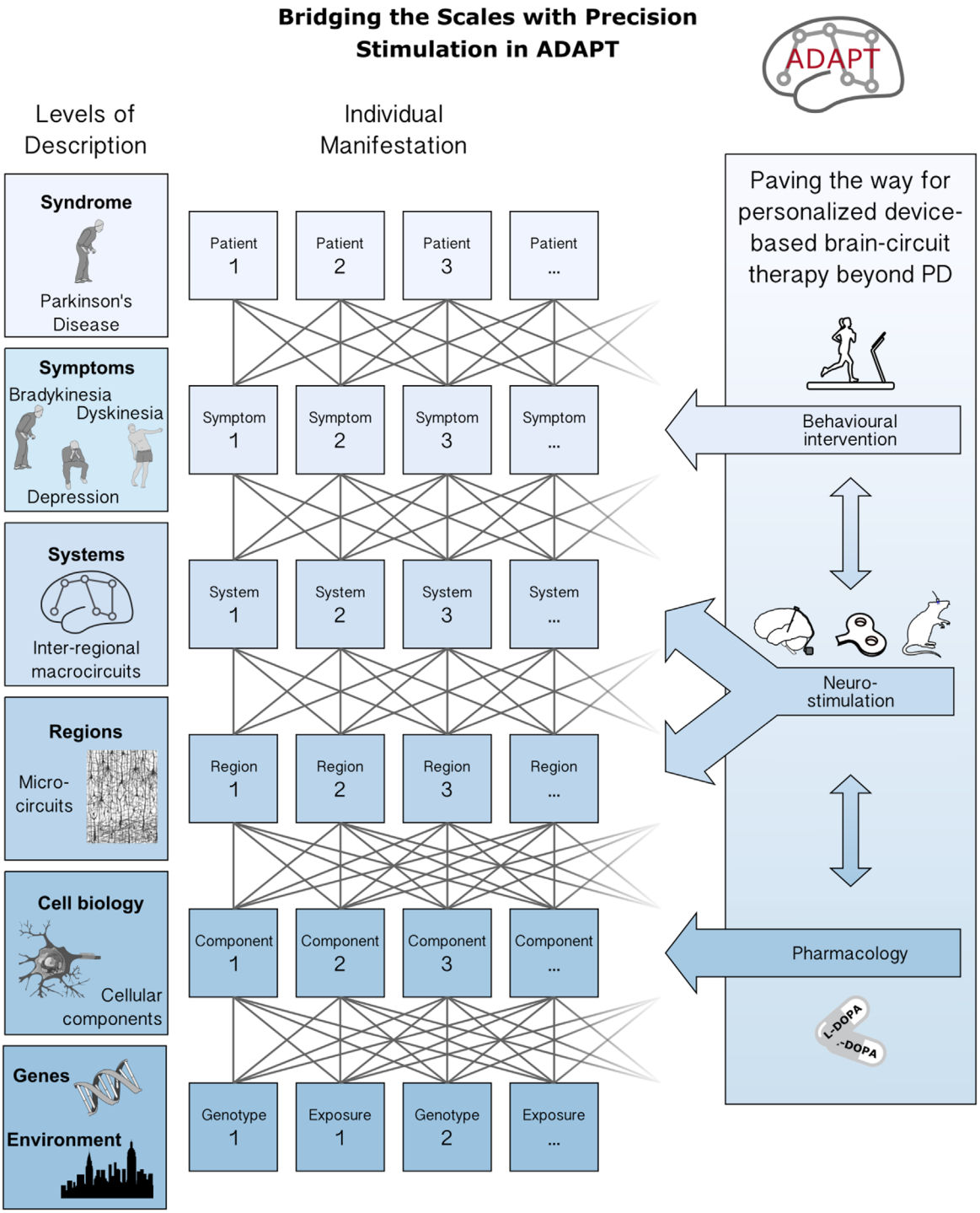
At the same time, we will test how non-invasive cortical stimulation can normalize the dysfunctional brain circuits. We will use this knowledge to develop novel brain stimulation therapies that primarily target the dysfunctional cortex. ADAPT-PD will greatly advance the mechanistic understanding of cortico-basal ganglia circuit dynamics in health and PD and create a powerful hub for causal brain circuit discovery, paving the way for personalized device-based neurostimulation, with therapeutic implications beyond PD.

IMPACT

Using a multimodal and multiscale approach, we will investigate how the cortico-basal ganglia circuit is altered in Parkinson's disease as well as levodopa-induced dyskinesia. Based on this knowledge we will develop treatments with tailored non-invasive and invasive brain stimulation.

FACTS

Funding: 35 mill. DKK Lundbeck Foundation Collaborative Projects grant
Period: 2021 – 2026
Led by: Professor Hartwig Siebner
Partners: Professor Andrea Kühn, Charité Universitätsmedizin in Berlin, Germany, and Professor Angela Cenci Nilsson, Lund University, Sweden


Bridging the Scales with Precision Stimulation in ADAPT
ADAPT
Levels of Description
Individual Manifestation
Syndrome
Parkinson's Disease
Symptoms
Bradykinesia
Dyskinesia
Depression
Systems
Inter-regional macrocircuits
Regions
Micro-circuits
Cell biology
Cellular components
Genes
Environment
Patient 1
Patient 2
Patient 3
Patient ...
Symptom 1
Symptom 2
Symptom 3
Symptom ...
System 1
System 2
System 3
System ...
Region 1
Region 2
Region 3
Region ...
Component 1
Component 2
Component 3
Component ...
Genotype 1
Exposure 1
Genotype 2
Exposure ...
Paving the way for personalized device-based brain-circuit therapy beyond PD
Behavioural intervention
Neuro-stimulation
Pharmacology
L-DOPA
-DOPA

VIA15 - BRAINMAP

THE DANISH HIGH RISK AND RESILIENCE STUDY

Children of parents with schizophrenia and bipolar disorder are at high risk for developing mental illnesses. Studies of groups at high risk for schizophrenia and bipolar disorder provide opportunities to gain insight into the processes that contribute to or protect against the emergence of symptoms. The Danish High Risk and Resilience Study – VIA 15 includes 15-year-old adolescents whose parents have been treated for bipolar disorder, schizophrenia disorders or none of these disorders. VIA 15 is the second follow-up study of a Danish cohort of 522 children who have already been studied at the age of seven (VIA 7) and eleven (VIA 11). When children took part in VIA 11, they underwent magnetic resonance imaging of the brain at the DRCMR or the Centre for Integrative Neuroscience (CFIN), Aarhus University. We are now re-scanning the children at the age of 15. Half of the children will additionally be examined with EEG at the DRCMR or with MEG at CFIN.

The design and scope of brain mapping in the VIA 15 study is unique on a global scale. Since brain imaging is performed repeatedly, before puberty (i.e., at the age of 11) and during puberty (i.e., at the age of 15), we have the opportunity to identify patterns of abnormal structural and functional brain maturation. We will particularly focus on developmental changes of brain networks involved in social cognition, reward processing, and executive functions. Furthermore, the brain imaging-based measures of brain network function and structure will be linked to the environmental, genetic, clinical, and neurocognitive data. This will enable us to elucidate underlying pathophysiological mechanisms and develop models predictive of risk, disease initiation and development, and resilience. Ultimately, this will contribute to early disease detection and the development of more personalized preventive interventions and treatment strategies.

FACTS

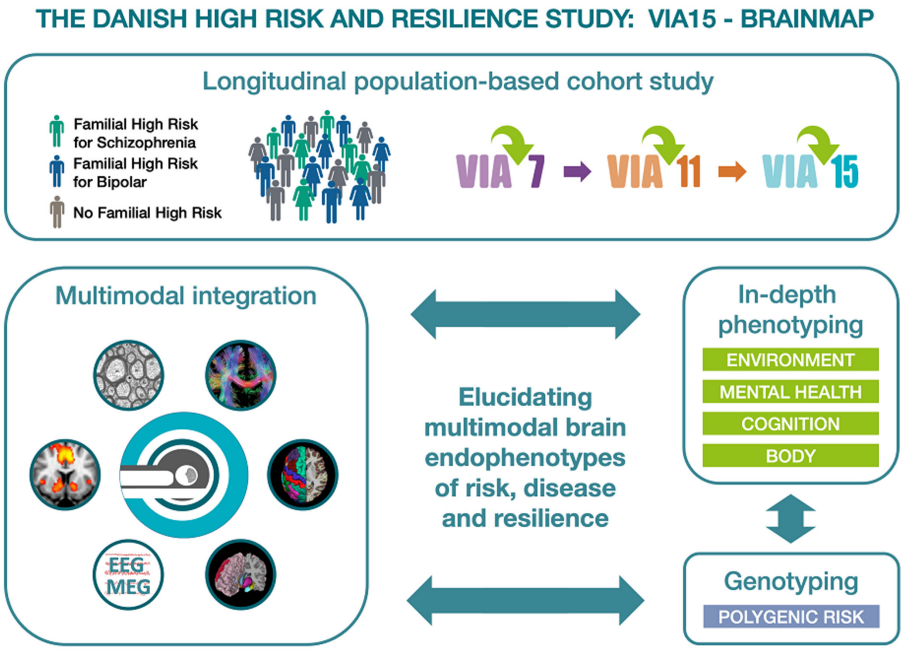
VIA 15 started in 2021 and is led by Prof. Merete Nordentoft from the Research Unit, Mental Health Center Copenhagen, University of Copenhagen.

The VIA 15 research group involves multiple clinical and research centres across Denmark.

VIA 15 received funding from the Lundbeck Foundation, the Mental Health Services of the Capital Region of Denmark and the Novo Nordisk Foundation.

IMPACT

The combination of a multidimensional assessment of cognition, physical activity, environment, and genetics with multimodal imaging in VIA 15 allow to differentiate factors that veer children on paths to health or to illness. The VIA 15 Brainmap study allows to identify brain risk and resilience markers which may help to develop targeted treatments that prevent the transition to these disorders.



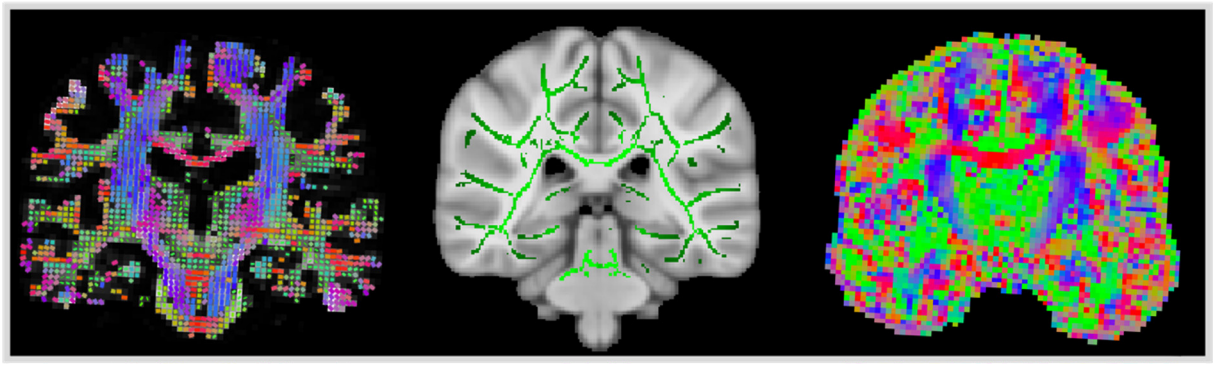
THE LISA STUDY

4 ROUNDS OF DATA COLLECTION COMPLETED – 2 MORE TO GO!

Exercise is generally considered good for brain health, but there are still many unresolved questions such as who will benefit the most, the type of exercise, how much and at what intensity. In the LISA study, the 4th round of data collection was finished during 2021. This is quite an accomplishment and would not have been possible without the collaboration between us at DRCMR, the Institute of Sports Medicine at Bispebjerg Hospital, and the department of Public Health at the University of Copenhagen. As a result, we now have a database with brain scans of over 300 individuals scanned at 4 time points. The MRI battery consists of structural scans, diffusion weighted imaging, perfusion, and resting state connectivity. The longitudinal nature of this dataset provides us with the unique opportunity to map individual brain trajectories in relation to physical fitness. Physical activity is, after all, central to the LISA study since its primary aim is to understand the effects of two different 1-year resistance training programs (high intensity vs. moderate intensity) in comparison to a non-exercising control condition.

What is evident in many exercising studies on brain structure and function is the large variability in response, and how difficult it is to understand the effects of physical training on brain structure and function in aging. The LISA study is no exception. In the first two studies published on the LISA data in 2020 (Gylling et al., 2020a, 2020b), the results showed that, even though some of the strength parameters improved over time, there was no influence on total hippocampal volume. Nevertheless, there was large individual variability in both physical parameters and hippocampal volume. This raises the question of whether there are some individuals that are responding to exercise with concomitant improvements in strength and brain variables, whereas other people are non-responders and would potentially require a different type of training than was provided here.

To precisely map the different trajectories of physical and brain parameters over time will be an important next step to further understand how staying physically fit can translate into maintaining a brain in shape. The large number of individuals and amount of data collected allows us to perform such analyses, which is a unique asset of the LISA-study - and something that will keep us busy in the years to come.



With diffusion weighted imaging it is possible to create a skeleton of the white matter tracts. In the LISA study, we can use these images to understand whether physical fitness is shaping the long-term consequences age has on these tracts.

UPCOMING KEY PROJECTS

During 2021 several researchers at DRCMR received major funding for new prestigious projects. The projects are now starting up and will be carried out during the coming years at DRCMR and at partner institutions.
Read about some of the projects here

OPTIMISTIC AND PESSIMISTIC DOPAMINE SIGNALS IN THE HUMAN BRAIN: A MAPPING AND MODELLING STUDY IN HEALTH AND PARKINSON'S DISEASE

This project is funded by a Sapere Aude: DFF Starting grant from the Independent Research Fund Denmark given to Research Fellow David Meder. The project is based on a new theory about how the brain's dopamine system works. The dopamine system allows us to generate adaptable behavior and vigorous movement. Dopamine cells release dopamine when we are positively surprised, but also when we initiate an action. The importance of dopamine is seen in Parkinson's disease where the degeneration of dopamine cells leads to impairments in motor function and motivation. A new theory suggests that dopamine cells react differently to rewards. Some are "optimistic" (they expect high rewards and are thus rarely positively surprised), while others are "pessimistic". It is, however, unknown, whether this is the case for the human brain. If so, this theory might explain several disease symptoms, such as apathy, anhedonia and motor impairments. David wants to use MR-scans to probe the human brain for "optimistic" and "pessimistic" dopamine neurons. Additionally, the plan is to map the loss of dopamine neurons in Parkinson's disease patients and investigate, whether the individual pattern of cell loss can explain some of their symptoms. The project will involve a tight collaboration with Brain Prize winner Ray Dolan and his lab, and with Mark Hallett at the NIH. The results might change our understanding of dopamine's role in reward, motivation and movement but also why Parkinson's patients develop their symptoms.

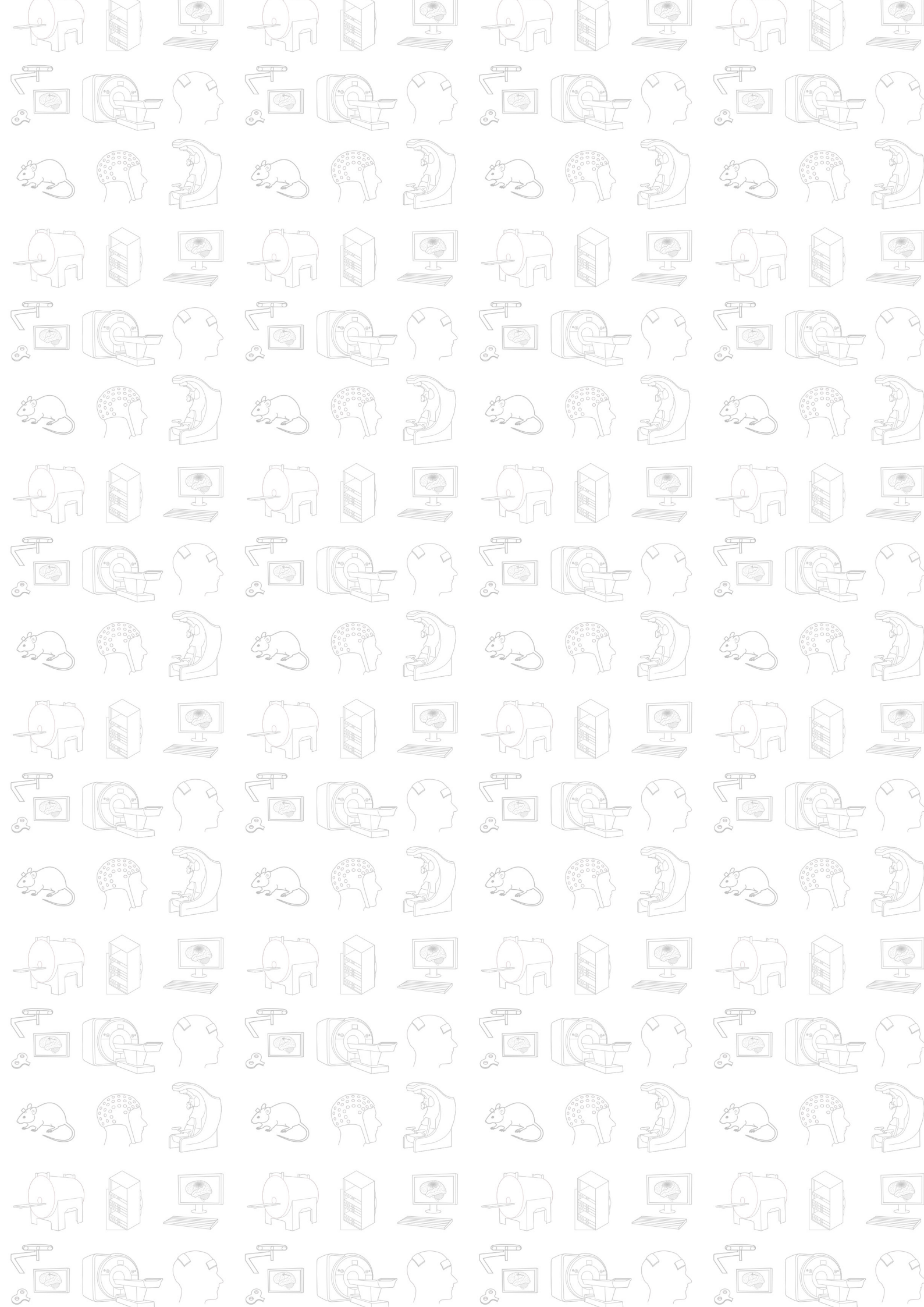
From DRCMR: Research Fellow David Meder and additional staff to be recruited.

MAPPING THE LATERAL PREFRONTAL CORTEX: IMPROVED PARCELLATION AND LAMINAR MODELS

The project is funded by the Lundbeck Foundation as part of the foundation's LF & NIH BRAIN Initiative. The initiative provides funding for researchers at Danish research institutions to join NIH BRAIN Initiative projects. The grant has been awarded to Oula Puonti at DRCMR for a collaboration with Dr. Bruce Fischl and Dr. Juan Eugenio Iglesias on two NIH BRAIN Initiative projects running at the Athinoula A. Martinos Center for Biomedical Imaging (Massachusetts General Hospital). The BRAIN projects: "Imaging and Analysis Techniques to Construct a Cell Census Atlas of the Human Brain" (1U01MH117023-01, PI: Dr. Fischl) and "Open-source software for multi-scale mapping of the human brain" (1RF1MH123195-01, PI: Dr. Iglesias), aim to develop novel imaging and computational techniques to build a cellular atlas of the human cortex and apply it to study brain structure and function from MRI data.

The LF & NIH project focuses on a specific cortical area called the lateral prefrontal cortex, which takes part in many executive functions such as planning and short-term memory. Studying the microstructure of the lateral prefrontal cortex is the key to understanding the organizational basis of its function and how this relates to behavior. Using MRI to study the microstructure, often called "in-vivo histology", has the potential to establish markers of the underlying cortical microstructure, which could also be used to diagnose and track brain diseases. However, the full realization of in-vivo histology is limited by our inability to accurately detect cortical layers, the defining feature of the cortical architecture, from the currently available MRI data. To tackle this challenge, we will build models of the microstructure and the cortical layers of the lateral prefrontal cortex using post-mortem brain samples and apply these models to MRI scans of the living human brain. Using detailed models with high-resolution MRI data allows us to infer the microstructure of the cortex even when it is not directly visible in the MRI scans.

From DRCMR: Postdoc Oula Puonti, Prof. Axel Thielscher, Assoc. Prof. Esben Thade Petersen, Prof. Hartwig R. Siebner and additional staff to be recruited.



RESEARCH AT DRCMR

OUR VISION

Mapping brain dynamics to promote health and to tailor therapy. We use advanced magnetic resonance imaging to create knowledge about the brain –knowledge that can be used to optimize treatments in individual patients and to boost public and individual health, potential, and well-being.

OUR MISSION

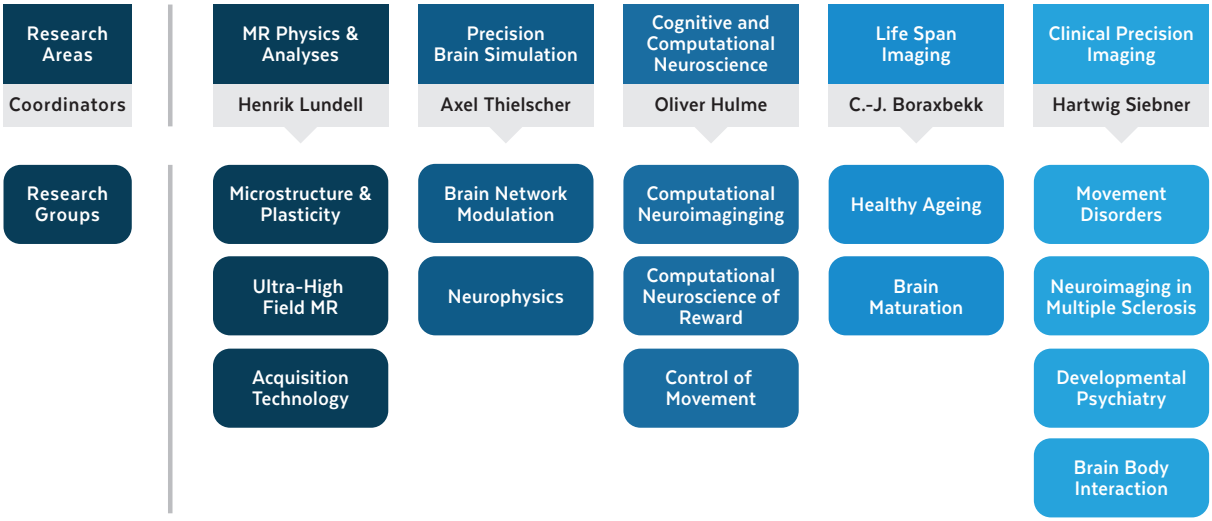
We use brain mapping to unravel causal dynamics in the human brain.

We study beneficial brain dynamics that secure physical and mental health as well as detrimental brain dynamics that cause brain disorders across the lifespan.

IMPACT

This knowledge will help us tailor therapeutic interventions in the brain dynamics expressed in individual patients (precision medicine).

And in general contribute to future efforts to boost public and individual health, potential, and well-being.


Research Areas
Coordinators
Research Groups
MR Physics & Analyses
Henrik Lundell
Microstructure & Plasticity
Ultra-High Field MR
Acquisition Technology
Precision Brain Simulation
Axel Thielscher
Brain Network Modulation
Neurophysics
Cognitive and Computational Neuroscience
Oliver Hulme
Computational Neuroimaginging
Computational Neuroscience of Reward
Control of Movement
Life Span Imaging
C.-J. Boraxbekk
Healthy Ageing
Brain Maturation
Clinical Precision Imaging
Hartwig Siebner
Movement Disorders
Neuroimaging in Multiple Sclerosis
Developmental Psychiatry
Brain Body Interaction

MR PHYSICS AND ANALYSES

While the research at DRCMR is multidisiplinary and involves a number of different techniques, MR-based methods are at the core of most projects. The continuous development of new methods enables new research questions to be raised. We take active part in the forefront of methods research and follow the achievements of the MR community closely to reach new goals in neuroscientific and clinical research.

MR methods range from high resolution anatomical imaging to studying brain anatomy in better detail, quantitative imaging and spectroscopic techniques reflecting different microstructural molecular features of tissue to dynamic imaging methods tracing neuronal activation and physiology. Increasing interest is also put into body imaging, e.g. the heart and the liver.

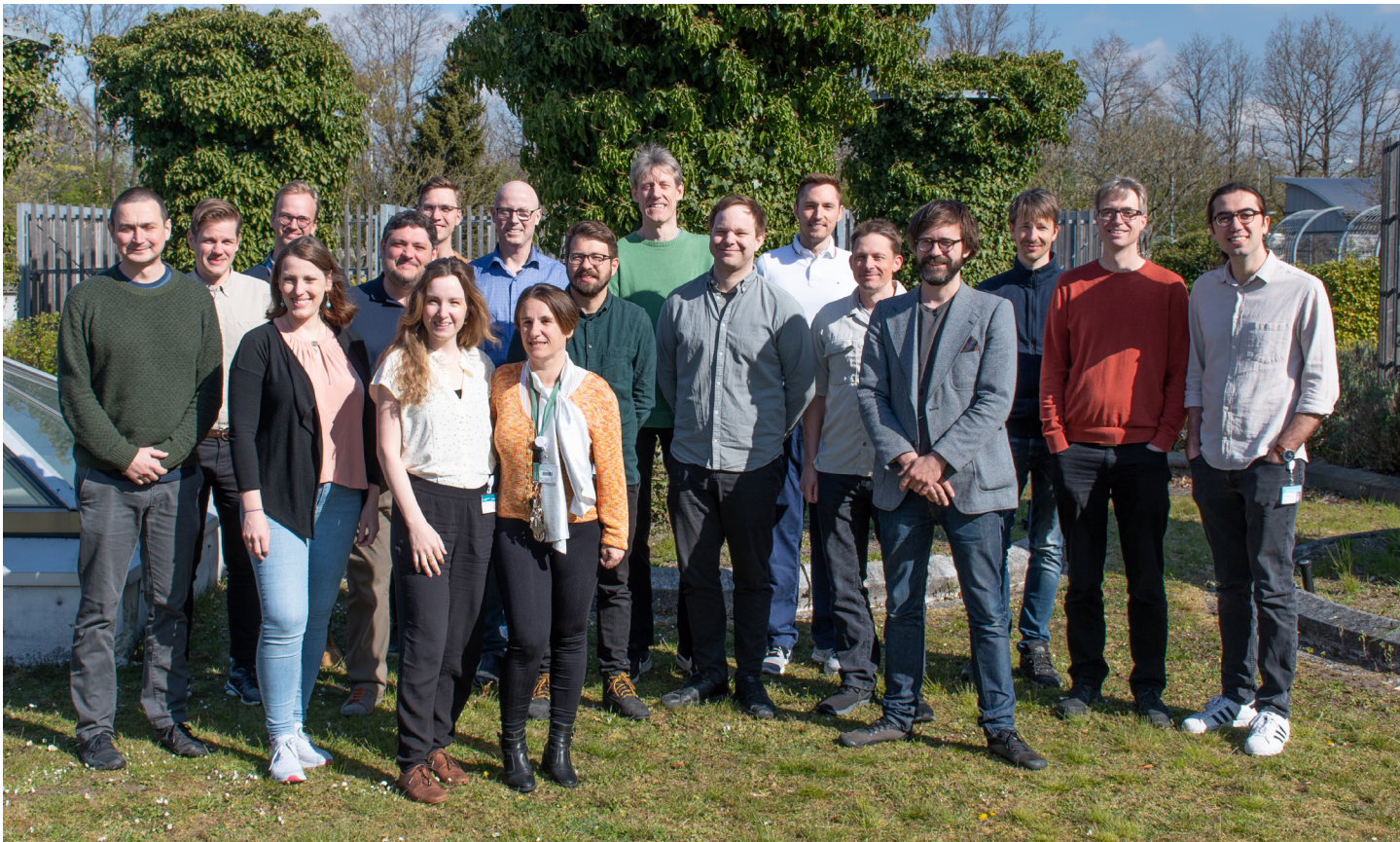
In our work, ultra-high field MRI is crucial for innovation in experimental and clinical research as well as the integration of multimodal approaches during the scanning session. Translation of experimental methods in preclinical and ultra-high field settings to clinically feasible routines is also in the heart of our work. This requires efforts in the construction of new hardware, scanner sequences and not at least computational methods to analyse new types of data. We have a particular interest in spectroscopy, diffusion, perfusion and functional MRI but are also extending to combined approaches, e.g. using MRI and transcranial magnetic stimulation.

To unleash the powers of new methods, we coordinate our work with other research areas at the department as well as external collaborators in Denmark and internationally. This ensures the synergy needed to span from basic research to clinical work. The MR Physics and Analysis research area is coordinated by Senior Researcher Henrik Lundell.

Microstructure & Plasticity

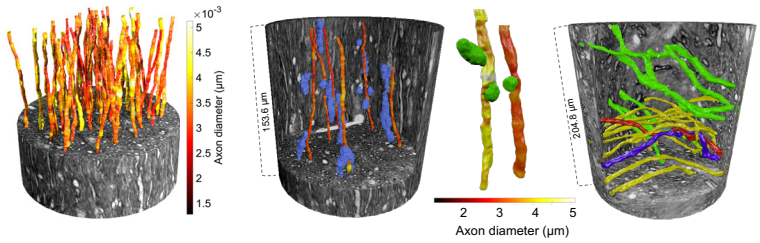
Ultra-High Field MR

Acquisition Technology



MICROSTRUCTURE AND PLASTICITY

In 2019-21 the MaP group continued to advance our multi-modal integration analysis of tissue microstructure, combining 3D phase-contrast synchrotron imaging (SRI), 3D EM, and MRI. Actually, we realized a kind of hybrid imaging because the same tissue had first been MRI scanned, then prepared for SRI and EM experiments, and finally histogly. As part of the MAX4Imagers project, Mariam Andersson and collaborators analysed single axon morphometry and its myelin thickness in monkey brain images, using MRI and the ESRF synchrotron in Grenoble, France. We showed how axon 3D morphology appears to be formed by its local environment of vessels, cell bodies and the mysterious vacloues (PNAS, 2020). Similarly, Mette Lindhøj is realising 3D imaging of sperm cell movement using SRI. It is a highly complex in vivo imaging issue where new staining techniques are developed to detect the cells with SRI, and here, 3D EM is used as verification. In collaboration with DTU and Gubra APS, we have started exploring Light-Sheet Flourence Microscopy (LSFM) imaging of cleared brains that provide micrometer resolution of smaller brains. Here, Johanna Perens has established an image registration framework to align the Allan mouse atlas into iDISCO cleared brains and LSFM (Neuroinformatics, 2020). Naturally, our key modality is MRI. We applied tensor-valued diffusion MRI in multiple sclerosis patients to estimate micro-Fractional Anisotropy (μFA) which is independent of fibre orientation compared with FA obtained from DTI. Results indicates that FA appears more sensitive to fibre architecture than expected whereas μFA shows a steady decrease in WM from healthy and with disease progression (Brain Comms, 2020). Henrik Lundell and Samo Lasic have
contributed to a new textbook with a chapter on the fundamental theory of diffusion encoding with free gradient waveforms for microstructural imaging.



Synchrotron imaging of axons. Left: 3D segmentation of axons diameter variation in Corpus callosum. Middle: Axon morphology can be modulated by vacuoles (green). Right: Crossing fibre region.

GROUP MEMBERS

- **Assoc. Prof. Tim B. Dyrby**
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- Postdoc Yi He
- Postdoc Tram Nguyen
- Postdoc James Breen-Norris
- Postdoc Samo Lasic
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- PhD stud. Sara Hesby Andreasen
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- PhD stud. Sidsel Winther

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- Prof. Tim Salditt
- Prof. Charles Liberman
- Prof. Torsten Dau
- Prof. Jon Sporring

HOMEPAGE

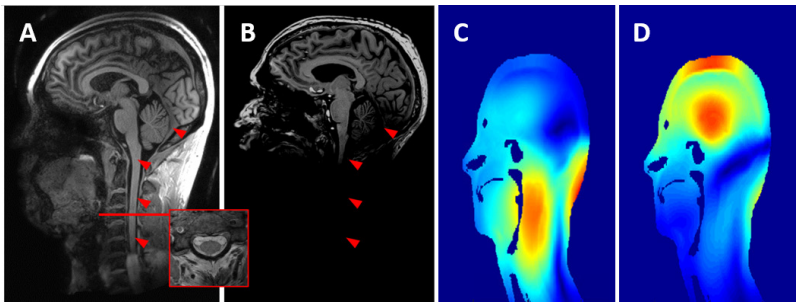
www.drcmr.dk/map

PUBLICATIONS

29, 40, 55, 59, 65, 68, 69, 75, 74, 101, 110, 120, 124, 135, 152, 177, 190, 206, 214

ULTRA-HIGH FIELD MR

The vision of the Ultra-High Field MR group is to enable cutting-edge spectroscopic and image-based research that keep our research within aging, metabolic and neurodegenerative diseases at the absolute forefront. We have a particular focus on the metabolic and neuro-chemical aspects of aging and how they manifest in disease. The hope is that we eventually, at an early stage, can separate healthy aging from unhealthy aging that leads to disease such as dementia or Parkinsonism. To achieve this we want to unleash the full potential of the 7 tesla MR system through innovation. Software solutions include novel sequences that deliver new clinical information as well as new ways to speed up the acquisition of existing modalities. Consistent image quality, also at extreme high-resolution in patients that may move during scanning, is achieved using advanced motion correction and reacquisition schemes. Hardware solutions include advanced RF coil designs which improve both coverage and homogeneity of the acquired images by means of multiple transmit coils. This allows us to target new structures such as the carotid arteries or the brainstem, both challenging regions at ultra-high field. We achieve this progress via strong collaborations between DRCMR, DTU Health Tech and Technological University of Eindhoven, the Netherlands. Fluctuations or imperfections in the constantly changing field gradients, used to encode the MR images, result in reduced image quality. To overcome this, we collaborate with the Niels Bohr Institute on the development of optical magnetometers that do real-time monitoring of the actual field at different positions within the scanner. The overall goal is to have a self-calibrating system operating at the optimal RF transmit field (B1) while having full control over the static field (B0), at all times, thereby improving speed and image quality even further.



RF field inhomogeneity and coverage is an issue at 7 tesla (A vs B). The solution (A) is based on a shielded coax cable coil array. It improves coverage and allows to steer the RF field to defined target areas such as neck or brain (C vs D).

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- Research Fellow Anouk Marsman
- Postdoc Vanessa Wiggermann
- MR Clinical Scientist Jan Ole Pedersen
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- Assoc. Prof. Lars G. Hanson
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- PhD stud. Sadri Güler
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- Prof. Eugene Simon Polzik
- Prof. Jeroen Hendrikse
- Prof. Dennis Klomp
- Prof. Andrew Webb
- Prof. Matthias van Osch
- Assoc. Prof. Itamar Rohnen
- Dr. Karin Markenroth Bloch
- Assoc. Prof. Gunther Helms
- Prof. Ulrik Pedersen-Bjergaard
- Prof. Michael Kjær

HOMEPAGE

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PUBLICATIONS

42, 83, 118, 176, 196

ACQUISITION TECHNOLOGY

Research focus:

- Motion and artefacts
- Phase-sensitive MRI
- MRI safety

The robustness, sensitivity and specificity of MRI is improved using fundamental physics and advanced analysis.

Many patients cannot lie still as needed for high-quality MRI. Funded by SDC, Malte Laustsen and his PhD supervisors in collaboration with Mads Andersen (Philips Healthcare) and Kristoffer Madsen, developed correction of MRI compromised by motion tracked with an EEG system. The quality is similar to MR navigators that prolong MRI.

MR Current Density Imaging (MRCDI) is developed with Axel Thielscher's Neurophysics group and partners. Postdoc Cihan Göksu, in particular, improved the resolution while addressing imperfections. The unique precision is now 0,1 nT in 4 minutes, which can improve electrical brain stimulation. Conducting material may cause burns during MRI. Hence, PhD student Froði Gregersen (funded by SDC) designed new safe electrodes almost eliminating stray fields interfering with MRCDI. The enabling of stronger currents and stimulation at 7T were added benefits. Froði's PhD that also addressed physiological noise handling in MRCDI was succesfully defenced late 2021.

The successes in MRCDI made us take on the challenge of directly mapping neural activity, funded by a Lundbeck Experiment grant. It relies on phase-sensitive MRI that will also be used by PhD student Peter Rasmussen for mapping transcranial ultrasound during brain stimulation.

Lars G. Hanson teaches MRI safety and techniques worldwide (lectures, 180,000 YouTube views, countless downloads - see www.drcmr.dk/MR). In 2020, a Bloch Simulator rewrite was released, www.drcmr.dk/BlochSimulator, with new functionality and accelerated 3D graphics, even on smartphones as a free app.

Most studies involve the MR section, DTU Health Tech, including hyperpolarized MRI and MR monitoring of brain tumors during radiotherapy.

GROUP MEMBERS

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- PhD stud. Froði Gregersen
- PhD stud. Malte Laustsen

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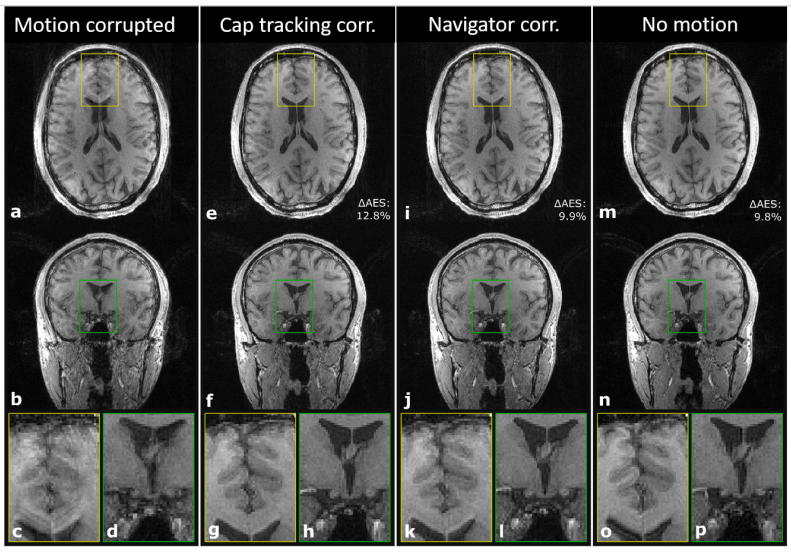
- Prof. Klaus Scheffler
- Dipl.-Ing. Gregor Schäfers

HOMEPAGE

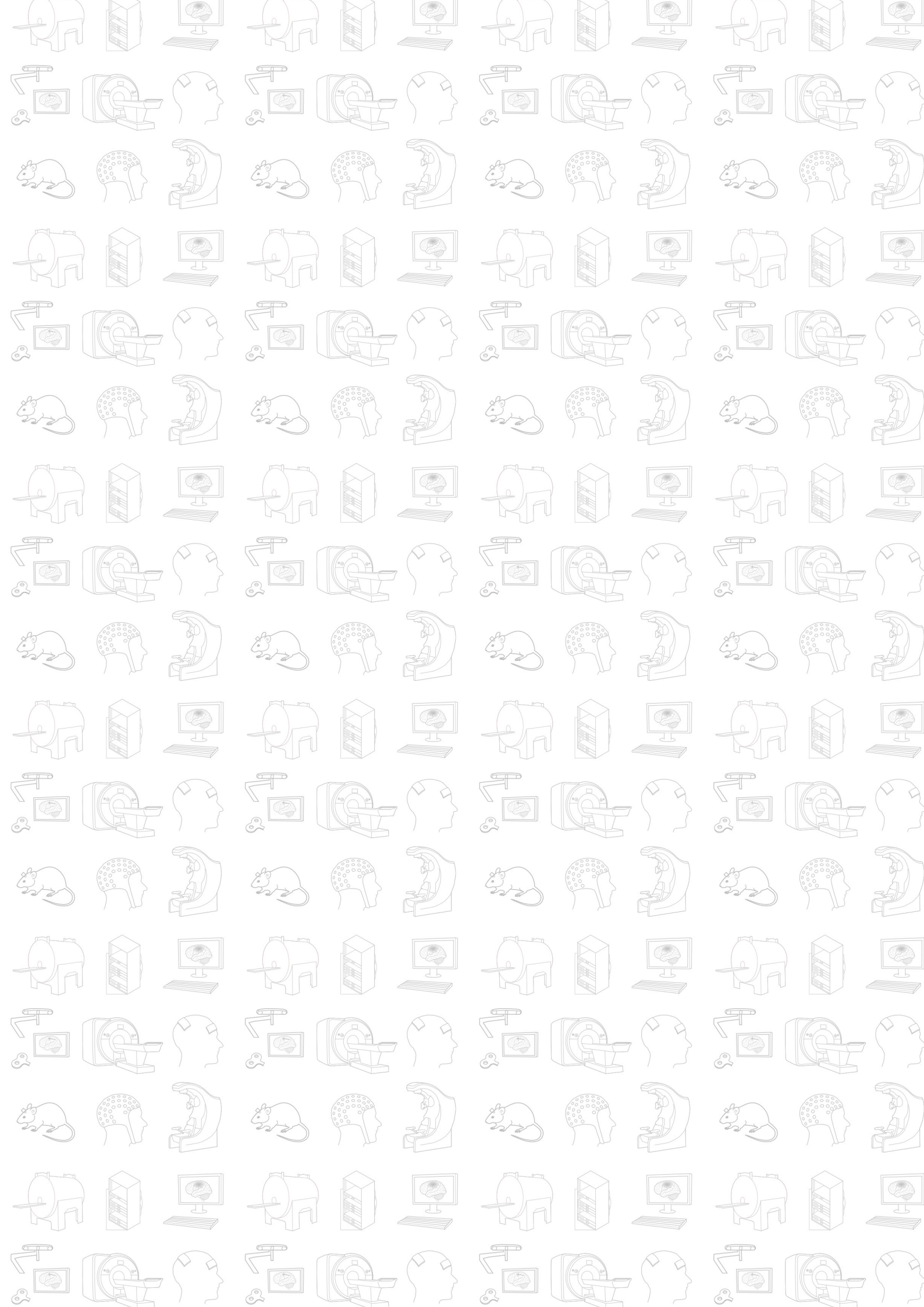
www.drcmr.dk/acquisition

PUBLICATIONS

20, 51, 172, 175, 208, 236



Brain MR images without and with motion correction using either a new tracking cap, or navigators prolonging scans. An image recorded in absence of motion is shown for comparison. Both methods show drastic reduction of errors and similar quality.



PRECISION BRAIN STIMULATION

Towards causal neuroscience

Non-invasive Transcranial Brain Stimulation (TBS) techniques directly interact with intrinsic brain activity and can induce long-lasting effects on human brain function. These features make them unique complements to neuroimaging techniques such as MRI that are correlative in nature, with limited possibilities to determine whether the measured brain activity patterns play critical roles in the observed behavior. In contrast, combining TBS with neuroimaging in a perturb-and-measure approach can reveal causal insights into the function and dynamics of the complex brain networks that underlie our thoughts, feelings and actions. TBS can also shape and normalize dysfunctional brain activity patterns that underlie neuropsychiatric diseases, making it a promising therapeutic option.

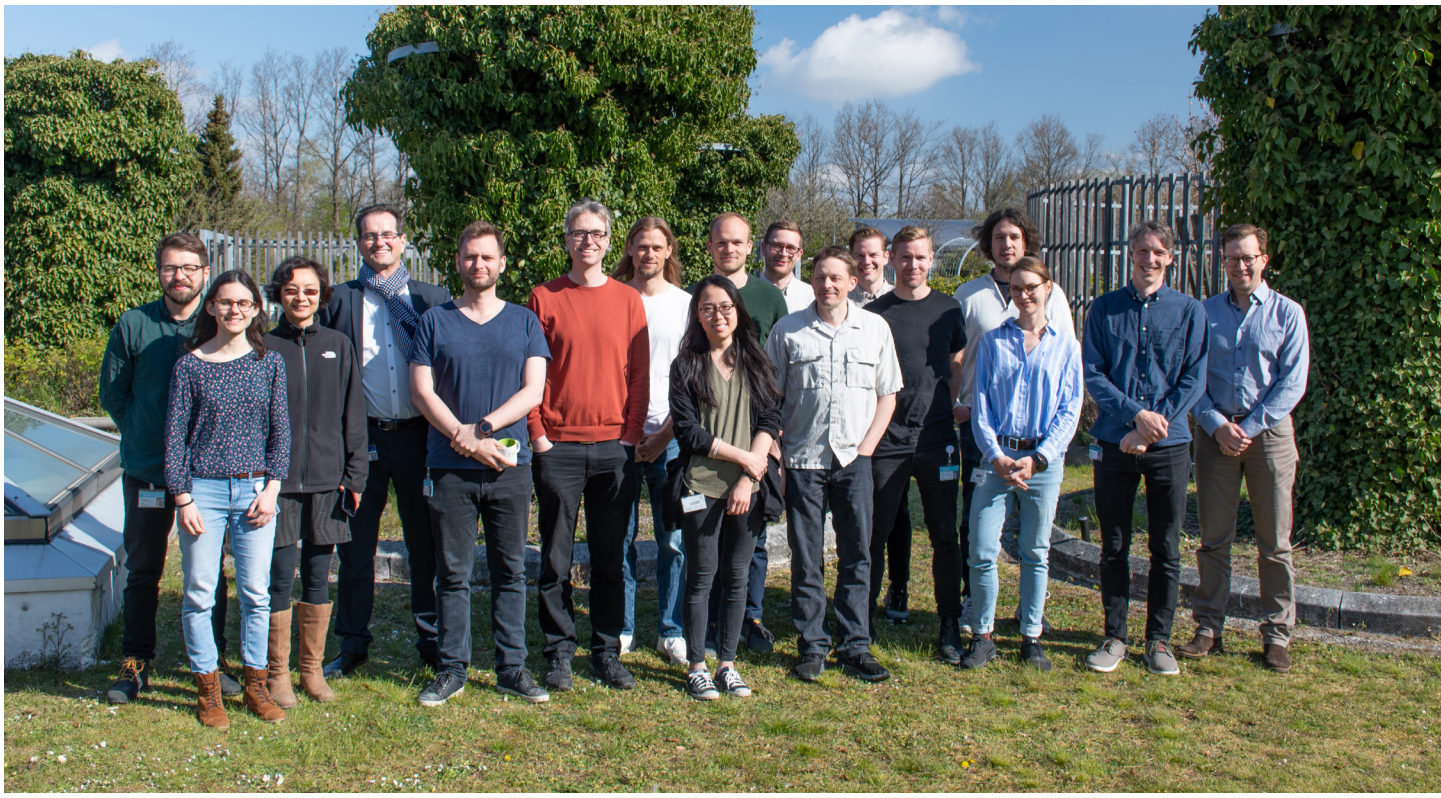
Yet, our understanding of how TBS affects the brain activity is still limited, which reduces its specificity when used as a neuroscience or therapeutic tool, and prevents a systematic optimization of the treatment efficacy.

Mission and Vision

We strive to advance TBS as a unique interventional tool to study causal brain dynamics and enhance cognitive, affective and motor function in health and disease. We aim to overcome current limitations through innovative approaches that shape electrical signaling in the brain with unprecedented spatial, temporal, and functional precision. Our goal is personalized TBS interventions that integrate neuroimaging-based phenotyping with computational dose control of the stimulation patterns in the brain to increase the specificity of the stimulation effects and minimize their inter- and intraindividual variability. We will exploit the potential of precision TBS, tailored to the individual brain, to uncover the causal dynamics of the human brain and translate these insights into powerful neuropsychiatric therapies for the 21st century.

A unique infrastructure for brain stimulation

The DRCMR houses a unique infrastructure to support 'brain imaging informed' and '-controlled' TBS. This includes five state-of-the-art laboratories where all TBS modalities can be applied independently or combined. Brain activity can be continuously monitored with EEG, offering open- and closed-loop applications. One laboratory is equipped with the first robotic TMS-system in Scandinavia for investigator-independent, automated transcranial magnetic stimulation. Neuro-navigated TMS-fMRI and TES-fMRI on a state-of-the-art 3T MR system enable measurements of the immediate and lasting stimulation effects on brain activity. Last but not least, personalized computational modeling of stimulation fields is supported by dedicated software infrastructure on the DRMCR computer cluster.



Brain Network Modulation

Neurophysics

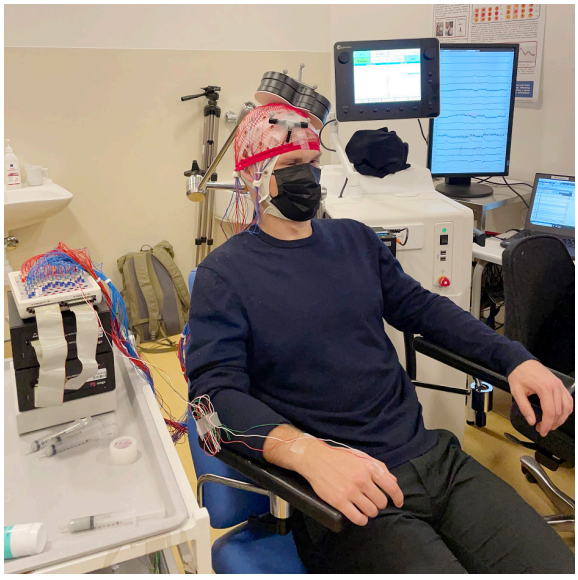
BRAIN NETWORK MODULATION

The Brain Network Modulation group employs transcranial brain stimulation to examine and shape the function of brain circuits, merging basic and clinical research with state-of-the art brain mapping. The group continuously improves methodological aspects of brain stimulation to optimize its spatial and functional precision.

Mind the periphery! - The group uses electrophysiological (MEP, EEG) and MR-based brain mapping techniques to delineate how transcranial brain stimulation functionally "engages" the targeted brain circuits. In a study on healthy volunteers, we used EEG to record the cortical responses evoked by transcranial magnetic stimulation (TMS). We found that peripheral co-stimulation of the somatosensory and auditory system can produce "non-transcranial" TMS-evoked potentials that constitute an inherent source of ambiguity in TMS-EEG studies (NeuroImage 185:300-312).

Modulating oscillatory brain activity - In a collaborative study that was conducted by Giovanni Pellegrino and colleagues in Venice, we showed that transcranial direct current stimulation (TDCS) over the sensorimotor regions inhibits cortical gamma synchrony evoked by click trains (Human Brain Mapping 40:2736-2746). This paper received the Best Paper of-the-Year award from the HBM editorial board in 2019.

"The state is the art" - We successfully used EEG to trace oscillatory brain activity online during transcranial brain stimulation of the motor cortex. This enabled us to align the time point of stimulation directly to the ongoing brain activity in the stimulated cortex. We were able to deliver TMS pulses at distinct power levels or a specific phase of the pericentral mu-rhythm (Brain Stimulation 12:1261-1270 and 14:713-722). Such state-informed brain stimulation opens up new ways of exploring and tuning human brain function.



Brain-circuit centered approach to precision neurostimulation of brain disorders.

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- Senior researcher Anke Karabanov
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- Research Fellow David Meder
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- Postdoc Syoichi Tashiro
- Postdoc Angela Mastropasqua
- Postdoc Mikkel Malling Beck
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- PhD stud. Allan Lohse
- Phd stud. Lærke Krohne
- PhD stud. Sofie Nilsson
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- Research asst. Marjolein Piek
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- Stud. Rasmus Brygman Lange
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- Senior researcher Raffaele Dubbioso
- Prof. Angelo Quartarone
- Senior researcher Til Ole Bergmann
- Research fellow Virginia Conde
- Senior Researcher Giovanni Pellegrino

HOMEPAGE

www.drcmr.dk/brain-network-modulation

PUBLICATIONS

52, 53, 184

NEUROPHYSICS

Our vision is to boost the efficiency of non-invasive Transcranial Brain Stimulation (TBS) and to make it a relevant therapy for neuropsychiatric diseases. A main focus of our research is on the personalization of existing TBS methods to increase their clinical efficacy. TBS can modulate neural plasticity and normalize function in the targeted disease-related brain networks at a level of spatial specificity that surpasses any other non-invasive method, in particular pharmacological approaches. However, the efficacy of TBS is still hampered by a large inter-individual variability of the treatment outcome.

Our group has pioneered the use of computational dosimetry methods for the personalized control and optimization of the current flow patterns induced by transcranial magnetic and electric stimulation in the brain (www.simnibs.org). Our working hypothesis is that an individualized dose control will help to reduce the outcome variabilty of TBS and by that increase its clinical impact. In internal and international collaborations, we aim to validate the predictions of personlized dosing approaches and to demonstrate their value in predicting the physiological brain responses to stimulation. To this end, we have successfully implemented novel MR methods to measure the current flow patterns induced by TBS. We are currently combining these measurements with functional MRI measurements of the physiological brain responses to transcranial electric stimulation. Finally, we are establishing low-intensity transcranial ultrasound stimulation (TUS) in our lab, which is emerging as a method with improved spatial precision compared to established TBS methods. In particular, we are excited to explore its potential in focally targeting deep brain regions, which is not feasible with other TBS methods.

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- Postdoc Cihan Göksu
- Postdoc. Cristina Pasquinelli
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- Postdoc Hasan Hüseyin Eroglu
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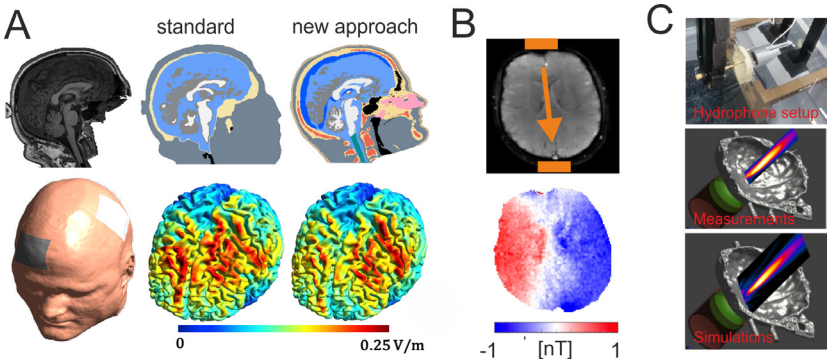
- Prof. Koen van Lempuut
- Prof. Dr. Klaus Scheffler
- Assist. Prof. Hyunjoo Jenny Lee
- Prof. Agnes Flöel
- Prof. Thomas Knösche
- Prof. Gottfried Schlaug
- Prof. Michael Siniatchkin
- Franz Bødker, PhD

HOMEPAGE

www.drcmr.dk/neurophysics

PUBLICATIONS

1, 4, 13, 18, 20, 27, 34, 56, 57, 58, 60, 61, 81, 82, 105, 128, 132, 133, 148, 153, 154, 167, 170, 172, 175, 186, 198, 199, 202, 210, 212, 216, 220, 222, 229, 236, 242, 244



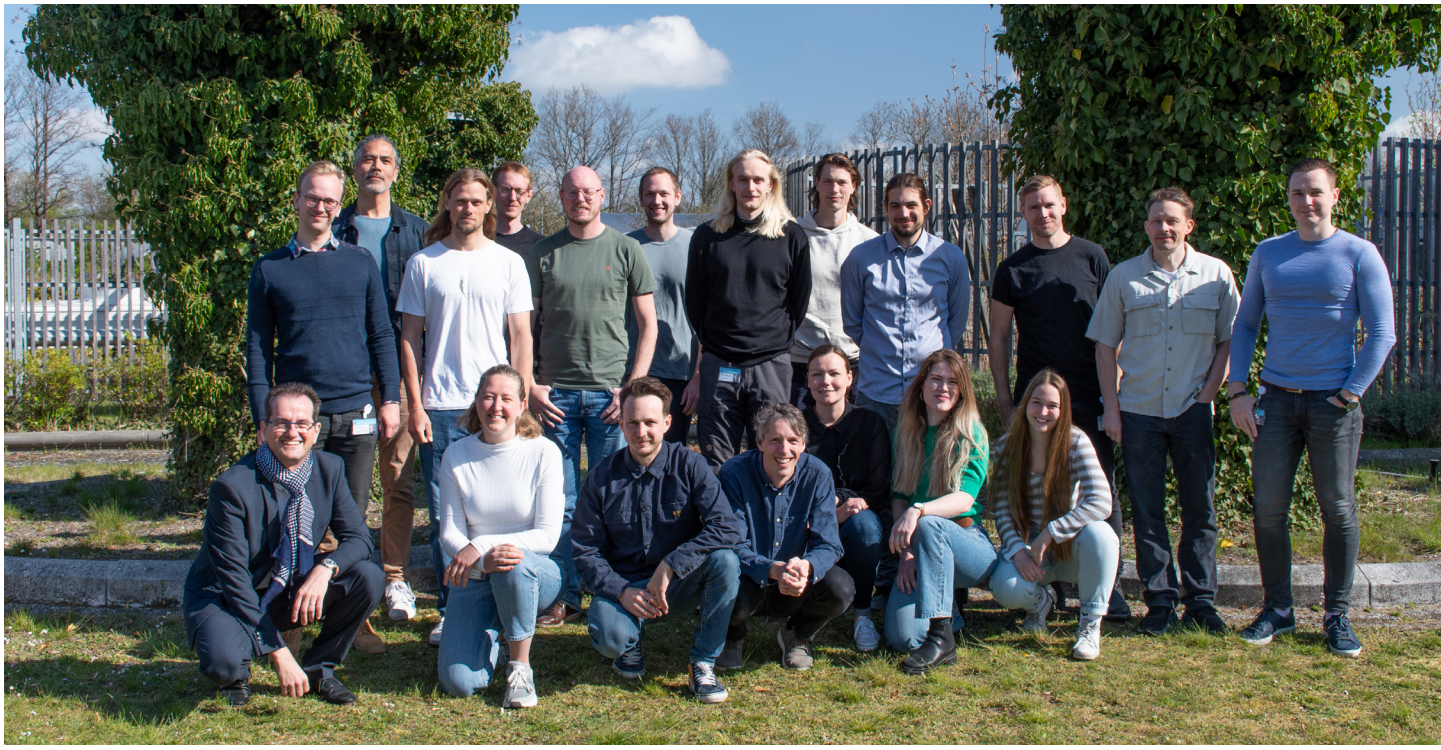
A) Our new whole-head segmentation method ensures accurate dose estimates even for clinical-grade MR images. B) Highly sensitive MR current density images to validate computational dose calculations. C) Simulation and measurement of ultrasound wave.

COGNITIVE AND COMPUTATIONAL NEUROSCIENCE

Both cognitive and computational neurosciences constitute major research themes here at DRCMR. What exactly is cognitive and computational neuroimaging? The word cognitive refers to a focus on cognition, a wide spectrum of mental faculties that we all take for granted. Learning, decision-making, attention, reasoning, memory, language, and motor control are all examples of the faculties we rely on as part of our mental toolkit. Cognitive neuroscience, naturally, is the subfield of neurobiology charged with investigating the neurobiological underpinnings of these faculties. Computational Neuroscience, on the other hand, is a subfield in which mathematical tools are used to develop and test theories of brain function. Putting this all together, cognitive and computational neuroimaging thus studies the neural basis of cognition from a computational perspective, using neuroimaging as its primary technique.

Our research area's long-term vision is to pioneer new methods for bridging computational modelling of cognition and neuroimaging, and to use this to understand the brain's functions and dysfunctions. Principal among these efforts is to develop advanced multi-modal methods for fitting computational models in parallel to individual neural elements; an approach that will allow us to change the way we ask questions about how computational variables are encoded by, and mapped across, the brain. We have several groups of researchers pursuing research along a diversity of frontiers.

The computational neuroscience of reward group seeks to build and test fundamental theories of reward value that are grounded in our physiology and evolutionary history. They combine neuroimaging with homeostatic and hormonal interventions, studying how these modulate basic rewards such as sugar consumption. The reward system is also studied in the context of economic decision making, combining computational modelling of reward valuation, with the neuroimaging of reward responses at high resolution. The motor control group is investigating how the brain engages in motoric control of its body with a particular focus on the hand, skill-learning, optimizing motor action. The group is currently focusing on combining computational techniques, with neuroimaging, magnetic stimulation and optogenetics to better understand and treat Parkinson's disease. The computational neuroimaging group engages in machine learning research that aims to improve the modeling and analysis of neuroimaging data from EEG, to fMRI, as well as diffusion & structural data. Their particular focus for the future is on building causal models of neuroimaging data and its relation to cognition.



Computational Neuroimaginging

Computational Neuroscience of Reward

Control of Movement

COMPUTATIONAL NEUROIMAGING

The Computational Neuroimaging group conducts research in modelling and analysis of neuroimaging data from several modalities, including functional and structural magnetic resonance imaging, electrophysiology, brain stimulation and behavior. The methodological focus is on applied statistical machine learning and spans from simple supervised linear models to non-linear and unsupervised learning.

Efficient feature extraction methods are important as neuroimaging experiments are generally high-dimensional and often cover several modalities with markedly different noise characteristics. To this end, the Computational Neuroimaging group works on developing unsupervised decomposition methods, which can improve generalization performance of prediction algorithms based on functional connectivity data, especially when faced with datasets recorded across several sites and acquisition manufacturers.

In active machine learning, the idea is to actively plan data acquisition while it is ongoing to optimize a learning objective. This has the potential to vastly improve efficiency of the data acquisition process but is a demanding endeavor in neuroimaging as it requires more sophisticated model and online learning. A key concept in this setting is uncertainty quantification as it enables the model to be aware of its shortcomings and thereby spend time on acquiring data which enable it to learn what it does not already know. Consequently, the Computational Neuroimaging group both develops efficient models with uncertainty quantification and real-time data analysis, in an effort to enable more efficient treatment and data acquisition procedures in the future.

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- PhD Stud. Jesper Duemose Nielsen

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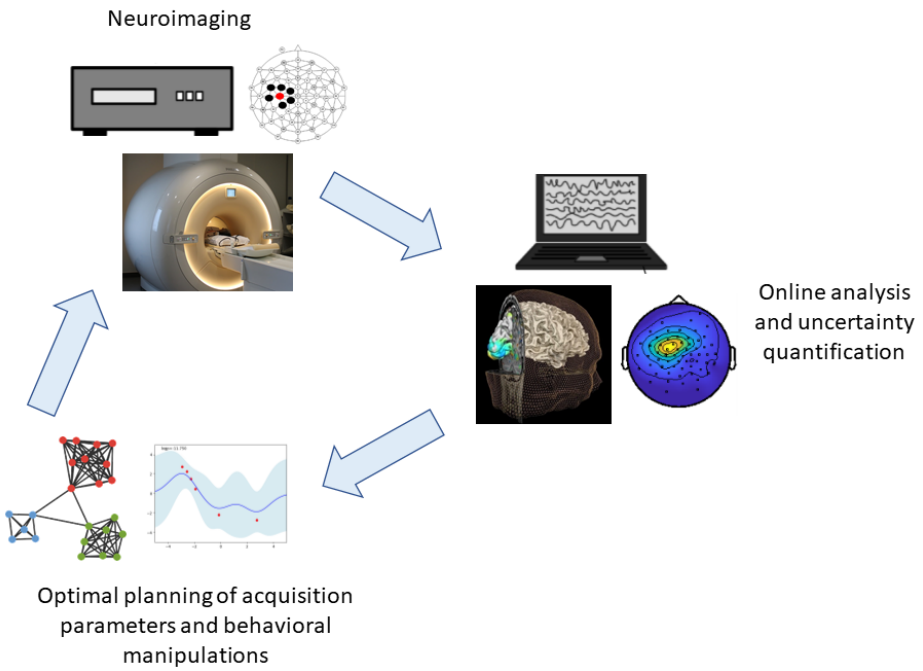
- Prof. Rong Xue
- Prof. Nathan W. Churchill
- Prof. Raymond Chan

HOMEPAGE

www.drcmr.dk/computational-neuroimaging

PUBLICATIONS

22, 36, 41, 49, 58, 64, 85, 147, 185, 208, 223



Active data acquisition procedures have the potential to improve the data collection procedure. In this setting, online analysis and uncertainty quantification is used to optimally inform future data collection procedure in a closed loop.

COMPUTATIONAL NEURO-SCIENCE OF REWARD

Our main research interest concerns the brain's reward system. Put simply: how does it work, and why?

We explore theories that constrain how it should work, and then test the predictions of these theories against behavioral, physiological, and neuroimaging data. There are two strands to the group's research agenda:

The first strand asks, how do reward computations shape behavior to regulate the physiological systems of the body. Specifically, how are the values of primary rewards such as food and water, configured by homeostatic states, and how should they be configured according to the constraints of survival. We are particularly interested in how models of this sort could provide a unified explanatory account of basic behavioral phenomena such as risk preferences, loss aversion, and temporal discounting. This work involves collaboration with endocrinologists, metabolic scientists, food scientists, and computational neuroscientists.

The second strand draws on a concept in physics known as ergodicity, and is the basis of the group's connection to the London Mathematical Laboratory. Ergodicity here refers to thinking carefully about the types of averages that are relevant to behaviour, with a particular emphasis on how decisions unfold over time. We are interested in the constraints that ergodicity imposes on decision-making, and whether such considerations can also offer a unified account of a number of disparate behavioral phenomena. We recently received funding from the Novo Nordisk Foundation to work together on experiments that expose subjects to different dynamical settings, testing how these dynamics modulate reward computations, and risk-taking behavior.

The group is committed to open science, and all future experiments will pre-register and release all code, materials, and data wherever possible. We also teach courses on the methods most central to our research, namely Bayesian statistics, as well as Bayesian modelling of cognition and the brain.

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- Research Assistant Iyadh Chaker
- Visiting Stud. Kamil Bonna
- Visiting Stud. Felix Hubert
- Junior Researcher Benjamin Skjold Frederiksen

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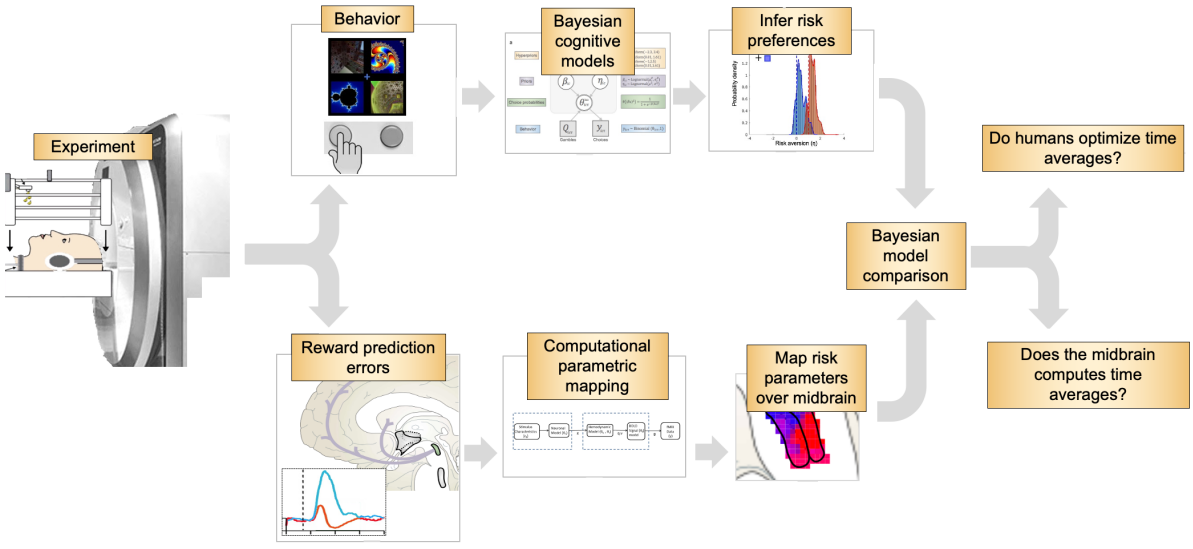
- Dr. Alex Adamou
- Dr. Mark Kirstein
- Dr. Yonatan Berman
- Prof. Sten Madsbad
- Assoc. Prof. Tobias Andersen
- Assoc. Prof. Christoffer Clemmensen
- Postdoc Claus Brandt
- Prof. Duda Kvitsiani

HOMEPAGE

www.drcmr.dk/reward-group

PUBLICATIONS

28, 146, 189, 197, 200



An overview of the methods deployed in our upcoming research project on ergodicity and the brain. It shows how the different methods combine to allow us to ask how the reward system computes time averages when making risky decisions.

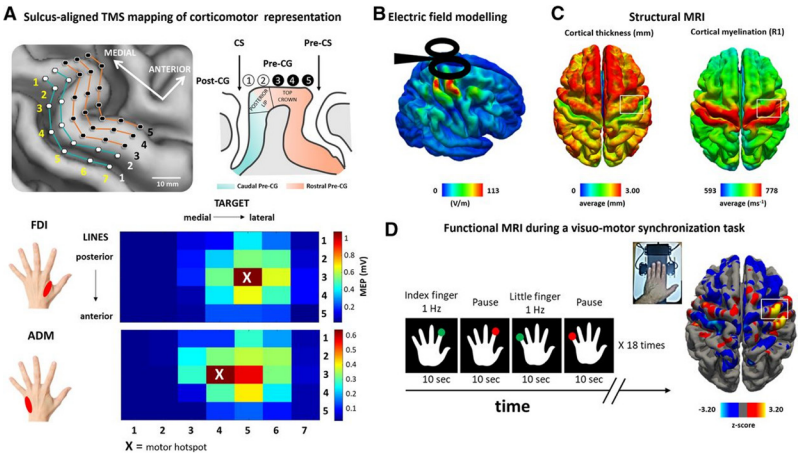
CONTROL OF MOVEMENT

Combining neuroimaging, neuromodulation and computational modelling of sensorimotor networks, the Control of Movement (CoMo) group studies how the brain orchestrates movements. We are particularly interested in clarifying the specific role of the motor cortex and basal ganglia. We meet every week to discuss new findings in movement neuroscience and relate these findings to our own research.

Our group uses structural MRI and neuronavigated TMS mapping of the hand representation of the motor cortex to study use-dependent cortical plasticity. In a recent study, we showed that immobilization and motor practice act in synergy to increase skilled motor performance and bring about changes in the cortical motor representation of hand muscles (Raffin & Siebner 2019).

Our group employs task-based functional MRI to map brain activity during motor tasks. In young individuals, we found that discrete finger sequences are widely represented in human striatum (Andersen et al., 2020). Specific sequences could be discriminated based on the distributed activity patterns in left and right striatum, but not by average differences in single-voxel activity. Multiple bilateral clusters in putamen and caudate nucleus belonging to motor, associative, parietal and limbic territories contributed to classification sensitivity. Our findings suggest that the basal ganglia integrate motor, associative and limbic aspects in the control of sequential overlearned behaviour.

The motor representations of the hand are located in a characteristic knob-like structure in the precentral gyrus, called the precentral motor hand knob (Dubbioso et al., 2021). We combined structural and functional MRI of the motor hand knob with neuronavigated TMS mapping of cortico-muscular representations of hand mucles. We found that the cortical myelin content of the M1-HAND predicts the localization of the muscle presentations in the precentral hand knob. The myelin content also correlated positively with the temporal precision of finger tapping movements. This is the first study to show that myelination of the precentral motor cortex is tightly coupled with the cortical control of the hand.



Schematic depiction of our approach to study sensorimotor control (reproduced from Dubbioso et al., 2021). Neuronavigated sulcus aligned mapping of the precentral gyrus with TMS maps reveals rostrocaudal and mediolateral position of motor representation of hand muscles (A). Site of activation confirmed to the pericentral area by modelling the induced electric field (B). Quantitative MRI couples microstructural underpinnings, in this case cortical myelination (C), to functional measures of cortical control of the hand and dexterity. (D).

GROUP MEMBERS

- **Prof. Hartwig R. Siebner**
- Postdoc Lasse Christiansen
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- Research Fellow Leo Tomasevic
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- Postdoc Kit Melissa Larsen
- Postdoc Mikkel Malling Beck
- Postdoc Søren Asp Fuglsang
- Postdoc Kasper W. Andersen
- Postdoc Angela Mastropasqua
- PhD. Stud./postdoc Mads A.J. Madsen
- PhD Stud. Janine Kesselheim
- PhD Stud. Sofie Nilsson
- PhD Stud. Allan Lohse
- PhD Stud. Line Korsgaard Johnsen
- PhD Stud. Marie Louise En-Ting Liu
- PhD Stud. Christopher Fugl Madelung
- PhD Stud. Valdemar Uhre
- PhD Stud. Christian Skoven
- PhD Stud. Anna Lind Hansen
- PhD Stud. Julia Steinhardt
- Research Asst Vytautas Labanauskas
- Research Asst Valeska Slomianka
- Research year Scholar Marie Trolle Bonnesen
- Stud. Nicole Hueng
- Stud. Marta Marques
- Stud. Felix Schmidt
- Intern Janka Hauffe
- Intern Domenico Voso
- Intern Marieke Anne Heyl
- Intern Daniel Semrád

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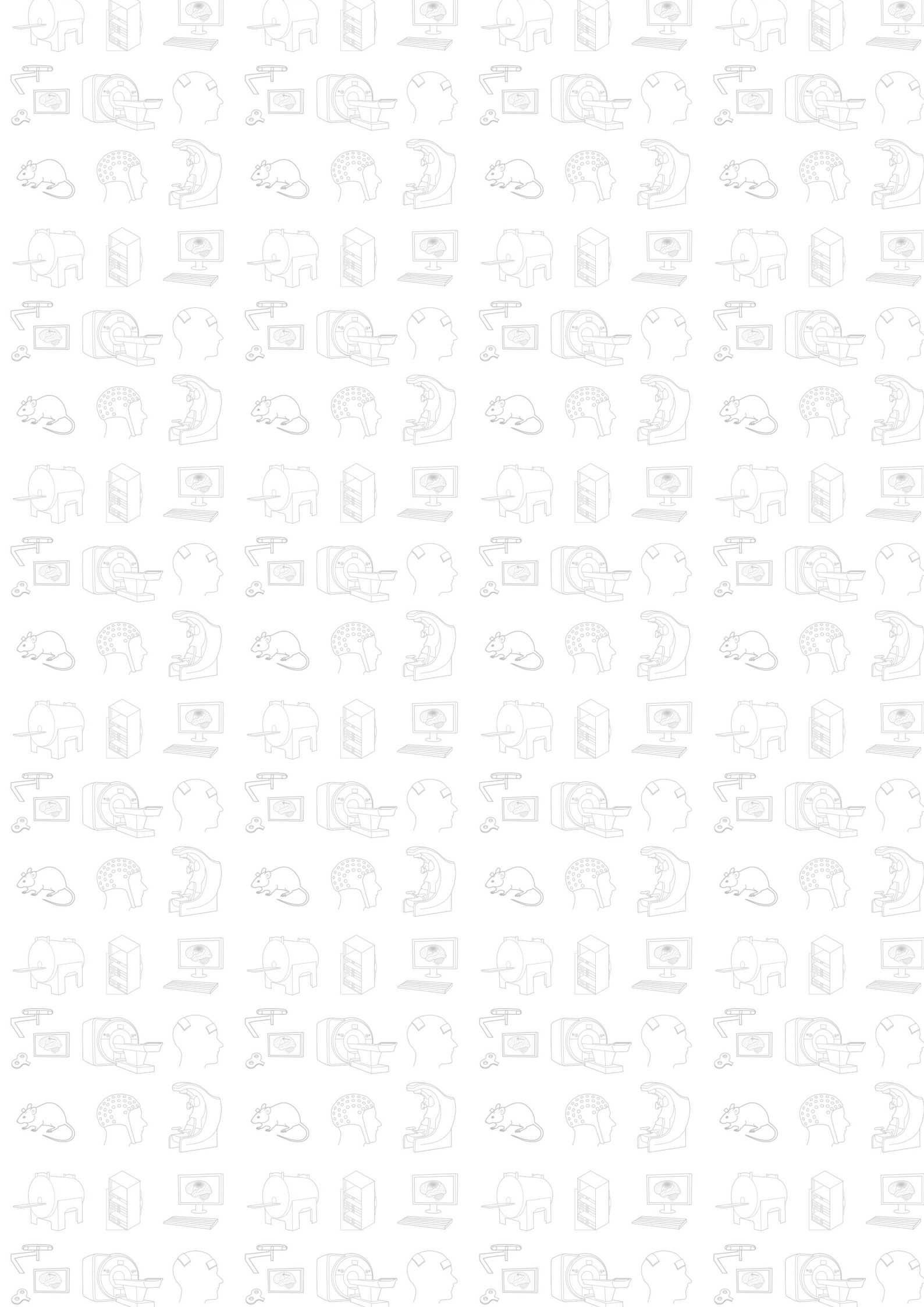
- Assoc. Prof. Mitsuaki Takemi
- Postdoc Estelle Raffin
- Neurologist Raffaele Dubbioso
- Prof. John Rothwell
- Prof. Angelo Quartarone

HOMEPAGE

www.drcmr.dk/control-of-movement

PUBLICATIONS

15, 33, 67



LIFESPAN IMAGING

Mapping of brain and behavioural changes across the lifespan

Lifespan imaging centres around understanding the development of brain structure, function and chemistry throughout the lifespan. We are interested in both normal and pathological development, and in understanding the drivers, either biological or socio-environmental, of such development. Ultimately, we would like to predict whether individuals are at risk of negative development, and to provide recommendations for interventions that may alter such a trajectory for a particular person.

A multi-dimensional prospective approach

We tackle these questions using a multi-dimensional prospective approach that combines state-of-the-art multimodal imaging techniques with advanced analysis methods and perform elaborative assessments of biological, physical, environmental and behavioural variables. We believe that the key lies in longitudinal data, with repeated measurements of the same individuals. We also perform various intervention studies testing effects on brain health from e.g. physical exercise or cognitive training. In our studies we have both healthy individuals, and specific patient groups.

We have established expertise and research infrastructures for detailed cross-sectional and longitudinal assessments of large cohorts and nurture active and elaborative regional, national and international collaborations.

The last years we have recruited many new talented young researchers whom you can read more about in specific sections of this report.

Our passion

In all our projects we strive for high academic standards, innovative methods and techniques, and an ambitious, fun and diverse environment.

Healthy Ageing

Brain Maturation

HEALTHY AGEING

The vision for the Healthy Ageing group is to identify and optimize sustainable interventional strategies for maintained brain health throughout life.

In the past years, some key results involve brain metabolism, multimodal brain-age prediction and physical exercise interventions. For example, we have utilized the improved resolution of 7T MRI and addressed the link between brain metabolism and cognitive ageing, showing higher levels of glia-related metabolites in older individuals, which correlated negatively with working memory performance. The collaboration between the Ultra-High Field MR group and the Healthy Ageing group becomes particularly rewarding since it allows us to combine state of the art metabolic imaging and answer important questions in cognitive ageing research. We further showed how physical fitness was identified as a predictor of brain maintenance in a multimodal image analysis of brain-age prediction. This work was in collaboration with Umeå Center for Functional Brain Imaging (UFBI). Lastly, it should be highlighted that we have published the first results from our large intervention study, the LISA-study. Although the first sets of analyses didn't support the expected intervention effect on our primary target hippocampus volume, the results revealed large individual differences in the trajectories of hippocampal decline, which is what we now are looking further into. This will allow us to understand why some individuals may respond well to exercise whereas others do not seem to get a similar effect, which is a central question in aging research.

In the years to come, we will continue to focus on multimodal characterization of brain ageing. We will combine large longitudinal data sets with experimental work and continue to contribute with knowledge about how to take care of brain function, structure, and chemistry throughout the lifespan.

GROUP MEMBERS

- **Prof. Carl-Johan Boraxbekk**
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- Research Fellow Anouk Marsman
- Postdoc Kasper Winther Andersen
- Postdoc Naiara Demnitz
- Postdoc Anna Plachti
- Postdoc Leise Borg
- PhD stud. Anna Lind Hansen
- PhD stud. Line Korsgaard Johnsen
- Intern. Katrine Høj Jensen

EXTERNAL COLLABORATORS

- Prof. Lars Nyberg
- Prof. Erik Lykke Mortensen
- Prof. Michael Kjær

HOMEPAGE

www.drcmr.dk/healthy-ageing

PUBLICATIONS

5, 10, 24, 32, 94, 102, 103, 105, 106, 115, 118, 149, 168, 176, 203, 209, 219

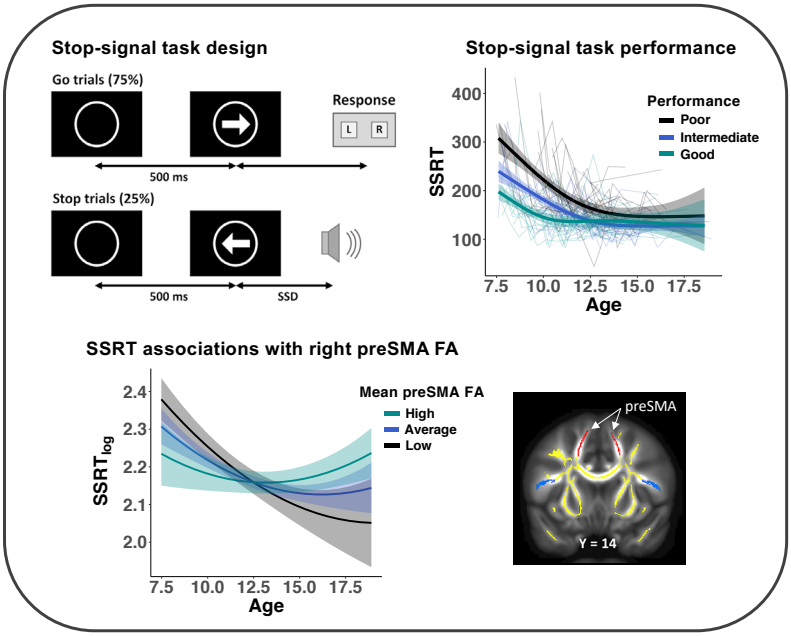
During 2020 we, as most other groups around the world, moved our meetings online, but together we managed to maintain research productivity and scientific discussions

BRAIN MATURATION

The brain maturation group studies brain and behavioral development during childhood and adolescence in health and disease, and the impact of genetic, biological and environmental factors. We address critical questions regarding the factors that place young people at risk for e.g. developing cognitive or emotional problems.

A key project is the longitudinal HUBU project, including 95 children aged 7-13 years. Between 2007-16, the participants were assessed up to 12 times. Since 2017, the HUBU project has been part of the Horizon 2020 project Lifebrain, in which we are partners. Lifebrain integrates data of existing large prospective brain imaging cohorts, incorporating more than 5000 participants aged 4-90 years and 27000 examinations. Lifebrain aims to build a solid knowledge foundation for understanding how brain, cognitive and mental health can be optimized throughout the lifespan. As part of the data enrichment for Lifebrain, we collected the 13th HUBU assessment in 2019. In 2020, we published the first longitudinal HUBU paper reporting on individual differences in the development of response cancellation (the ability to stop a no-longer required manual response) and associations with the white matter underlying the presupplementary motor area (preSMA, see Figure). Recently we have been focusing on characterizing individual differences in the maturational trajectories of brain (micro)structure.

In 2020, we wrapped up the Glucocorticoid project, which examined potential long-term effects of glucocorticoid treatment for non-cerebral diseases in children aged 7-14 years. The results from our last two papers suggest that previous glucocorticoid treatment may be associated with long-term alterations in subcortical grey matter volumes as well as hippocampal and uncinate fasciculus microstructure. Overall, the project resulted in two PhD theses and five journal papers.



Top: Poor performing children at baseline caught up with the initial good performers at the age of 13 years. Bottom: Children with lower mean right preSMA fractional anisotropy (FA) improved the most in response cancellation (i.e., lower SSRTlog).

GROUP MEMBERS

- **Assoc. Prof. Kathrine Skak Madsen**
- Senior researcher William F.C. Baaré
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- Postdoc Louise Baruël Johansen
- PhD stud. Jonathan Holm-Skjold
- Stud. Marie Frederikke Garnæs
- Research Asst. Maud Ottenheijm

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- Prof. Wesley Thompson
- Postdoc Marybel Robledo Gonzalez
- Prof. Sven Kreiborg
- Prof. Jesper Mogensen
- Prof. Katrine Pagsberg
- Prof. Peter Uldall
- Senior Researcher Martin Vestergaard
- Assoc. Prof. Morten Mørup
- Prof. Rogier Kievit
- Lecturer Delia Fuhrmann
- Assoc. Prof. Øystein Sørensen
- Prof. Kristine Walhoved
- EU Lifebrain partners

HOMEPAGE

www.drcmr.dk/brain-maturation

PUBLICATIONS

25, 84, 94, 121, 173, 219

CLINICAL PRECISION IMAGING

Magnetic Resonance Imaging (MRI) is the premier technique for brain imaging. A large array of MRI technologies is available, which can detect early and subtle disease-related abnormalities and monitor dynamics in the individual brain. Unmatched resolution and versatility renders MRI indispensable for the diagnosis and medical care of citizens living with a brain disorder. Therefore, MR-based brain imaging is routinely used in all regional hospitals as a diagnostic tool and as non-invasive tool to monitor disease progression.

Technical advancements and innovations continue to expand the possibilities of brain MRI to map how brain disorders affect the brain's structure, function, and metabolism. We exploit and expand the enormous biomedical potential of MRI to establish MR-based precision medicine as a powerful interface between diagnostic radiology and the clinical neurosciences. Our clinically oriented neuroimaging research covers a wide range of psychiatric and neurologic disorders as well as the entire life span.

Pushing the specificity of MR-based brain imaging of brain diseases

We strive to boost the role of MRI as a clinical tool that can help neurologists, neurosurgeons, and psychiatrists to tailor their therapy to the individual needs of their patients. Our goal is to identify clinical MR-based markers that provide relevant information about the individual risk or prognosis with respect to the course of disease or response to treatment. While many MRI-based brain readouts are highly sensitive to a disease process, they often provide limited information about its underlying neurobiological mechanisms. We therefore focus on improving the specificity of MR-based brain mapping methods. Only if the MRI method reliably reflects a relevant disease-causing process, will it provide mechanistic insights and neurobiological meaning. We validate advanced MRI-based brain readouts in clinical proof-of-concept studies and apply them in clinical trials as secondary outcome measures.

We are in a unique position to conduct clinical MRI research

The Clinical Precision Imaging area capitalizes on the specific expertise and outcomes of the MR Physics & Analyses areas and our method groups. Our clinical MR research draws on the neuroradiological expertise available at our center. In recent years, we successfully strengthened our ties with the clinical neuroscience community in the Capital Region of Denmark and set up novel collaboration projects with the clinical research group at our hospital, especially with gastroenterology (Prof. Flemming Bendtsen, Prof. Lise Lotte Gluud, Senior Researcher Johan Burisch), endocrinology (Prof. Sten Madsbad, Senior Researcher Kirstine Nyvold Bojsen-Møller), and infectiology (Prof. Thomas Benfield).

Movement Disorders

Neuroimaging in Multiple Sclerosis

Developmental Psychiatry

Brain Body Interaction

MOVEMENT DISORDERS

The Movement Disorders group bridges clinical, computational and cognitive neuroscience to advance the pathophysiological understanding of movement disorders. Our research primarily focuses on Parkinson's disease (PD) and dystonia.

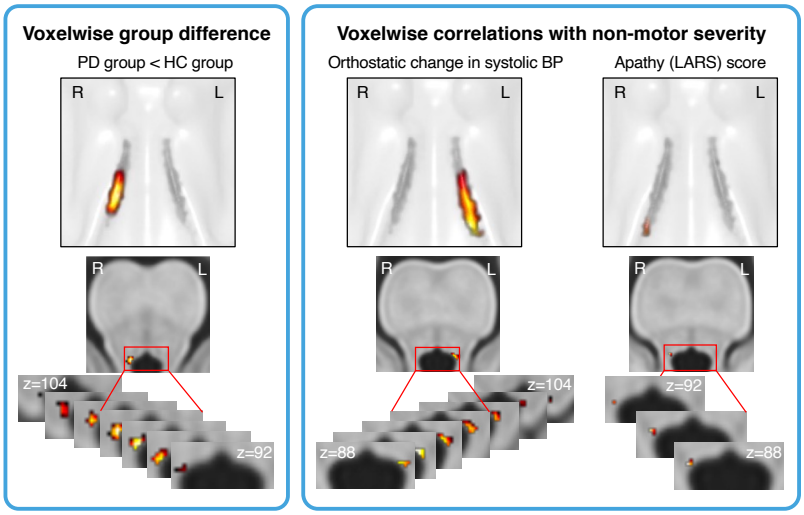
We use the ultra-high field (7 tesla) MR scanner in order to map the structural integrity of midbrain nuclei at high resolution. This allows us to investigate the relationship between the individual spatial pattern of neurodegeneration in Parkinson's disease and the patient's clinical symptoms.

We apply computational models of learning and decision-making to probe disease-induced changes in brain and behavior. Observing which parameters of the model are changed in the disease can then lead to a mechanistic understanding, explaining not only that there are disease-induced changes, but how the changes occur at the neural and symptomatic level.

We also use brain stimulation to explore dysfunctions of brain networks, but also as a promising therapeutic tool.

Current key projects are the 7-tesla and the ADAPT-PD projects. In the 7T project, we investigate structure and function of two neurotransmitter systems that are altered in PD, dopamine and noradrenaline. For example, we can show that the main noradrenergic nucleus, the locus coeruleus (LC), does not degenerate uniformly but with a certain spatial pattern and that cell death in different parts of the structure correlates with different non-motor symptoms (Madelung et al., 2022, MovDis).

In the ADAPT-PD project, we focus on investigating dysfunctional circuit dynamics in cortico-basal ganglia (CBG) projections to improve motor and non-motor function in PD. It is a multi-modal project involving different techniques (invasive and non-invasive recordings as well as brain stimulation) to be used in animal models and PD patients.



Patients with Parkinson's disease (PD) have a lower neuromelanin signal (CNR) in the right locus coeruleus (LC), indicative of the degeneration of noradrenergic neurons. The degeneration is not homogeneous but concentrated on middle and caudal parts of the LC. Loss of LC neuromelanin signal correlates with the degree of orthostatic hypotension and apathy in patients supporting a role of the LC in the development of non-motor symptoms in PD.

GROUP MEMBERS

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- Postdoc Mikkel Malling Beck
- Postdoc Mona El-Sayed Hervig
- Postdoc Naiara Demnitz
- Postdoc Søren Asp Fuglsang
- Stud. Anders Elkjær Lund
- PhD stud. Christopher Fugl Madelung
- PhD Stud. Birgitte Liang Chen Thomsen
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- Intern Janka Marlene Hauffe
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- Prof. Andrea Kühn
- Prof. Ray Dolan
- Prof. Mark Hallett

HOMEPAGE

www.drcmr.dk/movement-disorders

PUBLICATIONS

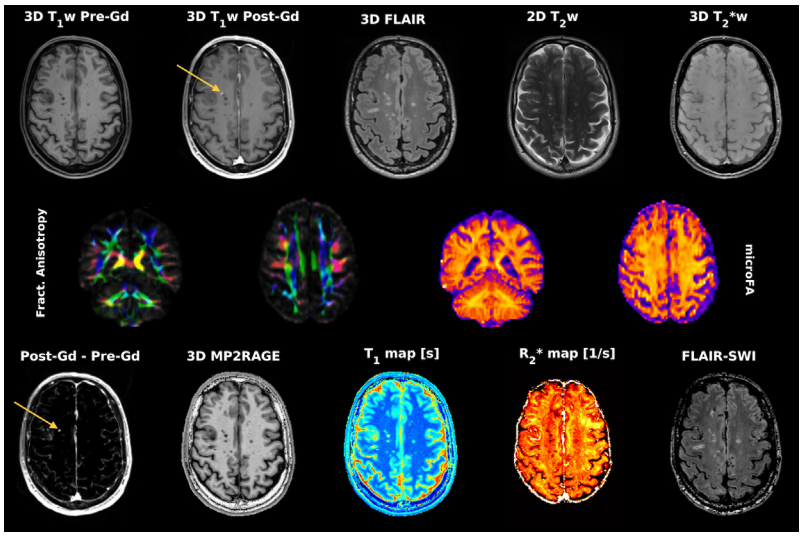
6, 16, 17, 30, 63, 89, 104, 114, 119, 146, 179, 213, 222, 230

NEUROIMAGING IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a complex autoimmune-mediated, demyelinating and neurodegenerative disease, and is the leading, non-traumatic cause of neurological disability in young adults.

Magnetic Resonance Imaging (MRI) allows to readily detect white matter brain and spinal cord changes that develop due to MS. MRI abnormalities are important to the diagnosis and monitoring of MS. However, in particular assessing only white matter lesions as a hallmark for MS limits the sensitivity and specificity of MRI as a clinical tool.

The NeuroImaging in Multiple Sclerosis (NiMS) group aims to look beyond white matter lesions, pushing the frontiers of MRI to capture other MS-related tissue damage and to uncover the pathophysiological mechanisms of MS. With a strong focus on multi-modal imaging, including a wide range of structural and quantitative MRI techniques as well as non-MRI modalities, e.g. transcranial magnetic stimulation (TMS), we have explored the specific role of cortical demyelination in motor dysfunction. Our 7T MRI results have shown that cortical lesions in the sensorimotor hand area have a negative effect on hand sensorimotor function and cortico-spinal conduction. Now, we are exploring the global contribution of cortical demyelination to disease progression in primary-progressive MS and are establishing new computational frameworks aimed at 7T MRI in the search of novel imaging biomarkers. Further human and pre-clinical 7T work aims to disentangle cell type specific morphological changes in MS pathology (C-MORPH), by combining diffusion and spectroscopic imaging properties. Finally, together with the Reader Centre and the Danish MS Centre, NiMS is coordinating DanNORMS, a large, multi-site, phase 3 Danish clinical trial assessing the non-inferiority of two treatments for relapsing MS, including MRI procotol development, image review and analysis for all sites.



Multi-modal MRI data as acquired for DanNORMS. High-quality structual and quantitative MRI are obtained at 3T, allowing for the qualitative and quantitative analysis of both MS lesions and other brain tissues. Arrows highlight an enhancing lesion.

GROUP MEMBERS

- **Prof. Hartwig R. Siebner**
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- Senior researcher Henrik Lundell
- Research Fellow Nathalie Just
- Postdoc Vanessa Wiggermann
- Postdoc Mads A.J. Madsen
- Postdoc Christian Bauer
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- PhD stud. Carmen Moreno Genis
- Research Asst Sofus A. Drejer Nygaard, MD
- Research Asst Valeska Slomianka
- Stud. Helena-Céline Arøe Stevelt
- Research Asst Mie Arnau Martinez
- Research radiographer Jasmin Merhout
- Research radiographer Sascha Gude

Research technologist Sussi Larsen

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HOMEPAGE

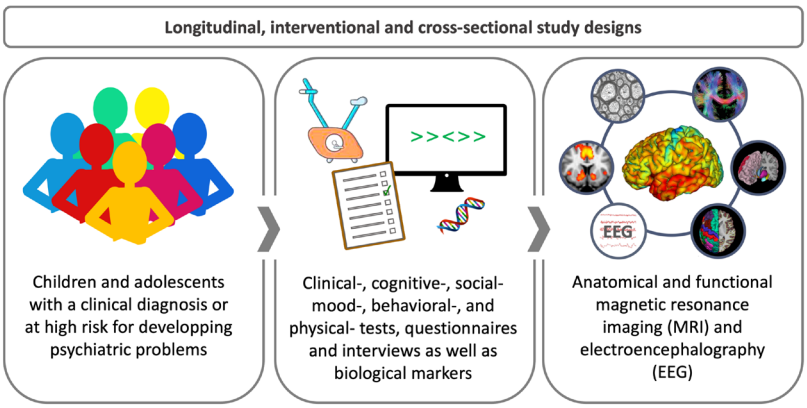
www.drcmr.dk/neuroimaging-in-multiple-sclerosis

PUBLICATIONS

75, 136, 160, 195

DEVELOPMENTAL PSYCHIATRY

Many psychiatric disorders have their onset in childhood, adolescence, or early adulthood, pointing to a neurodevelopmental origin. Having a long-standing interest in the neurodevelopmental aspects, our research is geared to improve the prediction and characterization of psychiatric disorders across the lifespan. We wish to contribute to the development of new personalized strategies for prevention and treatment by identifying new treatment targets. Our research is highly interdisciplinary. In close collaboration with our clinical partners, we employ state of the art multimodal brain imaging, and advanced modelling approaches to elucidate, characterize and monitor neurobiological and neurocognitive trajectories of brain development. By applying a longitudinal approach, we wish to identify abnormal neurodevelopmental trajectories that are associated with increased risk or resilience. Our work is centered around two key projects, The Danish High risk and Resilience study (VIA) and the Treatment Effects of family-based Cognitive Therapy in children and adolescents with Obsessive compulsive disorder (TECTO). VIA is a national longitudinal study of 522 11-year-old (VIA11) children born to parents with or without a diagnosis of either schizophrenia or bipolar disorder, now followed up at age 15 (VIA15). TECTO combines a randomized clinical trial and longitudinal case-control design in pediatric patients with obsessive-compulsive disorder. As part of the VIA 11 study, Anna V. L. van Themaat successfully defended her PhD thesis "From early information processing to higher-order cognitive functioning in children with familial high risk of schizophrenia or bipolar disorder" in October 2020 and Line Korsgaard Johnsen will defend her PhD thesis "Brain function correlates of interference control in children with familial high-risk of schizophrenia or bipolar disorder" in 2022.



General study designs, assessments and outcome measures.

GROUP MEMBERS

- **Postdoc Kit Melissa Larsen**
- Senior researcher William F.C. Baaré
- Prof. Hartwig Siebner
- Assoc. Prof. Kathrine Skak Madsen
- PhD stud. Line Korsgaard Johnsen
- PhD stud. Anna V. L. van Themaat
- PhD stud. Valdemar Uhre
- Research Fellow Leo Tomasevic
- Senior Researcher Kristoffer Hougaard Madsen
- Postdoc Søren Asp Fuglsang
- Senior Researcher Oliver Hulme
- Research Fellow David Meder
- Research Fellow Enedino Hernández-Torres
- Stud. Simon Yamazaki Jensen
- Stud. Benthe Emke Vink
- Stud. Ditte Høier Frantzen
- Stud. Mathilde Marie Hansen

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- Prof. Katrine Pagsberg
- Prof. Anne Amalie Elgaard Thorup
- Prof. Kerstin Plessen
- Prof. Thomas Werge

HOMEPAGE

www.drcmr.dk/developmental-psychiatry

PUBLICATIONS

21, 37, 43, 113, 116, 141, 169, 217, 218, 241, 245

BRAIN-BODY INTERACTION

This group focuses on the interaction between the central nervous system and other organ systems of the body. Impaired central control of physiological processes lie at the core of many diseases and complications to these. The group aims to cast light on this previously overlooked aspect using cutting-edge MRI methods.

The group was started in 2020 and the initial focus was on establishing a framework for future projects. Moving on, the main project has been an investigation on complications to diabetes mellitus. With a focus on autonomic dysfunction and neurovascular coupling, this project will investigate the brain-gut axis as well as control of cerebral perfusion. New methods have been established and recruitment and investigations are ongoing.

GROUP MEMBERS

- **Consultant Mads Barløse**
- Prof. Hartwig R. Siebner
- Head of Department Claus Leth Petersen
- Prof. Carl-Johan Boraxbekk
- Assoc. Prof. Esben Thade Petersen
- Postdoc Christian Bauer
- PhD Student Joakim Ölmestig

EXTERNAL COLLABORATORS

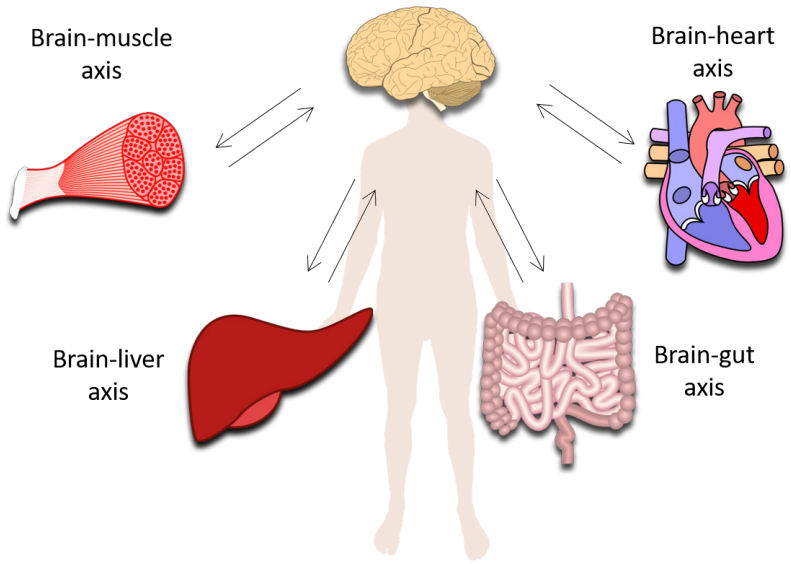
- Prof. Sten Madsbad
- MD, PhD Christian Stevns Hansen
- Consultant Jens Hove
- Prof. Michael Kjaer

HOMEPAGE

www.drcmr.dk/brain-body-interaction

PUBLICATIONS

213



Schematic representation of the research targets of the group.

INFRASTRUCTURE

INFRASTRUCTURE

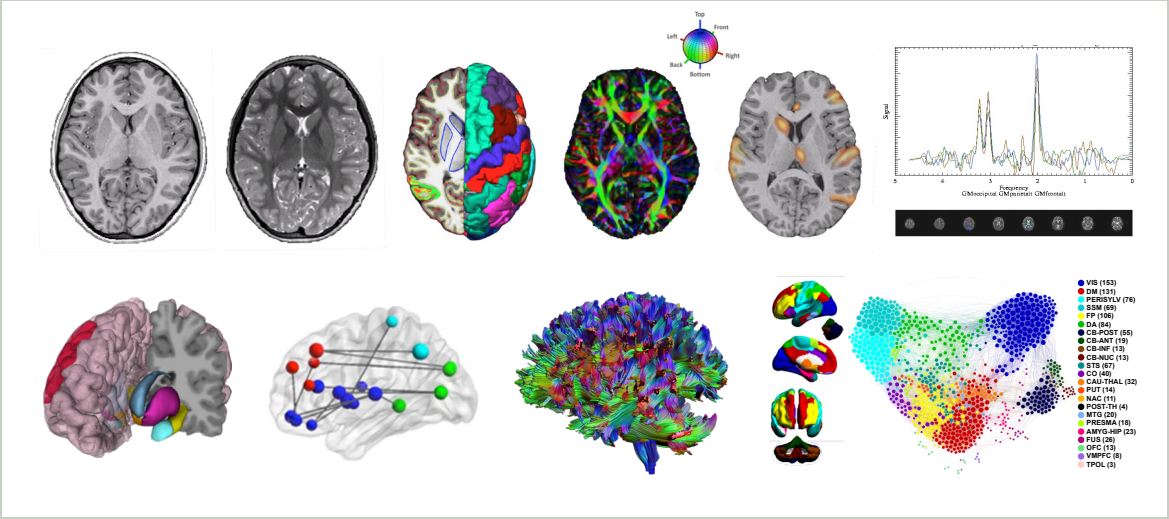
SCANNERS

1 x 7.0 tesla
1 x 7.0 tesla preclinical
3 x 3.0 tesla
2 x 1.5 tesla
1 x MRI simulator

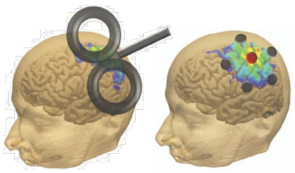
LABS

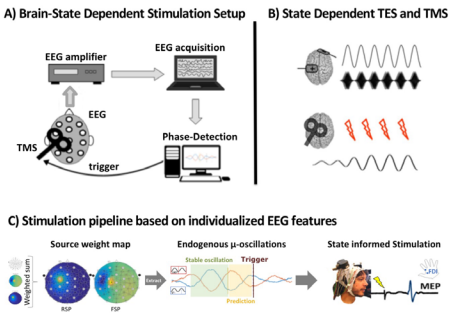
2 x Non-invasive brain stimulation
1 x EEG
2 x Non-invasive brain stimulation & EEG
1 x Hardware
1 x Preclinical including optogenetics
1 x GM-level 2 preclinical

STRUCTURAL, FUNCTIONAL AND NEUROCHEMICAL MRI

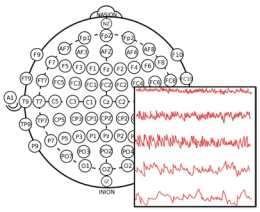


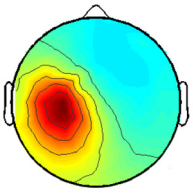
NON-INVASIVE PRECISION BRAIN STIMULATION

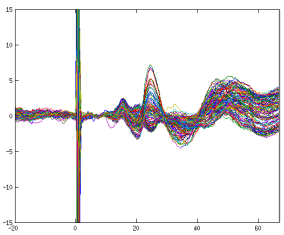




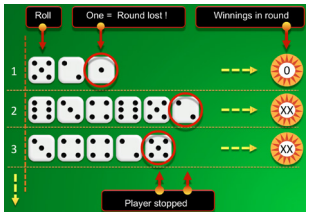
ELECTROENCEPHALOGRAPHY (EEG)







BEHAVIOURAL ASSESSMENTS

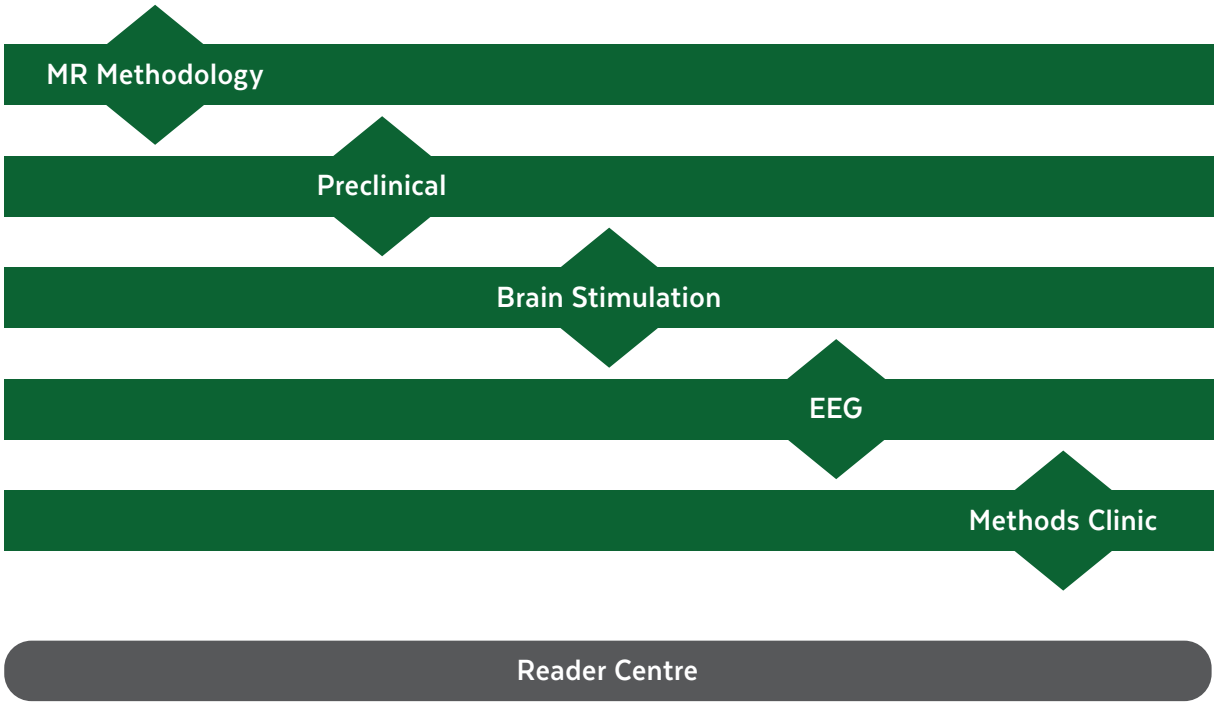


METHOD GROUPS

Overlapping and supporting the DRCMR research groups presented in the previous section, we have six method groups that support the research infrastructure at DRCMR. These groups follow the latest developments within their respective areas of expertise and ensure that the methods used in our research are state-of-the-art. Each method group is headed by a group leader and the groups meet on a regular basis to discuss and plan their activities.

MR Methodology

Preclinical



Brain Stimulation

EEG

Methods Clinic

Reader Centre

MR METHODOLOGY

The MR Methodology group supports the research activities that involve magnetic resonance (MR) at DRCMR.

MR is a cornerstone in the research at the department and is in many projects often used in conjunction with other independent methodologies. In this group, we support the MR acquisition part of these projects.

The centre has 7 MR scanners of which four are used for both research and clinical purposes. Clinic: two 3T Siemens Prisma and Verio and two 1.5T Siemens Espree and Avanto, and research two Philips Achieva systems (3T and 7T). We also have a pre-clinical Bruker BioSpec system (7T) used for animal research, post mortem imaging and method development on phantoms. In the MR Methodology group, we try to synchronize the data acquisition and quality, and try to maximize the potential of the different systems.

Part of this work is to pioneer new techniques, exchange sequences between our own systems and with other sites around the world. An important aspect of this work is also to monitor data quality and to plan hardware repairs and updates. Work is also done on adopting cutting edge hardware built by our collaborators or in our own workshop. Furthermore, we organize the mandatory MR safety training for all staff at DRCMR.

GROUP MEMBERS

- **Senior Researcher Henrik Lundell**
- **Research Fellow Vincent Boer**
- Assoc. Prof. Lars G. Hanson
- Clinical Physicist Lasse Rahbek Søndergaard, PhD
- Assoc. Prof. Tim Dyrby
- Prof. Axel Thielscher
- Assoc. Prof. Esben Thade Petersen
- Assoc. Prof. Kristoffer Hougaard Madsen
- Postdoc Vanessa Wiggermann

EXTNERAL COLLABORATORS

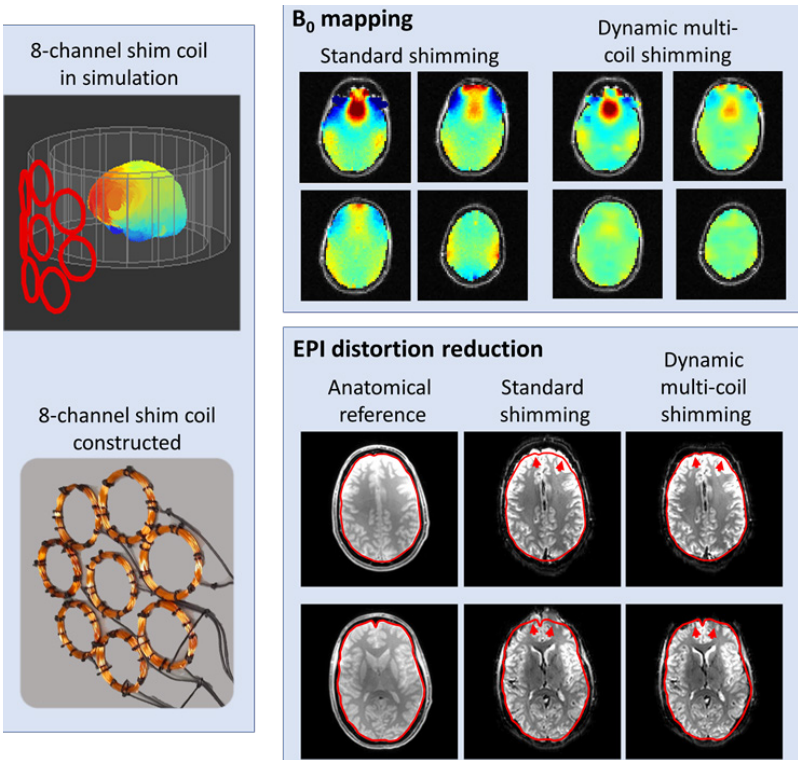
- Jan Ole Pedersen, PhD
- Karen Kettless, PhD

HOMEPAGE

www.drcmr.dk/mr-methods

PUBLICATIONS

2, 11, 40, 42, 83, 120, 178, 191, 227



In the MR Methodology group we developed an 8 channel shim coil for improved B_0 magnetic field homogeneity in the brain. This reduces image distortion for fast imaging techniques (EPI) used in high field MRI scanners.

PRECLINICAL GROUP

Our vision is to integrate our basic research with the human research in a translational forward (rodent-to-human) and backward (human-to-rodent) approach with the ultimate goal of improving the treatment and diagnosis of brain disorders. Our research spans from multi-modal microstructural, functional and metabolic imaging in combination with brain stimulation and other interventions with potential therapeutic relevance.

Our preclinical research facilities are now fully up and running. Our first studies are in their final stages whilst we are embarking on new exciting projects. Christian Skoven has established an optogenetic brain stimulation framework used to measure functional responses and conduction delays of optically stimulated brain networks. To understand optical brain simulation, Christian has explored a wide range of optical stimulation paradigm parameters to select an optimal set for brain stimulation. As part of the Novo Nordisk synergy project "UHeal", James Breen-Norris has established an extreme ex vivo imaging setup to image the trimmed guinea pig cochleae – the cochleae are miniscule i.e. approx. 0.5 mm in diameter and the structures of interest are below 100 um in length. The aim is to map hearing loss expressed as the loss of spiral ganglion nerve fibres as measured with diffusion MRI. Yi He received a MSCA postdoc stipend to link functional and structural MRI. He has published his work on an animal model of demyelination to explore how the tensor-valued diffusion MRI protocol for estimating the μFA metric is sensitive enough to detect pathology. In 2021, we welcomed Nathalie Just from France who joined the "C-MORPH" project. She is experienced with MR Spectroscopy and its combination to optogenetics. Mattias Rickhag has joined us from University of Copenhagen on the project "ADAPT-PD" and has experience with chemogenetics and animal models of Parkinson's disease.

GROUP MEMBERS

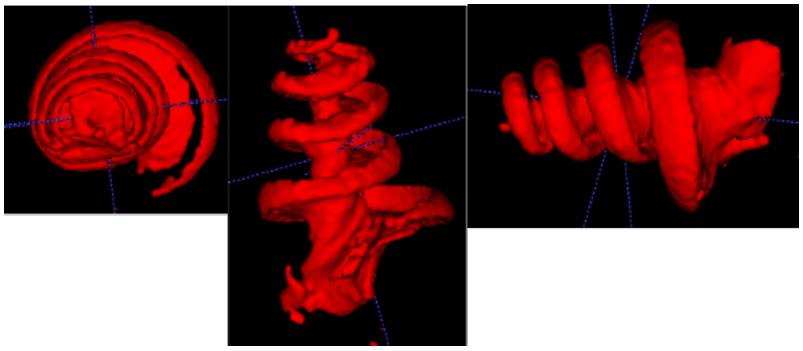
- **Assoc. Prof. Tim B. Dyrby**
- Senior researcher Henrik Lundell
- Senior Researcher Karl Mattias Rickhag
- Research Fellow Nathalie Just
- Postdoc Yi He
- Postdoc James Breen-Norris
- Postdoc Marco Pizzolato
- Research technologist Sascha Gude
- PhD stud. Christian Skoven
- PhD stud. Mariam Andersson
- PhD stud. Cristina Pasquinelli
- PhD stud. Freja Østergaard
- PhD stud. Sidsel Winther

HOMEPAGE

www.drcmr.dk/preclinical-research

PUBLICATIONS

40, 55, 65, 101, 177, 205, 214



3 Different views of a Guinea cochlear soft tissue segmented from an image acquired using a 7T bruker scanner with a cryoprobe rendered in 3D.

BRAIN STIMULATION

A range of Transcranial Brain Stimulation (TBS) techniques have emerged over the last decades. These techniques have become versatile neuroscientific tools and show therapeutical potential to treat circuit dysfunctions in brain disorders. At DRCMR, TBS is used extensively to modulate and map brain activity both in health and disease. The Brain Stimulation Methods Group facilitates, supports, and advances all forms of transcranial brain stimulation research at DRCMR. We support ongoing research aiming at ensuring quality of the experimental work – from the design of experiments to data acquisition and analysis. We work on improving state-of-the-art stimulation protocols by taking individual brain anatomy, the activation history of the brain, and its neural state at the time of stimulation into account. We develop in-house protocols for combining TBS with neuroimaging in order to inform stimulation parameters and ensure both spatial and temporal precision.

All forms of TBS do not only stimulate the brain transcranially, but cause concurrent stimulation of peripheral neural structures. Depending on the TBS method and stimulation settings, peripheral off-target effects include auditory, somatosensory, visual, or vestibular co-stimulation. Our group strives to capture, mitigate and control for these off-target effects of TBS.

The group has a strong focus on education: We provide in-house teaching in all brain stimulation techniques and organized international graduate-level workshops. In 2019 and 2021 young scientists from across Europe, America and Asia participated in our NTBS Winter School and Copenhagen Brain Stimulation (CoBS) School.

Since May 2019 the group has been headed by Postdoc Lasse Christiansen. The Brain Stimulation Methods group meets every second Monday and welcomes all researchers at DRCMR who wish to use TBS in their research.

GROUP MEMBERS

- **Postdoc Lasse Christiansen**
- Senior researcher Anke Karabanov
- Research Fellow Mikkel C. Vinding
- Postdoc Angela Mastropasqua
- Phd stud./postdoc Mads A.J. Madsen
- PhD Stud. Marie Louise Liu
- PhD Stud. Mia Kolmos
- PhD Stud. Lærke Krohne
- Phd stud. Janine Kesselheim
- Phd stud. Allan Lohse
- Research Asst Valeska Slomianka
- Research Asst Vytautas Labanauskas
- Stud. Felix Schmidt
- Stud. Martha Marques
- Stud. Maud Ottenheijm

HOMEPAGE

www.drcmr.dk/tms-group

PUBLICATIONS

41, 81, 167

Keeping the spirit high during Covid-19 pandemic with and without robotic assistance.

ELECTROENCEPHALOGRAPHY

The Electroencephalography (EEG) group is a method group, which main role is to provide support to researchers at DRCMR facilitating them in performing studies at the highest scientific level. Among the EEG group tasks there are training in laboratory usage, support in planning and carrying out experiments. We also provide advanced data analysis methods and supervision in using them. Another task of the EEG group is to develop methods that are requested for a specific study, with the main focus on those where EEG is used in combination with a brain stimulation technique. For example, recently we have proposed a hybrid electrode to record EEG signal immediately before and after transcranial electric stimulation (see figure). The hybrid electrode overcame the spatial limitation when combining these two techniques, where stimulation and recording electrodes could not be placed on the same spot on the scalp. We have also developed software able to detect phase and amplitude of brain rhythms in real time to inform the transcranial magnetic stimulation (TMS) and perform brain state dependent stimulation protocols.

GROUP MEMBERS

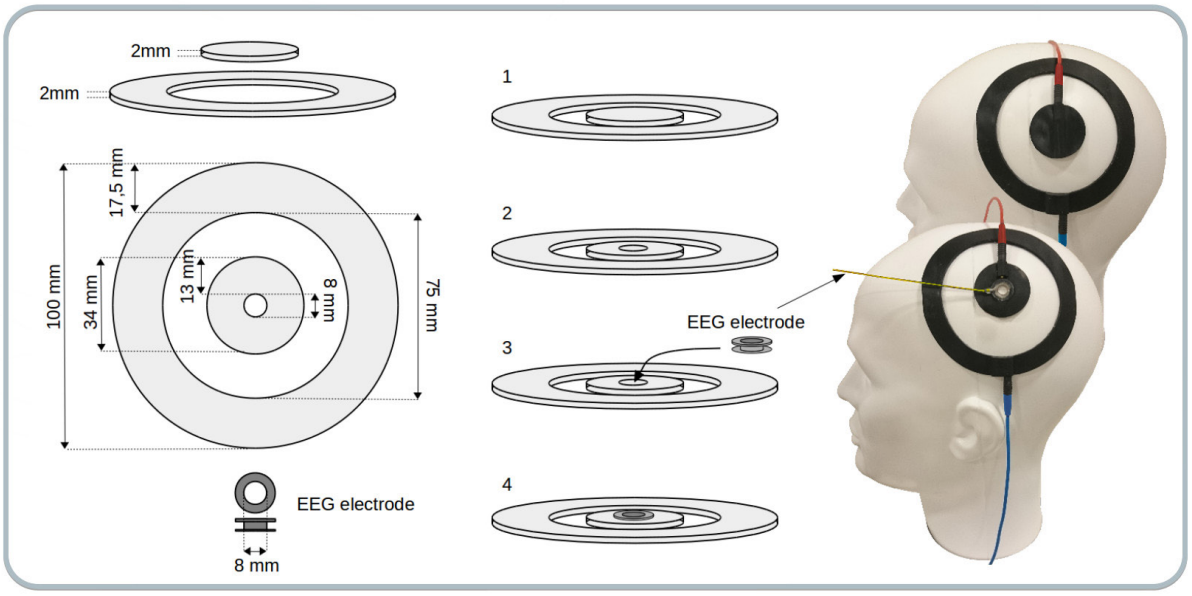
- **Research Fellow Leo Tomasevic**
- Postdoc Angela Mastropasqua
- Postdoc Melissa Larsen
- Research Fellow Mikkel C. Vinding
- Postdoc Monica Biggio
- Postdoc Mikkel Malling Beck
- Postdoc Syoichi Tashiro
- PhD stud. Janine Kesselheim
- PhD stud./postdoc Mads A.J. Madsen
- PhD stud. Anna Hester V. L. v.Themaat
- MD Sebastian Strauss
- Stud. Felix Schmidt
- Stud. Albert Orero Lopez
- Stud. Adam Ryszczuk

HOMEPAGE

www.drcmr.dk/eeg

PUBLICATIONS

13, 22, 41, 60, 98, 140, 185, 224



The design of the hybrid electrode modified from the publication by Tashiro et al. "Probing EEG activity in the targeted cortex after focal transcranial electrical stimulation" in Brain Stimulation (2020 May-Jun;13(3):815-818).

METHODS CLINIC

We are an informal group that operates a weekly clinic open to all members of DRCMR, and their collaborators. We aim to answer audience questions pertaining to statistical analysis and computational modelling of data. We can take questions from any domain (behavioral, neural, physical etc.), and any data modality (behavior, cognitive, MRI, fMRI etc.). We can help with any step in the scientific chain, from conception, coding, data formatting, experimental design, analysis, and interpretation, also including help with the review process. Often attendees will present a few slides, characterising their question, otherwise just verbally outlining what they want to ask. The answers can take anything from one to 90 minutes. The meetings are chaired and organized by senior researchers Ollie Hulme and Kristoffer Madsen. The questions are answered by the group of attendees as a whole. Attendance is voluntary but recommended for all researchers as a function of their needs.

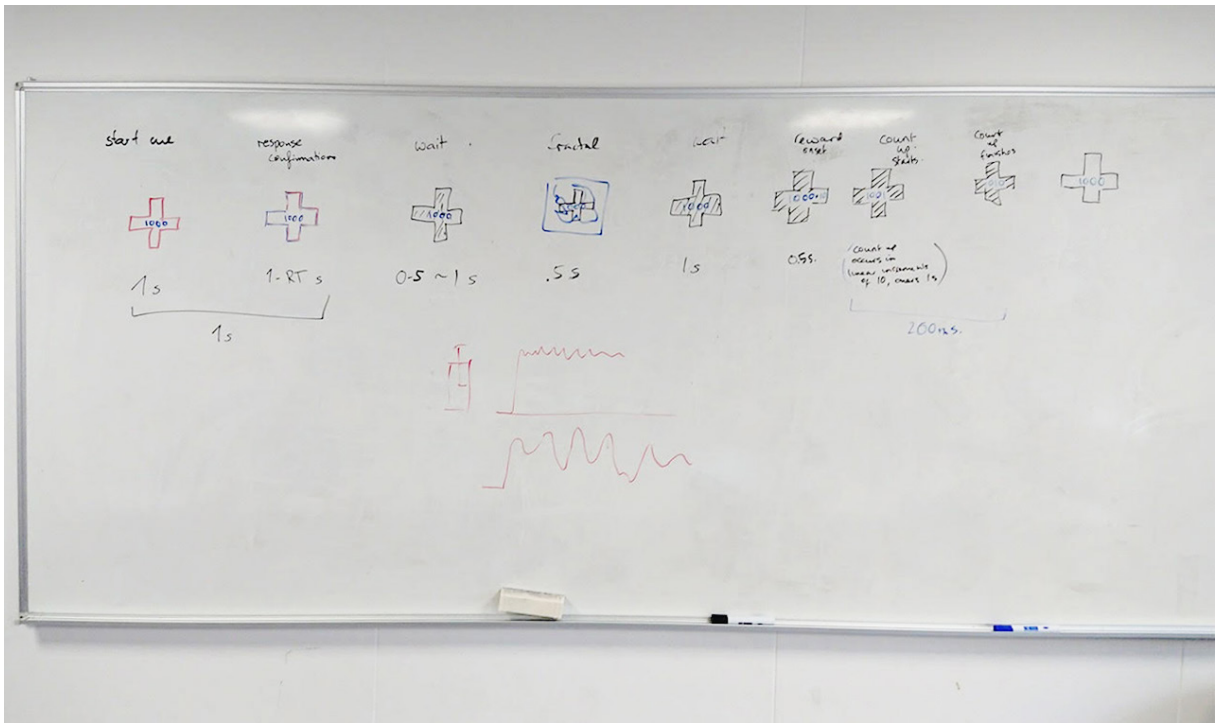
ORGANIZED BY

- **Senior Researcher Oliver Hulme**
- **Assoc. Prof. Kristoffer H. Madsen**

Clinic meetings are open to all members of DRCMR and their collaborators

HOMEPAGE

www.drcmr.dk/methods-clinic



Perhaps unsuprisingly, we use whiteboards to sketch out our problems and ideas.

READER CENTRE

Large cohort studies, clinical trials and biomedical research demand effective data management and even more specific and robust MRI techniques. The DRCMR Reader Centre takes pride in supporting such studies from idea to quality-assured results. This includes study planning, study coordination, MRI scan logistics, big data handling, ROI and lesion delineation, manual and automated data analysis, stakeholder communication and much more. All of these tasks are undertaken with a strong focus on continuous quality assurance while maintaining flexibility in regard to the needs of the individual study.

Lesion delineation and assessment is one of the focus areas of the centre, especially lesions related to multiple sclerosis and white matter hyperintensities (WMH). Drawing on the combined skills of the group and researchers at DRCMR, the Reader Centre has further refined its sensitive and reproducible algorithms to render the evaluation of lesions and lesion size more automatic and less dependent upon subjective assessment. Thus, the Reader Centre offers analysis of advanced structural MRI measures, such as brain segmentation, atrophy, lesion quantification and cortical thickness. Although most studies in the Reader Centre focus on the brain, MR images of other organs are also analysed in some studies, e.g. the spinal cord, liver and leg muscles.

The Reader Centre supports several research groups at DRCMR, e.g. the Healthy Ageing and the Neuroimaging in Multiple Sclerosis groups, but is also a partner in several investigator-driven clinical studies with the Danish Multiple Sclerosis Center. A major current undertaking is that the Reader Centre is co-ordinating the imaging part of the national multi-centre clinical trial DanNORMS in collaboration with the Danish Multiple Sclerosis Center.

GROUP MEMBERS

- **Research Manager Karam Sidaros**
- Senior researcher Henrik Lundell
- Research Radiographer Jasmin Merhout
- Research Technologist Sascha Gude
- Research Radiographer Hanne Schmidt
- Research Technologist Sussi Larsen
- Postdoc Vanessa Wiggermann
- Research Fellow Enedino Hernández-Torres

EXTERNAL COLLABORATORS

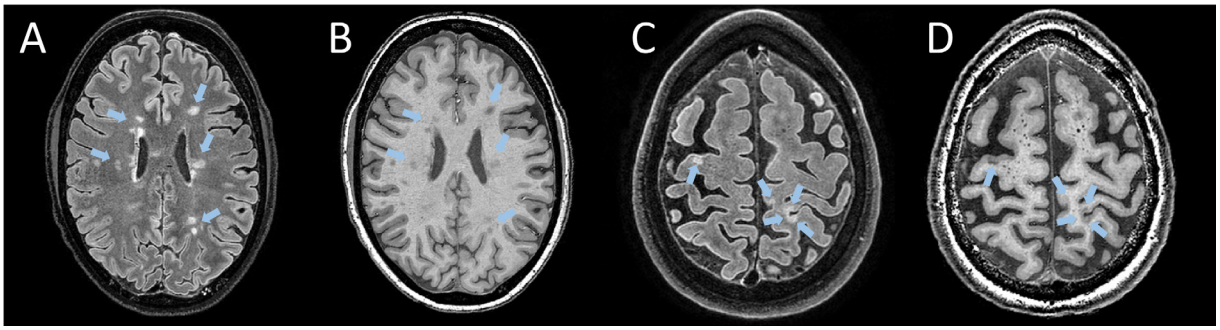
- Danish Multiple Sclerosis Center, Rigshospitalet
- Center for Healthy Ageing, University of Copenhagen
- Department of Clinical Medicine, Bispebjerg Hospital

HOMEPAGE

www.drcmr.dk/reader-centre

PUBLICATIONS

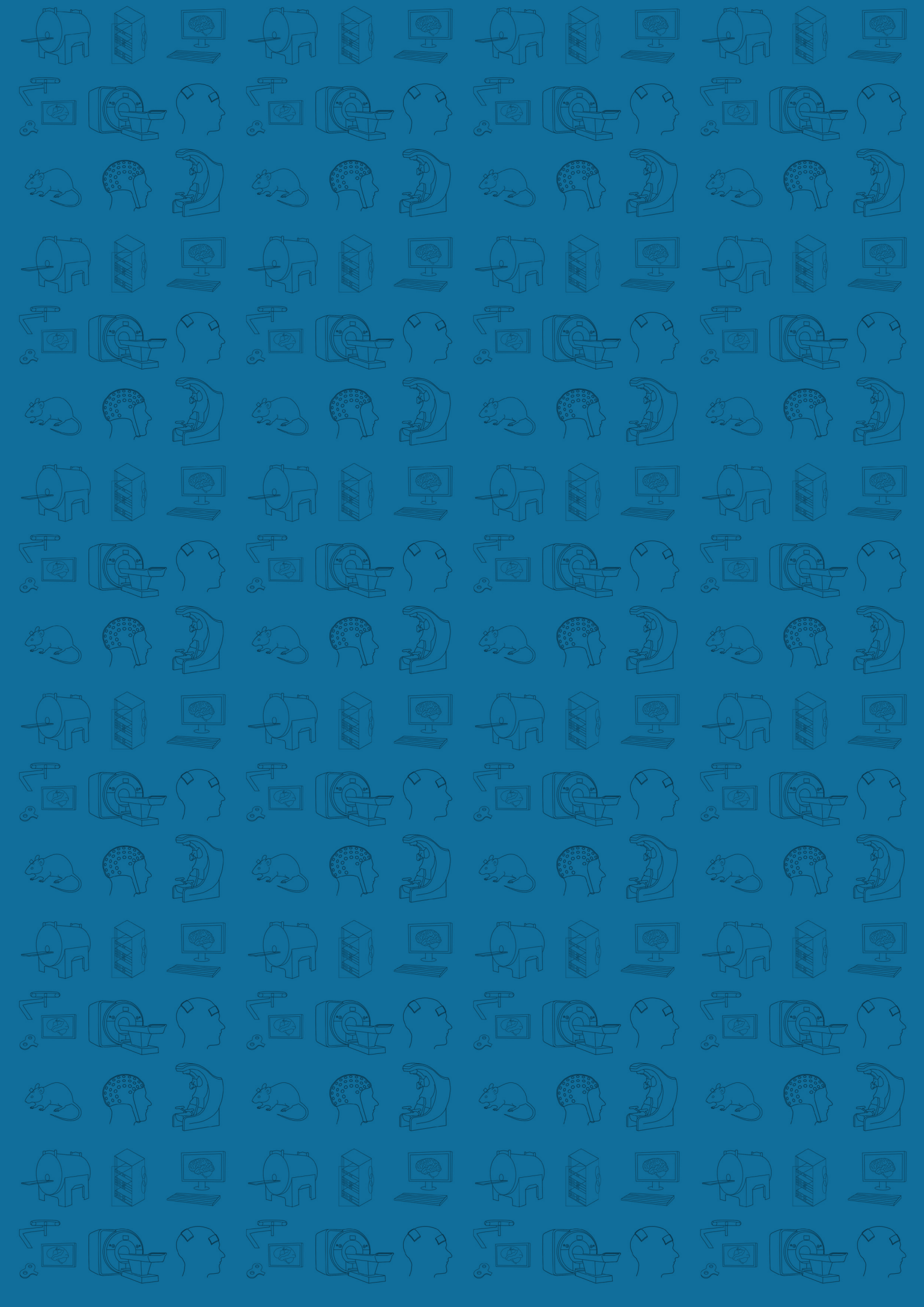
3, 68, 102, 103, 109, 160, 166, 180, 195



Example of MS lesions on 7T images in white matter: (A) FLAIR, (B) T1-weighted images; and in cortical grey matter: (C) FLAIR, (D) T1-weighted images.

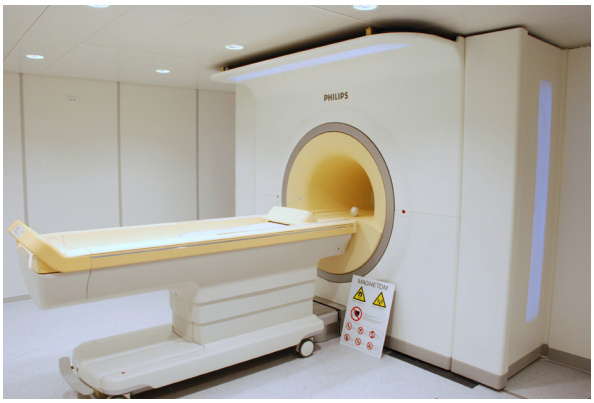
ACTIVITIES

2019-2021 have been three dynamic years with many engaging activities and events at DRCMR. Our researchers have been extremely active, and their research results have attracted attention from Danish media, led to new collaborations and resulted in interesting events.



ADVANCEMENTS AT THE NATIONAL 7T FACILITY

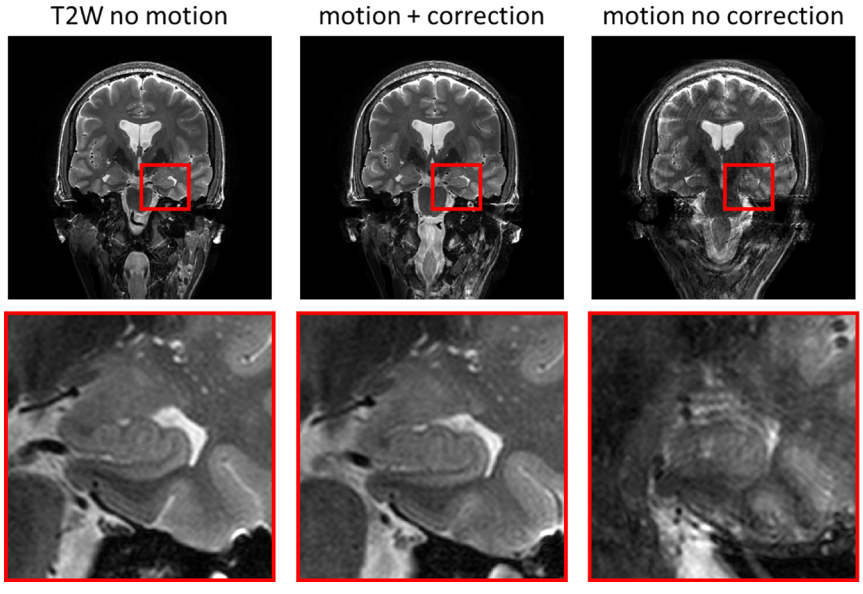
The aim of the Danish National 7 Tesla Project is to provide a state-of-the-art facility for cutting-edge imaging research open to all researchers in Denmark. The installed 7 tesla ultra-high field human MR scanner is equipped with the latest hardware and it will keep Denmark in a leading position within imaging research. This setup fosters close collaborations across centres, both nationally and internationally, and the good synergy will therefore ensure a fast progress, not only within imaging sciences but also in basic science and clinical research. The scanner, which has been on the field since 2015, and officially in use since 2016, has a steady flow of running projects from both within DRCMR as well as from external partners. As for other fields, Covid-19 also had an impact on 7T studies, mainly during the lock-down in March/April 2020, but in general, most studies have luckily managed to keep going without severe delays.



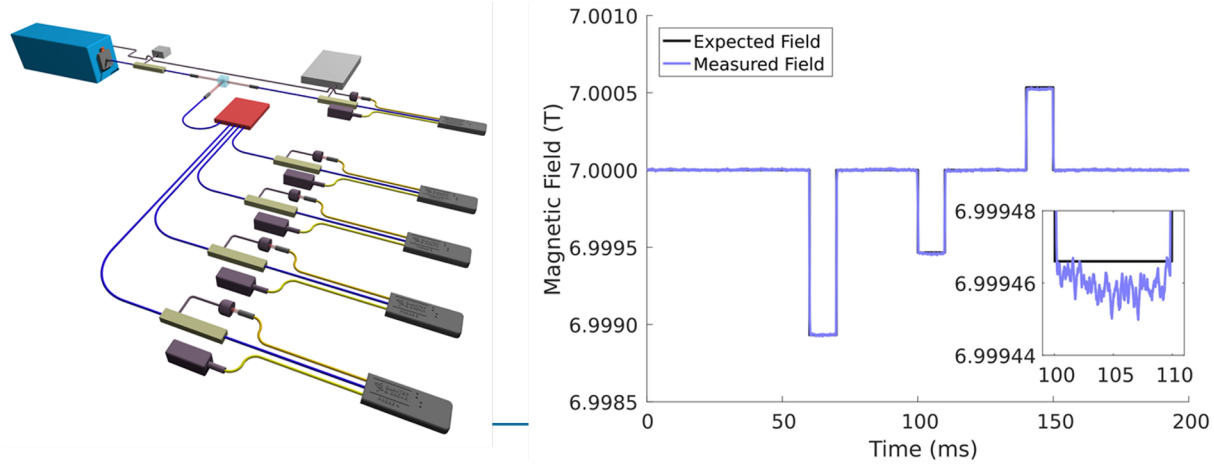
The Philips 7T scanner at DRCMR.

HARDWARE AND SOFTWARE DEVELOPMENTS FOR ULTRA-HIGH FIELD MRI

To keep our facility at the absolute forefront within Ultra-High Field MRI, an essential part of our continued research and development lies in improving the robustness and quality of the signal we receive. One strength of ultra-high field MRI is its ability to acquire very high resolution images. However, high resolution images result in rather long acquisition times, typically above 10 minutes, which significantly increases the risk of motion as compared to a typical 2-3 min. clinical imaging sequence. Therefore, we have made innovations that improve the sensitivity to motion by means of prospective motion correction using interleaved navigators during image acquisition. In this interleaved motion correction (iMoCo) approach developed by Vincent Boer (DRCMR) and Mads Andersen (Philips Healthcare), navigator images are acquired every few seconds, and potential motion is detected and corrected for by updating the image position and reaquiring corrupted data. This makes high resolution imaging possible in patient populations that



Effects of motion and motion correction on high-resolution T2-weighted 7T images. Top row: coronal T2-weighted images acquired at 7T without motion (left), with motion (right) and with motion and motion-correction implemented in the sequence (middle). The bottom row shows a zoom in of the outlined red squares in the top row.

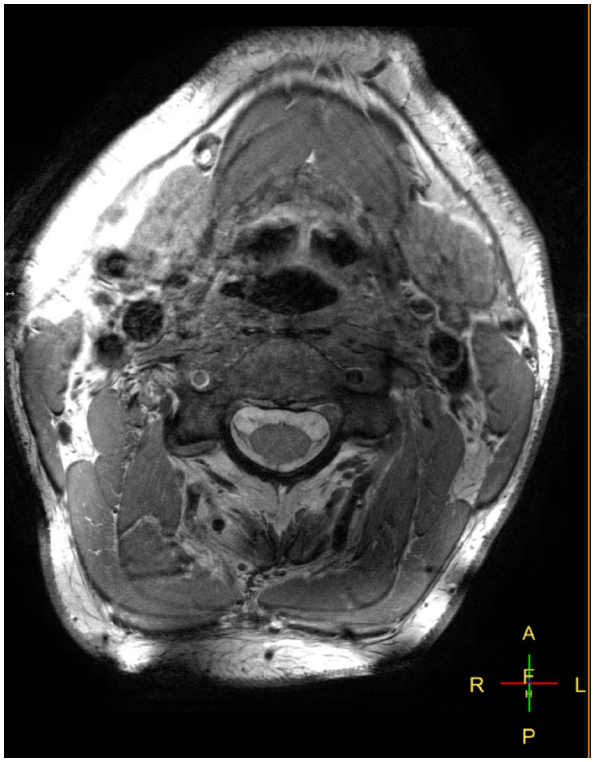


Left: Prototype of 4-channel quantum sensing optical field probe that can monitor the actual magnetic field in the scanner. Right: The field probe can detect minute changes in the magnetic field.

typically have a hard time staying still while being scanned, such as children and patients with motion disorders or dementia.

In addition, the field inhomogeneity gets more pronounced at higher field strength, where even breathing can distort B0 sensitive images such as the ones used in fMRI. Advanced shim abilities beyond the conventional 2nd or 3rd order shim systems are needed to improve or overcome this. A setup that can control up to 64 local shim coils independently has been established at DRCMR, and 8 dedicated shim coils for improved brain scans have been developed and tested by Vincent Boer and Jan Ole Pedersen (Philips Healthcare). Other innovations for correcting field inhomogeneities include the development of an all-optical field probe that continuously monitors the actual field within the scanner. This means that gradient imperfections and possibly breathing-related changes in the B0 field can be corrected for in the reconstruction process. Currently, a prototype exists with four probes, and the plan is to further improve the system and expand it to 16 or more probes. This exciting quantum sensing PhD project by Hans Stærkind (DRCMR/NBI) is a collaboration between DRCMR and Prof. Eugene Polzik at the Niels Bohr Institute.

Finally, specific absorption rate (SAR) used to control the allowed heating of the tissue is another restricting factor which effects get stronger at higher field strength. This is the reason why for instance no body coil exists for systems at 7 tesla or above, and it has resulted in a limited range of commercial coils with a correspondingly small spatial coverage. We therefore actively participate in the development of novel RF coil designs which improve both coverage and homogeneity of the acquired images by means of multiple transmit coils. The first coil we developed is a coil that targets the carotid arteries and spine, a challenging region at ultra-high field. This project is performed in collaboration with Prof. Hanne Christensen from Bispebjerg Hospital, who plans to investigate carotid dissection in details not seen before. We base our coil designs on a recent shielded coaxial coil approach, and we have established a strong collaboration between DRCMR, DTU (Assoc. Prof. Vitaliy Zhurbenko) and Technological University of Eindhoven, The Netherlands (Assoc. Prof. Irena Zivkovic) where both are co-supervisers on Sadri Güler's (DRCMR/DTU) PhD project which will ensure that we stay at the technological forefront in ultra-high field RF coil development.

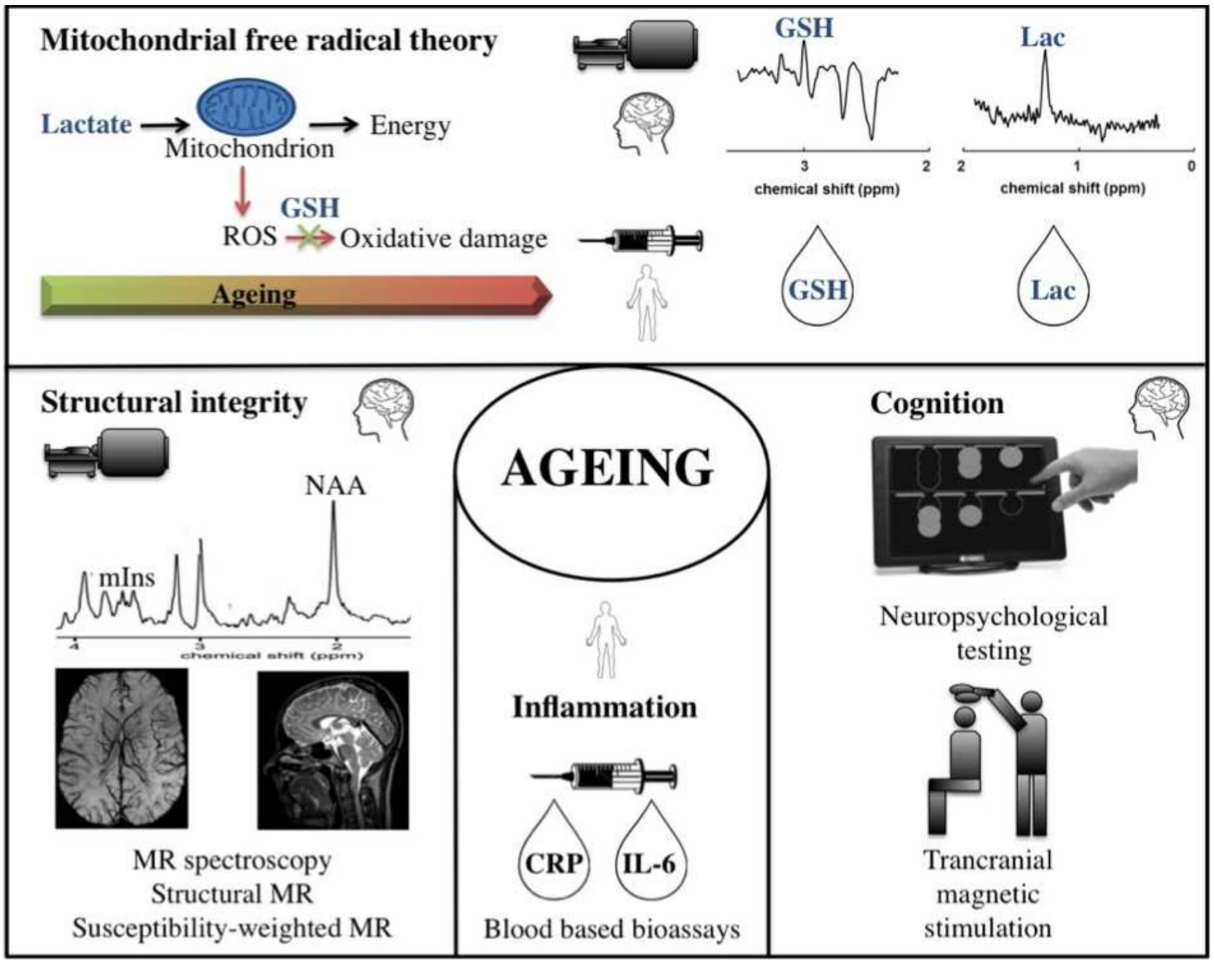


The first 7T carotid image from Denmark!

CLINICAL RESEARCH USING ULTRA-HIGH FIELD MRI

The Danish National 7T Project is a great success with many ongoing research studies being performed, new ones are in the planning, and the first ones have been completed. The projects range from high resolution functional and anatomical imaging in epilepsy, migraine, multiple sclerosis and Parkinson's Disease patients, to metabolic assessment of glycogen in the liver and muscle in diabetis and other diseases.

One of the initial PhD studies, completed by Anna Lind and supervised by Anouk Marsman, was a comprehensive ageing study where metabolic variations in different brain regions and their relation to cognition at different ages was investigated. At 7T, both the spectral resolution and intrinsic signal-to-noise ratio improve, which is ideal for spectroscopy. This technique can separate and quantify different metabolites in the brain in-vivo. One of the main findings in this study was that regional myo-inositol, creatine, and choline levels are higher at older age and scale negatively with visuospatial working memory. This study was the first to investigate normal ageing in several brain regions using 7T 1H-MRS and the findings indicate that glia-related metabolites could be valuable in future cognitive ageing studies.



One of the first 7T studies was a comprehensive ageing study that investigated metabolic variations in different brain regions and their relation to cognition at different ages.

STRATEGIC EFFORTS

The DRCMR leadership has planned a series of strategy meetings to work on a number of topics related to the DRCMR research strategy. The first two such meetings were held in 2021 as lunch-to-lunch meetings at external venues. At the first meeting, we discussed the strategy for the preclinical research at DRCMR. All DRCMR staff involved in preclinical research as well as key collaborators from the Bispebjerg Hospital and the University of Copenhagen were invited to the meeting. The meeting resulted in specific collaborative efforts and channels being set up.

Preclinical strategy seminar held in August 2021.

The second meeting addressed data governance at DRCMR and involved all researchers involved with handling data at DRCMR. At the meeting we identified focus areas covering a variety of topics such as data management, documentation, training, pre-registration, structure, archiving, automation, legality, version control, infrastructure and education. We plan on following up these strategic efforts with similar meetings in 2022 onwards.

Data governance seminar held in September 2021.

GLOBAL EXCELLENCE 2014-2020

In 2014, the DRCMR was announced as one of the winners of the Global Excellence Award of Region Hovedstaden (The Capital Region of Denmark), and in 2017, the Regional Council decided once again to award the DRCMR the prize.
With the re-announcement, the status of the department as the winner of Global Excellence was prolonged to the year 2020. In addition, the prize was accompanied by a grant of 1.5 million DKK in total. The grant has been used to attract international researchers and practitioners, as well as to conduct international symposia, workshops and similar.
The Global Excellence prize is a prize awarded by the Capital Region of Denmark to outstanding research environments at hospitals and universities in the Capital Region, whose efforts are considered world-class when it comes to research, development and deployment of new knowledge about technologies and new kinds of treatments in the Danish healthcare system.

At DRCMR we have benefitted a lot from the Global Excellence Prize. Besides the actual grant, the prize has helped us focus our strategic efforts within and outside the Capital Region. It has increased the awareness of the high level of research that we conduct at DRCMR and has thus opened doors to stakeholder institutions.
The Capital Region of Denmark has decided to discontinue the Global Excellence prizes and has introduced the concept of Clinical Academic Groups to replace the Global Excellence centres instead.

"The Global Excellence Award is a mark of quality of which we are proud."
- Head of Research, Hartwig Siebner

GLOBAL EXCELLENCE AT THE DRCMR

The Global Excellence prize has given us the unique chance to invite the best and most relevant speakers from all over the world. With the aid of the Global Excellence programme, we received the world's leading international researchers that inspired us to ensure innovative research ideas, to conduct high quality research, and to generate new international collaborations. The Global Excellence prize has played an important and contributing role in performing research on a first-rate level which has strengthened our international profile. The outcomes have led to the development and implementation of treatment methods and products for the benefit of patients.
Unfortunately, due the Covid-19 pandemic, we were only able to invite a limited number of international speakers to give Global Excellence talks at DRCMR during 2020.

GLOBAL EXCELLENCE SEMINAR PROGRAM 2019-2020

Date	Speaker	Affiliation	Title of talk
15-01-2019	Mark Hallett	National Institute of Neurological Disorders and Stroke, US	Parkinsonian Bradykinesia
22-02-2019	Mark Mühlau	Munich Center for Neurosciences,	MRI in MS -- the clinical perspective
08-03-2019	Bente Pakkenberg and Mikkel Vestergaard Olesen	Research Laboratory for Stereology and Neuroscience, Bispebjerg Hospital	Stereology applied to the central nervous system using histologic sections and MRI
04-04-2019	Jason Stockmann	Harvard Medical School	Quantitative MRI: Methods and Experimental Studies
Research, Massachusetts General Hospital, US	Beyond B0 shimming: New Applications of Local B0 Field Control Using Multi-Coil Arrays	Prof. of Neuroscience at the Department of Physiology, Development and Neuroscience at the University of Cambridge, UK	Neural signalling of reward and reward-based decisions
12-04-2019	Patrick Fisher	Dept. Neurology and Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet	The Psychedelic Brain: Neuroimaging psilocybin effects in humans
17-04-2019	Dirk Jancke	Institut für Neuroinformatik, Ruhr University Bochum	Imaging TMS-induced plasticity in animal models
10-05-2019	Søren Kyllingsbæk and Thor Grünbaum	University of Copenhagen	A Computational Model of Intention Selection
07-06-2019	Henning Friis	Danscatt	Bio-imaging at the world's most powerful x-ray sources
17-09-2019	Pedro Cavaleiro Miranda	University of Lisbon, Portugal	Modelling of transcutaneous spinal cord direct current stimulation
20-09-2019	Tonya White	Erasmus University Rotterdam, Netherlands	Pediatric population neuroimaging and the Generation R study
11-10-2019	Rani Moran	Max Planck UCL, Centre for Computational Psychiatry and Ageing Research	The effects of Model-Based inference on credit assignment in reinforcement learning
25-10-2019	James Rowe	University of Cambridge, UK	Multimodal challenges in FTD
31-10-2019	Alizee Lopez-Persem	University of Oxford, UK	The brain valuation system and its role in decision making
01-11-2019	Rune Berg	Department of Neuroscience, Univ. Of Copenhagen, Denmark	The enigmatic spinal cord: the black box of motor control
08-11-2019	Quentin Huys	Max Planck UCL, Centre for Computational Psychiatry and Ageing Research	The return of sadness: relapse after antidepressant discontinuation
15-11-2019	Steve Fleming	Wellcome Centre for Human Neuroimaging, UCL	Consciousness, state spaces and computational psychiatry
29-11-2019	Zeb Kurth-Nelson	Max Planck UCL, Centre for Computational Psychiatry and Ageing Research	A distributional code for value in dopamine-based reinforcement learning
02-12-2019	Yonatan Berman	London Mathematical Laboratory, UK	Ergodicity as a model of intertemporal decision-making
06-12-2019	Semir Zeki	Division of Biosciences, UCL	The Visual Brain's Multiple Visual Hierarchies Operate Asynchronously
17-01-2020	Claire Francesca Meehan	Department of Neuroscience, University of Copenhagen	Going Out With a Bang? Excitability, Motoneurone Disease and the Mid-Life Crisis
24-01-2020	Sebastian Weichwald	Copenhagen Causality Lab at the Statistics and Probability Theory Section	Causal inference in neuroimaging
07-02-2020	Tobias Hauser	Max Planck UCL, Centre for Computational Psychiatry and Ageing Research	The brain juices that make you noisy: The role of catecholamines in choice inconsistencies
14-02-2020	Elliott Wimmer	Max Planck UCL, Centre for Computational Psychiatry and Ageing Research	Episodic memory retrieval is supported by rapid sequential replay

FOCUS ON COLLABORATION

Collaboration plays a vital role in research, especially at DRCMR. Researchers with different educational backgrounds and skills form an extremely cross-disciplinary research team, spanning medicine, psychology, physics, biology, data science and engineering. Yet, without our numerous collaborators we wouldn't be able to conduct the cutting-edge research we are currently pursuing at DRCMR! Our collaborators inspire our scientific environment and enrich our research.

STRONG TRANSLATIONAL COOPERATION

As a research centre situated at Hvidovre Hospital, our research is conducted with the objective to improve diagnosis and/or treatment of patients – or with the objective to improve prevention and promote health and wellbeing. We have strengthened our translational research by reinforcing the collaborative ties with the clinical research groups at our own hospital, Amager and Hvidovre Hospital, but also with other hospitals in the Capital Region of Denmark, especially Bispebjerg and Frederiksberg Hospital. We have strong collaborative ties with Bispebjerg and Frederiksberg Hospital thanks to Hartwig Siebner´s affiliation to the Department of Neurology as Head of Research of the Movement Disorders Research Program and a collaboration on healthy aging between Prof. CJ Boraxbekk (DRCMR) and Prof. Michael Kjær´s group at the Institute og Sports Medicine. But many other collaborations have also been established with research groups at Herlev and Gentofte Hospital and Rigshospitalet. We are currently in the process of starting new projects with Hillerød Hospital as well.

The Capital Region of Denmark has also emphasized the need for better integration of research activities among universities and hospitals in the region. The Greater Copenhagen Health Science Partners have funded several Clinical Academic Groups which bring together researchers and clinicians in strong clinical research groups with a shared vision. We appreciate the initiative, and so far, DRCMR takes part in the Academic Alliance on Physical activity and sport in clinical medicine (imPAct), led by Professors Michael Kjær and Flemming Dela.

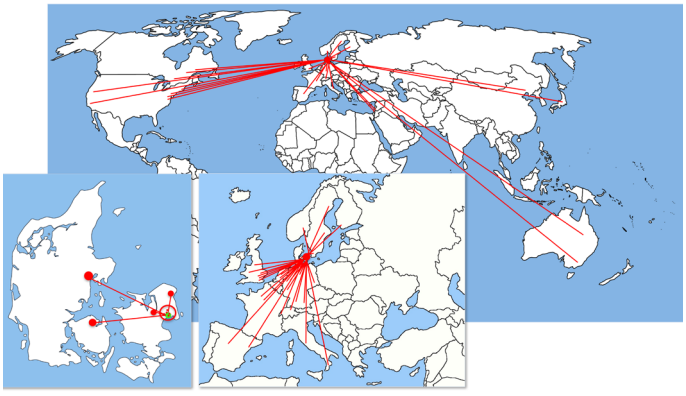
NEW COLLABORATIONS AND VISITING PROFESSORSHIPS

In 2019, DRCMR had two visiting professors: Professor Ray Dolan from University College London and Professor James Rowe from The University of Cambridge. Professor Ray Dolan was a visiting professor at DRCMR for a 6-month visit, funded by the Lundbeck Foundation. The visit was valuable for DRCMR, particularly for those working in the cognitive and computational neurosciences. During the visit, our weekly research meeting was host to around eight talks by different members of Ray's research institute, where we heard about topics such as hippocampal replay in planning and problem-solving, computational psychiatric approaches to depression and OCD, consciousness and metacognition, and neuro-aesthetics to name a few.

Professor James Rowe has been a close collaborator of DRCMR for many years. In 2019, this collaboration was strengthened thanks to a 5-month visiting professorship at the DRCMR, generously funded by the Lundbeck Foundation. James is a world-leading expert in frontotemporal dementia, Parkinson's disease and other neurodegenerative diseases. It was especially the movement disorders group that benefited from his engagement with ongoing projects, helpful comments and advice. Two of his lab members from the University of Cambridge also visited DRCMR and kindly shared their expertise on the post-processing of ultra-high-resolution imaging data of different brain stem nuclei such as the locus coeruleus.

INTERNATIONAL COLLABORATIONS

We work together with many research sites all over the globe. In the field of biomedical 7T MRI, we closely collaborate with



our colleagues at the Swedish 7T MR centre in Lund, but also within two European brain imaging networks "EUFIND" and "ASAP SYNTAU" on brain imaging of neurodegenerative brain diseases, causing dementia or atypical forms of parkinsonism. Both projects were funded by the EU Joint Project on Neurodegenerative Disease Research (JPND). In the last two years, we have strengthened synergistic research within Europe thanks to multilateral collaborations in especially H2020-funded projects such as LifeBrain, STIPED, TRABIT and bilateral collaborations with research groups in Germany, The Netherlands, Switzerland, United Kingdom, Italy, Sweden, Norway, and France. We are particularly proud about the marked increase in transcontinental collaborations with China, Japan, Korea, Australia, and the USA in recent years. Running synergistic projects together, exchanging students, researchers, knowledge, and ideas help us to maintain a vibrant research environment.

UNIVERSITIES IN THE CAPITAL REGION OF DENMARK

We continuously aim at enforcing our ties with our local university partners in the Capital Region of Denmark. We work together with researchers from multiple departments spanning four faculties at the University of Copenhagen. We also have a very fruitful collaboration with the Department of Technology at University College Copenhagen. Our closest regional university collaborations are with the Technical University of Denmark, where we have had strong ties with the Department of Applied Mathematics and Computer Science, and the Department of Health Technology (formerly Department of Electrical Engineering) for more than a decade. We have also the last few years started collaborations with the Department of Physics. As a hospital-based research centre with a strong emphasis on biomedical technology, we offer an important hub bridging the technology-oriented research carried out at DTU with the clinically and applied research pursued at several academic hospitals in the Capital Region.

INDUSTRIAL COLLABORATION

We have for many years had a strong collaboration with the vendors of our MR-scanners, namely Siemens and Philips. We have close interactions with them on the latest developments and have held several joint workshops with Philips with a focus on technical optimizations at ultra-high field. Through the Innovation Fund Denmark project, Precision-BCT, we have engaged in new collaborations with Magventure and Localite on precision brain-circuit therapy.

ACADEMIC ALLIANCES

We encourage our researchers to have academic affiliations and to integrate their research as well as their research groups with other academic research environments. We believe that academic alliances make our researchers grow and enrich our local research environment with new possibilities, ideas and inspiration. Currently, we have one shared professorship and four shared associate professorships with DTU, one shared senior associate lectureship with University College Copenhagen and one professorship shared with University of Umeå. In addition, Tim Dyrby is currently also associated to École Polytechnique Fédérale de Lausanne (EPFL) in Lausanne as visiting Professor. And finally, Prof. Hartwig Siebner is professor at University of Copenhagen and also affiliated to Bispebjerg and Frederiksberg Hospital.

AXEL THIELSCHER

Prof. in neurophysics and neuroimaging

Technical University of Denmark, Department of Health Technology (DTU-HealthTech), Center for Magnetic Resonance

TIM DYRBY

Assoc. prof. in multi-modal medical image analysis

Technical University of Denmark, Department of Applied Mathematics and Computer Science (DTU-Compute), Section for Image Analysis and Computer Graphics

LARS G. HANSON

Assoc. prof. in magnetic resonance imaging

Technical University of Denmark, Department of Health Technology (DTU-HealthTech), Center for Magnetic Resonance

ESBEN THADE PETERSEN

Assoc. prof. in ultra-high field MRI

Technical University of Denmark, Department of Health Technology (DTU-HealthTech), Center for Magnetic Resonance

KRISTOFFER HOUGAARD MADSEN

Assoc. prof. in statistical machine learning for functional neuroimaging

Technical University of Denmark, Department of Applied Mathematics and Computer Science (DTU-Compute), Section for Cognitive Systems

KATHRINE SKAK MADSEN

Senior assoc. lecturer in neuroimaging

University College Copenhagen, Department of Technology

CARL-JOHAN BORAXBEKK

Prof. of cognitive neuroscience of aging

University of Umeå, Sweden

Faculty of Social Science, Center for Demographic and Aging Research (CEDAR) // Umeå Center for Functional Brain Imaging (UFBI)

HARTWIG SIEBNER

Clinical Prof. with focus on precision medicine

University of Copenhagen, Faculty of Health and Medical Sciences, Institute of Clinical Medicine,

(sponsored by the Lundbeck Foundation - Grant Nr. R186-2015-2138).

And

Head of Research at Movement Disorders Research

Copenhagen University Hospital Bispebjerg and Frederiksberg, Department of Neurology

THE DRCMR IN THE NEWS!

The researchers at DRCMR and collaborators have not only been very productive during the last three years, they have also produced extremely interesting results. These results have triggered the interest of several Danish media and have resulted in DRCMR contributing to a number of articles/TV-shows/radio-programmes. Below you get a short insight on what has been of particular interest for the media in 2019-2021.

PROVOKING THE BRAIN

In the children's TV-news program "DR Ultra Nyt", Anna Lin Lundsgaard took a look at what happens in a child's brain when it is being provoked. For assistance, she teamed up with Associate Professor Kristoffer H. Madsen and let him measure the visible changes in the host's brain activity using functional MRI while she looked at pictures provoking her. Anger and provocation are typically associated with activities near the brain stem, including amygdala. Also, a number of bodily reactions are ready to prepare the body for a fight or an escape. Prior studies have shown how areas in the frontal lope are connected with a regulation of those emotions which surfaces when we are being provoked or getting angry. This regulation makes it possible for us to keep the situation under control and prevents us from reacting violently.

TV host Anna Lin Lundsgaard and Associate Professor Kristoffer H. Madsen.

Based on the DR Ultra program "DR Ultra Nyt" televised on 30 October 2019.

IS OKTOBERFEST GOOD FOR THE BRAIN?

"Politiken" Journalist Lars Igum Rasmussen drank a total of 69 alcohol units while celebrating Oktoberfest in Munich (and this was in only three days). Three days before the departure for the famous beer party in Munich, Lars Igum Rasmussen's and his friend's brains were MR scanned, and with the help of other tests, DRCMR researchers were to see how the large quantities of beer affect his and his friend's brains when the intoxication had diminished.
DRCMR researcher David Meder and PhD students Line Korsgaard Johnsen and Anna Hester Ver Loren van Themaat carried out the experiments and the analysis for Politiken.

"I have a slower brain, I am worse at remembering and concentrating, and I am in lack of energy." According to tests made, these are the results of three days of massive intake of beer at the Oktoberfest in Munich. "But I'm ready to go again".

Research Fellow David Meder and journalist Lars Igum Rasmussen.

Based on the article in Politiken on 19 October 2019.

SOCIAL MEDIA AND THE BRAIN

The model Cecilie Haugaard and her boyfriend Christopher have started a project in which the skills of a DRCMR researchers are used. In the TV series "Cillemouse - den falske virkelighed" [in English: "Cillemouse - the fake reality] on TV2play, the model Cecilie Haugaard investigates different aspects of social media. In an episode of the TV series "Cillemouse – den falske virkelighed", released on 10 April 2019, DRCMR and Researcher David Meder contributed with an MRI of Cecilie Haugaard's brain while she was looking at both happy and angry faces. This research project was performed a few years earlier when a larger group of subjects went through the same scanning process, revealing that the brain interprets smiles as 'rewarding', leading to the release of dopamine.

Photo: Shutterstock

Based on an episode of "Cillemouse – den falske virkelighed" on TV2Play on 10 April 2019.

A 7T STUDY: CORTICAL LESIONS IN THE HAND MOTOR AREA

...and its effects on hand function for people with multiple sclerosis

MENNESKER Af Cæcilie Dohn Christensen

MØD EN FORSKER

Hvert år uddeler Scleroseforeningen over 10 millioner kroner til forskning.

Mads Alexander Just Madsen
Cand.scient. i human fysiologi, ph.d.-studerende på Hvidovre Hospital på forskningsafdelingen for magnetisk resonansbilleddannelse.

[ORDBOG]

5 HURTIGE

Mads kan se ind i din hjerne

Hvad er formålet med projektet?

Hvordan kan projektet komme mennesker med sclerose til gavn?

Hvad har det betydet for projektet at få midler fra Scleroseforeningen?

Mads fortæller om hele projektet på www.scleroseforeningen.dk/mads

28 · MIT LIV MED SCLEROSE · NR. 1 · 2019

PhD Student Mads Alexander Just Madsen is doing research on how to develop new methods to be able to locate certain kinds of damages in the brain. It might make it easier in the future to reach an earlier and correct diagnosis for people with sclerosis. Mads received a grant from Scleroseforeningen and his project was featured in their magazine.

Based on an article published by Scleroseforeningen in January 2019.

FUTURE SCANNING METHODS WITH UNIQUE POSSIBILITIES

The uncertainty of how a life with multiple sclerosis will develop may be something of the past when Senior Researcher Henrik Lundell reaches his goal with his ambitious research project which is funded by the European Research Council. The project aims to develop new scanning techniques to better understand multiple sclerosis, which will support physicians in predicting outcome and choosing the most efficient treatment. The new methods will focus on the brain cells and how they interact, and through this data determine with great likelihood how the disease will develop.

FORSKNING Af Sara Bangsbo · Foto: Hvidovre Hospital

Fremtidens scannings-metoder skaber unikke muligheder

Frygten for, hvordan livet med sclerose vil udvikle sig, kan blive fortid, når den danske hjerneforsker Henrik Lundell kommer i mål med sit ambitiøse forskningsprojekt, som han har modtaget 11 millioner kroner til.

[ORDBOG]

"Vi vil udvikle tekniske metoder, der kan give os en langt bedre forståelse af sygdommen, så læger kan bruge den viden til at forudsige sygdomsforløbet og finde den helt korrekte behandling hurtigt."
Henrik Lundell

24 · MIT LIV MED SCLEROSE · NR. 1 · 2019

Based on an article published by Scleroseforeningen in January 2019.

NEW YEAR, NEW DECISIONS: HOW DO YOU HELP YOUR BRAIN TO MAKE THE RIGHT CHOICES?

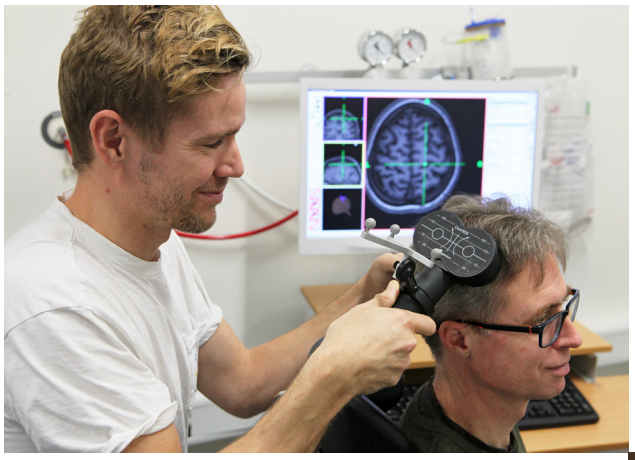
The New Year resolution is all about doing better in the upcoming year, but if you actually intend to accomplish your goals, it might be helpful to dig into the mechanisms behind decision-making.

What is actually going on in the brain when we make decisions? When we experience something good, we get rewarded, which happens when the brain releases dopamine. It causes us to want to repeat the action. Research Fellow David Meder from DRCMR explains that the reward system in the brain affects how we make decisions. Even app-developers work with a clear aim of using this mechanism. Bonuses or extra prizes added in a game. And after experiencing a winning, sub-conscientiously, we pick up the phone to play the game again in an attempt to feel the dopamine pleasure again. A reward.

Postdoc David Meder. Photo: Communication AHH.

Based on an interview at Videnskab.dk on 6 January 2020.

RESEARCH AIMS AT IMPROVING ELECTROMAGNETIC TREATMENT OF DEPRESSION



Senior Researcher Axel Thielscher is focusing on finding an alternative treatment of depression other than electroshock by using transcranial magnetic stimulation (TMS) which consists of electromagnetic coils which are placed on the head, creating a magnetic field. The varying magnetic field from the coils induces low electrical streams in the top layer of the brain, affecting the way the brain cells are communicating. However, our brains have different shapes and sizes as well as structure, which means that there is no such thing as a standard treatment.

The goal is to find out why and how to individualize the treatment to make sure that the magnetic stimulation hits accurately and provides the right simulation dosage, also called computational dosimetry.

Also, researchers hope to be able to use TMS to treat patients diagnosed with anxiety, OCD and cocaine addiction, and treatment of patients with Parkinson's disease can make successful use of TMS.

Based on article in "Magasinet Dynamo – DTU" no. 61, published in June 2020.

HALLOWEEN AND THE NEURAL REACTIONS

Research Fellow David Meder and Senior Researcher Kristoffer Madsen participated in the TV program “Manipulator” in November 2019. Here they told TV host Anne Glad about what a good scare does to our brain.

Based on the program on DR1 entitled ““Manipulator II - Halloween” aired on Tuesday 29 November 2019.

RESEARCH FELLOW DAVID MEDER ON “SOMMEREN PÅ P4” OVER THE SUMMER

Twice in July 2021, you had the opportunity to listen to Research Fellow David Meder when he was interviewed on the radio, channel P4, in the series “Sommeren på P4”.

On 7 July 2021, at 8:40 AM, the talk was about the growing use of cellular phones and time spent in front of a computer screen, and how it affects the brain. Is it turning into an addiction? And how does reducing the use of cellular phones and computers during the holidays affect the brain?

On 21 July 2021, at 8:40, the focus was around the everyday life in world filled with technology. How does the brain cope with that? And what about the flow of thoughts that appear when we put away the gadgets?

NEWLY APPOINTED PROFESSOR AT DRCMR

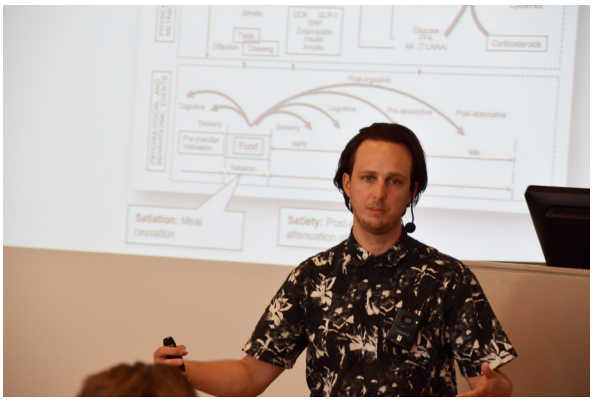
On 1 May 2021, Axel Thielscher was appointed professor at the Technical University of Denmark (DTU), Department of Health Technology. His research focuses on testing the mechanisms of action of non-invasive brain stimulation methods and on identifying the factors that cause variability in the stimulation outcome and hamper the clinical efficacy of non-invasive brain stimulation. His vision is to transform transcranial brain stimulation (TBS) into an effective medical treatment by personalizing established TBS methods and introducing novel TBS approaches with complementary application profiles.

Based on article in Dagens Medicin, published 11 august 2021.

RESEARCH DAY AT HVIDOVRE HOSPITAL

DRCMR researchers participated actively at the yearly Research Day at Hvidovre Hospital on 24 May 2019. Professor Hartwig Siebner and Senior Researcher Oliver Hulme gave a joint presentation together with Professor Sten Madsbad and Postdoc Maria Svane from the Dept. of Endocrinology on the Brain-Gut axis, gut hormones, appetite, obesity, and type-2 diabetes. The presentation also described the long-term collaboration between the two departments exemplified by the OmniSaM project which aimed to delineate neural systems underpinning satiety, and its interaction with behavior and endocrine systems.

Although the Research Day at Hvidovre Hospital is a yearly event, it was cancelled in 2020 and 2021 due to the Covid-19 pandemic.



Senior Reseacher Oliver Hulme presenting at the Hvidovre Hospital Research Day 2019.

PhD student Anna Ver Loren van Themaat presenting her poster at the Hvidovre Hospital Research Day 2019.

DRCMR POSTERS AT THE ANNUAL RESEARCH DAY AT HVIDOVRE HOSPITAL 2019:

Anna Ver Loren van Themaat
Electrophysiological measures of interference control in children at familial risk for schizophrenia or bipolar disorder

Christian Skoven
Can lasers shed light on the effects of human brain stimulation?

Christopher Fugl Madelung
Nuclear MRI in Parkinson's disease: Imaging brainstem changes in the substantia nigra and locus coeruleus using ultra-high field MRI

Fróði Gregersen
Design of electrode leads reducing heating at skin junctions during MRI

Line Korsgaard Johnsen
Functional brain imaging correlates of interference control in children at high risk of schizophrenia or bipolar disorder

Mads Alexander Just Madsen
Focal TACS of the primary motor hand area at individual mu and beta rhythm – effects on cortical excitability and intracortical inhibition

Marie Louise Liu
Patient-tailored Transcranial Direct Current Stimulation to improve stroke rehabilitation

Oula Puonti
Effect of anatomy on the electric fields induced by transcranial electric stimulation

Sofie Nilsson
Grasping motivation: Approach and Avoidance behavior is represented in grasping and slipping hand-movements

Valdemar Uhre
Cognitive Behavioral Therapy for Obsessive-Compulsive Disorder in Children and Adolescents. A Systematic Review with Meta-Analysis and Trial Sequential Analysis

POSITIONS OF TRUST

Hartwig Siebner:

- Editor-in-Chief, Neuroimage Clinical
- Senior Editor, Editorial Board of Neuroimage
- Board member, Editorial board, Brain stimulation
- Chairperson, Steering group, Danish Society for Medical Magnetic Resonance (DSMMR)
- Chairperson, Scientific Advisory Board, Danish Parkinson Association
- Vice-chairperson, Steering group member of the National Danish 7T MRI project
- Member, Steering group, National Swedish 7T MRI project, since 2016
- Member, Steering group, National MR-scanner project at "Børneriget"
- Member, Steering group, Nordic Chapter, International Society for Magnetic Resonance in Medicine (ISMRM)
- Member, Research Executive Committee, Copenhagen University Hospital Amager and Hvidovre
- Member, Steering group, NeuroGrad PhD School, Faculty of Health & Medical Sciences, Univ. of Copenhagen
- Member, International Advisory Board member, German Center for Brain Stimulation

Carl Johan Boraxbekk:

- Editorial Board member of Translational Sports Medicine
- Reviewer of grant proposals for French National Research Agency; Wallenberg foundation Sweden; Dutch National Research Foundation; UK Research and Innovation, BBSRC
- Reviewer of Professorship at Einstein Foundation Berlin
- Chair of the Aging theme of MIRAI - a Japanese-Swedish research collaboration

Henrik Lundell:

- Grant reviewer: French National Research Foundation (ANR) and France and Wings for Life, Austria
- Board Member: ISMRM Nordic Chapter

Leo Tomasevic:

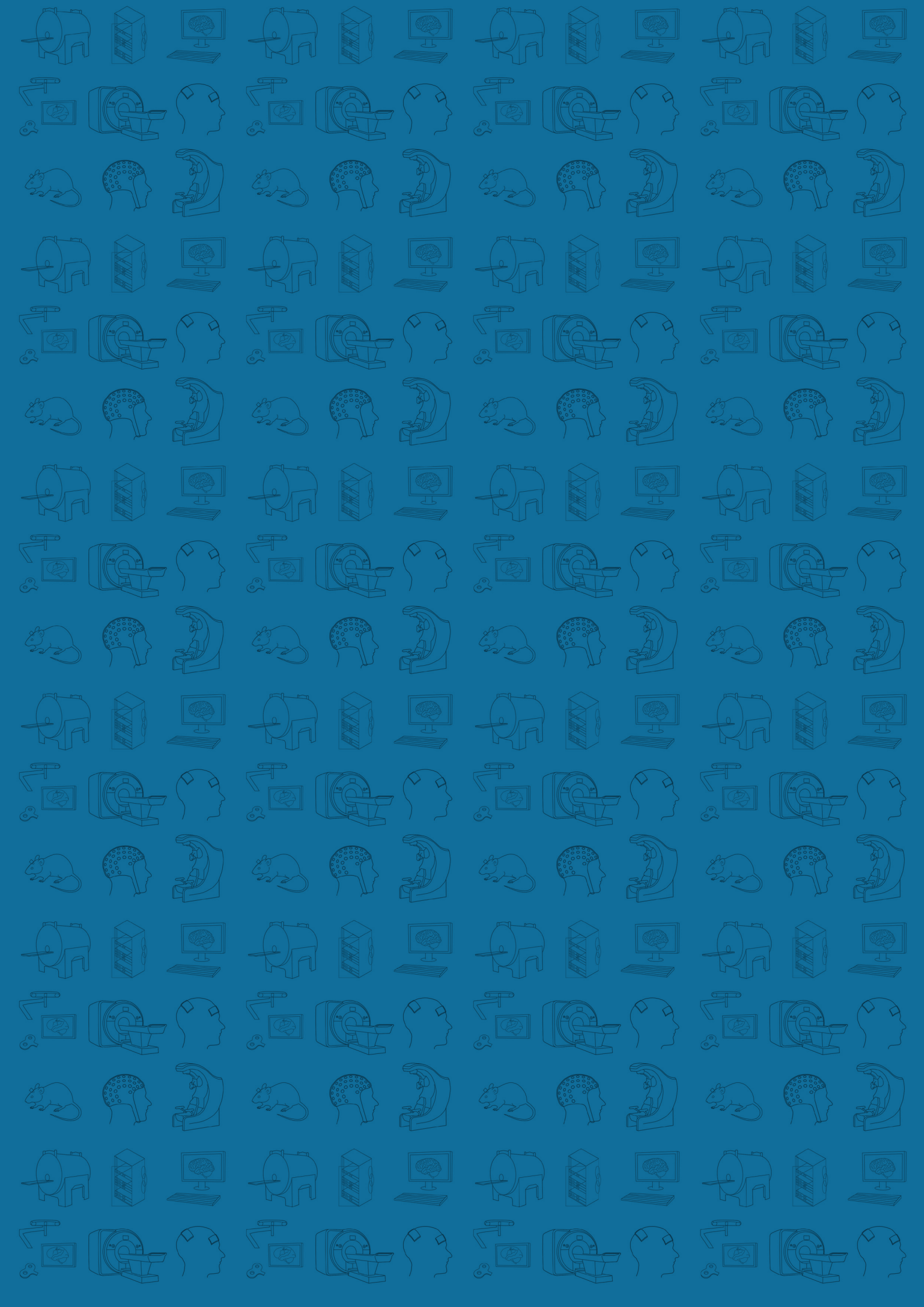
- Board member of Associazione Ricercatori e Scienziati Italiani in Danimarca (ARSID)
- Grant reviewer of the Italian Multiple Sclerosis Society (AISM-FISM)
- Member of Clinical Neurophysiology

Lars G. Hanson:

- Academic Editor, "Concepts of Magnetic Resonance Part B"
- Consultant, "Work Group on Revision of EFOMP Policy Statement 14 – Safety of MRI",
- EFOMP: European Federation of Organisations for Medical Physics
- Grant Reviewer for "Netherlands Organisation for Scientific Research, NWO"
- Consultant for a working group formed by the European Federation of Organisations For Medical Physics for revising the MR safety policy.
- Grant reviewer for UK Research and Innovation
- Grant Reviewer for Dutch Research Council.

FOCUS ON EDUCATION

An education in neuroimaging is challenging for many reasons and there are a number of problems faced by most neuroimaging centres. Apart from removing ferrous-metallic objects from every possible pocket, these include issues as basic as how to understand one another. Part of the challenges is that students come from diverse backgrounds, mathematics, physics, biology, medicine, economics, psychology, and even further afield, each with their own terminologies, and the range of topics and techniques to master is often very wide. Typically, it is hard for a student to know what it is they need to know, and what it is they do not know. Our solution to this problem is to provide a wide-ranging curriculum that covers all the basic knowledge and skills necessary to follow what is going on at DRCMR and to be able to make an intellectual contribution whatever the topic. The curriculum comprises several courses and modules that most students are expected to take whilst at DRCMR.



EDUCATIONAL CURRICULUM AT DRCMR

At DRCMR we provide a wide-ranging curriculum that covers all the basic knowledge and skills necessary to perform the research we carry out. We have evolved our previous annual course called *Foundational Skills for Neuroimaging* to a new course called *Analysis & Modelling, Brain & Behaviour*. The course teaches all students the main concepts of frequentist and Bayesian statistics and how these are used in neuroimaging. The course offers both a theoretical introduction to the field as well as a practical introduction to relevant statistical software that can be used. Due to the Covid-19 lockdown, the course was run as a book club in the first instance.

The internal *DRCMR Methods course* is a series of lectures and exercises that cover every major technique used at DRCMR. *Scanner safety* and scanner license courses are organized by the MR Methodology group. These courses give students the basic, necessary training to work in an MR environment, and the scanner license is the qualification that students need to acquire in order to autonomously operate an MR machine. Our yearly *MRI acquisition course* teaches the fundamental physics underlying the MR techniques employed at DRCMR. The course introduces MRI starting from a level requiring little or no MR experience. Lectures cover MR understanding, acquisition methods and parameters.

The yearly *Basic Introduction to Neuroanatomy course* introduces neuroanatomy to students and researchers who do not have any formal neuroanatomy training. The course also focuses on how basic neuroanatomy translates to MR images.

Image: Dejan Bozic © 123RF.COM

Once or twice a year (depending on the need), we also have a *Matlab course*, which teaches the basic programming skills needed to understand and develop scripting for data analyses to students with no prior programming experience.

Every autumn, we have our annual *Copenhagen Brain Stimulation Week*, formerly called *NTBS (Non-invasive transcranial brain stimulation) Winter school*, which is an intensive four-day workshop providing participants with in-depth knowledge of the most common non-invasive transcranial brain stimulation techniques followed by a one-day international symposium on the latest developments within brain stimulation.

Finally, our research areas organize week-long thematic *PhD courses* on their research in cooperation with the Graduate Programme in Neuroscience at the University of Copenhagen, Neurograd. The courses are arranged approximately once a year. In 2019, the Cognitive and Computational Neuroscience research area organized a course entitled Cognitive and Computational Neuroimaging: A Practical Course for Building and Testing Models of Mind, Brain, and Behaviour, and in 2020, the Life Span Imaging research area organized a course called Tracing brain and behavioural changes across the lifespan.

PHD COURSES

2019: COGNITIVE AND COMPUTATIONAL NEUROIMAGING

The PhD course on Cognitive and Computational Neuroimaging took place between 29 April - 3 May 2019 at DRCMR. The aim of the course was to combine theoretical models of cognition with neuroimaging, to ask how cognitive processes are encoded and enacted by the brain. Cognition was taken in the broadest sense to include any mental or behavioral process. However, the course primarily focused on four key cognitive domains: sensory perception, reward, decision-making and motor action, and it was divided into four phases: 1) Finding your question 2) Building your cognitive models 3) Designing your experiment 4) Presenting your experimental design. The course was fully booked – with a total of 20 students attending the course and 11 local and international teachers.

Students were divided into small groups and guided by experts they went through each stage of these four phases, culminating in a group presentation at the end, in which their chosen experiment were presented and scrutinized by the rest of the course attendants and instructors.

The course was organized by Oliver Hulme and members of the cognitive and computational research area and in collaboration with Prof. Hartwig Siebner and members of DRCMR and in collaboration with the Graduate School of Health and Medical Sciences, University of Copenhagen.

2020: TRACING BRAIN AND BEHAVIOURAL CHANGES ACROSS THE LIFESPAN

In January 2020 the "Lifespan Imaging" research area organized a PhD course on the influence of intrinsic and extrinsic factors and personalized health care. Insight into how the human brain and behaviour changes and is affected by biological, bodily or physical, and environmental factors, across the lifespan is pivotal in understanding behavioural and neurobiological risk for pathology, and for understanding health, resilience and potential. The course included lectures given by experts in the field and built on the latest research findings from neuroimaging and behavioural studies.

The course highlighted specific intrinsic, e.g. genes, hormones, immune system and extrinsic factors, e.g. nutrition, gut microbiota and physical activity, which influence brain and behavioural development and aging. Deviations from the typical pattern of brain and behavioural trajectories were illustrated by examples of neurological and psychiatric disorders.

Fundamental methodological and neuroscientific questions regarding lifespan neuroscience, including study designs and data analytical approaches were addressed, and questions such as what is a "good" or "bad" lifespan trajectory in terms of brain function and structure?" were debated.

The course was organized by Professor Carl-Johan Boraxbekk and the members of the Lifespan Imaging research area and offered together with the Faculty of Health and Medical Sciences, University of Copenhagen.

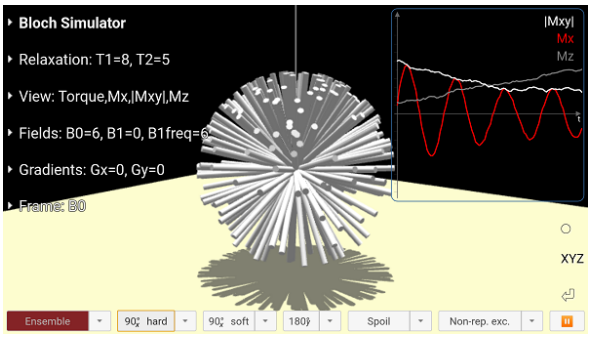
Main themes:

1. Population neuroscience across the lifespan
2. Brain and behavioural changes across the human life span
3. Identifying patterns of change over time and causality: data analyses strategies
4. Intrinsic and extrinsic factors influencing brain and behaviour across the lifespan
5. Towards personalized health care

MRI ACQUISITION COURSE

MRI is extremely flexible and therefore also challenging to learn. In fact, MRI is not one, but hundreds of techniques that all rely on some common basic ingredients that can be combined to measure a wealth of physiologically important parameters. Once a year, an introductory MRI course is offered at the DRCMR to provide new MR users the necessary understanding. During seven weekly 3-hour sessions, the participants gain insight into the basis of MRI and some of the many techniques used to probe structure and function of the living body. This includes aspects of anatomical imaging, spectroscopy, functional imaging and measurements of molecular motion.

Spin dynamics are challenging to explain and understand. Even the simplest measurement requires "excitation" for example, which involves rotation of the tissue magnetization around the scanner's strong magnetic field, and simultaneous rotation around an orthogonal axis, that is itself rotating. The traditional approach to teaching consequently involves considerable hand-waving, but 3D computer graphics offer much improved possibilities. Years ago, software was therefore developed for the course and has since been used by thousands. This so-called "Bloch Simulator" (http://drcmr.dk/bloch) needed a complete rewrite due to evolution of web technologies. A new version was therefore introduced in 2020, and beyond an improved user experience, it offered many new possibilities for interactive exploration of MR concepts and techniques. It was quickly adopted by the MR community worldwide and is used extensively for teaching.



METHOD GROUPS
FOR RESEARCH DEVELOPMENT AND TRAINING

There are several methods groups at DRCMR, each having a different set of aims and competences. There is no single template and each group is organized differently, however most groups meet on a weekly basis to discuss challenges, acute issues, new developments in the field, status of the labs, new projects, participation or organization of courses, workshops, and much else. Most groups have core members and then a large number of peripheral members attending meetings on a more ad hoc basis.

The method groups are essential for developing our research practices, as well as for ongoing methods training. Despite their diversity, the groups generally have three common aims: 1) Update and perform quality assurance on all methodology relevant for research in general and 2) Spread knowledge about innovative, upcoming methods and implement relevant novelties in an open and accessible manner for research staff and, finally, 3) Educate and support both students and researchers in methods relevant for specific experiments.

METHODS GROUPS AT DRCMR:

- MR Methodology
- Methods Clinic
- EEG - The Electroencephalography Group
- Brain Stimulation
- Preclinical

Read more about the focus of each group at pp. 66-73.

COPENHAGEN BRAIN STIMULATION WEEK

In November 2019, the 5th international '**Non-Invasive Brain Stimulation (NTBS) Winter School**' took place at DRCMR. The course, hosted by the Precision Brain Stimulation research group, features 4 days of interactive lectures in the morning and hands-on experience in the lab in the afternoon. More than 20 students, researchers, engineers and clinicians from around the world participated.

In 2021 the course resumed as the '**Copenhagen Brain Stimulation Week (CoBS)**'. Despite challenging circumstances, we again managed to gather more than 20 participants interested in NTBS. The 2021 CoBS also included a free online workshop, featuring renowned international experts within the field and more than 130 attendees from all around the world.

The course provides in-depth knowledge of NTBS, spanning from physical and physiological basics all the way to clinical application. In the evening, participants had the opportunity to attend social events intended to spur further networking.

"I really enjoyed the week! Fully appreciated the great organization, the variety of lectures and practical sessions. Everyone was extremely helpful, open to questions, explained everything in a hands-on manner."

-Varvara Mathiopoulou, 2021
CoBS attendee.

TO BE OR NOT TO BE A STUDENT AT DRCMR

Every year we enroll a considerable number of students (BSc, MSc and PhD's), interns, volunteers, research year students and student assistants at DRCMR. Students are very important for our research milieu – they contribute to research and we consider it our responsibility to educate future researchers. We are keen on providing the best possible frames for the students with focus on a rich learning environment to help them pursue their research dreams. The students normally join a research group, where they take part in theoretical and methodological discussions together with more established researchers at group meetings. Most of our students are also a valuable resource when experiments are carried out in our labs and many students even run their own experiments as part of their projects. The students come from many different countries and with many different backgrounds. We find that this diversity helps create an ambitious and collaborative research milieu.

YOU CAN MEET THREE OF OUR STUDENTS HERE:

Benjamin – MSc student from Denmark

Name: Benjamin Skjold Frederiksen
Age: 25 years
Study: Masters student at the Technical University of Denmark

I am very interested in understanding not just how humans behave but why we see this behaviour emerge. During my Master's degree, I was fortunate to be associated with the Computational Neuroscience of Reward Group at DRCMR, where I got to be part of a project that experimentally investigates emerging theories within behavioural economics that seek to end the misuse of terms such as "irrational behaviour".

At DRCMR, you have a great deal of responsibility for your research, but at the same time there is always someone close, who is happy to help - this counts all the way from other students and PhD-fellows to senior researchers. And due to the highly interdisciplinary work environment, you further have great opportunities to obtain skills and knowledge in other areas.

DRCMR was my first experience with a real research environment and was ultimately the reason that I decided to pursue a career in academia, which I now am as a PhD-fellow at the Technical University of Denmark. My time at DRCMR was heavily impacted by the Covid-19 pandemic, yet I am very happy I got the opportunity and highly encourage other students to look into the possibilities at DRCMR – you will not regret it!

Nina – Biomedical Engineering (BSc) student from Denmark

Name: Nina Braad Iskov
Age: 23 years old
Study: Bachelor student in Biomedical Engineering at the Technical University of Denmark (DTU) and University of Copenhagen (KU) Psychology student at the University of Copenhagen, Denmark.

For my bachelor thesis I wanted to combine my passion for the human brain and medical imaging. For this purpose, DRCMR was the perfect place to conduct my thesis. My bachelor partner and I became a part of the Neurophysics group, that works on advancing non-invasive transcranial brain stimulation methods, which relies on accurate modelling of the head. Our job was to improve a brain segmentation algorithm by implementing information about the spatial layout of the cortex derived from quantitative MRI.
In order to become more familiar with related research within neuroscience, we were invited to multiple meetings, in which we also got to present our project and get feedback. We got the opportunity to be a part of an interdisciplinary and positive environment, which was an enriching experience.
Since day one at DRCMR, everyone was open and helpful, which made us feel incredibly welcomed. We had a buddy who showed us around and introduced us to everyone working there. Even though we were only there for a couple of months, it clearly felt like we belonged. We generally felt a huge interest in our project from others, which was very motivating. We also highly valued the support from our office colleague, who was so kind and provided us with biscuits and juice.

Nikki – Intern from the USA

Name: Nicole Leewuen Hueng
Age: 25 years old
Study: Master student in Cognition and Communication at the University of Copenhagen, Denmark.

I started off as an intern in the fall of 2020 after hearing about DRCMR from a former student assistant. Despite all the setbacks COVID threw at us, I felt like I still learned so much from everyone here. Even though I was just a master's student intern with a not as strong neuroscience background, everyone made me feel welcome. I felt comfortable asking questions and socializing with people from different research backgrounds. Knowing that I wanted to keep learning about research, I decided to extend my time as a master's thesis student for the spring. It's pretty cool to say that I scanned brains for my thesis, and I never in a million years thought I would do something like this. DRCMR provided me with a taste of what research was like, as well as a great network of people who genuinely want everyone to succeed. .

THE DRCMR STUDENT GROUP

WHO ARE WE?

The DRCMR student group consists of PhD students, Research assistants, BSc and MSc students, visiting Interns, and "research year" medical students. We meet on the last Friday of every month to have lunch together, have discussions and listen to talks on different subjects.

OUR PURPOSE

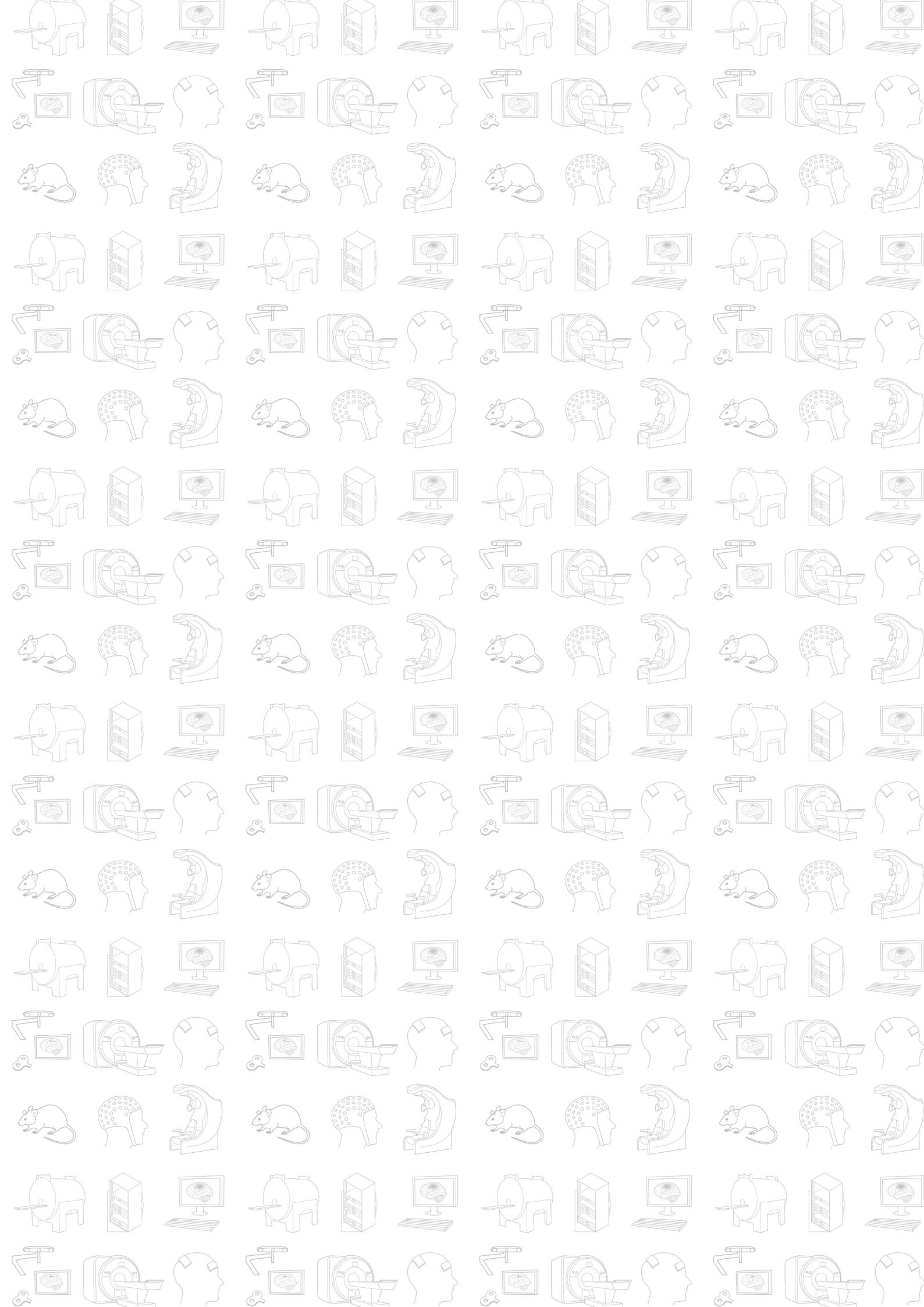
We form the basis of a student network and encourage both academic and social exchanges between students at DRCMR.

The talks given at the DRCMR student meetings are meant to lay the foundation for an academic toolbox that students can make use of during their studies, and to prepare students for their future careers. The presentations are given either by students themselves, or invited speakers, and are often angled towards overarching research-related topics. In example, presentations include "How to write an article" and "How to find grants".

Moreover, the student group acts as a forum for open discussion between students. The student group representatives work closely with the leadership to deliver the student consensus on various matters, in order to ensure an optimal study and work environment at DRCMR.

The student group meetings are also meant as a place where students can ask any question and receive advice from their peers. In this way, students new to DRCMR can quickly get to know their new workplace and colleagues. The student group is a place for academic growth, but also for having fun and experiencing the Danish "hygge" – we have, for example, revived the old tradition of going for after-work "Friday beers" - somethings that is open for all DRCMR staff..

Some of the members of the DRCMR student group.



DISSERTATIONS

16 PhD candidates defended their theses at DRCMR in 2019–2021. Here we present selected candidates and their projects.

The PhD's where done in collaboration with The University of Copenhagen and The Technical University of Denmark.

INHIBITORY CONTROL OF ACTION IN HEALTH AND DISEASE

Allan Lohse

SUMMARY

To make appropriate choices, inhibitory action control is a fundamental cognitive process, allowing us to only produce actions when they are adequate in the given context. One core region mediating this control is the pre-supplementary motor area (preSMA). In my thesis, I investigated the role of the preSMA in action control in two specific settings. In both cases, I inhibited the preSMA with rTMS to investigate changes in action control. In the first study, I measured healthy participants' trait and state impulsivity (questionnaire scores and gambling behavior, respectively) and could show that the association between both measurements (high trait impulsivity was associated with riskier gambling behavior) was uncoupled upon preSMA stimulation. This suggests a prominent role of the preSMA in the control of impulsive behavior. In a second study, I investigated Parkinson patients with levodopa-induced dyskinesia, which are involuntary movements caused by the intake of dopaminergic medication. Here I could show that rTMS successfully reduced excessive preSMA activity, together with a reduction in dyskinesia severity and prolonging the time to dyskinesia onset. Together, this shows that the preSMA is important in the control of voluntary (study 1) and involuntary behavior (study 2).

SUPERVISORS

Prof. Hartwig R. Siebner, DRCMR
Research Fellow David Meder, DRCMR
Assoc. Prof. Annemette Løkkegaard, BBH

UNIVERSITY

University of Copenhagen

DATE OF DEFENCE

May 11th, 2020

WORKING TODAY

Resident (Neurology) at Rigshospitalet

FROM EARLY INFORMATION PROCESSING TO HIGHER-ORDER COGNITIVE FUNCTIONING IN CHILDREN WITH FAMILIAL HIGH RISK OF SCHIZOPHRENIA OR BIPOLAR DISORDER

Anna Hester Ver Loren van Themaat

SUMMARY

Children born to parents diagnosed with schizophrenia or bipolar disorder have a higher risk to develop these disorders themselves. The present dissertation aimed at investigating several functional abnormalities that are common to schizophrenia and bipolar disorder, in children with familial high-risk of schizophrenia (FHR-SZ) or of bipolar disorder (FHR-BP) as part of the Danish High Risk and Resilience Study (VIA) using electroencephalography (EEG) and cognitive tasks.

We found that the level of global functioning of the children was associated with the latency of the EEG component related to detecting changes in an acoustic environment. Children at FHR-SZ and FHR-BP showed higher variability in their response timing when resolving a visuomotor conflict task. This finding correlated with the amplitude of the P300 EEG component that were found to be reduced in the high-risk children. Finally, children at FHR-SZ and FHR-BP showed comparable developmental trajectories (from age 7 to 11) of visual attention to children with no FHR. Longitudinal studies are fundamental to provide insights on whether our findings serve as transitory or persistent features and whether these may serve as a predictor for later illness onset, or possibly, may serve as protection from developing such disorders.

SUPERVISORS

Prof. Merete Nordentoft, Mental Health Centre
Prof. Hartwig R. Siebner, DRCMR
Prof. Kerstin Jessica Plessen, Univ.Hoso. Lausanne
Assoc. Prof. Bob Oranje, Mental Health Centre
Research Fellow Leo Tomasevic, DRCMR

UNIVERSITY

University of Copenhagen

DATE OF DEFENCE

October 9th, 2020

WORKING TODAY

Clinical psychologist in the Netherlands

NORMAL, REGIONAL AGEING OF BRAIN METABOLITES IN RELATION TO COGNITIVE AGEING AND INFLAMMAGING

Anna Lind Hansen

SUMMARY

The aim of this thesis was to use 7 tesla 1H-MRS to describe differences in brain metabolite levels across three age groups, a younger (18-26 years old), a middle (39-50 years old) and an older (69-79 years old) group, and to link these differences to cognitive ageing and inflammaging. We investigated five main metabolites; the glia-related myo-inositol (mIns), total creatine (tCr) and total Choline (tCho) and the neuron-related total N-acetylaspartate (tNAA) and glutamate (Glu). We measured these metabolites in four brain regions: anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), hippocampus and thalamus. A visuo-spatial working memory (vsWM) was used as a proxy for cognitive ageing and inflammaging was probed by measuring systemic concentrations of the proinflammatory markers C-reactive protein (CRP), interleukin 8 (IL-8) and tumor necrosis factor a (TNF-alpha).

We observed that ageing was primarily related to elevated levels of glia-related metabolites and found links between systemic inflammation, glia-related metabolites and cognitive ageing. The results in this thesis suggest that glial cells may play a central role in cognitive ageing and may be part of the basis of the biological and chemical changes linking systemic inflammation and cognitive ageing.

SUPERVISORS

Prof. Hartwig R. Siebner, DRCMR
Research Fellow Anouk Marsman, DRCMR
Prof. Carl-Johan Boraxbekk, DRCMR
Assoc. Prof. Esben Thade Petersen, DRCMR/DTU

UNIVERSITY

University of Copenhagen

DATE OF DEFENCE

June 15th, 2020

WORKING TODAY

Project Coordinator at Bavarian Nordic in the Integration Management Office

STRUCTURAL CORRELATES OF FATIGUE IN MULTIPLE SCLEROSIS ASSESSED WITH MRI

Christian Bauer

SUMMARY

Fatigue is one of the most common symptoms in multiple sclerosis (MS). It is reported as one of the most invalidating symptoms in the majority of the patients. The origin of fatigue still remains elusive and there is an unmet need for objective measurements. MS diffusively attacks the whole CNS, and affects the grey (GM) and white matter (WM) independently. The aim of this project was to investigate whether motor fatigue was associated with the degree of GM- and WM alterations. We investigated the corticospinal tracts (CST), which are responsible for the motor output, and cortical and subcortical regions involved in motor performance. Forty-six MS patients underwent diffusion weighted imaging (DWI) and clinical magnetic resonance imaging (MRI) along with 25 healthy controls (HC). The results revealed apparent increased anatomical connectivity (AC) in the left and dominant CST in fatigued patients compared to non-fatigued patients and HC. Contrarily, increased AC in the right CST was found in non-fatigued patients compared to HC. In general, increased connectivity was found in the bilateral CST among patients compared to HC. Fatigue was not associated with atrophy or lesion load. The results suggest that motor fatigue is related to central motor fibres and crossing fibre systems.

SUPERVISORS

Prof. Hartwig R. Siebner, DRCMR
Research Fellow Kasper Winther Andersen, DRCMR
Assoc. Prof. Tim B. Dyrby, DRCMR
Assoc. Prof. Kathrine Skak Madsen, DRCMR
Prof. Finn Sellebjerg, DMSC

UNIVERSITY

University of Copenhagen

DATE OF DEFENCE

December 16th, 2019

WORKING TODAY

Postdoc at DRCMR and lecturer at University College Copenhagen

SAFETY AND DOSE ESTIMATION OF TRANSCRANIAL FOCUSED ULTRASOUND STIMULATION (TFUS)

Cristina Pasquinelli

SUMMARY

Transcranial focused ultrasound stimulation (TFUS) is a non-invasive brain stimulation (NIBS) technique, which has a smaller spatial focus and can reach deeper targets in the brain compared to other NIBS modalities. Despite its proven modulatory effects on humans and animals, investigations to establish the method's foundations are missing, although indispensable for its safe and reliable usage. The first aim of the PhD project was to collect information on TFUS possible harmful effects. TFUS appeared to be safe in the majority of the published studies in humans and animals, except for two papers that reported microhaemorrhages in a subgroup of animals. However, further studies are necessary to demonstrate the reproducibility of the observed effect and to investigate its cause. The second aim of the project was to find a procedure, based on computer simulations informed by CT images of the skull, for accurate dose control. We investigated how a correct model of the transducer is important when simulating complex and realistic scenarios like human experiments. Finally, a promising initial test demonstrated the possibility of combining new CMUT-based TFUS transducers with fMRI in rodents, to allow assessing the brain network response to the stimulation in future studies.

SUPERVISORS

Assoc. Prof. Axel Thielscher, DRCMR/DTU
Assoc. Prof. Lars G. Hanson, DRCMR/DTU
Assoc. Prof. Hyunjoo J. Lee, KAIST

UNIVERSITY

Technical University of Denmark

DATE OF DEFENCE

October 4th, 2019

WORKING TODAY

Postdoc at DRCMR

SYSTEMATIC ARTIFACTS IN CURRENT-INDUCED MAGNETIC FIELD MEASUREMENTS BY MRI

Fróði Gregersen

SUMMARY

Computational models of the electrical properties of the human head are increasingly used in neuroscientific research to estimate induced electric fields in non-invasive brain stimulation methods or to estimate the origin of signals measured by electro- and magnetoencephalography. However, the anatomical complexity of the human head makes accurate head modeling challenging. To create reliable head models it is important to validate their accuracy.

A good candidate for non-invasive validation is magnetic resonance current density imaging (MRCDI). MRCDI uses an MR scanner to measure magnetic fields in the brain created by currents injected through the skull. Computational head models can be validated by comparing measured and simulated magnetic fields. MRCDI of the human brain is challenging since only tiny currents can be safely applied.

The aim of the thesis was to improve MRCDI of the human brain. First, new MRCDI-optimal current injection electrodes were designed. With the new MRCDI-optimal electrodes, unwanted magnetic fields from currents flowing in the electrode leads were reduced. The second aim was to reduce the influence of physiological noise on the MRCDI measurements. This was achieved by designing faster MR imaging methods than previously used in MRCDI.

SUPERVISORS

Assoc. Prof. Lars G. Hanson, DTU & DRCMR
Prof. Axel Thielscher, DTU & DRCMR
Prof. Rong Xue, CAS

UNIVERSITY

Technical University of Denmark

DATE OF DEFENCE

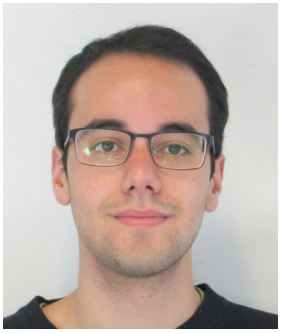
November 30th, 2021

WORKING TODAY

Postdoc at DTU and DRCMR

COMPUTATIONAL MODELLING AND OPTIMIZATION OF ELECTRIC FIELDS GENERATED BY TBS

Guilherme Bicalho Saturnino



SUMMARY

Transcranial brain stimulation (TBS) uses electrodes or magnetic coils to create an electric field in the brain that alters its activity, without the need of surgery and with minimal side effects. These methods are widely used in neuroscience research and are steadily gaining importance in the treatment of neurological and psychiatric disorders. However, the electric fields created by TBS methods in the brain are affected by the individual head anatomy in complex ways. This causes an interindividual variability of the applied stimulation dose that is likely a major factor of the variable TBS effects observed in practice in research and clinical applications. In the thesis, we investigated and validated computational methods to simulate and optimize these electric fields with the goal of improving the reliability and efficiency of those TBS methods.

SUPERVISORS

Assoc. Prof. Axel Thielscher, DRCMR and DTU
Assoc. Prof. Kristoffer Hougaard Madsen, DRCMR and DTU
Prof. Lars Kai Hansen, DTU

UNIVERSITY

Technical University of Denmark

DATE OF DEFENCE

November 20th, 2020

WORKING TODAY

Ørsted, developing computational models for offshore wind energy

PROFILING THE INPUT-RESPONSE RELATIONSHIP OF NON-INVASIVE TRANSCRANIAL BRAIN STIMULATION

Janine Kesselheim

SUMMARY

Non-invasive transcranial brain stimulation can modulate intrinsic brain activity, but large variations in the effects hamper its use as a therapeutic tool. I attempted to delineate the input-response relationships of two widely applied techniques, transcranial magnetic stimulation (TMS) and transcranial alternating current stimulation (TACS), to optimize stimulation parameters and minimize variability.

Both repetitive TMS (rTMS) using patterned pulses with intervals matching the periodicity of corticospinal volleys recorded after a single TMS pulse and bipolar TACS at beta-frequency (b-TACS) can induce plasticity, but more research is needed to overcome the present culprits: acute online effects are not well understood and the input-response relationships lack thorough investigations. I therefore probed online effects of TMS at I-wave periodicity and b-TACS on intracortical excitability to optimize TMS parameter setting and individualize TACS dosing. My studies revealed novel insights into online effects of both techniques: study I yielded input-response patterns that are useful to optimize rTMS at I-wave periodicity, while study II revealed a non-selective input-response pattern that indicates "target engagement" but could not solve the dosing problem of TACS interventions.

SUPERVISORS

Prof. Hartwig Roman Siebner, DRCMR
Assoc. Prof. Anke Ninija Karabanov, NEXS
Research Fellow Leo Tomasevic, DRCMR

UNIVERSITY

University of Copenhagen

DATE OF DEFENCE

August 19th, 2020

WORKING TODAY

Home carer

THE EFFECT OF MOTIVATION ON RESPONSE INHIBITION IN CHILDREN WITH TOURETTE SYNDROME

Katrine Maigaard

SUMMARY

Tourette syndrome is a neurodevelopmental disorder characterized by multiple tics. Most children with Tourette syndrome experience a decrease of symptoms as they mature, which may reflect compensatory adaptions in cognitive control. Although some aspects of cognitive control can be improved by external motivation, knowledge of how motivation influences the capacity to suppress tics is severely limited. The overall objective of this study was therefore to investigate the impact of prospect of reward on inhibition in children with Tourette syndrome, using a modified Simon task during functional magnetic resonance imaging.

We found that children with Tourette syndrome made fewer errors and managed interference with greater ease than typically developing controls in the fastest trials. Furthermore, we found heightened activity in inhibitory regions of the prefrontal cortex in children with Tourette syndrome in these trials. Finally, we found that the prospect of a reward improved performance in all children without regard to diagnosis. Together, our results reveal alterations in behavioural and neural correlates of response inhibition in children with Tourette syndrome, which we interpret as a compensatory higher global inhibition, presumably as the result of daily tic inhibition.

SUPERVISORS

Prof. Kerstin Jessica Plessen, Child and Adolescent Mental Health Centre Copenhagen
Prof. Hartwig Siebner, DRCMR

UNIVERSITY

University of Copenhagen

DATE OF DEFENCE

May 6th, 2019

WORKING TODAY

Copenhagen Affective Disorder Research Center

THE IMPACT OF CORTICAL LESIONS ON SENSORIMOTOR FUNCTION IN PATIENTS WITH MULTIPLE SCLEROSIS - A 7T MRI STUDY

Mads Alexander Just Madsen

SUMMARY

Multiple sclerosis (MS) is a chronic, autoimmune disorder, causing widespread inflammation and demyelination of white and grey matter in the central nervous system. However, the clinical impact of cortical lesions is underappreciated because they are difficult to detect using conventional clinical magnetic resonance imaging (MRI) at 1.5 or 3T.

The overarching purpose of this PhD thesis was to investigate the potential of 7T MRI to visualize cortical lesions and to characterize their contribution to clinical sensorimotor impairment. By combining data from a systematic review with empirically collected data from Danish MS patients, it was clear that 7T MRI enables visualization of cortical lesions to an extent that is not possible at lower field strengths. Cortical lesions were visible on 7T MR images in the vast majority of patients, but patients with a progressive disease course had a higher cortical lesion load than relapsing remitting patients. 7T MRI is also capable of visualizing cortical lesions to an extent that reflect their clinical relevance both on a global brain level, but also in highly specific areas of the brain. Specifically, I showed that cortical lesions in the sensorimotor hand area associates with decreased sensory and motor function in the contralateral hand.

SUPERVISORS

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Assoc. Prof. Esben Thade Petersen, DRCMR

UNIVERSITY

University of Copenhagen

DATE OF DEFENCE

October 25th, 2021

WORKING TODAY

Postdoc at DRCMR

MULTI-MODAL MICROSTRUCTURAL IMAGING OF BRAIN WHITE MATTER

Mariam Andersson

SUMMARY

The axons are the communication cables of the brain. Since their discovery, they have been described as cylindrical. Their diameters reflect how fast signals are conducted along them and potentially act as a biomarker of some neurodegenerative diseases, such as Multiple Sclerosis. A non-invasive estimation of axon diameter is possible with diffusion magnetic resonance imaging (MRI), through the fitting biophysical models that describe the expected shapes of the white matter microstructures to the diffusion MRI signal. However, in these, axons are again described as cylinders.

Here, we mapped the 3D microstructure of the white matter in the monkey brain, and characterised the shapes of cells, blood vessels and axons using synchrotron x-ray imaging. The axons exhibited varying diameters and trajectories along their lengths, often in response to other structures in their local environment. We showed that the true non-cylindrical axonal shapes – in addition to challengeing our knowledge of how axons conduct signals – caused an overestimation of axon diameter with diffusion MRI. We then simulated the diffusion MRI process and demonstrated how powder averaging techniques can give more accurate estimates of axon diameter, even in very complex axonal shapes.

SUPERVISORS

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Assoc. Prof. Vedrana Andersen Dahl, DTU
Assoc. Prof. Martin Bech, Lund University
Senior Researcher Henrik Lundell, DRCMR

UNIVERSITY

Technical University of Denmark

DATE OF DEFENCE

June 3rd, 2021

WORKING TODAY

Postdoc at DRCMR

MAGNETIC RESONANCE IMAGING BASED MICROSTRUCTURAL MARKERS OF BRAIN DAMAGE AFTER SEVERE TBI

Sara Hesby Andreasen

SUMMARY

The aim of this thesis is an examination of how structural MRI can capture the severity of the microstructural shear-strain induced axonal injury, known to be the decisive injury for functional long-term outcome in severe TBI. Fourteen patients with severe TBI were examined with whole-brain MRI. Susceptibility weighted imaging (SWI) was used to index traumatic microbleeds, and diffusion measures fractional anisotropy (FA) and mean diffusivity (MD) were used as indexation of TAI. Clinical severity was defined as the duration of posttraumatic amnesia (PTA).

Results and interpretation: A correlation between the regional expression of microbleeds and TAI was only found in the central and deep territories of the brain, suggesting that the microvascular lesions may be an independent pathology trait in severe TBI, rather than a proxy-marker of TAI. Furthermore, this study found two patterns of diffusion weighted imaging changes were associated with the duration of PTA, namely a global expression of diffuse white matter microstructural injury and a preferential damage in the central and deep territories of the brain predisposed a worse outcome. This result suggests that clinical severity of TBI increases with depth of white matter injury.

SUPERVISORS

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Research Fellow Kasper Winther Andersen, DRCMR
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Consultant Lars-Peter Kammersgaard, TBI Unit

UNIVERSITY

University of Copenhagen

DATE OF DEFENCE

June 19th, 2020

WORKING TODAY

Roskilde Hospital, Department of Neurology

FUNCTIONAL AND STRUCTURAL IMAGING IN TRAUMA-AFFECTED REFUGEES WITH POSTTRAUMATIC STRESS

Sigurd Wiingaard Uldall

SUMMARY

The overall aim of the present PhD project was to study neural activity and microstructural properties of white matter in trauma-affected refugees with posttraumatic stress disorder (PTSD). We collected fMRI data during a monetary incentive delay task and while participants viewed positive visual stimuli, both before and after having imagined a personal traumatic memory. These results suggest that a reduced prefrontal and occipital reinforcing signal of reward may adversely affect the experience of pleasure in refugees with PTSD. Furthermore, the association between the presence of secondary psychotic symptoms and reduced anticipatory reward processing in the associative striatum may reflect a mechanism by which abnormal reward signals in the basal ganglia facilitates psychotic symptoms across psychiatric conditions. Finally, the results may also imply that PTSD is associated with compromised structural connectivity in fibre tracts involved in top-down dysregulation of the hippocampus, amygdala and insula by mPFC, in relation to contextual processing deficits, exaggerated fear and symptoms of avoidance and dissociation. This points to symptom-specific functional and structural brain changes in patients with PTSD which may be relevant for future treatment-studies.

SUPERVISORS

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UNIVERSITY

University of Copenhagen

DATE OF DEFENCE

September 30th, 2019

WORKING TODAY

Psychiatry fellowship, Psychiatric Centre Ballerup

COMPUTATIONAL IMAGING BIOMARKERS OF MULTIPLE SCLEROSIS

Stefano Cerri

SUMMARY

Multiple Sclerosis (MS) is a chronic disease of the central nervous system, characterized by the formation of lesions in the brain and marked atrophy. MRI scans are the primary tool used by clinicians to detect lesions and atrophy patterns. Manually labeling white matter lesions and many brain structures on MRI scans is time-consuming, prone to inter-rater variability. For such reasons, many automatic tools have been proposed in the literature. However, these methods fall well below the threshold of what is required in clinical applications.

In this thesis, we first focused on the development of a method for simultaneously segmenting white matter lesions and dozens of brain structures. The method is adaptive to scanner and contrast changes. It also has competitive lesion segmentation performance compared to benchmark methods while segmenting 41 brain structures.

We then extended this method to track brain changes and lesion evolution accurately on longitudinal MRI scans. This extension leads to more temporally consistent segmentations than its cross-sectional counterpart while being able to better detect biological changes in the brain.

We made the proposed methods publicly available as part of the neuroimaging package FreeSurfer, with approximately 50000 licenses worldwide.

SUPERVISORS

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Dr. Annemie Ribbens, Icometrix

UNIVERSITY

Techical University of Denmark

DATE OF DEFENCE

June 29th, 2021

WORKING TODAY

Research Fellow at Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School

WHO WE ARE

“Coming together is a beginning, staying together is progress, and working together is success.”

- Henry Ford

DRCMR STAFF 2019–2021

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COMING TO DRCMR

We have welcomed many new talents during 2019-2021. They bring valuable knowledge and experience from their previous positions and help us develop and grow.

Here we introduce the postdocs and research fellows who are new to DRCMR the past three years and a bit about their backgrounds.

Angela Mastropasqua

I came to work as a Postdoc at DRCMR in June 2020. During my PhD in Munich, at the Graduate School of Systemic Neurosciences GSN-LMU, I focused on the use of multi-techniques, such as transcranial magnetic stimulation (TMS), electroencephalography (EEG), and eye-tracking to investigate the causal role of brain regions involved in cognitive processes. Here, I have the great opportunity to continue working with non-invasive brain stimulation (NIBS) and neuroimaging, applying these techniques to the investigation of clinical conditions. I am currently working in a new teamwork project, Precision-Brain Circuit Therapy (Precision-BCT) aimed at developing a personalized brain stimulation approach to restore brain function in treatment resistant depression. My research focus is on the use of EEG measures to examine the effect of TMS and to establish optimized neurostimulation protocols for clinical interventions.

The DRCMR is a unique place that offers a collaborative and interdisciplinary work environment and excellent resources. I look forward to sharing and improving my scientific skills working with great colleagues.

Anna Plachti

I came to DRCMR in May 2020. During my PhD, I studied the functional and structural differentiation patterns of the hippocampus across the lifespan and in pathology at the Research Centre Juelich, Germany. My current project at the DRCMR is about negative emotionality traits, which are assumed to be risk factors for psychiatric disorders such as anxiety and depression. My primary aim is therefore to uncover structural brain networks that distinguish individuals with positive and negative emotionality traits. In addition, I am also interested in identifying the environmental and genetic factors that influence these networks in order to predict who will suffer from which type of psychiatric disorder in the future.

Working at DRCMR is a great opportunity for me to learn about diffusion weighted imaging and to focus more on the lifespan aspect of personality and brain maturation. Through the close international collaborations, I hope to learn a lot and to further develop my research career as an independent scientist.

Enedino Hernández-Torres

After finishing my PhD in physics, I spent five years as a post-doctoral fellow and four years as a research associate in Vancouver, Canada. During this time, I worked with several MRI techniques such as susceptibility weighted imaging (SWI), diffusion tensor imaging (DTI), myelin water fraction (MWF) to study various diseases, including multiple sclerosis, concussion, and bipolar disorder. I was also involved in studies of knee cartilage and animal models of spinal cord trauma. I have vast experience in the development of frameworks for data analysis, including image registration and tissue segmentation. In this context, I have developed graphical user interfaces for image analysis and image visualization for quality assurance purposes. I joined the DRCMR as a research fellow in June 2020 to contribute with my experience in data analysis in several projects, mainly VIA11. By collaborating with the different interdisciplinary research teams at DRCMR, I aim to apply my experience and to learn new analysis techniques. My goal is to establish standardized methods for data analysis that can facilitate organization and analysis of current and future data at DRCMR.

Fang Cao

I work at DRCMR as a Postdoctoral Researcher. Before coming to DRCMR, I was a postdoc at INRIA Rennes, France, where I applied non-linear optimization algorithms to estimate MRI parameters quantitatively. Earlier, I received a PhD in Signal and Information Processing and did a bachelor's degree in physics.

My current research is in the area of medical image processing. I work in the Neurophysics group, headed by Axel Thielscher, with a focus on the Precision BCT (Brain-Circuit Therapy) project. My contribution to the project carried out at DRCMR and DTU Health Tech is to optimize the open-source software SimNIBS (Simulation of Non-invasive Brain Stimulation). Our goal is to develop a real-time application to simulate the electric field induced by Transcranial Magnetic Stimulation (TMS).

Working at DRCMR has been a great privilege to me. The institute offers a unique, extraordinary working environment with excellent neuroimaging facilities and rich collaboration and interdisciplinary work opportunities. I have enjoyed interacting with and learning from researchers with different backgrounds and competencies. It is truly inspiring to work here, and I look forward to contributing to DRCMR while developing my research capabilities and learning skills for my future scientific career.

Hasan Hüseyin Eroglu

I came to work as a Postdoctoral Researcher at DRCMR in November 2019. During my PhD studies, I contributed to the design and implementation of an Induced Current Magnetic Resonance Electrical Impedance Tomography (ICMREIT) system which is based on switching of gradient coils of an MRI scanner and inducing electrical currents in volume conductors to be imaged. After my PhD, I investigated interaction of electrical currents in conductive fluids with the static magnetic field of an MRI scanner, which results in magnetohydrodynamic (MHD) flow of the fluid. Currently, I have been working with the Neurophysics group, headed by Axel Thielscher, to develop reconstruction methods for Magnetic Resonance Electric Impedance Tomography (MREIT) which aims to improve Transcranial Direct Current Stimulation (TDCS) of the human brain by means of accurate computational dose control. In DRCMR, I have found the chance to apply my experience to explore electrical conductivity imaging of human brain. By using and combining numerous hardware (scanners, stimulators, instrumentation devices, application specific electrodes and cable structures) and software tools (i.e. SIMNIBS, segmentation and meshing scripts), I have been learning how to make different approaches for the effective implementation of the electrical conductivity imaging of the human brain.

Lasse Christiansen

I joined DRCMR in May 2019 following a 1-year postdoc at the University of Copenhagen. I did my PhD program in the quondam 'Copenhagen Neural Control of Movement' at the Panum Institute, where I studied neural plasticity in relation to motor control, learning and brain stimulation. Subsequently, I joined The Miami Project to Cure Paralysis, University of Miami where I focused on non-invasive models for inducing and enhancing spinal plasticity to promote motor recovery in spinal cord injured individuals.

Working at DRCMR has been a very good experience so far. I really enjoy the international atmosphere, and the in-house cross disciplinary expertise has been a benefit to my understanding of the physics and neurophysiological background of NTBS. The possibility of combining brain stimulation with brain imaging provides new opportunities when exploring neural control of movement as well as neural plasticity underlying changes in sensorimotor control.

Here at DRCMR, I am working on multimodal mapping of sensorimotor integration in the cerebral cortex. I use non-invasive brain stimulation paradigms to induce plasticity and MRI protocols to inform stimulation parameters and evaluate the neural effects of stimulation. In addition, I head the Brain stimulation Methods group, where we focus on optimizing data acquisition and analysis in relation to brain stimulation.

Mattias Rickhag

I joined DRCMR in May 2021 as a senior researcher and have a background in experimental neuroscience from University of Copenhagen. My research has focused on animal models with emphasis on the dopamine system and I have developed platforms to understand neuronal circuits in disease by use of viral-genetic tools. I will provide DRCMR with strong expertise within the basal ganglia circuit biology, brain lesion models, and application of genetic tools. Here, I will implement viral-based technologies to gain deeper insights into how particular neuronal circuits govern motor behaviour in animal models of Parkinson's disease. As part of a Lundbeck Foundation Collaborative Grant, I will establish novel transgenic mouse lines that allows labelling and manipulation of distinct cortical circuits. With these unique genetically modified animal systems, we can control activity of selected neurons in a spatial and temporal fashion and monitor behavioural readouts in parkinsonian mouse models. This is part of a collaboration with both Department of Neuroscience at the University of Copenhagen and Lund University. The project will clarify how cortical projections instruct motor behaviour in mice and how the selective targeting of distinct cortical inputs can restore normal motor function in animal models of Parkinson's disease. I am looking forward to establishing these technologies at DRCMR, which offers a vibrant energizing neuroscience centre with inspiring colleagues.

Michal Považan

My long-term research interests revolve around the development of MR methods and their application in clinical and scientific settings, most notably within the field of MR spectroscopy (MRS). During my studies in Bratislava and Vienna, and later in Peter Barker's lab at Johns Hopkins University, I have been engaged in numerous studies involving collaboration with departments of nuclear medicine, psychiatry, oncology, and neurology, as well as other sites across U.S. and Europe.

I joined the DRCMR team in August 2021 as a postdoctoral researcher in The Lundbeck Foundation funded project "HiReSpect". This project aims to combine the MRS methodology for detecting the neurotransmitter levels with non-invasive brain stimulation to uncover the biochemical dynamics that underlie the motor activation. The DRCMR with a close-knit multidisciplinary group of researchers and a cutting-edge biomedical methodology provides a perfect opportunity to expand my knowledge and try to answer some of the current neuroscientific challenges.

Mikkel C. Vinding

I joined DRCMR in September 2021 after nearly six years at Karolinska Institutet in Stockholm, Sweden, where I previously worked with magnetoencephalography (MEG) methods and primarily in Parkinson's disease. At DRCMR, I am privileged to be part of the ADAPT-PD project on individualised precision-based brain stimulation in patients diagnosed with Parkinson's disease. Within the project, I am responsible for the electroencephalographic (EEG) experimental branch and will help identify EEG markers of dyskinesia and other movement symptoms that can be used as targets for direct stimulation using transcranial magnetic stimulation (TMS).

My academic interests are the role of motor control in health and disease, and how to use electrophysiological (EEG/MEG and similar methods) to uncover the neural mechanisms of motor control. I am therefore very excited to be part of DRCMR and work together with the excellent researchers here, who have much knowledge and expertise in this field. I will further help to develop the EEG methods and expand the EEG research at DRCMR.

Mikkel Malling Beck

I came to work as a postdoc at DRCMR in September 2021 after finishing my PhD at the Department of Nutrition, Exercise and Sports at the University of Copenhagen. During my PhD, I studied development of motor control and motor learning in children, adolescents and adults using behavioural analyses and electrophysiological techniques, including electroencephalography (EEG) and transcranial magnetic stimulation (TMS). My current work at DRCMR focuses on combining these two methods, TMS and EEG, to characterize and further the understanding of early brain responses to magnetic stimulation. Working at DRCMR has been a great experience so far. The core of DRCMR features a collaborative and interdisciplinary work environment with state-of-the-art neuroimaging and brain stimulation facilities. This makes DRCMR an exciting place to work with plenty of room for professional and personal development and I look forward to developing my research skills and competencies.

Naiara Demnitz

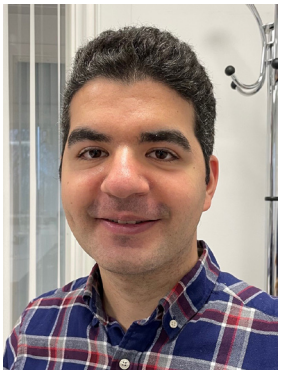
I came to DRCMR in August 2020 to work as a postdoctoral researcher in the Healthy Ageing group, led by Carl-Johan Boraxbekk. The overarching aim of my research is to understand how modifiable lifestyle factors can help promote healthy brain ageing. To that end, I combine structural magnetic resonance imaging (MRI) and neuropsychological assessments to characterise the relationship between lifestyle factors, such as physical activity, and the brain structure and function of older adults.

Prior to moving to DRCMR, I completed my PhD at the University of Oxford and worked as a postdoc at Trinity College Dublin, where I held an Atlantic Fellowship for Equity in Brain Health. During my PhD, I investigated the effects of a 12-month physical exercise intervention (the REACT study) on the brain structure and function of older adults. At DRCMR, I hope to build on my previous work to further explore individual differences in the effects of physical activity on the ageing brain. For example, DRCMR hosts a unique and state-of-the-art MRI dataset, the LISA study, which will enable me to investigate if and how sex moderates the beneficial effects of physical activity. For this, the extensive expertise in interventional studies and neuroimaging methods available at DRCMR will be invaluable resources and will certainly provide a rich learning environment for me to develop my research skills.

Nathalie Just

I am an MR physicist. I come from France but I have spent most of my career in many different laboratories across Europe. I obtained my PhD in 2004 from the University of London and the Institute of Cancer Research (Sutton, Surrey, UK) and after a short stay in industry, I rehearsed my academic career in the Center for Biomedical Imaging of EPFL (Lausanne, Switzerland). There, I started to work on fMRI and fMRS in rodents at high field strength (9.4 and 14T). Since then, the development of fMRS techniques for rodent applications became one of my major research areas. After nearly 10 years in Switzerland, I joined the University Hospital of Münster (Germany) to combine fMRS and optogenetics in the rat cortex for the first time. In 2019, I went back to France where I obtained my habilitation. I worked at INRAE on non-invasive methods to investigate hypothalamic neurogenesis in the sheep brain. I arrived at DRCMR in May 2021 to work on the development of Diffusion-weighted MRS in rodents on our Bruker 7T. Of course, new ideas for improved functional metabolic outcomes are in the pipeline, notably with chemo-genetics! In addition, my research always focuses on translational outcomes.

Seyedsina Hosseini



I came to DRCMR and the Technical University of Denmark (DTU) to work as a Postdoc in December 2020. During my Ph.D. studies at Aarhus University, I was working with tiny devices in the brain, operated by ultrasonic waves to help people with Parkinson's disease (PD) through optogenetics.

My current project is investigating the characteristics of the skull applicable in Transcranial Ultrasound Stimulation (TUS). TUS is emerging as a new non-invasive brain stimulation method that can achieve a highly focused stimulation also of deeper brain areas. By that, it offers unique new prospects for the treatment of neuropsychiatric diseases.

Dose control for TUS is very challenging because the waves are strongly affected by the human skull, which has rather complex and inhomogeneous acoustic properties. In my current project, under the supervision of Senior Researcher Axel Thielscher and Senior Researcher Lars G. Hanson, we will develop new methods for the individualized modelling of the acoustic human skull properties from computed tomography (CT), magnetic resonance imaging (MRI), and calibration measurements. Our aim is to provide more accurate and robust dosing methods that will be a cornerstone for clinically effective and safe TUS applications.

Working at DRCMR is an interesting experience for me since we have an interdisciplinary environment with nice collaboration as well as prestigious facilities.

I look forward to strengthening my knowledge and experience with my new colleagues at DRCMR.

Simon R. Steinkamp

After completing my PhD in Psychology at the Research Centre Jülich in Germany, I joined the Computational Neuroscience of Reward group lead by Oliver Hulme at DRCMR in August 2021 as a postdoc.

The main project I am working on is the "Ergodicity Experiment". Together with our collaborators at the London Mathematical Laboratory, we are investigating how concepts from ergodicity economics are expressed in human behaviors like decision making and reward learning. I am especially interested in modeling the underlying brain activity in the reward system during these cognitive processes. For example, addressing the question whether populations of dopamine neurons encode a heterogeneous or homogenous reward signal, which requires the development and implementation of new brain mapping methods.

My background is in computational cognitive neuroscience, with a focus on attentional processes both in audition and vision, using neuroimaging methods such as fMRI and EEG. During my PhD, I have investigated the effects of attentional orienting along the meridians of the visual field and contributed to a computational modeling approach, that simultaneously models behavioral and fMRI responses. With my work at DRCMR I build on my computational modeling experience and want to further develop my skills in this field and am excited to learn more about ergodicity economics. Furthermore, I am looking forward to the international collaborations and cherish the commitment to open-science practices.

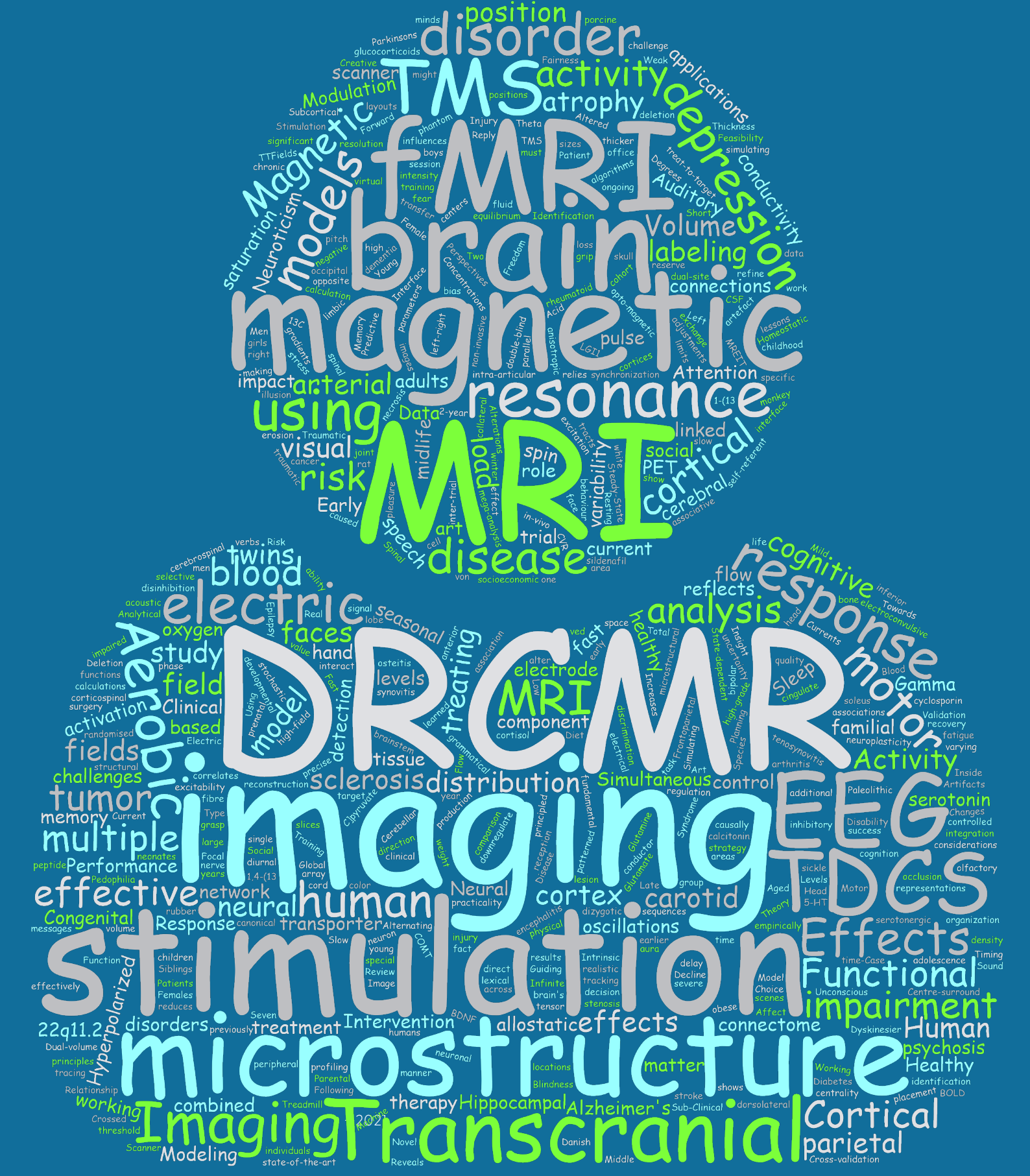
Vanessa Wiggermann

I joined the DRCMR in May 2020 as a Postdoc after completing my PhD in physics at the University of British Columbia, Vancouver, Canada. My PhD was focused on developing and assessing quantitative MRI techniques for their potential to image the myelin state of the brain. My research has been mainly aimed at the study of multiple sclerosis, an immune-mediated, demyelinating, neurodegenerative disease, which is one of the most common causes of disability in young people.

To join the Neuroimaging in MS and Ultra-High Field MR groups at the DRCMR and specifically the CLiMS project (Cortical Lesions in MS) is an exciting opportunity. It allows me to pursue my goal of working with ultra-high field MRI and expand my MRI knowledge in different areas while contributing with my expertise to the CLiMS project, which aims to identify the impact of individual cortical lesions on hand function.

Moving from Canada to Denmark was a big step, but the welcoming and collaborative atmosphere at the DRCMR and exciting first six months in the project have made this an easy transition. I look forward to starting the next projects that are currently being planned and to integrating myself further at the DRCMR.

PUBLICATIONS



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