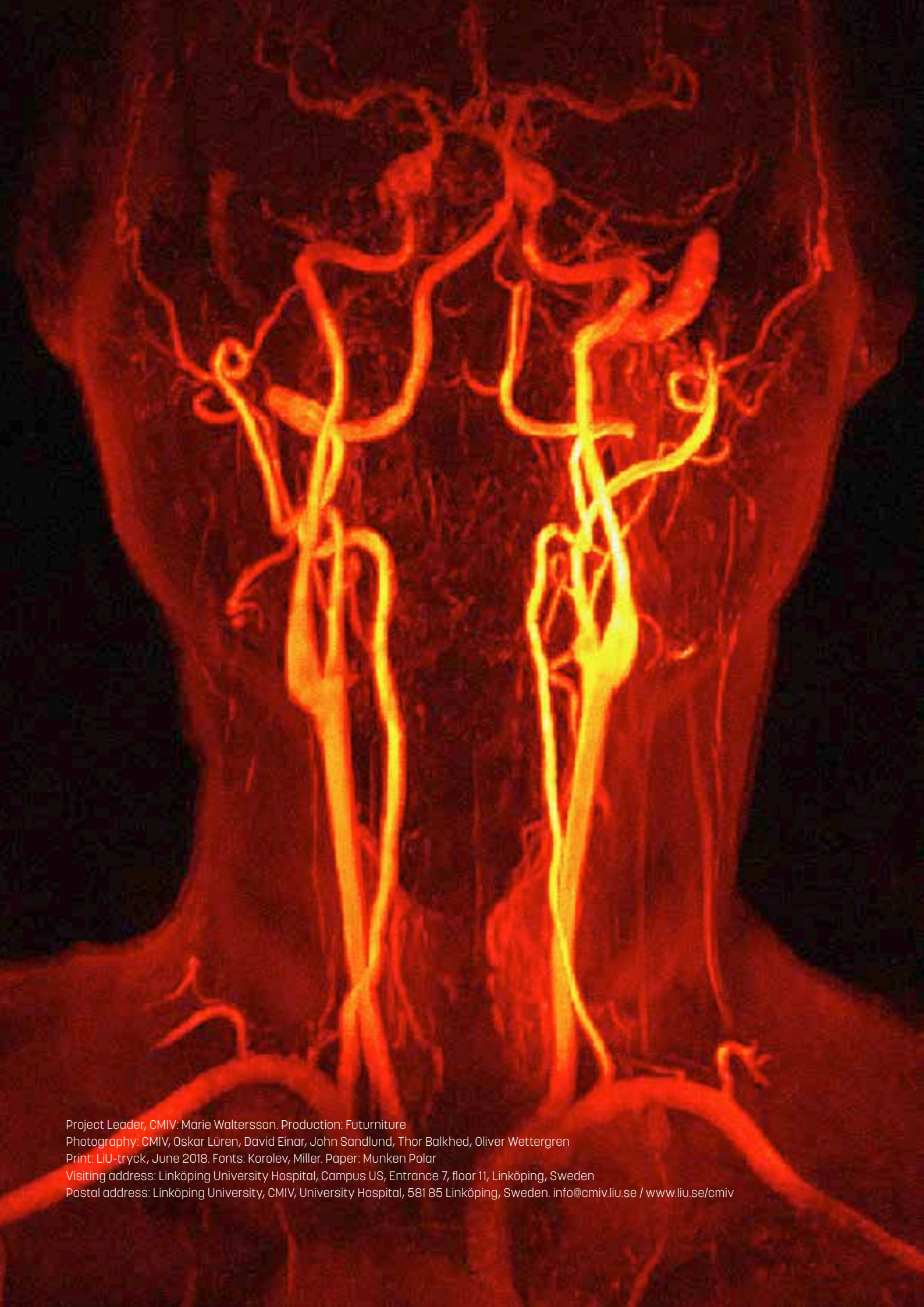
Welcome to the exciting world of CMIV

ANNUAL SCIENTIFIC REPORT 2017

LINKÖPING UNIVERSITY



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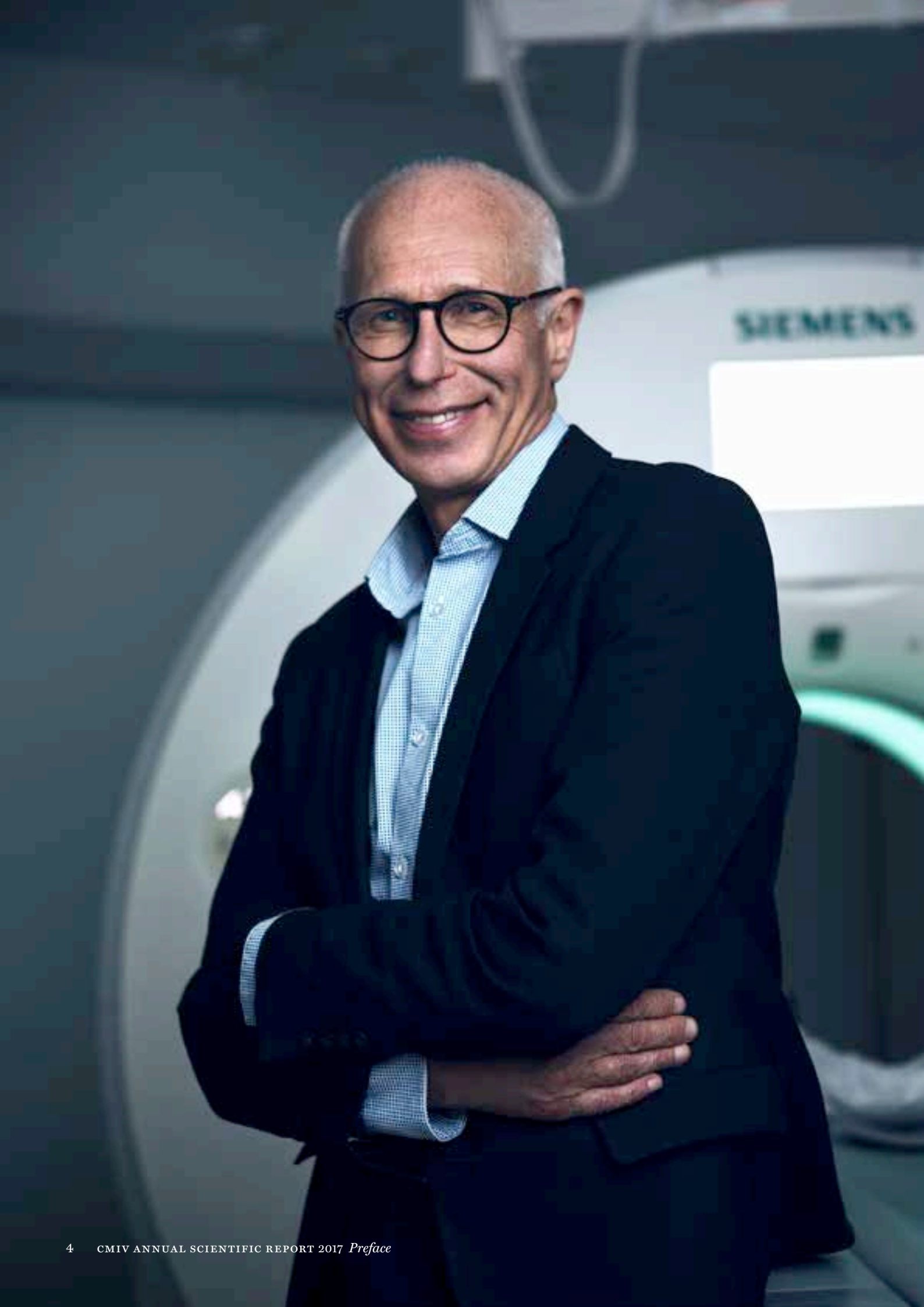

SIEMENS

Preface

Looking back at 2017 I see many amazing accomplishments, both from CMIV as a whole, as well as from individual research groups and supporting staff. CMIV continues to grow and we have welcomed quite a few new researchers and with them new exciting projects.

During the spring we started up AIDA, a national arena for artificial intelligence (AI) research in medical imaging. The arena has evolved during the year and the future is looking very promising in this field. Proposals from financiers to expand this strategic project have already been presented. The researchers, who have joined AIDA, comes from all over Sweden bringing different knowledge to the table.

The flagship projects of 2017 are complementing each other and represents CMIV well in showing different areas and how we work close to the clinic, combining technical and medical knowledge. The PRECIIS project is a national effort to bring increased precision to orthopedics in particular by bringing new radiology tools closer to the orthopedics planning and follow-up. The RTMS project is part of an international consortium striving to find new treatments for alcohol addiction using non-invasive brain stimulation. The third project develops new methods for risk assessment of carotid plaque rupture. The methods are based on visualization of plaque composition and hemodynamic effects on the vessel wall.

Our back projection VR theater "Wrannesalen" has during the year been upgraded, as one of the first installations in the world, with a newly developed 6P RGB laser projector that delivers exceptional image quality with outstanding 4K 2D & 3D images. A new sound system and the ability to record lectures and seminars in real time has been added. A feature that has been tested in the Master's Program for radiology nurses, that has been introduced at CMIV during the year.

In the beginning of the fall it was finally time for "Röntgenveckan 2017" in Linköping – the annual Swedish radiology meeting hosted by CMIV and the radiology department in Linköping and planned since two years. The meeting was a great success with approximatively 1500 participants and high class lectures.

In the past year there was a record number of dissertations at CMIV graduate school, with many theses from the radiology department.

To summarize, 2017 was yet another successful year for CMIV with excellent future-oriented interdisciplinary research that resulted in high impact publications, patient benefit and several awards during the year. All thanks to the outstanding individuals at CMIV as well as the unique twinning between medical and technical research in a clinical setting.

Anders Persson
DIRECTOR OF CMIV

Highlights

As always, a lot has happened during the past year. CMIV is continuing to grow with new researchers and projects. During 2017 there was an extra focus on meetings, both large as Röntgenveckan and smaller as the MedTech Week fitting into the Wranne theatre. Here you will find the highlights of the year.

Medtech Week

DURING MEDTECH Week 2017 CMIV hosted a talk show on how new technology can solve some of the health care challenges of today. The discussions were based on some of the most promising life science projects in the region. The talk show was a collaboration between Linköping University, Region Östergötland and the local industry.

The Kings Medal

THE SWEDISH ROYAL COURT announced on the Swedish National Day that the Professors Anders Persson and Anders Ynnerman would be awarded the kings medal of the eight size with a ribbon of the Seraphim order. They where awarded the medal for significant efforts in medical imaging. The medal ceremony was held at the Royal Castle in Stockholm.

Vetenskapens Värld

IN AN EPISODE of the scientific magazine "Vetenskapens värld" on Swedish national TV Professor Anders Persson talked about the new computed tomography(CT) tools developed by CMIV researchers to diagnose heart disease. By using modern CT methods many patients can avoid invasive procedures. These procedures are both expensive for the health care and pose a risk for the patient.

Upgrade of the Wranne Theatre

AFTER A THOROUGH procurement process the Wranne theatre was finally upgraded with a 6 laser beam backlight projector from Barco and a new glass screen. The system has 4K resolution and an advanced 3D system that ensures the high brightness level, increased contrast ratio and vivid colors needed for our medical images. The system includes a recording system with possibility to show prerecorded and live streamed lectures online.

The Wranne theatre is used for seminars, visiting groups, conferences and education. The new system will give a new dimension to our medical images. The stereo-images are an important element in the anatomy classes for medical students.

Pathology 2020

AS A CONCLUSION of the Vinnova financed project "Optimized Flows and IT Tools for Digital Pathology" a joint effort was made with the EXDIN project and the Swedish Society of Pathology to host the workshop "Pathology 2020". The workshop gathered representatives for the pathology departments all over Sweden as well as representatives for the industry and politicians to discuss how Swedish pathology should move on and evolve in one common direction with common goals. Pathology has much to gain from a national approach to standardization, data storage and shared workload. During the workshop the life science coordinator of the Swedish government Anders Lönnberg spoke about the importance of Swedish pathology coming together and creating a national plan.

AIDA

THE CMIV INITIATIVE "Analytic Imaging Diagnostic Arena" (AIDA) was awarded 11 million SEK from VINNOVA with the motivation:

"AIDA is considered to be a well-reasoned investment in implementing image diagnostics using artificial intelligence in medical care. The project is expected to have a great potential to contribute to an improvement and more personalized care and thus a better health economy."

AIDA is a national arena for research and innovation on artificial intelligence, AI, for medical image analysis. The base is in Linköping but the arena is national. Here, academia, healthcare and industry will meet to translate technical advances in AI technology into patient benefit in the form of clinically useful tools. AIDA is part of the national Strategic Innovation Program Medtech4Health, a joint initiative by VINNOVA, Formas and the Swedish Energy Agency.

CMIV Annual Conference

THE CMIV ANNUAL conference is an opportunity for the researchers to come together and discuss their research. For the PhD students it is a golden opportunity to meet senior researchers and get comments on their projects during the poster session. This year the conference was opened up for anyone interested to learn more about what is happening at CMIV and held at the university hospital instead of at a remote conference center.

The conference was introduced by Per Magnusson, research director at Diagnostic Center, Region Östergötland; Fredrik Elinder, Prodean at the Faculty of Medicine and Health Sciences and Magnus Borga, CMIV researcher and cofounder of AMRA AB, as representatives from Region Östergötland, Linköping University and the industry.

New Radiography Master Courses

DURING THE AUTUMN semester of 2017, radiography courses to be included in Bachelor's and Master's degrees were introduced by the Department of Medical and Health sciences at LiU in collaboration with CMIV. The lectures were held in the Wranne Visualization Theatre using state-of-the-art laser projection and professional recording equipment. The courses were designed to support distance learning, with lectures, demonstrations and student presentations recorded and made available via a digital learning platform. Additional courses will be introduced during the following semesters.

One of the lecturers where MR physicist and senior researcher Anders Tisell, who talked about MRI technology during the course "Technique and Methodology in Medical Image Science".

Artificial Intelligence and Deep Learning in Medical Imaging

IN OCTOBER CMIV together with Visual Sweden hosted a course in artificial intelligence and deep learning for pathologists and radiologists. The aim of the course was to give physicians more knowledge about AI for them to be able to set demands and actively take part in deciding what would make a difference in clinical practice and ultimately to participate in the development of future AI tools. It is only when we have a close collaboration between the industry and healthcare that we will see implementation of useful AI tools.

Both participants and teachers agreed on that artificial intelligence is nowhere close to replacing radiologists or pathologists, if they ever will, but has great potential to be a valuable tool in increasing efficiency and precision in patient care.

Röntgenveckan

IN SEPTEMBER it was time for Linköping to host the National Radiology Congress, Röntgenveckan. This year's congress was organized by the Radiology Department at Linköping University Hospital together with CMIV.

The theme of the week was Integrated Diagnostic. Many world leading speakers held interested keynote lectures, eg. Prof Harnsberger, Utah, Prof Krestin, Rotterdam and Prof Siegel, Maryland. With many local talents together with a big and interesting exhibition and a captivating social program the week turned out to be a great success.

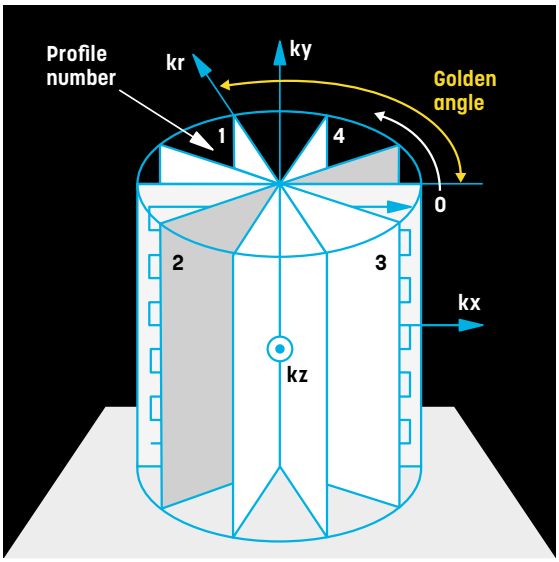
Behind the annual meeting are the Swedish Society for Radiology and the Swedish Society for Radiology Nurses.

Professor Ric Harnsberger, University of Utah.

Inauguration by Vice-Chancellor Helen Dannetun, CEO Region Östergötland Ditte Pehrsson-Lindell and County Governor Elisabeth Nilsson.

Forsell lecture by Associate Professor Sven-Göran Fransson, Region Östergötland.

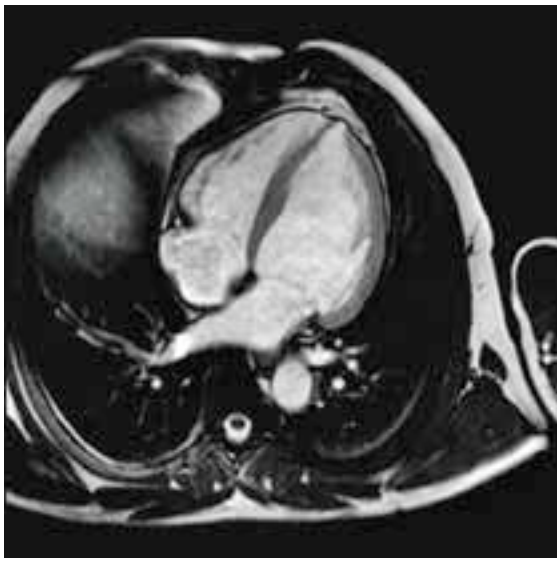
Information is gathered using novel imaging equipment.



Raw data is processed using complex calculations and algorithms.

CMIV Imaging Chain

When CMIV was initiated, the vision was to gather all the components of medical imaging and visualization in one place. At the same time a whole new type of research environment where scientists, technicians and medical doctors could work close together with immediate access to the patients would be created. A place where there was no distance between research and clinical needs. Since the start in 2002, CMIV has grown into the vision and it is now our everyday routine.



Important findings are visualized in a comprehensive way.

Images and findings are used in patient care.

Today, CMIV conducts focused front-line research within multidisciplinary projects providing solutions to tomorrow's clinical issues. The mission is to develop future methods and tools for image analysis and visualization for applications within health care and medical research.

CMIV has a unique constellation in which research at the university provides the opportunity for clinical benefit in the region while the industry benefits nationally and internationally. The activities aim to combine different demands where the university seeks publications in high quality journals and the region wishes that the research and development come to patient benefit. CMIVs organization centrally located within the university hospital creates conditions that combine these requirements. Results from basic research at universities can be utilized in clinical research, resulting in scientific publications, and better patient care.

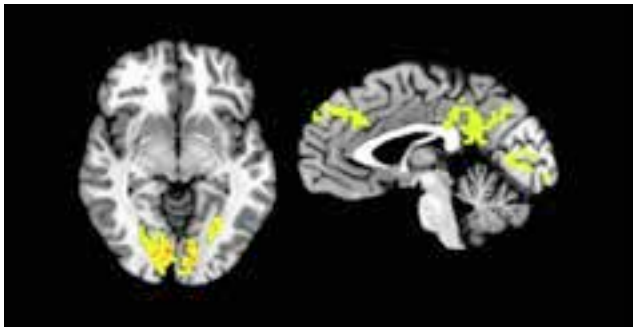
The research projects at CMIV are all part of the imaging chain. Projects move dynamically through the chain and researchers from different disciplines work together to reach the goal of patient benefit. Focused research and development in all steps of the chain is important to continue to improve quality of care. In this way a technical solution in one medical field may be found useful in other fields as well. Fitting in as it is or, moving back down the chain, inspire to new solutions no one even thought was possible. ■

Flagship Projects

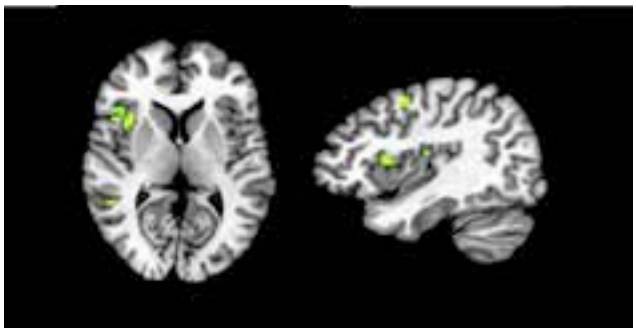
The 2017 flagship projects were elected through a faculty nomination process and from these the CMIV scientific council selected three projects that together best represent the broad and multi-disciplinary research at CMIV. They all complement each other regarding modalities, project stage and medical research area.

Effects of rTMS Targeting the Insula on Alcohol Use

Among the adult population that consumes alcohol at some level, around 10 % are having a problematic consumption. Just under half of them are considered having an alcohol addiction. Craving alcohol and an impaired ability to stop drinking despite adverse consequences are key features of alcohol addiction. This project aims to find a noninvasive brain stimulation method that can be used as treatment for addiction.



Alcoholics looking at images of alcoholic beverages vs alcoholics looking at images of non-alcoholic beverages.
We see higher activity in visual cortex/dorsal attention network when they look at the alcoholic beverages. Meaning that they are investing more attentional resources on drug related stimuli.
We expect less of a contrast in non-alcoholic people.



Alcoholics treated with TMS compared to alcoholics treated with SHAM TMS show an enhanced anterior insula activity when looking at alcoholic beverages compared to non-alcoholic beverages.
This possible suggests that the TMS treatment (controlled for placebo) reorganizes insular activity in alcoholics.

Functional imaging studies of the brain have shown that activation of the insula in response to drug cues is positively correlated with cravings. High insula activity during a simple decision-making task is associated with relapse to drug use. This is consistent with the notion that disrupted insula function contributes to impaired decision making, resulting in continued drug use despite negative consequences.

For example, chronic cocaine users have been shown to have grey matter loss in the insula. Similar reductions in insular volume and cortical thickness have been reported in alcoholics. Modulation of insula activity may therefore represent a novel therapeutic approach in addiction.

Irene Perini is one of the researchers in the project. She has a background in neuropsychology and neurophysiology research with MRI as the primary tool.

– We are interested in the insula because it has been shown that lesions in this area reduce craving for drugs. The insula is involved in processing the internal states of the body. It is processing the way we feel, Irene explains.

However, non-invasive methods to modulate the activity of this structure have not been availible until recently.

A small pilot study suggested that repetitive transcranial magnetic stimulation (rTMS), a non-invasive tool for neuromodulation, can reduce craving and cue reactivity in cocaine and opiate users.

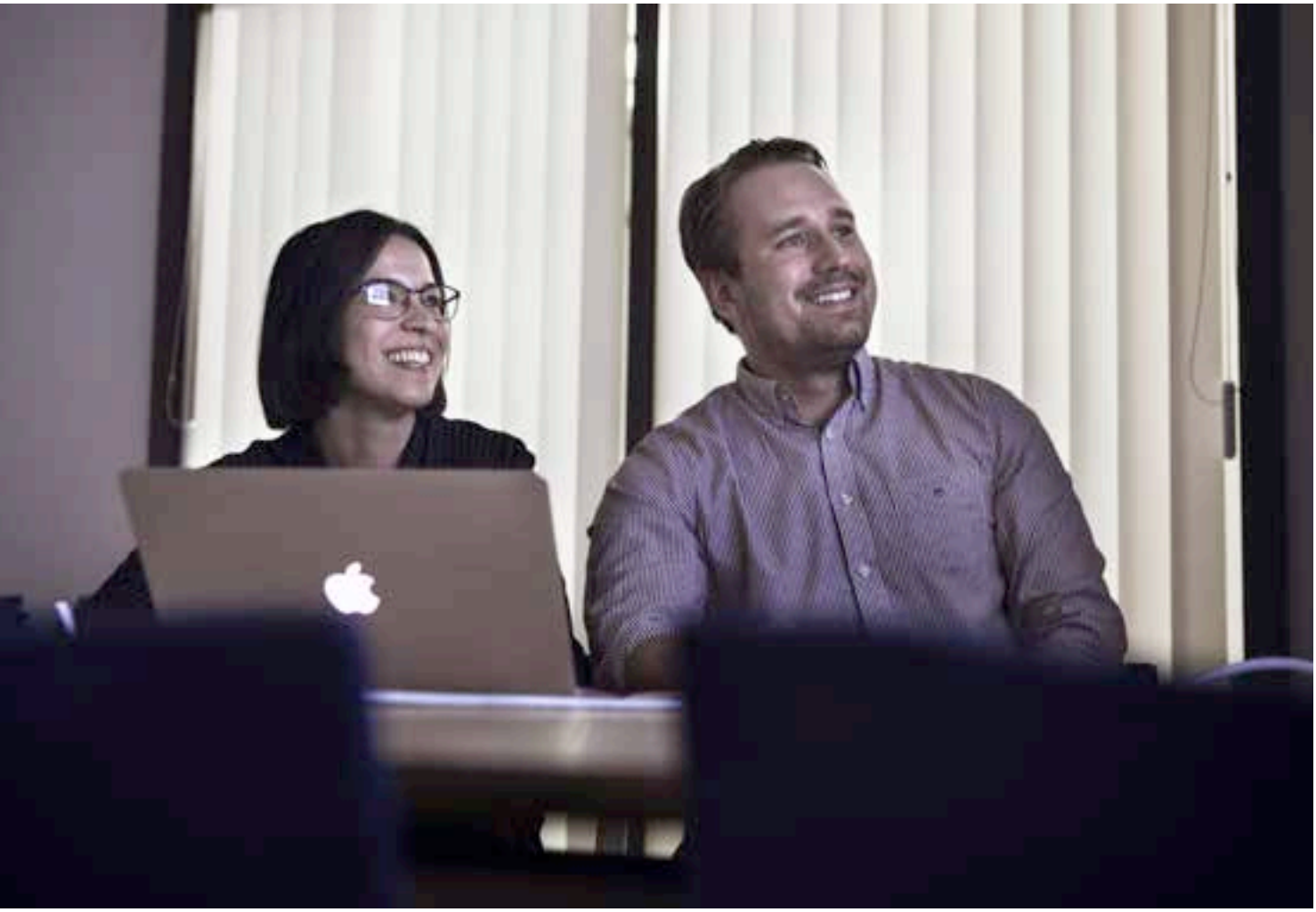
– The idea is to alter the activity in the insula to see how this is going to impact their behavior. With rTMS you can excite the brain activity or inhibit the activity depending on the frequency you use, Irene says.

In these studies, rTMS has typically been applied to a superficial structure of the brain. However, the insula is located deeper into the brain and therefore no study has to date evaluated whether modulation of insula activity using rTMS would reduce alcohol craving and use. The present study uses a novel coil, designed to allow "deep TMS", to examine whether stimulation of the insula offers a novel alcoholism treatment.

– The objectives of the project are to investigate the effects of rTMS targeting the insula on alcohol use and neural responses in alcohol-dependent patients, Irene continues.

The project is part of a bigger international consortium with 11 other partners. In Israel one of the partners is doing the same study but with another brain area.

The study population consists of treatment seeking alcohol dependent subjects, who have first completed standard alcohol withdrawal treatment if needed. The participants first undergo an MRI scan to collect resting state, DTI and structural data, and then



"It is very motivating to work with research that is directly aimed at helping the patients"

Irene Perini

receive one of two treatments: Active (10Hz) rTMS; or sham stimulation, both targeting the insula bilaterally. rTMS sessions will be conducted five times per week, for 3 weeks, for a total of 15 sessions. A second MRI scan is obtained at the end of the treatment phase to assess changes in resting state connectivity, and to evaluate insula activity in tasks known to activate this structure.

The primary outcome measures are alcohol consumption during the follow-up phase and insula fMRI responses during tasks known to induce insula activation. A number of secondary and exploratory measures are also assessed, including objective biomarkers of alcohol consumption.

– Coming from basic research, I have never worked with clinicians before. Now we work with clinicians in every project. That has been an insight for me. Thanks to this relationship between research and clinic work we get access to and help with recruiting the patients. It is very motivating to work with research that is directly aimed at helping the patients, Irene concludes. ■

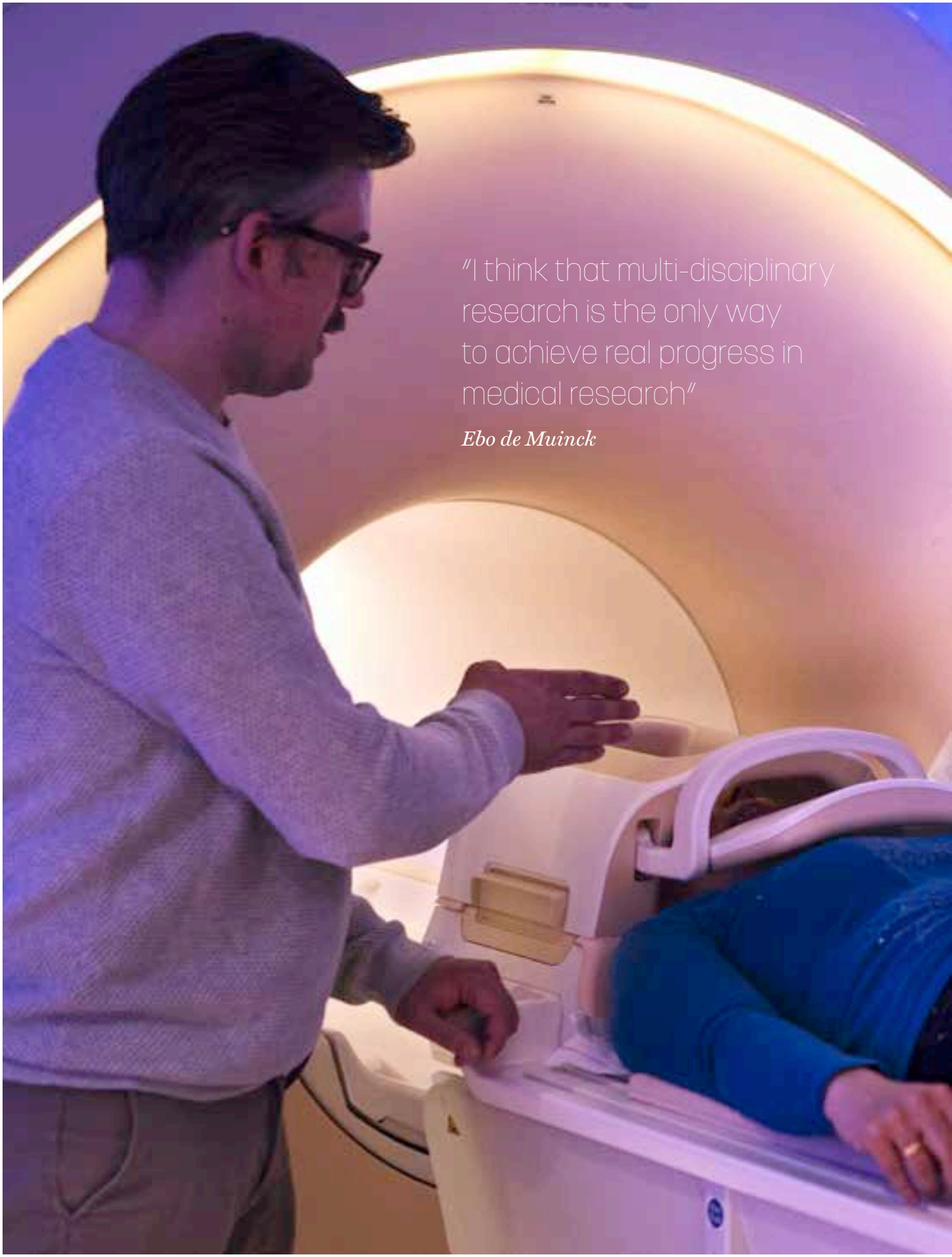
PROJECT INFORMATION

Project Name
Effects of repetitive transcranial magnetic stimulation (rTMS) targeting the insula on alcohol use and neural responses in alcohol-dependent patients

Project Leader
Markus Heilig, Department of Clinical and Experimental Medicine, Center for Social and Affective Neuroscience

Main Project Participants
Irene Perini, Andreas Löfberg, Hanna Karlsson, Paul Hamilton, Robin Kämpe, Åsa Axén

Grants
The Swedish Medical Research Council
EU-funded Horizon 2020 project SyBil-AA


"I think that multi-disciplinary research is the only way to achieve real progress in medical research"
Ebo de Muinck

Carotid Plaque Assessment

Worldwide, the most common cause of death is cardiovascular disease and the dominant cause of cardiovascular disease is atherosclerosis. Individuals with an atherosclerotic plaque in the carotid have an increased risk of future heart attack, stroke and cardiovascular death. This project develops new methods for improved identification of carotide plaques that are associated with increased cardiovascular risk. To this end it combines quantitative magnetic resonance imaging (MRI) of plaque composition with blood flow parameters.

Atherosclerosis is caused by accumulation of fat, primarily cholesterol in the wall of arteries. When the fat builds up in the arterial wall it causes thickening of the vessel wall and the thickened area bulges out into the vessel. These thickened areas are called atherosclerotic plaques.

Strokes resulting from blood clots that migrate to the brain from plaque in the carotids cause 2.5 % of all deaths. Today, plaques that cause more than 70 % constriction of the carotid in stroke patients are removed surgically to avoid future strokes. The hypothesis is that the blood clots are formed when the plaque surface rupture.

Professor Ebo de Muinck is a cardiologist with experience from combining clinical work with cardiovascular research and one of the project leaders behind the project.

– The composition of the plaque is affecting the rupture risk. Plaque with a large amount of fat and blood are more prone to rupture, Ebo explains.

However, studies show that only half of the removed plaques have ruptured. Also, removing the plaque is far from a complete safe guard against future stroke.

– We believe that the blood flow around the plaque also is an important factor for the development of blood clots. If there is a turbulent flow, blood clots could form despite an intact plaque surface.

Unfortunately, current clinical tools are insensitive to these effects. Consequently, there is a clear and urgent need to improve carotid plaque assessment in order to more accurately assess risk of progression and rupture in patients as well as to improve risk management in patients with carotid plaques.

– In this project we aim to improve carotid plaque risk assessment both for better assessment of overall cardiovascular risk and for better decision support in which patients will benefit from surgery, Ebo continues.

The project will develop tools for automated visualization and quantification of carotid plaque composition and hemodynamic effects on the vessel wall. This will be achieved by combining advanced quantitative magnetic resonance imaging methods with novel image analysis.

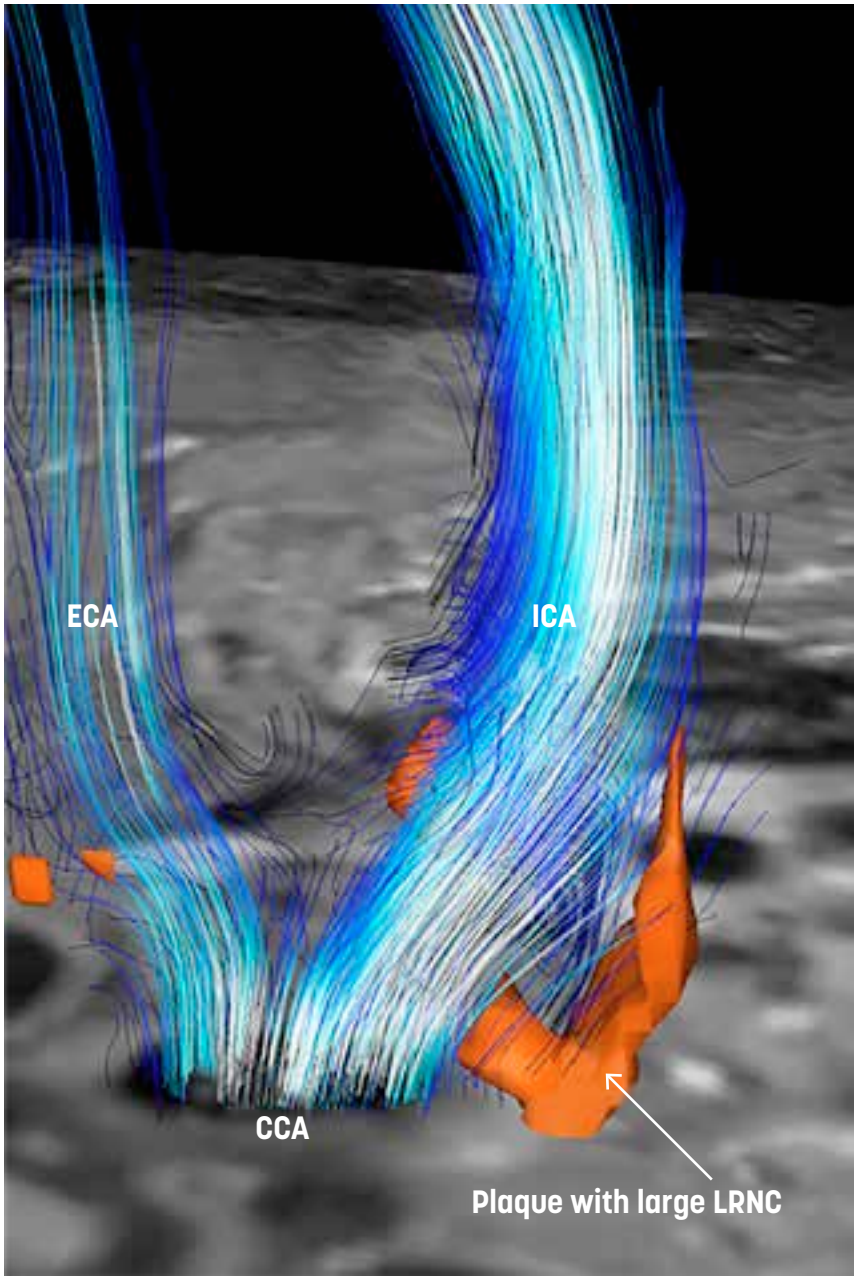
– In this way, we will automatically identify plaque severity based on the extent of fat and blood within the plaque. Similarly, we will provide assessment of impact of turbulent flow on the vessel wall.

The methods will be evaluated in patients with carotid atherosclerotic plaques to optimize and establish the reliability of the technical developments in a clinical setting.

– We have two study groups, one smaller patient group with high risk carotid plaque and one larger group with volunteers from the SCAPIS population, not previously treated for cardiovascular symptoms.

The different approaches to cardiovascular risk management will be explored in patients with carotid plaques and serial imaging with the new imaging methods will be used to assess the effect of these different interventions on key risk factors.

Successful implementation of the project will enable new approaches for risk stratifying carotid plaques clinically and improved cardiovascular risk management. This will not only improve the selection of patients for



preventive care and surgery, but also, through improved management, reduce healthcare costs.

Ebo started off as a cardiologist and researcher with interests in imaging methods in the Netherlands and after eight years at Dartmouth Medical School in New Hampshire as a researcher he came back to Europe. CMIV was a contributing factor in choosing Linköping.

– I think that multi-disciplinary research is the only way to achieve real progress in medical research. But it requires that all team members are willing to move beyond their 'comfort zone' and are willing to work in areas where not they but other team members are the experts. This requires humility, patience and courage. ■

FIGURE. Joint visualization of quantitative fat (orange) MRI data using the proposed method and blood flow (blue/white) where whiter color indicates higher velocities. Arrow: A high-risk plaque with a large lipid-rich necrotic core (LRNC) is clearly visualized in the carotid sinus. CCA, ECA, ICA = common, external and internal carotid artery.

PROJECT INFORMATION

Project Name
Carotid plaque assessment

Project Leader
Petter Dyverfeldt, Department of Medical and Health Sciences, Division of Cardiovascular Medicine
Ebo de Muinck, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

Main Project Participants
Toste Länne, Miguel Ochoa Figueroa, Marcel Warntjes, Sandeep Koppal, Magnus Ziegler, Elin Good

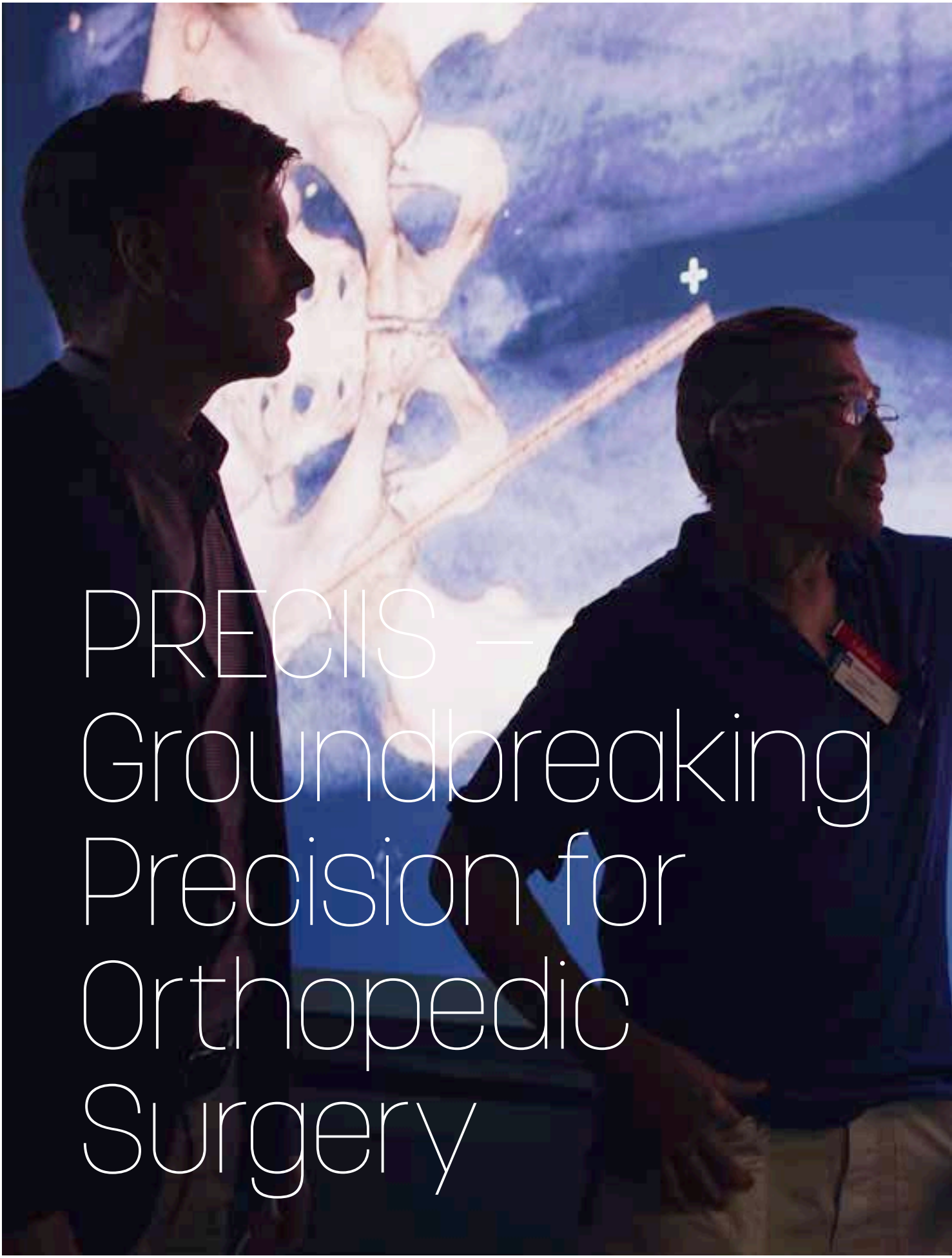
Grants
Swedish Research Council (2014–2017, 2018–2021)

Key publications

Koppal S, Wratjes M, Swann J, Dyverfeldt P, Kihlberg J, Moreno R, Magee D, Roberts N, Zachrisson H, Forssell C, Länne T, Treanor D, de Muinck E.
Quantitative Fat and R2* Mapping In-Vivo to Measure Lipid-Rich Necrotic Core and Intraplaque Hemorrhage in Carotid Atherosclerosis. Magnetic Resonance in Medicine 2017; 78(1):285-96.

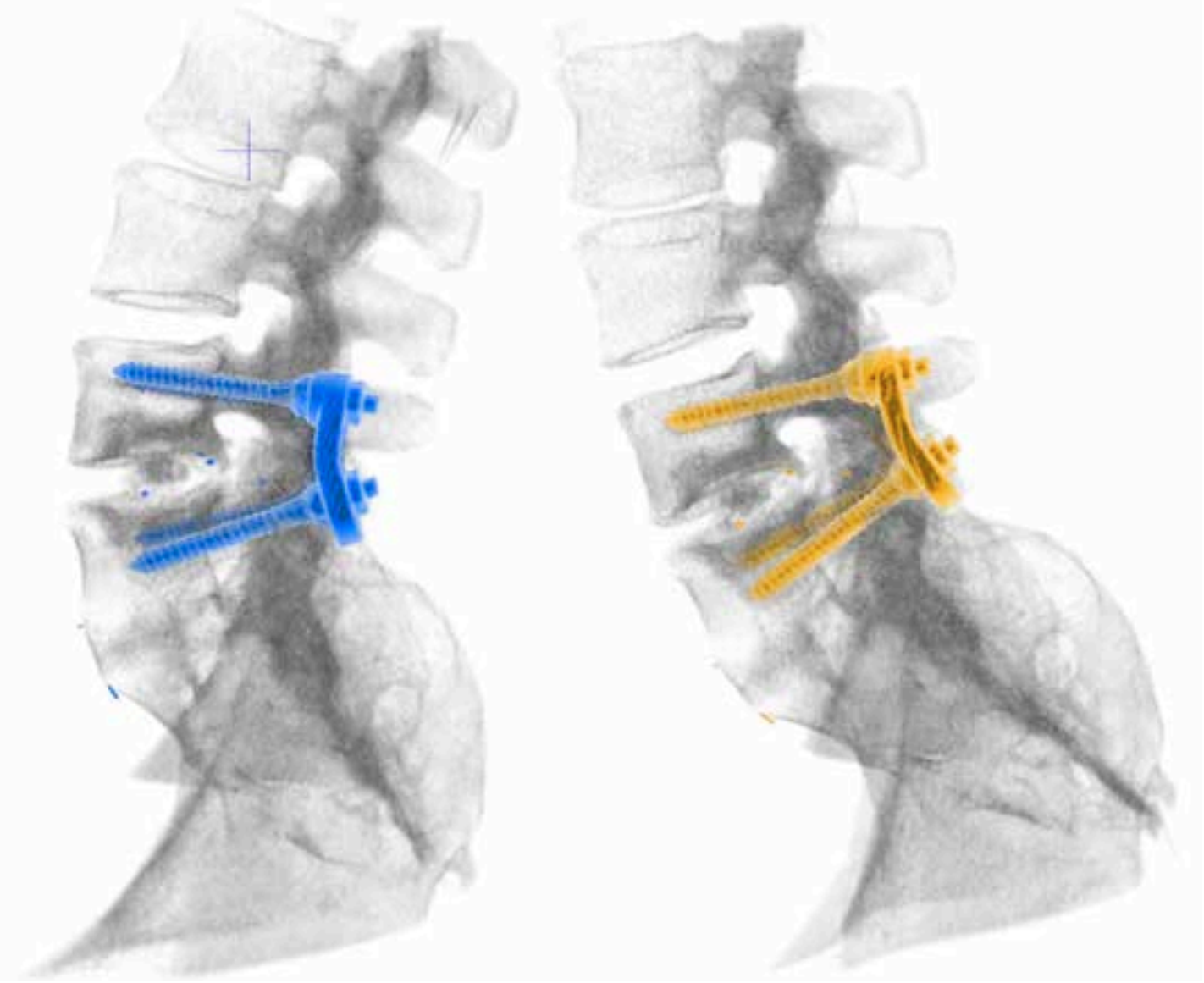
Ziegler M, Lantz J, Ebbers T, Dyverfeldt P.
Assessment of Turbulent Flow Effects on the Vessel Wall using 4D Flow MRI.
Magn Reson Med 2017; 77(6):2310-9.

Good E, Länne T, Wilhelm E, Perk J, Jaarsma T, de Muinck E
High-grade carotid artery stenosis: A forgotten area in cardiovascular risk management.
European journal of preventive cardiology 2016; 23(13):1453-60.



PRECIIS – Groundbreaking Precision for Orthopedic Surgery

Orthopedic surgery is a heavy health economy factor in Sweden and across the globe. This project aims towards significantly better outcomes and patient safety at a significantly lower cost, through ground-breaking improvement of precision in orthopedic surgery. Higher precision is necessary to meet strong healthcare needs: less invasive surgery, more individualized care, earlier detection of complications and more efficient resource use in the surgical workflow.



The need of implant surgery is increasing, partly due to the ageing population, partly due to increasing patient demands on mobility. There are, however, quality issues in orthopedics; in Sweden, for instance, care-related injuries occur at 15 % of the procedures leading to an additional healthcare cost of >1 billion SEK/year.

In this project a portfolio of innovations providing ground-breaking precision improvements will be developed and validated in a close collaboration between industry, healthcare and academia. The project consortium consists of 14 organizations within these three sectors, where Sectra is the project coordinator and together with CMIV run the overall project management.

Solutions will be developed in five tracks, implant movement, patient movement, implant logistics, 3D print and pre-per-post integration, where CMIV primarily will be involved in patient movement and pre-per-post integration. Finally, the project also contains a sixth track that will ensure a patient-centric view on innovation requirements, and that will work towards making the increased precision a professional norm in orthopedics.

Finding the source of a mobility problem can be difficult. More advanced diagnostic methods would be of great use, as there are many treatment options in surgery and physical therapy when you know what the cause is. The patient movement project develops a detailed analysis suitable for clinical routine based on combining CT images with camera-based motion capture technology, as well as time-resolved CT.

Hans Tropp, an orthopedic surgeon since 1990 with long experience of research in movement analysis, is project manager in the subproject.

– I have always tried to solve orthopedic problems with biomechanical methods. If you consider the movement you will get much better results in orthopedics.

In this project a CT image of the patient's joint is combined with a movement analysis of the patient.

– In this way we can visualize how the patient moves and how the joints are adjusting to compensate for the injury. We can study what part of the joint that is provoked when the patient feels pain.

The project is a collaboration between the orthopedic clinic in Linköping, Sectra and Qualisys.

– For me, it is very important that there are engineers in the project who

"For me, it is very important that there are engineers in the project who are interested in clinical problems"

Hans Tropp

are interested in clinical problems.

The subprojects in Preciis benefit from each other.

– The Preciis subprojects are so close to each other that spinoff effects are constantly being created. As an example, we can use the 3D print project to create a model from the CT images to validate our method, both the software and the method as a whole.

Traditionally, the orthopedic surgeon's workflow for physical material (the implants) has been separated from the handling of digital images. A cornerstone here is to amalgamate these two areas, so that new innovative solutions can be created based on seamless couplings between digital and physical counterparts. Great opportunities are provided by modern imaging technology, which until now has not reached its full potential in orthopedic applications.

– There is a focus on production in orthopedics and often there is not much evaluation of the patient's problems available beforehand leading to more or less guessing about what the problem is. Developing methods that can diagnose and visualize patient problems are really quite important, Hans explains.

Bringing the orthopedic and radiology departments closer together is of great importance for these kinds of initiatives to thrive.

– I think it would be best to have the radiologists on board from the beginning. In fact, I would like to collaborate with a dedicated radiologist, who does the image review in the same way as you have a thoracic radiologist working with the heart specialists, Hans concludes. ■

PROJECT INFORMATION

Project Name
PRECIIS – Groundbreaking precision for orthopedic surgery

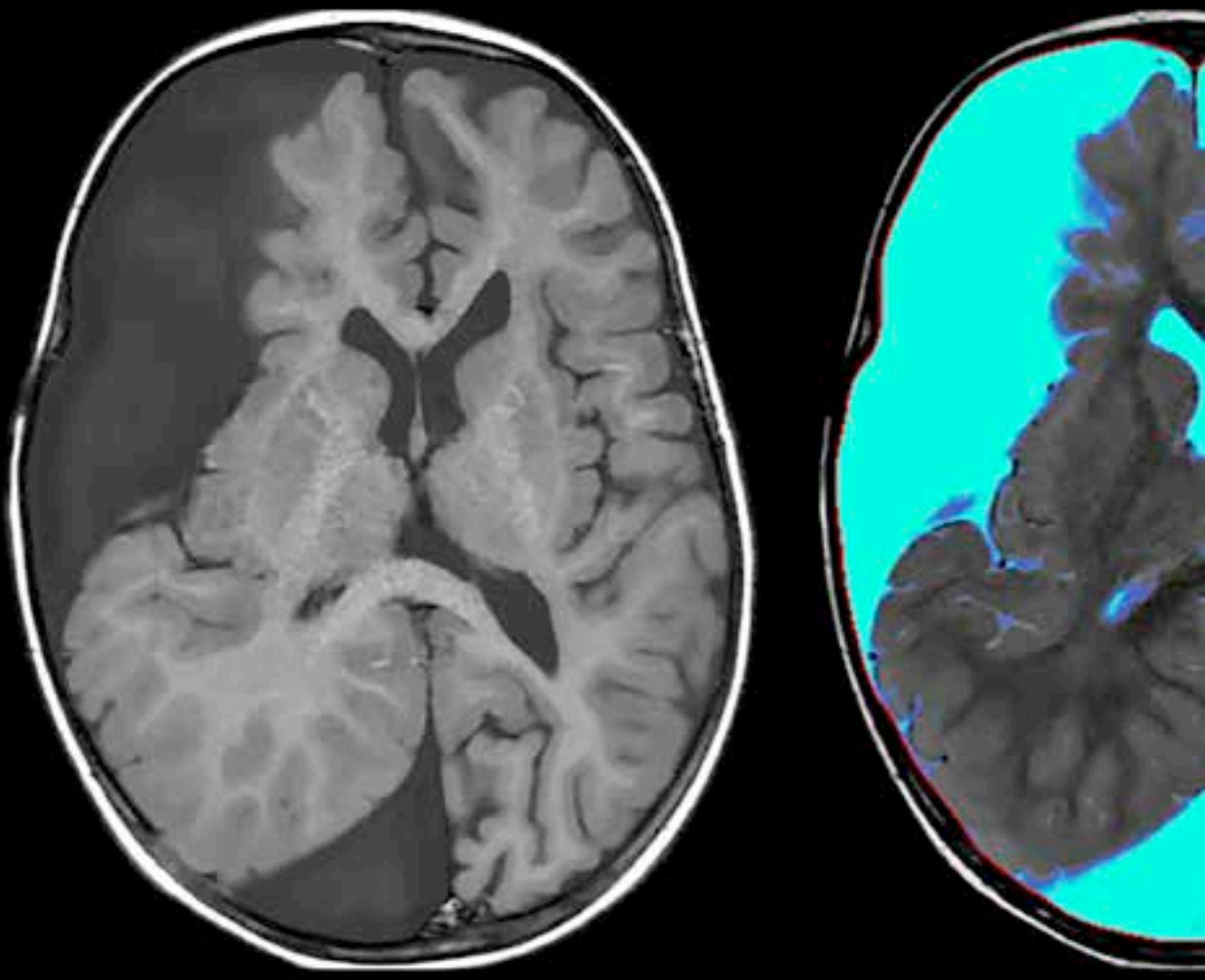
Project Leader
Claes Lundström, Department of Science and Technology, Division of Media and Information Technology

Main Project Participants
Erik Sundén, Daniel Jönsson, Hans Tropp, Håkan Gauffin, Anders Persson, Marie Waltersson, Joanna Kvist, Olof Sandberg, Stefan Lindholm, Ulrica Vach

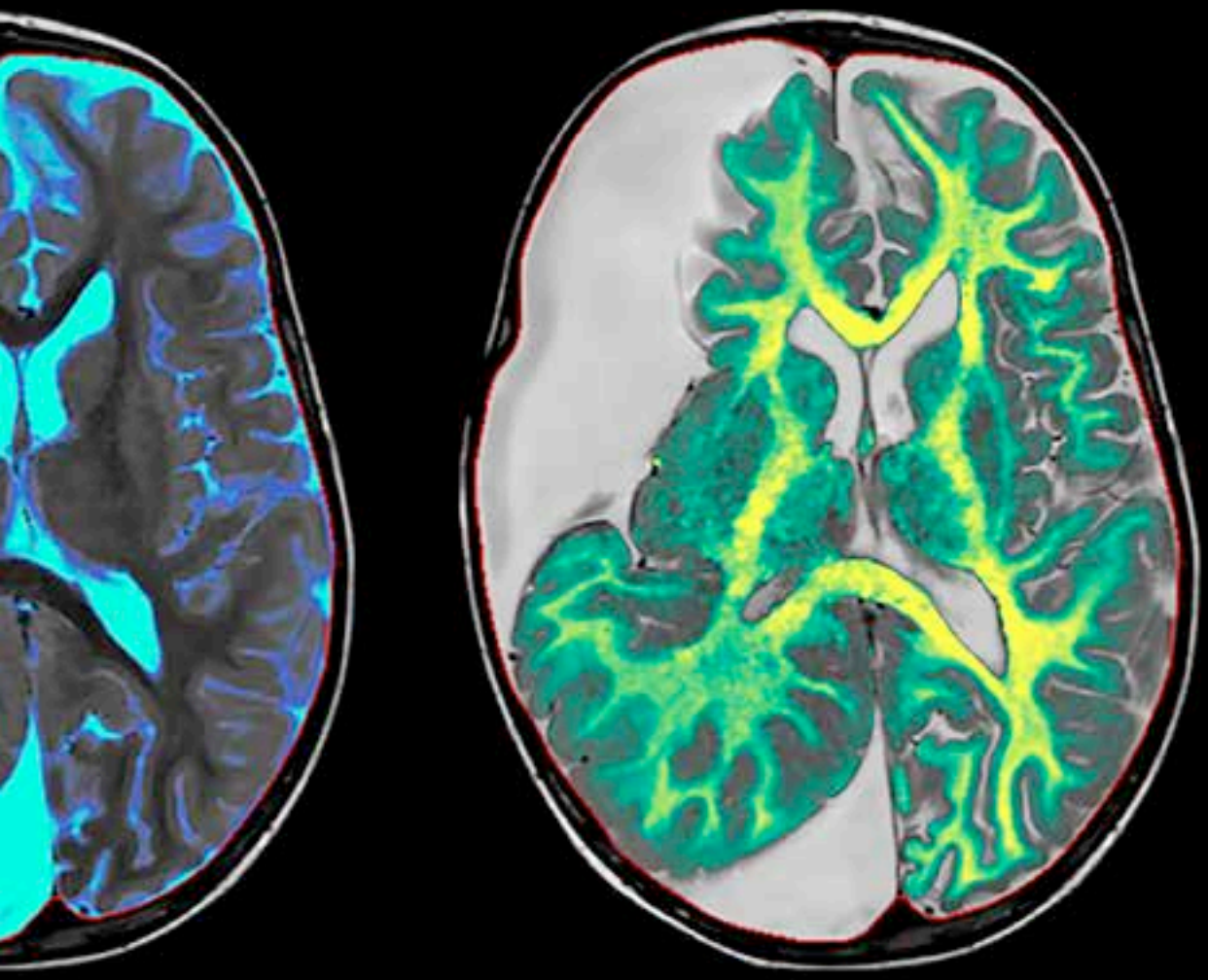
The project consortium also includes the following organizations: Sectra, Ortopedikliniken Region Östergötland, Ortopedikliniken Karolinska Sjukhuset, Capio Movement, Ortopedkliniken Danderyds sjukhus, Ortopediavdelningen Sahlgrenska Universitetssjukhuset, Ortopedikliniken Uddevalla Sjukhus, Landstingens Ömsesidiga Försäkringsbolag, Reumatikerförbundet, Zimmer Biomet Sweden, Wematter, Qualisys, OssDsign

Grants
Vinnova 2017–18

Key publications
Anterior Spinal Overgrowth is the Result of the Scoliotic Mechanism and is Located in the Disc, Brink et al. (incl Hans Tropp, Ludvig Vavruch, and Marcus Malmqvist), Spine 2017.



Research Projects



The research within CMIV is based on innovations in medical image science and visualization. Future directions will strengthen the interdisciplinary approach to enhance the possibilities of image-based diagnosis and treatment. At CMIV research is conducted within several medical problem areas, combining a number of technologies for new application within clinical routine, medical research and dissemination of information. Here you will find a selection of the research projects at CMIV.

PROJECT INFORMATION

Project Name
Seeing Organ Function

Project Leader
Anders Ynnerman, Department of Science and Technology, Division for Media and Information Technology

Main Project Participants
Anders Ynnerman, Magnus Borga, Tino Ebbers, Maria Engström, Markus Heilig, Ingrid Hotz, Matts Karlsson, Hans Knutsson, Peter Lundberg, Anders Persson, Karin Wårdell

Grants
KAW

Key Publications
Sebastian Sten, Karin Lundengård, Suzanne T Witt, Gunnar Cedersund, Fredrik Elinder, and Maria Engström. »Neural inhibition can explain negative BOLD responses: A mechanistic modelling and fMRI study.« NeuroImage, 2017;158:219–231.

Snehlata Shakya, Nazre Batool, Evren Özarslan, and Hans Knutsson. »Multi-Fiber Reconstruction Using Probabilistic Mixture Models for Diffusion MRI Examinations of the Brain« Modeling, Analysis, and Visualization of Anisotropy. Springer, Cham, 2017. 283–308.

Jönsson, Daniel, and Anders Ynnerman. »Correlated Photon Mapping for Interactive Global Illumination of Time-Varying Volumetric Data.« IEEE Transactions on Visualization and Computer Graphics 23, no. 1 (2017): 901–910.

POPULAR SCIENTIFIC SUMMARY

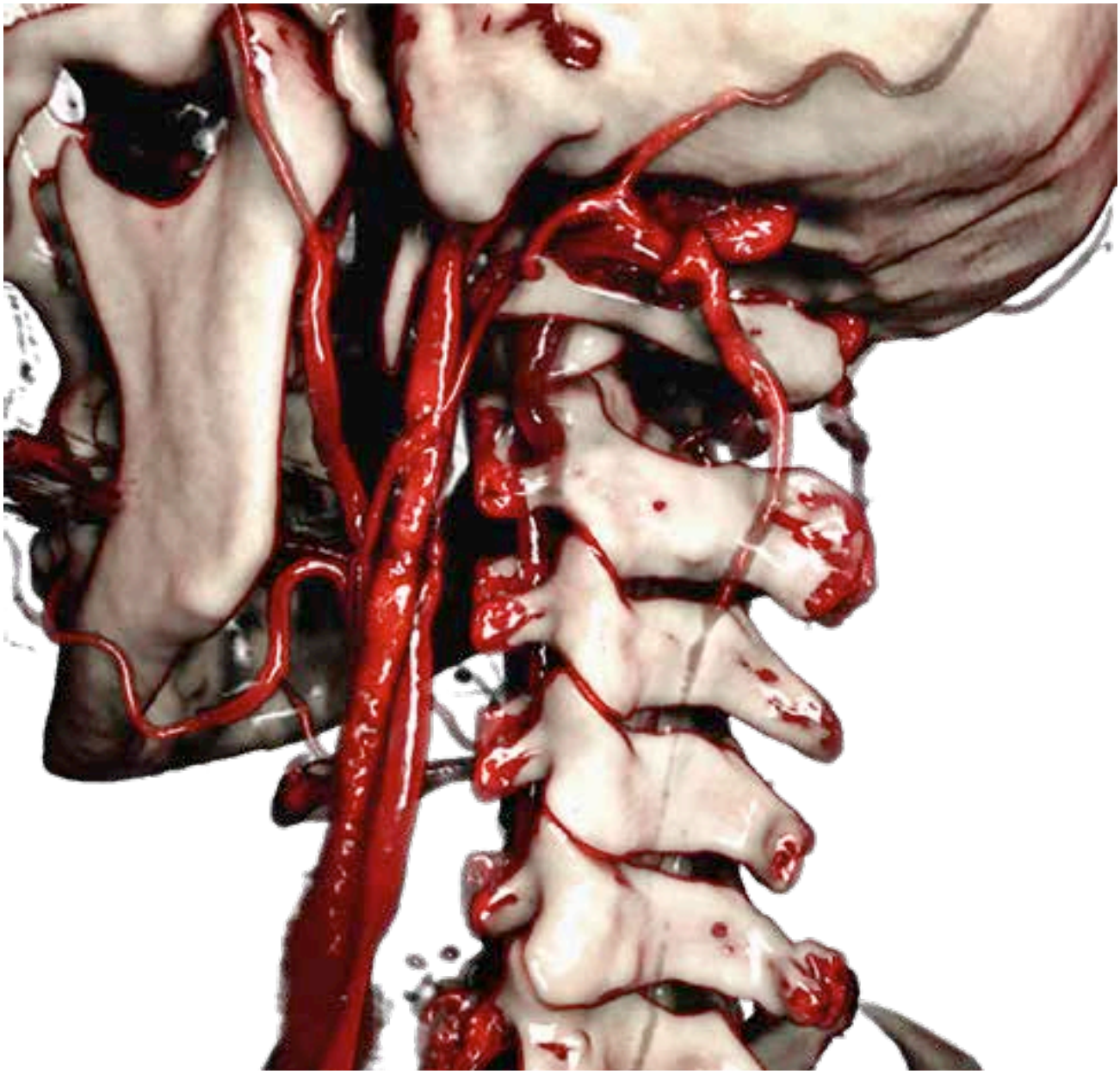
ANDERS YNNERMAN

Seeing Organ Function

The main cause of death in our part of the world is cardiovascular disease and the fastest growing cause of death is degenerative brain diseases. In this project, we hope to contribute to the health care fight against these diseases. The goal is to create image-based patient-specific models that explore organ function through simulation, enable breakthroughs in research on organ function and to use patient-specific functional organ models in the diagnostic workflow.

In the diagnosis of cardiovascular diseases anatomical measurement of arterial constriction may be supplemented with patient-specific estimates of the constriction effects on blood pressure and flow. Simulation and MRI Measurements of the three-dimensional blood flow provide a deeper insight into disease mechanisms in e.g. heart failure.

Diagnosis of degenerative brain diseases require the centers controlling brain functions, and the connections between them, to be localized. New MRI techniques can provide this infor-



mation and also provide the basis for image-based measurement of disease severity in e.g. Alzheimer's disease.

This project focus on the heart and the brain since they are two of the most vital organs in the human body. Different types of functional imaging are progressively complementing the traditional imaging for both these organs, and there is strong medical motivation for accelerating this progress. The Seeing organ function project takes on the urgent task of developing new methods to capture, process and present this rich functional information.

The project finances several Postdocs with different technical background, all working on parts of the research agenda. Here, CMIV provides the perfect environment for such a project as it brings together expertise ranging from medicine, over medical visualization to image analysis and biomedical engineering. All the research teams have worked together in multidisciplinary projects for a long time which is of great advantage.

Using image-based heart models it is now possible to simulate patient-specific blood flow in the heart with an incredibly high resolution. 3D visualization of the blood flow and the possibility for interaction provides completely new insights into the functionality of the heart.

Progress, can also be seen in the analysis of the electrical activity of brain cells fusing data of different types from various image sources or using novel mathematical models to reconstruct neuronal fibers from diffusion imaging data. ■

PROJECT INFORMATION

Project Name
Clinical Implementation of Synthetic MRI

Project Leader
Marcel Warntjes, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

Main Project Participants
Ida Blystad, Stefan Tell, Peter Lundberg, Maria Engström, Tino Ebbers, Ebo de Muinck, Peter Johansson, Elna-Marie Larsson, Tobias Granberg, Wolf Zech

Key Publications
Quantitative MRI for analysis of peritumoral edema in malignant gliomas. Blystad I, Warntjes JBM, Smedby Ö, Lundberg P, Larsson EM, Tisell A. PLoS One. 2017 May 23;12(5):e0177135.

Myelin Detection Using Rapid Quantitative MR Imaging Correlated to Macroscopically Registered Luxol Fast Blue-Stained Brain Specimens. Warntjes JBM, Persson A, Berge J, Zech W. AJNR Am J Neuroradiol. 2017 Jun;38(6):1096–1102.

Rapid Magnetic Resonance Quantification on the brain: Optimization for Clinical Usage. JBM Warntjes, O Dahlqvist Leinhard, J West and P Lundberg. MagnReson Med 2008;60:320–329.

POPULAR SCIENTIFIC SUMMARY

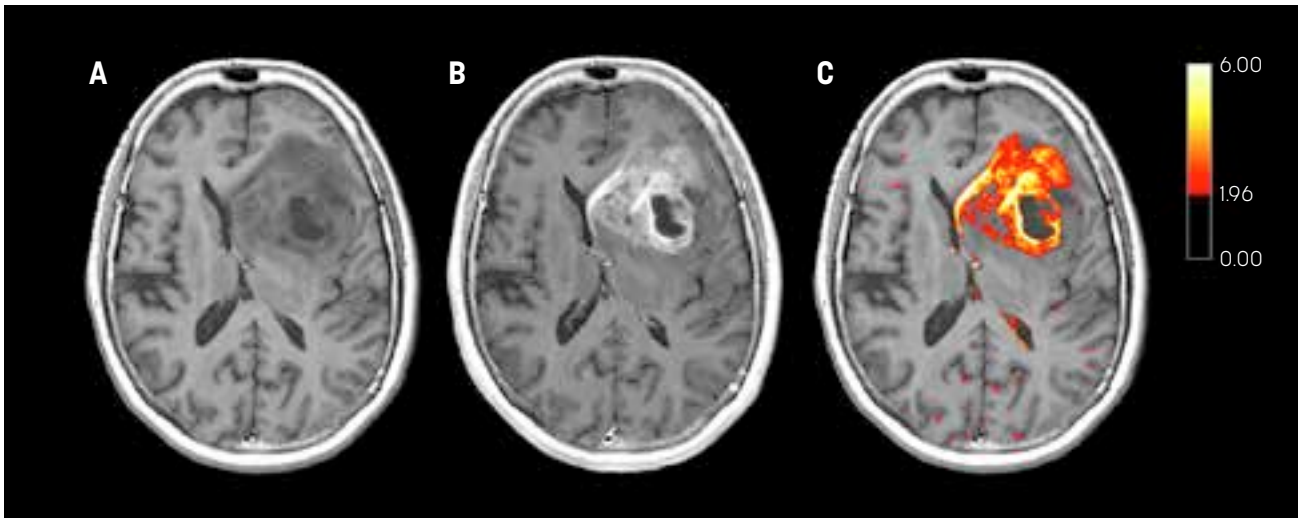
MARCEL WARNTJES

Clinical Implementation of Synthetic MRI

Synthetic MRI is a technique to quantify physical properties of a patient using Magnetic Resonance Imaging (MRI). Based on these physical properties a range of conventional MR images can be recreated as well as tissue can be recognized and assessed automatically. This means that a relatively short scan time of 5–7 minutes is sufficient to reproduce a large part of a normal MR examination and, additionally, to provide more objective means of patient follow-up.

A close collaboration between researchers at CMIV and the university hospitals in Linköping, Umeå, Örebro, Uppsala and Göteborg ensured the clinical relevance of the technique. A number of technical and clinical studies were performed to validate the various aspects of synthetic MRI on scan time reduction and automatic brain segmentation. A spin-off company, SyntheticMR AB, was created to ensure an installable, safe product including the necessary regulatory requirements. After this initial prototype phase more hospitals have been involved, among which a number in the EU, US and Japan to introduce synthetic MRI as a standard procedure into the clinical workflow.

All major MR vendors, GE Healthcare, Philips Healthcare and Siemens



Example of synthetic MRI on a glioma patient, showing a T1W axial slice before and after administration of Gadolinium contrast media. The difference, caused by leakage of Gd through the blood-brain-barrier can be measured in absolute numbers, expressed as significance on the right side. These measurements can result in more objective assessment of the patients.

Healthineers now offer synthetic MRI as part of their product, based on the CMIV spin-off. More and more hospitals are starting to get familiar with the technique. An increasing number of clinical projects are ongoing to validate the time reduction on the MR scanner and to assess the robustness of the technique on diseases such as Multiple Sclerosis, hydrocephalus, cancer and dementia in clinical practice.

A unique feature of synthetic MRI is the possibility to measure myelin in the brain, an important biomarker for the health of the nervous system. A study on 12 human cadavers was performed at CMIV to validate this method. A large study was conducted at the Cincinnati Children's Hospital where myelin was measured in 120 healthy children to obtain a reference developmental curve for the age 0–20 years old. Synthetic MRI is also tested on other applications such as bone metastases, cartilage assessment, automatic detection of gliomas and assessment of plaque vulnerability. A major breakthrough worked on currently is the development of a 3D version of the sequence allowing high resolution images in three planes simultaneously.

In the history of MRI general images were acquired which were then subjectively interpreted by radiologists. With the advent of synthetic MRI we believe that this is going to change dramatically: Scan times will be shorter and the decision support will be more based on numbers and statistics.

Automated analysis can make the work of the radiologist both faster and more objective. The technique is available on the major scanner brands, which will decrease the variation between different hospitals. Synthetic MRI is a clear example of excellent cooperation between universities, hospitals and commercial companies, made possible by CMIV. ■

PROJECT INFORMATION

Project Name
Assessment of cardiovascular blood flow using 4D flow MRI

Project Leader
Tino Ebbers, Department of Medical and Health Sciences, Division of Cardiovascular Medicine & Department of Science and Technology

Main Project Participants
Tino Ebbers, Carl-Johan Carlhäll, Jan Engvall, Petter Dyverfeldt, Jonas Lantz, Merih Cibis, Hojin Ha, Belén Casas Garcia, Mariana Bustamante, Federica Viola, Magnus Ziegler, Jakub Zajac, Alexandru Fredriksson

Grants
Swedish Research Council 2011–2013
European Research Council 2013–2017

Key Publications
Ha H, Lantz J, Ziegler M, Casas B, Karlsson M, Dyverfeldt P, Ebbers T. Estimating the irreversible pressure drop across a stenosis by quantifying turbulence production using 4D Flow MRI. Scientific Reports 2017;7:46618.

Eriksson J, Zajac J, Alehagen U, Bolger AF, Ebbers T, Carlhäll C-J. Left ventricular hemodynamic forces as a marker of mechanical dyssynchrony in heart failure patients with left bundle branch block. Scientific Reports 2017;7:2791.

Dyverfeldt P, Bissell M, Barker AJ, Bolger AF, Carlhäll CJ, Ebbers T, Francois CJ, Frydrychowicz A, Geiger J, Giese D, Hope MD, Kilner P, Kozerke S, Myerson S, Neubauer S, Wieben O, Markl M. 4D Flow CMR Consensus Statement. J Cardiovasc Magn Reson 2015; 17:174.

POPULAR SCIENTIFIC SUMMARY

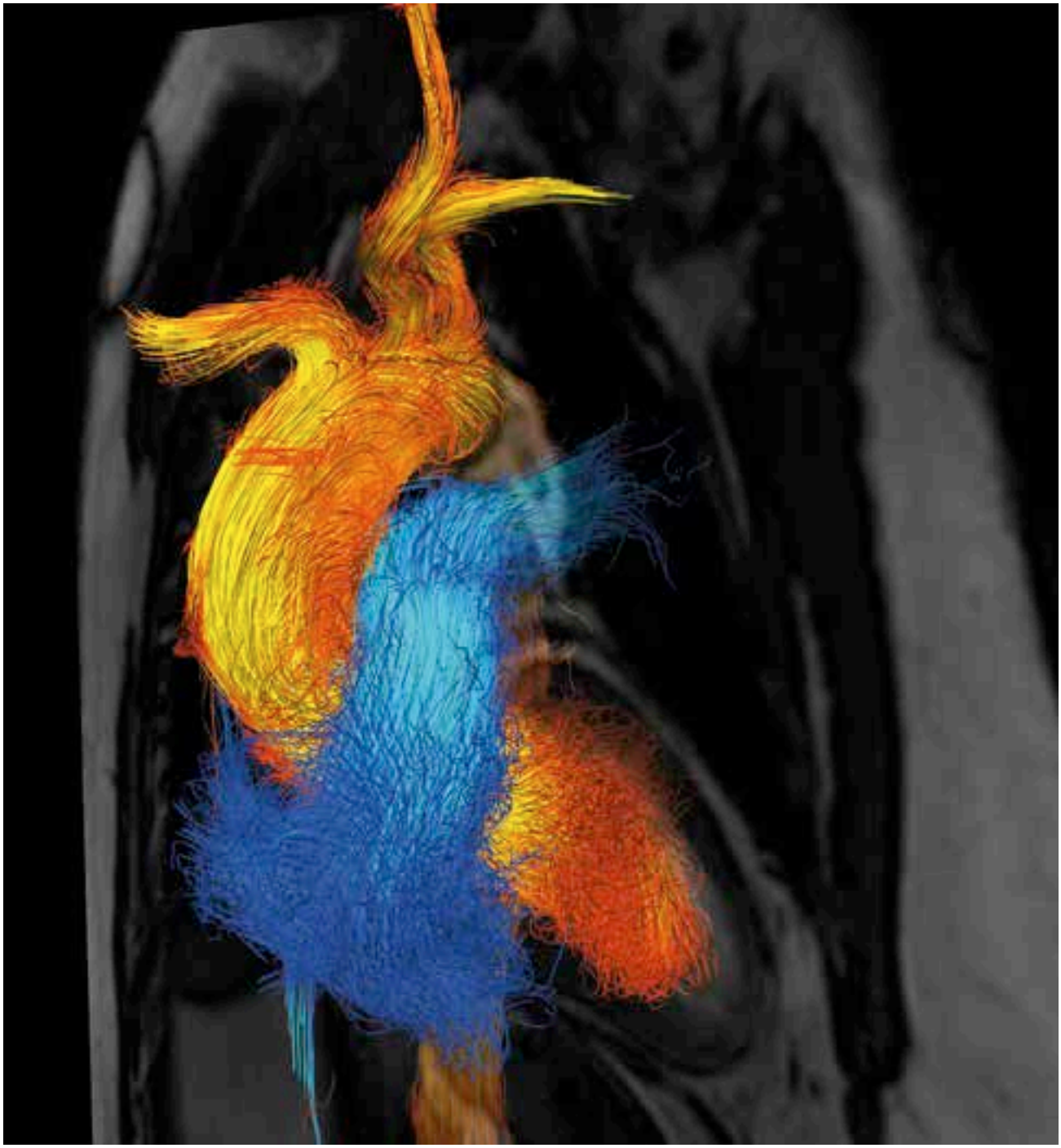
TINO EBBERS

Assessment of Cardiovascular Blood Flow Using 4D Flow MRI

The primary purpose of the cardiovascular system is to drive, control and maintain blood flow to all parts of the body. The heart acts as the pump in this system, and has as task to move blood through the body. Using a complex and ingenious interplay between muscle contraction and valve function, it fulfills this task amazingly efficient during rest and exercise for about a hundred years.

Sometimes small abnormalities occur at birth or by disease, cardiovascular diseases are often found in obesity, diabetes and an aging population. The heart can compensate for these to some extent, but they can also lead to inefficient pump function and sometimes to a cascade of more severe abnormalities.

Despite the primacy of flow, cardiac diagnostics still rely almost exclusively on tools focused on morphological assessment. Flow characteristics are often assumed rather than measured directly. Suitable non-invasive tools for characterizing and measuring



flow dynamics are needed to push our medical effectiveness to the next level.

Imaging that is focused on answering the most relevant questions, with an eye towards tangible improvements in diagnosis, therapy and outcomes can facilitate treatment of cardiac patients with higher quality and lower costs.

The objective of this project is to develop the next generation of methods for the non-invasive quantitative assessment of cardiac diseases and therapies by focusing on blood flow dynamics, with the goals of earlier and more accurate detection and improved management of cardiac diseases.

The project has developed a method for flow quantification using MRI which allows for simultaneous measurement of time-resolved, three-dimensional (time + 3D = 4D) blood flow velocity and turbulence intensity. This method reveals blood flow patterns in the heart and the large vessels.

Cardiovascular blood flow is still to a large extent unknown. In order to define relevant parameters, development of analysis and visualization approaches and studies of normal and abnormal blood flow have to be performed in chorus.

Studying cardiovascular blood flow dynamics in patients and healthy subjects will improve our understanding of the roles of flow dynamics in health and disease, leading to improved cardiac diagnostics, novel assessments of pharmaceutical, interventional, and surgical therapies, and promoting exploration of new avenues for management of cardiac disorders. ■

PROJECT INFORMATION

Project Name
Non-invasive imaging of the interrelationship between blood flow and vascular disease

Project Leader
Petter Dyverfeldt, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

Main Project Participants
Magnus Ziegler, Jonas Lantz, Marcus Lindenberger, Martin Welander, Sandeep Koppal, Elin Good, Carl-Johan Carlhäll, Tino Ebbers, Ebo de Muinck, Toste Länne

Grants
Swedish Research Council
Forskningsrådet i Sydöstra Sverige (FORSS)

Key Publications
Ziegler M, Lantz J, Ebbers T, Dyverfeldt, P. Assessment of turbulent flow effects on the vessel wall using four dimensional flow MRI. Magnetic resonance in medicine 2017; 77 (6), 2310–2319.

Ha H, Lantz J, Haraldsson H, Casas B, Ziegler M, Karlsson M, Saloner D, Dyverfeldt P, Ebbers T. Assessment of turbulent viscous stress using ICOSA 4D Flow MRI for prediction of hemodynamic blood damage. Scientific reports 2016, 6.

Dyverfeldt P; Bissell M; Barker AJ; Bolger AF; Carlhäll CJ; Ebbers T; Francois CJ; Frydrychowicz A; Geiger J; Giese D; Hope MD; Kilner P; Kozerke S; Myerson S; Neubauer S; Wieben O; Markl M. 4D Flow CMR Consensus Statement. J Cardiovasc Magn Reson 2015; 17(1):174.

POPULAR SCIENTIFIC SUMMARY

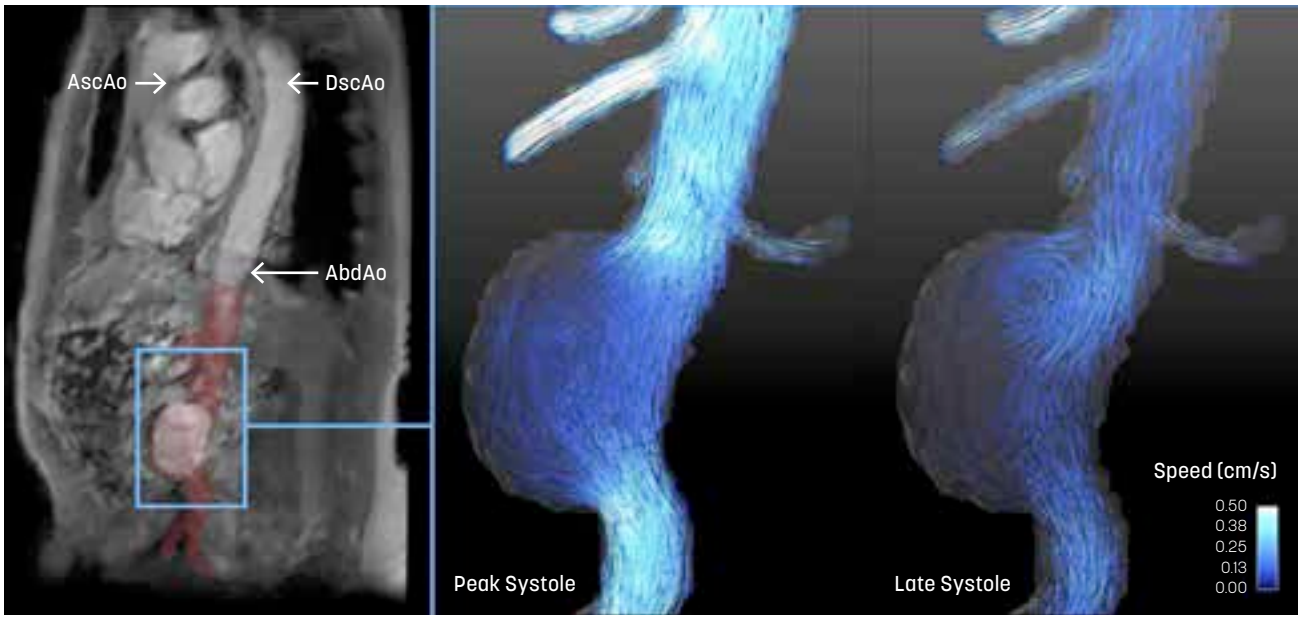
PETTER DYVERFELDT

Non-Invasive Imaging of Blood flow and Vascular Disease

The main purpose of our arteries is to distribute blood flow to the organs of our body. Arteries can sometimes become constricted and this may affect the blood flow to downstream vasculature. Today, the risk that a constriction affects the blood flow is assessed based on the size of the constriction. It has been known for quite some time that abnormal blood flow is both an indicator of arterial disease and a risk factor for disease progression. Unfortunately, appropriate tools for measuring these flow effects in humans have been lacking. Consequently, we still use measures such as the size of a constriction to assess the status of the blood flow.

The purpose of this project is to develop methods for the determination of some of the most important aspects of blood flow.

Many arterial diseases are related to atherosclerosis. The atherosclerotic disease process starts when we are young with deposition of fat in the arterial wall. This early process does not affect the size of our arteries but it does make them stiffer. Arterial stiffness alters the pressure wave that the heart generates when it contracts. Altered pressure wave is a strong marker of several cardiovascular diseases. Today's methods can only measure this in a few arteries, and the information that can be obtained represents an average. However, arterial stiffness varies within an artery. If we could measure these variations, we could increase and improve the clinical applicability of pressure wave measurements.



The more advanced stages of atherosclerotic disease are characterized by large deposits of fat in the arterial wall. These deposits, plaques, constrict the arterial lumen. The plaques may rupture, which can cause stroke or a heart attack. The blood flow in constricted arteries can become turbulent. Several studies indicate that turbulent forces increase the vulnerability of the plaques and their risk of rupture. Today's techniques for assessing the effects of flow on the vessel wall focus on forces that exist also in normal blood flow in healthy arteries. However, methods that permit assessment of the impact of turbulent forces do not exist.

We develop methods for the determination of pressure wave velocity and the effects of turbulent flow on the vessel wall. In achieving our goals, we plan to use an advanced magnetic resonance imaging (MRI) technique referred to as 4D flow MRI, which permits comprehensive assessment of time-varying three-dimensional (time + 3D = 4D) blood flows. This technique has the potential to unveil information about key aspects of blood flow. However, dedicated research efforts are needed to realize this potential.

Being able to measure aspects of blood flow that have previously not been measurable will lead to an increased understanding of the interrelationship between blood flow and vascular disease. It will also open up for new ways to assess and risk-stratify vascular disease. This will offer improved care for the vast population of patients with vascular disease and financial benefits for the health care. ■

FIGURE. The complex hemodynamics of Abdominal Aortic Aneurysms (AAA) can be investigated using 4D Flow MRI.
Left panel shows an anatomical image in a sagittal orientation, with an AAA delineated in red.
Centre panel shows a streamline visualization of flow in the aneurysmal sac at peak systole.
Right panel shows a streamline visualization of flow in the aneurysmal sac at late systole, where a large vortex has formed at the proximal edge of the sac.
AscAo = Ascending Aorta, DscAo = Descending Aorta, ThoAo = Thoracic Aorta, AbdAo = Abdominal Aorta.

PROJECT INFORMATION

Project Name
DOPPLER-CIP

Project Leader
Tino Ebbers and Jan Engvall, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

Main Project Participants
Johan Kihlberg, Petter Dyverfeldt, Eva Olsson, Carl-Johan Carlhäll, Lars-Åke Levin, Magnus Husberg, Magnus Janzon

Grants
EU grant, 2010–2014

Key Publications

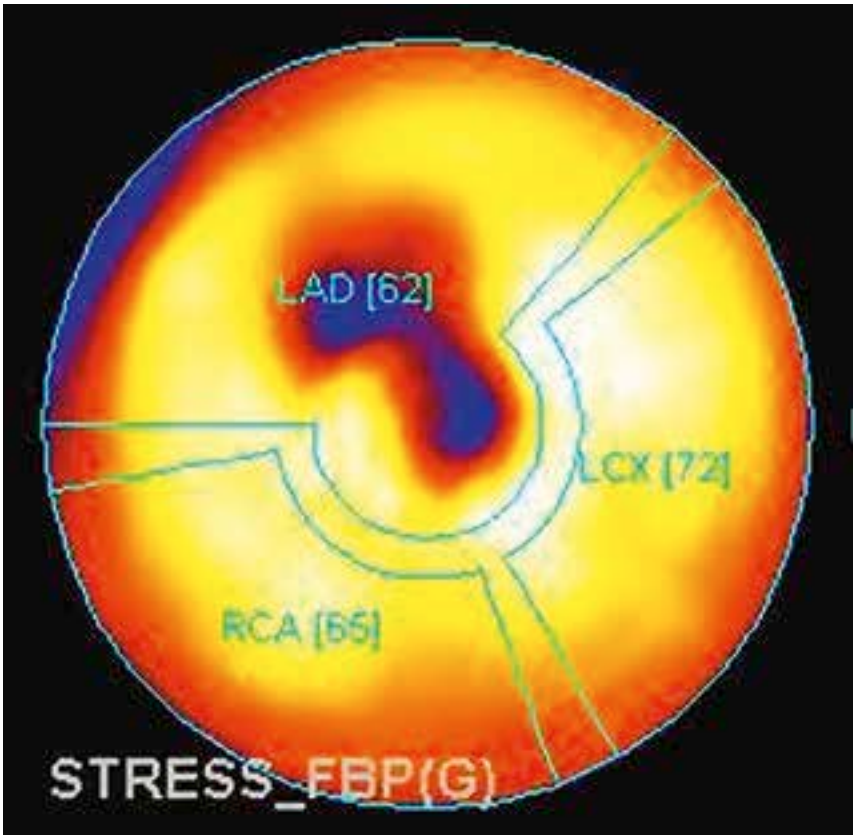
Kihlberg J, Haraldsson H, Sigfridsson A, Ebbers T, Engvall J.
Clinical experience of deformation imaging using DENSE for detecting abnormal cardiac segments.
Journal of Cardiovascular Magnetic Resonance 2015;17:50 doi: 10.1186/s12968-015-0155-8.

Queirós S, Barbosa D, Engvall J, Ebbers T, Nagel E, Sarvari S, Claus P, Fonseca J, Vilaça J, D'hooge J.
Multi-center validation of an automatic algorithm for fast myocardial segmentation in 3D cine CMR datasets.
EHJ Cardiovascular Imaging 2015 Advance Access published October 22, 2015, doi:10.1093/ehjci/jev247.

Morais P, Queirós S, Heyde B, Engvall J, D'hooge J, Vilaça JL.
Fully automatic left ventricular myocardial strain estimation in tagged Magnetic Resonance Imaging.
Phys Med Biol. 2017 Aug 7;62(17): 6899–6919. doi: 10.1088/1361-6560/aa7dc2.PMID: 28783715.

POPULAR SCIENTIFIC SUMMARY

JAN ENGVALL & TINO EBBERS

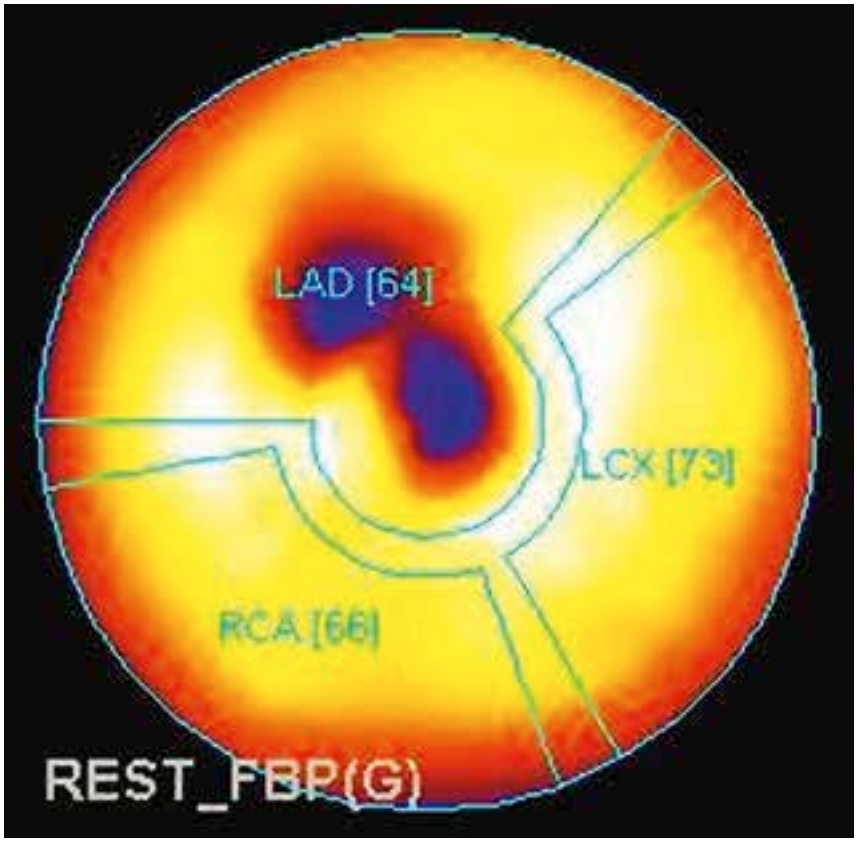


DOPPLER-CIP

Coronary artery disease is the most prevalent cause of cardiovascular disease. It is defined by the narrowing and occlusion of coronary arteries with subsequent imbalance between myocardial oxygen consumption and supply. This imbalance causes either myocardial cell death (infarction) or chronic ischemia (viable myocardium), both leading to changes in the shape of the heart (morphologic remodeling) and functional deterioration. In the long term, patients suffer from heart failure or die.

Restoring blood flow to a region of chronic ischemia can stop the process of remodeling and allow partial or full recovery of function. The current therapeutic approaches are either to restore blood flow by mechanical dilatation of the stenosed coronary vessel (i.e., balloon angioplasty, PCI) or by surgically bypassing the stenosis (coronary artery bypass grafting). Preprocedural investigations as well as the therapeutic measures undertaken are costly and carry a considerable risk for the patient.

The response of chronically ischemic myocardial cells to therapy depends on many factors. Little is known, however, about the exact relation between these pathophysiologic factors and functional



recovery of the myocardium for a given therapeutic strategy.

Therefore, the purpose of DOPPLER-CIP is to determine the optimal noninvasive parameters (myocardial function, perfusion, ventricular blood flow, cell integrity) for the prediction of left ventricular morphologic and functional remodeling in chronic ischemic patients.

DOPPLER-CIP is a multi-center observational study. All patients with ischemic heart disease included in this study undergo at least two noninvasive stress imaging examinations at baseline. The presence/or absence of left ventricular (LV) remodeling will be assessed after a follow-up of 2 years, during which all cardiac events will be registered.

After completion, DOPPLER-CIP will provide evidence-based guidelines toward the most effective use of cardiac imaging in the chronically ischemic heart disease patient. The study will generate information, knowledge, and insight into the new imaging methodologies and into the pathophysiology of chronic ischemic heart disease.

In Linköping, almost all 192 patients have undergone at least three stress imaging tests. We will have an excellent opportunity to compare the different modalities in our local material. The patients in this study have helped us develop new MRI-based methods for the measurement of wall motion abnormalities and for 3D-visualization of intracardiac blood flow.

The study closed on March 31, 2015, and had a closing event in Leuven, Belgium, April 25–26 2015. Several manuscripts are in preparation from the different core-labs. Based on evidence-based efficiency of different imaging technologies, researchers at CMT in Linköping will provide a cost-effectiveness analysis of the methods used to image coronary heart disease. ■

PROJECT INFORMATION

Project Name
SCAPIS-Echo

Project Leader
Jan Engvall, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

Main Project Participants
Carl Johan Östgren, Toste Länne, Fredrik Nyström, David Kylhammar, Meriam Åström Aneq

Grants
KAW
Swedish Heart and Lung Foundation

Key Publications
Bergström G, Berglund G, Blomberg A, Brandberg J, Engström G, Engvall J, Eriksson M, de Faire U, Flinck A, Hansson MG, Hedblad B, Hjelmgren O, Jansson C, Jernberg T, Johnsson Å, Johansson L, Lind L, Löfdahl CG, Mellander O, Östgren CJ, Persson A, Sandström A, Schmidt C, Söderberg S, Sundström J, Toren K, Waldenström A, Wedel H, Vikgren J, Fagerberg B, Rosengren A.
The Swedish CArdioPulmonary BioImage Study (SCAPIS): objectives and design.
J Intern Med. 2015 Dec;278(6):645-59. doi: 10.1111/joim.12384. [Epub ahead of print]. PMID:26096600.

Maret E, Liehl M, Brudin L, Todt T, Edvardsen T, Engvall JE.
Phase analysis detects heterogeneity of myocardial deformation on cine MRI.
Scand Cardiovasc J. 2015 Jun;49(3): 149-58. [Epub ahead of print] PMID: 25752486.

POPULAR SCIENTIFIC SUMMARY

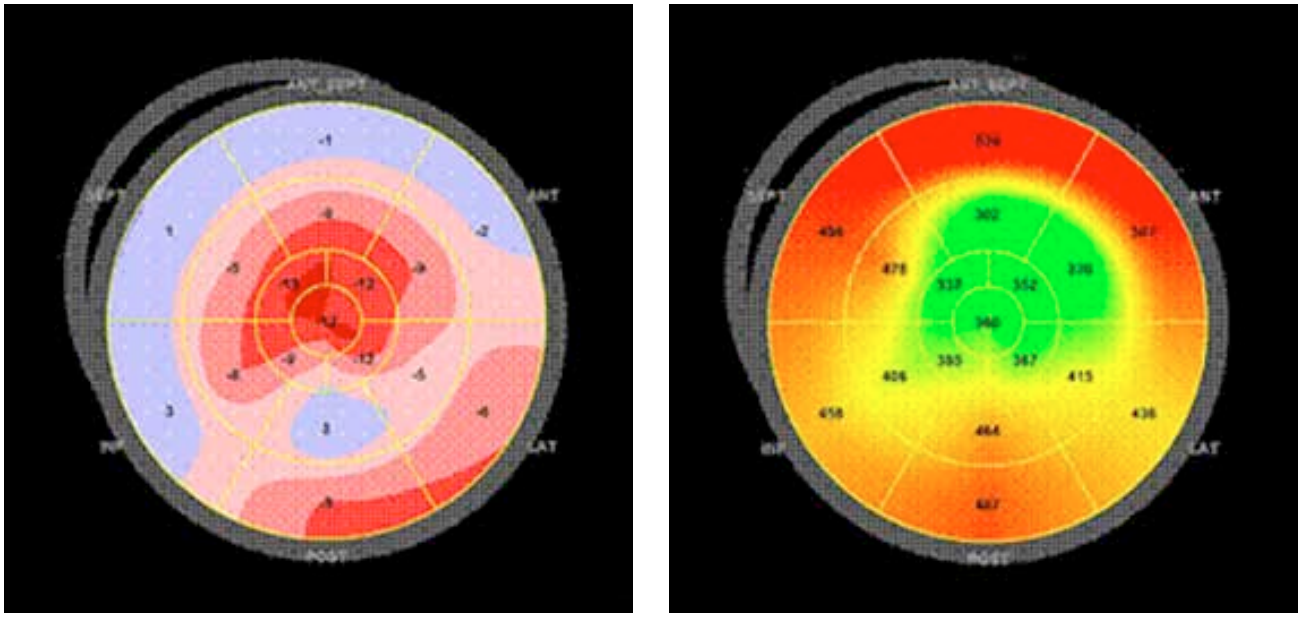
JAN ENGVALL

SCAPIS-Echo

Swedish Cardio Pulmonary bioImage Study (SCAPIS), is a large-scale national population study initiated by The Swedish Heart and Lung Foundation and supported by the Wallenberg Foundation. The study is lead by a national research group in collaboration with the University Hospitals in Sweden.

SCAPIS is aiming for improved diagnosis and treatment of cardio-vascular and lung disease. In total 30 000 healthy individuals in the age of 50–64 years will be examined in the study. Of these 5 000 will be examined in Linköping. The participants' lungs and cardiovascular system are examined with computed tomography and ultrasound. All the collected data will be saved in a knowledge bank, which will be a national resource used for research.

Coronary artery stenosis is the most prevalent cause of cardiovascular disease. Atherosclerotic disease is initiated in early life, advancing with age and eventually creating severe coronary



Polar plot representation of the amplitude of peak strain (left), time-to-peak strain (right) and the calculated standard deviation of peak strain, (red box right). The green area of the right polar plot shows normal temporal relationship between segments. The red basal area denotes mechanical dispersion, which in this case is located in the areas that have reduced strain amplitude (blue in the left polar plot).

stenosis or occlusion. In the Scapis pilot study, about 50 % of participants aged 50–64 had plaque in their coronary arteries. Disease progression is however unpredictable. Recent studies have shown that the risk of future coronary events is related to the presence of plaque.

However, other studies have shown that myocardial function is another powerful predictor of prognosis. A third predictor has been suggested, namely the presence of mechanical dispersion. Mechanical dispersion has been thought to represent the mechanical effect of electrical dispersion, which in itself represents an electrical instability that could be derived from previous myocardial scarring.

We hypothesized that the presence of mechanical dispersion would predict an increased risk of future cardiac events in the Scapis population.

Therefore, the purpose of Scapis-echo is to determine global longitudinal strain amplitude and peak systolic dispersion in the Linkoping Scapis population of 5 000 participants 50–64 years of age. The participants undergo an echocardiographic study as an additional part of their evaluation in Scapis, which also performs coronary CT and an extensive mapping of cardiopulmonary risk factors.

Inclusion will be completed in 2018 and future cardiovascular events in the cohort followed through Swedish disease registries. ■

PROJECT INFORMATION

Project Name
SCAPIS-Health

Project Leader
Carl-Johan Carlhäll, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

Main Project Participants
Tino Ebbers, Olof Dahlqvist Leinhard, Peter Lundberg, Carl Johan Östgren, Toste Länne, Fredrik Nyström, Jan Engvall, Eva Swahn, Markus Karlsson, Nils Dahlström, Bengt Norén, Amir Razavi, Wolf Bartholomä, Federica Viola, Petter Dyverfeldt

Grants
KAW
Swedish heart and lung foundation

Key Publications
Bergström G, Berglund G, Blomberg A, Brandberg J, Engström G, Engvall J, Eriksson M, de Faire U, Flinck A, Hansson MG, Hedblad B, Hjelmgren O, Jansson C, Jernberg T, Johnsson Å, Johansson L, Lind L, Löfdahl CG, Mellander O, Östgren CJ, Persson A, Sandström A, Schmidt C, Söderberg S, Sundström J, Toren K, Waldenström A, Wedel H, Vikgren J, Fagerberg B, Rosengren A.
The Swedish CArdioPulmonary BioImage Study (SCAPIS): objectives and design. J Intern Med. 2015 Dec;278(6):645-59. doi: 10.1111/joim.12384. [Epub ahead of print]. PMID:26096600.

Nasr P, Forsgren MF, Ignatova S, Dahlström N, Cedersund G, Leinhard OD, Norén B, Ekstedt M, Lundberg P, Kechagias S. Using a 3% Proton Density Fat Fraction as a Cut-Off Value Increases Sensitivity of Detection of Hepatic Steatosis, Based on Results From Histopathology Analysis. Gastroenterology. 2017 Jul;153(1):53-55.e7. doi: 10.1053/j.gastro.2017.03.005. Epub 2017 Mar 9.

POPULAR SCIENTIFIC SUMMARY

CARL-JOHAN CARLHÄLL

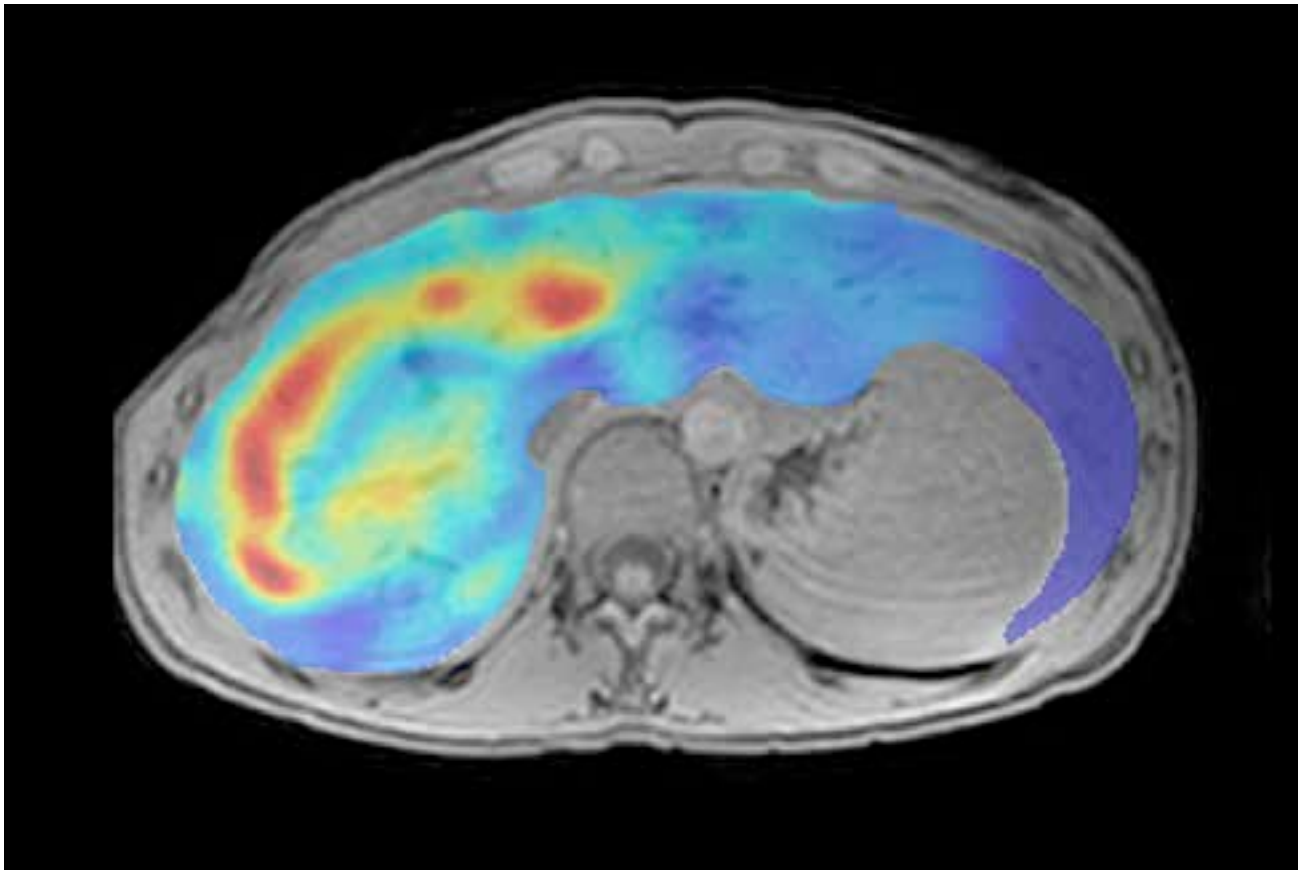
SCAPIS-Health

Swedish Cardio Pulmonary bioImage Study (SCAPIS), is a large-scale national population study initiated by The Swedish Heart and Lung Foundation and supported by the Wallenberg Foundation. The study is lead by a national research group in collaboration with the University Hospitals in Sweden.

SCAPIS is aiming for improved diagnosis and treatment of cardiovascular and lung disease. In total 30 000 healthy individuals in the age of 50–64 years will be examined in the study. Of these 5 000 will be examined in Linköping. The participants' lungs and cardiovascular system are examined with computed tomography and ultrasound. All the collected data will be saved in a knowledge bank, which will be a national resource used for research.

The overall aim of the HEart-Adipose tissue-Liver TrusT (HEALTH) project is to establish a relationship between cardiovascular disease, liver disease and ectopic fat storage in a cohort with Type 2 Diabetes Mellitus (T2DM), something that has never been done previously.

We hypothesize that advanced MRI-based measurements of the heart, liver and body composition in combination will relate stronger to adverse cardiac



remodeling, cardiovascular events, and metabolic disease compared to individual mesurements.

At CMIV in Linköping we intend to study the relationship between measurements with highly advanced MR methods on heart (e.g., myocardial deformation/fibrosis/fat, blood flow), liver status (e.g., fibrosis, liver fat, iron), ectopic fat infiltration (visceral, intramuscular and pancreatic), and body composition (total abdominal fat tissue, occurrence of brown fat, and fat-free muscle volume). We will also study how such MRI-based measurements, individually and in various combinations, can relate to adverse heart remodeling, cardiovascular events and metabolic disease.

It would also be of great value to supplement with a longitudinal follow-up of the same research subjects after two years to study how long-term changes in the estimated MRI-based measurements relate to adverse cardiac remodeling, cardiovascular events, and metabolic disease.

The study subjects will be recruited from the SCAPIS cohort. The study will involve 100–250 persons with T2DM (as reported in SCAPIS forms) and 100 control subjects without T2DM. Patient recruitment is active and will continue during 2018. ■

FIGURE. Image showing liver elasticity in a patient with chronic liver disease. Elasticity is a measure of how stiff the liver is and is a measure of fibrosis in the liver.

PROJECT INFORMATION

Project Name
Histological and Functional Changes in Left Ventricular Function Due To Aortic Stenosis

Project Leader
Éva Tamás, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

Main Project Participants
Eva Nylander, Jan Engvall, Tino Ebbers

Grants
Svenska Läkarsällskapets Projektanslag 2014–2016

Key Publications
Tamás É, Broqvist M, Olsson E, Franzén S, Nylander E.
Exercise Radionuclide Ventriculography for Predicting Post-Operative Left Ventricular Function in Chronic Aortic Regurgitation. J. Am. Coll. Cardiol. Img. 2009;2;48–55.

Kvernby S, Warntjes MJ, Haraldsson H, Carlhäll CJ, Engvall J, Ebbers T.
Simultaneous three-dimensional myocardial T1 and T2 mapping in one breath hold with 3D-QALAS.
J Cardiovasc Magn Reson. 2014 Dec 20;16:102. doi: 10.1186/s12968-014-0102-0.

POPULAR SCIENTIFIC SUMMARY

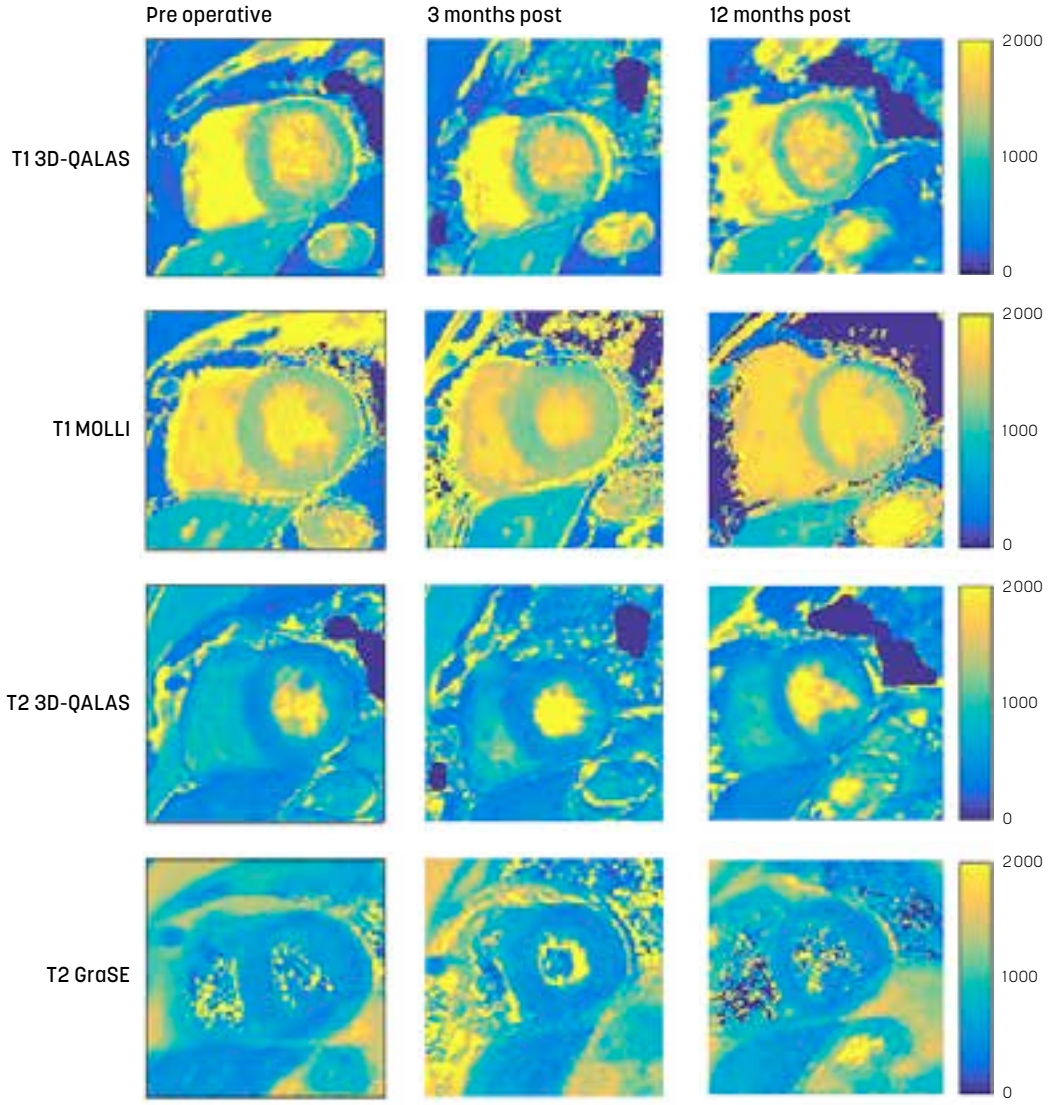
ÉVA TAMÁS

Changes in left Ventricular Function due to Aortic Stenosis

Aortic valve stenosis (AS) is the most common valvular heart disease in Europe (46.4%). Mostly elderly patients suffer from AS and due to the expanding population above 60 years this patient group is steadily increasing. Current treatment of aortic valve disease is prosthetic aortic valve replacement (AVR).

Operation is indicated when the valve disease affect hemodynamics and left ventricular function (LVF). Present guidelines suggest surgery when patients are presented with symptoms and/or echocardiographic parameters. These manifestations are fairly crude as both symptoms and left ventricular dilatation are appearing late in the natural history of the aortic valve disease. Furthermore, we showed previously that symptoms and LVF do not correlate.

In order to be able to keep up performance the LV compensates minor changes by hypertrophy. Further changes present even at histological level as diffuse fibrosis. It is known that regional fibrosis e.g. after myocardial infarction leads to impaired ventricular



function. However, there is no information available in the medical literature on exactly how diffuse fibrosis affects LVF and whether these are reversible. Thus, understanding how fibrotic changes of the heart muscle are connected to the impairment of LVF could give valuable information.

Previous studies have verified fibrotic regions following myocardial infarction on cardiac magnetic resonance imaging (CMRI). Thus CMRI was proved to be a useful diagnostic modality for myocardial viability and this knowledge has already been translated to clinical practice. While fibrosis is focal and concentrated in myocardial infarction there is no in-vivo information on the distribution of the fibrotic tissue in the mass of the human heart muscle in aortic valve disease which makes validation of CMRI images by means of histology necessary.

In our ongoing study we validate CMRI (special sequences developed at CMIV) as a diagnostic tool for diffuse myocardial fibrosis and to evaluate the effect of fibrosis on myocardial function. We hypothesize that the amount and the location of the fibrotic tissue can be connected to impairment of LVF in severe aortic valve disease. By using CMRI we intend to gain information on whether this impairment is reversible following surgery.

In addition to histological and functional studies at rest we plan to survey the anaerobe (physical) capacity by performing cardiopulmonary exercise testing pre- and postoperatively and study the relationship between physical performance capacity, fibrosis and LVF. ■

PROJECT INFORMATION

Project Name
Quantitative Assessment of Trabecular Bone Structure

Project Leader
Örjan Smedby, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Eva Klintström, Rodrigo Moreno, Torkel Brismar

Grants
Swedish Research Council (VR-NT)
VINNOVA/EuroStars 2015–17

Key Publications
Klintström E, Klintström B, Pahr D, Brismar TB, Smedby Ö, Moreno R. Direct Estimation of Human Trabecular Bone Stiffness Using Cone-Beam Computed Tomography. Accepted for publication in Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology.

Klintström B, Klintström E, Smedby Ö, Moreno R. Feature Space Clustering for Trabecular Bone Segmentation. In: Sharma P, Bianchi FM, editors. Image Analysis: 20th Scandinavian Conference, SCIA 2017, Tromsø, Norway, June 12–14, 2017, Proceedings, Part II. Cham: Springer International Publishing; 2017. p. 65–75. DOI:10.1007/978-3-319-59129-2_6.

Chowdhury M, Klintström B, Klintström E, Smedby Ö, Moreno R. Granulometry-Based Trabecular Bone Segmentation. In: Sharma P, Bianchi FM, editors. Image Analysis: 20th Scandinavian Conference, SCIA 2017, Tromsø, Norway, June 12–14, 2017, Proceedings, Part II. Cham: Springer International Publishing; 2017. p. 100-8. DOI:10.1007/978-3-319-59129-2_9.

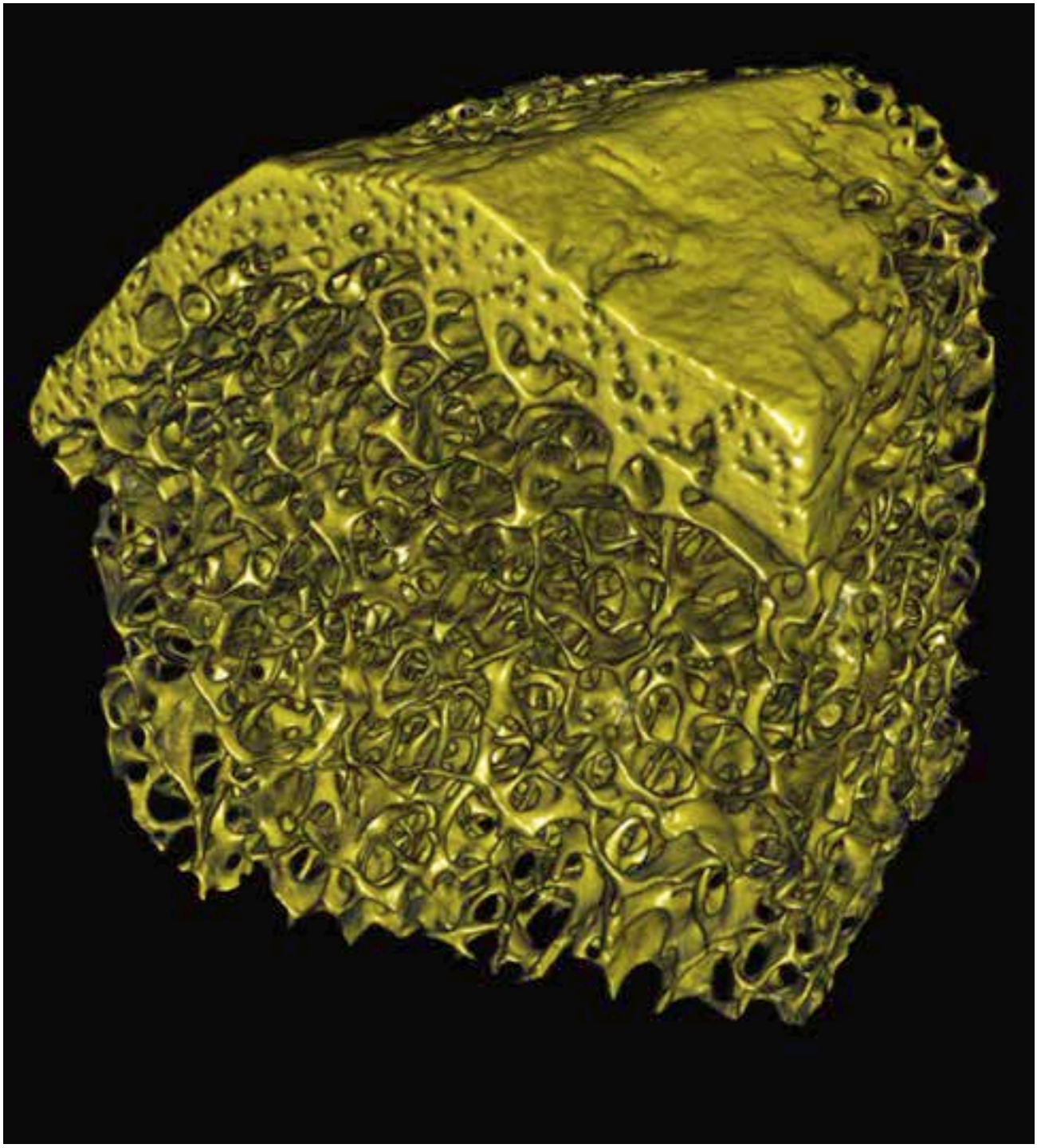
POPULAR SCIENTIFIC SUMMARY

ÖRJAN SMEDBY

Quantitative Assessment of Trabecular Bone Structure

Patients suffering from osteoporosis have an increased risk of fractures. When studying this in patients the amount of calcium in the bone is usually measured since this is reduced in osteoporosis. However, the condition is also characterized by a change in the internal structure of the bone, which may be more important for its strength than the reduced calcium content. The internal structures of the bone are called trabeculae, and they are usually portrayed as either narrow rods or flat plates. Earlier, the 3D microstructure could only be studied in bone specimens removed from the body, where properties such as the spacing and thickness of the trabeculae and the number of branching points can be measured.

This project aims to study this structure in the living human by using methods available in a radiological department, in particular different types of computed tomography (CT) methods. Since the trabeculae often are less than



0.2 µm thick, the limited resolution of the radiological methods may be a problem. Therefore, we have focused on developing new image processing techniques for as accurate measurements as possible in the available images.

To study how the structure of the bone differs between different directions we use mathematical concepts called tensors. With these rather abstract tools, we can estimate the strength of the bone, which is what really matters for the patient. We have shown that our predictions agree well with results from Finite element modeling (FEM), a computational method that requires much longer time even on very fast computers.

We have also studied how the type of tissue structure that is present in trabecular bone can be characterized and enhanced using tensor methods. In addition to bone structure this may be useful also for e.g. identifying vessels in CT or MRI images.

The studies have resulted in the doctoral dissertation »Image Analysis for Trabecular Bone Properties on Cone-Beam CT Data« which Eva Klintström defended on Oct 26, 2017.

In the future, we hope that our methods will be useful in particular to evaluate the effects of treatment against osteoporosis. With better tools to measure the structure of the bone trabeculae it will be possible to draw such conclusions at an earlier stage, hence the number of subjects and the observation times in clinical trials may be reduced. ■

PROJECT INFORMATION

Project Name
Visualization of spinal deformities

Project Leader
Hans Tropp, Dept of Spine Surgery, Region Östergötland

Main Project Participants
Ludvig Vavruch, Marcus Malmqvist, Håkan Gauffin

Grants
Vinnova Preciis 2017

Key Publications
Ludvig Vavruch, Daniel Forsberg, Nils Dahlström, Hans Tropp.
Vertebral Axial Asymmetry in Adolescent Idiopathic Scoliosis. In Press Spine Deformity.

de Kleuver M, Faraj SSA, Holewijn RM, Germscheid NM, Adobor RD, Andersen M, Tropp H, Dahl B, Keskinen H, Olai A, Polly DW, van Hooff ML, Haanstra TM.
Defining a core outcome set for adolescent and young adult patients with a spinal deformity.
Acta Orthop. 2017 Sep 15:1–7.

Brink RC, Schlösser TPC, Colo D, Vavruch L, van Stralen M, Vincken KL, Malmqvist M, Kruyt MC, Tropp H, Castelein RM.
Anterior Spinal Overgrowth Is the Result of the Scoliotic Mechanism and Is Located in the Disc.
Spine 2017 1;42(11):818–822.

POPULAR SCIENTIFIC SUMMARY

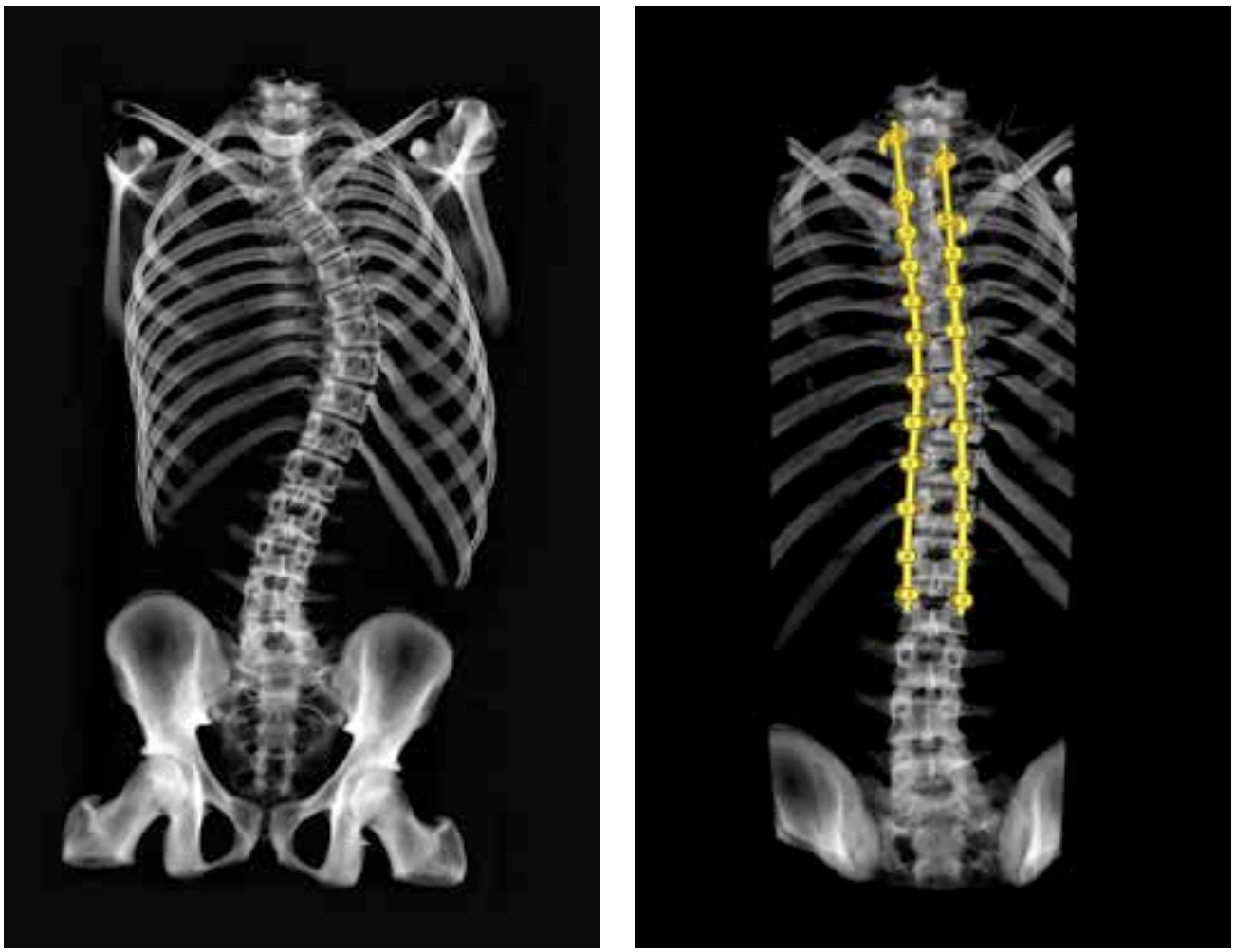
HANS TROPP

Visualization of Spinal Deformities

Spinal deformities not only cause changes in posture but can also be associated with severe pain, breathing complications, as well as heart complications. Treatment options include braces for mild to moderate cases of scoliosis, whereas severe cases often require surgery, both to halt progression and to preferably correct the already existing deformity.

Scoliosis is a three-dimensional (3D) structural deformity that affects the spine on both regional and local levels. The induced deformity is regional, in the sense that a group of vertebrae are affected, forming a scoliotic curvature. This deformity is typically described with a single measure, for example the Cobb angle. The Cobb angle measures the angle of the spine as seen on frontal radiographs. However, although widely used in clinical practice, the Cobb angle is incapable to fully describe a spinal deformity.

On the other hand, the deformation is local, because each vertebra is individually deformed; for example,



A CT before and after surgical treatment of idiopathic scoliosis.

sagittal or coronal wedging can occur in each vertebra.

Our project aims to develop new methods for visualization and calculation of spinal deformities. The methods are based on computed tomography (CT) and integration of CT and motion capture. Our main application will also be valuable for studying femro-acetabular impingement (FAI) which is a very common functional problem among young athletes. We perform a CT followed by functional testing of the patient. ■

PROJECT INFORMATION

Project Name
Health effects of resistance training on postmenopausal women

Project Leader
Mats Hammar, Department of Clinical and Experimental Medicine, Division of Obstetrics and Gynecology
Magnus Borga, Department of Biomedical Engineering, Division of Medical Informatics

Main Project Participants
Anna-Clara Spetz Holm, Lotta Lindh Åstrand, Hanna Lindblom, Olof Dahlqvist Leinhard, Heriberto-Rodriguez-Martinez, Marie Rubér, Peter Söderkvist, Pontus Boström, Emilia Berin, Sofia Thorell

Grants
Swedish Research Council

Key Publications
Romu T, West J, Spetz-Holm A-C, Lindblom H, Lindh-Åstrand L, Hammar M, Dahlqvist Leinhard, Borga M. The effect of flip-angle on body composition using calibrated water-fat MRI. Submitted to ISMRM 2016, Singapore.

Borga M., Virtanen Kirsi A., Romu T., Dahlqvist Leinhard O. Persson A., Nuutila P., Enerbäck S. Brown adipose tissue in humans: detection and functional analysis using PET (Positron Emission Tomography), MRI (Magnetic Resonance Imaging), and DECT (Dual Energy Computed Tomography), accepted for publication in: Methods in Enzymology Volume 537: Methods of Adipose Tissue Biology, 141–159, 2014.

Berin E, Hammar ML, Lindblom H, Lindh-Åstrand L, Spetz Holm AC. Resistance training for hot flushes in postmenopausal women: Randomized controlled trial protocol. Maturitas. 2016 Mar;85:96–103. doi: 10.1016/j.maturitas.2015.12.015. Epub 2016 Jan 3.

POPULAR SCIENTIFIC SUMMARY

MATS HAMMAR & MAGNUS BORGA

Health Effects of Resistance Training on Postmenopausal Women

Today's women will live more than a third of their lives after menopause, which is characterized by a series of clinical signs and symptoms including vasomotor symptoms (hot flushes and sweating), sleep and mental disturbances. Other important changes are osteoporosis and loss of muscle mass, which is replaced by accumulation of white fat. Inflammatory changes in the fat tissue also occur with immunologic and metabolic dysfunctions as consequences such as increased risk of cancer and cardiovascular disease.

Vasomotor symptoms like hot flushes and sweating are reported by about 75 % of all menopausal women. Until about ten years ago almost every other middle-aged woman in the Western world used hormone therapy (HT) with combined estrogens and synthetic progesterone, which effectively diminishes vasomotor symptoms. Since HT, however, has been shown to increase the risk of cardiovascular and thrombo-embolic disease as well as breast cancer there is a need for alternative therapies.

Already in the early nineties (as the first group worldwide) we reported that vasomotor symptoms were less prevalent in women who participated in regular physical exercise. Women who were randomized to regular exercise re-

ported decreased vasomotor symptoms and increased quality of life.

The purpose of this study is to establish health effects from 15 weeks of structured resistance training on postmenopausal women. The participating women are coached by a skilled physiotherapist and the training is individualized.

In the beginning and end of the study clinical outcomes as vasomotor symptoms, well-being, Body Mass Index, muscle strength and mass are measured. White and brown adipose tissue as well as browning of fat are measured with MRI. Also, production of myokines as irisin and adipokines, immunological markers and genetic variables (length of telomeres) are analyzed. By means of structured interviews we investigate how to best stimulate women to change life-style and why some women will not be successful.

The study is a close collaboration between clinical medicine, the participating gym, laboratory biomedicine, caring sciences and physiotherapy, as well as advanced technology at CMIV. The results could easily and rapidly be implemented into clinical routine and may have extensive health benefits on the aging population.

In November 2016 we included and randomized the 65:th woman and by March 2017 all women had gone through the 15 weeks of intervention or being in the control group. Thereafter blood analyses and all other analyses will be performed. Already a test-retest investigation has been performed with a number of MRI investigations performed twice.

Furthermore we have decided to prolong the study including all measurements after 24 months. We now investigate all women who have been long-term compliant to regular exercise and compare with women who are again sedentary. This prolongation of the study will go on until summer 2019. ■

POPULAR SCIENTIFIC SUMMARY

LENNART PERSSON

Impact of Vitamin D on Physical Training in Patients with COPD

Muscle waste and inactivity is a great problem among patients with chronic obstructive pulmonary disease (COPD) and structured physical training is known to have many beneficial effects on these patients.

Many patients with COPD exhibit vitamin D deficiency, which in addition to COPD may act negatively on the skeletal muscle. Today it is still not well known how deprivation of this vitamin may interfere with muscle function and the ability of these patients to fully gain the benefits of physical training.

The goal of the present project is to identify mechanisms behind vitamin D deficiency- and COPD dependent muscle pathology applying the very latest technology, which include the 31P-MRS and serological biomarkers, and to find out the impact of vitamin D deficiency in an interventional doubleblind trial of vitamin D3 supplementation and placebo.

If successful, the study will lead to a better understanding about the role of vitamin D deficiency on the muscle waste observed among many COPD patients. Indeed, vitamin D may become a crucial vitamin to supplement before physical training is started.

The present study will include patients with stable but advanced COPD exhibiting deficiency of vitamin D and significant weakness of the breathing muscle. In a blinded fashion patients are randomized to physical training (at hospital supervised by physiotherapist

twice a week and at home monitored by a training diary once a week for 8–10 weeks) with the study medication Vigantol (vitamin D3) or placebo (miglyol). Ongoing treatments with vitamin D and calcium are temporarily stopped at inclusion. Vigantol is administered orally as a daily dose of 4 000 IU starting from the day of randomization and continuing throughout the training period.

Primary outcome is respiratory muscle strength measured as the maximal inspiratory pressure (MIP). Among secondary outcomes studies on muscle strength and endurance of the dominant leg, metabolism of the quadriceps muscle of the dominant leg at rest and exercise (employing 31P-magnetic resonance (MR) spectrometry) and quantification of muscle, fat and bone tissues of the dominant leg (using MR) will be performed. ■

PROJECT INFORMATION

Project Name
Impact of Vitamin D on Physical Training in Vitamin D Deficient Patients with COPD

Project Leader
Lennart Persson, Department of Pulmonary Medicine, Region Östergötland

Main Project Participants
Magnus Kentson, Apostolos Sioutas, Mikael Forsgren, Kristina Tödt, Petra Jacobson, Linda Vainikka, Per Leanderson, Peter Lundberg

Grants
The Swedish Heart and Lung Foundation
Medical Research Council of Southeast Sweden (FORSS)

PROJECT INFORMATION

Project Name
Semiautomatic Liver Volume Determination and Segmentation

Project Leader
Nils Dahlström, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Mikael Forsgren, Chunliang Wang, Amir Razavi, Markus Karlsson, Peter Lundberg, Ola Persson

POPULAR SCIENTIFIC SUMMARY

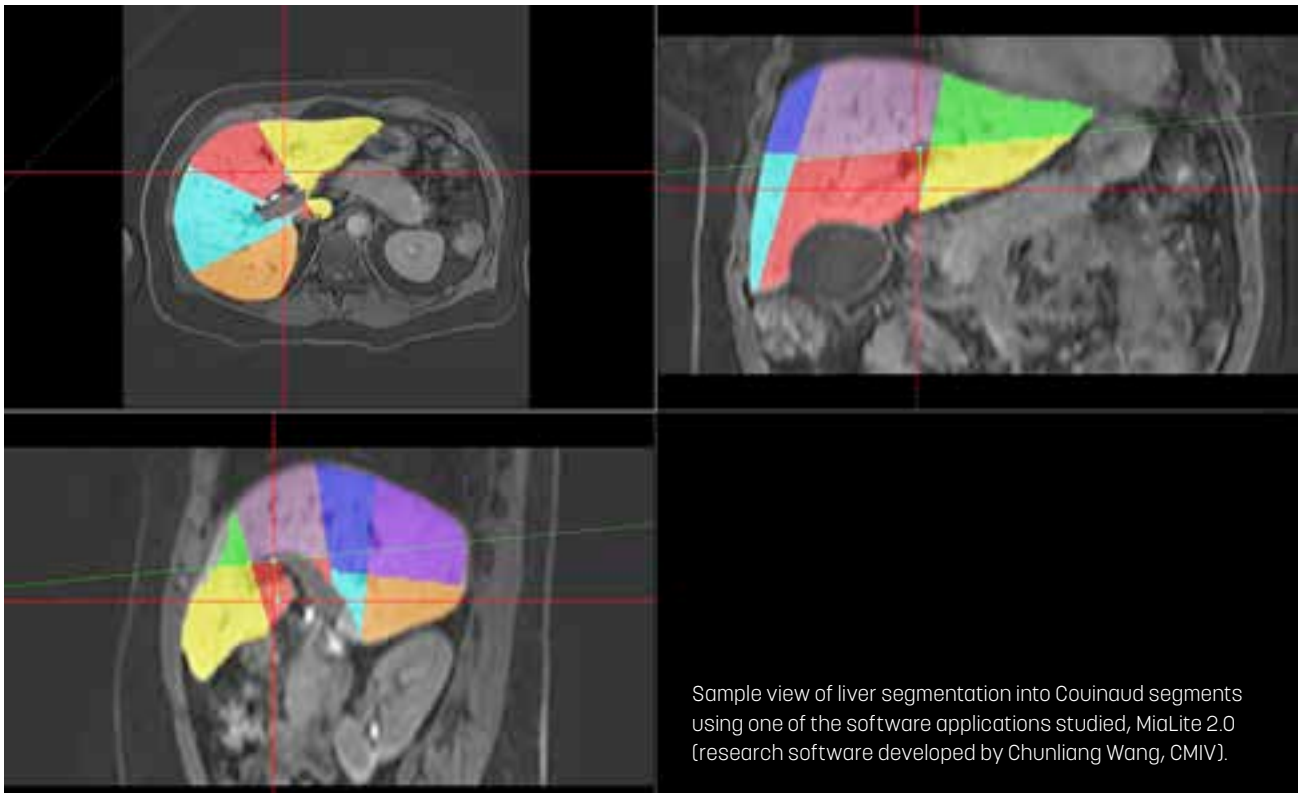
NILS DAHLSTRÖM

Semiautomatic Liver Volume Determination and Segmentation

There are many types of liver diseases occurring through many different mechanisms. Diffuse liver disease for example is a rapidly growing problem in the Western world and includes conditions such as viral infection (hepatitis) and non-alcoholic fatty liver disease. Other types are alcohol-induced liver disease and focal liver disease.

Common for all liver diseases is that they may lead to the formation of fibrosis, inflammation and ultimately, cirrhosis. Many forms are mainly discovered at a late stage when there is a loss of liver function. At this stage liver resection or transplantation may be the only available treatment. The evaluation of liver function is then crucial for reliable treatment planning.

Magnetic resonance imaging (MRI) offers a noninvasive method to monitor liver function using liver specific contrast agents. However, in developing system biology models for describing the pharmacokinetics of hepatocyte-specific contrast medium, it is important to estimate the total liver volume and preferably also liver segment volumes. Although tools for



Sample view of liver segmentation into Couinaud segments using one of the software applications studied, MiaLite 2.0 (research software developed by Chunliang Wang, CMIV).

liver segmentation using datasets from computed tomography have become easily available, useful applications aimed at MRI datasets are lacking.

Thus, a sub-project within the Liver Function Evaluation project was formed to evaluate software that was compatible with the late hepatobiliary phase 3D datasets from examinations of patients with diffuse liver disease.

The first objective of this study is to compare the measured total liver volumes from several semi-automatic liver segmentation tools and a fully automatic application (developed in-house), with manual, detailed segmentation in a separate software environment serving as »ground truth«.

Preliminary results show that a fully automatic segmentation is feasible and has a precision that is sufficient for clinical use. Both semi-automatic applications were found accurate but have quite different user interfaces, sometimes complicating the measurement task.

Another objective is to provide the total liver measurements needed for modeling the individual liver function estimates in quantitative MRI studies (e.g. LIFE and HIFI), and also introduce the means for segment-based liver function modeling.

In 2016 the in-house application was extended to include segmentation of the liver into the classical Couinaud segments, producing 3D masks defining the shape and volume of each segment. This feature is currently not readily available for MRI datasets in clinical segmentation or surgery planning applications, which rely on CT studies. The measurement of liver segmental volumes will permit segmental liver function assessment in the NILB, LIFE and HIFI studies. ■

PROJECT INFORMATION

Project Name
Whole body MRI based fat and muscle measurement

Project Leader
Olof Dahlqvist Leinhard, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Magnus Borga, Janne West, Anette Karlsson, Thord Andersson, Mikael Forsgren, Per Widholm, Thobias Romu, Jennifer Linge

Key Publications

Linge J, Borga M, West J, Tuthill T, Miller MR, Dumitriu A, Thomas EL, Romu T, Tunón P, Bell JD, Dahlqvist Leinhard O.
Body Composition Profiling in the UK Biobank Imaging Study
Accepted for publication in Obesity, 2018.

Middleton MS, Haufe W, Hooker J, Borga M, Dahlqvist Leinhard O, Romu T, Tunón P, Szeverenyi N, Hamilton G, Wolfson T, Gamst A, Loomba R, Sirlin CB.
Repeatability and accuracy of an, MRI-based, semi-automated analysis method for quantifying abdominal adipose tissue and thigh muscle volumes, and hepatic proton density fat fraction.
Radiology 283 (2), 438–449, 2017.

Lidell M, Betz M, Dahlqvist Leinhard O, Heglind M, Elander L, Slawik M, Mussack T, Nilsson D, Romu T, Nuutila P, Virtanen K, Beuschlein F, Persson A, Borga M, Enerbäck S.
Evidence for Two Types of Brown Adipose Tissue in Humans. Nature Medicine, Volume 19(5):631–634, 2013, DOI:10.1038/nm.3017.

POPULAR SCIENTIFIC SUMMARY

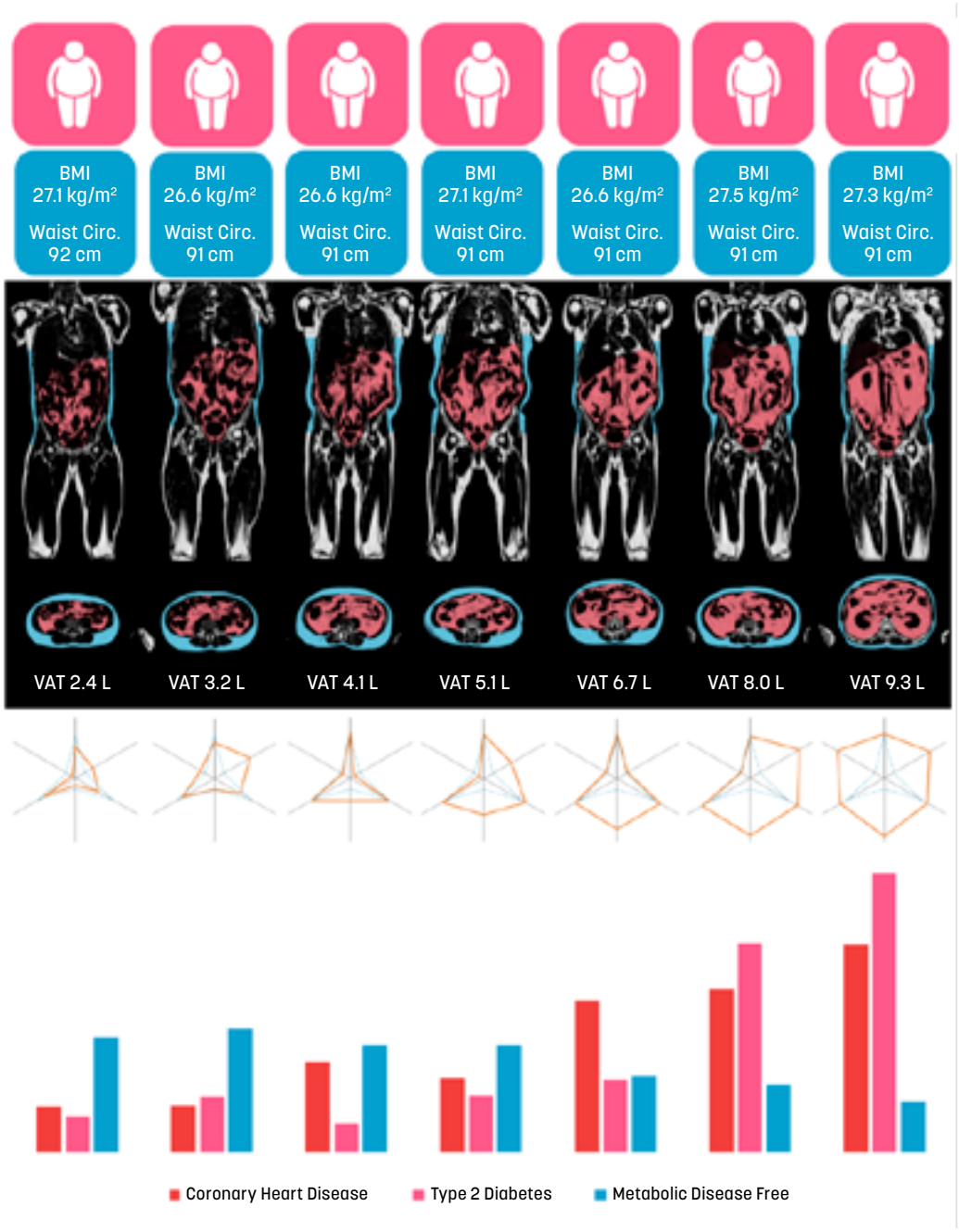
OLOF DAHLQVIST LEINHARD

Whole Body MRI-based Fat and Muscle Measurement

The metabolic syndrome is a disorder involving alterations of the normal biochemical processes in the body. High blood pressure, high blood sugar level, excess body fat around the waist and abnormal cholesterol increase the risk of heart disease, stroke and diabetes. In the metabolic syndrome several of these risk factors occur together, dramatically increasing the risk further.

Body Mass Index (BMI), weight and waist circumference do not tell the whole story about the metabolic syndrome. A better understanding of the effect of drugs and life style requires biomarkers reflecting where and how the body stores fat, builds muscles and reacts on physical exercise. Fat stored diffusively in and in between the internal organs is much more dangerous than fat stored as subcutaneous fat and weight gain due to increased muscle mass is rather positive than negative for your health.

Body composition measurement with magnetic resonance imaging (MRI) enables safe and accurate quantification of fat and how it is stored in the body. The technology can determine diffuse storage of fat in the liver, pancreas and muscles, fat stored between the internal organs in the abdomen, and subcutaneous fat. The technique also



allows quantification of the volume and muscle fat infiltration of muscles. The project has resulted in a clinical product available through the CMIV spinoff AMRA AB.

In this project we develop a technique for detailed analysis of fat and muscle tissue in the body based on very rapid whole-body MRI examinations. The technique is now applied in large-scale research studies to provide a better understanding about different body composition phenotypes. Today more than 30 000 subjects have been scanned using our method in various research studies proving the large-scale feasibility of whole body MRI body composition assessment. This vast number of subjects scanned also enables association of body fat distribution to metabolic health.

To support visualization of differences in body composition we have developed the body composition profile allowing quick visual comparison of a patients body composition to the average body composition of metabolic disease free subjects. In the figure an example of body composition profiling of seven different male subjects with identical BMI and waist circumference in the UK Biobank imaging study are shown with associated predicted probabilities for being metabolic disease free, having type 2 diabetes and coronary heart disease.

We apply the technique in a number of clinical studies ranging from large scale population studies like the UK Biobank imaging study to smaller interventional clinical trials investigating specific fat compartments or individual muscles following orthopedic rehabilitation and progression in muscular dystrophies. Furthermore, we use the technique to provide better understanding of Sarcopenia and Cachexia, the decline of muscle tissue and fat tissue associated with ageing and catabolic disease processes. ■

PROJECT INFORMATION

Project Name
PRESTO-CAN for three-dimensional functional MRI

Project Leader
Peter Lundberg, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Maria Magnusson, Olof Dahlqvist Leinhard, Helene van Ettinger-Veenstra

Grants
Swedish Research Council (VR),
Cancerfonden
Knowledge foundation

Key Publications
Magnusson M, Dahlqvist Leinhard O, Brynolfsson P, Thyr P, Lundberg P. 3D Magnetic Resonance Imaging of the Human Brain – Novel Radial Sampling, Filtering and Reconstruction. In: Proceedings of the 12th IASTED International Conference on Signal and Image Processing, Acta Press, 2010.

Magnusson M, Dahlqvist Leinhard O, Brynolfsson P, Lundberg P. A 3D-plus-time radial-Cartesian hybrid sampling of k-space with high temporal resolution and maintained image quality for MRI and fMRI. In: Proceedings of the 19th Scientific Meeting & Exhibition of ISMRM, Montréal, Québec, Canada, 2011.

Magnusson M, Dahlqvist Leinhard O, van Ettinger-Veenstra H, Lundberg P. FMRI Using 3D PRESTO-CAN – A Novel Method Based on Golden Angle Hybrid Radial-Cartesian Sampling of K-Space In: Proceedings of the 20th Scientific Meeting & Exhibition of ISMRM, Melbourne, Australia, Montréal, 2012.

POPULAR SCIENTIFIC SUMMARY

PETER LUNDBERG

PRESTO-CAN for Three-Dimensional Functional MRI

The magnetic resonance images (MRI) are not produced directly by the MRI scanner. Instead raw data from the scanner is temporary stored in the so called k-space. The raw data comes in to k-space as sinus waves of different frequencies. These frequencies can then be transformed into images by a mathematical operation. This is called reconstruction. Normally, the frequency measurements are performed in thin 2D slices of the body which are reconstructed and combined in a stack to form an image volume. Occasionally, k-space is measured directly in 3D with a square pattern called Cartesian sampling pattern (figure 1, left).

In contrast to the 3D Cartesian geometry, our method PRESTO-CAN samples k-space using a hybrid between a radial geometry and a Cartesian geometry (figure 1, right). The large steps in the angular direction gives a fast recording of the important information located in the center of k-space.

As seen to the right in figure 1, there are more densely sampled data in the inner part of k-space. It has been shown that by removing parts of the inner over-sampled k-space at certain time points, the temporal resolution can be further increased. However, this gives a more complicated sampling pattern and a non-trivial reconstruction. PRESTO-CAN has shown to provide excellent temporal resolution and satisfactory image quality.

The method was developed having functional MRI (fMRI) applications in mind. In fMRI, MRI-volumes are recorded during a time period when

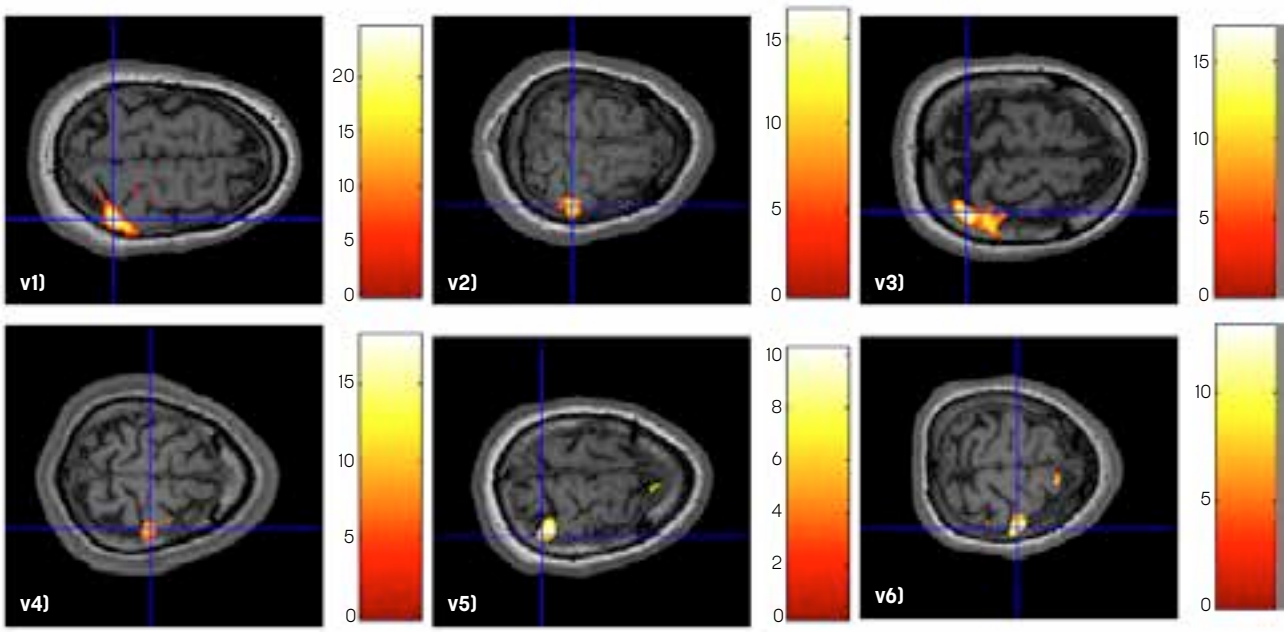


FIGURE 2. fMRI-activation in left fingers motor cortex computed from MRI-data based on PRESTO-CAN for six different volunteers.

a person/patient performs a particular task. By analyzing the MRI time sequence, it is possible to detect brain activity. Accordingly, it is desirable with a high time resolution.

A major advantage of the PRESTO-CAN sequence is that it allows for whole brain coverage. We are currently finishing a comparative fMRI study between PRESTO-CAN and conventional techniques, like EPI. Figure 2 shows left fingers fMRI-activation in six different volunteers computed from MRI-data based on PRESTO-CAN. The rather simple geometry of PRESTO-CAN makes it easy to include standard procedures for speeding up the data acquisition further, such as parallel imaging which can be combined with unique 3D motion correction schemes. These possibilities will be investigated further. ■

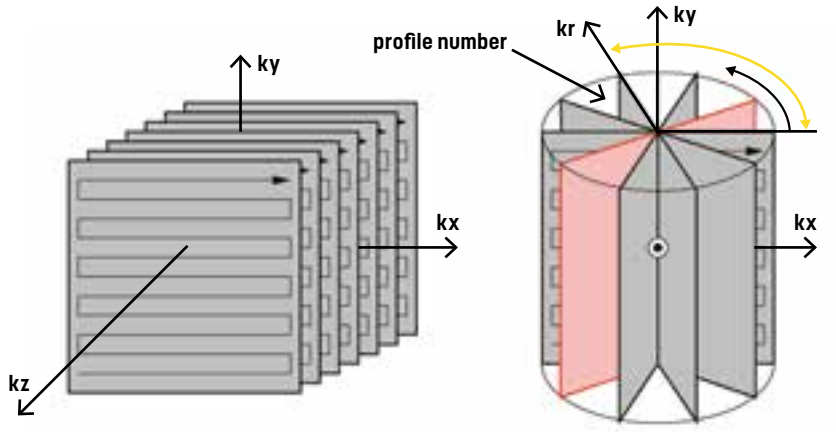


FIGURE 1. Left: 3D Cartesian sampling of k-space. Right: PRESTO-CAN sampling of k-space.

PROJECT INFORMATION

Project Name
MR-Mammography 3.0 (BREASA): Pharmacological Prevention of Breast Cancer Monitored Using a Novel Comprehensive Magnetic Resonance-Based Protocol

Project Leader
Peter Lundberg, Department of Medical and Health Scienses, Division of Radiological Sciences

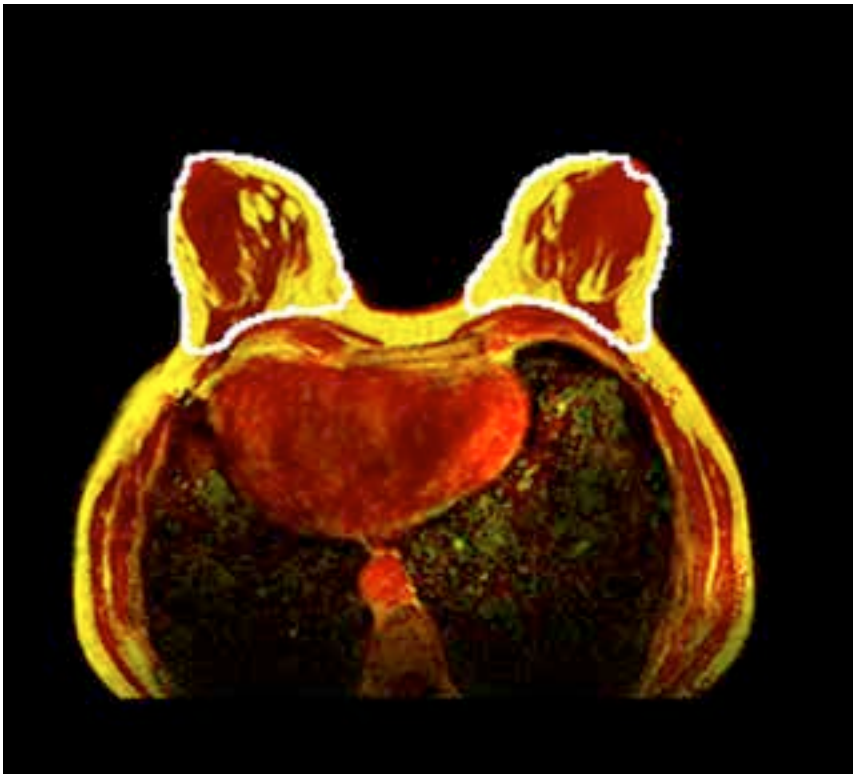
Main Project Participants
Magnus Borga, Charlotta Dabrosin, Olof Dahlqvist Leinhard, Thobias Romu, Mikael Forsgren, Johan Kihlberg, Nicholas Kinnunen, Pantelis Gialias, Anna Rzepecka

Grants
LiU-Cancer
Cancerfonden

Key Publications
Abrahamsson A, Rzepecka A, Romu T, Borga M, Dahlqvist Leinhard O, Lundberg P, Kihlberg J, Dabrosin C, »Dense breast tissue in postmenopausal women is associated with a pro-inflammatory microenvironment in vivo«, Oncoimmunology, 5(10), 2016.

POPULAR SCIENTIFIC SUMMARY

PETER LUNDBERG



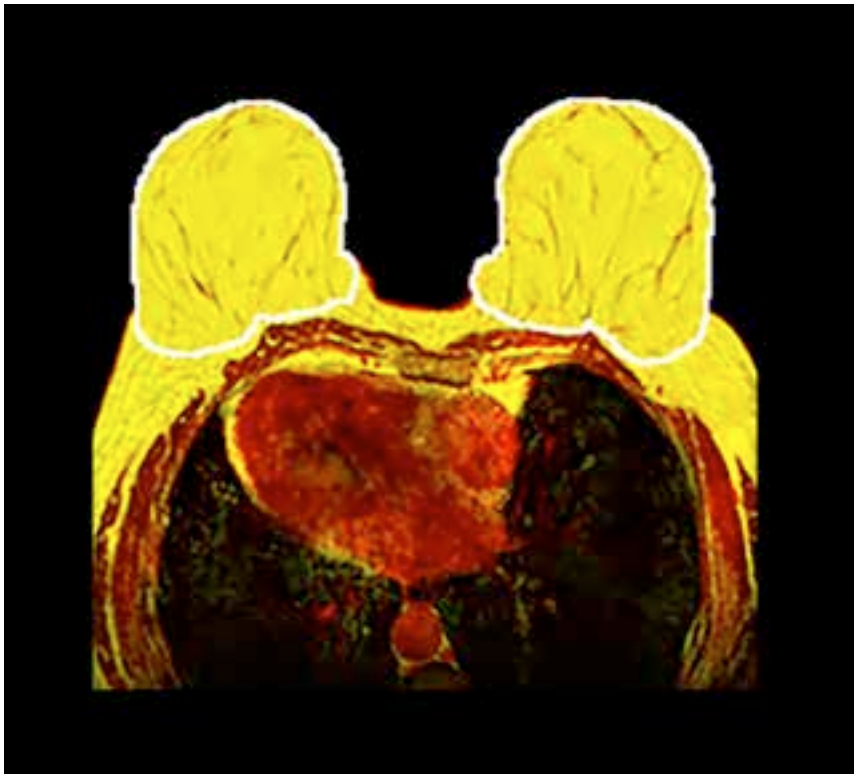
BREASA

Breast cancer is the most common form of cancer in women with a life-time risk of over 12 %. A major risk factor for breast cancer is breast density. Women with dense breasts have been shown to have a four- to six-fold increased risk of developing breast cancer.

Dense breast tissue contains higher amounts of stroma, including collagen, and less fat tissue. Conflicting results regarding a difference in the amounts of epithelial cells have been reported, although it varies only between 1–6 % and the proliferation of these cells is also very low. Hence, the underlying biological mechanism(s) of a higher breast cancer risk of dense breast tissue is to date unexplored.

In addition to dense breast tissue, exposure to sex steroids such as estradiol is an established risk factor for breast cancer. An inflammatory microenvironment has also been associated with increased risk of cancer and a reduced risk of breast cancer has been reported in women who regularly use anti-inflammatory drugs.

Despite the wide use of mammo-



MR-quantification of lean tissue fraction in postmenopausal women attending the regular mammography screening program. The images are representative for dense (left) and non-dens (right) breasts.

graphy as a general screening tool for breast cancer, this method has a painfully high false-negative rate (about 10–25 %).

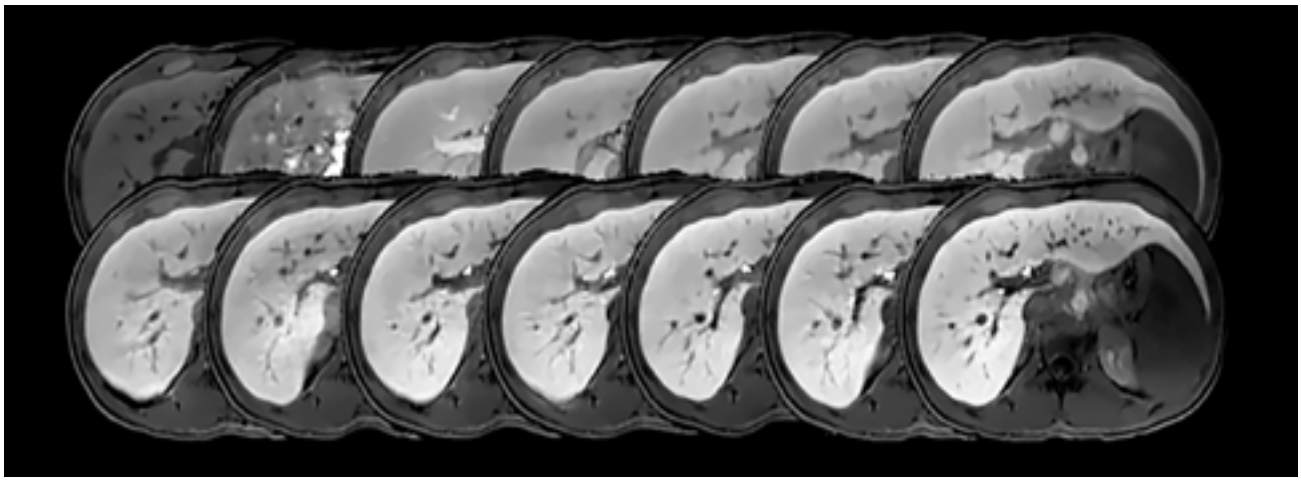
Today, there is growing interest in using Magnetic Resonance (MR) for breast cancer screening, in particular in the younger population as the higher density of the younger breast can obscure underlying lesions in mammography. The absence of ionizing radiation also makes MR a particularly interesting tool for clinical research on breast cancer risk factors.

In order to perform studies involving MR and MR-based risk assessment and diagnosis, a clinically useful MR protocol has recently been developed. The protocol has been developed, implemented at CMIV and used in a pilot study on 40 female subjects. Furthermore, methods for quantifying clinically relevant parameters from the MR data have been explored.

The aims of BREASA are to further validate a comprehensive MR protocol, and also to investigate the clinical relevance for the derived MR-based parameters in a cohort of subjects that are treated using an anti-inflammatory agent. Will the treatment affect the levels of inflammatory biomarkers, and will it affect the quantitative assessment of stroma, associated imaging biomarkers and the tissue? The ultimate long-term end-point is whether the treatment will reduce the risk for breast cancer. ■

POPULAR SCIENTIFIC SUMMARY

PETER LUNDBERG



Liver Function Evaluation

The liver is an important organ involved in vital processes as metabolism and removal of toxins. The western way of life is putting a high strain on the organ and liver diseases are consequently increasing. Liver Function Evaluation is a clinical research project that with the help of magnetic resonance (MR) will develop new methods for diagnosing liver disease. The new technology is expected to result in safer liver surgery and better treatment of diffuse liver diseases.

Many malignant liver diseases are diagnosed when they are in an advanced stage and the liver may be seriously damaged. At that time, surgery or liver transplantation is often the only curable treatment option. In order for the patient to survive a liver tumor operation, a healthy piece of the liver has to be left in the body. The liver is then growing during 4–5 weeks to regain almost full size and function. The first week after the surgery is a critical time since the small sized liver has to manage the job of a full liver.

Today, determination of how much of the liver to remove is difficult as only a rough estimate of the liver function can be made. Occasionally, patients may suffer from liver failure following radical surgery. On the other hand, some patients are wrongly judged unfit for surgery when the rough estimate suggests that they will not survive the procedure. With a better estimate of size and function in the liver residue more patients could be surgical candidates.

With the help of MR it is possible to measure several parameters in the liver without invasive procedures. The MR also enables a better overview of the liver status as a whole compared to

biopsies, as they only show status at the location where the sample is taken. If the biopsy is extracted from the wrong area there is a risk that important information is overlooked.

The magnetic resonance technology may, among other things, be used to measure the amount of fat in the liver, measure the uptake of a contrast agent to get an idea of how well the liver works and measure levels of many different elements, including iron and phosphorus compounds. In this project multimodal methods for analyzing the liver is developed.

One of the MR methods used is elastography. The examination shows fibrosis, formation of connective tissue, in the liver. The connective tissue makes the liver less flexible and impairs its normal elasticity. During MR mechanical vibrations are sent into the patient´s body. The vibrations are propagated differently depending on the flexibility of the tissue. Through registration of the different vibrations the MR-scanner can separate healthy tissue regions from diseased. ■

PROJECT INFORMATION

Project Name
Liver Function Evaluation

Project Leader
Peter Lundberg, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Stergios Kechagias, Mattias Ekstedt, Per Sandström, Olof Dahlqvist Leinhard, Nils Dahlström, Mikael Forsgren, Markus Karlsson, Thobias Romu, Patrik Nasr, Johan Kihlberg, Anna Lindhoff Larsson, Gunnar Cedersund, Bengt Norén, Tommy Johansson, Torkel Brismar, Martin Henriksson, Lars-Åke Levin

Grants
VINNOVA 2013-2017;
Swedish Research Council (VR/NT) 2015–2018/2019

Key Publications

Nasr P, Forsgren MF, Ignatova S, Dahlström N, Cedersund G, Leinhard OD, Norén B, Ekstedt M, Lundberg P, Kechagias S.
(2017) Using a 3 %o Proton Density Fat Fraction as a Cut-Off Value Increases Sensitivity of Detection of Hepatic Steatosis, Based on Results From Histopathology Analysis. Gastroenterology. 2017 Jul;153(1):53–55.e7. doi: 10.1053/j.gastro.2017.03.005. Epub 2017 Mar 9.

Homeyer A, Nasr P, Engel C, Kechagias S, Lundberg P, Ekstedt M, Kost H, Weiss N, Palmer T, Hahn HK, Treanor D, Lundström C.
(2017) Automated quantification of steatosis: agreement with stereological point counting. Diagn Pathol. 2017 Nov 13;12(1):80. doi: 10.1186/s13000-017-0671-y.

Forsgren MF, Norén B, Kihlberg J, Dahlqvist Leinhard O, Kechagias S, Lundberg P.
(2015) Comparing hepatic 2D and 3D magnetic resonance elastography methods in a clinical setting – Initial experiences. Eur J Radiol Open. 2015 Apr 28;2:66–70. doi: 10.1016/j.ejro.2015.04.001. eCollection 2015.

PROJECT INFORMATION

Project Name
The neurocorrelates of meditative practice

Project Leader
Rozalyn Simon, Department of Medical and Health Sciences, Radiological Sciences

Main Project Participants
Maria Engström

Grants
FORSS
Alzheimerfonden

Key Publications
Rozalyn Simon and Maria Engström. The default mode network as a biomarker for monitoring the therapeutic effects of meditation. Frontiers in Psychology, 2015; 6:776.

M. Engström, J. Pihlsgård, P. Lundberg, and Birgitta Söderfeldt. Functional magnetic resonance imaging of hippocampal activity during silent mantra meditation. Journal of Alternative and Complimentary Medicine, 2010;16:1253-1258.

M. Engström and B. Söderfeldt. Brain activation during compassion meditation: a case study. Journal of Alternative and Complimentary Medicine, 2010;16:597-599.

POPULAR SCIENTIFIC SUMMARY

ROZALYN SIMON

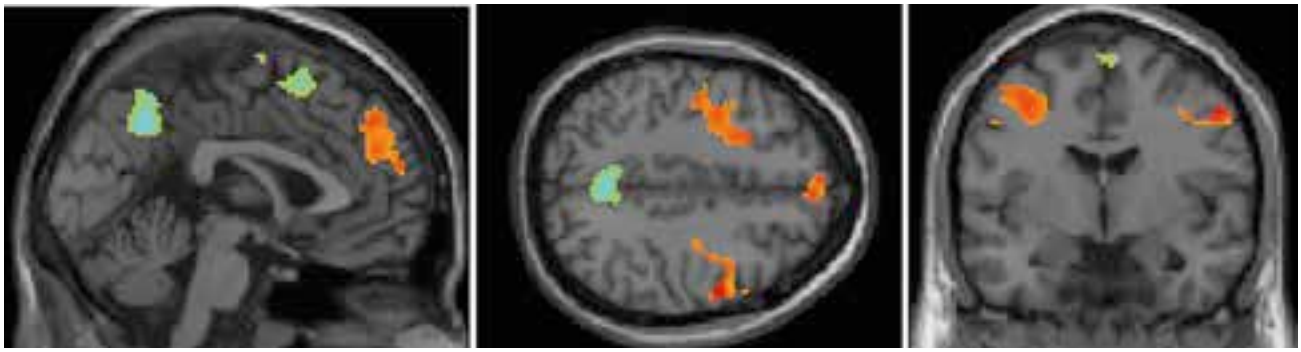
The Neurocorrelates of Meditative Practice

When an individual is in a quiet state of rest, thought-related activity in the brain doesnot cease. This activity can be recorded by functional magnetic resonance imaging (fMRI) and represented as constellations of anatomic regions in the brain that co-activate during cognition called resting state networks. Although there are a number of such networks, the default mode network (DMN) became the first, and now the most extensively studied of the many known resting state functional networks. Network activation has been associated with specific mentation including autobiographical memory, self-reflective thought, envisioning future events, mind wandering, and considering the thoughts and perspectives of others. Abnormal DMN activity – such as distractive mind wandering during tasks or excessive rumination – has been associated with a number of psychological disorders such as schizophrenia, anxiety, depression, attention deficit hyperactivity disorder (ADHD), and Alzheimer's disease (AD).

As research strengthens the link between anatomical regions of the DMN and psychological disorders, much interest has been directed toward non-pharmacological means of harnessing the brains inherent neuroplasticity and altering patterns of behavior within this network. One promising method of achieving this goal is through meditation training.

Meta-analyses examining the speci-

Data from five zen meditators showing differences in the Default mode network between focused attention meditation on breath versus resting state. Increases in red, decreases in activity in green.



Activations in the default mode network for meditators during rest alone.

fic neurocorrelates of meditation have shown reductions in DMN activity as a primary outcome of meditation practices. In addition, modulation of DMN activity through meditative training has been demonstrated to help individuals concentrate and increase their present awareness, thus reducing mind wandering activities and improving cognition. Functional magnetic resonance imaging (fMRI) has been used to successfully visualize changes in the DMN resulting from meditative practices such as Vipassana and Mindfulness-based stress reduction (MBSR).

Although there is evidence that meditation practice alters DMN activity, the specific neurocorrelates based on the type of meditation practiced remain unclear. For example, what regions of the brain are active when one focuses their attention on the breath? How does open awareness of one's thoughts affect emotional centers of the brain?

In this project we are investigating the neural correlates of meditative practice in both experienced and novice meditators. Our goal is to identify regions of the brain affected by three specific types of meditation techniques by fMRI and EEG. To date the project has examined experienced meditators, novices, and controls practicing techniques common to Buddhist meditation. These examinations include fMRI and DTI, as well as number of neuropsychological evaluators and first-person reports. We will be investigating cognitive activations, functional connectivity between regions, changes in gray and white matter, and changes in the quality of life resulting from meditative training.

Research-based evidence indicates that these practices, when used efficiently, could prove effective not only in the delay of cognitive dysfunction, but also in the enhancement of grey matter density and neuron plasticity in specific regions of the brain. By determining these neurocorrelates, it is our intention to effectively employ very specific meditative techniques as a means for the individual to regain control over irregular DMN activity and connectivity while providing a new perspective on the value of the present moment. ■

PROJECT INFORMATION

Project Name
Sleep Abnormality Network Description: Modeling and Analysis in Neuroimaging (SAND:MAN)

Project Leader
Maria Engström, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Natasha Morales-Drissi, Suzanne Witt, Anne-Marie Landtblom, Tove Hallböök, Atilla Szakacs, Thomas Karlsson, Henriettae Ståhlbrandt, Peter Lundberg, Anders Tisell, Sofie Tapper, Alexander Wessén, Helena Gauffin

Grants
FORSS 2012–2018

Key Publications
Suzanne T Witt, Natasha Morales Drissi, Sofie Tapper, Anna Wretman, Attila Szakács, Tove Hallböök, Anne-Marie Landtblom, Thomas Karlsson, Peter Lundberg, Maria Engström.
Evidence for cognitive resource imbalance in adolescents with narcolepsy. Brain Imaging and Behavior, 2017. doi: 10.1007/s11682-017-9706-y.

Natasha Morales Drissi, Attila Szakács, Suzanne T Witt, Anna Wretman, Martin Ulander, Henrietta Ståhlbrandt, Niklas Darin, Anne-Marie Landtblom, Tove Hallböök, Maria Engström.
Altered brain microstate dynamics in adolescents with narcolepsy. Frontiers in Human Neuroscience, 2016;10:369.

M. Engström, T. Hallböök, A. Szakacs, T. Karlsson, A.M. Landtblom.
Functional magnetic resonance imaging in narcolepsy and the Kleine-Levin Syndrome. Frontiers in Neurology, 5:105, 2014.

POPULAR SCIENTIFIC SUMMARY

MARIA ENGSTRÖM

Modeling and Analysis in Neuroimaging

In this project, we investigate brain function in patients with sleep disorders. Our ongoing study is about brain function and body composition and their relation to clinical symptoms in adolescents with narcolepsy.

Narcolepsy is characterized by daytime sleep attacks, poor nighttime sleep, and sudden loss of muscle tonus (cataplexy) caused by the loss of certain neurons in the hypothalamus: a central structure in the brain. These neurons produce the neurotransmitter, orexin, that takes part in the regulation of sleep and wakefulness, and also body metabolism. Orexin deficiency is one hypothesis behind weight gain at narcolepsy onset.

To investigate the relation between brain function and clinical symptoms in narcolepsy, we use functional MRI (fMRI) and simultaneous electroencephalography (EEG), quantitative MRI and body fat imaging. We have shown that adolescents with narcolepsy have altered resting state brain dynamics. Compared to healthy controls, they are less likely to stay in a specific brain microstate, related to the default mode network, which is active when the brain is at rest. We concluded that narcolepsy might be accompanied with a disruption in the default mode network that is disease specific. This conclusion was supported by our second study where we investigated working memory function. Many patients with narcolepsy complain about subjective working memory problems, but research has not found objective evidence. In our study, we neither found signs of working memory performance deficits nor specific brain dysfunction related to working memory. However, we did find an imbalance of cognitive resources manifested by decreased activation of the default mode network pointing to a dysregulation within the sustained attention system, which could be the origin behind self-reported cognitive difficulties in narcolepsy.

Preliminary data from quantitative MRI show structural changes in the brain stem in patients with narcolepsy. Figure 1A shows areas with lower R2 relaxation rate, a finding that could be related to neuromelanin containing brain stem nuclei or myelin. We observed that the aberrant brain stem region was functionally connected to the cerebellum and the thalamus together with other subcortical areas (Fig. 1B). We also have preliminary data that shows that narcolepsy patients have increased subcutaneous fat volume (Fig. 2) with a trend level relation to orexin measured in cerebrospinal fluid (CSF). ■

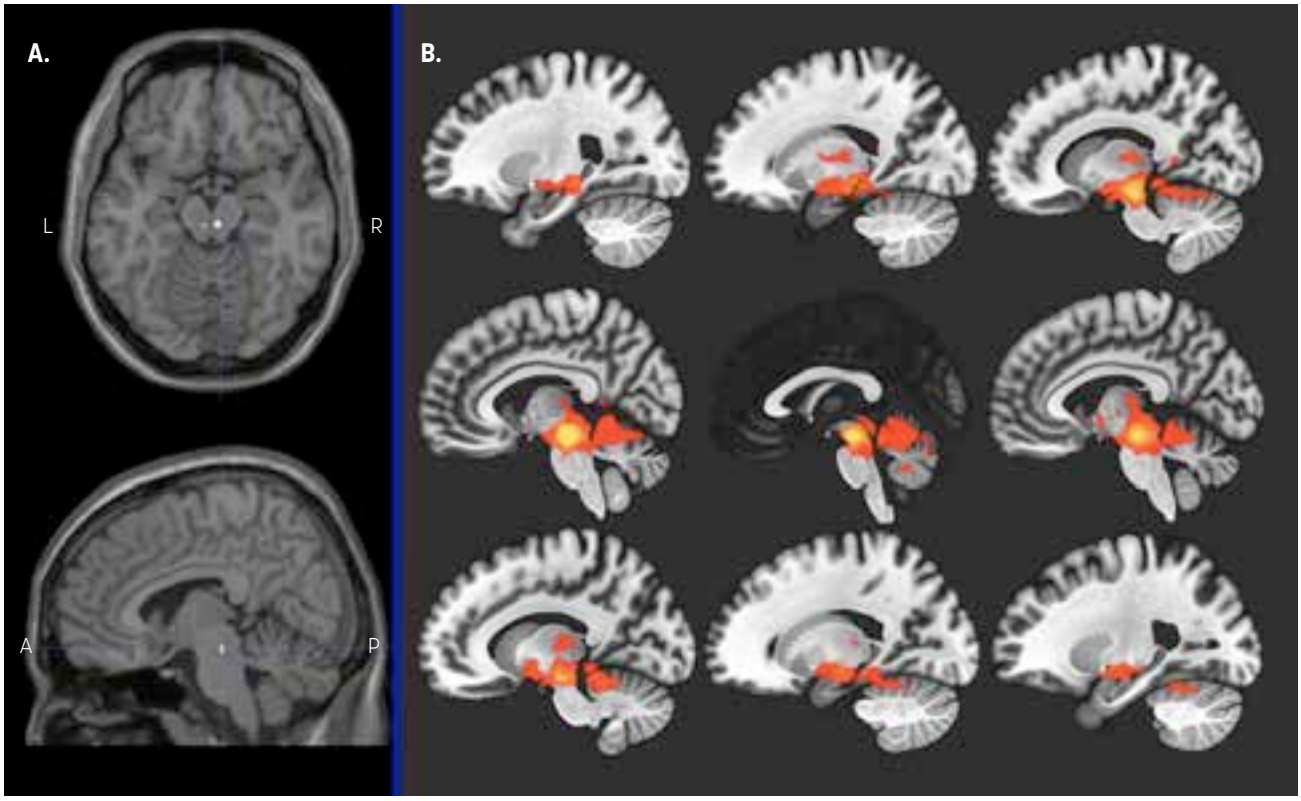


FIGURE 1A. Brain stem structural changes in narcolepsy. **FIGURE 1B.** Brain stem functional connectivity.

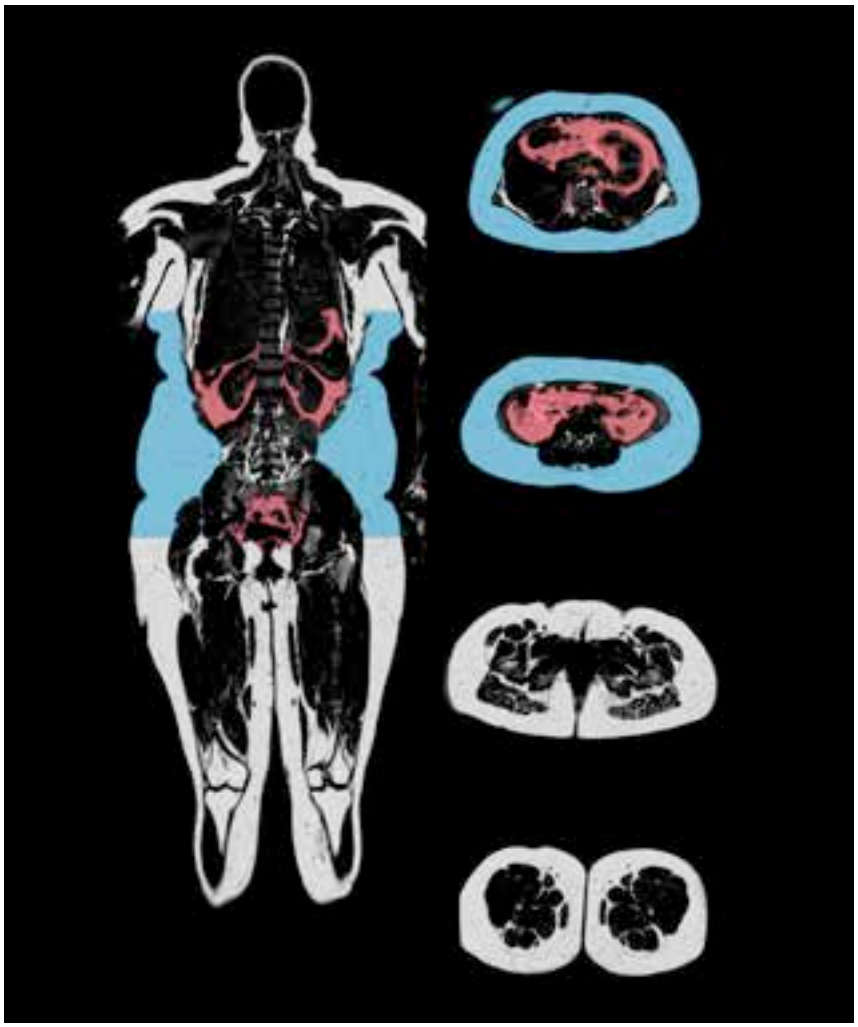


FIGURE 2. Narcolepsy patient with increased subcutaneous fat volume.

POPULAR SCIENTIFIC SUMMARY

MARIA ENGSTRÖM

Mathematical Modelling of Mechanisms in the Human Brain

By functional magnetic resonance imaging (fMRI) we can visualize brain areas that are activated by certain tasks or sensory stimuli. Despite that fMRI is widely used in both research and in the clinic, the biological mechanisms behind the brain activation maps are largely unknown. This means that we do not have information about e.g., neurotransmitters that underlie the fMRI signal.

This lack of information can be overcome by mathematical modelling and systems biology where different hypotheses describing e.g., neurotransmitter action are translated to mathematical equations (= models). These models are tested against experimental data: if a model cannot explain data the hypothesis is rejected, if a model can explain data it is further investigated and tested against new data. In this way, we can get information about neurotransmitters etc. and we can also predict new data (Figure 1).

We have shown that a model based on neurotransmitter influence on the brain's blood flow can explain and predict fMRI data. Importantly, we have rejected the hypothesis of brain metabolism being the driving force behind fMRI. According to our model, if metabolism is driving fMRI then glucose levels need to be depleted during brain activation. That is not biologically plausible.

The fMRI signal can be positive or negative with respect to baseline (Figure 2A–B). Positive signals are strongly correlated to neuronal activity, but less is known about the negative signals. Recently we have shown that neural inhibition can explain negative signals. When the brain is activated there are interactions between the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA. When the GABA effect is dominant, our model shows that the fMRI signal turns negative (Figure 2B).

Our modelling approach can advantageously be used to study pharmacological effects. We have shown that working memory activation in certain brain areas are influenced by the GABA modulator diazepam (Figure 2C). At diazepam administration, the fMRI signal changes from positive to negative and this can be explained by enhanced GABA effect on the calcium influx in neuronal cells (Figure 2D).

In summary, by our modelling approach we can firmly reject hypotheses that cannot explain data, we can get information about hidden variables e.g., neurotransmitter action, and we can explain pharmacologically induced brain responses. The next step is to advance the model by including improved descriptions of synaptic activity and descriptions of blood flow – blood volume interaction. We are aiming to define model-based biomarkers of brain function, that is to say biomarkers that can express brain activation in terms of biological properties. ■

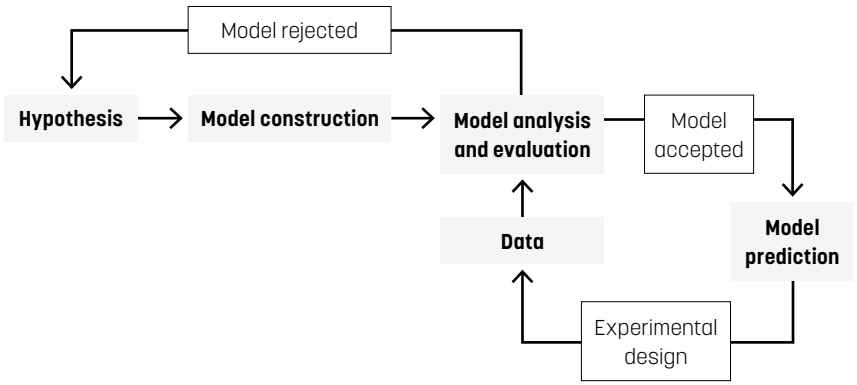


FIGURE 1. Schematic overview of the iterative modelling workflow used in the project.

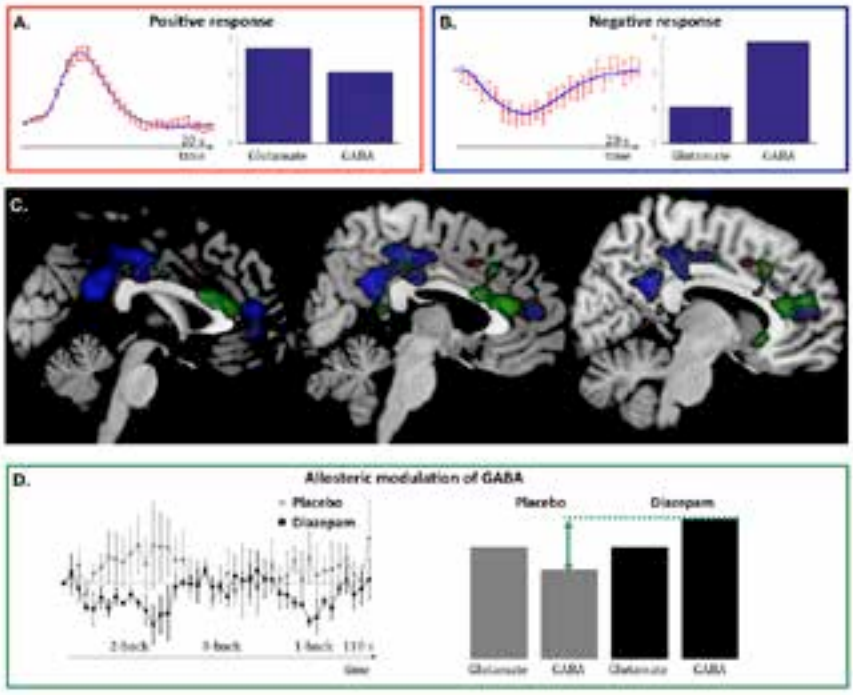


FIGURE 2. Relation between neurotransmitters and positive and negative brain responses.

A. Typical positive fMRI signal (left) and model simulations of the neurotransmitters glutamate's and GABA's effect on calcium influx in neural cells (right).

B. Typical negative fMRI signal (left). The graph to the right shows that the inhibitory neurotransmitter GABA has a dominant effect at negative fMRI signals.

C. Activation maps from a working memory task in three sagittal slices showing positive responses in red and negative responses in blue. Green areas show brain activation correlated to the GABA-modulator diazepam.

D. The fMRI signal from a working memory task, n-back, with three difficulty levels; 2-back being the most difficult task (left). During the placebo session, the signal is predominantly positive and during the diazepam session it is mostly negative. The graph to the right shows the effect of glutamate and GABA on the calcium influx. Diazepam has a modulating effect that increases the GABA effect keeping GABA concentration constant.

PROJECT INFORMATION

Project Name
Ab Initio Mathematical Modelling of Mechanisms in the Human Brain

Project Leader
Maria Engström, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Karin Lundengård, Sebastian Sten, Natasha Morales-Drissi, Gunnar Cedersund, Fredrik Elinder, Susanna Walter

Grants
Swedish research council 2015–2018
FORSS 2014–2018

Key Publications
Sebastian Sten, Karin Lundengård, Suzanne T Witt, Gunnar Cedersund, Fredrik Elinder, Maria Engström. Neural inhibition can explain negative BOLD responses: a mechanistic modelling and fMRI study. NeuroImage, 2017;158:219-231.

Karin Lundengård, Gunnar Cedersund, Sebastian Sten, Felix Leong, Alexander Smedberg, Fredrik Elinder, Maria Engström. Mechanistic mathematical modelling tests hypotheses for the neurovascular coupling in fMRI. PLOS Computational Biology, DOI:10.1371/journal.pcbi.1004971, 2016.

Karin Lundengård. Mechanistic Modelling – a BOLD response to the fMRI information loss problem. Linköping University medical dissertations, No. 1591, 2017.

PROJECT INFORMATION

Project Name
Neuroimaging of decoding and language comprehension in young very low birth weight adolescents

Project Leader
Nina Nelson Follin, Department of Clinical and Experimenta Medicine, Division of Childrens and Women's Health

Main Project Participants
Helene van Ettinger-Veenstra, Carin Widén, Maria Engström, Thomas Karlsson, Ingemar Leijon

Grants
FORSS

Key Publications
Van Ettinger-Veenstra Helene, Widen Carin, Engström Maria, Karlsson Thomas, Leijon Ingemar, Follin Nelson Nina.
Neuroimaging of decoding and language comprehension in young Very Low Birth Weight (VLBW) adolescents: indications for compensatory mechanisms. PLoS ONE 2017 12(10): e0185571.

POPULAR SCIENTIFIC SUMMARY

NINA NELSON FOLLIN

Neuroimaging of Language Comprehension in Low Birth Weight Adolescents

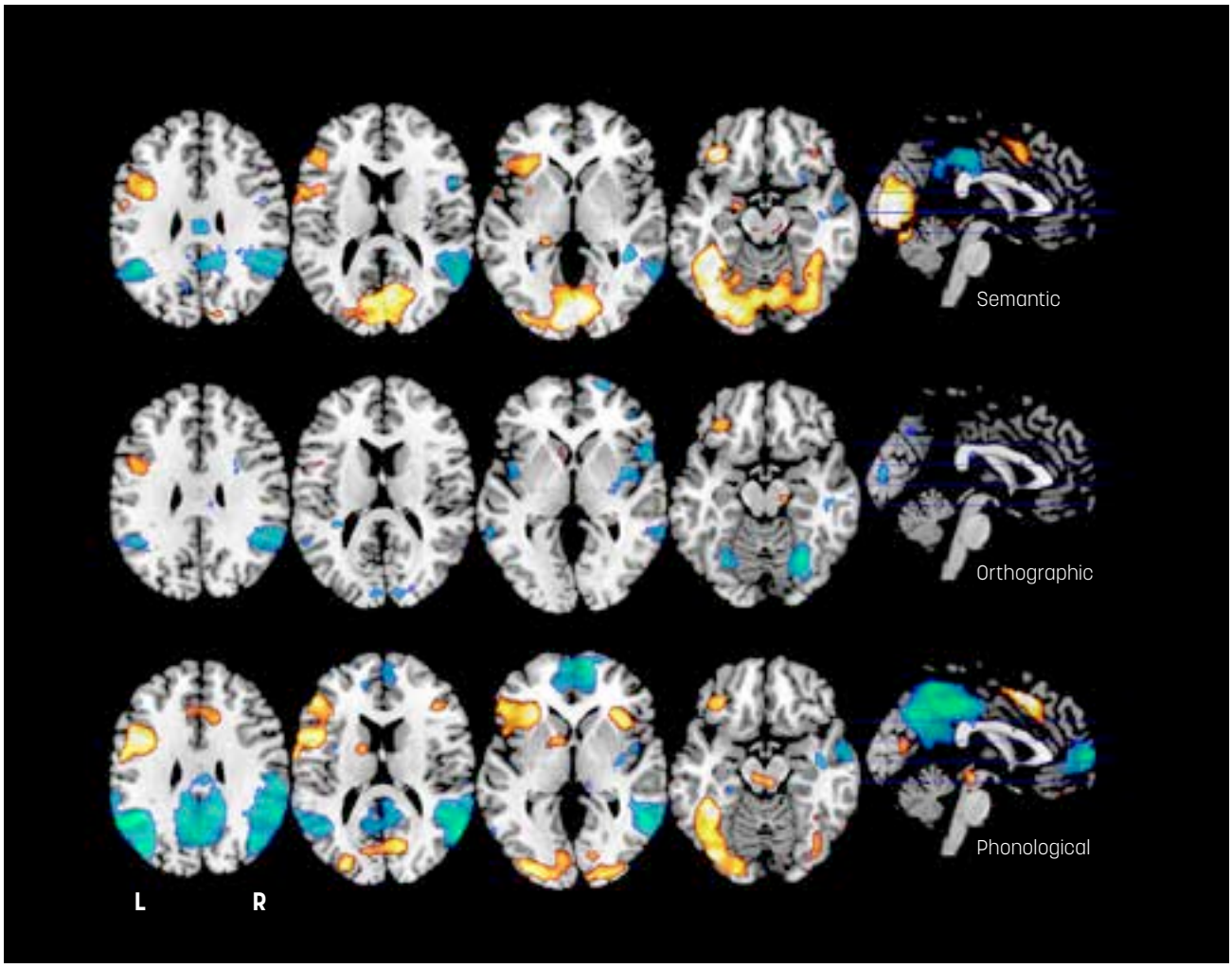
Children that are born preterm with a very low birth weight have an increased risk of developing impairments in the cognitive and behavioral domains. We investigated whether their neural pathways would reflect impaired decoding and language comprehension, and we investigated correlations of cognitive performance to neural changes.

Thirteen adolescents between 12–14 years that were born around 30 weeks (normal gestation time is around 38–40 weeks) with a birth weight of under 1 500 gram were compared to 13 adolescents born with normal birth weight (above 2 500 gram).

We obtained functional magnetic resonance images (fMRI) during three different types of language processing, namely phonological processing of how a word sounds, orthographic processing of how a word is spelled, and semantic processing of in which semantic category a word belongs (see Figure).

Our results showed that indeed adolescents with very low birth weight have different neural activation during different types of language processing when compared to normal birth weight term-born controls. We observed a difference in neural activation between birth weight groups for phonological as well as semantic processing in the left inferior frontal gyrus. Different parts of this region are involved in either phonological or semantic processing, and our results support the hypothesis that children born with very low birth weight may compensate for a dysfunctional phonological processing system.

Performance differences on the three fMRI language tasks showed not to be significant between groups, but there was an interaction effect of higher accuracy on the semantic task with increased left angular gyrus activation within the very low birth weight group. In addition, we found that the very low birth weight group had impaired performance on the WISC Block Design test that tests for spatial processing. We



suggest that this decreased performance may have been influential in development of decoding pathways but does not affect reading ability performance directly. The aberrant neural activation and deactivation pattern for reading ability components appears to be effective in compensating for potential underperformance on decoding and language comprehension tasks and cannot directly be explained as cognitive impairment effects. ■

FIGURE. Phonologic, orthographic, and semantic processing evoked neural activation (warm/orange) and deactivation (cool/blue) for all participants.
Results showed that the phonological decoding activation pattern was more widespread for very low birthweight adolescents, while during orthographic and semantic processing, activation was reduced.

PROJECT INFORMATION

Project Name
Visualizing the clinical model of chronic pain: towards a better understanding of pain behavior and treatment

Project Leader
Björn Gerdle, Department of Medical Health Sciences, Division of Community Medicine

Main Project Participants
Helene van Ettinger-Veenstra, Peter Lundberg, Peter Alföldi, Martin Södermark, Thomas Graven-Nielsen, Anna Sjörs, Maria Engström

Grants
FORSS Swedish Research Council
Danish National Research Foundation

Key Publications
Van Ettinger-Veenstra Helene, Lundberg Peter, Alföldi Peter, Södermark Martin, Graven-Nielsen Thomas, Sjörs Anna, Engström Maria, Gerdle Björn. Chronic Widespread. Pain patients show disrupted cortical connectivity in relation to pain sensitivity, psychological strain, and as an effect of experimental pain. Arthritis & Rheumatology submitted.

POPULAR SCIENTIFIC SUMMARY

BJÖRN GERDLE

Visualizing the Clinical Model of Chronic Pain

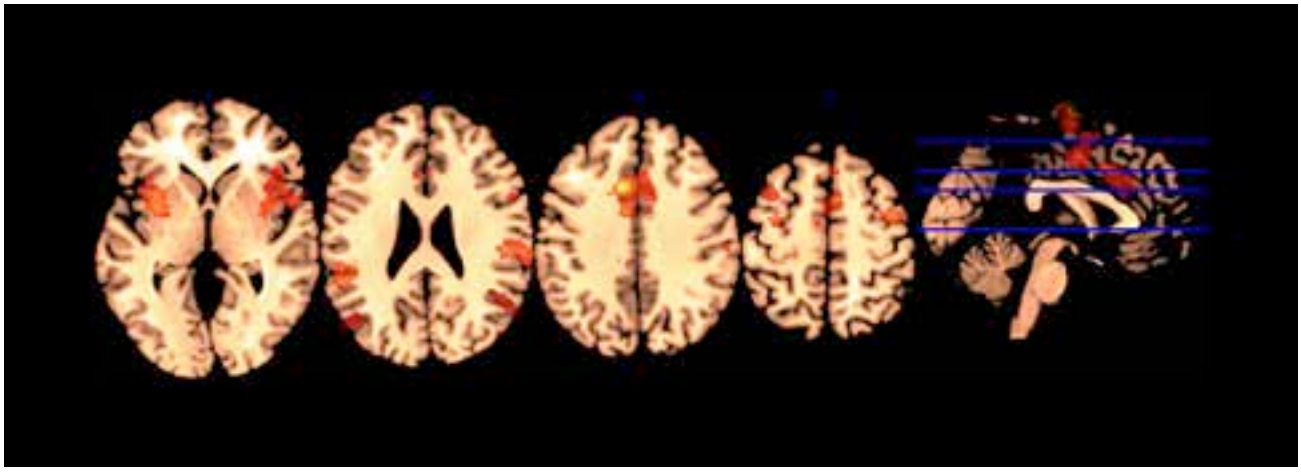
A considerable group of all patients that have a chronic pain condition (up to 25 %)will develop a more widespread pattern of chronic pain. Chronic widespread pain (CWP) is considered the worst chronic pain condition, affects predominantly women, and results in many negative effects such as work absence and a poor quality of life. An important subgroup of chronic widespread pain is fibromyalgia (FM) syndrome; these patients also develop hyperalgesia which is an increased sensitivity to pain.

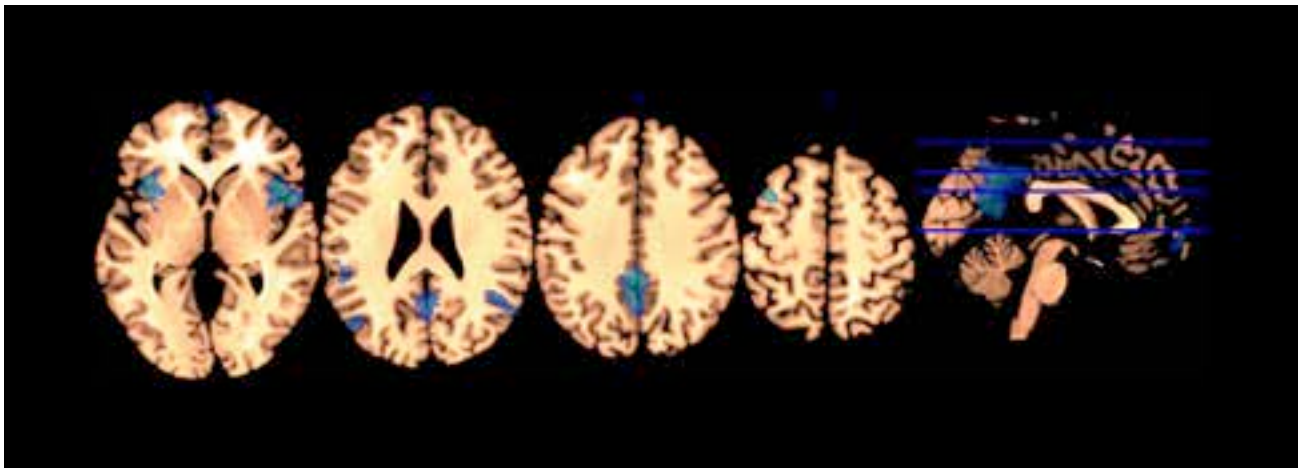
This project aims to understand the interactions between pain and psychological characteristics of CWP and FM in relation to chronic pain pathophysiology. Neural alterations have been observed in the pain processing regions and prefrontal cognitive control regions with task-based functional magnetic resonance imaging (fMRI), as well as (rs-)fMRI in intrinsically active neural networks that consist of interconnected regions and represent different functions of the brain.

The default mode network (DMN) that is involved in introspective processing and the salience network (SN) that processes salient stimuli including pain and filters information to support behavioral choice are such affected intrinsic neural networks.

As the DMN and SN are affected by acute pain, the observed disruption in chronic pain has yet to be disentangled from the perception of current, acute pain. Moreover, the neural influence of psychological aspects such as comorbid depression and anxiety symptoms are poorly documented in CWP. How are the altered neural patterns in FM related to chronic habitual pain and acute pain, and how are they influenced by psychological characteristics?

We used rs-fMRI to measure intrinsic





neural network connectivity. Our first study showed a short-term neuroplasticity of SN and DMN resting state networks directly after acute pain stimulation in CWP. In normal healthy controls, the DMN as well as the SN showed strong within-network connectivity, but low or even negative between-network connectivity. Patient effects were dependent on pain sensitivity (pressure pain detection threshold), and psychological strain (which included depressive and anxiety symptoms).

The results of this study demonstrate a complicated interaction of psychological strain, pain sensitivity, and experimental pain processing in relation to functional connectivity changes in DMN and SN for CWP patients. These effects are dissimilar from current findings on FM and chronic non-widespread pain. ■

FIGURES. These figures show the correlation of connectivity with higher pain sensitivity within the chronic widespread pain (CWP) patient group.

Top figure in warm/orange: connectivity between the anterior cingulate and insular nodes of the salience network (SN) are more strongly connected for CWP patients who are more sensitive for pain, measured at baseline. This is an augmentation of the normally high connectivity within the SN. Also, these SN regions are more strongly connected to the default mode network (DMN), in specific the lateral parietal nodes. Normally, connectivity between networks is low.

Bottom figure in cool/blue: after receiving painful pressure pain, the connectivity pattern for pain sensitive CWP patients changed from the baseline pattern towards decreased connectivity within the SN (insulae) as well as decreased connection between SN and DMN (posterior cingulate cortex).

PROJECT INFORMATION

Project Name
Brain-gut interactions in IBS

Project Leader
Susanna Walter, Department of Clinical and Experimental Medicine, Division of Neuro and Inflammation Sciences

Main Project Participants
Rozalyn Simon, Maria Engström, Peter Lundberg, Suzanne Witt, Nawroz Barazanji, Olga Bednarska, Anna-Karin Norlin, Åsa Keita, Felipe de Meira, Adriane Icenhour, Sigrid Elsenbruch

Grants
AFA

Key Publications
Brain functional connectivity is associated with visceral sensitivity in women with Irritable Bowel Syndrome. Icenhour A, Witt ST, Elsenbruch S, Lowén M, Engström M, Tillisch K, Mayer EA, Walter S. Neuroimage Clin. 2017 Jun 2;15:449-457. 2017.

Vasoactive Intestinal Polypeptide and Mast Cells Regulate Increased Passage of Colonic Bacteria in Patients With Irritable Bowel Syndrome. Bednarska O, Walter SA, Casado-Bedmar M, Ström M, Salvo-Romero E, Vicario M, Mayer EA, Keita ÅV. Gastroenterology. 2017 Oct;153(4): 948-960.

Insular brain metabolites are related to somatic symptom burden and cognitive coping in Irritable Bowel Syndrome (IBS). A. Icenhour, O. Bednarska, S. Tapper, A. Tisell, P. Lundberg, S. T. Witt, S. Elsenbruch, S. Walter. (oral presentation). Neurogastroenterology & Motility; nr. 38, Volume 29, 2017 Issue Supplement S2.

POPULAR SCIENTIFIC SUMMARY

SUSANNA WALTER

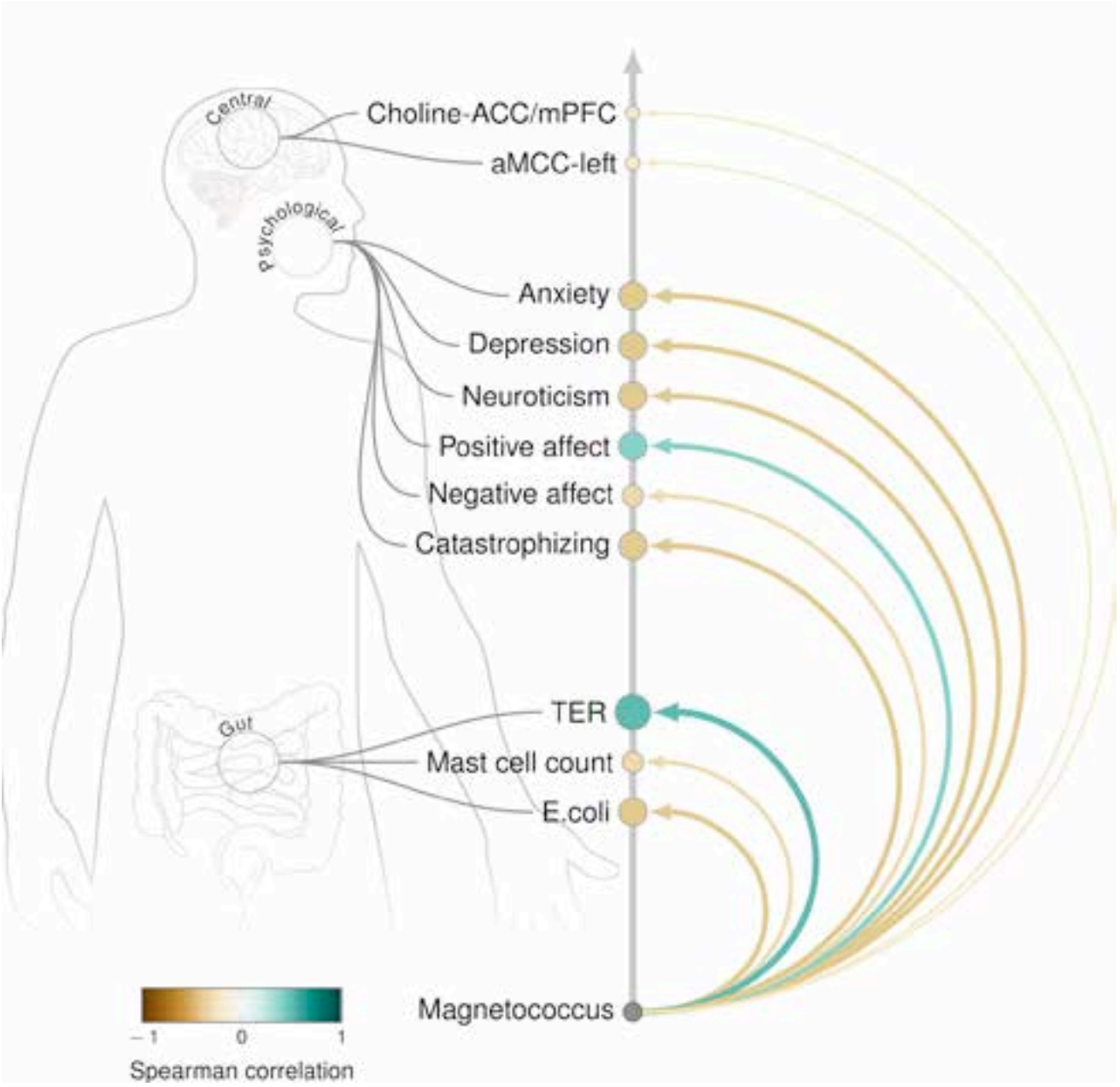
Brain-Gut Interactions in IBS

Irritable bowel syndrome (IBS) is a chronic disorder characterized by abdominal pain and alterations in bowel habits (diarrhea, constipation, or both in an alternating pattern). IBS is also associated with mental and physical comorbidity such as anxiety, depression, fatigue and other chronic pain syndromes. Despite advances in modern medicine, IBS remains a persistent, disabling, and costly problem.

IBS is a disorder of dysregulated brain–gut homeostasis involving peripheral and central mechanisms. An increasing body of evidence strongly supports both the role of peripheral factors such as disturbed microbiota composition, mucosal barrier or gut immune function. Also alterations in bidirectional interactions between the brain and gut microbiota are believed to be responsible for the pathophysiology of irritable bowel syndrome (IBS).

To date research has identified several components, both in the gut and the central nervous system (CNS), that are considered important in the IBS pathophysiology, however, no studies have measured both CNS and gut functions in the same patient population within the same period of time. Additionally, evidence of what pathways and mechanisms actually link together the gut and brain function is very limited.

In this ongoing study, we investigate multiple factors along the gut-brain axis in the same sample and within the same time period, both in patients with well-established IBS and healthy controls. We investigate gut related colonic mucosal function, gut microbiota and brain functional connectivity, magnetic resonance spectroscopy for the detection of neurotransmitter density in the brain, and brain structure. ■


Central
Choline-ACC/mPFC
aMCC-left
Psychological
Anxiety
Depression
Neuroticism
Positive affect
Negative affect
Catastrophizing
Gut
TER
Mast cell count
E.coli
Magnetococcus
−1
0
1
Spearman correlation

PROJECT INFORMATION

Project Name
Clinical, psychosocial and imaging studies of fatigue in multiple sclerosis

Project Leader
Anne-Marie Landtblom, Department of Clinical and Experimental Medicine, Division of Neurology.
Maria Engström, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Thomas Karlsson, Gullvi Flensner, Andreas Tolf

Grants
Swedish Research Council (VR)

Key Publications
Flensner G, Ek AC, Söderhamn O, Landtblom AM.
Sensitivity to heat in MS patients: a factor strongly influencing symptomology – an explorative survey. BMC Neurol 2011;11:27.

Engström M, Flensner G, Landtblom AM, Ek AC, Karlsson T.
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POPULAR SCIENTIFIC SUMMARY

ANNE-MARIE LANDTBLOM & MARIA ENGSTRÖM

Clinical, Psychosocial and Imaging Studies of Fatigue in MS

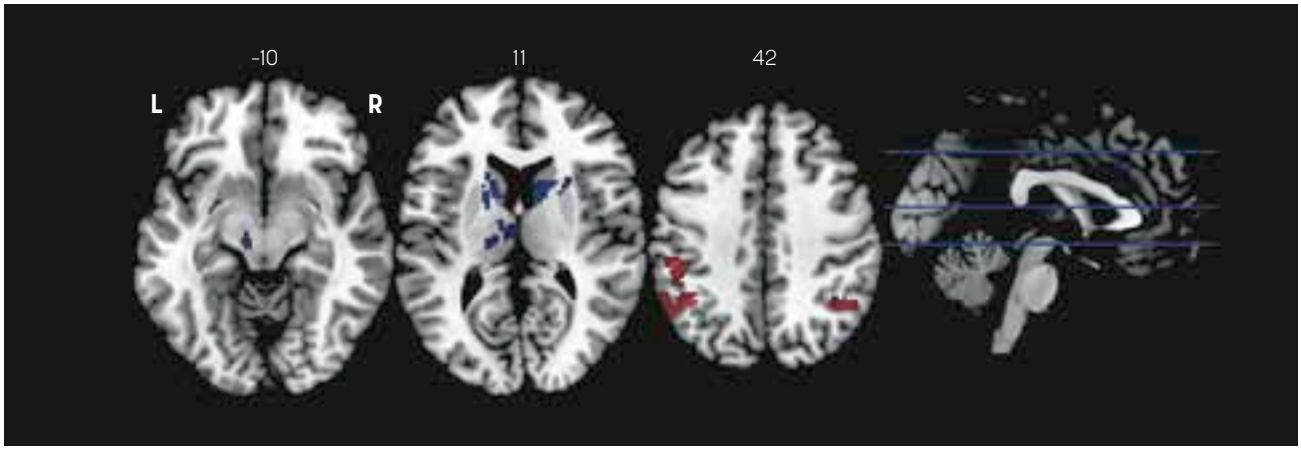
Multiple Sclerosis (MS) is an inflammatory disease affecting the nerve cells of the brain and spinal cord. The disease damages the nervous system communication resulting in a wide range of physical and mental symptoms. Fatigue, extensive tiredness and exhaustibility, is a common symptom of multiple sclerosis (MS). Fatigue is often found to be a more decapitating symptom than paresis. In this project we have aimed to describe fatigue from an epidemiological, psychosocial (effect on employment), physiological (coupling to heat sensitivity), clinical (effect on cognition) and interventional (cryotherapy) point of view.

Fatigue can be either peripheral or central. The neuronal mechanisms are not fully uncovered but the hypotheses for central fatigue involve the feedback loops between the basal ganglia and the motor cortex.

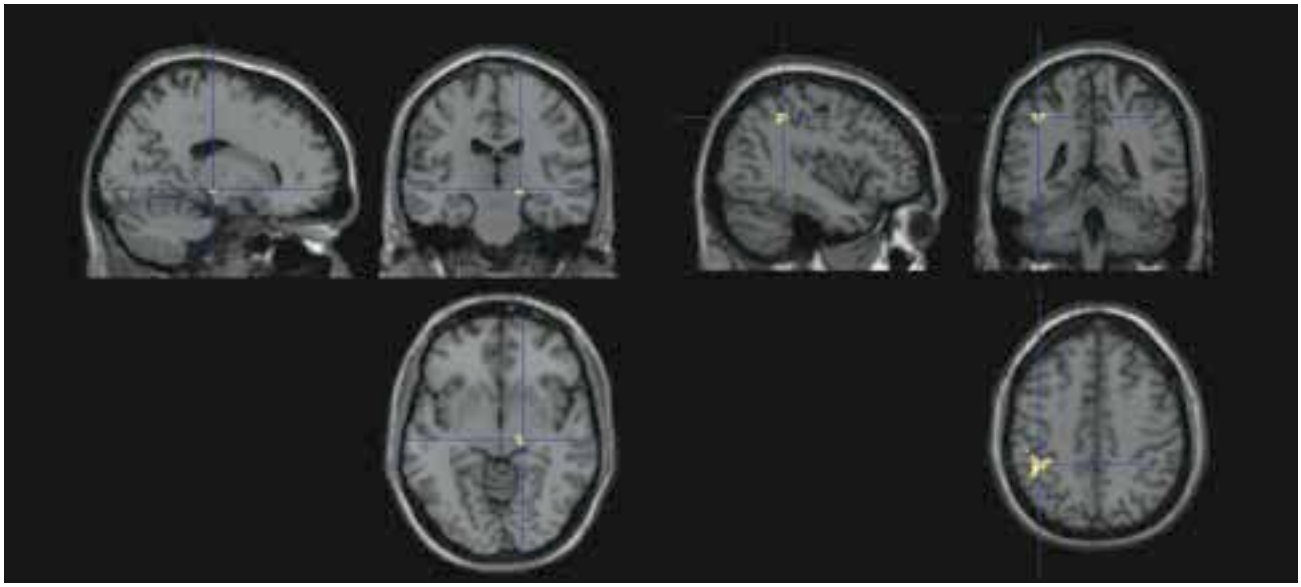
We have used functional magnetic resonance imaging of the brain (fMRI) to investigate the neuronal activity involved in the enhancement of cognitive problems due to fatigue among patients with MS. In fMRI, changes to the blood flow in the brain are measured. Increased blood flow corresponds to increased activity in that area of the brain. The patients were performing verbal tasks during the scan. A control group of healthy participants were also investigated. The patients were then examined in the same way after having a treatment with cryotherapy, i.e. having put on an active cooling garment with running cold water to lower the body temperature. The measurements were repeated to see if the cooling had improved the cognitive functions.

The fMRI experiments showed correlation between activation in specific areas of interest in the brain and perceived fatigue during the working memory tasks. The areas activated were the right substantia nigra and the left posterior parietal cortex. Neuropsychological investigations revealed clear effects on the working memory in the patients with MS and fatigue compared with the control group.

It is important to describe fatigue to gain acceptance for this decapacitating symptom. It is of great relevance to continue to investigate the physiological mechanisms behind the symptom.



Differences in brain activation between MS participants and healthy participants in regions of interest in the brain. The red colour represents areas that were more activated in MS participants compared to controls, and the blue colour represents areas that were less activated in MS participants compared to controls.



Brain activation with positive correlation to perceived fatigue during the working memory task. The images show activation in regions of interest: the right substantia nigra and the left posterior parietal cortex.

The results of this study now have identified areas of the brain that are involved.

Analysis of results after intervention with a cooling garment is now terminated. Here the fMRI analysis revealed some responders who are of great interest. We now prepare a manuscript that contribute to the work of determine the physiological background of MS fatigue. In a collaboration with Uppsala university, we also plan to integrate our findings with an ongoing study of the effects of blood stem cell transplantation (PhD student Andreas Tolf). ■

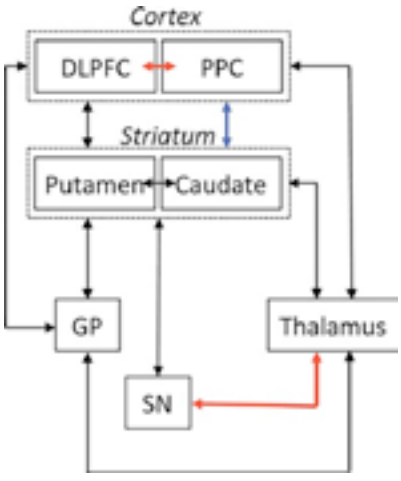


FIGURE. Schematic diagram of the thalamo-striato-cortical circuits, which describes the results of the present study. The red arrows describe couplings between areas that were more strongly connected in MS participants than controls during the working memory task. The blue arrow describes the coupling between areas that were more weakly connected in MS participants. DLPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; GP, globus pallidus; SN, substantia nigra.

PROJECT INFORMATION

Project Name
Clinical, imaging and memory investigation in KLS patients

Project Leader
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Maria Engström, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
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Grants
Kleine Levin Foundation, USA

Key Publications
Engström M, Karlsson T, Landtblom AM. Thalamic activation in the Kleine-Levin syndrome. SLEEP, 2014;37(2):379–386.

Engström M, Landtblom AM, Karlsson T.
New hypothesis on pontine-frontal eye field connectivity in Kleine Levin syndrome. J Sleep res 2016; Dec;25(6):716–719.

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POPULAR SCIENTIFIC SUMMARY

ANNE-MARIE LANDTBLOM & MARIA ENGSTRÖM

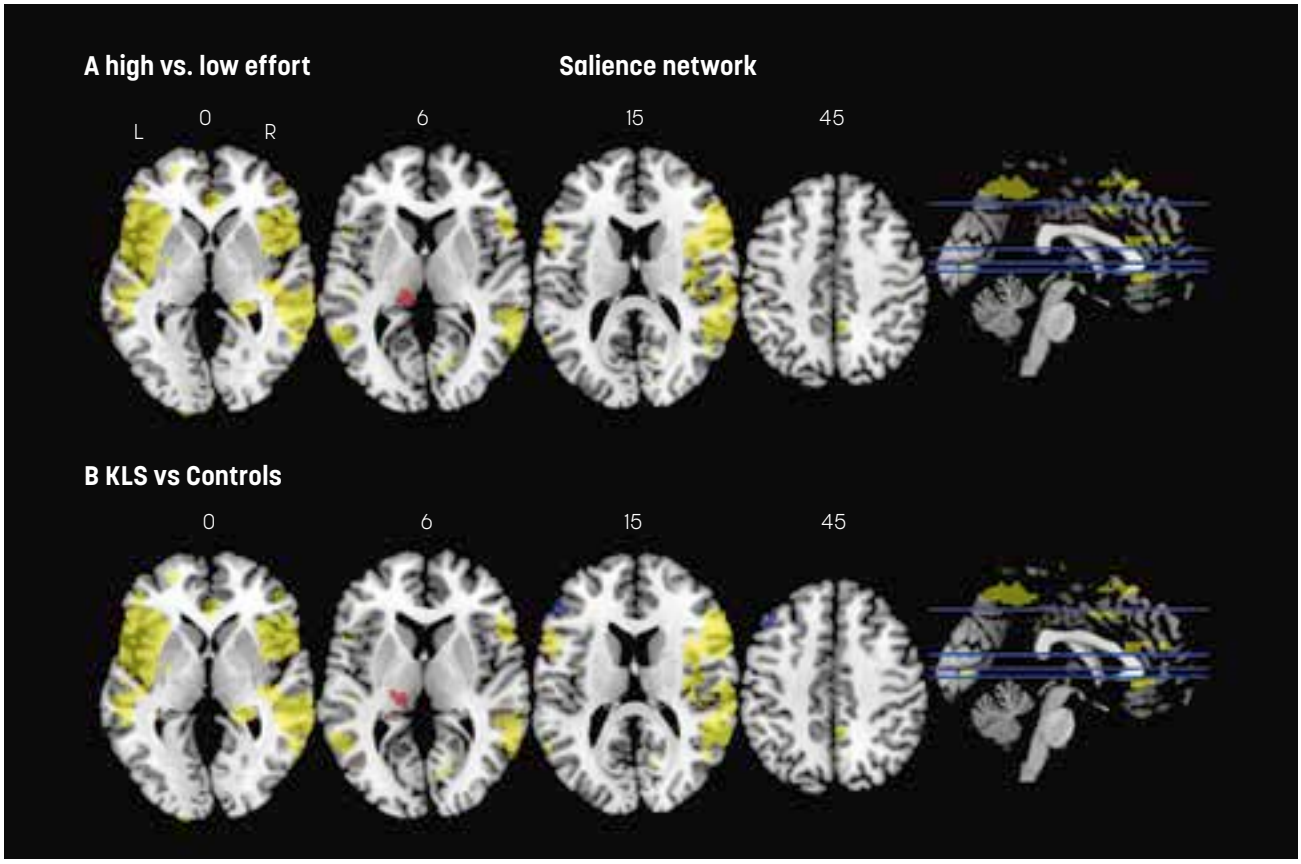
Clinical, Imaging and Memory Investigation in KLS Patients

Sleep disorders in young individuals are acknowledged as a growing problem. Some disorders increase, especially delayed sleep phase syndrome (DSLP), but also narcolepsy as a consequence of the Pandemrix vaccinations. Some of the rarer sleep disorders are hard to diagnose, especially the periodically occurring hypersomnia, Kleine-Levin syndrome (KLS). The diagnostic tools used are mainly clinical, but in narcolepsy also laboratory.

We have developed laboratory tools to support the diagnosis of the Kleine-Levin syndrome, including neuropsychological testing to identify working memory deficits. We also used measures of cerebral blood flow in our diagnostic set up for KLS. Over the years we have gathered a large number of KLS patients from the Nordic countries (n=30) who take part in clinical and scientific procedures. This gives us the opportunity to compare young individuals with the disorder.

In this study we examined frequency, duration and the type of sleep periods the patients had. We also performed basic investigations including blood flow measurements in the brain (fMRI), where increased blood flow corresponds to increased activity in that part of the brain. The fMRI measurements were combined with cognitive tests of the working memory and also neuropsychological investigations. The tasks had varying difficulty and therefore required different effort levels. Measurements were also performed in resting state.

Our results show that there are areas in the brain that are activated differently in patients with KLS compared with healthy individuals. The differences between patients with KLS and healthy controls were demonstrated in the resting state. In activated state during the working memory test, patients with KLS showed increased activation in some parts of the brain while other parts were less activated compared with healthy individuals. The differences in activation in these areas could be used to part the KLS patients from the healthy individual in most of the cases; hence the techniques have the potential to be developed into diagnostic tools of KLS. In addition, using fMRI we have observed and reported that cerebral centers for regulation of eye movements are involved and this corresponds to clinical symptoms.

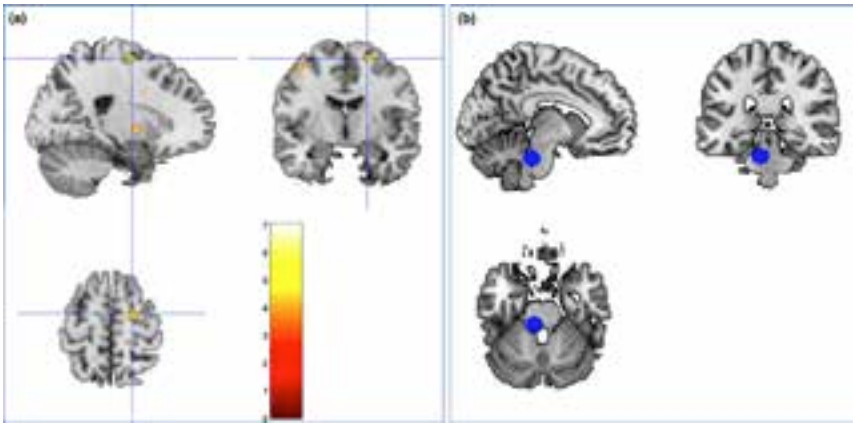


Functional connectivity in the salience network
Neural processing is often performed by an integrated network of several regions in the brain. Functional connectivity studies investigate the interaction of regions within these networks. Yellow areas show the network in selected slices. Red and blue areas show connectivity differences.

(A) Red colour denotes regions that are more strongly coupled to the network at a high effort level compared to a low effort level. Blue colour denotes regions that are more strongly coupled to the network at a low effort level. (B) Regions that are more strongly (red) respectively more weakly (blue) coupled to the network in patients with periodic idiopathic hypersomnia (KLS) compared to healthy individuals at the high effort level.

Our latest contribution in this project concerns the pontine–frontal eye field connectivity in patients with KLS. We could demonstrate a lower connectivity between the left dorsal pons and the right frontal eye field. Interestingly, the patients often report on visual disturbances which we now aim to scrutinize.

In KLS, two additional studies regarding genetics are now being terminated. We aim to conclude the full picture with genetics, imaging, physiologic and clinical findings. We have also expanded the studies into physiology i.e. the role of body temperature and certain CSF metabolites in relation to sleep episodes in collaboration with Uppsala University. Upcoming studies with an Eye Tracker will be of certain interest in relationship to the recent findings concerning eye field connectivity. ■



Pontine-frontal eye field connectivity in patients with Kleine-Levin syndrome (KLS).
(a) Patients with KLS had significantly lower connectivity between the left dorsal pons and the right frontal eye field. The cross-hair is located at the most significant voxel for the difference in connectivity between healthy controls and patients with KLS. The colour bar indicates the t-statistic values. Images were thresholded at an uncorrected P-value of 0.001 for visualization purpose. Peak P = 0.041, corrected for multiple comparisons at the whole brain level.
(b) The location of the seed region in the left dorsal pons. For visualization of the connectivity results and the pontine seed region, the standard Montreal Neurological Institute (MNI) template available in SPM8 was used.

POPULAR SCIENTIFIC SUMMARY

ANNE-MARIE LANDTBLOM

Clinical and Imaging Studies of Multiple Sclerosis

Multiple Sclerosis (MS) is an inflammatory disease affecting the nerve cells of the brain and spinal cord. The disease damages the nervous system communication resulting in a wide range of physical and mental symptoms. The symptoms may occur in isolated attacks or build up over time.

Together with inflammation, destruction of the insulating covers of nerve cells and the formation of lesions in the central nervous system are the main characteristics of MS. However, not all MS patients have the typical lesions in the brain. In fact, MS could be seen as a generic group for a variety of disease patterns and this perspective may help the endeavors to find more specific treatment in the future.

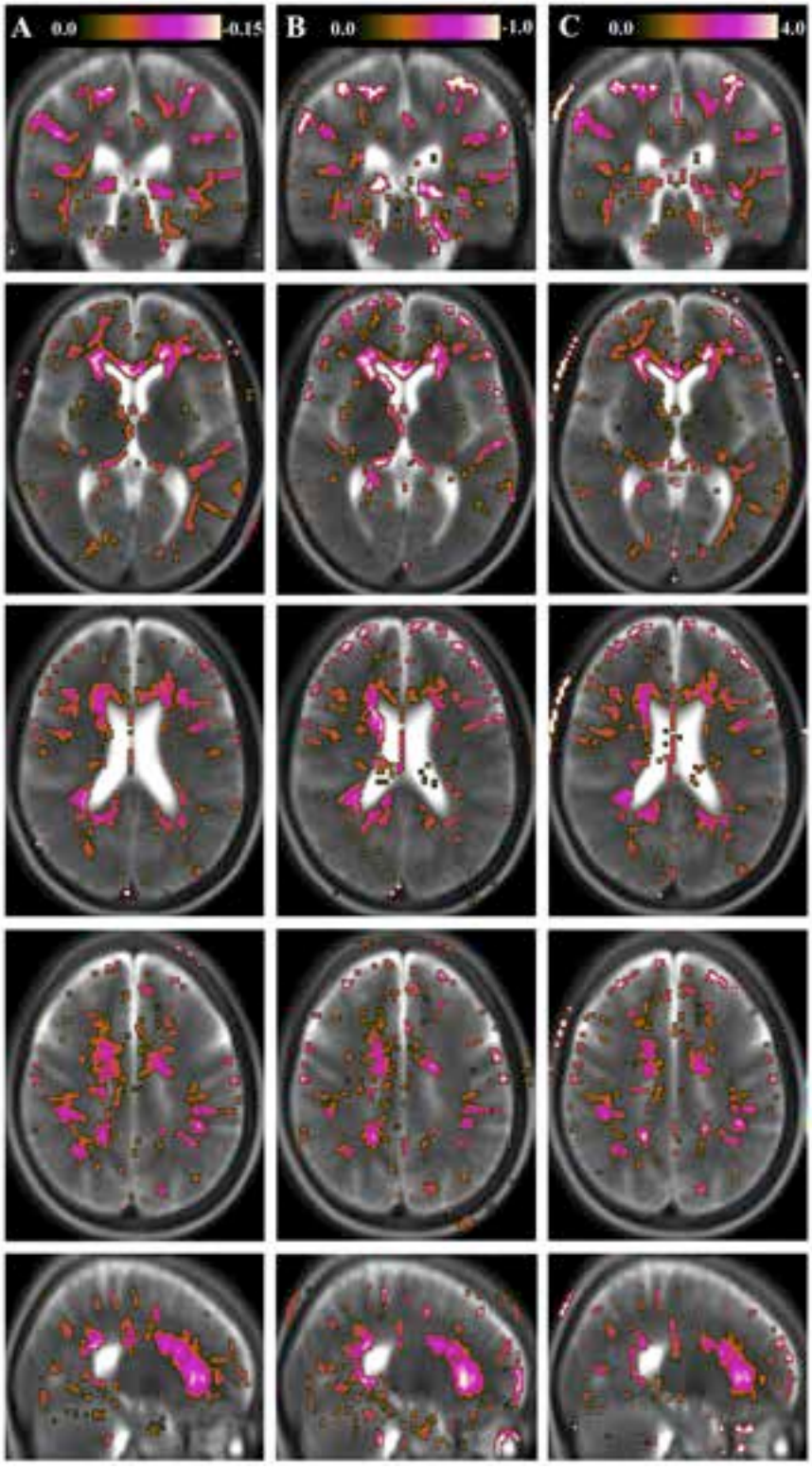
Since not all patients have lesions in their brain, they cannot be the only explanation for the neuronal damage. Patients without lesions (MR negative) have almost equal disability from the disease. New methods that can look deeper into the cause of MS is therefore of great interest. In addition to standard MRI quantitative MRI (QMR) is a new promising method, that can add information and also visualize RF in a graph, giving the opportunity for studies.

A new field that attracts interest in MS imaging, are the so called Diffuse Appearing White Matter lesions or DAWN. In our studies of MR negative patients, we also encountered such lesions and reported a correlation to atrophy.

With magnetic resonance (MR) techniques we can measure the levels of different metabolites in the brain. High levels of some substances reflect healthy tissue whereas others reflect damage. Using this method we have followed MS patients treated with the pharmaceutical Copaxone. Copaxone has been shown to decrease the lesions and slow down the progression of the disease. The results showed that the treatment improved the metabolite status.

In addition, the effects of the contrast agent Gadolinium on QMR have been investigated and reported. We also demonstrated multiparametric imaging in MS, combining radiological results with disability measures (Figure).

Unspecific lesions in cerebral white matter can be seen both in MS and cerebral arteriosclerosis and is therefore often hard to use as basis for a diagnosis. A possibility to discriminate these lesions regarding their origin would be a valuable tool for diagnosis and we have therefore performed a pilot project aiming to develop an MR method



to determine such differences using QMR. Results of this study including 20 patients revealed a trend that may help in differentiating demyelinisation and cerebral ischemia. This will be investigated further. The project is now being expanded through cooperation with Uppsala University, where another 50 patients will be examined, i.e. with MS and cerebral ischemia respectively. ■

FIGURE. Geometrical representation of the correlation of tissue parameters and clinical measures.
Shown as the color overlay is the slope of the voxel-based correlation with Expanded Disability Status Scale (EDSS).
EDSS is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time.

PROJECT INFORMATION

Project Name
Clinical and Imaging Studies of Multiple Sclerosis

Project Leader
Anne-Marie Landtblom, Department of Clinical and Experimental Medicine, Division of Neurology

Main Project Participants
Peter Lundberg, Olof Dahlqvist Leinhard, Marcel Warntjes, Anders Tisell, Örjan Smedby

Grants
Swedish Research Council (VR)

Key Publications

West J, Aalto A, Tisell A, Dahlqvist Leinhard O, Landtblom AM, Smedby Ö, Lundberg P.
Normal and Diffusely Abnormal White Matter in Patients with Multiple Sclerosis, Assessed with Quantitative MR. PLOS one 2014 Apr 18;9(4):e95161. Doi:10.1371/journal.pone. 0095161. eCollection 2014.

Warntjes M, Tisell A, Landtblom AM, Lundberg P.
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Engström M, Warntjes M, Tisell A, Landtblom AM, Lundberg P.
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PROJECT INFORMATION

Project Name
Working Memory in Visual Noise

Project Leader
Mary Rudner, Department of Behavioural Sciences and Learning, Disability Research Division

Main Project Participants
Josefine Andin, Emil Holmer, Victoria Stenbäck, Krister Schönström

Grants
Swedish Research Council 2016–2020

Key Publications
Rudner M, Orfanidou E, Cardin V, Capek C.M, Woll B & Rönnberg J (2016). Pre-existing semantic representation improves working memory performance in the visuospatial domain. Memory & Cognition, 44(4), 608–620.

Rudner M, Toscano E and Holmer E (2015). Load and distinctness interact in working memory for lexical manual gestures. Front. Psychol. 6:1147.

Cardin V, Smittenaar C.F, Orfanidou E, Rönnberg J, Capek C.M, Rudner M & Woll B. (2016). Differential activity in Heschl's gyrus between deaf and hearing individuals is due to auditory deprivation rather than language modality. NeuroImage, 124, 96–106.

POPULAR SCIENTIFIC SUMMARY

MARY RUDNER

Working Memory in Visual Noise

Explicit working memory processing comes into play when speech communication takes place under adverse conditions, for example in background noise or when one of the communicating parties has a hearing impairment.

Age-related hearing loss is associated with age-related cognitive decline and temporal lobe atrophy. In particular, the effect of hearing loss strikes at episodic memory more than working memory, while no such effect is found for visual loss in hearing individuals. It has been suggested that while hearing loss keeps working memory in trim by requiring continual activation in communicative situations, episodic memory declines because of disuse.

Profoundly deaf individuals often prefer sign language communication, even when they use technical aids such as cochlear implants (CI) to access acoustic information. This applies especially in noise, where the CI is ineffective because it cannot separate signal from noise.

Acoustically noisy situations are often visually noisy, i.e. the visual signal

may be degraded in various ways, and it is likely that explicit working memory capacity comes into play during sign language communication in such adverse conditions. Thus, congenitally profoundly deaf sign language users without CI can help us test the theory that age-related sensory loss in preferred modality of communication drives episodic memory decline under the disuse hypothesis. Support for the theory will be obtained if visual loss is associated with greater age-related decline in episodic memory than in working memory in this group.

Video gaming enhances cognition in both younger and older hearing adults, potentially counteracting the effects of age-related sensory decline on memory systems. However, it is not known whether video gaming enhances cognition in deaf individuals who use visual (sign) language.

The proposed project constitutes the first two testing phases in a longitudinal study, which as the first scientific investigation of its kind will examine how visual noise influences working memory for sign language and the neural networks that support it. We will also investigate how sensory loss, sign language knowledge and video gaming experience influence the dynamic relation between episodic and working memory.

The overarching goal of the project is to test whether current memory models are neuro-cognitively robust across the modalities of sign and speech. It will generate knowledge that can be applied in hearing rehabilitation, design of the built environment and digital communication interfaces. ■

PROJECT INFORMATION

Project Name
Neuroaffective Effects of Electroconvulsive Therapy for Major Depressive Disorder

Project Leader
Markus Heilig, Department of Clinical and Experimental Medicine, Center for Social and Affective Neuroscience

Main Project Participants
Paul Hamilton, Pia Nordanskog, Åsa Axén, Robin Kämpe

POPULAR SCIENTIFIC SUMMARY

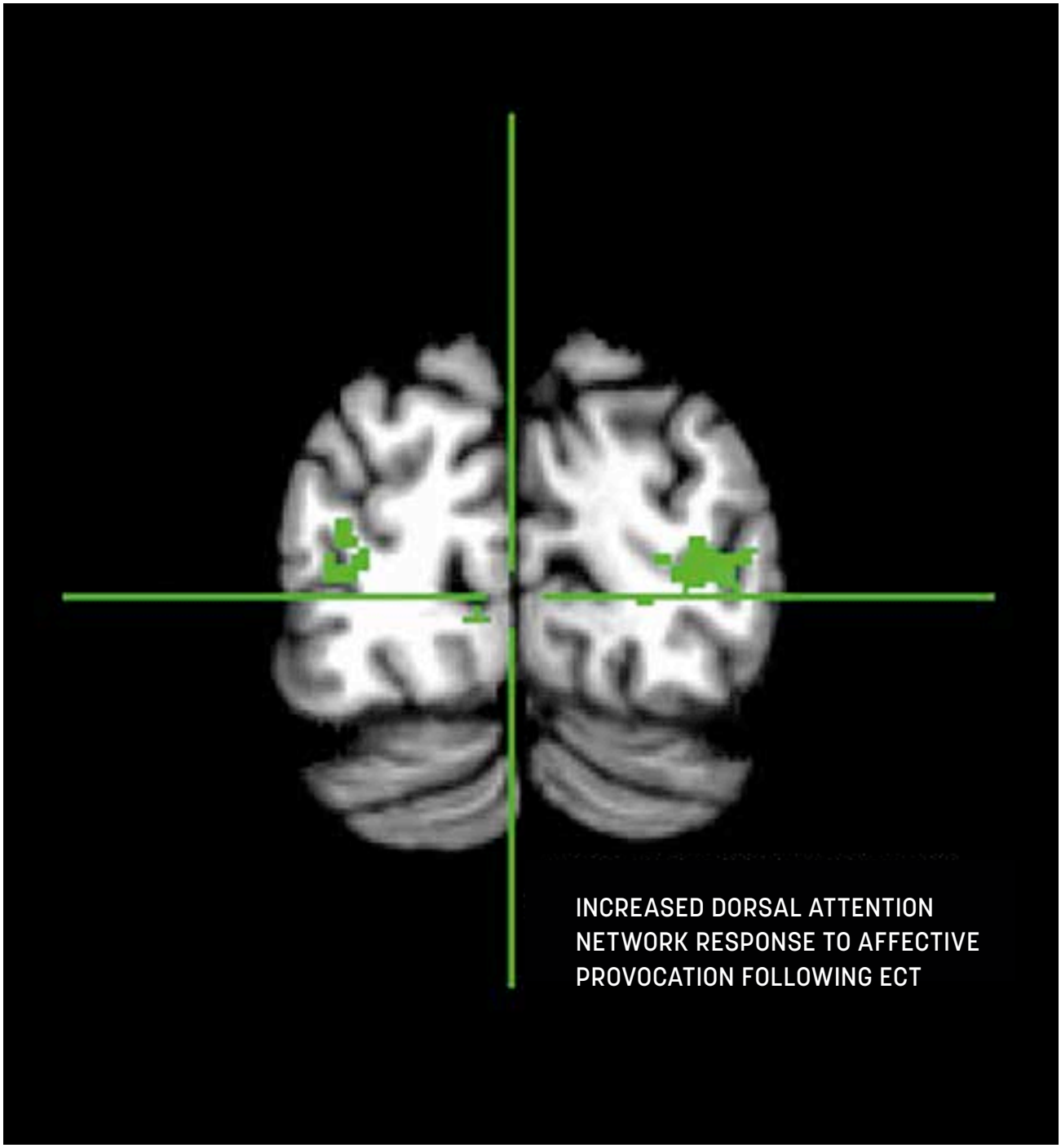
MARKUS HEILIG

Neuroaffective Effects of Electroconvulsive Therapy for MDD

Major depressive disorder (MDD) is a highly debilitating psychiatric condition that affects 20–30 % of people at some point during their lifetime. Major depression leads all diseases in terms of years of productive life lost due to illness.

In acute cases of MDD, individuals can become entirely incapacitated or worse; pose a significant danger to themselves. In such acute cases, immediate amelioration of depressive symptomatology is required. Only a small handful of currently implemented courses of treatment can achieve such immediate effects – among these treatments, the most broadly applied is electroconvulsive therapy (ECT).

While effective, ECT is burdensome, requiring the patient to be anesthetized and to receive electrical stimulation sufficient to cause a grand mal seizure and concomitant side effects, including significant (but transient) autobiographical memory impairment. Given this, it is desirable to investigate the neural underpinnings of ECT's thera-



INCREASED DORSAL ATTENTION NETWORK RESPONSE TO AFFECTIVE PROVOCATION FOLLOWING ECT

peutic effects so that we might develop equally effective treatments that are less burdensome to patients.

In a study currently underway, we are collecting neural structural and functional data in depressed patients during a course of ECT – just prior to receiving ECT for the first time, following eight weeks of receiving ECT, and eight weeks after completion of the course of ECT.

Preliminary analyses of functional neuroimaging data show intriguing functional changes in the brain as a result of ECT. Before ECT, for example, depressed patients show a pattern of affective flattening in which they react little, either neurally or behaviorally, to affective provocation with pictures. After ECT, however, depressed patients show robust response in the brain's visual attention network (see Figure 1) to emotionally provocative stimuli.

Further, in a task requiring patients to perform a challenging task to receive money, prior to ECT patients strongly activate a network subserving self-relational processing when they believe they are about to fail at the task. Following ECT, however, patients no longer strongly activate these structures as they anticipate failure at this challenging task.

As we continue collecting and analyzing these neuroimaging data, we will further delve into the neural underpinnings of ECT effects and how to implement them with less burdensome treatment modalities such as transcranial magnetic stimulation, which can focally stimulate a brain region of interest without detrimental side effects. ■

POPULAR SCIENTIFIC SUMMARY

MARKUS HEILIG

Brain Correlates to Affective Processing

The aim of this project is to contribute to the understanding of the intense affects and difficulties with affect regulation that is noted clinically in adolescents with non-suicidal self-injury (NSSI) disorder and Autism Spectrum disorder (ASD) compared to healthy controls. This project includes three experiments in the MRI scanner. The first experiments in 40 healthy adolescents is concluded. The data collection regarding the other two experiments will be concluded at the beginning of 2018.

The purpose is to investigate how the two clinical groups respond to different types of stress (social stress, exposure to emotionally charged images) and light touch to investigate whether there are psycho-biological differences with regard to neural correlates compared to healthy controls.

In order to address these aims the following paradigms are tested in the Magnetic Resonance Imaging (MRI) scanner:

Matching of images
Emotionally negative pictures taken from a set of normative stimuli, are shown to the subjects to investigate cerebral responses following emotional processing. This task has previously been shown to result in activation of insular cortex in response to negatively valenced affective images.

Online game paradigm
Social interactions are particularly relevant during adolescence. Neural systems are not fully developed for processing emotional reactions, and in clinical samples these systems may also have been affected by trauma. Rejection or other negative social interactions are some of the most powerful stressors for humans. Here the subjects participate in a novel paradigm which mimics everyday interactions in a social media context. The paradigm induces the feeling of being accepted or rejected by other participants. It also investigates brain correlates to seeing others being liked or disliked. This task is based on two relevant aspects in the adolescents' world: 1) the importance of feeling included in a group. 2) the importance of social media when it comes to acceptance or rejection.

Touch paradigm
Light touch to the skin by a conspecific is the affiliative behavior that is important for the development of a close attachment between mother and child. This type of social-affective touch is one of the strongest signals of a successful attachment bond between parents and offspring during early childhood, and later life in close relationships. Lightly touching the skin activates two different systems of neurons that signal to the brain. Here tactile soft brush strokes are delivered to the skin of the right dorsal forearm in a proximal-distal direction. After each stimulation the subjects are asked to rate the pleasantness and intensity of stroking on a visual analog scale (VAS). ■

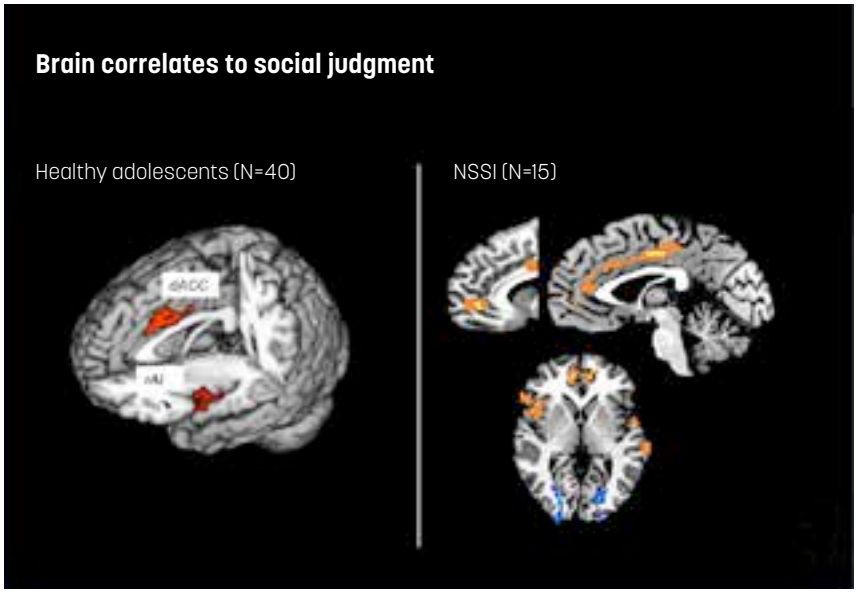


FIGURE 1 (left). One of the aims of this project is to contribute to the understanding of the brain mechanisms behind social processing in healthy subjects and in clinical groups. Here we provide findings in healthy adolescents and preliminary results in ASD and NSSI groups. The experiment in the healthy adolescents group is concluded and now submitted for publication. Healthy participants activate the salience network when they feel judged by others, during online social interaction.

FIGURE 1 (right). The salience network activates to direct our cognitive resources towards relevant stimuli in the environment. We conclude that this activation is involved in properly attributing salience to self-relevant social stimuli, a function that is disrupted in several disease states. Preliminary findings in NSSI and ASD groups show some degree of overlap but important differences, which will be further explored. The NSSI group activates the cingulate to a higher extent than the healthy subjects, possibly due to a higher sensitivity to judgment by others.

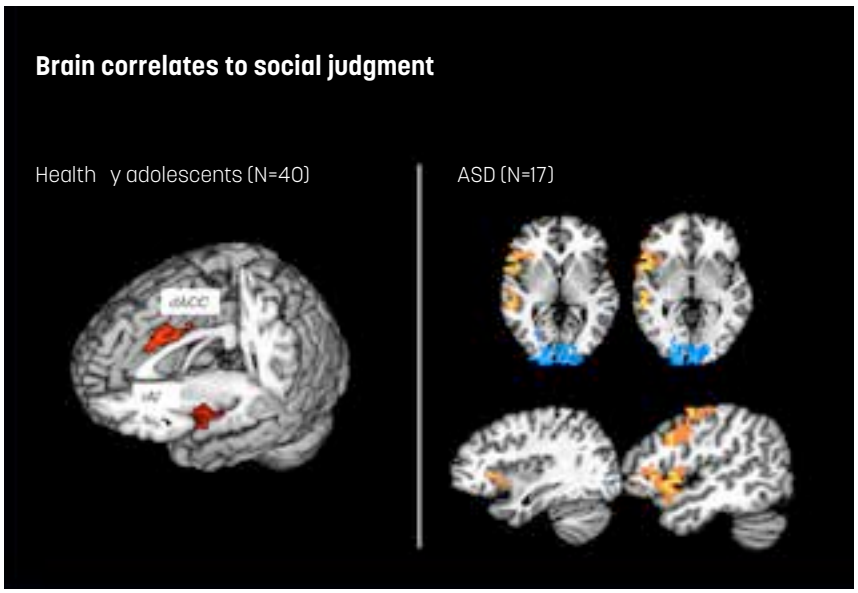


FIGURE 2 (right). On the other hand the ASD group fails to activate the cingulate activity, suggesting an altered activity in the salience network following social judgment.

PROJECT INFORMATION

Project Name
Brain correlates to affective processing in typical individuals and clinical groups

Project Leader
Markus Heilig. Center for Social and Affective Neuroscience. Department of Clinical and Experimental Medicine

Main Project Participants
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Grants
The Swedish Medical Research Council
EU-funded Horizon 2020

PROJECT INFORMATION

Project Name
Brain correlates to affective processing in individuals exposed to early life trauma

Project Leader
Markus Heilig, Department of Clinical and Experimental Medicine, Center for Social and Affective Neuroscience

Main Project Participants
Åsa Kastblom, Paul Hamilton, Robin Kämpe, Irene Perini

Grants
The Swedish Medical Research Council

POPULAR SCIENTIFIC SUMMARY

MARKUS HEILIG

Brain Correlates to Affective Processing in Individuals Exposed to Early Life Trauma

The purpose of the study is to investigate whether individuals who during childhood have been exposed to traumatic events – sexual, emotional or physical abuse – are at increased risk for developing substance use or other psychiatric disorders. Importantly, this group of individuals is selected using prospective registry and not subjective retrospective report.

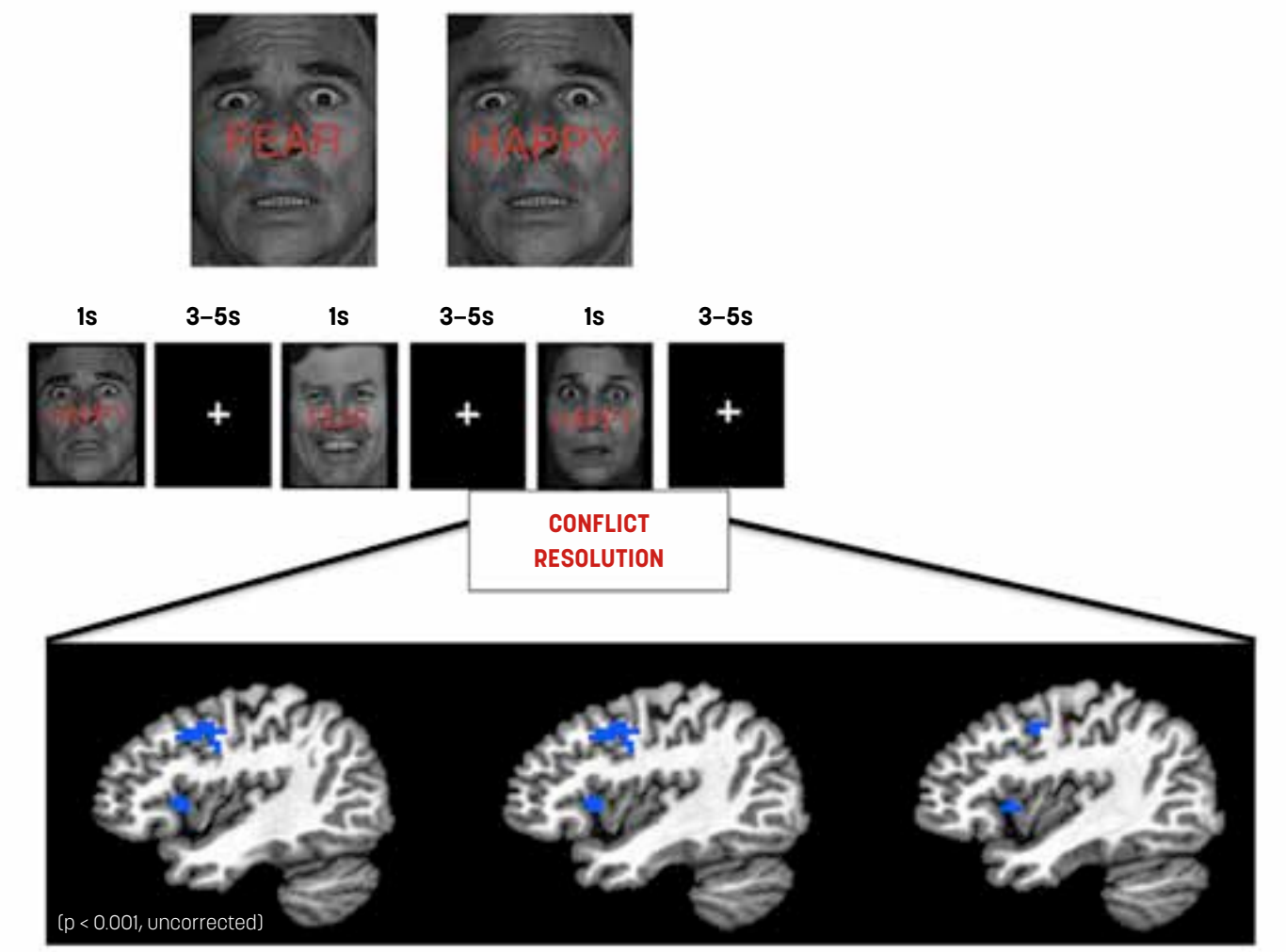
The specific aim regarding the MRI data collection of this project is to investigate experimentally whether the regulation of affect and stress responses differs in individuals who have experienced early trauma, compared to controls.

In order to address these aims the following paradigms are tested in the Magnetic Resonance Imaging (MRI) scanner:

Matching of images
Emotionally negative pictures takes from a set of normative stimuli, are shown to the subjects to investigate cerebral responses following emotional processing. This task has previously been shown to result in activation of insular cortex in response to negatively valenced affective images.

Matching alcohol and non-alcohol images
Alcohol related and non-alcohol related pictures are shown to the subjects to measures brain responses to alcohol related stimuli. Brain responses to alcoholic, compared to non-alcoholic images are assessed.

Emotion conflict task
Brain mechanisms following emotional regulation have been previously



described in healthy subjects and in patients with generalized anxiety disorder. Participants are instructed to identify the underlying facial emotion (fearful or happy) while ignoring an overlying emotional distractor (emotion word: "FEAR" or "HAPPY"). Trials vary such that the emotional distractor words are congruent or incongruent with the underlying facial expression. This task has been used to successfully discern between brain mechanisms involved in two components of emotional regulation: conflict monitoring and conflict resolution. Differences in behavioral and cerebral patterns between generalized anxiety patients and healthy controls have been shown. Behavioral and brain results will be investigated in this population group and compared to healthy controls. ■

PROJECT INFORMATION

Project Name
Modulating inflammation in the central nervous system in major depression via inflammatory cytokine blockade

Project Leader
Paul Hamilton, Department of Clinical and Experimental Medicine, Center for Social and Affective Neuroscience

Main Project Participants
Markus Heilig, Martin Samuelsson, Sandra Boda, Elisabeth Paul, Åsa Axén, Gisela Öhnström

Grants
The Swedish Medical Research Council

POPULAR SCIENTIFIC SUMMARY

PAUL HAMILTON

Modulating Inflammation in the CNS in Major Depression

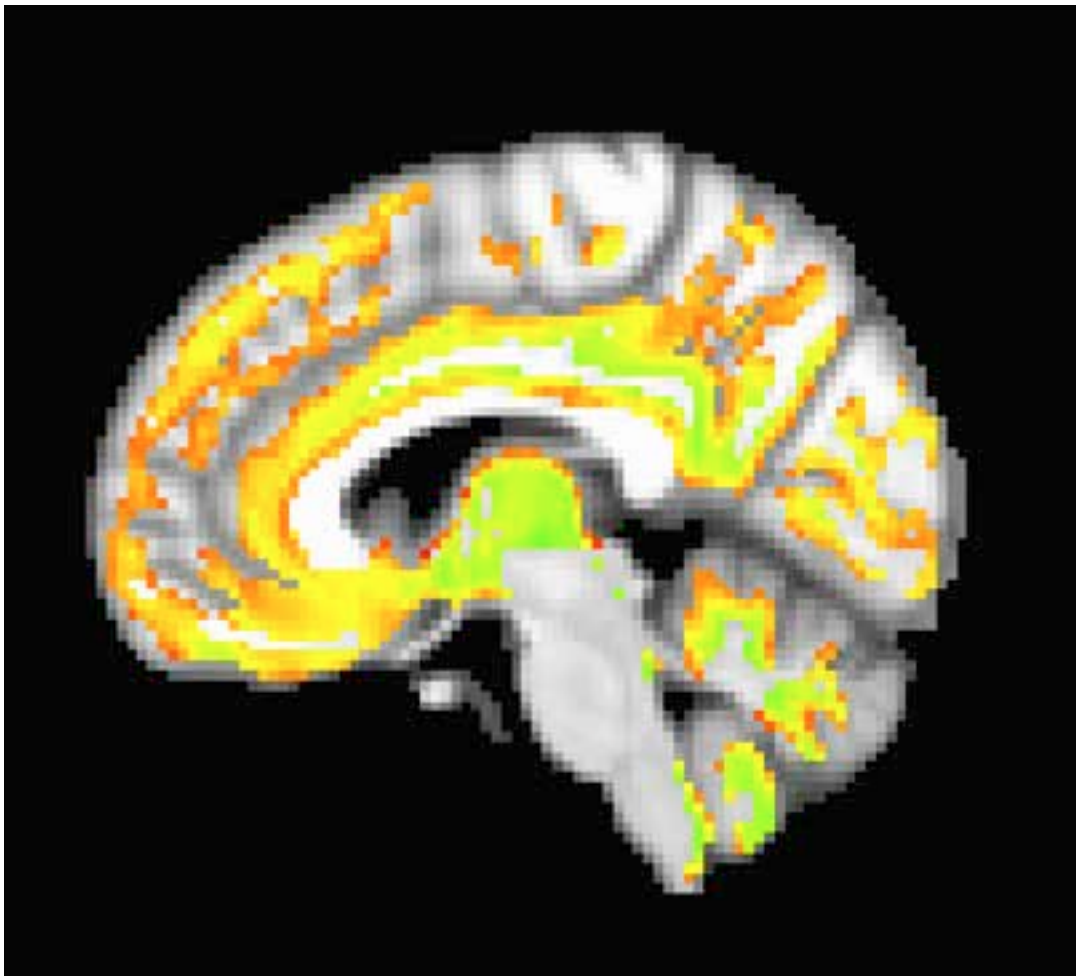
Major depressive disorder (MDD) is a leading contributor to the global burden of disease and is projected to be the second leading cause of global disability burden by the year 2020.

In depression, this loss is the result of heightened mortality from suicide and cardiovascular illness as well as significantly diminished daily functioning in workplace and family contexts.

A critical symptom of depression is a diminished interest in and engagement with previously pleasurable daily activities. Importantly, scientists have observed similarities between this pattern of behavior in MDD and "sickness behavior" characterized by decreased food consumption, inactivity, and social withdrawal that occurs in response to viral and bacterial infection.

Given the significant role of inflammation in mediating sickness behavior, inflammation in depression has been increasingly examined in recent years. Investigations of inflammation in MDD have been motivated, in particular, by high rates of comorbidity of MDD with primary inflammatory conditions – like multiple sclerosis – and findings showing that patients receiving immune system activating interventions for viral infections are more likely to subsequently develop a depressive episode. Based on these findings, we are currently investigating the biological and clinical effects of blocking inflammatory activity in MDD.

The primary objective of our study



is to evaluate the efficacy of tocilizumab – an anti-inflammatory drug that inhibits the effects of interleukin-6, an inflammatory cytokine implicated in MDD – in reducing measures of inflammation in the central nervous system. Secondarily, we will examine the effects of administering tocilizumab on depressive symptoms.

To realize these objectives, individuals diagnosed with MDD will be asked to enroll in a double-blind, placebo-controlled treatment study in which half of participants will receive tocilizumab and the other half will receive an equal volume of matched placebo every week for four weeks.

One week before and one week after four weeks of treatment or placebo, participants will be asked to provide cerebrospinal fluid (CSF), and magnetic resonance imaging (MRI) data. From the CSF, we will determine whether anti-inflammatory treatment reduces levels of chemical signaling of inflammation in the brain. On the MRI data, we will apply a specialized algorithm for calculating levels of cerebral microedema or swelling at a small spatial scale in the brain.

Using these data, we will see whether anti-inflammatory treatment affects swelling in the brain. At the conclusion of the study we hope to better understand central nervous system inflammation in depression as well as how we might reduce this inflammation toward therapeutic ends in MDD. ■

FIGURE. Preliminary group-average map of regional cerebral microedema levels in cortical and subcortical regions.

PROJECT INFORMATION

Project Name
Statistical Analysis of NeuroImaging Data

Project Leader
Anders Eklund, Department of Biomedical Engineering, Department of Computer and Information Science

Main Project Participants
Mattias Villani, Hans Knutsson, Per Sidén, Bertil Wegmann, Josef Wilzén, Xuan Gu, Jens Sjölund

Grants
Swedish Research Council

Key Publications
Eklund A, Lindquist M, Villani M,
A Bayesian heteroscedastic GLM with application to fMRI data with motion spikes, NeuroImage, 155, 354–369, 2017.

Eklund A, Nichols T, Knutsson H,
Reply to Brown and Behrmann, Cox et al., and Kessler et al.:
Data and code sharing is the way forward for fMRI, Proceedings of the National Academy of Sciences, 114, E3374-E3375, 2017.

Gu X, Eklund A, Knutsson H,
Repeated tractography of a single subject – how high is the variance?, Modeling, Analysis and Visualization of Anisotropy, 331–354, 2017.

POPULAR SCIENTIFIC SUMMARY

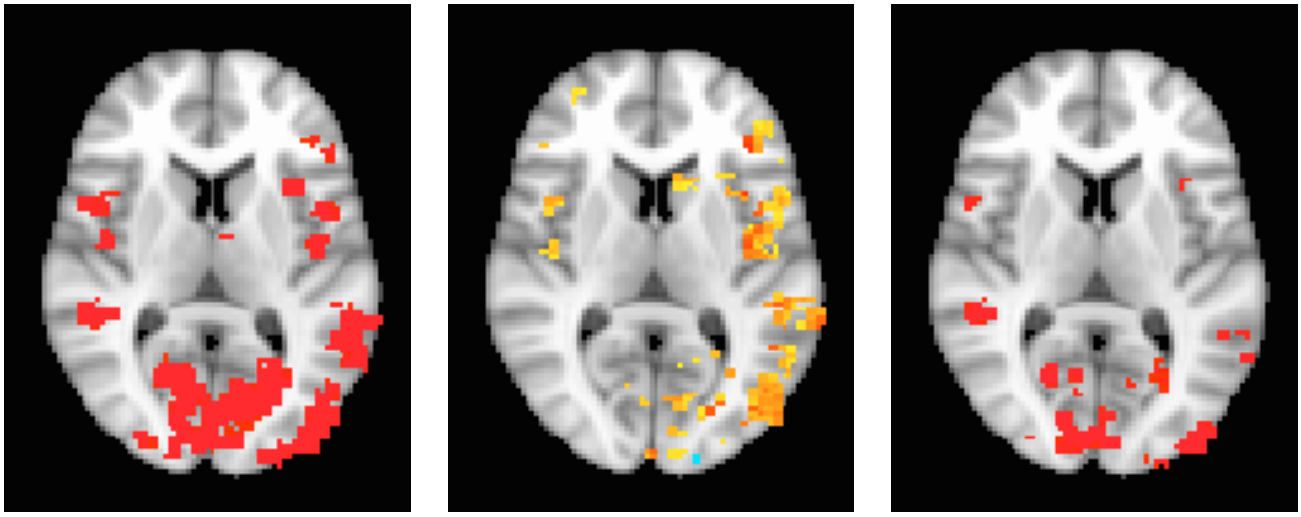
ANDERS EKLUND

Statistical Analysis of NeuroImaging Data

Functional magnetic resonance imaging (fMRI) is a popular tool for studying brain activity, as it can non-invasively image the human brain without any ionizing radiation. Similarly, diffusion MRI (dMRI) is a popular tool for studying brain connectivity, by for example measuring how easily water can travel along different directions.

From a statistical perspective, analyzing fMRI and dMRI data is a challenging task for several reasons. One reason is that the noise has a complex spatio-temporal structure, which is virtually impossible to simulate in a computer. Another reason is that there are several noise sources which distort the signal of interest, for example head motion, breathing and pulse. In this project we validate and improve existing statistical models for neuroimaging data.

In our latest work, we developed a new statistical model for fMRI data, which allows the variance to change over time. The model is very useful for fMRI data where the subject has moved its head during the experiment, which is a common problem for children as well as for some adult. By modeling that the variance is higher during head motion spikes, time points corresponding to head motion can automatically be downweighted, instead of discarding the dataset. ■



FIGURES. The image shows the detected brain activity for our (heteroscedastic) model (left), a standard (homoscedastic) fMRI model (middle) and the difference between the two models (right). Our model can detect more brain activity, by automatically downweighting time points where the subject has moved its head.

PROJECT INFORMATION

Project Name
Tissue Classification Using Dual Energy CT and Iterative Reconstruction

Project Leader
Åsa Carlsson Tedgren, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Alexandr Malusek, Maria Magnusson, Michael Sandborg, Gudrun Alm Carlsson

Grants
Cancerfonden 2013–2015, 2016–2018
Swedish Research Council 2017–2020

Key Publications
Malusek A, Karlsson M, Magnusson M, and Alm Carlsson G.
The Potential of Dual-energy Computed Tomography for Quantitative Decomposition of Soft Tissues to Water, Protein and Lipid in Brachytherapy. Physics in Medicine and Biology 58, pp. 771–785, 2013.

Kardell M, Magnusson M, Sandborg M, Alm Carlsson G, Jeute J and Malusek A. Automatic segmentation of male pelvis for brachytherapy of prostate. Radiation Protection Dosimetry, Vol. 169, Iss. 1–4, 2016.

Malusek A., Magnusson M, Sandborg M and Alm Carlsson G.
A model-based iterative reconstruction algorithm DIRA using patient-specific tissue classification via DECT for improved quantitative CT in dose planning. Medical physics, Vol. 44, Iss. 6, pp. 2345-2357, 2017.

POPULAR SCIENTIFIC SUMMARY

ÅSA CARLSSON TEDGREN

Tissue Classification Using Dual Energy CT and Iterative Reconstruction

Today's computed tomography (CT) images are affected by artifacts caused by the X-ray spectrum (beam-hardening artifacts). Due to the artifacts the CT-images are not completely quantitatively accurate. We have developed a mathematical method, an iterative algorithm, which eliminates these artifacts. With our dual energy iterative image reconstruction algorithm (DIRA) the pixels of the image are first classified into bone and soft tissue.

Bone pixels carry information about percentages of compact bone, red and yellow bone marrow. Soft tissue pixels carry information about percentages of water, protein and lipid. Consequently, DIRA provides quantitative information that can be used for improved medical diagnosis and treatment. As an example, DIRA can be used for determination of calcium content in the prostate.

The method is particularly important in radiation treatment planning using brachytherapy for prostate cancer where low-energy photons are used. A high calcium content in the prostate gland will change the spatial distribution of absorbed dose since it depends strongly on tissue's atomic number, Z.

Our quantitative CT algorithm is important also in proton radiation therapy where the spatial location of the dose maximum is sensitive to the atomic numbers of the patient tissues.

To verify the method, we applied DIRA to simulated projection data of the human pelvic region. The X-ray spectra were 80 and 140kV, photon noise was included, and the geometry was basically the same as for the CT-Scanner at CMIV.

Figure 1 shows conventionally filtered back-projection 80kV reconstructed images of the human pelvic region after 0 iterations in DIRA (left) and after 8 iterations in DIRA (right). It is apparent that the beam-hardening artifacts corrupt the image causing streaks after 0 iterations (corresponding to the conventional Filtered Back Projection (FBP) with water beam hardening correction) (left). These artifacts are to a large extent reduced after 8 iterations (right).

One key point in DIRA is to classify the soft tissue of the reconstructed images for 80 and 140kV into the base material triplet lipid, protein and water (LPW). The classification based on the 8th iteration is consistent with the true values and provides important quantitative information of the tissue, see figure 2. Recent publications include test of different noise levels, implementation on parallel CPU architecture and more advanced segmentation, see fig. 3. Ongoing research includes applications on new modalities of radiation therapy. ■

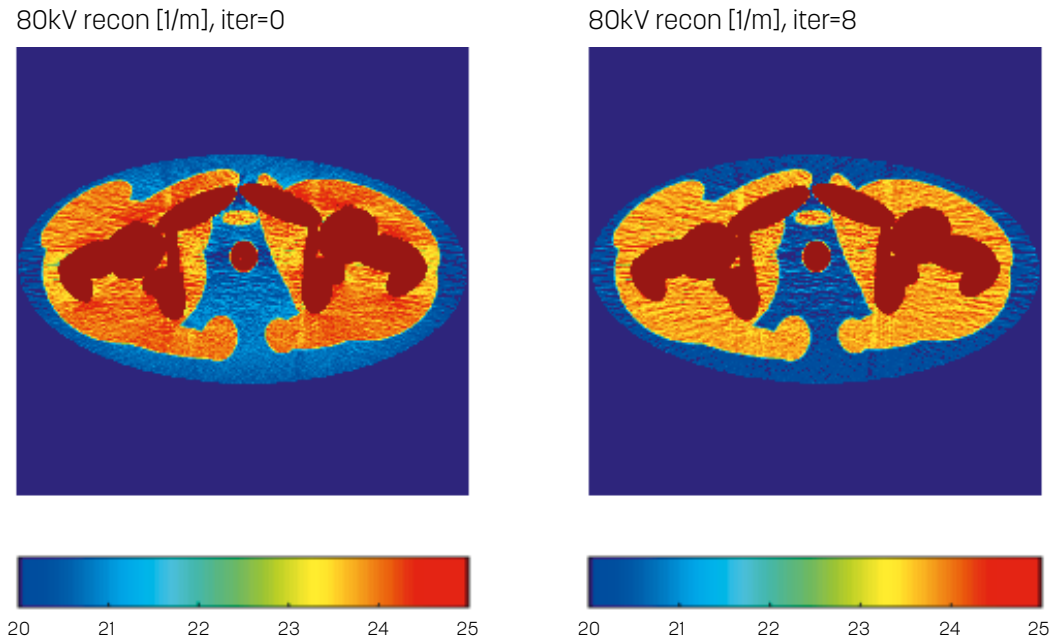


FIGURE 1. Suppression beam hardening artifacts in the human pelvic region from iteration 0 to iteration 8 in DIRA.

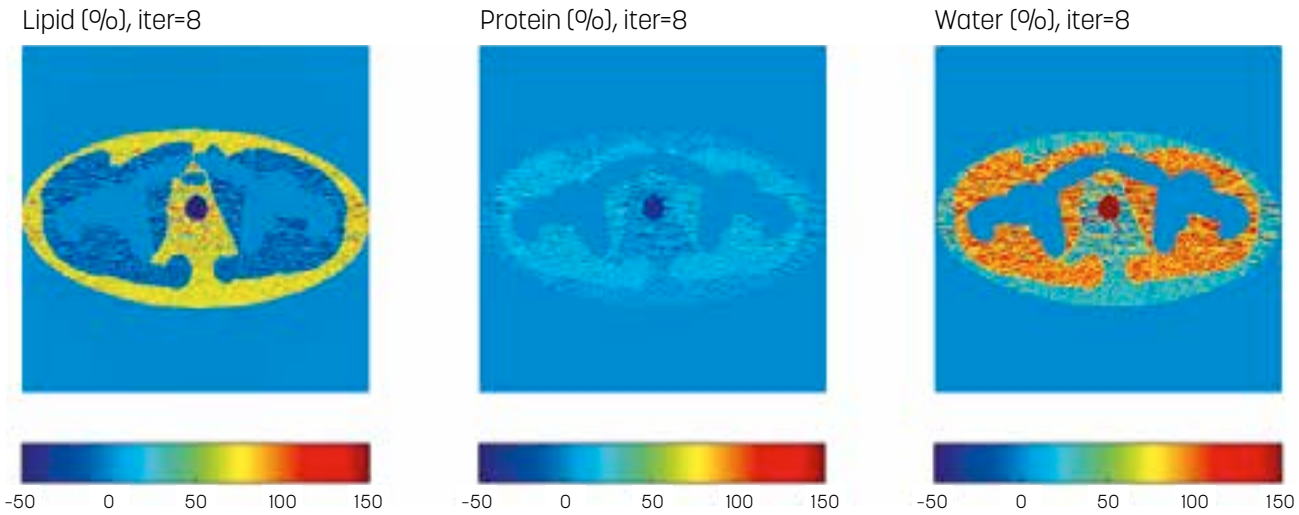


FIGURE 2. Soft tissue classification into lipid, protein and water (LPW) after 8 iterations of DIRA.

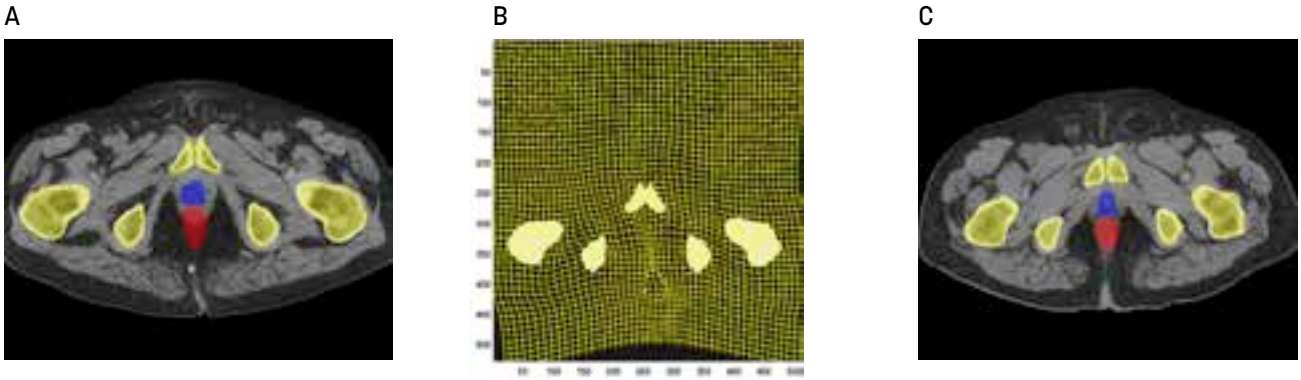


FIGURE 3. A) Automatic segmentation of the male pelvis to bone (yellow), prostate (blue) and rectum (red) using our algorithm JJ2016 (Master thesis by Julius Jeute).
(B) Transformation field calculated using the morphone algorithm and applied to the atlas bones.
(C) Automatic segmentation of a different patient using the same atlas image. Note that the figures show one slice only. The segmentation is automatically performed in the whole 3D dataset.

PROJECT INFORMATION

Project Name
Optimising radiographic techniques – dose versus image quality

Project Leader
Michael Sandborg, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Gudrun Alm Carlsson, Erik Tesselaar, Alexandr Malusek

Key Publications
Erik Tesselaar and Michael Sandborg. Assessing the usefulness of the quasi-ideal observer for quality control in fluoroscopy. Radiat. Prot. Dosim., 169, 360–364 (2016).

Erik Tesselaar, Nils Dahlström and Michael Sandborg. Clinical Audit of image quality in radiography using visual grading characteristics analysis. Radiat. Prot. Dosim., 169, 340–346 (2016).

Alexandr Malusek, Michael Sandborg, and Gudrun Alm Carlsson. Accurate KAP meter calibration as a prerequisite for optimization in projection radiography. Radiat. Prot. Dosim., 169, 353–359 (2016).

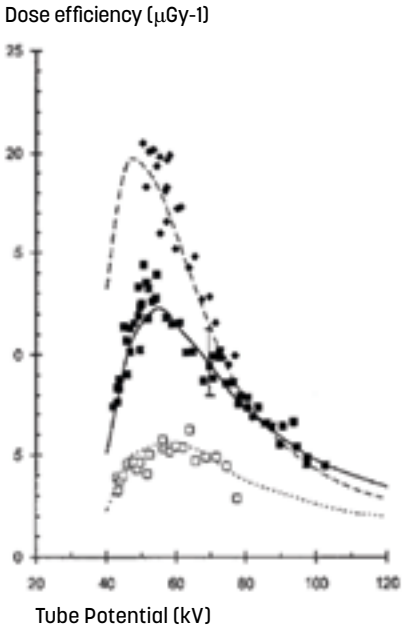
POPULAR SCIENTIFIC SUMMARY

MICHAEL SANDBORG

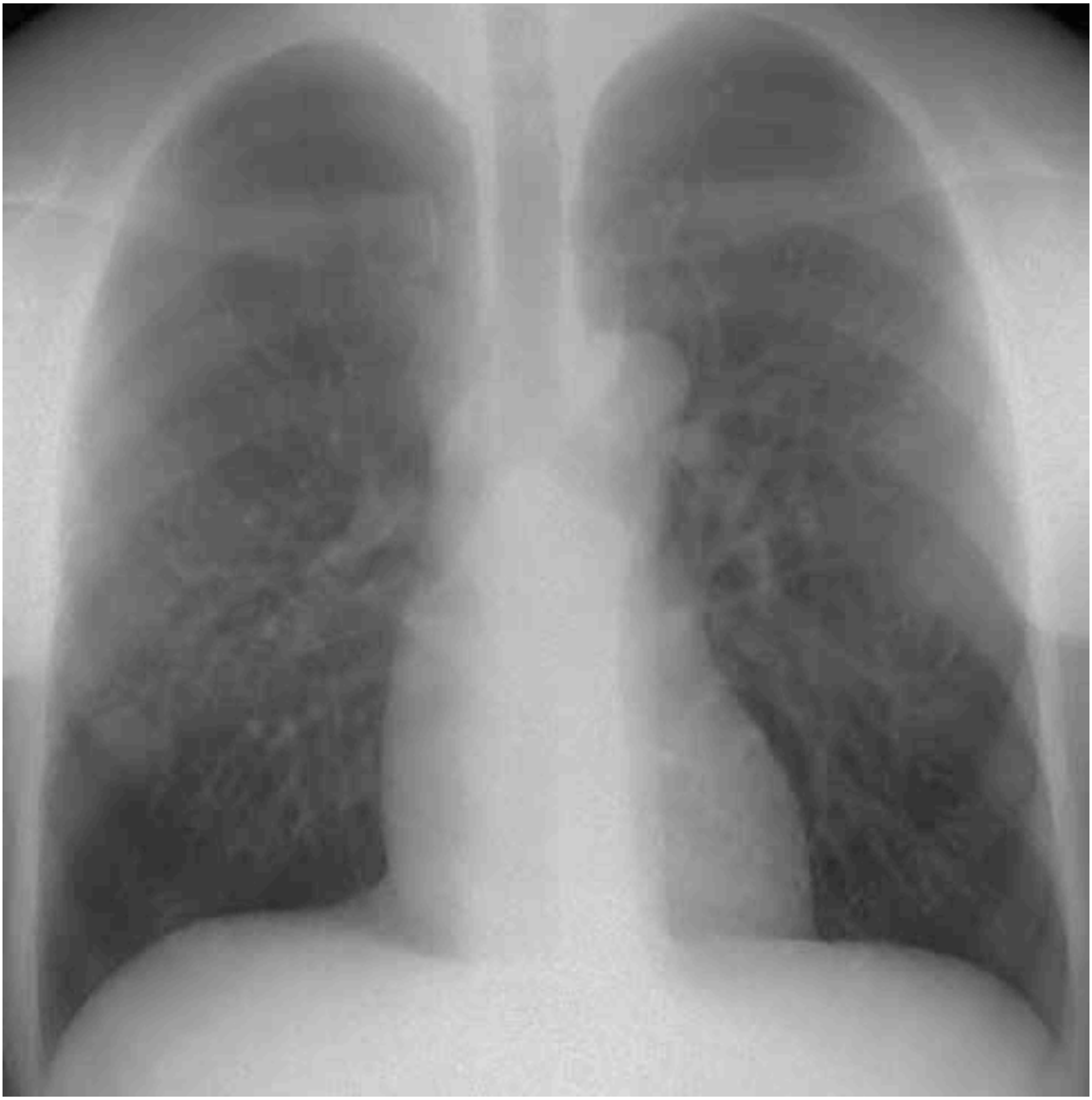
Optimising Radiographic Techniques – Dose Versus Image Quality

Humans have always been exposed to ionizing radiation. Today's increasing medical exposure is an important part of modern health care. The risk for individual patients due to exposure to ionizing radiation and the associated risk for lethal cancer is typically very small. This is particularly true compared to the expected clinical benefits, for example an accurate diagnosis and subsequent adequate treatment. However, since the number of x-ray examination (computed tomography in particular) increases steadily each year the medical community has a responsibility to minimise the radiation dose that patients are exposed to.

The procedure for this is called dose optimisation and aims to reduce the radiation associated risk while maintaining sufficient clinical image quality. Dose optimization requires that both image quality and patient exposure can be accurately measured and balanced against each other.



The figure illustrates how our virtual x-ray system was validated since the measured (single marker points) and calculated (lines) data both coincide and indicate that dose efficiency peaks at a tube potential of 50–60 kV.



Our aim is to develop and use a computer simulation model of the complete x-ray imaging system. To achieve this goal, we are validating a model called the virtual x-ray machine by exploring the correlation between subjective radiologists' assessment of image quality and the objective estimates from a so-called model observer. The validated model observer's assessment is then used to search for radiation dose-efficient settings of the x-ray machine. This cost-efficient strategy provides unique opportunities not only for evaluating today's x-ray machines, but also future machines before expensive prototype system are built. The whole medical imaging process can be optimised including image acquisition, image processing and pathology detection.

An example of a model observer is the signal-to-noise ratio when imaging the reduced blood flow in a coronary artery. The signal-to-noise ratio measures the accuracy by which this artery pathology can be detected in the images when the detection is limited by image quantum noise. Quantum noise typically increases as the patient exposure is reduced as fewer x-ray photons then contribute to image formation. Much in the same way as your camera images seem less clear when you take a photograph under poor light conditions.

The figure illustrates important results from our model observer. The y-axis shows that the dose efficiency (signal-to-noise ratio per exposure [μGy-1]) is highest (maximum) when the tube potential (x-axis) is approximately 55 kV. This tube potential hence minimises patient exposure for a fixed signal-to-noise ratio ('image quality'). This is a lower tube potential than commonly used in today's x-ray machines for coronary angiography and indicate that further dose reductions of up to 50 % are possible in clinical practice for the benefit of our patients. ■

PROJECT INFORMATION

Project Name
Finding High Risk Osteoporosis Patients with CT techniques

Project Leader
Mischa Woisetschläger, Department of Radiology, Region Östergötland.
Anna Spångeus, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

Main Project Participants
Eva Klintsröm, Benjamin Klintström

Key Publications
Soft tissue discrimination ex vivo by dual energy computed tomography (Persson) 2010; Eur J Radiol. 2010 Aug;75(2):e124-8.

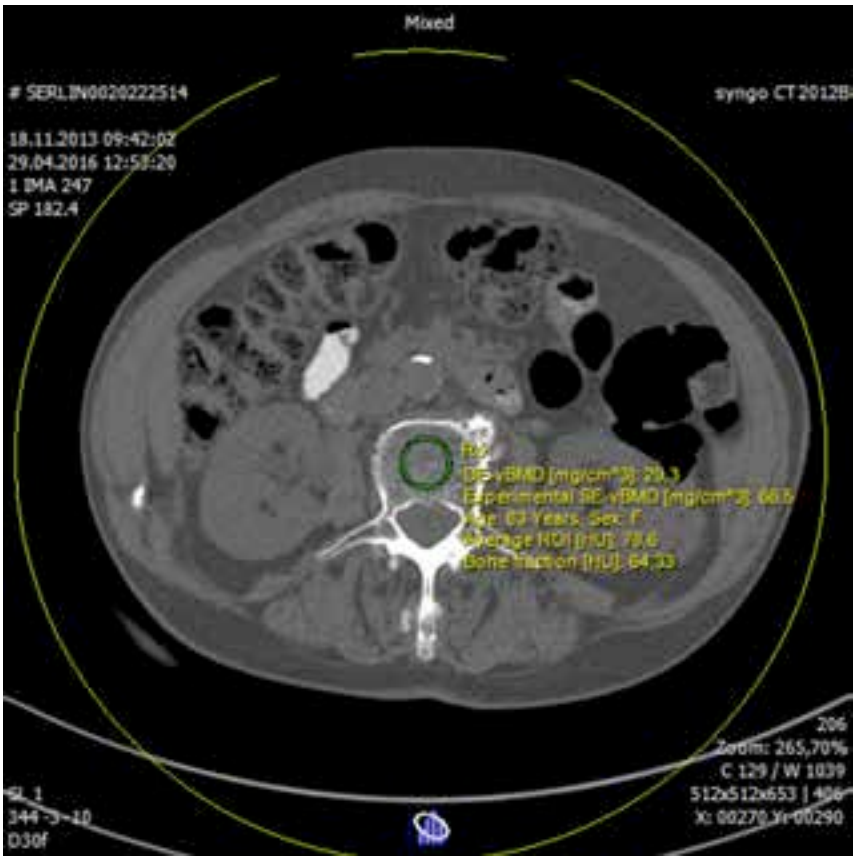
Klintström, E. et al., 2014. Trabecular bone structure parameters from 3D image processing of clinical multi-slice and cone-beam computed tomography data. Skeletal radiology, 43(2), pp.197-204.

POPULAR SCIENTIFIC SUMMARY

MISCHA WOISETSCHLÄGER & ANNA SPÅNGEUS

Finding High Risk Osteoporosis Patients with CT Techniques

Osteoporosis is one of the biggest endemic diseases in the western world especially in the Nordic countries. It implies great individual distress and Health economic problems. Early detection and treatment can avoid both individual suffering and save costs for the healthcare system by avoiding vertebral fractures and their rehabilitation costs as well as surgery costs for hip and radius fractures.



Results of the vBMD (volume BMD), measured by eXamine, the software application developed together with Siemens. The analysis is done on a dual energy scan without contrast.

Today many osteoporotic fractures are not detected in time because many different specialties are involved in a cumbersome process where patients are examined in the ER when having a low energy fracture or back pain. The orthopaedic surgeons will in this phase write a referral to the primary care doctor who will then write another referral to the endocrinologist for a DXA scan. The treatment induction is then made by the endocrinologist or the primary care doctor. This cumbersome process is prone to fail.

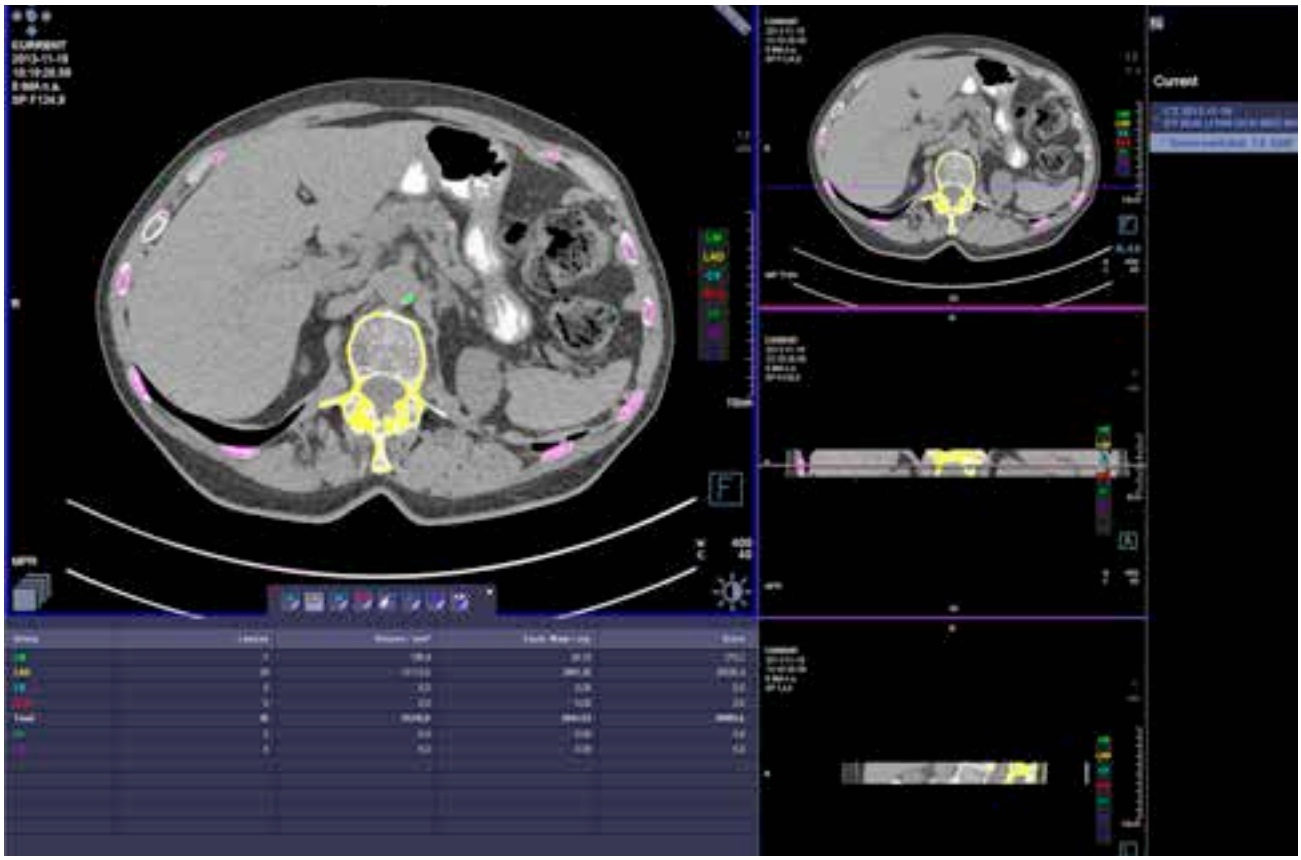
Our idea is to use different imaging techniques like MDCT scans, Cone beam CT, MRI, made for different indications at CMIV, including the lumbar spine and/or the hips to describe the risk for having osteoporosis and by that finding high-risk patients earlier.

In collaboration with Siemens Healthcare we developed a software with three component analysis that calculates the amount of bone mass. A dual energy 3-material decomposition algorithm is used to differentiate bone from soft tissue and fat attenuation. The algorithm uses material attenuation coefficients on different beam energy levels. The bone fraction of the three different tissues is used to calculate the amount of hydroxyapatite in the trabecular bone of the corpus vertebrae inside a predefined ROI.

Results show that there is a good correlation between our software solution and DXA scans in non-contrast examinations.

We also analysed the amount of prevertebral calcifications in the aorta as well as the degree of osteoarthritis in the lumbar spine and osteoarthritis in the facet joints. Results here show that the higher the calcifications in the aorta, the more osteoarthritis there is in the spine and the bigger the difference between the BMD measured in CT compared to DXA, showing that calcifications and osteoarthritis lead to false high BMD values in DXA scans.

In the second part of the project we have a collaboration with the RMV (Rättsmedicinlaverket). The goal of the project is to optimize CBCT (cone beam CT) techniques in order to be used more widely to detect high risk patients for osteoporotic fractures. CBCT is today mainly used in dentistry to make high resolution images of the mandibles and teeth. But recently CBCT is used more and more for examination of extremities. In the future we think applications of CBCT like in the new Multitome CAX from Siemens (a robotic radiology system for skeletal and lung examinations) can be used to make high resolution scans of the radius of fractured patients in the emergency setting and ideally even the lumbar spine in order to find high risk patients earlier. We also think it might be possible to use CBCT technique to obtain a DXA scan in the same session as the acute examination. ■



Results of the CaScoring analysis of the aorta with quantification of the amount of CaHA (Calciumhydroxyappatite) in the aorta. The results were used to proof that DXA scans are false too high in individuals with aortic calcifications compared to vBMD obtained in the same patients.

PROJECT INFORMATION

Project Name
Analysis of CT Liver Perfusion

Project Leader
Mischa Woisetschläger, Department of Radiology, Region Östergötland

Main Project Participants
Per Sandström, Bergthor Björnsson, Wolf Bartholomae, Lilian Henriksson, Petter Quick

Key Publications
Miles K, a et al.
Current status and guidelines for the assessment of tumour vascular support with dynamic contrast-enhanced computed tomography.
Eur. Radiol. 22, 1430-41 (2012).

Klotz E, et al.
Technical prerequisites and imaging protocols for CT perfusion imaging in oncology.
Eur. J. Radiol. 1–9 (2015). doi:10.1016/j.ejrad.2015.06.010.

Kalra M K, et al. Radiation Dose Reduction With Sinogram Affirmed Iterative Reconstruction Technique for Abdominal Computed Tomography. Journal of Computer Assisted Tomography 36, 339–346 (2012).

POPULAR SCIENTIFIC SUMMARY

MISCHA WOISETSCHLÄGER

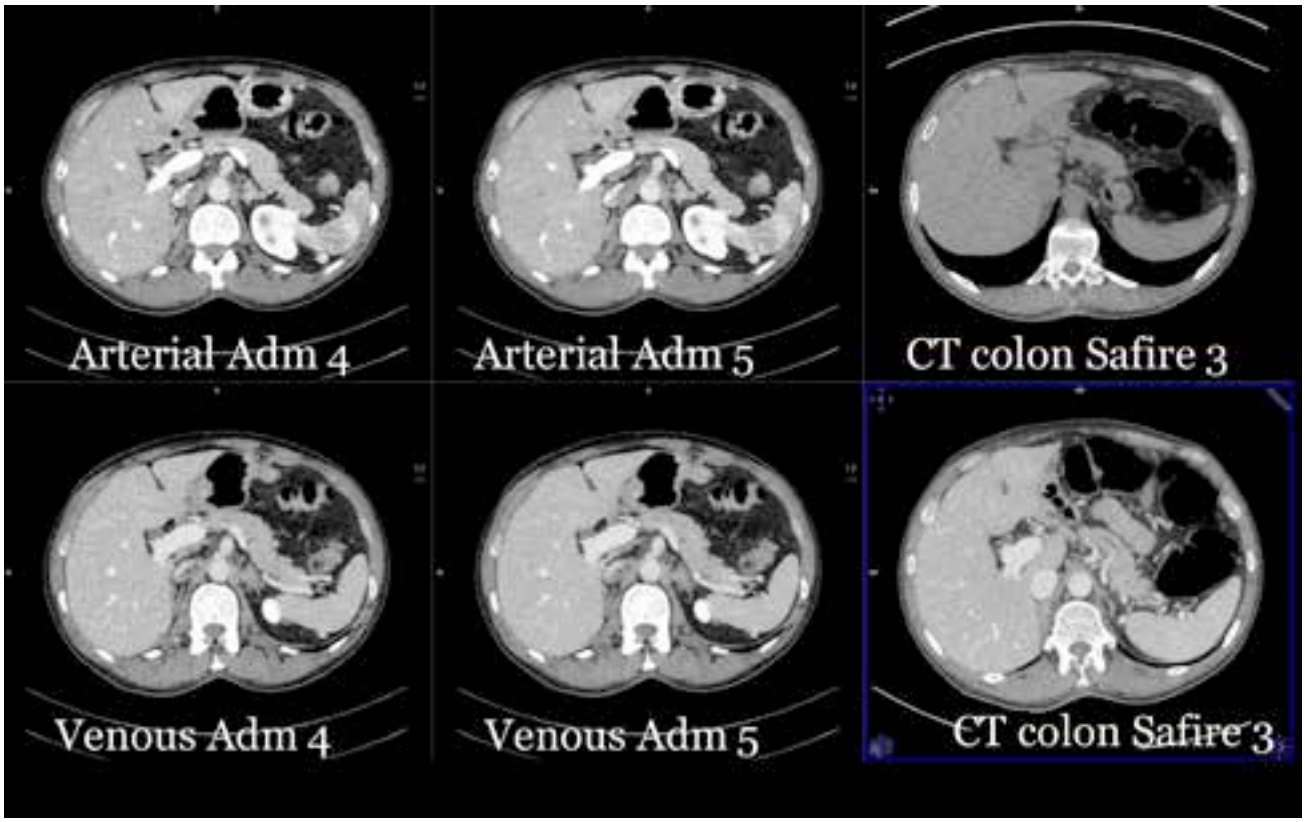
Analysis of CT Liver Perfusion

CT perfusion is a technique known since 1991. Despite its advantages in giving quantitative information about the blood flow and blood volume in tissues, i.e. tumours, the technique is not yet widely used in clinical practice. There are several reasons for this. One of the main reasons is the relatively high radiation dose and the restricted area of examination. Because of radiation issues and technical restrictions, so far only the region of known tumours or recently the upper part of the abdomen could be examined.

For the technique to be used in a more widely clinical setting, it would be preferable to examine the whole abdomen and be able to get images with acceptable image quality for review as well as getting quantitative information. Recently several technical advancements as iterative reconstruction kernels and low kilovolt examinations have had a major impact in lowering radiation dose and enhancing image quality in CT.

In this project we want to examine if it is possible to do low kilovolts CT perfusion examinations of the liver, including the whole abdomen to replace an abdominal four phase CT scan. For the first time, we examine patients with a 70 kV examination protocol and use a new iterative reconstruction kernel (Admire) to increase Image quality as well as getting quantitative information of the whole upper abdomen.

Patients with hepatocellular carcinoma (HCC) planned for a transarterial chemoembolization treatment (TACE) will be scanned with our CT perfusion



protocol as well as with a 4 phase CT (non contrast, late arterial, venous and late phase) before TACE and 3–4 weeks after TACE treatment.

The image quality of the four phase CT will be compared to the images of the perfusion CT. We will also analyse the quantitative results of the CT perfusion software and compare these with the visible results to analyse if the quantitative information can increase the radiologist confidence in deciding if lesions are HCC or nodules as well as the question about residual tumour after TACE treatment.

In the first part of the study we concentrate on lowering the radiation dose. In the second part we will examine if lesions are missed or under-diagnosed with the fixed time points of a four phase CT, compared to the continuous CT perfusion scan. We will then investigate if fewer sequences in a perfusion scan might be sufficient for the quantitative information. The last part will investigate if LI-RADS scores are changed when evaluating liver nodules only visibly as compared with adding the help of the quantitative perfusion information.

In summary, the goal of this project is to improve CT perfusion that it might replace todays 4 phase CT. For this to be realized CT perfusion should have at least the same dose as a 4 phase CT or lower and cover an area big enough for evaluation of organs (or whole abdomen). CT perfusion should also supply images that can be evaluated visually and be used in clinical practice together with the quantitative information. ■

FIGURE. CT perfusion scan with 1 series representing an arterial time point with admire reconstructions grade 4 and 5 and 1 series representing a venous time point with admire reconstructions grade 4 and 5, compared to a CT colon scan of the same patient with and without contrast agent, reconstructed with Safire 3. The CT perfusion scan is made with 70 Kv and 50ml contrast agent compare to the CT colon with 120Kv and 100 ml of contrast agent.

PROJECT INFORMATION

Project Name
Methods for high-quality illumination in interactive volume graphics

Project Leader
Anders Ynnerman, Department of Science and Technology, Division for Media and Information Technology

Main Project Participants
Daniel Jönsson, Joel Kronander, Timo Ropinski

Grants
The Swedish Research Council 2011

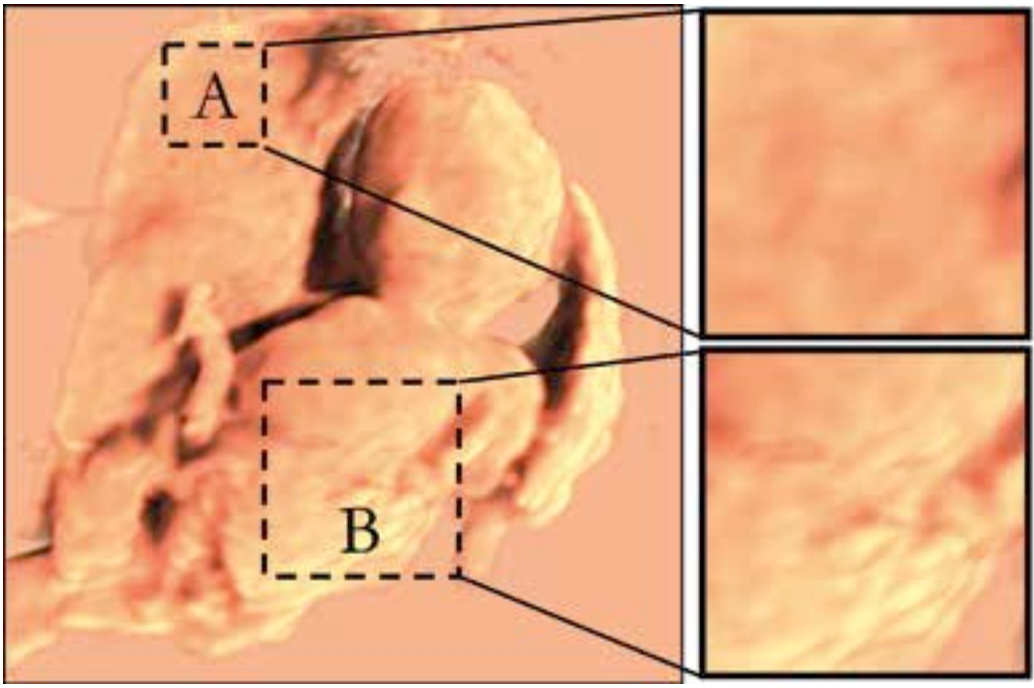
Key Publications
Correlated Photon Mapping for Interactive Global Illumination of Time-Varying Volumetric Data.
Daniel Jönsson, Anders Ynnerman, IEEE Transactions on Visualization and Computer Graphics (TVCG), Volume 23, Number 1, pages 901–910, 2017.

Interactive Visualization of 3D Scanned Mummies at Public Venues.
Anders Ynnerman, Thomas Rydell, Daniel Antoine, David Hughes, Anders Persson, Patric Ljung.
ACM Communications, Volume 59, Number 12, pages 72–81, 2016.

Efficient Visibility Encoding for Dynamic Illumination in Direct Volume Rendering.
Joel Kronander, Daniel Jönsson, Joakim Löw, Patric Ljung, Anders Ynnerman, Jonas Unger.
IEEE TVCG, Volume 18, Number 3, pages 447–462, 2012.

POPULAR SCIENTIFIC SUMMARY

ANDERS YNNERMAN



Methods for High-Quality Illumination in Interactive Volume Graphics

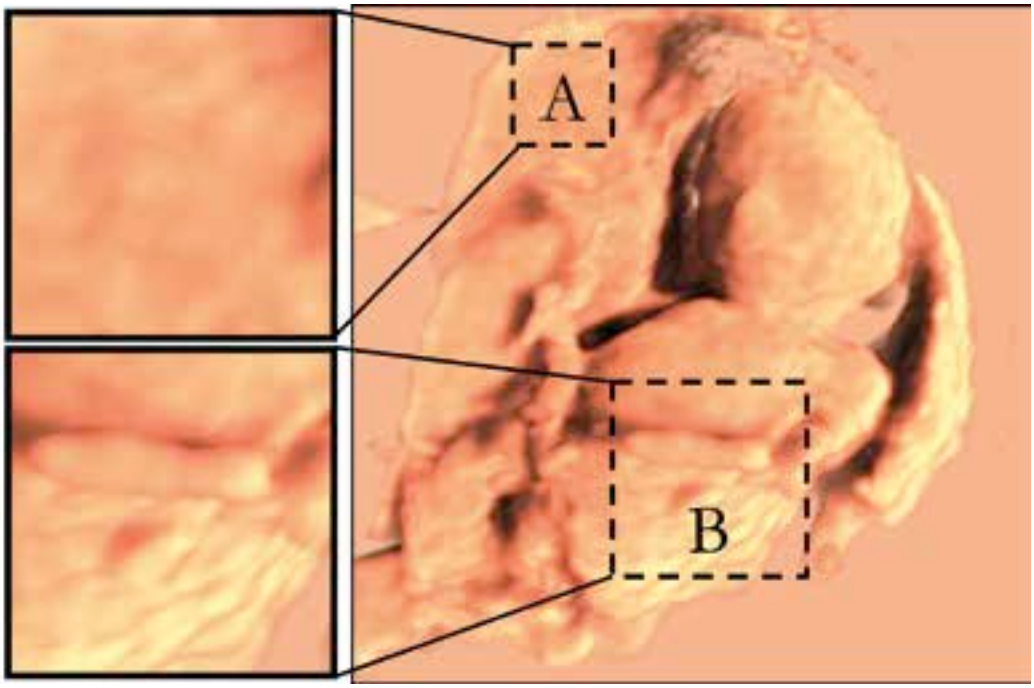


FIGURE. Highlights of two areas at different time-steps in a time-varying 3D ultrasound scan of a fetus. Region A changes little over time while a new feature appears in region B. By focusing the light transport computation on regions with highly changing areas, such as region B, we can reach interactive performance for time-varying volumetric data.

An essential ingredient in understanding the structures found in volumetric data is the ability to interactively change rendering parameters and camera settings. In this project we strive to increase the clarity of images and improve the perception of depth and detail by developing efficient algorithms for shading of volumetric data in real time. However, being able to perform simulations of the ways light absorbs and reflects, while still being able to interactively explore the data, is a computationally daunting task.

Several approaches to this problem exist but they reduce the physical accuracy of the light transport in the volume in order to maintain interactivity. Our research is therefore focused on developing efficient methods for simulating physically based light interaction of volumetric objects from computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound scans. The methods in our research mimick the real world matter-light interaction, while still allowing interactive data exploration.

This lifelike object-light interaction was previously not possible until we in this project were able to simulate realistic light interactions interactively using photon maps. The maps have a data structure that enables recording of the photons path history, thus avoiding costly recalculation of photon paths that did not change when altering light transport parameters.

By utilizing recent advances in hardware we have also shown how to perform selective light updates and reduce the memory footprint of a widely used light transport algorithm. This enables the user to interactively create advanced light setups with low memory overhead.

In our latest work, we have extended our methods to time-varying CT, MRI and ultrasound scans, thus enabling examination of organ functions with accurate shading. We show that the key to allow high quality illumination for time-varying data is to utilize the correlation between the changes in the data over time, illustrated in the figure below. By efficiently incorporating the information about changes in the data, we can reduce the light transport computation to the changing areas and thereby reach interactive performance. This work received an honorable mention for the best paper award at IEEE Visualization 2016. ■

PROJECT INFORMATION

Project Name
DROID – Diagnostic reference oncology imaging database

Project Leader
Caroline Bivik Stadler, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Daniel Forsberg, Martin Svenson, Mischa Woisetschläger, Nils Dahlström, Johan Blomma, Anna Bodén, Karin Skoglund, Jerónimo Rose, Ludwig Jacobsson, Darren Treanor, Claes Lundström, Martin Hedlund, Anders Persson

Grants
Visual Sweden 2017–2018

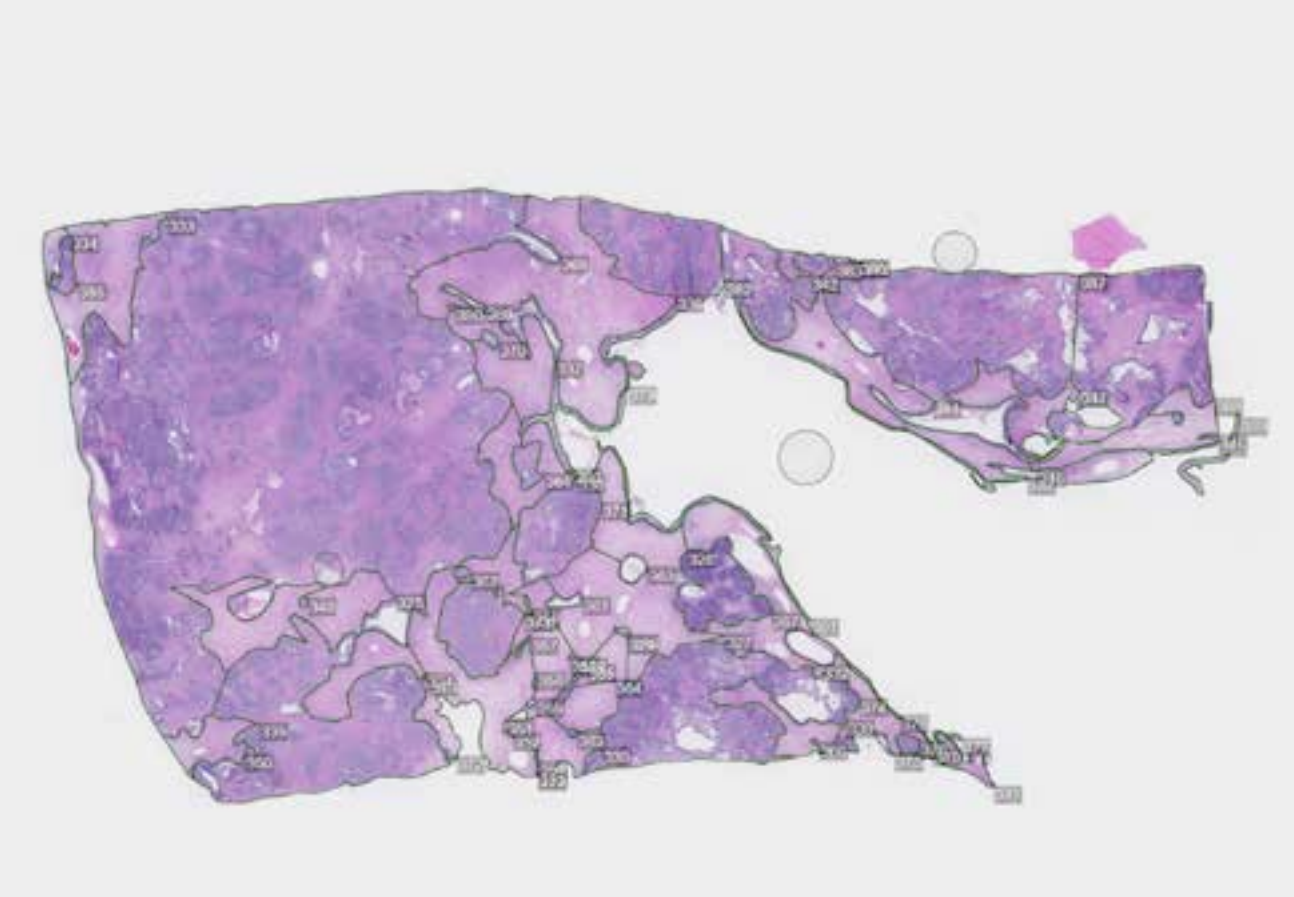
POPULAR SCIENTIFIC SUMMARY

CAROLINE BIVIK STADLER

DROID – Diagnostic Reference Oncology Imaging Database

The two very important disciplines in diagnostic medicine, radiology and pathology, spend more and more time and resources on cancer diagnoses. This puts the physicians under increasing pressure to deliver to the level required. The radiologists analyze images from computed tomography (CT) and magnetic resonance imaging (MRI), for them the challenges concern how to effectively handle the comparison between several follow-up studies in order to determine if a cancer tumor progresses, if it responds to treatment or if it is stable. The pathologists analyze tissue by surgery in high-resolution microscopes. The diagnostic work relates to classification, detection and quantification of image features. This specialty, based on subjective assessments, is difficult and time-consuming to learn to master.

Today, many physicians place their hope in different artificial intelligence (AI) based decision support systems that are expected to be able to both streamline and improve the quality of diagnostic work. The rapid development of AI and deep learning gives promises of future tools performing or assisting routine clinical tasks, e.g. automatically segment tumors in radiographic images and thereby facilitate consistent measurement of tumor size. Furthermore, the work of the pathologists could preferably be supported by more accurate and reproducible anal-



ysis provided by quantitative AI tools based on pattern recognition.

However, a huge challenge in this context is that the access to comprehensive image data, required to develop AI systems for these medical tasks, is severely limited, if available at all. The amount of high-quality data used for training is crucial and has a big impact on the performance of the system generated. The DROID-project is aiming to compile and publish an open image database, containing detailed annotations of oncological images from several different tissues, e.g. breast, ovarian, colon, skin, liver, skeleton and lymph. This database should be freely available for AI algorithm training for medical diagnostics.

Apart from CMIV the project involves Region Östergötland, Sectra and ContextVision. Clinical experts will collect images, mark contours of specific morphological patterns and label them with standardized anthologies. Based upon these annotated images, a number of AI-prototypes will be generated and trained. Henceforth, the results will be integrated into existing clinical IT-systems for evaluation of prospective end users in their normal workflow. The long-term goal of the project is to contribute to the large-scale use of AI in healthcare, particularly to the development and implementation of various AI decision support tools in cancer diagnostics. ■

FIGURE. A digital image of a pathological ovarian tissue stained with hematoxylin-eosin (H&E). Manual annotations have been made to contour the malignant tumor area.

PROJECT INFORMATION

Project Name
Digital Pathology

Project Leader
Claes Lundström, Department of Science and Technology, Division for Media and Information Technology

Main Project Participants
Darren Treanor, Jeroen van der Laak, Martin Hallbeck, Peter Lundberg, Stergios Kechagias, Daniel Forsberg, Martin Falk, Dharshana Jayewardene, Anna Bodén, Jeronimo Rose, Karin Skoglund, Arrigo Capitanio, Helén Richard, Christine Johansson, Sofia Jarkman

Grants
VINNOVA 2012–2014, 2015–2017

Key Publications
CF Lundström, HL Gilmore, PR Ros. Integrated Diagnostics: The Computational Revolution Catalyzing Cross-disciplinary Practices in Radiology, Pathology, and Genomics. Radiology 285 (1), 12–15, 2017.

JA Chow, ME Törnros, M Waltersson, H Richard, M Kusoffsky, CF Lundström, A Kurti .
A design study investigating augmented reality and photograph annotation in a digitalized grossing workstation.
Journal of Pathology Informatics, 2017;8(31).

H Kost, A Homeyer, J Molin, C Lundström, HK Hahn.
Training nuclei detection algorithms with simple annotations.
Journal of Pathology Informatics, 2017; 8.

POPULAR SCIENTIFIC SUMMARY

CLAES LUNDSTRÖM

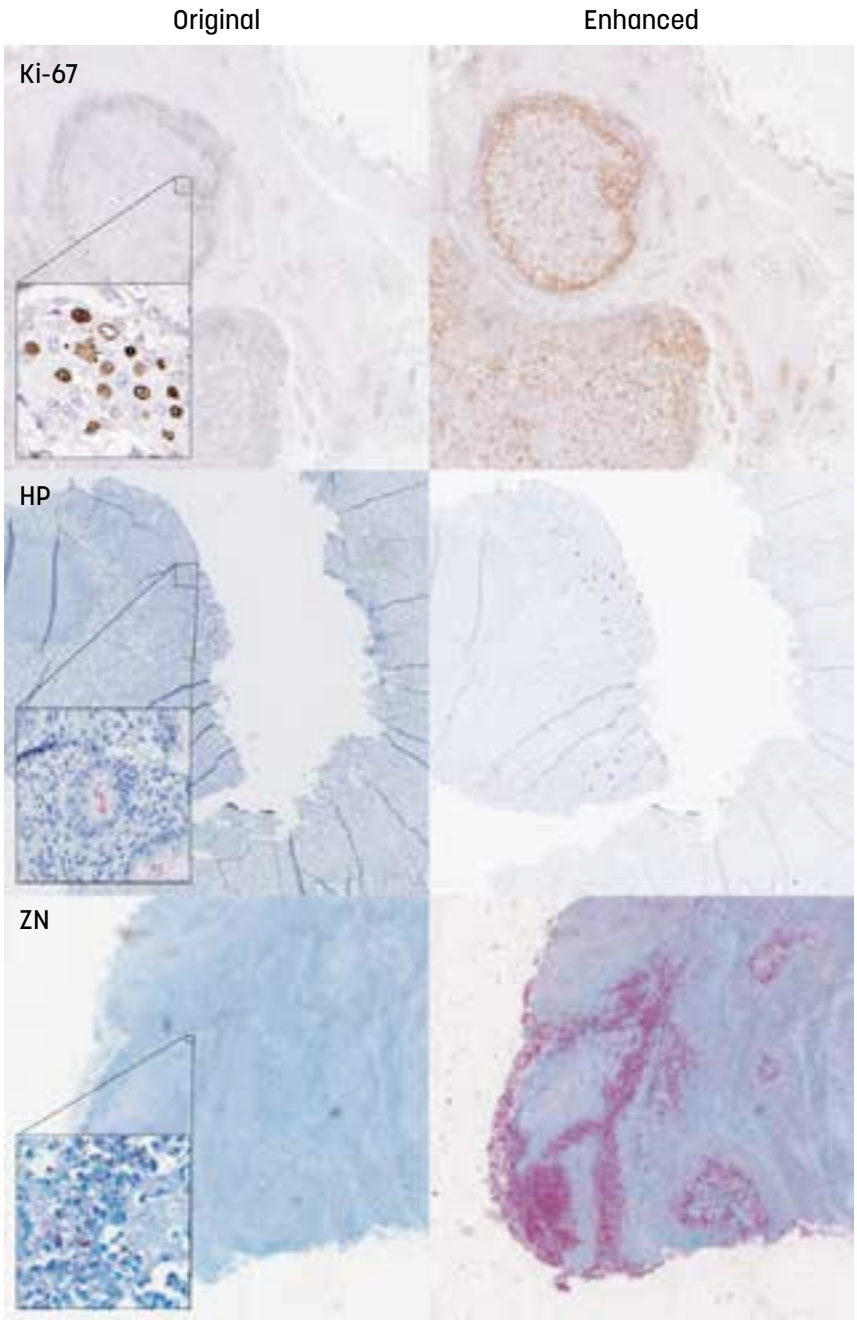
Digital Pathology

Diagnostic pathology is of crucial importance for health care, especially cancer care. Pathologists analyze tissue from the patient to determine its characteristics (histology). This knowledge is used to find the correct diagnosis and therapy. Due to lack of pathologists the waiting time for the pathology report is often long, with an anxious wait and delayed therapy for the patient as a result.

Digitization of the pathology workflow has the potential to increase both efficiency and quality of care.

In order to realize this potential, cross-disciplinary research efforts are needed that can combine clinical expertise with knowledge in image analysis and human-computer interaction.

The CMIV pathology group consists both of medical and technical researchers from the university and pathologists and lab assistants from the clinical pathology department at the hospital, all working together on research and development efforts close to clinical practice.



Today, most pathologists analyze histology samples in a microscope. In digital pathology the histology samples are instead scanned to create digital images of the tissue, which can be analyzed on a computer screen. While the pathologist is still responsible for the evaluation and diagnosis, the digital environment is a valuable tool for image analysis to detect, measure and grade diagnostic findings.

Analyzes of the pathology department show that digitization of the workflow from referral, finished preparation and scanning of samples to the pathologist´s workstation may result in a better overview of the workload, less administration and shorter turnaround times. Digital pathology also entails unique opportunities for collaborations between hospitals both regionally and worldwide as the digital samples can be sent instantly.

The CMIV research agenda in digital pathology tackles image analysis challenges such as correlating findings between radiology and histology in liver biopsies and increasing precision and efficiency in breast cancer histological grading. Visualization challenges for 3D histology are being addressed, in particular handling of the very large data sets at interactive speed. Furthermore, the possibilities to validate the clinical work are investigated and human-computer interaction aspects are explored. A common ground for the research projects is the focus on finding digital solutions that will work in the clinical setting. ■

PROJECT INFORMATION

Project Name
Quantitative MRI as a ground-breaking tool for post mortem imaging diagnoses

Project Leader
Anders Persson, Department of Medical and Health Sciences, Division of Radiological Sciences,
Wolf-Dieter Zech, Department of Medical and Health Sciences, Division of Radiological Sciences / Institute of Forensic Medicine Bern, University of Bern, Switzerland

Key Publications
N Schwendener, C Jackowski, A Persson, MJ Warntjes, F Schuster, Fabiano Riva, Wolf-Dieter Zech. Detection and differentiation of early acute and following age stages of myocardial infarction with quantitative postmortem cardiac 1.5 T MR. Forensic science international 270, 270, 248–254. 2016.

WD Zech, N Schwendener, A Persson, F Schuster, F Riva, C Jackowski. Detection and Differentiation of Early Acute and Following Age Stages of Myocardial Ischemia With Quantitative Postmortem Cardiac Magnetic Resonance. American Academy of Forensic Medicine. Las Vegas, Nevada, USA. 22.–27.02.2016.

WD Zech, N Schwendener, A Persson, MJ Warntjes, F Riva, Frederick Schuster, Christian Jackowski. Postmortem quantitative 1.5-T MRI for the differentiation and characterization of serous fluids, blood, CSF, and putrefied CSF. International journal of legal medicine 129 (5), 1127–1136.

POPULAR SCIENTIFIC SUMMARY

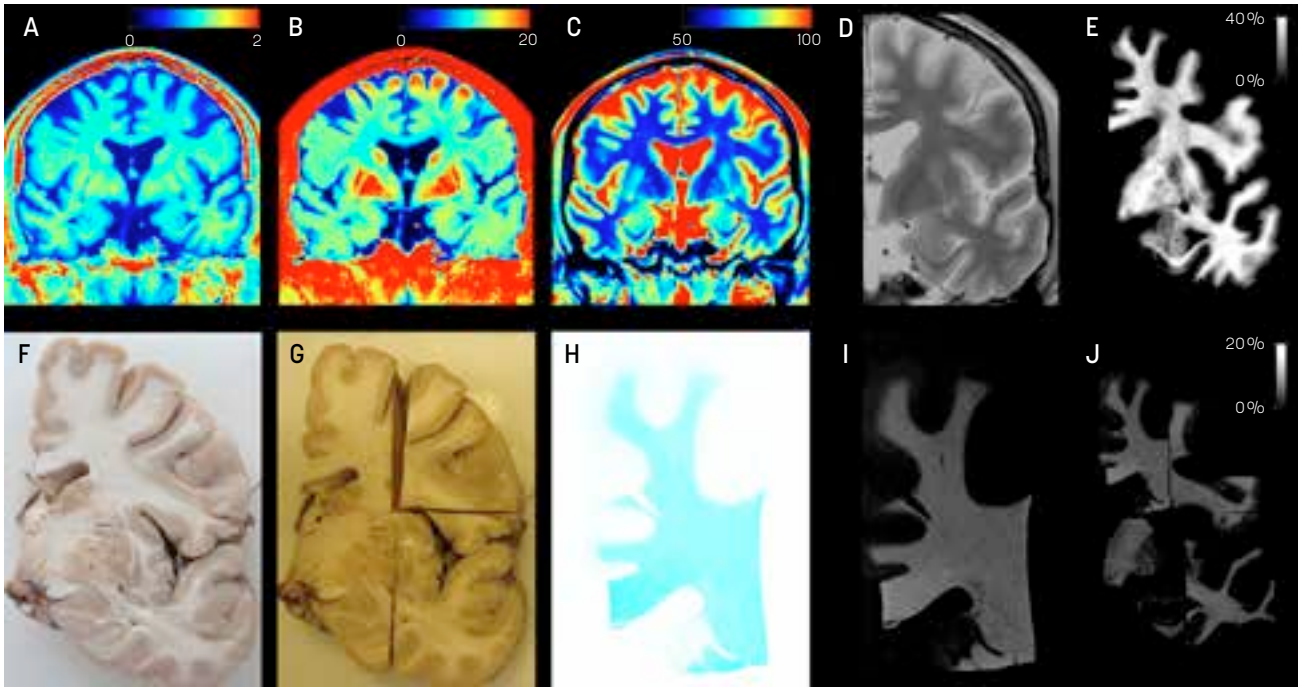
WOLF-DIETER ZECH & ANDERS PERSSON

Quantitative MRI as a Tool for Post Mortem Imaging

Autopsies are fundamental to current post-mortem information acquisition for medical education, validation of therapeutic strategies, medical quality control and national cause of death statistics. Nevertheless autopsy rates have dramatically declined over the last decades.

A solution to overcome this problem was thought to be provided by non-invasive imaging techniques such as post-mortem computed tomography and post-mortem magnetic resonance imaging (MRI). However, so far several natural and unnatural causes of death and relevant forensic findings cannot be visualized or recognized via post-mortem imaging. Hence, to this date the classic autopsy remains the gold standard for acquisition of relevant post-mortem data, especially in determining natural causes of death such as acute heart attack.

A substantial advancement required for post-mortem imaging to equal classic autopsy is related to post-mortem quantitative MRI. This approach is based on a recently developed MRI sequence that allows for rapid



The process for myelin evaluation on a male subject, 69 years old, acquired at a temperature of 10 degrees.

quantification of parameters called relaxation times and proton densities. These parameters can be measured by placing measuring fields in regions of interest in MR images.

It was found that each relevant pathology such as infarction, inflammation or tumors exhibit unique combinations of parameters. Therefore, the measured values can provide the radiologist and the forensic pathologist with relevant information for the determination of the cause of death.

In 2015 a research collaboration between CMIV, the Forensic Institute in Linköping and the Institute of Forensic Medicine in Bern / Switzerland had been started assessing post-mortem quantitative MRI data validated by autopsy findings. The data assessed in this international research collaboration will be used to create a whole body reference database for the quantitative MRI approach. The database will be used for advanced post-mortem MRI diagnostics of relevant pathologic findings. Moreover the database will provide a fundament for development of software that is able to automatically detect pathologic tissue.

The overall-goal of the research collaboration is to develop a fully automatic workflow that acquires quantitative MR post-mortem information from corpses that do not undergo a traditional autopsy. Once implemented in a wide-spread manner, post-mortem quantitative MR imaging is expected to result in more deceased people undergoing investigations of the cause of death and thereby increase the quality of medicine in general and substantiate the mortality statistics of our society. ■

Analytic Imaging Diagnostic Arena

Analytic Imaging Diagnostic Arena (AIDA) is a national arena for research and innovation in medical image analysis. AIDA is a cross-disciplinary collaboration aiming for largescale use of Artificial Intelligence (AI) in healthcare. Here, academia, healthcare and industry will meet to translate technical advances in AI technology into patient benefit in the form of clinically useful tools.

The national arena AIDA was formed in late spring 2017. AIDA is an initiative of CMIV but invites research projects from all parts of Sweden. The vision is to bring AI tools all the way from research to clinical practice and ultimately patient benefit. The research areas tackled are radiology and pathology.

Artificial Intelligence

Artificial intelligence, AI, is defined as the ability of machines to perform intelligent tasks. The term is often used on projects where systems are taught to perform intellectual tasks that are commonly performed by humans. Typically, this can involve generalization, reasoning or learning from past experience. Computers can be taught to do very complex tasks and can excel over humans in repetitive precise assignments. However, when it comes to being flexible and adapt to new conditions computers are far behind. This is where AI research has focused and now come a long way.

AI is a broad field including various branches of techniques to teach machines to be intelligent. The development in all these branches has been very strong during the recent years.

AI in Healthcare

The advances in modern AI fits perfectly into the healthcare vision of "precision medicine", the fully tailored treatment for each patient. In healthcare the use of AI is focused around algorithms and software that help physicians draw diagnostic conclusions. In radiology this can for example be a software that helps detect alterations not yet visible to the naked eye.

The AIDA projects work with population-level analyses using modern machine learning (e.g. deep learning) – which we refer to as Big Data Analytics. In machine learning computers are taught to learn from experience.

Deep learning is based on algorithms that through iterations of data processing adjust until they can recognize and categorize the data. The learning can be supervised, where the data which is used to train the algorithm is labeled, for example pathology images labeled as normal or tumor. Or it can be unsupervised, where where the data is unlabeled and the algorithm works with pattern analysis.

Big Data Analytics

Big data analytics can be a complement to traditional clinical studies. Instead of doing a large study giving one result to guide in the treatment of all patients, a new unique study can be made for each individual patient. Information that is routinely stored from all previous patients is used as decision support.

"It's a great possibility to meet other researchers and exchange ideas and knowledge. The competence and infrastructure offered by AIDA is fantastic"

Tomas Fröding

Large-scale analyses can be made for each new patient to find out what the best treatment would be based on how previous patients are doing.

The Challenge

Today the challenge lies in creating complete solutions that can be put to actual use in healthcare. Claes Lundström, the arena leader for AIDA explains the reason for starting up the arena.

– In recent years, two insights have grown stronger. On the one hand, we get more and more evidence of how powerful AI can be in imaging medicine. On the other hand, it is clear that very little AI reaches out in actual healthcare, so there are unresolved challenges.

Through previous large-scale projects Claes has experience of bringing research ideas and technical innovation into clinical practice.

– Collaboration is the deciding factor for successful technical innovations in healthcare. This applies even more to such a revolutionary opportunity as AI. Healthcare must drive development, the research must understand the real clinical challenges, and the industry create complete solutions that work in the complex reality.

A large part of AIDA consists of subprojects run by research and innovation groups throughout the country. Although being a national arena, AIDA has a physical core at CMIV in Linköping, where the projects meet and where the arena offers infrastructure and expertise.

– In order to fuel a national cooperation, a core is needed that can take extra responsibility for joint activities and infrastructure. Together, the triad CMIV, Sectra and Region Östergötland constitute a critical mass of leading expertise, which also has long experience of effective collaboration, making CMIV the perfect hub in this venture, Claes explains.

Large-Scale Goals

AIDA aims to lead big data analytics to real benefit in healthcare. This is done by creating a large-scale IT system launched in an environment as similar to a diagnostic department as possible with patients, equipment, personnel, etc.

The diagnostic tools developed within AIDA consist of decision support based on AI methods, emphasizing man-machine interaction. The scale in terms of number of patients should be so large that further scaling up to the entire region or even a whole country should be straightforward.

During 2017 nine projects were admitted to the AIDA program. There are projects both in pathology and radiology. The subjects span from using AI to automatically detect oral cancer in microscopy images of brush samples, to developing tools that visualize what regions and details in an image are important for the decision of the neural network.

To enable clinicians to participate and bring valuable diagnostic work to the projects AIDA offers clinical fellowships. There are currently four clinical fellows working with AIDA projects.

Great Timed Opportunity

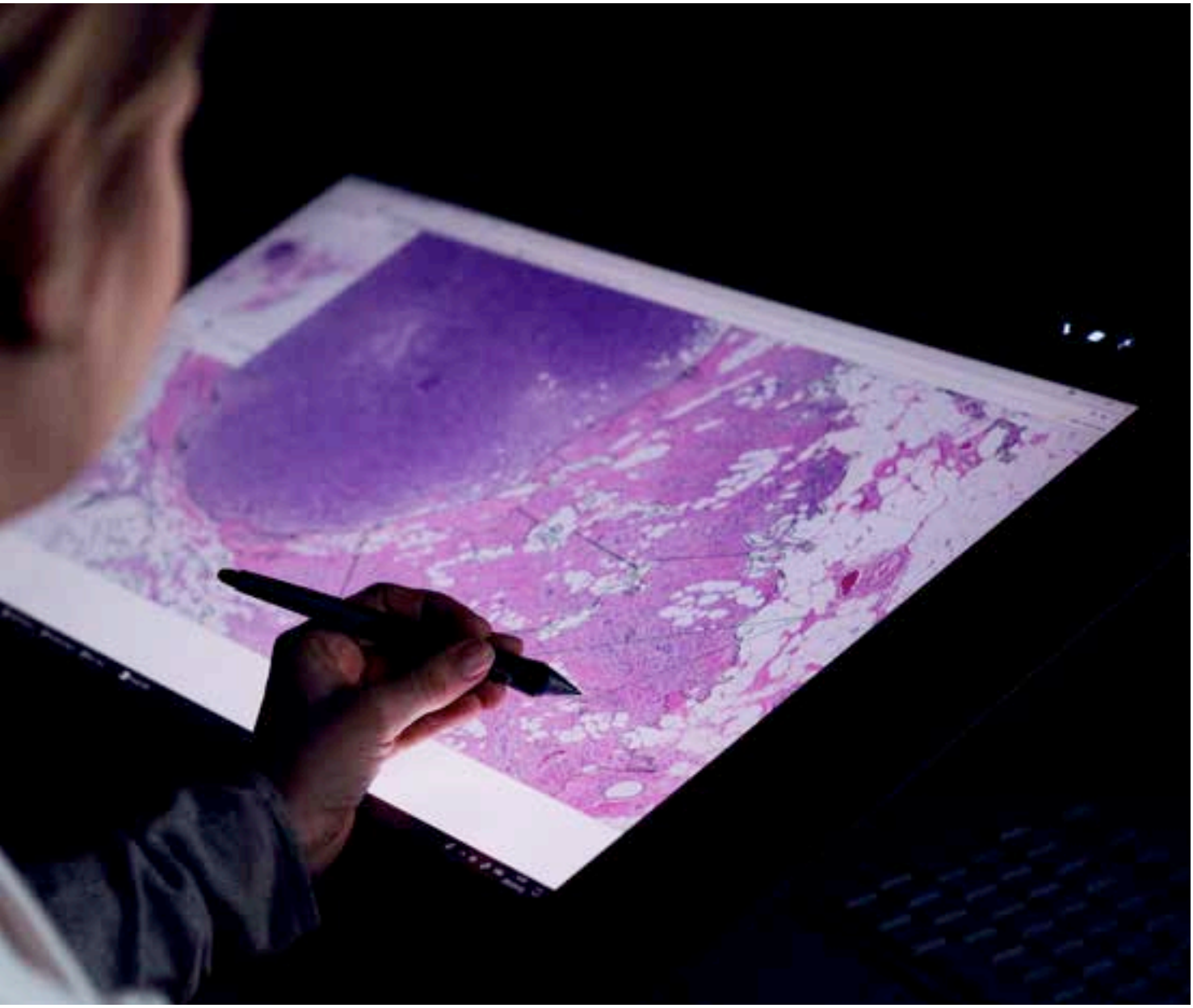
One of the clinical fellows in AIDA is Tomas Fröding from the Radiology Department at Nyköping hospital. He has been working in Nyköping for 16 years and finished his radiology training in 2007 but it was not until a few years back that he got involved with research.

– I met with a good friend of mine, Tobias Sjöblom, and together we came up with the idea that it would be interesting to teach computers to interpret radiology images.

Tobias Sjöblom, professor in cancer genetics at Uppsala University, is the project manager for the project "Automatic detection of lung emboli in CTPA examinations" where Tomas has his fellowship. The project focuses on automatic identification of blood clots in CT images of the lungs.

Both Tobias and Tomas were new to the research area and expertise in image analysis was brought in to the project by requiting a computer engineer.

– I was new to research and Tobias was new to radiology. Neither of us



had the computer knowledge needed to continue the project on our own. Ali Teymur Kahraman did his master thesis in the project and was the key to image analysis for us, says Tomas.

Ali stayed with the project and they continued working together. Tomas annotating the radiology images, Ali working the computers and Tobias as project manager. The timing of AIDA was perfect for them.

– After recruiting additional image analysis competence in Nataša Sladoje, we applied for funding from AIDA and at the same time I applied for a clinical fellowship to be able to spend more time on the project, Tomas continues.

Being part of AIDA means a lot to the project group and the project has reached a higher level. Although it is possible to work with the images at home it is an advantage to use the equipment on site at CMIV.

– It's a great possibility to meet other researchers and exchange ideas and knowledge. The competence and infrastructure offered by AIDA is fantastic. Being part of AIDA increases the chances of success and our goal is to implement an automatic system at radiology departments.

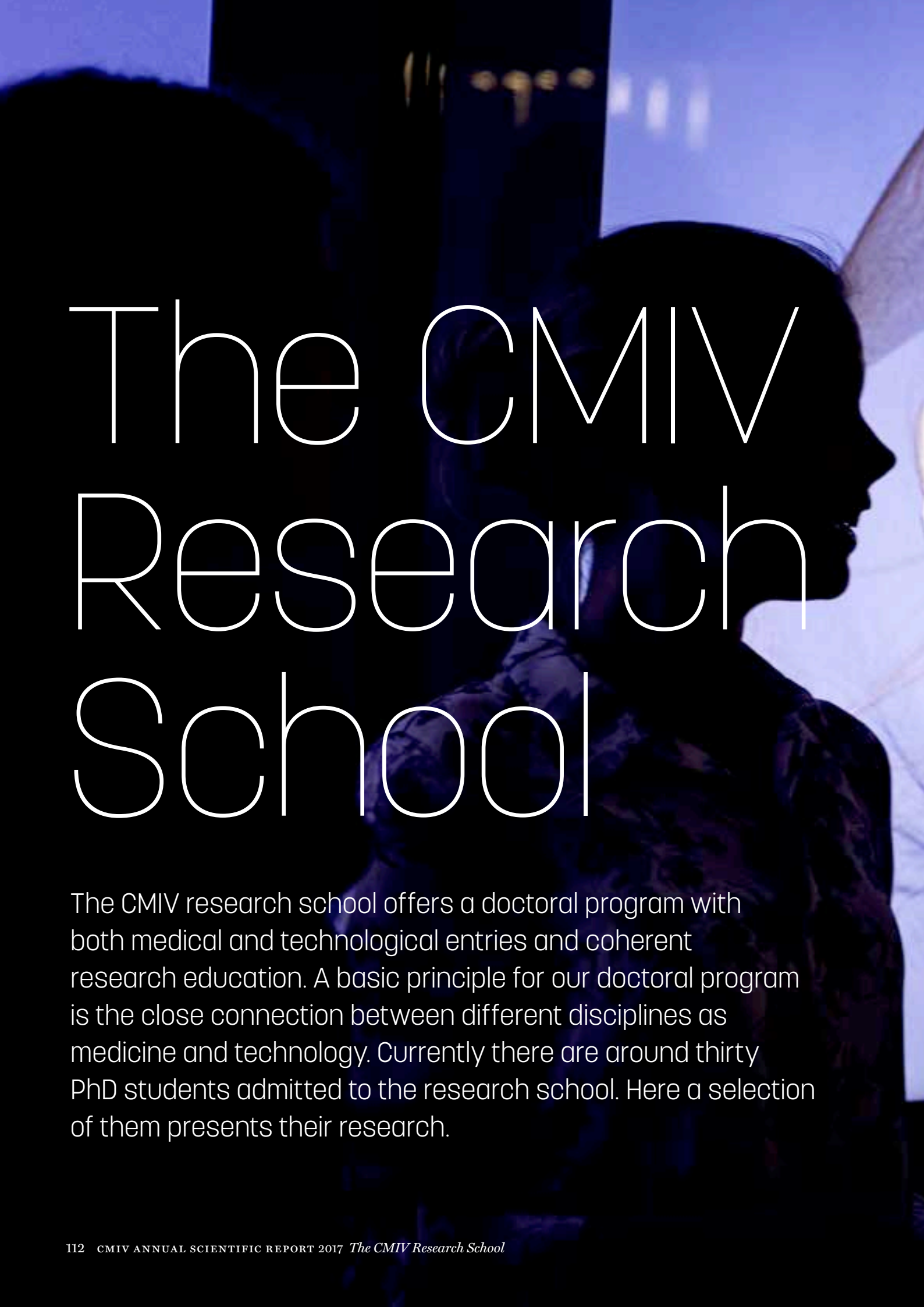
Medtech4Health

AIDA is part of the national Strategic Innovation Program Medtech4Health, a joint initiative by VINNOVA, Formas and the Swedish Energy Agency. Medtech4Health supports innovation in Swedish medical technology focusing on patient benefit. Reidar Gårdebäck is program director for Medtech4Health and explains why it is important to support projects like AIDA.

– AI and imaging medicine are of course central areas for us, and we believe that a national effort will strengthen our research and development in this field, as well as develop new modern tools to implement in healthcare. Tools that in the form of improved diagnostics will benefit both healthcare professionals and patients as well as provide an opportunity for improved health for patients.

The expectations on AIDA are high.

– We believe that AIDA will be a major part in putting Swedish imaging medicine in the international frontline of bringing AI into real benefit, Reidar concludes. ■



The CMIV Research School

The CMIV research school offers a doctoral program with both medical and technological entries and coherent research education. A basic principle for our doctoral program is the close connection between different disciplines as medicine and technology. Currently there are around thirty PhD students admitted to the research school. Here a selection of them presents their research.

ANETTE KARLSSON

Assessing Muscle Volume Using Magnetic Resonance Imaging

We have developed a method that can determine a patient's entire muscle volume, as well as the volume of separate muscle groups based on images from a 10 minute MR-scan. The method can also determine the amount of fat within the muscle, which is a sign that the muscle is injured.

The greatest health challenges of today are either obesity related or ageing related. While getting older, you start loosing muscles, a syndrome called sarcopenia. This may lead to immobility, falls, hip fractures, diabetes and more. In order to understand more about these kinds of syndromes and diseases we need detailed measures of muscle volume and fat infiltration. The possibility to measure the muscle volume and the amount of fat in the muscles is also a useful tool in finding the right treatment and rehabilitation for specific patients.

With an MR-scanner, images are created where all the soft tissue, for example liver, fat and muscles may be shown separately. A pair of images where the first only shows fat tissue while the second shows all the tissue containing water is shown in figure 1.

For the human eye, it is easy to distinguish e.g. the liver from the muscles, as the human knows where the liver is located and its shape. However, when calculating the volume of the muscles, each small image element must be included for each muscle group. This is too expensive why automatic solutions are needed.

For a computer, organs like the liver and the muscles look very similar as they have similar intensity values in the images (figure 1). The computer has no knowledge about where the liver is located or its shape. This method's solution is to manually pre-define the muscle groups within an image. When a new image with no pre-defined muscles is produced the old images are adapted so that they become as similar to the new image as possible. The adapted labels are in that process overlaid onto the new image and an automatic solution for the new muscles is achieved. The volume is calculated by a sum of all the small image elements. A typical result from our automatic muscle tissue segmentation method is shown in figure 2. ■

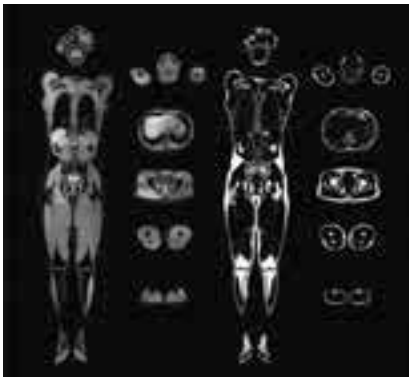


FIGURE 1. A paired magnetic resonance image where the left shows all the water within a whole body and the right shows all the fat.

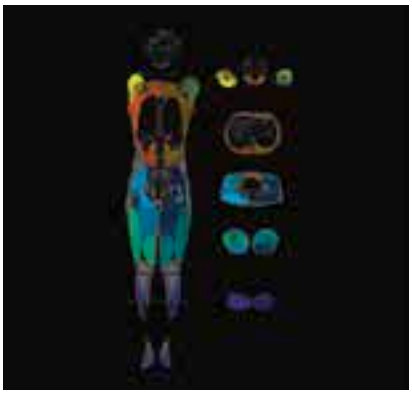


FIGURE 2. A typical result from the automatic method. The different muscle groups are shown in different colors. Grey color indicated that the automatic method has not considered that tissue as muscle tissue.

PROJECT INFORMATION

Supervisors
Magnus Borga, Olof Dahlqvist Leinhard, Ola Friman

Project
Fat- and Water Imaging Project
Quantitative Muscle Project
Brown Adipose Tissue Project

Background
Master of Science, Engineering Biology, specialization in Biomedical Engineering, The Institute of Technology, Linköping University, 2005–2011

Research Engineer, Department of Biomedical Engineering, Linköping University, Linköping 2011–2012

THOBIAS ROMU

Quantitative Water-Fat Imaging

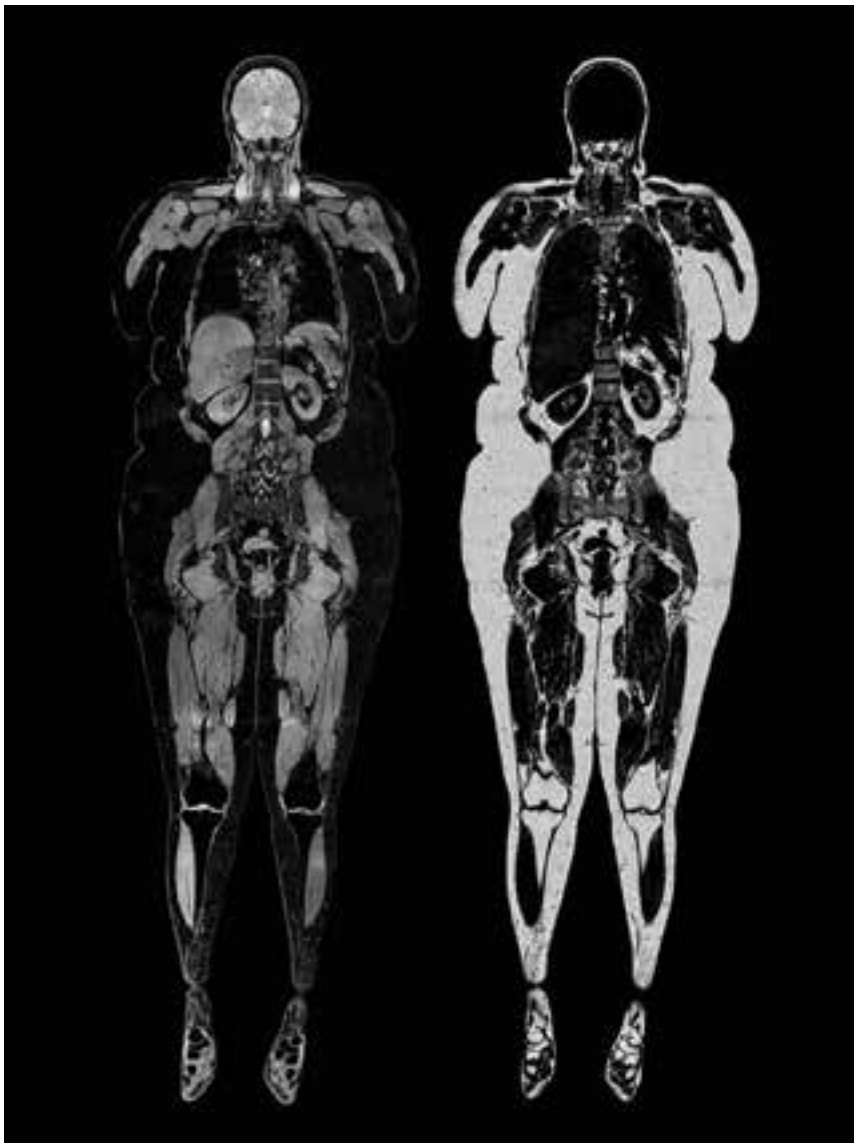
To study the distribution of various tissues within the human body we use a technique that separates water and fat in magnetic resonance (MR) images. An example of such images is seen in the figure. We calibrate the images in a way that every pixel in the fat image corresponds to the actual adipose tissue concentration. Furthermore, we use automatic segmentation through anatomical atlases to study the amount of fat in different compartments in a cost effective way.

White adipose tissue (fat tissue) volume is very hard to measure by imaging since it is the most variable tissue in the human body. Its total volume varies from a few per cent of a person's total volume, to several times the volume of other tissues. An application of regional adipose quantification is that excess of visceral adipose tissue (belly fat) indicates a heighten risk of diabetes type 2, cardio vascular disease and cancer, whilst subcutaneous adipose tissue may even act protectively. Thus, it becomes important to separate the two fat compartments when assessing the risk of obesity.

The problem is that current methods, such as waist circumference, are not accurate enough to make predictions on an individual level. At the same time, competing image based methods are too expensive and time consuming.

We have created an inexpensive method for analyzing water and fat separated images as well as protocols for speedy MRI accusation. We can cover the abdomen in 5–6 min, and the entire body in less than 10 min, making it possible to add the sequences to existing protocols without much cost. After the data acquisition the abdominal fat can usually be measured without user interaction, by a system which learns from prior examinations. However, no bodies are identical to each other, so we have developed tools for those few cases where the automatic method fails, and by using those tools the abdominal fat can be measured in 1–3 min. For every new case the method learns a bit more about the possible variations, so it will handle those variations better in the future.

Abdominal fat is not the only fat of interest. The same method is used to measure the amount of brown adipose tissue, a tissue which burns energy to produce heat. It is also used to quantify the subcutaneous adipose tissue volume, the liver and pancreatic fat concentration as well as the breast density, which is a strong predictor of breast cancer. ■



A water and fat image from a set of images covering the whole body.

PROJECT INFORMATION

Supervisors
Magnus Borga,
Olof Dahlqvist Leinhard

Background
MSc from Linköping University

MARIANA BUSTAMANTE

Automated Assessment of Blood Flow in the Cardiovascular System Using 4D Flow MRI

Changes in intracardiac blood flow patterns appear to be early markers of cardiac disease. Altered blood flow patterns have been observed in many cardiac diseases, often as a result of early remodeling of the cardiac chambers. These alterations have turned out to be extremely difficult to predict based on anatomy. Blood flow velocity can be measured in the whole heart using 4D Flow MRI, but manual analysis of this data has been shown to be extremely difficult and time-consuming.

Current methods for 4D Flow MRI data analysis have included some degree of automation. However, the bulk of the studies continue to rely on manual methods, especially when it comes to segmentation of the heart's chambers, necessary for the calculation of several important hemodynamic markers.

Due to the large amount of information included in a 4D Flow MRI acquisition, manual methods applied on them are tedious, hard to reproduce, and usually very time consuming. The aim of this project is to develop and evaluate tools for the assessment of 4D Flow MRI data that can be used in large groups of data, are mostly automatic, and consequently easy to use.

With this goal in mind, we proposed an improvement over the approach typically used for Phase-Contrast Magnetic Resonance Angiography (PC-MRA)

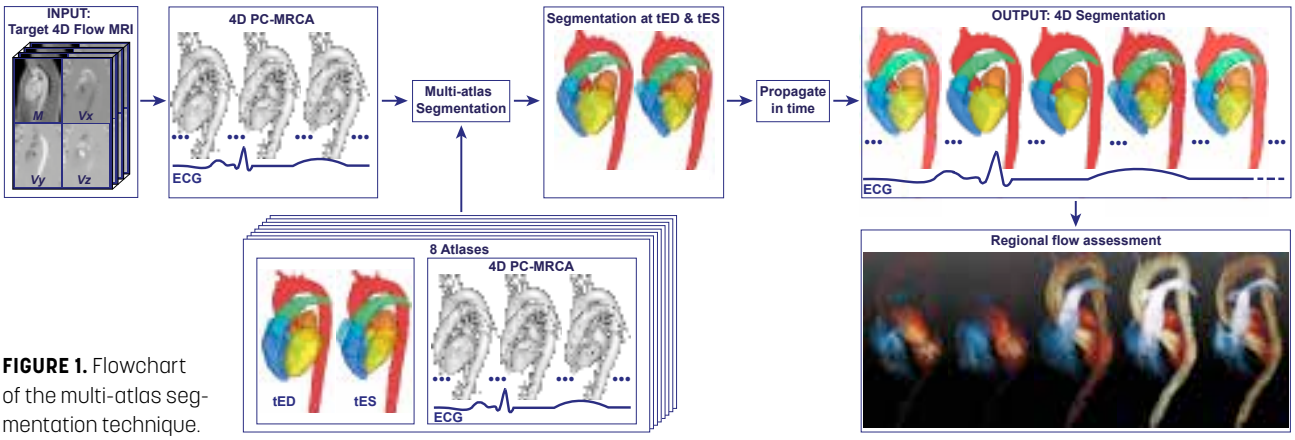


FIGURE 1. Flowchart of the multi-atlas segmentation technique.

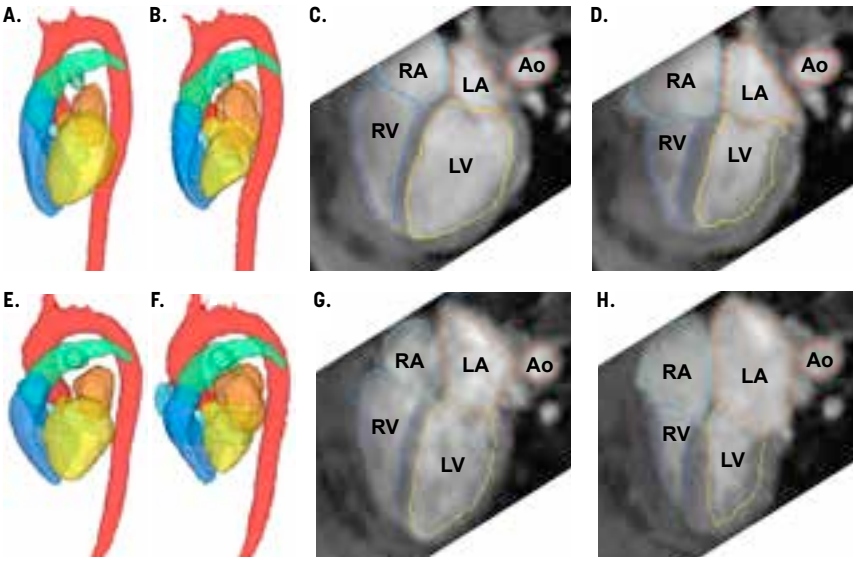


FIGURE 2. Segmentations obtained for two datasets at end-diastole (A, E, C, G) and end-systole (B, F, D, H). Visualized as an isosurface rendering (A, B, E, F), and superimposed over a four-chamber image of the heart (C, D, G, H). The regions included are: left ventricle (LV, yellow), left atrium (LA, orange), right ventricle (RV, dark blue), right atrium (RA, light blue), aorta (Ao, red), pulmonary artery (green).

data generation from 4D Flow MRI. Namely, a technique for the generation of a temporally resolved Phase-Contrast Magnetic Resonance CardioAngiography (4D PC-MRA) that includes the geometry of the lumen of the vessels, as well as the heart over the entire cardiac cycle. Using these angiographic images, we developed a multi-atlas segmentation technique in order to automatically segment the cardiac chambers and major thoracic vessels in 4D Flow MR images. See Figure 1 for a flowchart of the technique. Figure 2 shows two representative examples of the obtained segmentations.

Automation of the segmentation process offers some improvements to manual segmentation on large scale data by making the process faster, more reliable, repeatable and scalable. The proposed method results in segmentations suitable for the assessment of hemodynamic markers in 4D Flow MRI; consequently, increasing the feasibility of using this type of MR acquisitions in the clinical setting. ■

PROJECT INFORMATION

Supervisors
Tino Ebbers, Carl-Johan Carlhäll, Petter Dyverfeldt

Project
Assessment of cardiovascular blood flow using 4D Flow MRI (Heart4Flow)

Background
MSc Computer ScienceUppsala University, Sweden, 2010–2012

BSc Computer Engineering Simon Bolivar University, Venezuela, 2001–2006

BELEN CASAS

Improved Diagnosis and Management of Heart Disease by 4D Blood Flow Assessment; Stenotic Blood Flow

Narrowing of the valves of the heart, valve stenosis, prevents the valves from opening fully which obstructs the blood flow. The blood flow after the valve will be turbulent and produces a pressure drop across the valve. Such pressure drop will cause the heart to perform additional work to increase the driving pressure and maintain the blood flow through the vascular system. Over time, this causes adverse remodeling of the heart muscle. In many patients with valve stenosis, the heart's short-term compensatory mechanisms become less and less effective, ultimately leading to heart failure. It appears that the pressure drop over the valve is a crucial marker of the severity of the stenosis.

The current gold standard for measuring the pressure drop is catheterization, but this is an invasive procedure and cannot be applied routinely. In practice, the pressure drop is instead estimated non-invasively based on ultrasound measurements. This approach, however, does only work well for severe stenoses since mild pressure drops are masked by a pressure recovery phenomenon downstream of the stenosis. The irreversible pressure drop over the stenosis is directly related to the amount turbulence and a method monitoring this would be useful in detecting also mild stenoses.

The aim of this project is to propose and validate a non-invasive method to estimate irreversible pressure loss based 4D magnetic resonance imaging (MRI) measurements of the turbulent blood flow. Such a method should be suitable for assessment of mild, moderate and severe stenoses. In particular, it would be especially helpful for assessment of moderate and mild stenoses, for which current non-invasive methods often fail to provide a correct estimate of the pressure drop. ■

PROJECT INFORMATION

Supervisors
Tino Ebbers, Petter Dyverfeldt, Jonas Lantz, Carl-Johan Carlhäll

Project
Cardiovascular blood flow assessment

Background
MSc in Biomedical Engineering August 2010–March 2013, Linköping University (Linköping, Sweden)

MSc in Telecommunication Engineering, October 2003–March 2010, Universidad de Oviedo (Oviedo, Spain)

Systems engineer trainee April 2010–July 2010, EADS Astrium (Madrid, Spain)

ELIN GOOD

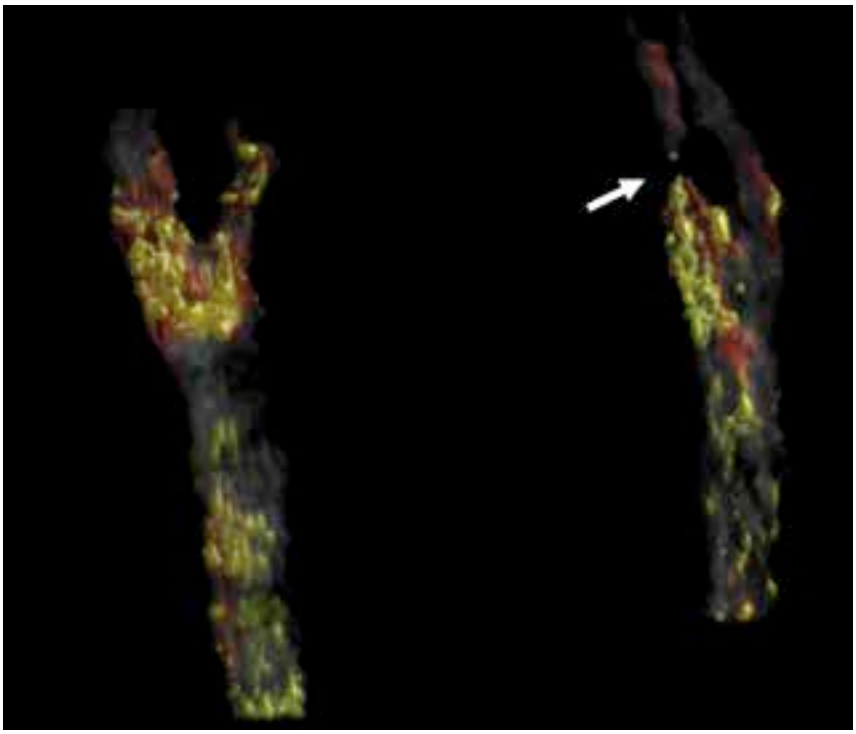
The CARMA Study

The most common cause of death in Sweden as well as in the rest of the world is cardiovascular disease. The primary cause is myocardial infarction and stroke, which most often steam from rupture of atherosclerotic plaques. Traditionally the degree of stenosis has been used as a measure for risk assessment, but in later years research has shown that the contents rather than the size of the plaque is correlated to plaque rupture. The factors most strongly associated with plaque rupture are blood (Intraplaque Hemorrhage, IPH) and fat (Lipid Rich Necrotic Cores, LRNC).

In the beginning of 2017 we included the first patients in the CARMA-study, a prospective study of 53 patients with carotid atherosclerosis. The study uses a repeated-measures design where assessments will take place at baseline, and after one year. During the past year we have consecutively included patients and invited them for their baseline visit and their first MRI of the carotid arteries.

For analysis of the plaques we use a quantitative MRI (qMRI) technique, which is a recently developed method used to quantify the amounts of fat (LRNC) and blood (IPH) inside the vessel walls and plaques. The patients will at two timepoints undergo a four-point Dixon and cardiac-triggered T1-weighted qMRI, detecting LRNC and IPH by registering the Dixon images against the T1w images. We use a 3T Philips Ingenia scanner located at CMIV.

Since there is a well-established link between systemic inflammation and the presence of atherosclerotic plaques we will also study the relationship between LRNC and IPH as measured by qMRI versus circulating markers of inflammation, data that is received from blood tests from the patients.



We anticipate that plaque component assessment with qMRI will refine the diagnostics and improve risk assessment for patients with atherosclerotic plaques in the carotids, the coronary arteries or elsewhere. This will facilitate the identification of high-risk individuals in need of, for example, surgical- or endoscopic interventions.

Currently we are planning for a second study, called the CARMA-PET Study, where we will invite a subgroup of the CARMA patients for complementary assessment of their carotid plaques, using a hybrid PET/MRI. ■

PROJECT INFORMATION

Supervisors
Ebo de Muinck, Toste Länne, Joep Perk, Petter Dyverfeldt

Project
The CARMA Study (Carotid ARtery MRI Assessment of atherosclerotic plaque)

Background
Medical school, Linköping University, medical degree 2011

Resident physisian in cardiology and internal medicine, Department of cardiology, Region Östergörland 2015–present

JENS SJÖLUND

Advanced MRI Techniques for Functional and Stereotactic Neurosurgery

Many brain disorders–e.g. tumors, vascular malformations and Parkinson's disease-can be treated either surgically or by focused radiation. The treated areas are often small and it is of course vital not to harm the surrounding healthy tissue. This places extremely high demands on the accuracy of the tools used by neurosurgeons; for example the Leksell Gamma Knife (a Swedish invention) can deliver focused radiation with accuracy better than one millimeter.

To take full advantage of this accuracy you need to know where to direct it, which is why you need imaging. This project deals with the imaging technique known as Magnetic Resonance Imaging (MRI). It was developed in the early 1970's by the chemist Paul Lauterbur and the physicist Sir Peter Mansfield, a feat for which they were awarded the Nobel Prize in physiology or medicine in 2003.

Since its introduction, the principles and applications of MRI have been subject to intense research. We strive to take these scientific land winnings and put them at the hands of those who make it matter–the neurosurgeons. Our emphasis is on segmentation, which means that an MR image is, more or less automatically, provided with a "map" that describes the locations of different anatomical and functional structures in the image. This map can comprise both the target of the treatment (e.g. a tumor) and normal, healthy, brain structures.

Accurate and robust segmentation methods have several clinical uses. The most obvious is to aid in defining the target of a treatment and identifying nearby structures which must be protected. To evaluate the effects of a procedure, new MR images are acquired and compared to the prior ones. Segmentation methods can facilitate this comparison by, for example, quantifying how much a tumor has shrunk. Yet another important application, specific to radiation therapy, is the need to accurately compute the radiation dose. This is something that typically requires additional X-ray imaging with little diagnostic gain, in particular for brain disorders. It is therefore desirable to do the dose calculations using only MR images. An important step in this direction is to use segmentation to identify tissue types that have different effect on the radiation (Figure).

A specific MR technique with an important role in this project is so called diffusion imaging, which provides means to segment nerve fibers by taking advantage of the fact that water travels easier along nerve fibers than across them. This could provide the neurosurgeon with a valuable insight into the wiring of the brain; allowing critical nerves to be spared, improving understanding of how epileptic seizures spread throughout the brain and facilitating treatment of conditions in which a nerve itself is the culprit (e.g. trigeminal neuralgia–one of the most painful conditions known to mankind). ■

PROJECT INFORMATION

Supervisors
Hans Knutsson, Mats Andersson

Background
M.Sc. in Engineering Physics, KTH Royal Institute of Technology 2007–2012

Research Scientist, Elekta Instrument AB, Stockholm, Sweden (2012–present)

SEBASTIAN STEN

Mathematical Modeling of Biological Mechanisms Underlying Brain Responses in fMRI

Brain activity is a continuously demanding process and therefore a large vascular system is required to supply the neuronal and glial cells with mainly glucose and oxygen. An adequate supply of glucose and oxygen is preserved during periods of increased neural activity by regulation of cerebral blood flow.

This regulation of blood flow can be seen in the blood oxygenation level dependent (BOLD) signal captured by functional magnetic resonance imaging (fMRI). Therefore, a connection between neural activity and blood flow changes, the so-called neurovascular coupling, exists.

Activity at the neural level can be inferred by indirect measurements of hemodynamic responses. These hemodynamic responses come in different forms. The most common shape is the positive BOLD response where the main signal increases above basal (See figure 1, red error bars): Another common shape is the negative BOLD response where the main response should lie below basal (see figure 1, blue error bars). How the neurovascular coupling translates neural activity to these hemodynamic responses remain elusive. Furthermore, the neurovascular coupling is shown to dysfunction in different neurological disorders.

Here, the use of mathematical modeling, where hypotheses formulated in words are translated into mathematical equations and evaluated in systematic way has been successful. We have developed a mathematical model, illustrated in figure 2, which is based on the most widely discussed hypothesis underlying neurovascular coupling, the neurotransmitter feed-forward hypothesis. This model is capable of describing and predicting both positive and negative BOLD-responses from a variety of fMRI-data. These results pave the way for a better understanding of how neural activity and hemodynamic responses are connected. The results also provide a new environment for testing of potential therapeutics and their effect on the neurovascular coupling. ■

PROJECT INFORMATION

Supervisors
Maria Engström, Gunnar Cedersund, Fredrik Elinder, Susanna Walter

Project
Methods for High-quality Illumination in Interactive Volume Graphics

Ab Initio Mathematical Modeling of Mechanisms in the Human Brain

Background
Bachelor degree in engineering biology, Linköping University, 2011–2014

Research preparatory course I–II 2014–2015

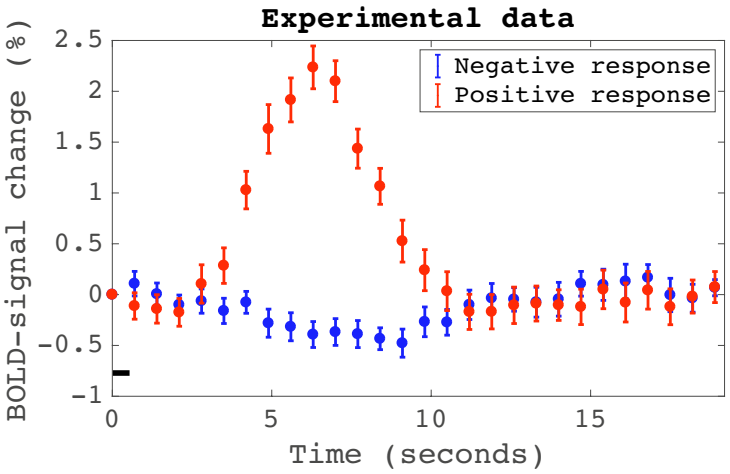


FIGURE 1.

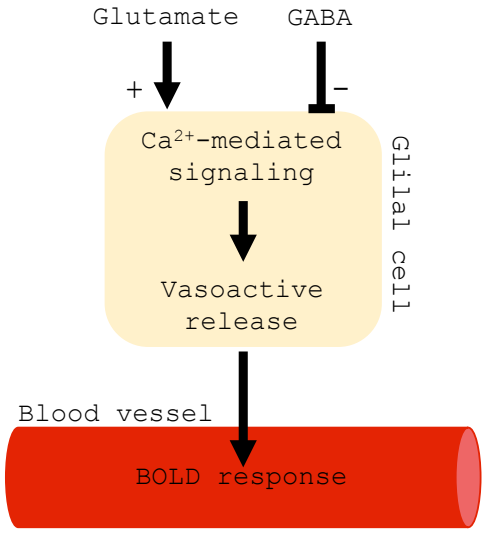


FIGURE 2.

BHARTI KATARIA

Evaluation of Optimization Methods for Abdominal Computed Tomography

In all diagnostic radiology examinations using ionising radiation, there is a desire for the best possible image quality (AHARA principle) and at the same time endeavor to keep the radiation dose to the patient as low as reasonably achievable (ALARA principle). The higher the dose the better the image quality as image noise is reduced, but this is not always necessary to make a diagnosis.

Abdominal Computed Tomography (CT) examinations deliver a high radiation dose to the patient. As one third of all CT examinations are abdominal optimization of these examinations is advocated.

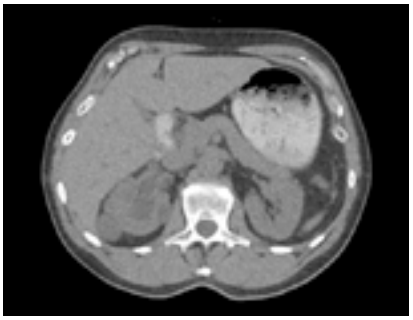
The purpose of this project is to find ways to optimize abdominal CT examinations by evaluating the dose reduction potential of different reconstruction and post-processing methods and the diagnostic value of a low-dose CT.

First we evaluated the dose reduction potential of an iterative (mathematical) reconstruction (IR) method, SAFIRE in a low-dose abdominal using SAFIRE strength 1. Image quality was improved with SAFIRE compared to Filtered Back Projection (FBP) and allowed for a 5–9 % dose reduction. The study revealed that the full potential of the algorithm had not been studied and further research was necessary.

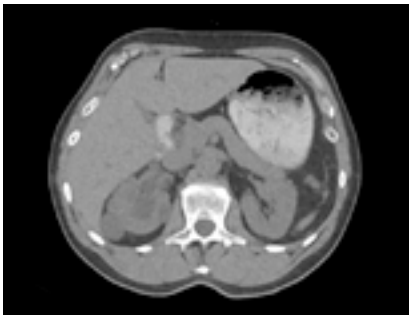
Due to technical advancements a model-based iterative reconstruction (IR) algorithm (ADMIRE) was made available, hence in the second study the potential dose reduction using ADMIRE strengths 3 and 5 in a standard dose abdominal CT was evaluated. The model-based IR algorithm improves image quality compared to FBP showing a positive correlation between ADMIRE strength and increase in potential dose reduction for all but one image criterion. Images produced at 70 % dose level were found to be superior in image quality compared to full dose images indicating that for the Somatom Force abdominal protocol, the dose can be reduced to 70 % without any change in algorithm.

Further investigation of this algorithm combined with other post-processing methods using visual grading experiments will reveal the amount of dose reduction that is possible in order to optimize abdominal CT examinations. ■

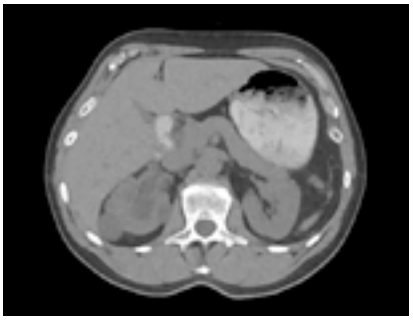
FBP 98 mAs



ADMIRE 3 98 mAs



ADMIRE 5 98 mAs



Visual image quality demonstration with images obtained in the same patient at 70 % dose level (98mAs) using dual source Siemens Somatom Force and reconstructed with Filtered Back Projection (FBP), ADMIRE 3 and ADMIRE 5.

PROJECT INFORMATION

Supervisors
Michael Sandborg, Örjan Smedby, Anders Persson, Hannibal Sökjer

Background
Diagnostic radiographer, Bristol School of Radiography in Great Britain April, 1980

Diagnostic Radiographer Nairobi, Kenya 1980–1985

Radiology department Vrinnevi Hospital in Norrköping 1986–2014 during which I graduated with a Bachelor´s (2008) and Master's (2013) degree in Medicine

Radiology Department in Linköping March 2014–present

LUDVIG VAVRUCH

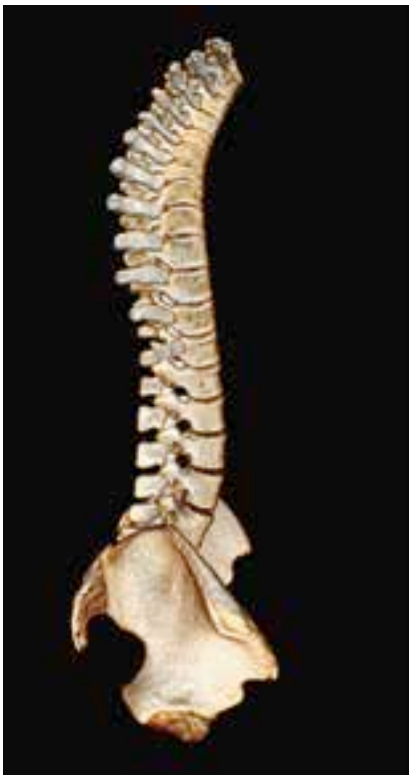
Idiopathic Scoliosis – Deformity in Three Dimensions

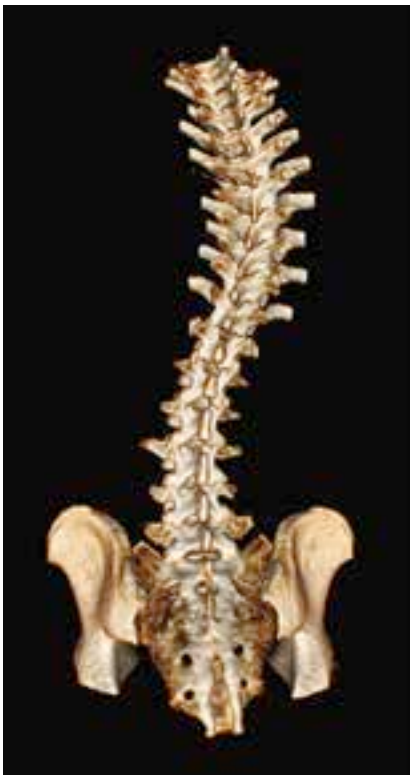
Scoliosis is a deformity of the spine with curvatures in the frontal as well as the sagittal plane. In addition, the vertebras in the deformity are rotated in the axial plane. Thus, scoliosis is a three dimensional spinal deformity. Traditionally the severity of each curvature has been evaluated by measuring the Cobb angle from standing radiographs. This angle is measured between the endplates of the vertebras in each curvature. It is desirable to be able to measure the vertebra rotation to fully understand the scoliotic curve.

Since scoliosis is a three-dimensional deformity, the importance of three-dimensional imaging has been pointed out as a necessity to better understand the condition, as well as getting better preoperative information.

One way to obtain three-dimensional images is to use low dose computed tomography images of the spine and then make three-dimensional reconstructions. Using this technique, it is easy to assess the spinal deformity as well as make precise measurements of each vertebra with concern to vertebral rotation and vertebral morphology.

The Cobb angle changes when going from standing to supine position. This is due to lesser gravitational loads in the supine position compared to when standing up. Since the patient is lying down during the CT examination we want to investigate how the Cobb angle changes from standing to supine position.





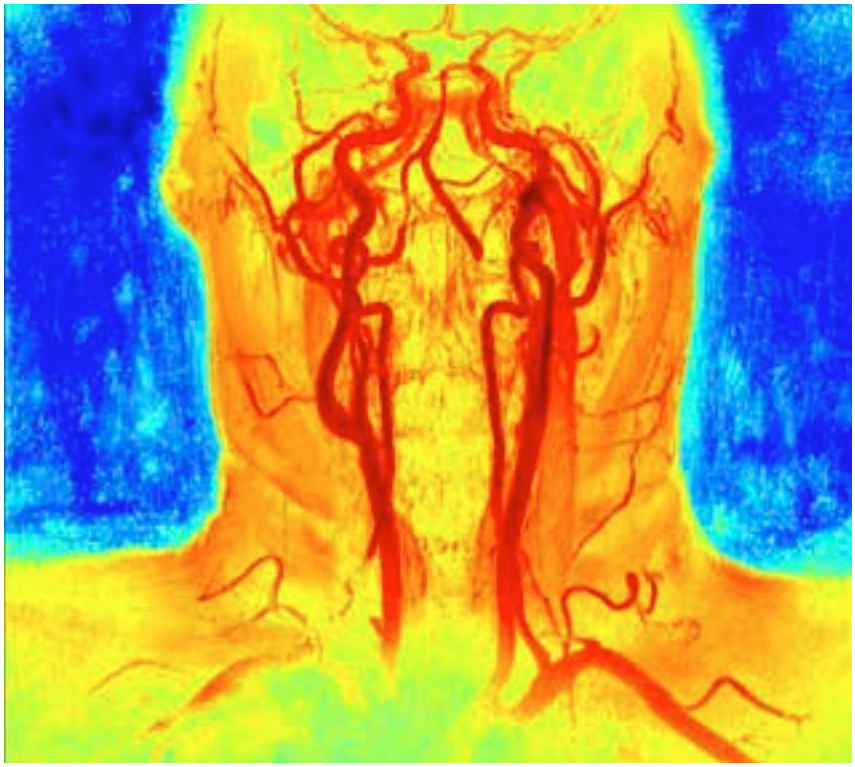
The vertebras in scoliosis are not just rotated they are also deformed. Therefore, we will analyze how the morphology is changed in scoliotic vertebras compared to vertebras from a control group without any known back disorder. We hope to obtain a better understanding of the etiology of idiopathic scoliosis.

Surgical correction is obtained using either a posterior or anterior approach to the spine. Little is known about the three-dimensional correction accomplished by the approaches. To learn more, preoperative low dose CT examinations will be compared with postoperative low dose CT examinations in three-dimensional reconstructions. There will be a two-year follow up to investigate how well the correction is preserved after surgery. The patients will also answer questionnaires to determine not only what correction is obtained with either approach, but also how satisfied the patients are postoperatively. ■

PROJECT INFORMATION

Supervisors
Hans Tropp, Nils Dahlström, Daniel Forsberg, Per Aspenberg

Project
Quantitative musculoskeletal imaging for assessment of idiopathic scoliosis



Stylized image of neck vasculature created using 4D Flow MRI imagery.

MAGNUS ZIEGLER

Improved Assessment of the Link Between Hemodynamics and Vessel Wall Disease

The aim of this research is to develop new methods for the assessment of vessel wall disease using novel hemodynamic markers from 4D Flow MRI. The forces exerted by blood flow dictate a continuous remodeling of the heart and vessels, and tend to create the optimal geometry for efficient flow under prevailing conditions. As a result, the healthy cardiovascular system has largely laminar flow. However, these forces appear to play a significant role in the pathophysiology of many common cardiovascular diseases. Through remodeling, irregularities in blood flow patterns and their associated forces caused by congenital or acquired diseases can lead to a cascade of more severe abnormalities.

MRI in general and 4D Flow MRI specifically offers the most powerful capabilities for in vivo flow assessment. 4D Flow MRI is a relatively new technique that allows quantitative assessment of the time-varying three-dimensional flow fields of the cardiovascular system. Using this technique, new, and more accurate assessments of the patient's cardiovascular system can provide clinicians with deeper knowledge and aid in both diagnosis and treatment.

For example, patients with aortic stenosis or coarctation of the aorta often have large levels of turbulent flow. Using 4D Flow MRI the amount of turbulence near the vascular wall can be quantified, and with this new information, we can study how this abnormal flow characteristic impacts the vessel.

Another exciting area of research involves examining how the blood flows through the complex geometries of abdominal aortic aneurysms. These localized bulges in the aorta can take a wide variety of shapes and sizes, and studying how flow impacts the vessel wall may help us predict the growth rate and rupture risk in a patient-specific way. ■

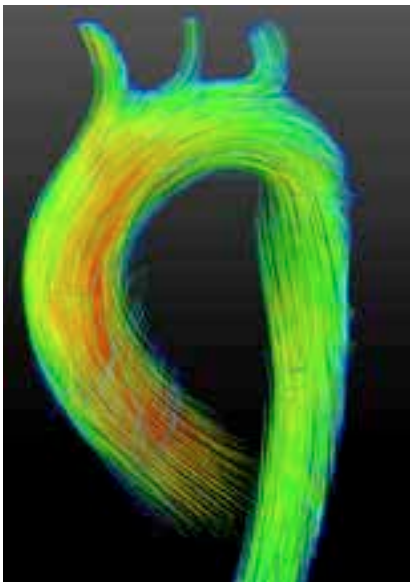
PROJECT INFORMATION

Supervisors
Petter Dyverfeldt, Tino Ebbers, Jonas Lantz, Carl-Johan Carlhäll, Ebo de Muinck

Project
Non-invasive imaging assessment of the interrelationship between blood flow and vascular disease

Background
Bachelor of Applied Science (B.A.Sc.) – Mechanical Engineering with Biomedical Specialization University of British Columbia, Vancouver, Canada, Graduated Spring 2012

Masters of Science (M.Sc.) – Biomedical Engineering, Chalmers Institute of Technology, Gothenburg, Sweden, Graduated Summer 2014



Streamline visualization of blood flow through the Aortic Arch in a healthy young volunteer created using 4D Flow MRI.

XUAN GU

Analysis of Diffusion MRI Data

Diffusion tractography is a magnetic resonance imaging method that uses the diffusion of water molecules to identify anatomical connections in the brain. The diffusion of water is hindered by obstacles as membranes and fibers and moves faster when following a structure instead of crossing it. Diffusion tractography is an important neuroimaging tool that can be used for studying brain connectivity and aiding brain surgery.

When using diffusion tractography to visualize neural connections it is important to acknowledge that the resolution of the method is not high enough to show an individual neuron. Therefore each voxel in the image represent a bundle of neurons. The result from the tractography is an estimation of the most probable direction of the bundle but there is a high probability that not all neurons are heading in the same direction. The result is that there is always a portion of uncertainty in the model. To improve the results distortion correction models can be used.

To see how consistent diffusion tractography is over time we investigated the test–retest reliability, using 32 diffusion datasets from a single healthy volunteer. We used two open source software's, FSL and Dipy, to run the analysis. A visual comparison of the results showed that diffusion along the cores of the corticospinal and cingulum gyrus tracts in the brain were common over the 32 datasets, for both FSL and Dipy.

We also observed that the degree of reproducibility of the results differed between the corticospinal and cingulum tracts. The difference may be explained by the fact that these tracts are not of the same size. Also, different parts of the brain may experience various degrees of distortions and artifacts due to head motion. Hence, the results indicate that distortions and head motion may be important uncertainty sources.

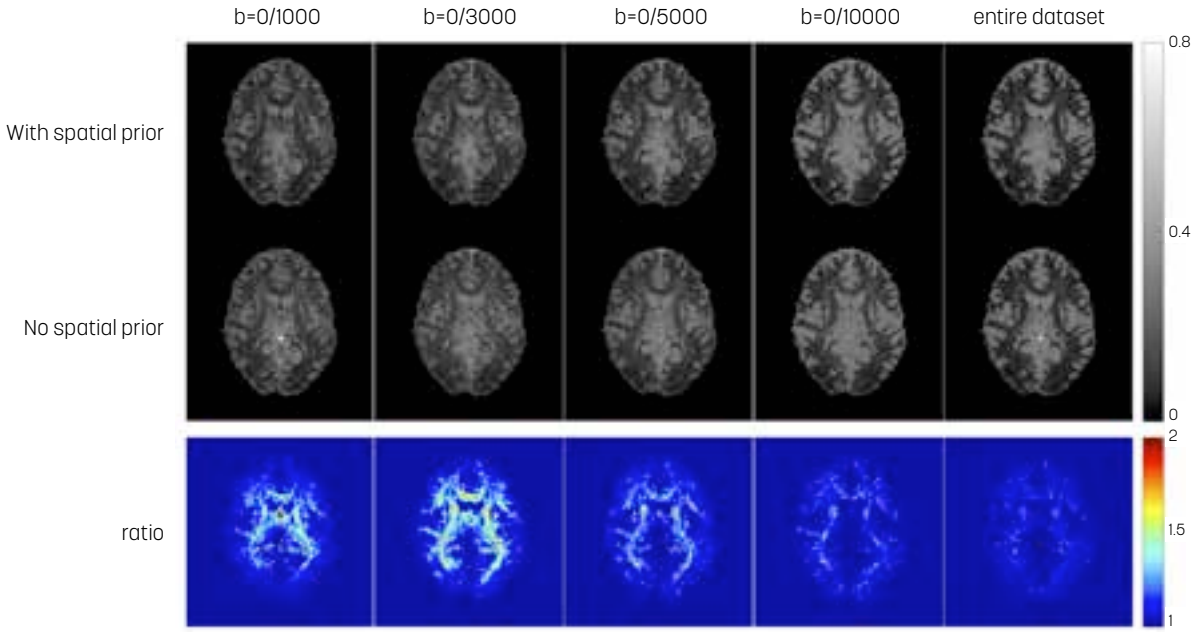
It was observed that the reproducibility increased if distortion correction was used, for both the corticospinal and cingulum gyrus tracts. The ball and stick model representing multiple fiber orientations was found to be able to reconstruct the most connections, however, at the cost of a longer processing time. We conclude that the tractography results obtained with the used software packages have a rather high reproducibility. ■

PROJECT INFORMATION

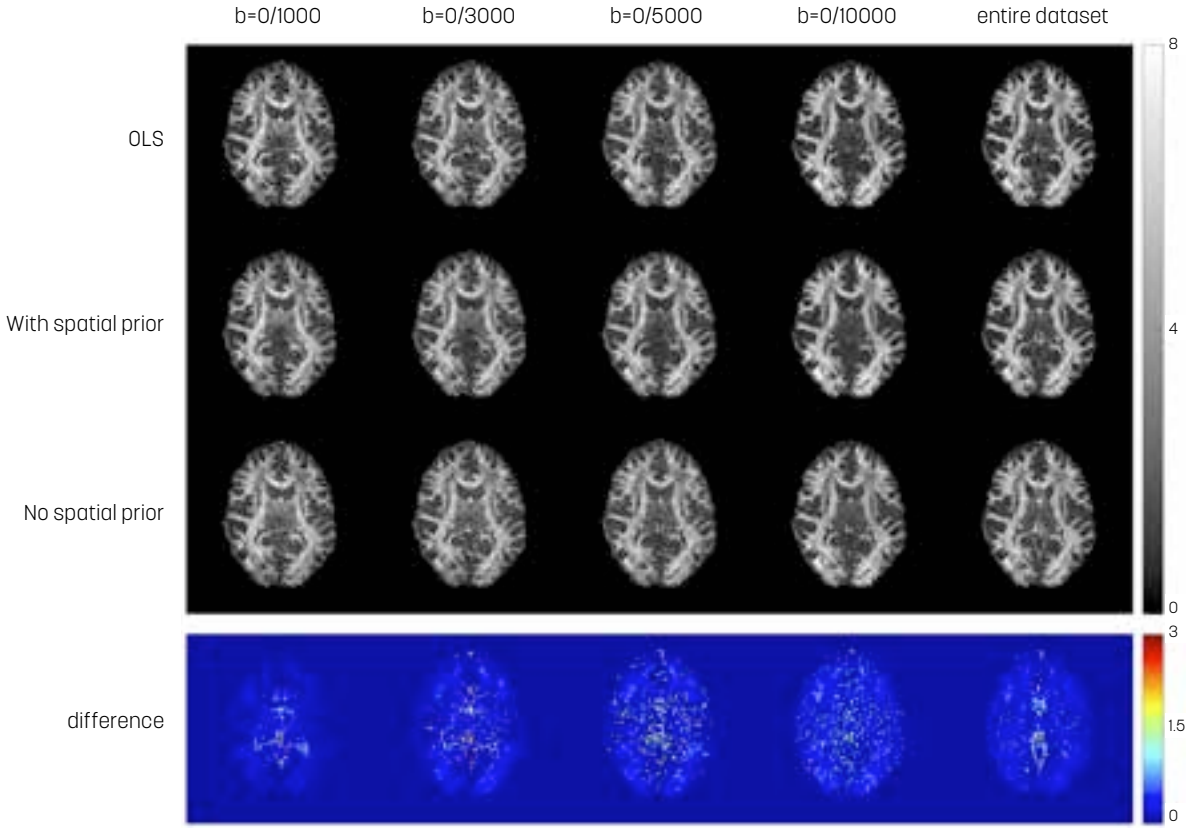
Supervisors
Anders Eklund, Hans Knutsson, Evren Özarslan, Malin Björnsdotter

Background
Bachelor of Engineering, Beijing University of Posts and Telecommunications, China

Master of Science, University of Southampton, United Kingdom



CV of FA maps calculated from the MCMC samples.



FA maps from three diffusion tensor estimation methods.

MARKUS KARLSSON

Early Characterization of Hepatic Inflammation, Fibrosis and Function

Today, a patient with liver disease often has to go through a liver biopsy to help the physician diagnose the condition, or see how much fat, iron or fibrosis there is in the liver. However, a liver biopsy is an invasive procedure, which is uncomfortable for the patients and carries some risk for complications. Therefore, my project is aimed towards using magnetic resonance imaging (MRI) to develop a noninvasive and quantitative tool-kit, which can be used for diagnosing and staging liver diseases. Such a toolkit should include methods for quantifying the amount of fat and iron in the liver, as well as staging how much inflammation and fibrosis there is. For late stages of liver diseases, there should also be methods for quantifying how much the liver function has been affected, e.g. when considering liver transplantations. So far, my work has mainly focused on measuring liver function. To measure liver function, we use a contrast agent called Gadoxetate. A contrast agent is a drug that makes parts of the images brighter and is given to a patient during an MRI-examination. Gadoxetate is a special contrast agent, which is accumulated in the liver cells, making the liver brighter than other organs in the images, (Figure). Today, Gadoxetate is commonly used in conventional liver radiology, where radiologists mainly use it to visualize tumors.

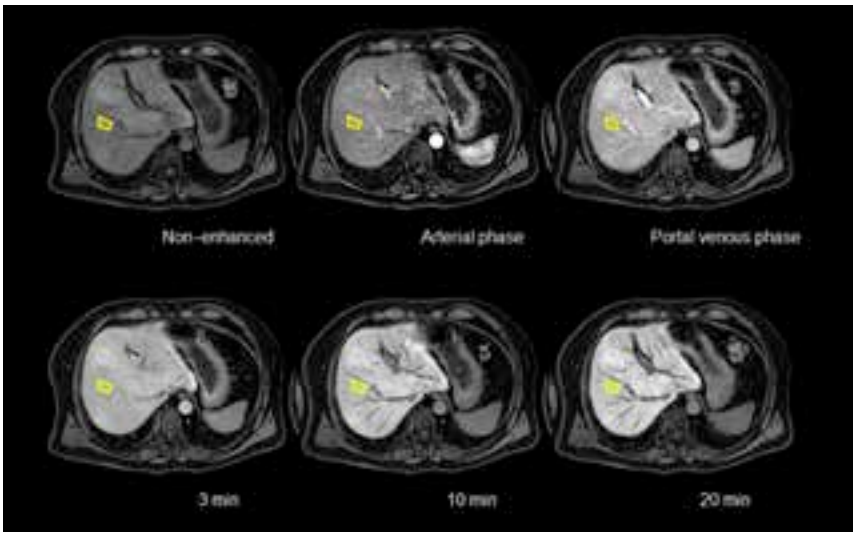
My research group has developed methods for using MR images to measure the concentration of contrast agent in the liver and other organs. Those methods can be used together with mathematical modeling to estimate rate by which Gadoxetate is transported into the liver cells. The transport rates can be used as biomarkers for liver function since the Gadoxetate are transported into the liver cells by proteins that are important for normal liver function. Therefore, we believe that if the transport rates are decreased, it is a sign that the general function of the liver has been impaired. ■

PROJECT INFORMATION

Supervisors
Peter Lundberg, Nils Dahlström, Gunnar Cedersund, Stergios Kechagias

Project
Non-invasive liver biopsy (NILB), Liver intrinsic function evaluation (LIFE), Hepatic inflammation and fibrosis investigation (HiFi), Heart, adipose tissue, and liver thrust (HEALTH)

Background
M.Sc. in Engineering Biology, Linköping University (2015)



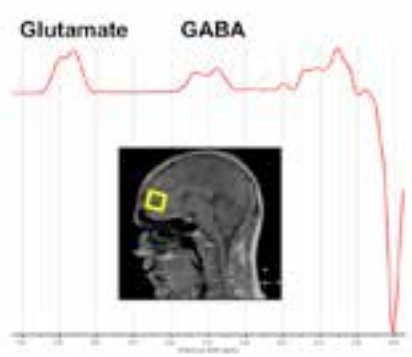
Examples of MR-images of the liver before (Non-enhanced) and at several time points after injection of Gadoxetate. As can be seen, the liver becomes brighter as more Gadoxetate is accumulated. The yellow square is the areawhere we measure the intensity used to calculate the Gadoxetate concentration.

SOFIE TAPPER

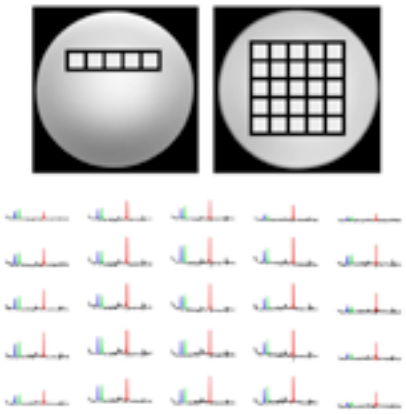
Neurotransmitter Imaging of the Human Brain

The neurotransmitters GABA and Glutamate are the main inhibitory and excitatory neurotransmitters in the central nervous system. An imbalance between these neurotransmitters may have a significant influence on the development of neurological diseases. Therefore, it is important to develop a clinical tool for reliable quantification of these neurotransmitters.

Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique that can be used to study metabolic changes in the brain. However, the challenges are exceptional when measuring GABA, as the concentration of GABA is about 40 000 times less than that of water, and there is an additional overlap in the spectrum with signals from other metabolites. Because of this overlap, a special editing MRS-technique (MEGA) is necessary for the quantification of GABA. Additionally, in clinical applications, it is desired to have minimal measurement time and measurement region, without any reduction of the quality of the measurement. Therefore, it is important to develop a novel method that reliably quantifies GABA and other metabolites. An MRS Imaging pulse sequence has been developed in collaborations with GyroTools (Zürich, Switzerland) that uses MEGA-semi-LASER pulses for full brain coverage, minimal chemical shift displacement error, and with spiral readout to limit the acquisition time. This sequence is currently in the validation phase and there are several challenges that needs to be resolved.



The GABA and Glutamate signals obtained from a GABA edited single-voxel MRS measurement.



Resulting spectra obtained using the developed MRSI sequence without GABA-editing measured on a phantom.

The developed methodology for GABA quantification is continuously applied in different clinical applications; diseases related to pain within the brain-gut axis (IBS), patients with essential tremor or Parkinson's disease that undergoes Deep Brain Stimulation (DBS) intervention, patients with sleep disorders such as Narcolepsy, and accumulation of manganese in the human brain affecting cognitive function. ■

PROJECT INFORMATION

Supervisors
Peter Lundberg, Anders Tisell, Peter Zsigmond

Project
Seeing Organ Function

Background
Master of Science (MSc) Applied Physics and Electrical Engineering, Signal and Image Processing, Linköping University 2008–2013

Research preparing course I-II 2013–2014

Research Assistant/Engineer, County Council of Östergötland, Department of Radiation Physics, 2014–2015

SOFIA KVERNBY

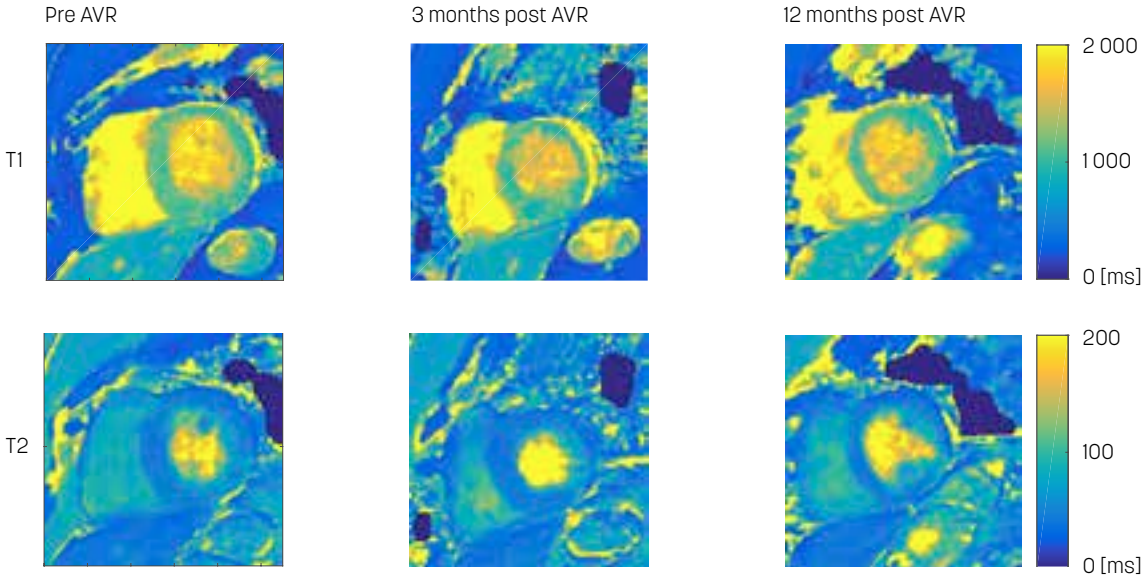


Illustration of mid-ventricular myocardial relaxation time maps with 3D-QALAS in a patient with severe aortic valve stenosis. Maps are acquired at three different time points: pre AVR, 3 months post AVR and 12 months post AVR.

Quantitative Assessment of Myocardial Tissue Characterization

The main goal of this project is to develop and evaluate quantitative approaches for the assessment of the myocardial function from magnetic resonance imaging (MRI).

The longitudinal relaxation time (T1) and transverse relaxation time (T2) are two parameters in MRI that describes the characteristics of a tissue. A functional change in a tissue often appears as changes in these parameters, thus a quantitative measure of T1 and T2 could help indicate functional changes.

We have in this project developed a new and fast 3D-method for quantifying relaxation times in the myocardium, the 3D-QALAS method. The method provides simultaneous quantification of both T1 and T2 relaxation times with full coverage of the left ventricular myocardium in one single breath hold. The 3D-QALAS method has been validated in both healthy volunteers and in patients with different cardiac pathologies.

In an ongoing study we include patients with severe aortic stenosis who will undergo aortic valve replacement surgery (AVR). In this patient group the left ventricle must generate a higher pressure to effectively move blood forward into the aorta. The increased pressure will normally affect the left ventricular wall and induce myocardial fibrosis. Since the fibrosis is diffusely spread over the myocardium and thus affecting the whole myocardium, it is not possible to see the changes in a normal weighted MR image. In quantitative images, like T1 maps and T2 maps, it is possible to make a numerical measure and thus compare values with normal values in healthy volunteers.

We are in this study interested to see whether magnetic resonance relaxation times, T1 and T2, can reflect changes in fibrotic tissue over time, from pre surgery to 12 months after the valve replacement. ■

PROJECT INFORMATION

Supervisors
Tino Ebbers, Marcel Warntjes, Jan Engvall, Agnetha Gustafsson

Background
Medical physicist Region Östergötland 2017–

PhD student in Cardiac Magnetic Resonance group 2013–

Medical physicist Region Östergötland, 2012–2014

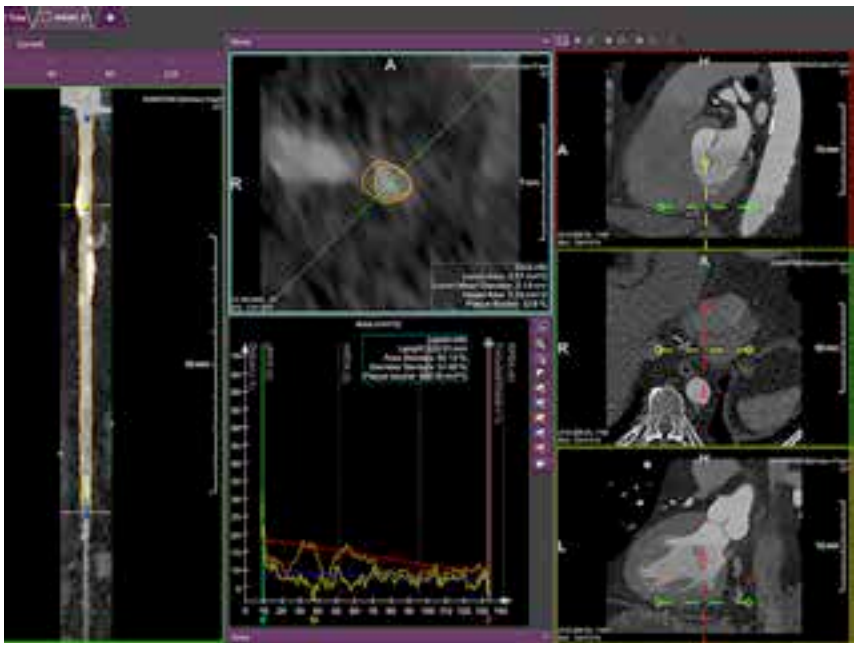
Master of Science in Medical Physics, Lund University, 2007–2012

LILIAN HENRIKSSON

Coronary Artery Computed Tomography: Stenosis Evaluation, Risk Stratification and Effects on Cardiac Hemodynamics

Coronary computed tomography angiography (CCTA) is a non-invasive examination method used to detect coronary artery plaques that might cause stenoses. Iodine contrast is injected intravenously during the examination and this makes it possible to see plaques in the vessel wall. CCTA has a high sensitivity for detection of coronary stenoses while the specificity is lower due to a tendency to overestimate the stenosis degree. It is especially calcified lesions that make the evaluation difficult as they cause so called blooming artefacts. These blur the edges of the plaque thus making it look larger than it actually is. Severe calcifications may even lead to undiagnostic CCTAs. As a result patients sometimes end up being unnecessarily sent for further evaluation with invasive coronary angiography. This method is considered to be the reference method for stenosis evaluation due to the possibility to measure the fractional flow reserve (FFR) or pressure caused by the stenosis.

One method that might increase the specificity of CCTA is to measure the transluminal attenuation gradient (TAG). The theory is that the contrast attenuation in the vessel reflects the flow of contrast through that vessel. By measuring the attenuation at small intervals throughout the vessel it is possible to calculate the linear regression coefficient. A stenosis will decrease the contrast flow and thereby increase the regression coefficient. The needed measurements can be made using the same software used for the ordinary CCTA evaluation.



There is no standardized method established regarding the CCTA for TAG measurements. One factor that probably affects the results is whether the CCTA was acquired during one or multiple heart beats since every heart beat changes the contrast attenuation slightly. This retrospective study will include one heartbeat CCTAs that have been followed up with invasive coronary angiography and FFR. All examinations have been acquired between August 2009 and March 2017 here in Linköping. The primary aim is to evaluate if TAG improves the specificity of CCTAs acquired during one heartbeat. We will also look at how often conventional angiography could have been avoided had a TAG measurement been done. Other than that the image quality will be checked to see how it affects the results. ■

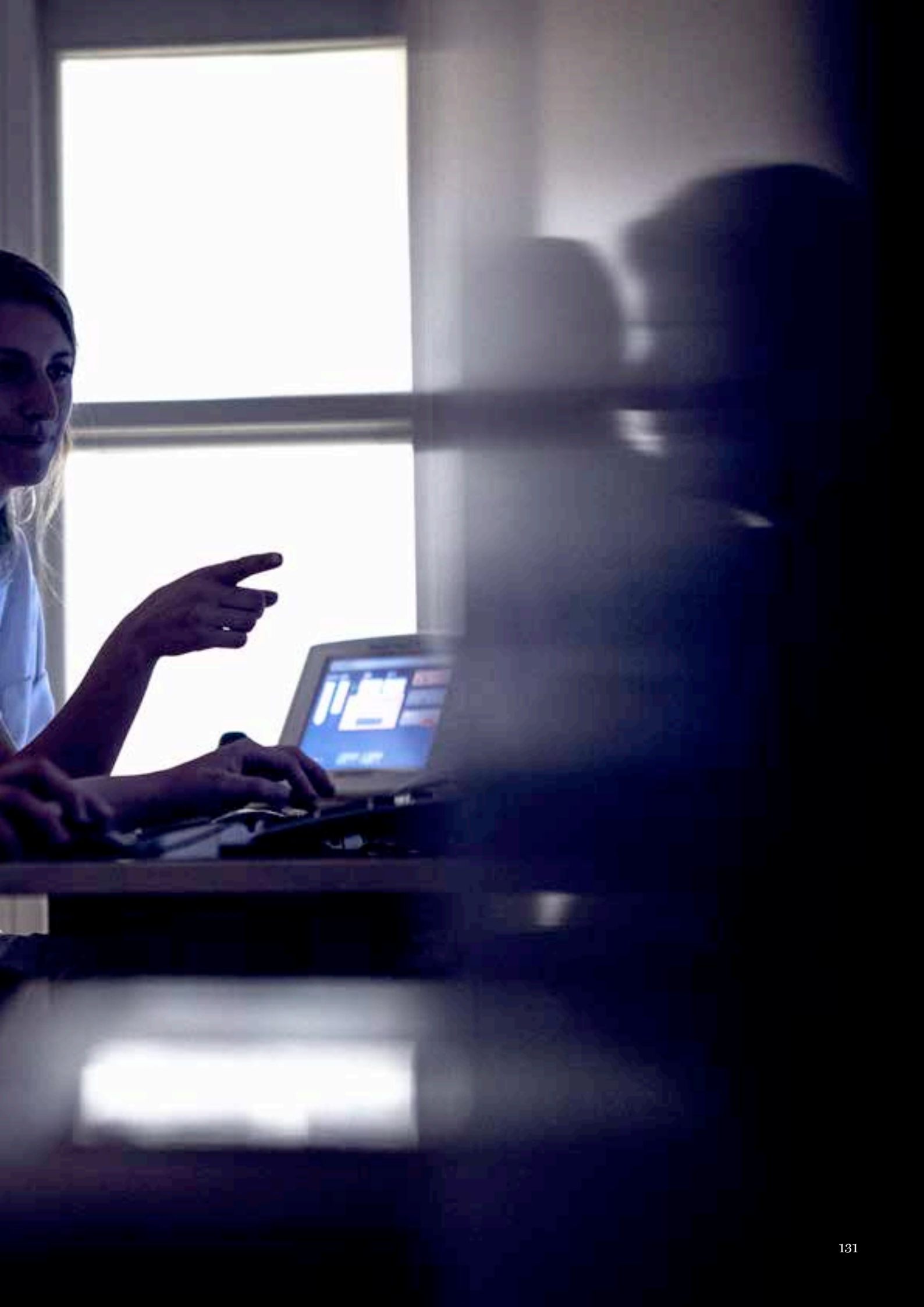
PROJECT INFORMATION

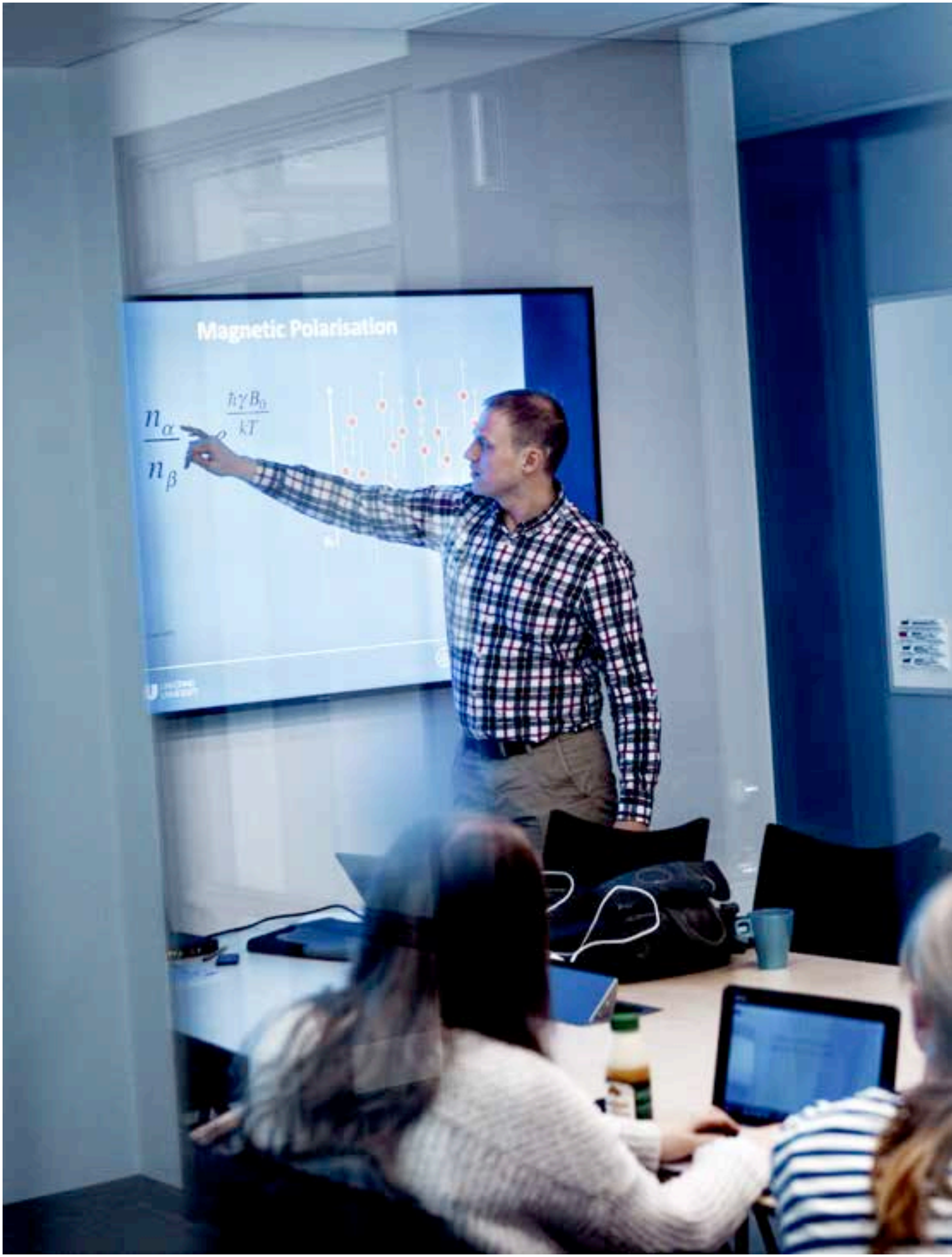
Supervisors
Anders Persson, Jan Engvall, Tino Ebbers, Mischa Woisetschläger

Background
Radiology nurse 2005, masters degree 2013

Dissertations

During 2017 six of the CMIV PhD students have finished their studies and defended their theses. The PhD students and the research school are an important part of CMIV and we are proud to present their theses here.




Magnetic Polarisation
$\frac{n_\alpha}{n_\beta} = e^{\frac{\hbar\gamma B_0}{kT}}$

EVA KLINTSTRÖM

Image Analysis for Trabecular Bone Properties on Cone-Beam CT Data

Linköping University, Department of Biomedical Engineering , Division of Biomedical Engineering

Trabecular bone structure as well as bone mineral density (BMD) have impact on the biomechanical competence of bone. In osteoporosis-related fractures, there have been shown to exist disconnections in the trabecular network as well as low bone mineral density. Imaging of bone parameters is therefore of importance in detecting osteoporosis. One available imaging device is cone-beam computed tomography (CBCT). This device is often used in pre-operative imaging of dental implants, for which the trabecular network also has great importance.

The aim of this project was to study how well the trabecular bone structure could be analyzed with computed tomography methods. In the in vitro studies fourteen or 15 trabecular bone specimens from the radius were imaged.

CBCT data of trabecular bone can be used for analyzing trabecular bone properties, like bone microstructure and bone biomechanics, showing strong correlations to the reference method of micro-CT. The results depend on choice of CBCT device as well as segmentation method used. The in-house developed code based on homogeneity thresholding is appropriate for CBCT data. The overestimations of BV/TV must be considered when estimating bone properties in future clinical dental implant and osteoporosis research. ■

IDA BLYSTAD

Clinical Applications of Synthetic MRI of the Brain

Linköping University, Department of Biomedical Engineering , Division of Biomedical Engineering

Magnetic Resonance Imaging (MRI) has a high soft-tissue contrast with a high sensitivity for detecting pathological changes in the brain. Conventional MRI is a time-consuming method with multiple scans that relies on the visual assessment of the neuroradiologist. Synthetic MRI uses one scan to produce conventional images, but also quantitative maps based on relaxometry, that can be used to quantitatively analyze tissue properties and pathological changes.

The general aim of this thesis was to apply synthetic MRI in different clinical settings and to evaluate its quality and potential use in different patient populations. Initial work was focused on the quality of the synthetic images and the possibility that they could replace conventional images. The subsequent studies were focused on the quantitative aspects of the sequence, with specific applications of relaxometry on multiple sclerosis (MS) and malignant gliomas.

The MS studies suggest that active lesions often have relaxation times and proton density that differ from non-enhancing lesions, but with some overlap. This makes it difficult to replace gadolinium-based contrast agent injection with synthetic MRI in the monitoring of MS patients. Analyses of the peritumoral area of malignant gliomas, revealed quantitative findings regarding peritumoral relaxation changes and non-visible contrast enhancement suggestive of non-visible infiltrative tumour growth. ■

MIKAEL FORSGREN

The Non-Invasive Liver Biopsy: Determining Hepatic Function in Diffuse and Focal Liver Disease

Linköping University, Department of Medical and Health Sciences, Division of Radiological Sciences

The number of people suffering from chronic liver disease is on the rise, likely due to the present 'western' lifestyle. As disease develops in the liver inflammation, fatty infiltration (steatosis), excessive scar tissue formation (fibrosis and cirrhosis), and iron loading manifests. Importantly, as the disease progresses there is concurrent loss of liver function. Currently, an invasive liver needle biopsy is required to determine the etiology and to stage or grade the pathophysiological manifestations. There are limitations with the biopsy for example risk of serious complications, sampling error, and sampling variability.

The main aim of this thesis was to develop and evaluate methods that can be used for a 'non-invasive liver biopsy' using magnetic resonance (MR). We also aimed to develop sensitive methods for measure liver function based on gadoxetate-enhanced MR imaging (MRI). The presented work is primarily based on a prospective study on c. 100 patients suffering from chronic liver disease of varying etiologies recruited due to elevated liver enzyme levels, without clear signs of decompensated cirrhosis. Our results show that the commonly used liver fat cut-off for diagnosing steatosis should be lowered from 5 % to 3 % when using MR proton-density fat fraction (PDFF). We also show that MR elastography (MRE) is superior in staging fibrosis. ■

KARIN LUNDENGÅRD

Mechanistic Modelling – a BOLD Response to the fMRI Information Loss Problem

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Functional Magnetic Resonance Imaging (fMRI) is a common technique for imaging brain activity in humans. However, the fMRI signal stems from local changes in oxygen level rather than from neuronal excitation. The change in oxygen level is referred to as the Blood Oxygen Level Dependent (BOLD) response, and is connected to neuronal excitation by the neurovascular coupling. The neurons affect the oxygen metabolism, blood volume and blood flow, and this in turn controls the shape of the BOLD response. This interplay is complex, and therefore fMRI analysis often relies on models. However, none of the previously existing models are based on the intracellular mechanisms of the neurovascular coupling. Systems biology is a relatively new field where mechanistic models are used to integrate data from many different parts of a system in order to holistically analyze and predict system properties.

This thesis presents a new framework for analysis of fMRI data, based on mechanistic modelling of the neurovascular coupling, using systems biology methods. The framework presented herein may serve as the basis for a new method for identification of both brain activity and useful potential biomarkers for brain diseases and disorders, which will bring us a deeper understanding of the functioning of the human brain. ■

JOHAN KIHLBERG

Magnetic Resonance Imaging of Myocardial Deformation and Scarring in Coronary Artery Disease

Linköping University, Department of Medical and Health Sciences, Division of Radiological Sciences

Although improved treatments have reduced the rates of acute complications from myocardial infarction, sequelae such as heart failure and sudden death threaten the future wellbeing of those patients. Secondary prevention after myocardial infarction is related to cardiovascular risk factors and the effect of the infarct on left ventricular function. Cardiovascular magnetic resonance imaging (CMR) is necessary to determine the size of the infarct scar and can with great precision determine left ventricular volumes, left ventricular ejection fraction, and deformation (strain and torsion).

The purpose of this thesis was to develop and evaluate improved CMR imaging techniques for patients with high risk of coronary artery disease (CAD), especially techniques used to detect infarct scarring and to measure myocardial deformation. Early detection of disease leads to early treatment that can improve prognosis. The improved techniques can also be used in other cardiac diseases and as robust research tools.

Patients with high risk of CAD were investigated using the displacement encoding with stimulated echoes (DENSE) sequence. DENSE was superior to the other methods investigated for strain and torsion measurement and can be used to describe myocardial deformation quantitatively and objectively. ■

OLIVIER CROS

Structural Properties of the Mastoid Using Image Analysis and Visualization

Linköping University, Department of Biomedical Engineering , Division of Biomedical Engineering

The mastoid, located in the temporal bone, houses an air cell system whose cells have a variation in size that can go far below current conventional clinical CT scanner resolution. Therefore, the mastoid air cell system is only partially represented in a clinical CT scan. Where the conventional clinical CT scanner lacks level of minute details, micro-CT scanning provides an overwhelming amount of fine details.

This thesis presents a statistical analysis determining the surface area to volume ratio of the mastoid air cell system of human temporal bone, from micro-CT scanning using methods previously applied for conventional clinical CT scans. To gain more knowledge about micro-channels, a local structure tensor analysis was applied where structures are described in terms of planar, tubular, or isotropic structures.

The knowledge gained from analysing the micro-channels as locally providing blood to the mucosa, led to the consideration of how inflammation of the mucosa could impact the pneumatization of the mastoid air cell system.

Last but not least, discovery of other structures, previously unreported in the literature, were also visually observed and briefly discussed in this thesis. Further analysis of these unknown structures is needed. ■

Equipment

Through unique collaborations with the industry it is possible for CMIV to always have the latest and most advanced equipment. This is a prerequisite for the successful research carried out at CMIV.

CT

The Siemens SOMATOM Force enables routinely performed exams at low kV settings (70–90 kV), even in adults. This is due to the system being equipped with powerful generators and X-ray tubes. The low kV settings allow for substantial reductions in contrast medium dose. Improvements have been made on the detector side as well with an increased number of detector rows and upgraded collimation.

The Force renders images with high spatial resolution and soft-tissue contrast. It contains two X-ray sources and two detectors, which can be used simultaneously. This in combination with a broader detector enables faster scans than before. High speed scanning is necessary for cardiac examinations as well as for restless patients. The two X-ray sources also provide the possibility for dual energy examinations with improved spectral separation.

The Siemens SOMATOM Definition Flash dedicated to the SCAPIS project also performs at low kV settings and has two x-ray sources and two detectors allowing the use of dual energy.

MRI

The Philips Ingenia 3.0T has a 70 cm bore. It is equipped with Xtend gradient system (up to 45mT/m–200 T/m/s) and two parallel RF transmissions (Multitransmit 4D), which adapt the RF signals to each patient. Multitransmit facilitates an increased image uniformity, contrast, and consistency, as well as faster imaging. A full range of receiver coils is available with analog-to-digital converters inside the coils (dStream RF). This samples the MR signal directly in the coil on the patient, and sends it to the reconstructor via a fiber-optic cable.

Our Philips Achieva 1.5T has a 60 cm bore and is equipped with Nova Dual gradients (up to 66 mT/m–160 T/m/s), and the latest software release and upgraded to dStream resulting in up to 40 % higher SNR, and a dynamic range that exceeds 185dB.

The Siemens 3T Prisma with a 60 cm bore is our latest MRI-scanner. The gradients are outstanding with 80mT/m@200 T/m/s simultaneously, which nicely facilitate fMRI and DTI studies. The software is the latest release and the coil concept offers high coil density using parallel transmit technology called TimTx TrueShape for cardiac, abdominal and musculoskeletal examinations.

A full research agreement with Philips Medical Systems and Siemens Healthcare allows all possible clinical as well as technical research applications.

In addition, we have access to a GE Signa 1.5T HDxt and Discovery 750 3.0T MRI system.

ULTRASOUND

CMIV has access to several clinical ultrasound scanners, Vivid E 9 with Echopac BT 13 software for echocardiography and Siemens S2000 for vascular studies, as well as a dedicated scanner GE Logic E9 and a Vevo high frequency scanner for vascular research.

PACS

Sectra radiology PACS is a comprehensive workstation, designed to optimize the workflow. It ensures quick and easy access to patient data and images and provides instant access to all the tools needed integrated on the desktop – including RIS and clinical applications.

For storage and handling of echocardiographic image data (for both research and clinical use), one of the largest installations of the GE Echopac system in the world is available. A number of advanced diagnostic workstations are available for clinical and research purposes.

VISUALIZATION

CMIV has its own Virtual Reality theatre with a capacity of 90 persons. The theatre is built around Barco DP4K-30L

6P Laser projector (21 000 lumens light output), with 4K resolution(4 096 × 2 160). The Barco Laser 3D has a native 6-primary color-3D system. The system uses a Barco E2 Image processor, 4K Native 12 bits/color 3D input/output. The computer to screen connections are run by the Lightware MX-33R Digital Crosspoint matrix. The Wirecast 7.3 Recorder system allows recording and online streaming.

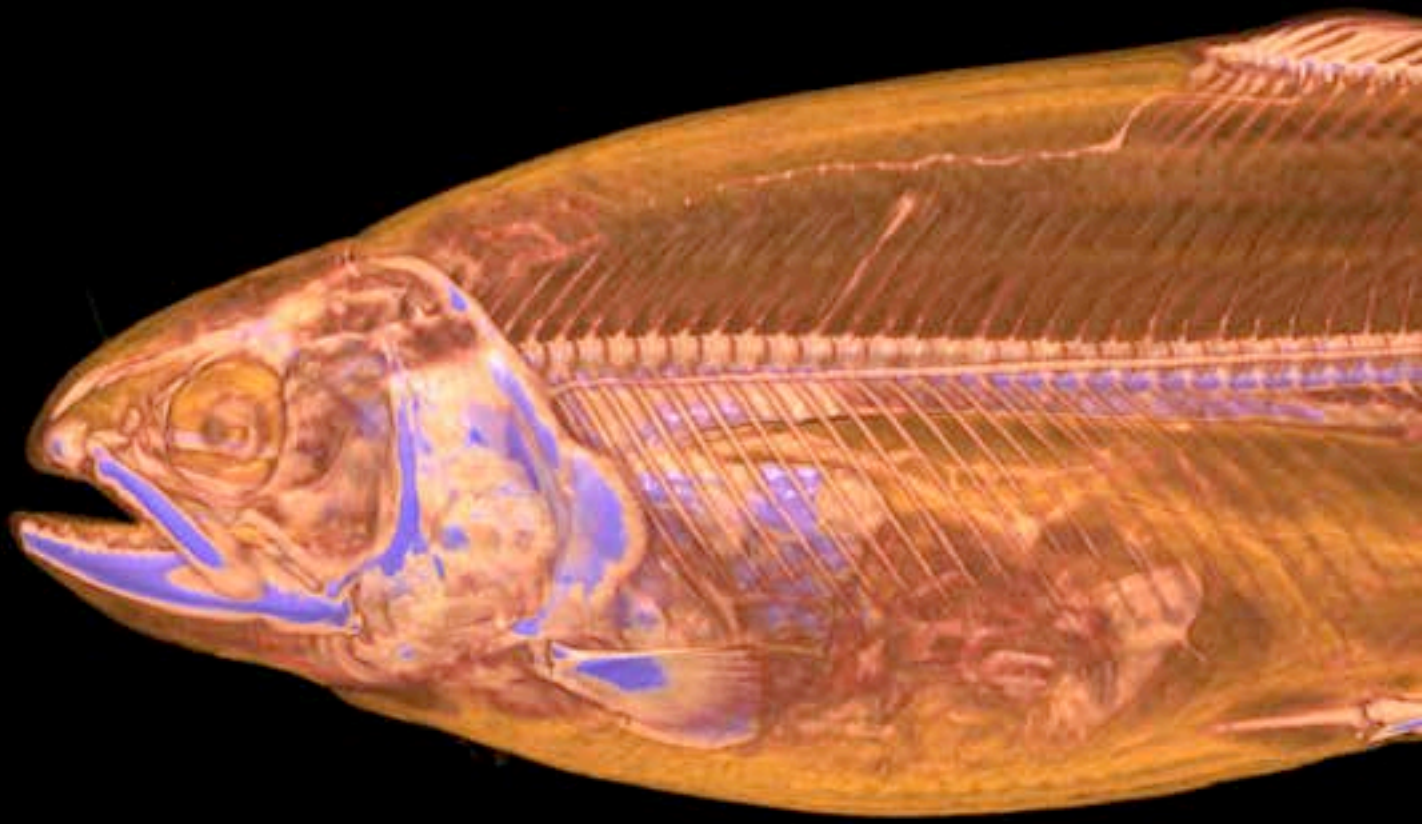
All computers at CMIV:s network can be used for video conference system, allowing for 1080p HD conference meetings or video broadcasting.

Several Advantage Workstations from GE Medical Systems are available at the hospital.

In addition to the theatre there is also a 55" Sectra visualization table and a wall mounted 85" Sectra visualization monitor with ten fingers multi-touch. The Visualization Table is a large interactive screen with an image display system that enables interaction with 3D human body images rendered from CT or MR.

DIGITAL PATHOLOGY SCANNER

A pathology glass scanner from Hamamatsu is available at CMIV. The Nanozoomer 2.0HT convert glas s slides into high-resolution digital data by high-speed scanning and has a capacity of scanning up to 210 glasses automatically. ■



Organization

CMIV is governed by its Board of Directors, with representatives from academia, healthcare and industry. The Scientific Council, appointed among the senior researchers affiliated with CMIV, manages the research agenda of CMIV. The day-to-day operations of CMIV are handled by a group of core staff.

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Catrin Nejdeby	Coordinator
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Petter Dyverfeldt	Clinical Scientist
Suzanne Witt	Clinical Scientist

Publications

As the CMIV researchers are also affiliated to a home department at Linköping University or another university and their research is primarily registered there it can be difficult to overview. We have made an attempt at putting together a list with the publications produced during 2017. Although not complete it still shows a good representation of CMIV.

Bibliometric Analysis

The bibliometric analysis has been provided by the Linköping University Library, department of Publishing Infrastructure. The citation data used in the analysis has been supplied by CWTS, Leiden University; data source: Clarivate Analytics Web of Science.

TABLE 1. **Norwegian Model, 2013–2017**

	Number of publications	Number of fractions
Journal articles – refereed	373	173.3
Conference publications	6	3.7
Chapters – other academic	25	11.3

Results	
% author shares level 2	12

Percentage of fractionalized publications published in journals / publishers of the highest scientific quality.

TABLE 2. **Open access, 2013–2017**

Articles	%
Articles	50
Conference publications	17
Chapters	28

Green open Access refers to articles, conference articles and chapters published in full text in DiVA. Gold open access is defined as publications where the article ISSN is registered in the Directory of Open Access Journals (DOAJ). Hybrid open access is defined as publications where registration in DOAJ is missing but open access may be availible through the DOI link.

TABLE 3. **Coverage in Web of Science, 2013–2017**

Publications in Web of Science	Number of publications	Number of fractions
Articles, reviews, letters, proceedings papers	360	160.9

Coverage	%
Articles	88
Conference Proceedings	0

FIGURE 1. **Number of fractionalized publications**

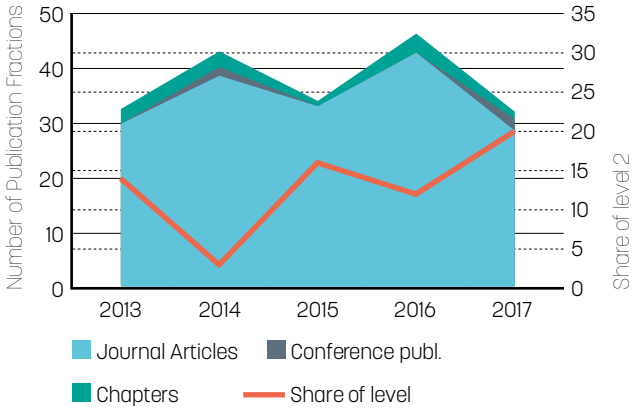

FIGURE 2. **Open access articles**

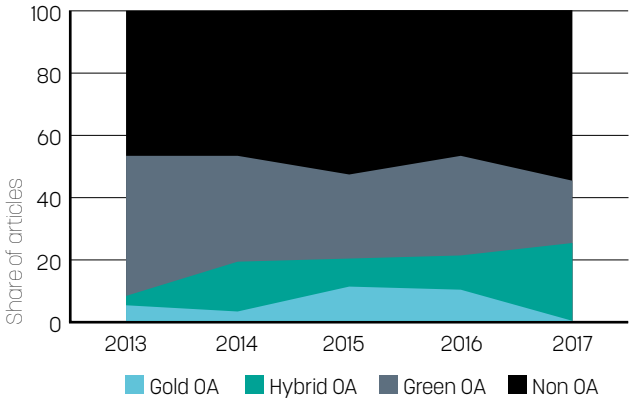

FIGURE 3. **Number of fractionalized journal articles: Coverage in WoS, 88 %**

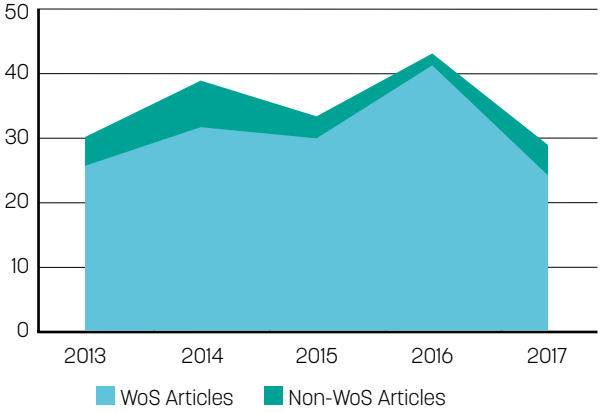

FIGURE 4. **Impact**

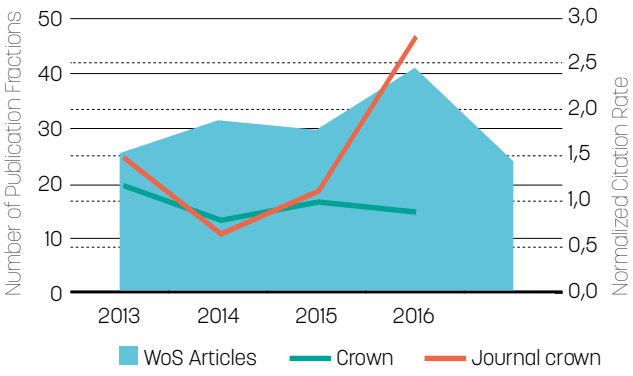

FIGURE 5. **Fractionalized journal articles in WoS: Co-authorships**

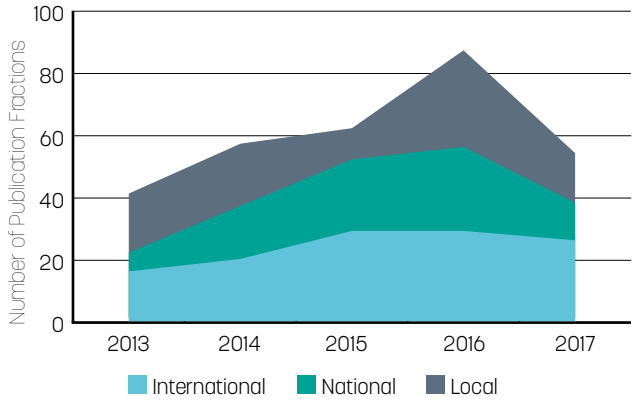

FIGURE 6. **Interdisciplinary publications**

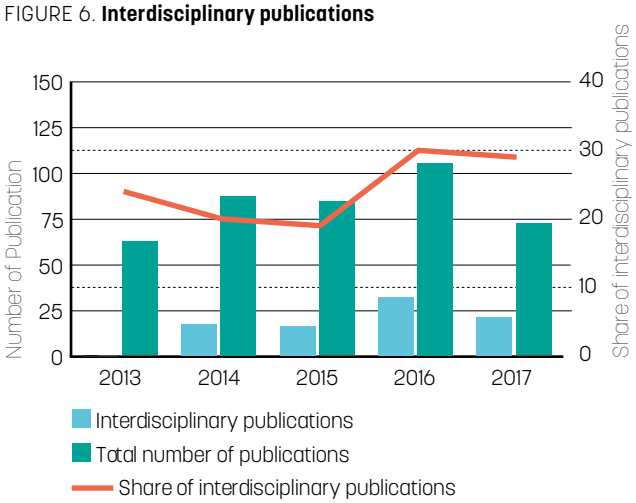

TABLE 4. **Citation analysis, 2013–2016**

Publications in Web of Science	Number of publications	Number of fractions
Articles, reviews, letters	246	108.9

Results, 2013–2016	%
Field-normalized citation rate (crown)	1.63
Share of top 10 %	11
Share of uncited publications	29
Field-normalized journal citation rate (journal crown)	0.9
Journal Impact Factor (JIF) ranking, mean	0.64

Crown: A measure of the impact of the articles included in the analysis. Provides a comparison value with an international average for the same field, year and article type, and where the value 1 corresponds to a world average.
Share of top 10 %: The percentage of publications that are among the 10 % most cited in the subject area during the time period
Journal Crown: A measure of the impact of the journals that the department published in. JIF Ranking mean: All journals within each subject category are ranked based on the JIF, and the number indicates how the journal in question is placed in the rankings. Ex 0.8 indicates that the journal is among the 20 % highest ranking.

TABLE 5. **Co-authorship, 2013–2017**

	%
Share of articles with international co-authors	40
Share of articles with national co-authors	28
Share of articles with local co-authors	30

TABLE 6. **Interdisciplinary authorship (LiU faculties), 2013–2017**

Number	101
Share	25 %

Publications 2017

CMIV affiliated researcher are written in bold.

PEER-REVIEWED ORIGINAL ARTICLE

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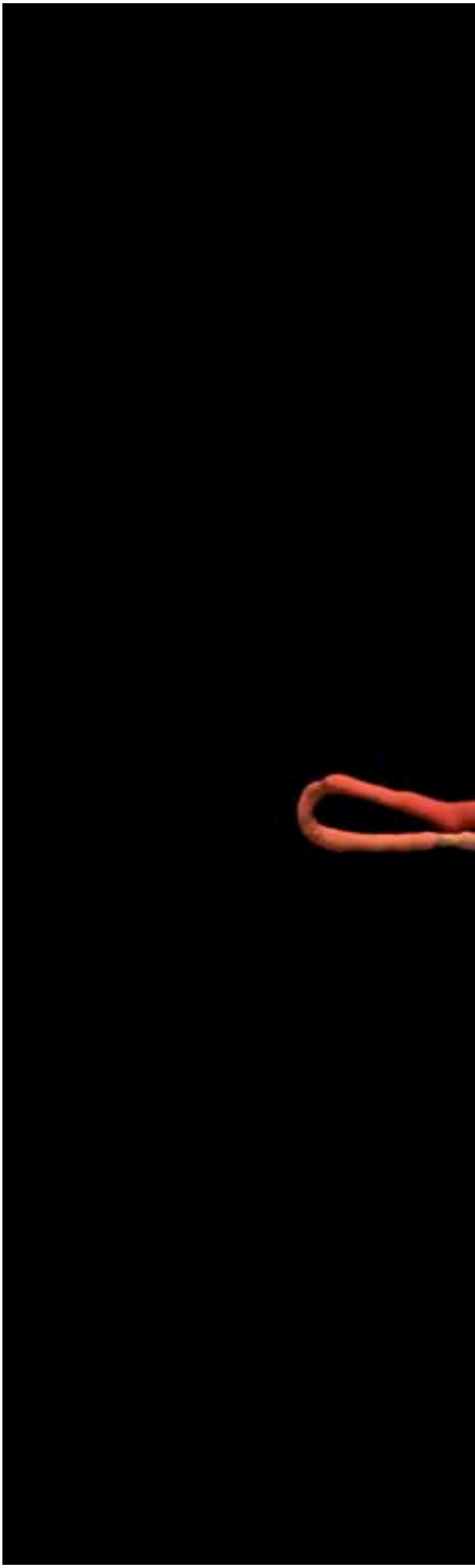
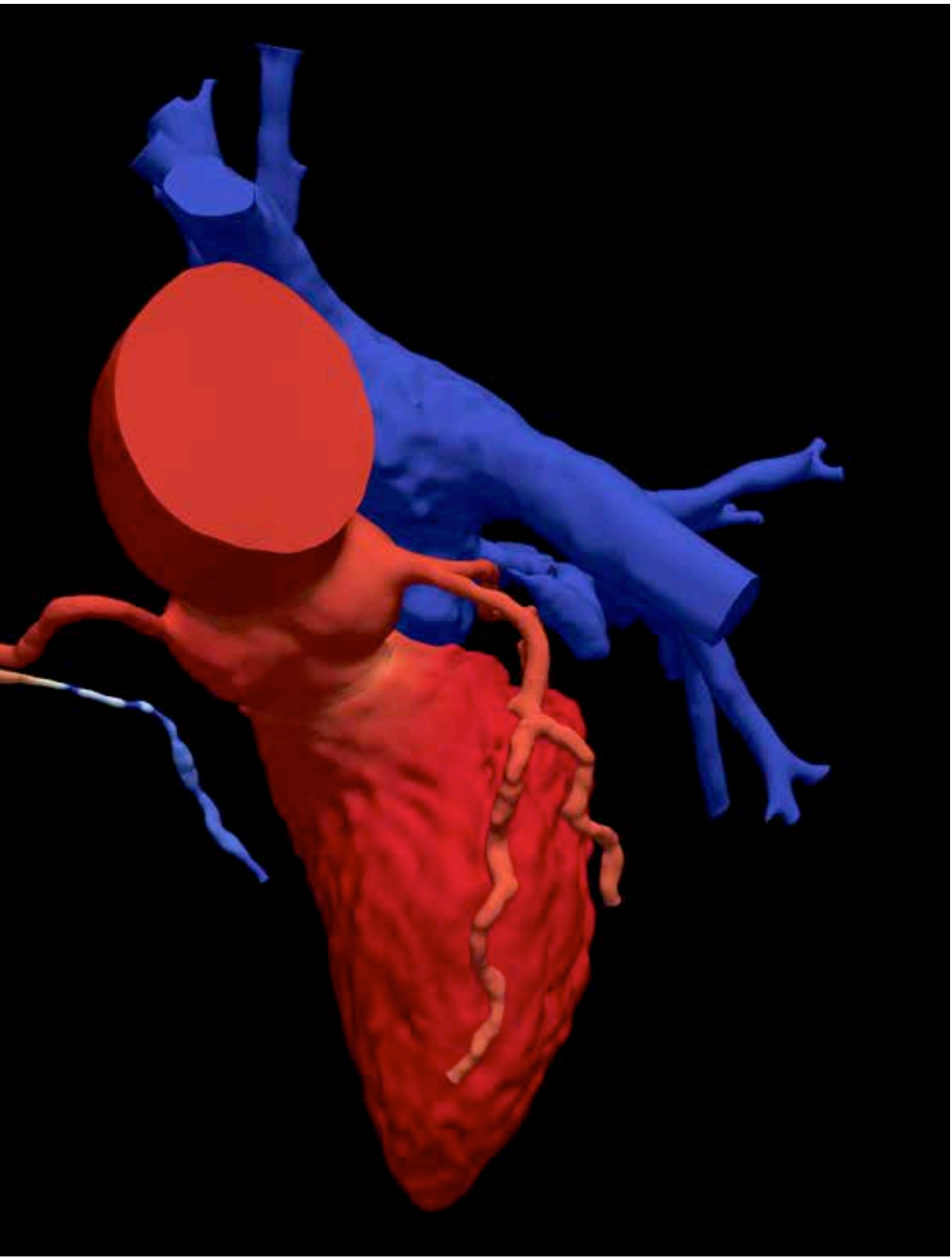




Annual Accounts

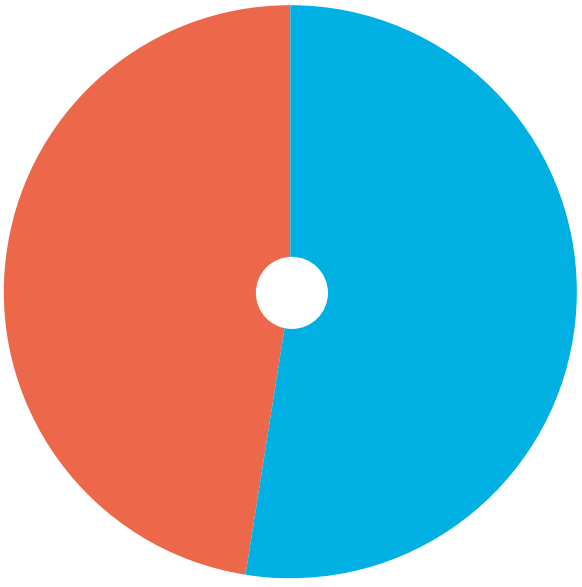
During 2017 CMIV had a turnover of more than 48 million.
The financial result for CMIV in 2017 was 1.3 million SEK.

This fiscal year we have continued to develop our infrastructure by upgrading our virtual reality theatre in Wrannesalen to a Barco laser projector system with a rear projector screen.

During 2017 CMIV had several ongoing grant research projects. VINNOVA announced funding of AIDA – Analytic Imaging Diagnostics Arena during spring 2017. This project will continue during 2017–2019 in it is first period. The VINNOVA-financed project "Bringing orthopedic implant surgery to the era of precision medicine" was continued in a larger scale during 2017, this project will continue until 2019. The project "Radsim: Simulation Based Training Program for CT Protocol, Iterative Reconstruction and Dual Energy Applications" continues. Radsim is funded by RSNA Research & Education Foundation. DROID (Open image database for AI-training) started during 2017, and will continue during 2018. DROID is funded by Visual Sweden. The Strategic Area of Forensic Science funded the project "New approaches to forensic wound assessment using post-mortem Dual Energy CT and Quantitative MRI" during 2017. Both the Faculty of Medicine and Health Sciences and the Faculty of Science and Engineering have continued to support CMIV:s work within the Digital pathology area. ■

ECONOMIC SUMMARY	2012	2013	2014	2015	2016	2017
Total Revenue	32 629	35 576	48 762	39 298	40 655	48 165
EXPENSES						
Staff expenses	–15 102	–16 756	–19 507	–18 593	–16 978	–15 772
Cost of premises	–2 145	–2 034	–2 058	–2 869	–9 135	–6 472
Misc. operating expenses	–7 653	–8 876	–17 334	–11 483	–12 158	–16 765
Depreciation expenses	–4 938	–5 336	–5 629	–4 980	–6 781	–7 819
Financial expenses	–125	–185	–102	–123	– 132	– 36
Total expenses	–29 963	–33 187	–44 630	–38 048	–45 184	–46 864
Result of Operations	2 666	2 389	4 133	1 250	–4 519	1 300

NUMBERS IN THOUSANDS OF SEK



Research Funding at CMIV 2010–2017

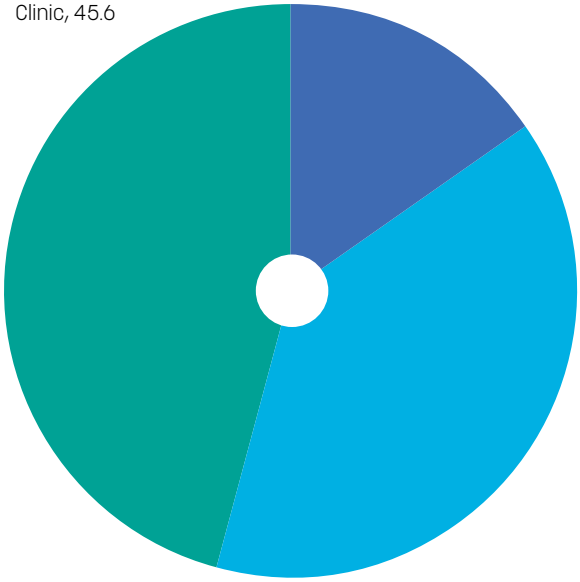
CMIV receives funding from research funds and the industry both directly to the R&D platform and to specific research projects. In addition, the affiliated researchers have their own funding; however, these grants will not be presented here.

External funds: 73 331 tkr
Industrial funds: 65 899 tkr

CT Research and Clinic, %

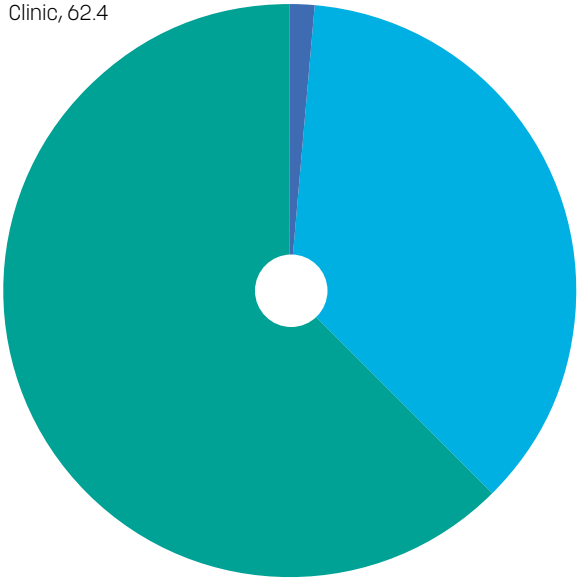
2017

Combined research and clinic, 15.5
SCAPIS, 38.8
Clinic, 45.6



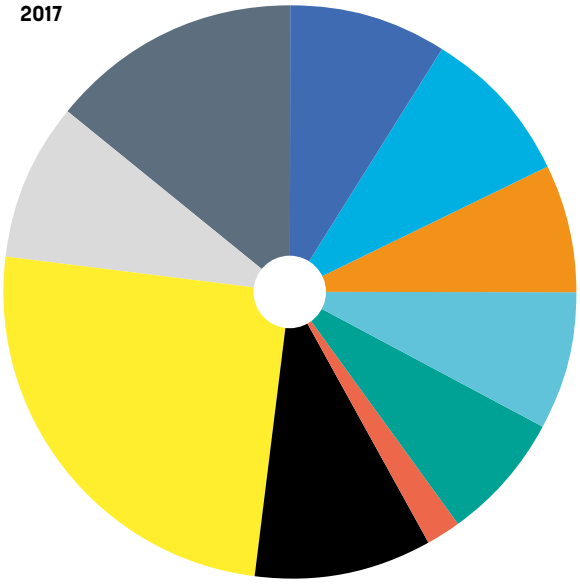
2016

Combined research and clinic, 1.6
SCAPIS, 36
Clinic, 62.4



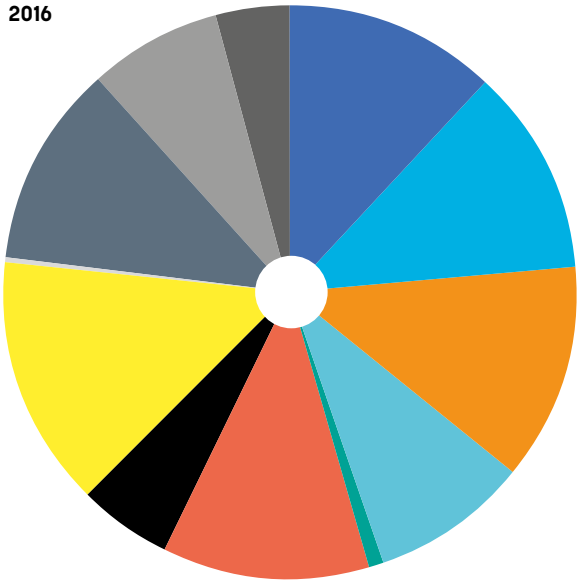
Distribution of Research on the MRI Cameras, %

2017



- Full body scan, 8.6
- Logistics, 9.0
- fMRI neuro, 6.6
- Cardiovascular, 8.1
- Combined Clinic / Research, 7.1
- Spectro neuro, 2.3
- Development time, 10.5
- CSAN neuro, 24.8
- SCAPIS, 9.0
- MSK, 13.9

2016



- Full body scan, 12
- Logistics, 11.8
- fMRI neuro, 12.4
- Cardiovascular, 8.9
- Industry, 0.6
- Combined Clinic / Research, 11.9
- Spectro neuro, 5.3
- Development time, 14.2
- Neuro, 0.1
- CSAN neuro, 11.5
- SCAPIS, 7.5
- MSK, 4

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