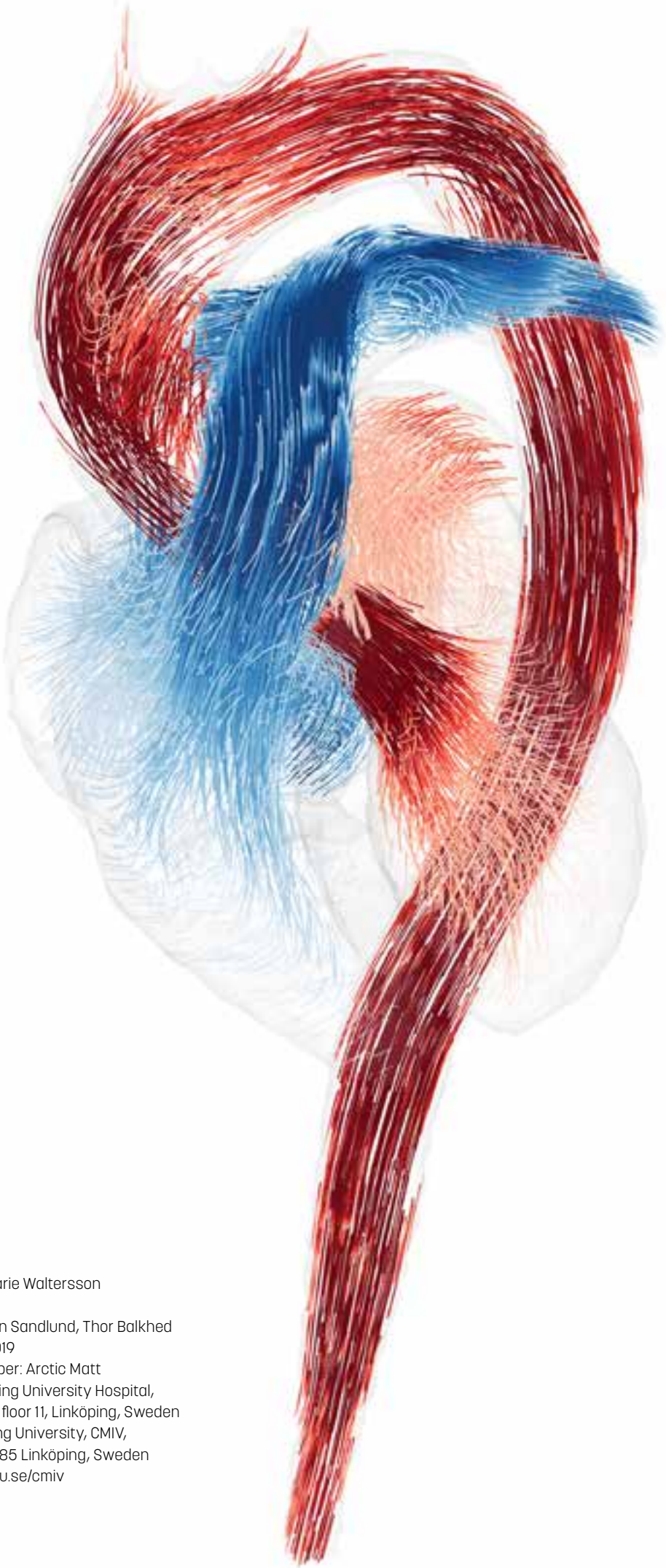
Welcome to the exciting world of CMIV

ANNUAL SCIENTIFIC REPORT 2018

LINKÖPING UNIVERSITY



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Print: LiU-tryck, June 2019
Fonts: Korolev, Miller. Paper: Arctic Matt
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Preface

In the beginning of 2018, we had the privilege to celebrate CMIV's 15th birthday with a jubilee conference showing how much we have accomplished over the years. Everything started in 2003 with no windows but an amazing view of the future. Four square meters and plain walls, our first office was nothing to boast about. But when you're planning to be first in the world to build a center that tears down traditional boundaries and allows people, ideas, creativity and production to flow freely, there are no blueprints or models to follow and the necessity for a spatial office limited.

The spectacular images and research that has been produced during the last 15 years may steal all the thunder but what actually makes CMIV stand out is the set-up. Placed at the very heart of Linköping University Hospital, in new much larger premises where unique multidisciplinary research environment attracts scientists, medical doctors, technicians, radiologists and a whole range of people with the most unexpected skill sets. All interacting with each other and where this becomes most apparent is still after 15 years the coffee room.

During 2018 I see many amazing accomplishments, both from CMIV as a whole, from individual research groups and supporting staff. CMIV continues to grow and one of the newest research areas AIDA, a national arena for artificial intelligence (AI) research in medical imaging, has evolved during the year and the project budget and number of fellowship researchers, from all over Sweden, has been doubled. At the end of the financial year, the total number of active simultaneously ongoing research projects at CMIV exceeded 80.

The flagship projects of 2018 are three outstanding projects that visualize the broad competence among the CMIV researchers. They represent CMIV well in showing different areas and how we work close to the clinic combining technical and medical knowledge. The first project, MR-based body composition, has developed a method for quantitative assessment of body composition using MRI. In the second project, 4D flow CT, images from computed tomography cardiac examinations has for the first time in the world been used to calculate and visualize patient specific heart function. The last flagship project, Statistical Analysis of NeuroImaging Data, validates and improves existing statistical models for fMRI data.

All in all, 2018 has been another great year at CMIV and I'm sure that 2019 will be even greater.

Anders Persson
DIRECTOR OF CMIV

Highlights

As always, a lot has happened during the past year. CMIV is continuing to welcome new researchers and projects. We started 2018 with our 15-year jubilee conference and continued the year with many prominent guests. Here you will find the highlights of the year.

FOTO: THOR BALKHED, LIU

4D Flow Simulation Using CT Comparable with MRI

IN A PUBLICATION in Radiology in 2018, CMIV researchers presented a study where they used information from computer tomography images to simulate the heart function of an individual patient. The publication was discussed in the editorial and highlighted by, amongst others, Aunt Minnie.

Modeling methods originally used to simulate flowing fluids and turbulence in the aeronautical and motor industries were applied on flow through the patient's heart and blood vessels. The modeling methods simulated the blood flow in a patient's heart with the aid of high-resolution CT images. The calculations needed were performed aided by computing power available at the National Supercomputer Centre (NSC) at Linköping University.

The results were verified against 4D flow MRI and the CT simulation provided very similar flow patterns and measurements compared with MRI.

NDP at ECDP in Helsinki

THE »NORDIC SYMPOSIUM on Digital Pathology« (NDP) was founded by the national project DigiPat and organized by CMIV. DigiPat was a collaboration between most Swedish pathology departments, Linköping University and industry partners with the goal to digitize Swedish pathology. After four successful annual meetings in Linköping the NDP of 2018 was co-organized with the »European Congress on Digital Pathology« (ECDP) in Helsinki.

The congress theme was digital diagnostics and intelligence augmentation, with focus on artificial intelligence for pathology.

CMIV 15 Years

IN THE BEGINNING of 2018 CMIV turned 15 years. This was celebrated with a jubilee conference. The jubilee speaker Anders Lönnberg spoke about the importance of collaboration between university, healthcare and industry for life science development. The jubilee speech was followed by talks by representatives of Linköping University, Region Östergötland and the industry. CMIV director Anders Persson told the CMIV story and several CMIV researchers presented their research. During the conference the guests were invited to an open house at the new CMIV facilities.

Jubilee speeker Anders Lönnberg and Chairman of the CMIV board Katrine Riklund.

Claes Lundström presenting the PRECIIS project.

The Swedish National Orthopedics Meeting

THE SWEDISH ANNUAL meeting in orthopedics 2018 was held in Karlstad. The theme for the week was »Future Orthopedics«. Through the national project PRECIIS, CMIV has extended knowledge about innovations and possibilities in precision orthopedics. CMIV therefore hosted a session presenting current and future possibilities of integrating radiology tools in orthopedics to increase precision.

Swedish Research Council

Research Grants from the Swedish Research Council

THE PURPOSE OF the research project grant from the Swedish Research Council is to give researchers the freedom to formulate by themselves the research concept, method and implementation, and to solve a specific research task within a limited period of time. The Swedish Research Council rewards research of the highest scientific quality in national competition.

In the 2018 call within Natural and Engineering Sciences Linköping University was granted 84 million SEK divided amongst 25 researchers and within Medicine and Health 75 million SEK divided on 22 researchers.

In the Medicine and Health call Carl-Johan Carlhäll received grants for his research on multi parametric MRI and atrial fibrillation. Anneli Peolsson was granted funding for her research on innovative rehabilitation in chronic whiplash associated disorders. Kajsa Igelström was granted a starting grant for her research on brain imaging techniques in neuro psychiatric syndromes. The starting grant gives junior researchers the opportunity to establish themselves as independent researchers.

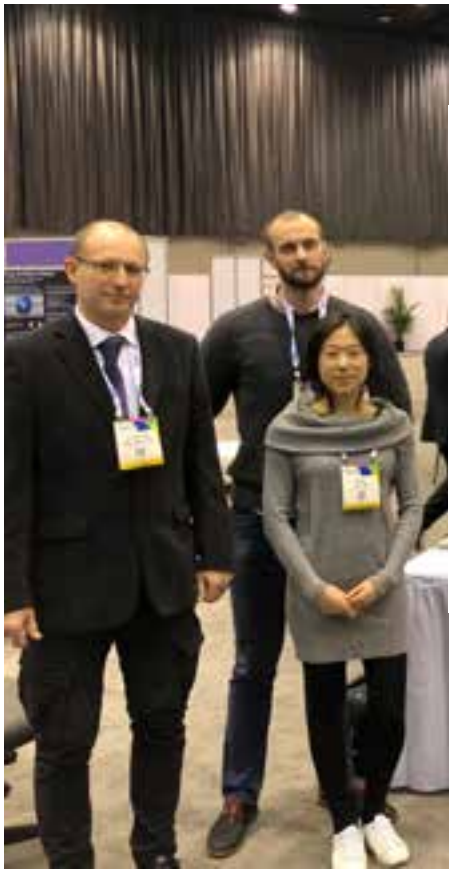
In the Natural and Engineering Sciences call Tino Ebbers received grants for his work on the cardiovascular functional avatar. Maria Engström received funding for a research project on imaging biomarkers in neuroradiology. Markus Henningsson was awarded a starting grant for his research on quantitative MRI measurements of perfusion in the heart.

Jenni Nordborg and the Swedish Life Science Office at CMIV

DURING THEIR VISIT to Region Östergötland the National Coordinator Life Sciences at the Government Offices, Head of Health Division at VINNOVA Jenni Nordborg also visited CMIV. The group was accompanied by the Research Director at Region Östergötland, Mats Ulfendahl, the Vice-Chancellor of Linköping University, Helen Dannetun and the Dean of the Medical Faculty at Linköping University, Johan Dabrosin Söderholm.

Anders Persson presented the ongoing research at CMIV and in particular the successful projects where region, university and industry collaborate to create real patient values. Torbjörn Kronander, CEO at Sectra participated and gave the industry view on the collaboration model. The life science office was established by the Ministry of Industry in the beginning of 2018 to coordinate policies, clarify priorities and accelerate the work previously initiated to create the conditions for a competitive life science industry in Sweden. Jenni Nordborg will continue at her position as Director of the Health Division at VINNOVA alongside her new assignment.

Jenni Nordborg and Johan Dabrosin Söderholm at the guided tour around CMIV.



RadSimCT

IN 2014 THE RSNA Derek Harwood-Nash Education Scholar Grant was awarded to the CMIV project RadSimCT. At RSNA this year the result from this project could be demonstrated. RadSimCT is a web-based educational tool for learning the principles of CT scanning in radiology and it is available to use for free. It is a vendor-neutral simulation software which utilizes images from actual CT examinations.

The RadSimCT team presenting the software at the RSNA exhibition in Chicago.

Anders Ynnerman, CMIV researcher and Professor in Scientific Visualization at Linköping University.

Innovation Minister Mikael Damberg Visited CMIV

INNOVATION MINISTER Mikael Damberg visited CMIV during his trip to Linköping to learn about cross-disiplinary research at LiU.

The IEEE Visualization Technical Achievement Award

ANDERS YNNERMAN, CMIV researcher and Professor in Scientific Visualization at Linköping University was appointed the 2018 IEEE Visualization Technical Achievement Award. He got the prize for contributions to medical visualization resulting in the development of virtual autopsies, which have had extraordinary impact in both medicine and communication of science to the public.

CMIV at ISMRM 2018

THE ANNUAL ISMRM meeting 2018 was held in Paris, France. The International Society for Magnetic Resonance in Medicine (ISMRM) is a multi-disciplinary nonprofit association that promotes innovation, development, and application of magnetic resonance techniques in medicine and biology throughout the world. CMIV contributed to the program with a great number of poster abstracts and oral presentations.

The CMIV Landscape

When CMIV was initiated, the vision was to gather all the components of medical imaging and visualization in one place. And at the same time create a whole new type of research environment where scientists, technicians and medical doctors would work close together with immediate access to the patients. A place where there were no distance between research and clinical needs. Since the start in 2003, CMIV has grown into the vision and it is now our everyday routine.

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 healthcare with the opportunity of clinical benefits, while the industry gain from the research with e.g. spin-offs. The activities aim to combine different demands were the university seeks scientific publications in high quality journals and the county council expects the research and development to come to patient benefit. CMIV's organization, fully embedded in the university hospital, creates conditions to successfully meet these requirements. Results from basic research at the university can be utilized in clinical research which can then result in scientific publications, and improved patient care.

Until recently we described the CMIV research projects as links in a sequential imaging chain. Projects move dynamically through the chain and researchers from different disciplines work together to reach the goal of patient benefit. While this still holds true, the picture is also growing more complex with the addition of new research areas as artificial intelligence and precision medicine.

We are in the middle of a paradigm shift for healthcare. Focused research and development in all steps of the chain are still important to continue improving quality of care. However, embracing new possibilities and letting the research grow in new dimensions is key to stay in the frontline of medical imaging. CMIV is now adapting its research to be in the forefront of this development. The advances in precision medicine are due to rapid development in a number of important areas that are groundbreaking by themselves. But their impact can also be greatly magnified if they are wisely combined. These areas include molecu-


STOP

lar biology, large-scale genetic sequencing and artificial intelligence.

Precision medicine can be defined as clinical, therapeutic and diagnostic methods for optimal disease management based on the patient's individual variations, often including a genetic profile. It provides more effective treatments, fewer adverse effects and increased survival. Examples of other advantages of precision medicine are increased possibilities to identify and thereby prevent or mitigate disease at an early stage, to make it easier for patients to manage their illness and shortening hospital stays.

The CMIV projects are not easily categorized as they move dynamically over research areas, always looking for new ideas from other fields. In an attempt to visualize the CMIV research areas we have created an overview table with the projects from the annual report and marked the main areas that the projects involve.

The categories used are divided in three main research areas; imaging data source, biomedical research area and technical research area. The main research areas consist of a number of sub-areas.

Imaging Data Source

The overall dominating data source at CMIV is magnetic resonance imaging (MRI). The method is versatile and allows great opportunities for project specific development. Another advantage is the use of volunteers not being restricted by radiation dose.

In computed tomography (CT), the development of low dose CT has opened up for larger prospective studies and at the same time clinical examinations can be used for potent simulations. CMIV have several exciting new studies in these fields. Another interesting field with an increasing contribution is microscopy, where the ongoing digitization of the clinical routine has opened up for new applications in image analysis and deep learning.

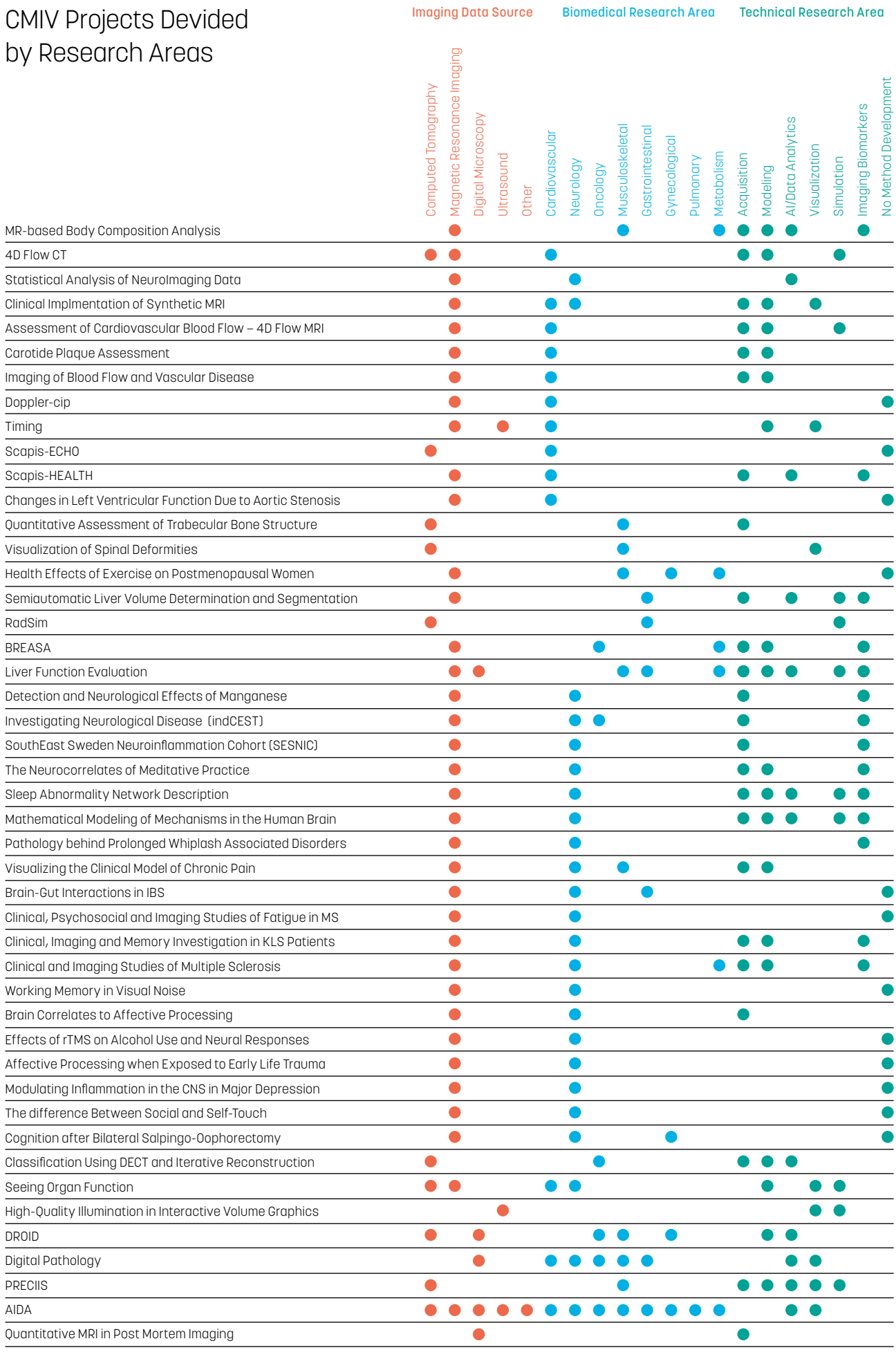
Biomedical Research Area

CMIV have strong traditions in the fields of cardiovascular and neurology research. Other strong areas are musculoskeletal and gastrointestinal research. However, with new constellations forming, projects are less focused on individual organs and instead have a more holistic approach.

Technical Research Area

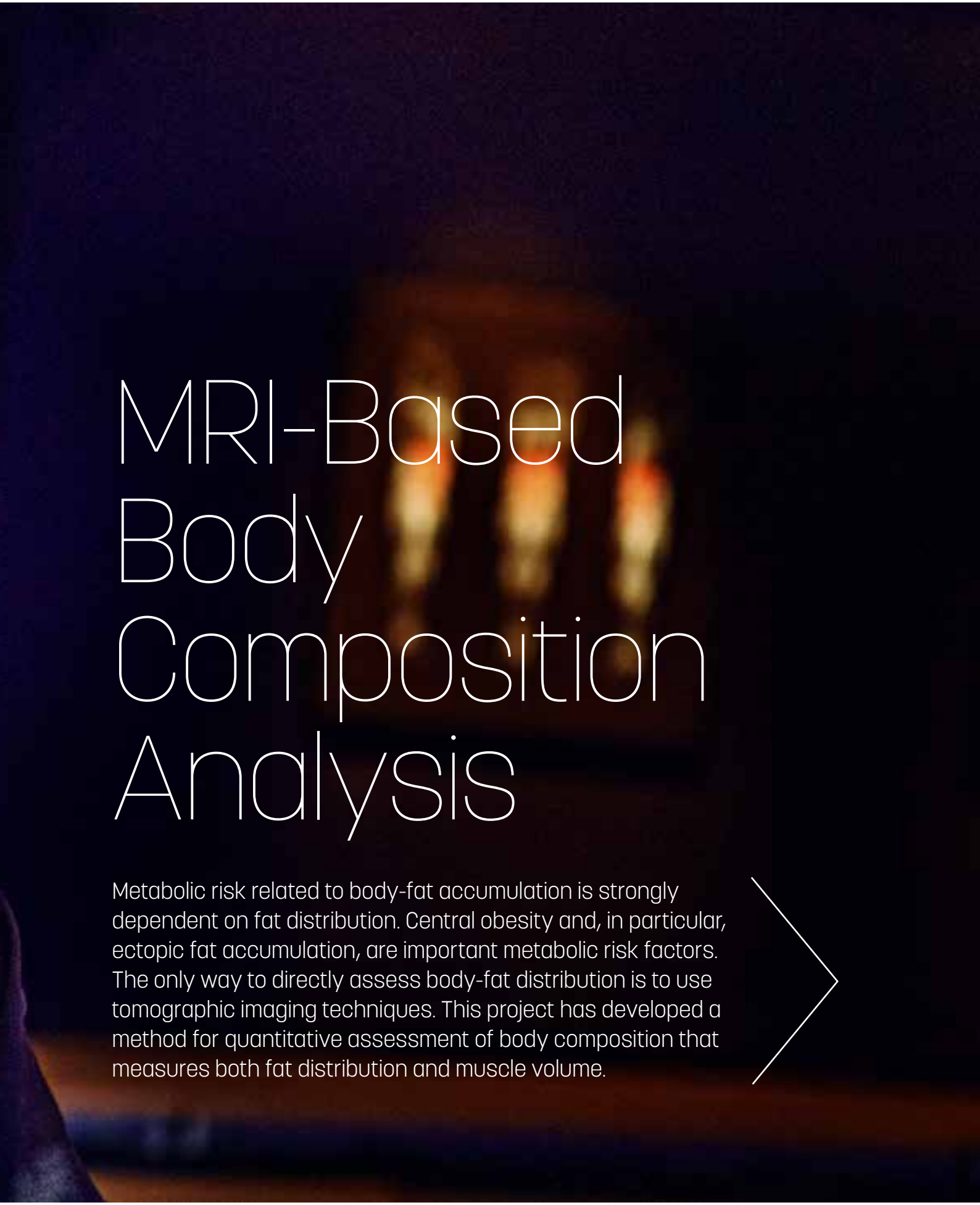
A foundational aspect of CMIV is that the research spans all the technical areas involved in the imaging chain. This type of cross-disciplinarity means that scientific efforts in one technology domain at CMIV is enriched by in-depth knowledge on the characteristics of preceding steps and on subsequent use of the results later in the chain. The overview shows that CMIV projects are fairly evenly distributed in terms of technical contribution, from data generation through acquisition and simulation to a wide range of analytics and visualization methods. ■

CMIV Projects Devided by Research Areas



Flagship Projects

The 2018 flagship projects were selected by the CMIV scientific council. The chosen projects complement each other in modalities, project stage and medical area and therefore well represent the broad and multi-disciplinary research at CMIV.



MRI-Based Body Composition Analysis

Metabolic risk related to body-fat accumulation is strongly dependent on fat distribution. Central obesity and, in particular, ectopic fat accumulation, are important metabolic risk factors. The only way to directly assess body-fat distribution is to use tomographic imaging techniques. This project has developed a method for quantitative assessment of body composition that measures both fat distribution and muscle volume.

PROJECT INFORMATION

Project Name
MRI-based Body Composition Analysis

Project Leader
Magnus Borga, Department of Biomedical Engineering, Division of Biomedical Engineering
Olof Dahlqvist Leinhard, Department of Medical and Health Sciences, Division of Radiological Sciences

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

Grants
AIDA (VINNOVA), 2018–2019

Key publications
Borga M et al.
Advanced body composition assessment: from body mass index to body composition profiling. J Investig Med. 2018 Jun; 66(5):1–9. doi: 10.1136/jim-2018-000722.

Linge J et al.
Body Composition Profiling in the UK Biobank Imaging Study. Obesity (2018) 26, 1785–1795. doi:10.1002/oby.22210.

Middleton M et al.
Quantifying abdominal adipose Tissue and Thigh Muscle Volume and hepatic Proton Density Fat Fraction: Repeatability and Accuracy of an MR Imaging-based, Semiautomated Analysis Method Radiology (2017) May, Volume 283: Number 2, 438–449. doi:10.1148/radiol.2017160606.

MRI
Musculoskeletal
Acquisition
Modeling
AI/Data analytics
Imaging Biomarkers

"We wanted to think freely, without limitations by the traditional boarderbetween image generation and postprocessing. This was where it all began."

Magnus Borga

Today, it is well known that the metabolic risk related to body-fat accumulation is strongly dependent on fat distribution. Central obesity and, in particular, ectopic fat accumulation, are important metabolic risk factors. Large amounts of visceral adipose tissue is associated with increased risk of cardiovascular disease, type-2 diabetes, liver disease, and cancer. But more importantly, it has been shown that disease risks tend to be related to specific patterns of fat accumulation.

The only way to directly assess body-fat distribution is to use tomographic imaging techniques. Magnetic resonance imaging (MRI) can also measure muscle volumes, muscle fat infiltration and other ectopic fat accumulation, which makes it a powerful tool for advanced body composition assessment.

Professor Magnus Borga is one of the researchers behind the body composition project. He is an engineer with roots in image processing and robot vision that moved on to medical image processing. His co-worker is senior lecturer Olof Dahlqvist Leinhard with a background in MR physics.

– I met Olof at CMIV. He was working with liver fat measurements and his focus was not to produce images for the radiologists to interpret but rather to use the MR camera as a measuring instrument. We started discussing how we could combine our specialties in MRI instead of seeing them as two separate problems. Olof was focused on how to prepare the camera to get the images you want while I was specializing in the postprocessing of the images, Magnus explains.

The two researchers started discussing how they could make the whole process more effective when data optimal for computer analysis is the primary goal instead of the image.

– We wanted to think freely, without limitations by the traditional boarder between image generation and post-processing. This was where it all began.

They started out with a project where they wanted to measure fat accumulation in individuals after a fast food intervention.

– To be able to measure fat accumulation in other parts of the abdomen than the liver we needed to know where we were measuring. This was a combined MR physics and image analysis problem and the result was the basis of our methodology, says Magnus.

Since then they have refined the measurement technique and can now measure in more detail and larger parts of the body, fat infiltration in the muscles as well as muscle volume.

– With the muscle and fat measurements, we can now provide a more complete picture of the body composition from a metabolic perspective. We have studied the reproducibility of the method and because no one has done this before we spent a lot of time and resources on exploring how to classify a normal body composition, Magnus continues.

MRI is not in itself a quantitative method. Magnus and Olof came up with a postprocessing technique that calibrated the images against the fat signal to produce a quantitative result. This technique was patented and placed in a spin-off company that they called AMRA. The company has

grown in parallel with the research.

– There is a symbiotic relationship between our research and AMRA. The research is providing knowledge and credibility to AMRA and the company allows the use of an industrial production process that would otherwise not be possible in a research environment. We are now in the process of analyzing 100 000 whole body scans.

The large study population allows the research group to use big data components to find correlations between body composition and other health aspects as heart disease prevalence. With follow up data it might be possible to predict disease outcome by looking at the body composition.

The identification of specific fat distributions associated with different diseases enables the development of more targeted and effective treatments. One example of how this research can be used is as a tool in clinical trials. As MRI-based body composition analysis greatly individualizes the description of the patient, it provides information that can identify and define the populations in clinical trials, bringing them one step closer to precision medicine. ■

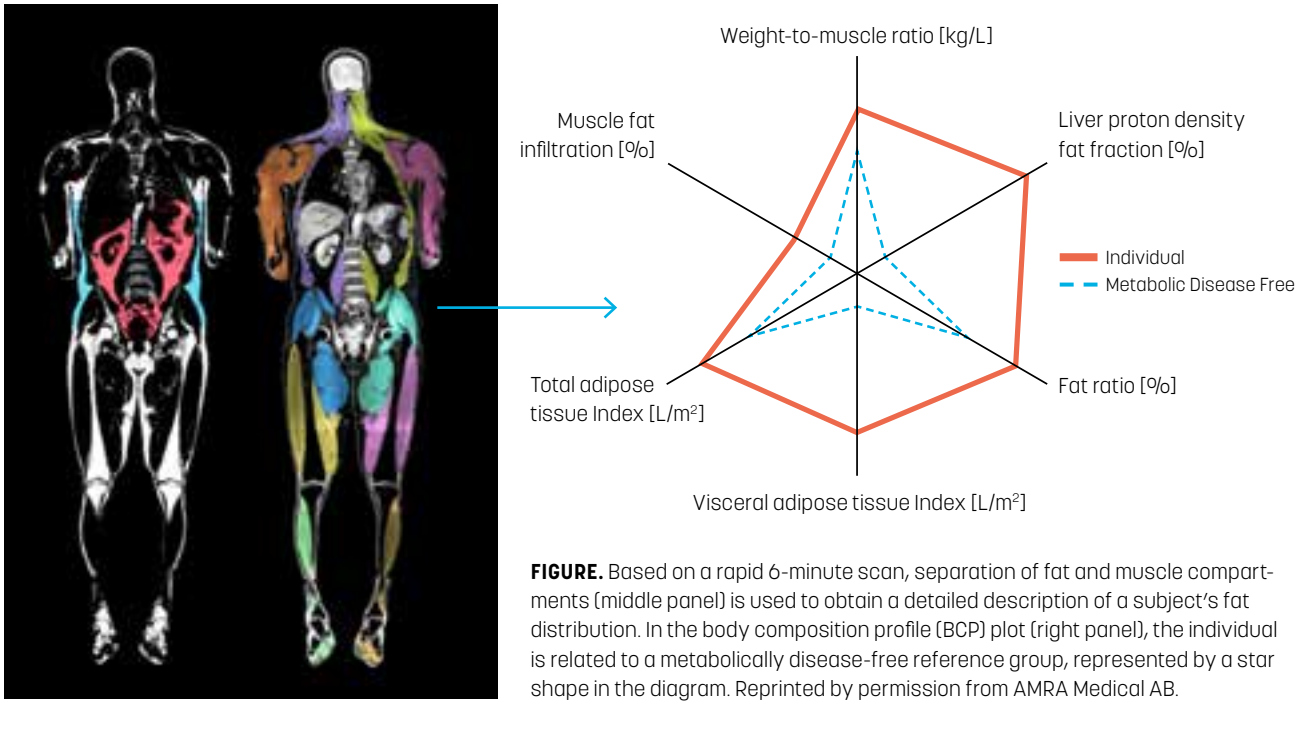
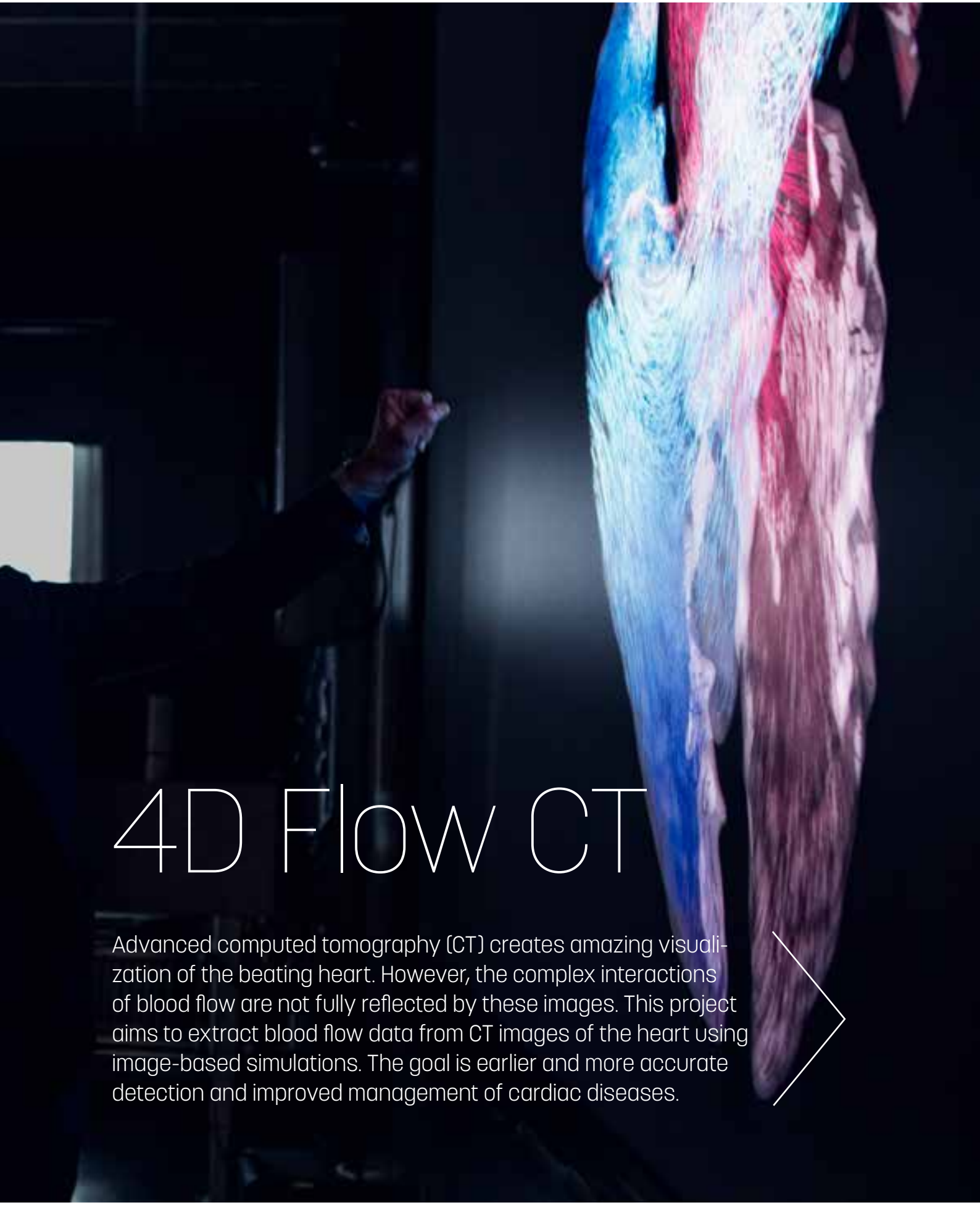


FIGURE. Based on a rapid 6-minute scan, separation of fat and muscle compartments (middle panel) is used to obtain a detailed description of a subject's fat distribution. In the body composition profile (BCP) plot (right panel), the individual is related to a metabolically disease-free reference group, represented by a star shape in the diagram. Reprinted by permission from AMRA Medical AB.



4D Flow CT

Advanced computed tomography (CT) creates amazing visualization of the beating heart. However, the complex interactions of blood flow are not fully reflected by these images. This project aims to extract blood flow data from CT images of the heart using image-based simulations. The goal is earlier and more accurate detection and improved management of cardiac diseases.

PROJECT INFORMATION

Project Name
Simulation of Time-Resolved, Three-Dimensional Cardiac Blood Flow from Computed Tomography (4D flow CT)

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

Main Project Participants
Anders Persson, Matts Karlsson, Carl-Johan Carlhäll, Jonas Lantz, Vikas Gupta, Lilian Henriksson, Sophia Beeck

Grants
KAW-Seeing organ function, 2012–2018
Swedish Heart Lung Foundation, 2019–2021

Key publications
Lantz J, Gupta V, Henriksson L, Karlsson M, Persson A, Carlhäll CJ, Ebbers T.
Intracardiac flow at 4D CT: comparison with 4D flow MRI. Radiology 2018: 289 (1), 51–58.

Lantz J, Henriksson L, Persson A, Karlsson M, Ebbers T.
Patient-specific simulation of cardiac blood flow from high-resolution Computed Tomography. Journal of Biomechanics Engineering 2016; 138(12).

Lantz J, Gupta V, Henriksson L, Karlsson M, Persson A, Carlhäll C-J, Ebbers T.
Impact of Pulmonary Venous Inflow on Cardiac Flow Simulations: Comparison with In Vivo 4D Flow MRI, Annals of biomedical engineering 2019; 47 (2), 413–424.

CT
MRI
Cardiovascular
Acquisition
Modeling
Simulation

"You need to have all the knowledge from simulation to clinical experience to succeed in creating something clinically useful."

Tino Ebbers

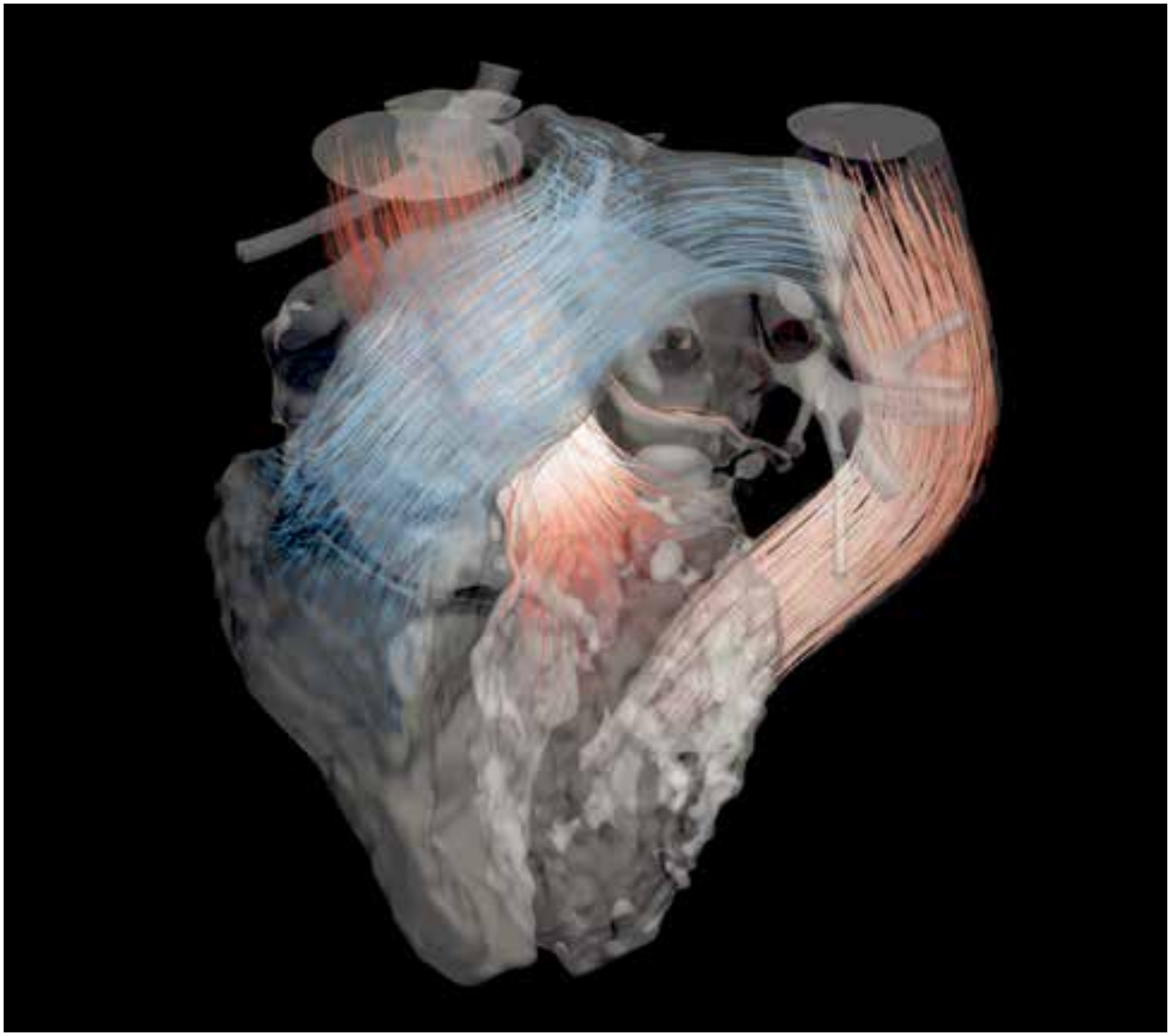
Advanced computed tomography (CT) allows for amazing visualization of the human body including the beating heart. However, the complex interactions of blood flow, which is crucial in the diagnosis and treatment planning of many diseases, are not fully reflected by these images. Magnetic resonance imaging (MRI) and ultrasound are able to measure functional data like blood flow, but at a low resolution. Furthermore, these techniques are not able to predict the changes in blood flow after surgical treatment.

Professor Tino Ebbers has long experience in imaging of the cardiovascular system, mainly using MRI. For the 4D Flow CT project he changed imaging technique to computed tomography (CT). He brought on board Professor Anders Persson who is world leading in CT imaging of the heart, Professor Matts Karlsson who is an expert in flow mechanics and simulation, and Professor Carl-Johan Carlhäll, for physiological knowledge.

– This project is really a collaboration. When we combined our three specialties we had all the knowledge we needed on site. Adding the computer power at National Supercomputer Centre we fast became world leading in the field, Tino says.

The research group aims to extract blood flow data from CT images of the heart using image-based simulations. The goal is earlier and more accurate detection as well as improved management of cardiac diseases.

Simulation of blood flow in the whole heart has so far mainly focused on exploration in simplified 3D models and validation with in vivo measurements are few. Even though many forms of functional imaging data and modeling approaches are currently available, a gap persists between mode-



ling and experimental research.

– You need to have all the knowledge from simulation to clinical experience to succeed in creating something clinically useful. And you need to be able to communicate to combine technology with medicine, Tino explains.

They have bridged the gap by developing and evaluating an approach in which intracardiac flow fields are computed based on patient-specific high-resolution cardiac CT data. The heart is segmented at one cardiac phase, and advanced registration techniques are used to track the heart wall. Using computational techniques usually employed by the automotive or aerospace industry, detailed intracardiac and vascular blood fields are obtained.

– Recently we have showed that our 4D Flow CT method can produce blood-flow patterns that are qualitatively and quantitatively similar to the current reference standard 4D Flow MRI.

While 4D Flow MRI can obtain accurate intracardiac flow fields, the use of computer tomography data allows for studying patient groups that cannot be studied using magnetic resonance imaging. The high resolution also allows the simulated data to reveal processes that couldn't be studied before, like the coagulation of blood or the occurrence of turbulence in the blood flow.

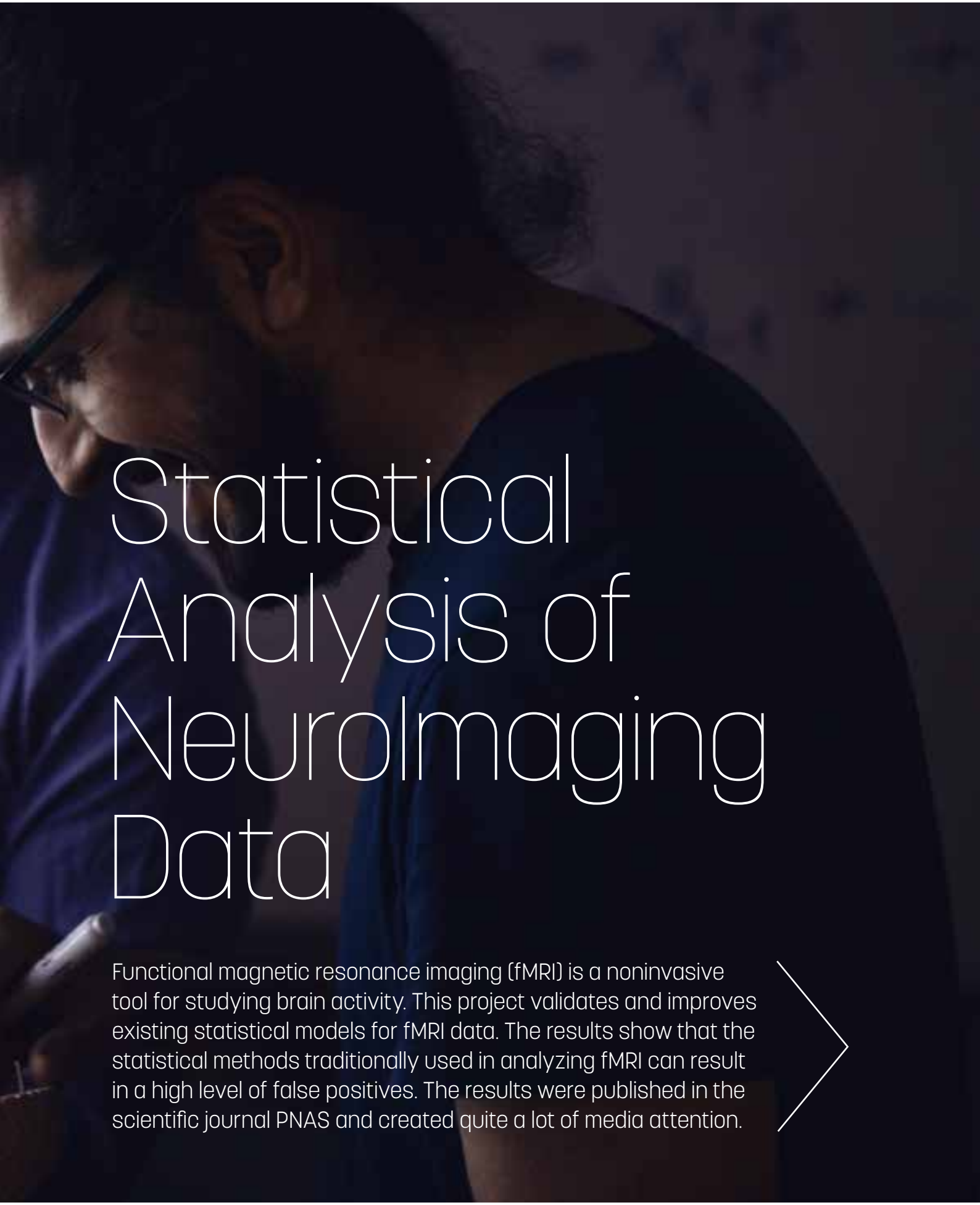
– One clinical application that we are exploring is in atrial fibrillation. The patients have an increased risk of blood cloths forming in the atrium and by migrating to the brain or coronary arteries they may induce a stroke or heart attack. We are building a model that can identify where the blood cloths are forming. The goal is that the information from our model may be used to identify patients at risk, Tino continues.

The simulation-based approach potentially allows for studies of what-if scenarios where different treatment options can be explored.

– With the CT data we can simulate what will happen if we change something. For example, if we simulate the exchange of a defect heart valve we can predict how it will affect the flow. This could be used to plan heart surgery in the future.

However, the heart is complex and adapts to changes. If the flow is inefficient due to a stenosis or a defect valve the heart will be enlarged to compensate. After a surgical intervention the heart will adjust to normal size. The model has to take this into account.

– The model is a simplified version of reality and we have to find a balance in how much information to include to come close enough to make it clinically useful, Tino concludes. ■



Statistical Analysis of NeuroImaging Data

Functional magnetic resonance imaging (fMRI) is a noninvasive tool for studying brain activity. This project validates and improves existing statistical models for fMRI data. The results show that the statistical methods traditionally used in analyzing fMRI can result in a high level of false positives. The results were published in the scientific journal PNAS and created quite a lot of media attention.

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, David Abramian

Grants
Swedish Research Council (2018–2021)
VINNOVA / ITEA3 IMPACT (2019–2021)
CENIIT (2018–2023)

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.
Cluster failure: why fMRI inferences for spatial extent have inflated false positive rates, Proceedings of the National Academy of Sciences (PNAS), 113, 7900–7905, 2016.

Eklund A, Knutsson H, Nichols T.
Cluster failure revisited: Impact of first level design and physiological noise on cluster false positive rates, Human Brain Mapping, 40, 2017–2032, 2019.

MRI
Neurology
AI/Data analytics

"I think that too few researchers are studying the actual method and how to analyze the data."

Anders Eklund

Functional magnetic resonance imaging (fMRI) is a popular tool for studying brain activity. It can non-invasively image the human brain without any ionizing radiation. The method can detect brain activity in correlation to tasks performed by the subject during the scan and is often used in neurology and psychology research.

From a statistical perspective, analyzing fMRI data is a challenging task for several reasons. One reason is that the noise created during the scan has a complex 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. Also, the MRI itself creates a variation of electronic noise.

– If you move your head it affects the magnetic field and that effect lingers for a while and does not only disturb the image in that moment but also the following images, says Associate Professor Anders Eklund.

Anders has one foot in biomedical engineering and the other in computer science with experience in fMRI method development, statistics and image analysis.

This project validates and improves existing statistical models for neuroimaging data. Most fMRI research projects use the method as a tool and does not reflect on the method itself.

– I think that too few researchers are studying the actual method and how to analyze the data. If everyone is analyzing their data with the same method and that method later on turns out to be wrong. Then a lot of studies will be affected.

Thinking about this Anders became more and more interested in how to analyze the data and how you can verify what is correct and what is not. This type of research requires large datasets where you can run multiple analyses on normal subjects.

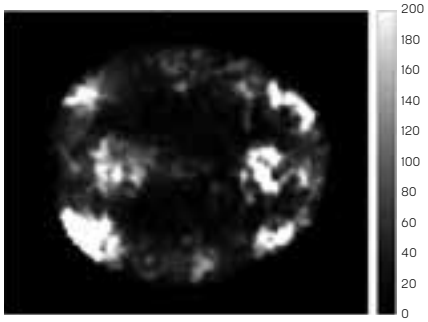
– We use open data available through data sharing. Even though we have great opportunities to scan and collect our own material at CMIV, it is very time consuming and expensive to scan 1000 subjects.

In this project Anders is collaborating with Mattias Villani who is a Professor in Bayesian statistics at Linköping University and Stockholm University. His background is in econometrics, analyzing economic time series.

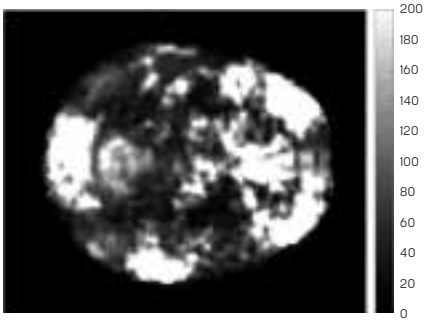
– In fMRI you have time series as well so we could apply most of the methods directly. After that the methods grew more and more advanced, Anders explains.

Another key player in the project is Professor Thomas Nichols from University of Oxford. He has long experience in neuroimaging statistics and became an important sounding board.

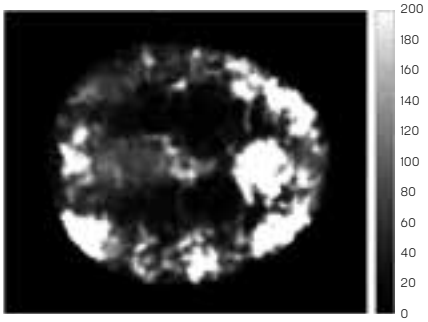
– I had plenty of time during my PostDoc for running all the analyses. Tom had a more pressed schedule but a lot of knowledge to contribute with. Despite communicating almost exclusively by email it turned out to be a perfect collaboration, says Anders.



Original fMRI data.



After cleaning the fMRI data with default ICA FIX.



After cleaning the fMRI data with retrained ICA FIX.

Anders and his colleagues found that the statistical methods traditionally used in analyzing fMRI can result in a high level of false positives. The results were published in the scientific journal PNAS and created quite a lot of media attention.

In a follow-up study the research group extended their work and responded to some of the questions and criticism the first article received.

– We previously showed that the non-parametric permutation test can perform better than commonly used parametric tests, as the permutation test is based on a lower number of statistical assumptions.

However, in a few cases even the permutation test produced invalid results.

– We investigated several ways to obtain nominal false positive rates, and finally discovered that physiological noise can disturb the group analyzes. To correctly model physiological noise requires monitoring of breathing and pulse during the fMRI experiment, Anders continues.

After eleven years of research on fMRI Anders is expanding his research into deep learning.

– I think that it is important not to get stuck in the same tracks for too long. The things I learn in my deep learning projects can give me inspiration for the fMRI research as well. That's also why my collaboration with Mattias Villani is so important. He brings other angles, coming from another field. ■

Research Projects

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

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, Peter Lundberg, Maria Engström, Tino Ebbers, Ebo de Muinck, Peter Johansson, Elna-Marie Larsson, Tobias Granberg

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

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2017 Jun;38(6):1096–1102.

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MRI
Cardiovascular
Neurology
Acquisition
Modeling
Visualization

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

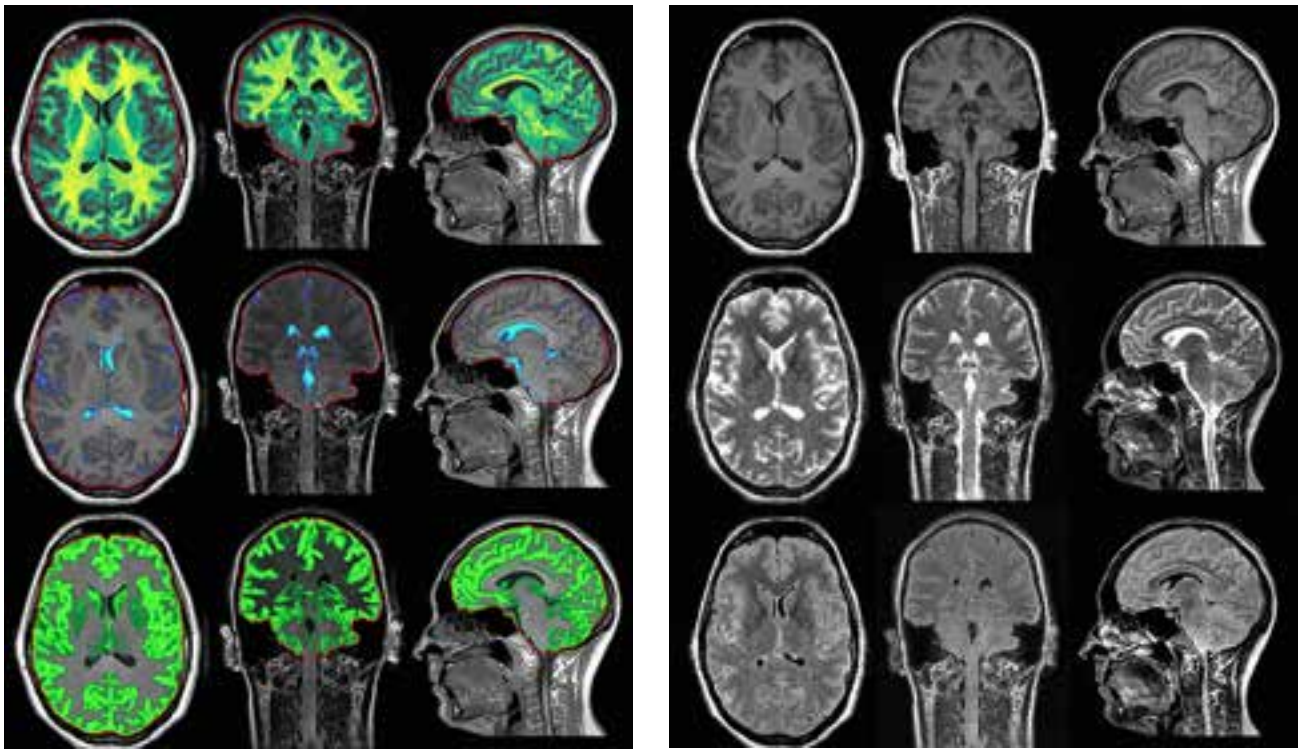


FIGURE. Example of synthetic MRI on a glioma patient, showing a T1W axial slice before and after administration of Gadolinium contrast media. The difference, caused by leakage of Gd through the blood-brain-barrier can be measured in absolute numbers, expressed as significance on the right side. These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

MRI
Cardiovascular
Acquisition
Modeling
Simulation

POPULAR SCIENTIFIC SUMMARY

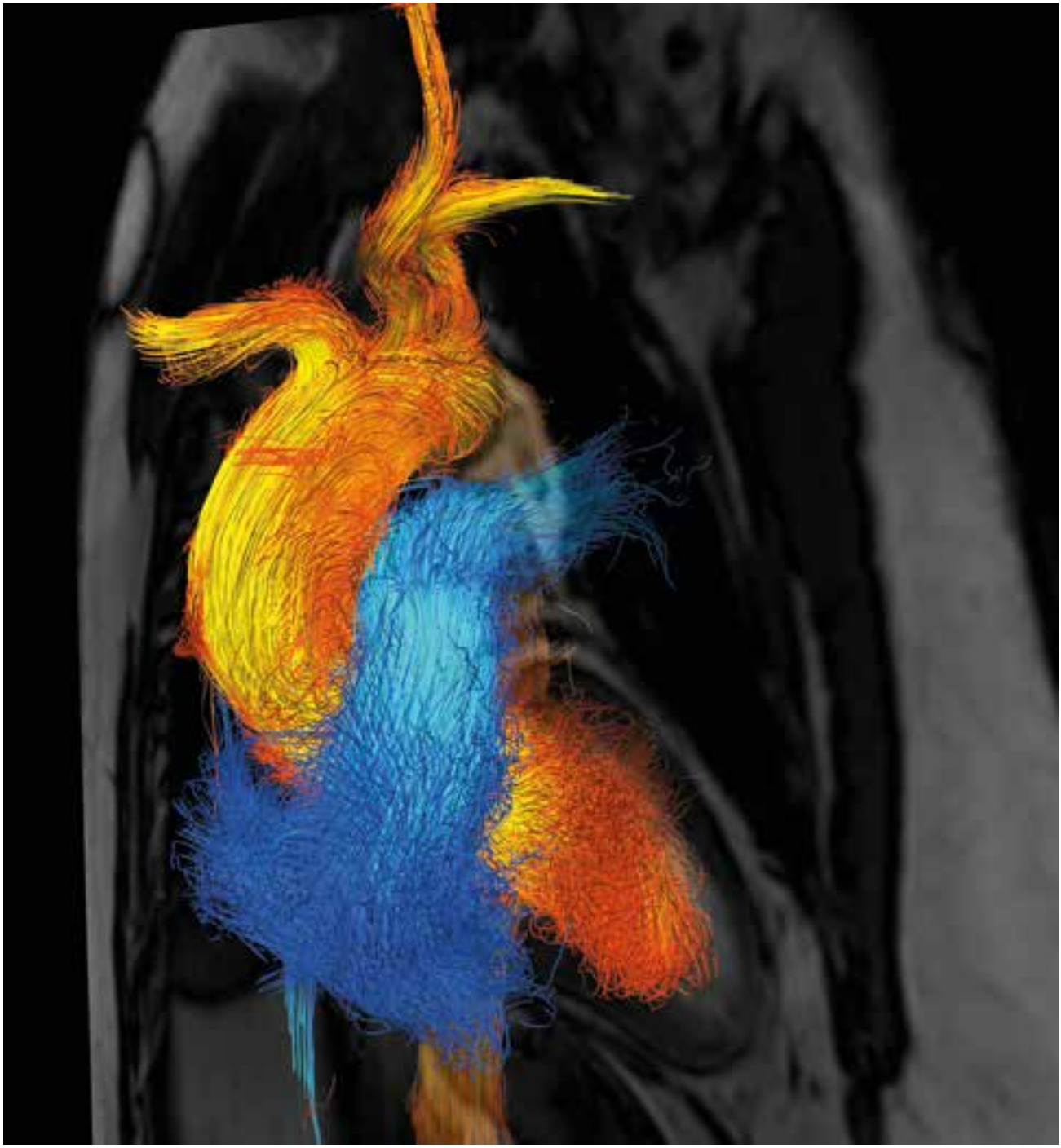
TINO EBBERS

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 with amazingly efficiency 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. ■

POPULAR SCIENTIFIC SUMMARY

PETTER DYVERFELDT & EBO DE MUINCK

Carotid Plaque Assessment

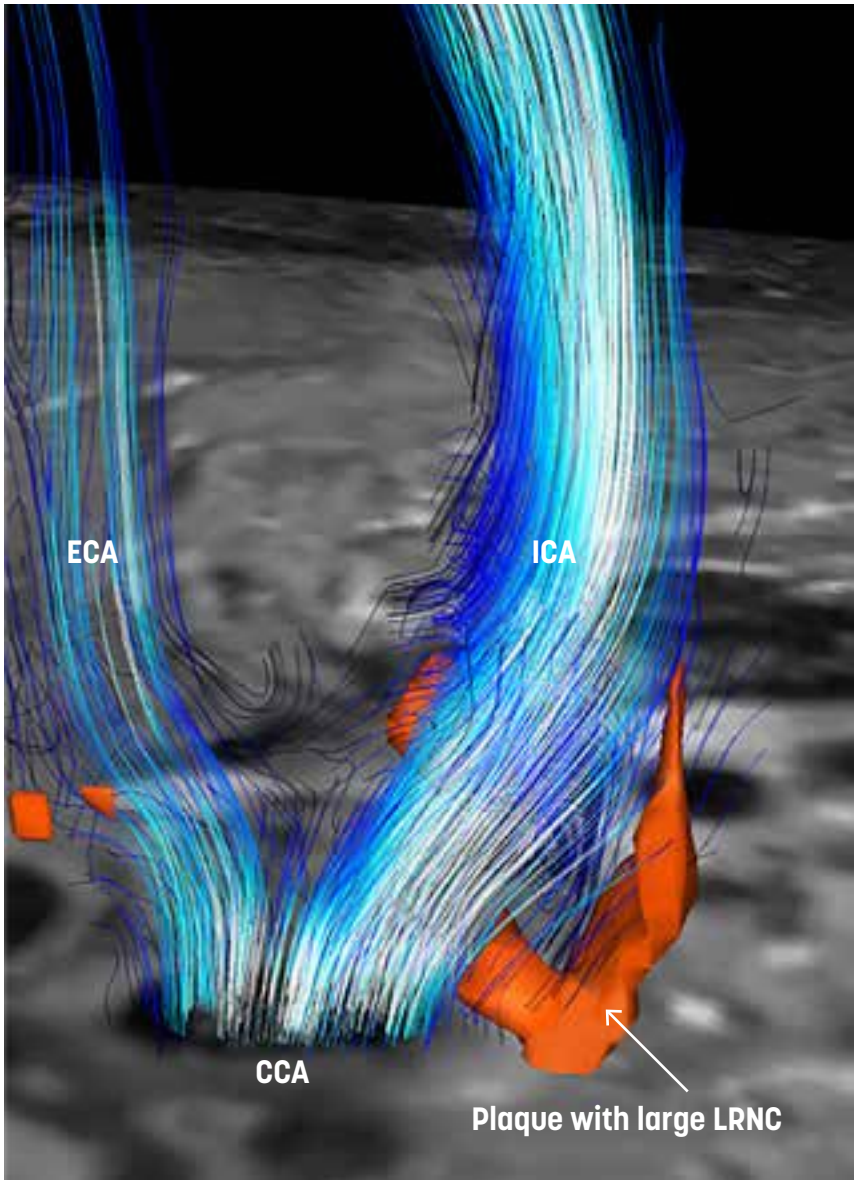
Worldwide, the most common cause of death is cardiovascular disease and the dominant cause of cardiovascular disease is atherosclerosis. A significant atherosclerotic plaque in the carotid increases the risk of future heart attack, stroke and cardiovascular death. This project develops methods for better risk assessment of carotid plaque by focusing on plaque composition and blood flow parameters rather than level of vessel constriction.

Atherosclerosis is caused by accumulation of fat, primarily cholesterol in the wall of the 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. The composition of the plaque is affecting the rupture risk. Plaque with a large amount of fat and blood are more prone to rupture. 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 rupture risk. Additionally, if there is stagnant 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.

The project develops tools for automated visualization and quantification of carotid plaque composition and hemodynamic effects on the vessel wall. This will be achieved by combining ad-



vanced 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 the 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.

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. ■

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
Miguel Ochoa Figueroa, Marcel Warntjes, Sandeep Koppal, Magnus Ziegler, Elin Good

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

Key publications

Koppal S, Warntjes 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.

MRI
Cardiovascular
Acquisition
Modeling

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, Marcus Lindenberger, Elin Good, Carl-Johan Carlhäll, Tino Ebbers, Ebo de Muinck

Grants
Swedish Research Council
FORSS

Key Publications
Ziegler M, Welander M, Bjarnegård N, Carlhäll CJ, Lindenberger M, Ebbers T, Länne T, Dyverfeldt P.
Visualizing and Quantifying Flow Stasis in Abdominal Aortic Aneurysms using 4D Flow MRI. Magnetic Resonance Imaging 2019; In press.

Ha H, Ziegler M, Welander M, Bjarnegård N, Carlhäll CJ, Lindenberger M, Länne T, Ebbers T, Dyverfeldt P.
Age-related vascular changes affect turbulence in the aortic blood flow.
Frontiers in Physiology 2018;9:36.

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), 2 310–2 319.

MRI
Cardiovascular
Acquisition
Modeling

POPULAR SCIENTIFIC SUMMARY

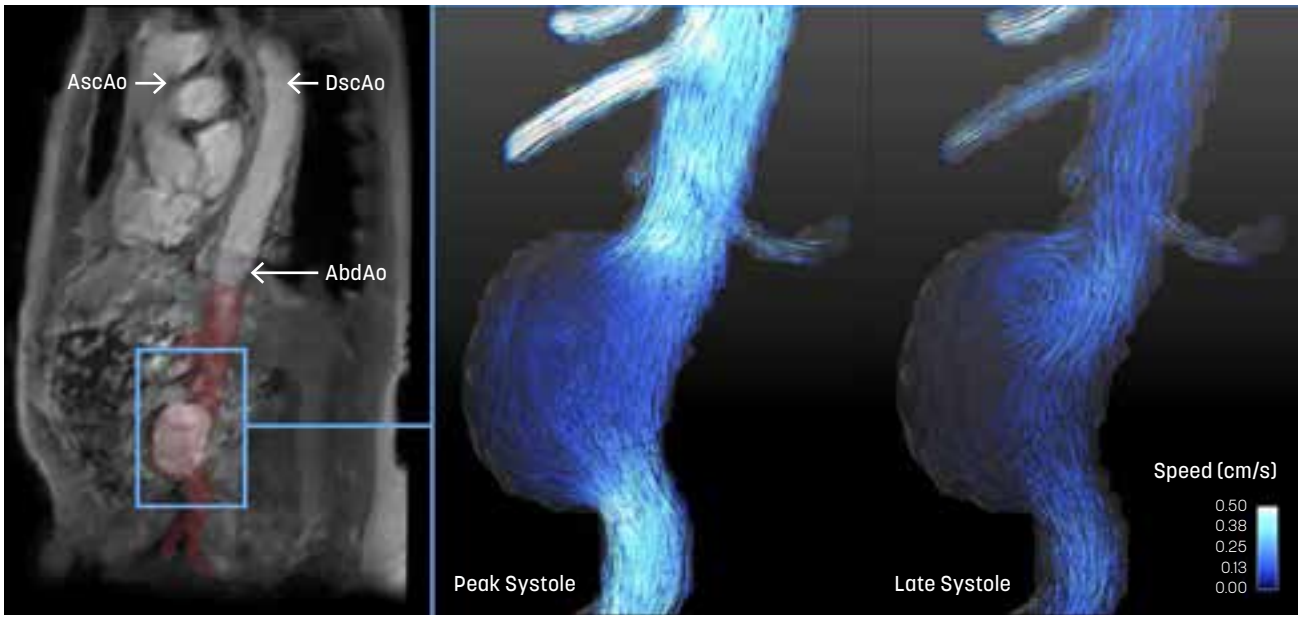
PETTER DYVERFELDT

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, Department of Medical and Health Sciences, Division of Cardiovascular Medicine
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

Pedrosa J, Queiros S, Bernard O, Engvall J, Edvardsen T, Nagel E, Dhooge J.
Fast and Fully Automatic Left Ventricular Segmentation and Tracking in Echocardiography Using Shape-Based B-Spline Explicit Active Surfaces. IEEE Trans Med Imaging. 2017 Aug 2. doi: 10.1109/TMI.2017.2734959. [Epub ahead of print]. PMID: 28783626.

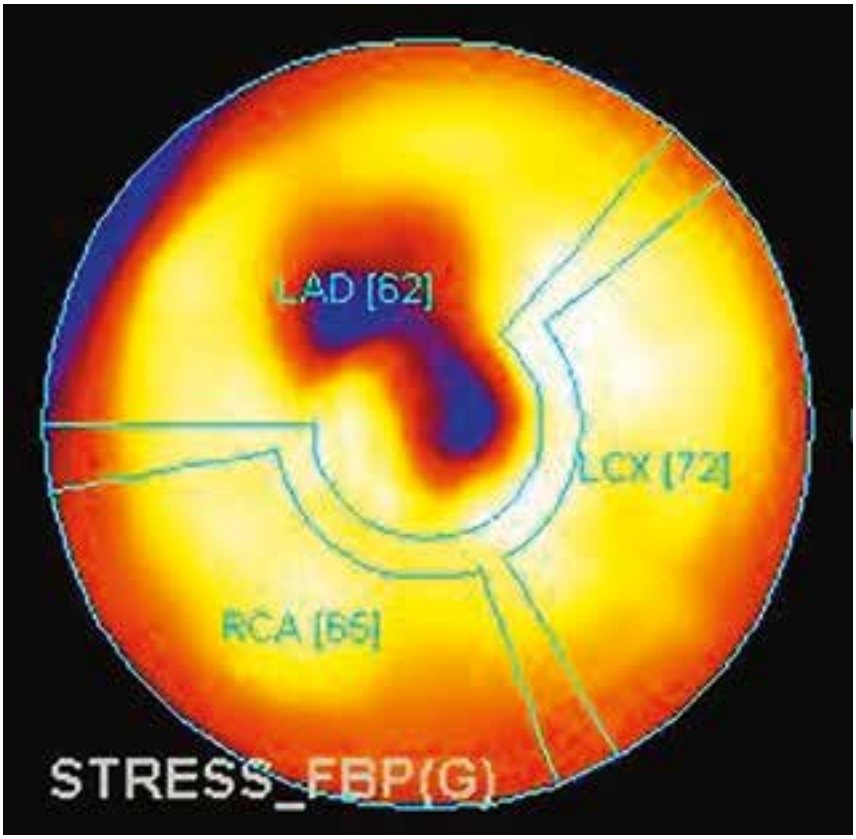
Myhre P, Omland T, Sarvari S, Rademakers F, Engvall JE, Hagve T, Sicari R, Zamorano JL, Monaghan M, D'Hooge J, Edvardsen T, Røsjø H on behalf of the DOPPLER-CIP Study Group. Cardiac Troponin T Concentrations, Reversible Myocardial Ischemia, and Indices of Left Ventricular Remodeling in Patients with Suspected Stable Angina Pectoris: a DOPPLER-CIP substudy. Clin Chem. 2018 Sep;64(9):1370-1379. doi: 10.1373/clinchem.2018.288894. Epub 2018 Jun 29. PMID: 29959147.

Bustamante M, Gupta V, Forsberg D, Carlhäll CJ, Engvall J, Ebbers T. Automated multi-atlas segmentation of cardiac 4D Flow MRI. Medical Image Analysis 2018; epub ahead of print. DOI: 10.1016/j.media.2018.08.003.

MRI
Cardiovascular

POPULAR SCIENTIFIC SUMMARY

JAN ENGVALL & TINO EBBERS

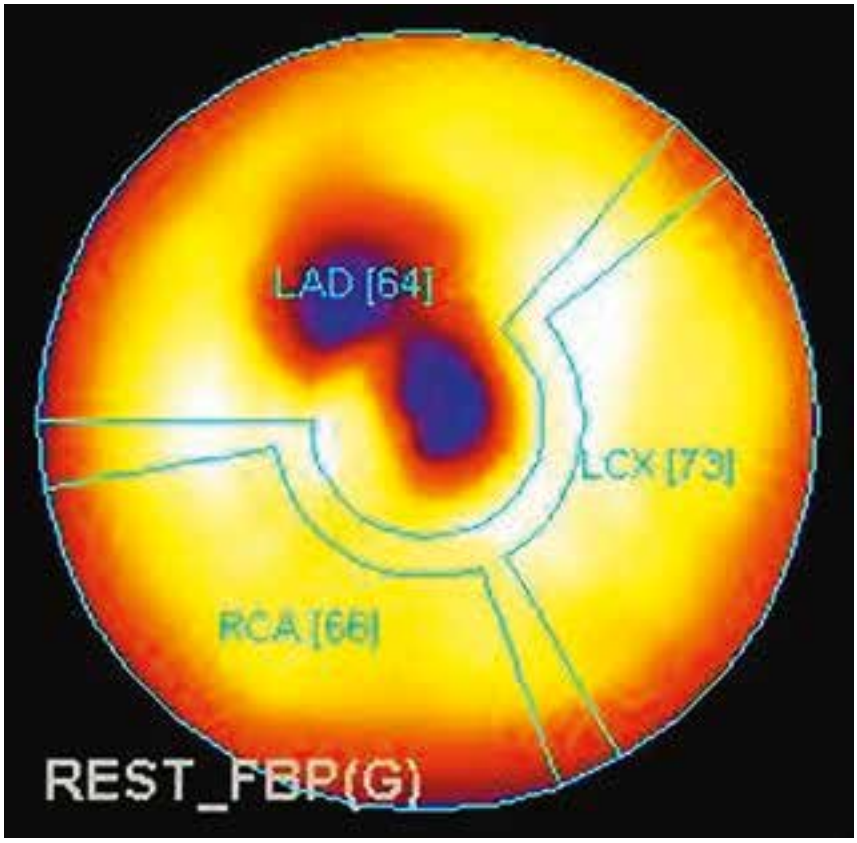


DOPPLER-CIP

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. ■

POPULAR SCIENTIFIC SUMMARY
JAN ENGVALL

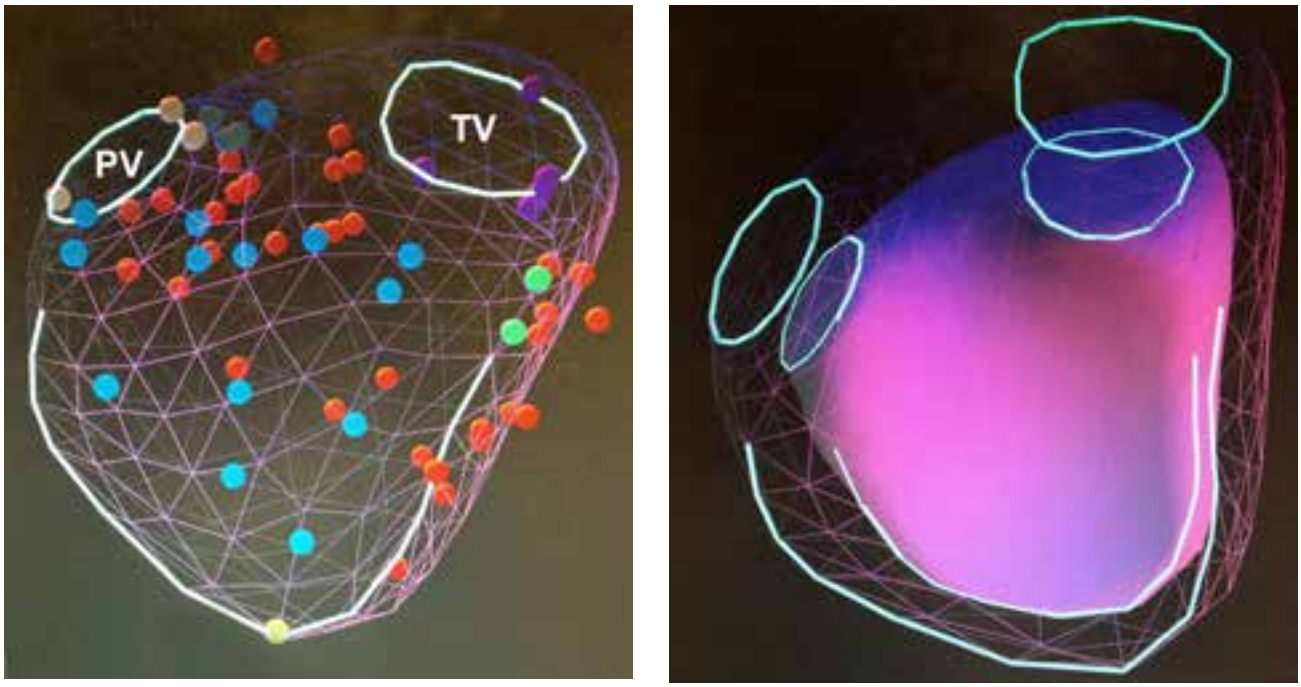


FIGURE 1. The image shows the initial reconstruction and the final result of a knowledge-based reconstruction.

TIMING

Congenital heart disease (CHD) is a global health problem. However, due to breakthroughs in the cardiovascular field over the last decades the survival of infants with CHD have increased. Today, most children with CHD survive to adulthood. However, these patients need lifelong treatment for their heart problems and often repeated cardiac surgeries.

Adult patients with CHD is now a relatively large patient group. Previously these patients had an increased risk of complications, but with improved surgical methods most patients can now expect a normal life span. CHD patients are a diverse patient group. They may suffer from one of several hundred different variants of heart disease, which contributes to the difficulty in researching them.

This project investigates methods to measure and characterize cardiac function in patients with CHD, mainly corrected Fallot, but also other severe conditions such as congenitally corrected transpositions with the anatomical right ventricle supporting the systemic circulation. During life, most of these patients will need to undergo repeated surgical procedures to replace heart valves and correct other problems. Some artificial heart valves need to be replaced after a number of years, and being able to predict when could mean

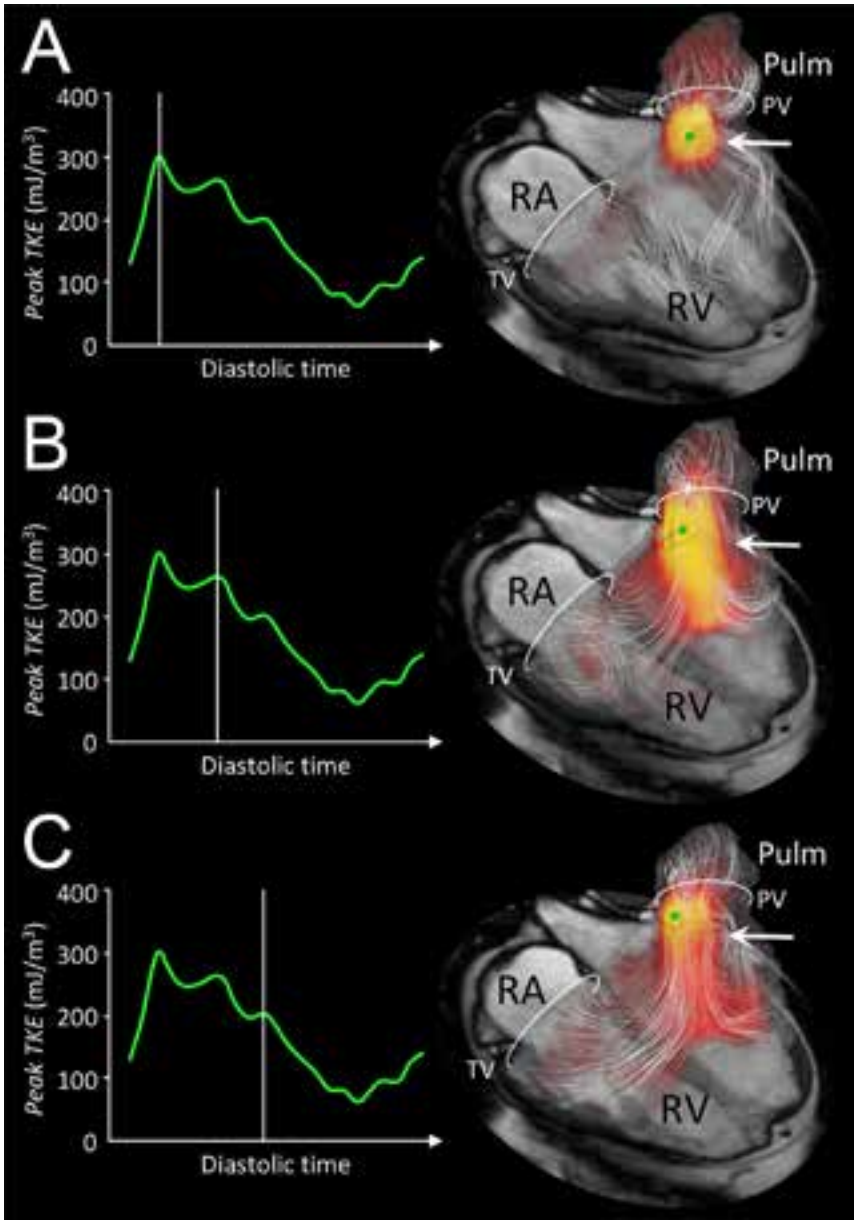


FIGURE 2. Image showing turbulence calculated at three diastolic time frames of the right ventricle (used by permission of the publisher Elsevier, J Magn Reson Imaging. 2018 Apr;47(4):1043-1053.

that operations are carried out at an optimal time and the number of operations that patients undergo during their lifetime would be fewer.

In total 80 patients have been screened and invited to participate in this study that has been ongoing since 2014.

The project involves the use of ultrasound 3D methods for calculation of volume and function compared to cardiac magnetic resocnance (CMR) used as a gold standard. The project has also provided new measures of intracardiac flow such as turbulence mapping of turbulent kinetic energy. As part of the project a collaboration with the university hospital in Utrecht resulted in an ultrasound study with »Knowledge-based reconstruction« (KBR). KBR uses multiple 2D slices acquired with a clinical 2D ultrasound scanner, stiched together using spatial information from a magnetic positioning system. ■

PROJECT INFORMATION

Project Name
TIMING

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

Main Project Participants
Aleksandra Trzbiatowska-Krzynska, Eva Swahn, Carl-Johan Carlhäll, Alexandru Fredriksson, Lars Wallby, Niels-Erik Nielsen, Petter Dyverfeldt, Tino Ebbers, Jan Engvall

Grants
Swedish Heart-Lung Foundation

Key publications

Fredriksson A, Trzebiatowska-Krzynska A, Dyverfeldt P, Engvall J, Ebbers T, Carlhäll CJ.
Turbulent kinetic energy in the right ventricle: Potential marker for risk stratification of adults with repaired Tetralogy of Fallot. J Magn Reson Imaging. 2018 Apr;47(4):1043–1053. doi: 10.1002/jmri.25830. Epub 2017 Aug 2.

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Trzebiatowska-Krzynska A, Driessen M, Sieswerda GT, Wallby L, Swahn E, Meijboom F.
Knowledge-based 3D reconstruction of the right ventricle: comparison with cardiac magnetic resonance in adults with congenital heart disease. Echo Res Pract. 2015 Dec 1; 2(4): 109-16 doi: 10.1530/ERP-15-0029.

MRI
Ultrasound
Cardiovascular
Modeling
Visualization

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, Fredrik Nyström, David Kylhammar, Meriam Åström Aneq, Lina Hult, Peter Blomstrand

Grants
KAW
Swedish Heart-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.

CT
Cardiovascular

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

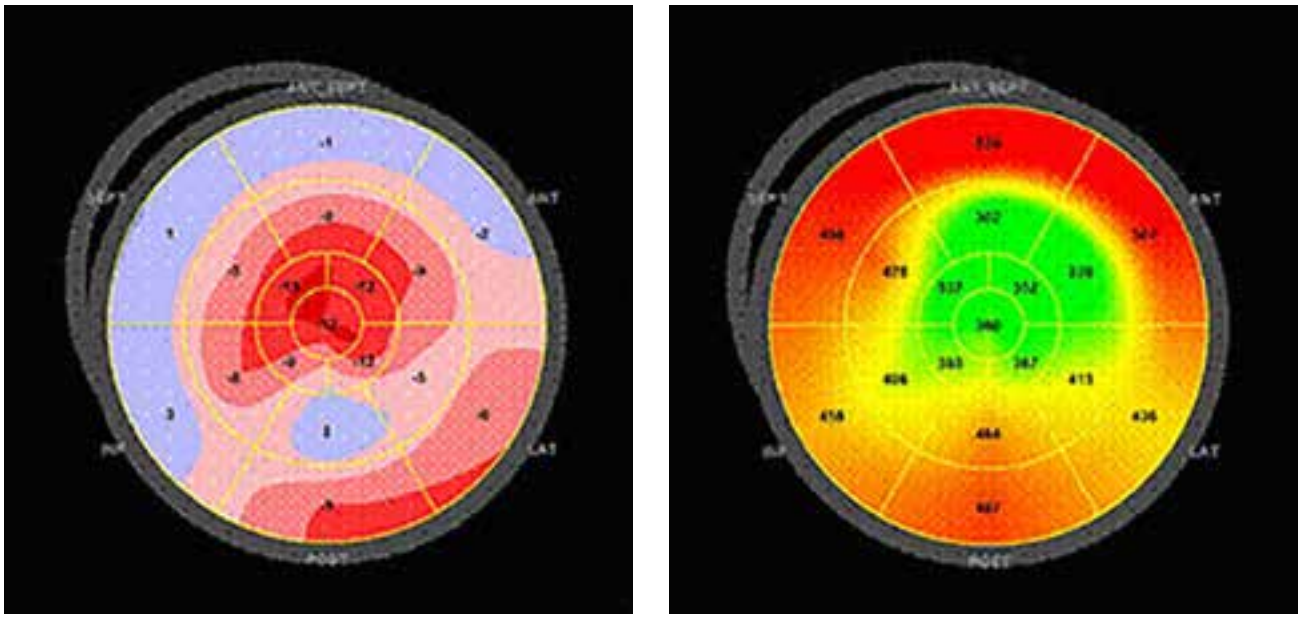


FIGURE. Polar plot representation of the amplitude of peak strain (left), time-to-peak strain (right) and the calculated standard deviation of peak strain, (red box right). The green area of the right polar plot shows normal temporal relationship between segments. The red basal area denotes mechanical 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, Fredrik Nyström, Jan Engvall, Eva Swahn, Markus Karlsson, Nils Dahlström, Bengt Norén, Amir Razavi, Wolf Bartholomä, Federica Viola, Petter Dyverfeldt

Grants
KAW
Swedish Heart-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.

MRI
Cardiovascular
Acquisition
AI/Data analytics
Imaging Biomarkers

POPULAR SCIENTIFIC SUMMARY

CARL-JOHAN CARLHÄLL

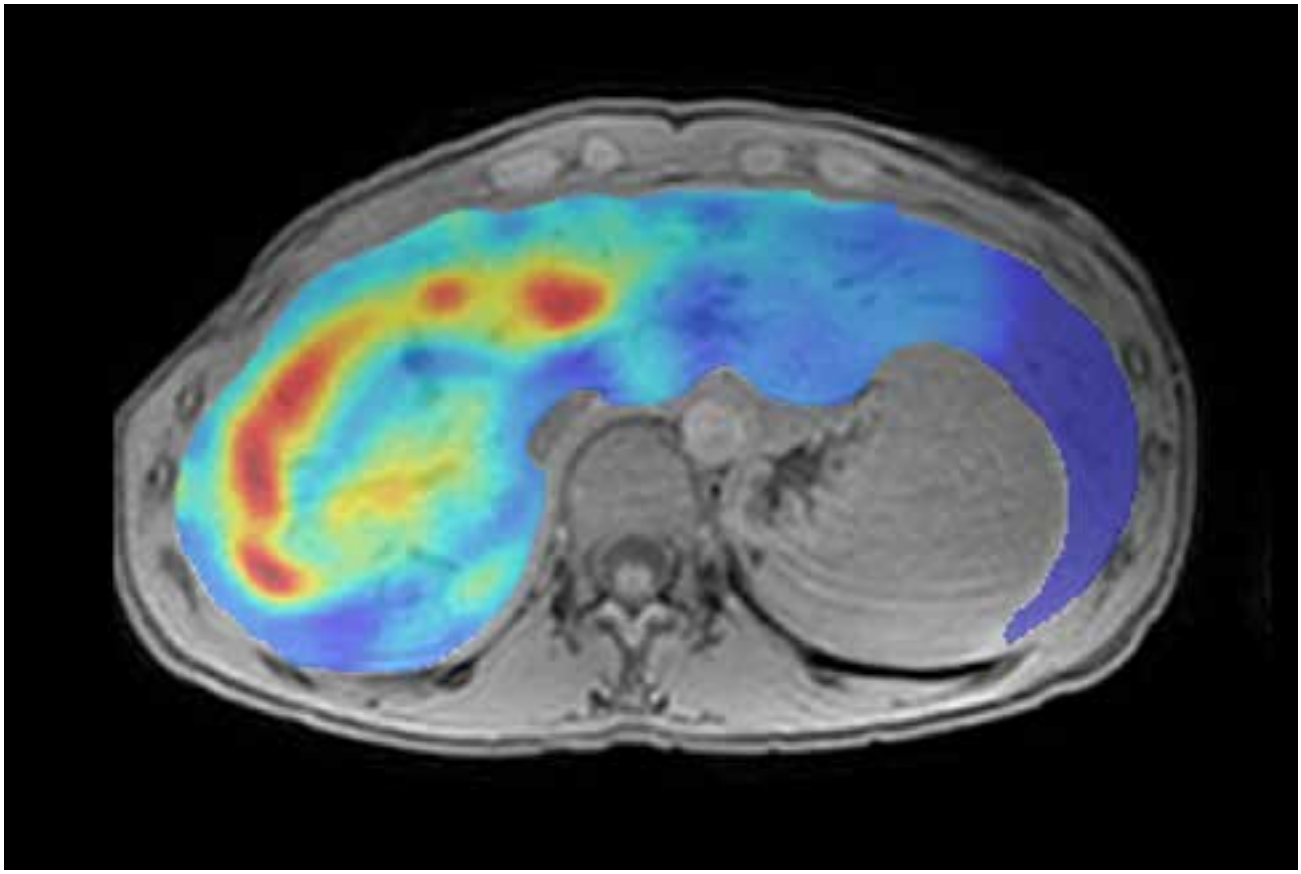
SCAPIS-Health

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

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.

MRI
Cardiovascular

POPULAR SCIENTIFIC SUMMARY

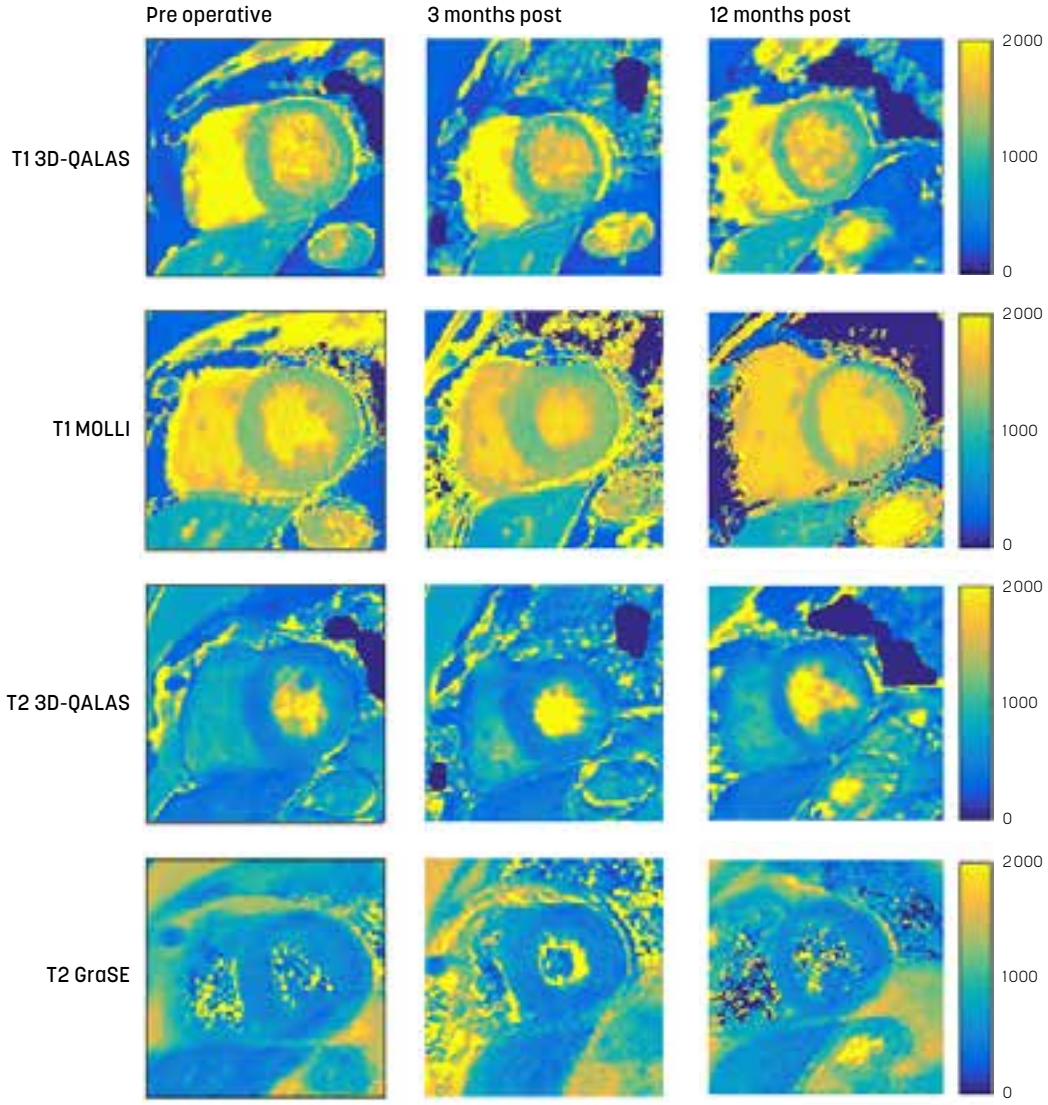
ÉVA TAMÁS

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
Eva Klintström, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Örjan Smedby, Rodrigo Moreno, Benjamin Klintström, Mischa Woisetschläger

Grants
VINNOVA/EuroStars 2015–2017

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.

Klintström E.
Image Analysis for Trabecular Bone Properties on Cone-Beam CT Data. Linköping: Linköping University Electronic Press; 2017. Linköping University Medical Dissertations, 1594.

CT
Musculoskeletal
Acquisition

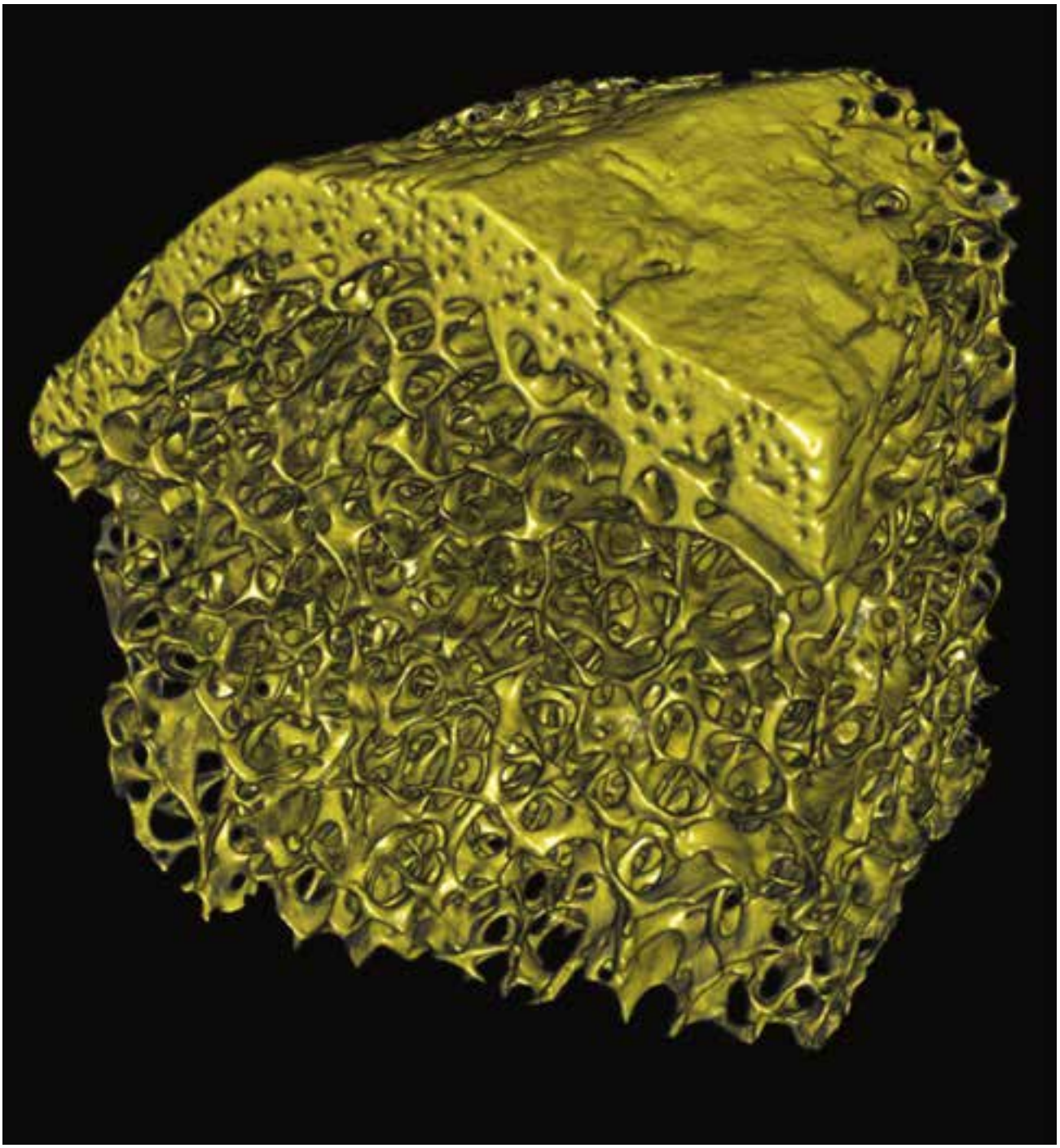
POPULAR SCIENTIFIC SUMMARY

EVA KLINTSTRÖM

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.

In collaboration with University of Iowa, analyzes of the data from the different CT and CBCT scanners are ongoing to evaluate the possibility for density measurements of the CBCT data.

A clinical study in collaboration with the Department of Endocrinology at Linköping University Hospital will start in March 2019.

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, Department of Clinical and Experimental Medicine, Division of Surgery, Orthopedics and Oncology

Main Project Participants
Marcus Malmqvist, Ludvig Vavruch, Håkan Gauffin

Grants
VINNOVA

Key Publications
Brink RC, Vavruch L, Schlösser TPC, Abul-Kasim K, Ohlin A, Tropp H, Castelein RM, Vrtovec T. Three-dimensional pelvic incidence is much higher in (thoraco)lumbar scoliosis than in controls. Eur Spine J. 2018 Aug 20.

Tropp H, Leivseth G, Berg S. Segemental motion after total disc replacement or fusion for discogenic lumbar back pain. J Orthop Res and Ther, 2018 in press.

Daghighi A, Tropp H, Dahlström N, Klarbring A, F.E.M. Stress-Investigation of Scolios Apex, The Open Biomedical Engineering Journal, Volume 12, (2018), 51–71.

CT
Musculoskeletal
Visualization

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

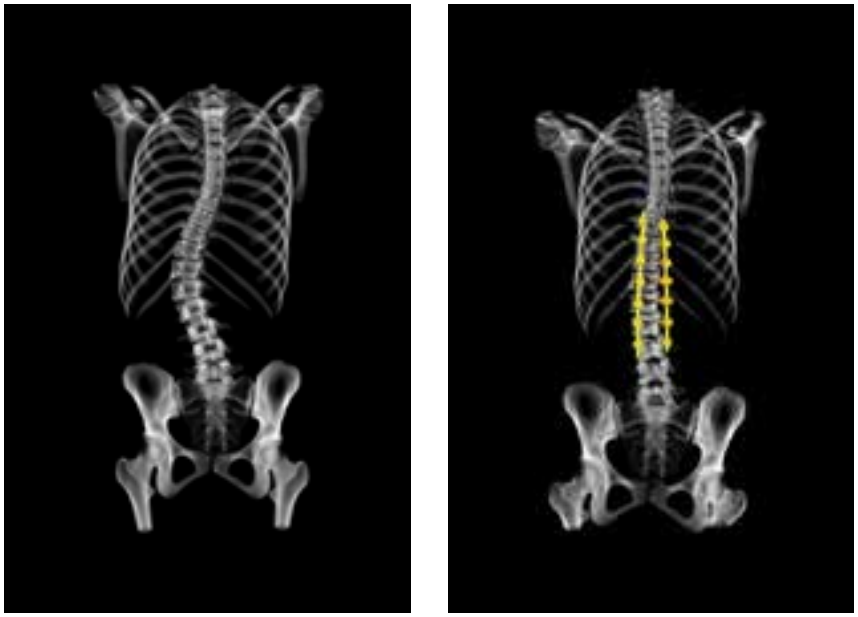


FIGURE 1. Posterior scoliosis correction.

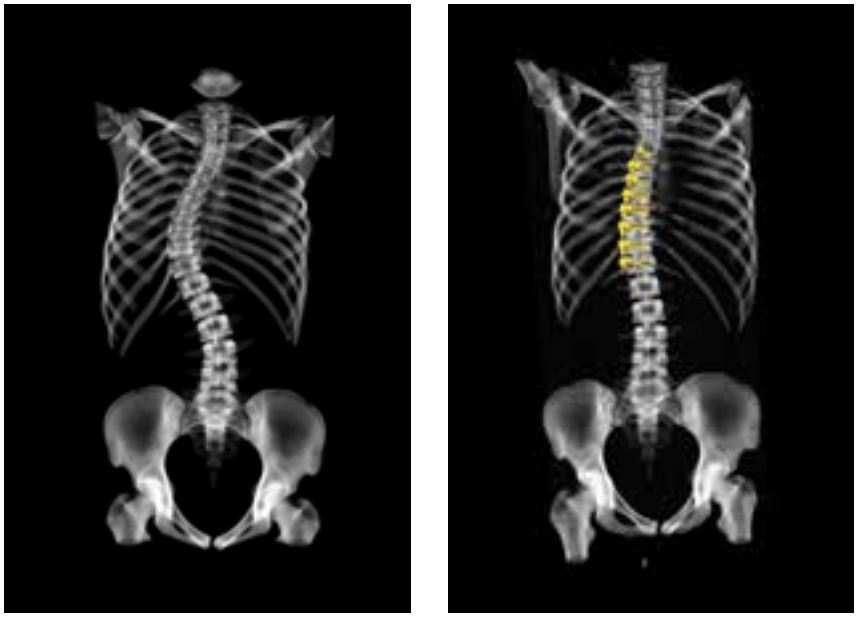


FIGURE 2. Anterior scoliosis correction.

is incapable of fully describe a spinal deformity.

On the other hand, the deformation is local, because each vertebra is individually deformed; for example, sagittal or coronal wedging can occur in each vertebra.

We study patients with idiopathic scoliosis and can use CT performed before and after surgical corrections. We include the pelvis in the examination which gives a possibility to study pelvic anatomy together with posture. The CT data is used for finite element analysis (FEM) of local loads as well as thoracic volume measurements. The vertebrae in idiopathic scoliosis show morphological changes and anterior overgrowth, probably due to »abnormal load upon a normal spine«. We compare the clinical and mechanical results after different methods for surgical corrections.

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 femuro-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.

MRI
Musculoskeletal
Gynecological
Metabolism

POPULAR SCIENTIFIC SUMMARY

MATS HAMMAR & MAGNUS BORGA

Health Effects of Exercise 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 thromboembolic 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. The results of the 15 weeks study have been analyzed as also the results from blood analyses on blood lipids and oxidative stress. A test-retest investigation has been performed with a number of MRI examinations performed twice.

The study has been prolonged 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 sedentary or less physically active. This prolongation of the study will go on until summer 2019 after which all analyses will be performed. ■

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

MRI
Gastrointestinal
Acquisition
AI/Data analytics
Simulation
Imaging Biomarkers

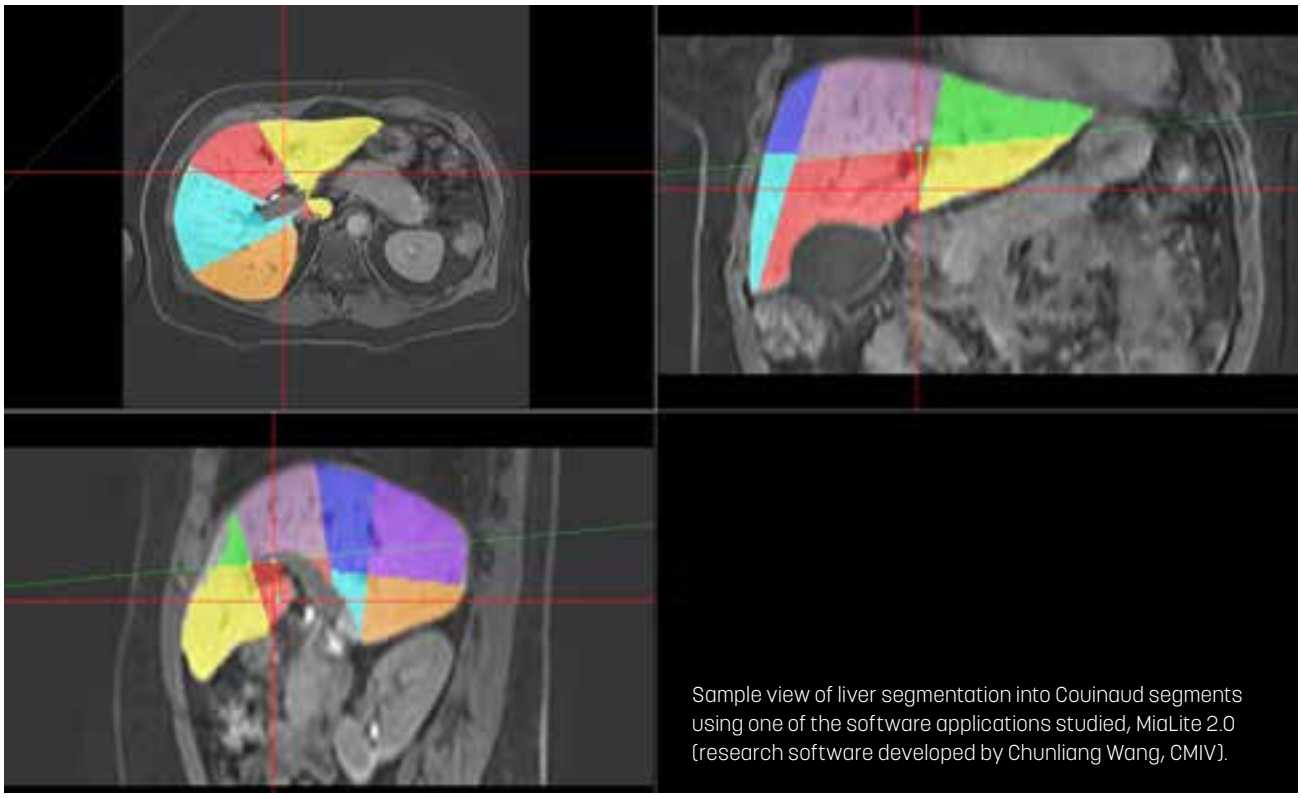
POPULAR SCIENTIFIC SUMMARY

NILS DAHLSTRÖM

Semiautomatic Liver Volume Determination and Segmentation

A common trait of diffuse liver diseases is that they may lead to the formation of fibrosis, inflammation and ultimately, cirrhosis. Since the liver can regenerate and thus compensate for some damage, liver diseases are often not discovered until 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. In developing system biology models for describing liver function, it is important to estimate the total liver volume and preferably also liver segment volumes. Although tools for liver segmentation using datasets from computed tomography have become easily available, useful applications aimed at MRI datasets are lacking. A sub-project within the Liver Function Evaluation project was



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).

formed to evaluate available software to measure 3D volumes of late hepatobiliary phase 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
RadSimCT: Simulation Based Training Program for CT Protocol, Iterative Reconstruction and Dual Energy

Project Leader
Anders Persson, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Alexandr Malusek, Nils Dahlström, Angie Liu, Filip Landgren, Peter Vorel

Grants
RSNA

Key publications
The RadSimCT Educational CT/DECT simulation software, www.radsimct.se

RadSimCT Linköping educational videos, www.youtube.com/channel/UCAZIWTAwZQEmDjSt-KaOTZw

CT
Gastrointestinal
Simulation

POPULAR SCIENTIFIC SUMMARY

ANDERS PERSSON

RadSimCT

Computed tomography (CT) scanning contributes to the largest portion of radiation in medical imaging, which calls for special attention to dose reduction in CT scanning. At the same time, prior studies have highlighted the lack of understanding of CT technologies, leading to high variability in CT protocols.

Several medical specialties including radiology have applied simulation-based training methods to improve learning and performance while improving safety of complex and sometimes life-saving procedures. In radiology, use of simulation techniques has been reported for interventional procedures and learning anatomy. Prior studies have demonstrated advantages of such simulation-based training over conventional didactic training.

The purpose of this research project was to develop and implement a web based educational tool for learning the principles of CT scanning in radiology. The tool allows users to set various scan parameters and instantly observe the effects of these changes. The result of this research, RadSimCT, is a vendor neutral simulation software which utilizes images from actual clinical CT examinations.

We believe that a simulation-based training of protocol optimization will enhance the caregivers (radiologists, physicists, technologists and in-training students) understanding of imaging protocols, dose reduction and optimization strategies. Our project has undertaken development of a simulation-based training software, based on real imaging CT data, for radiation optimization. The RadSimCT module include practical aspects of imaging parameters, radiation dose descriptors, image quality and dual-energy CT. The module contains both general and specific details that apply to all CT models from all major CT vendors. RadSimCT is a seamless bridge between the published resources and the practical implementation of optimal scanning practices.

The RadSimCT software has successfully been developed, validated and implemented in educational curricula. The software is now used in training of radiologists, technologists, physicists, and engineers in-training as well as in-practice at Linkoping University and there is inquiries from several other universities in Europe who want to use RadSimCT for both teaching and research projects. ■


RadSimCT
CT
DECT
Settings
About
Help
Load new series
C: 50, W: 500
Dose:7.62 mGy
190 keV
180 keV
170 keV
160 keV
150 keV
140 keV
130 keV
120 keV
110 keV
100 keV
90 keV
80 keV
70 keV
60 keV
50 keV
40 keV
Predicted CT-Value [HU]
1500
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500
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50
100
150
energy [keV]
Image 280 / 844
Patient: 20160219
Scatter Plot
Energy Dependence Plot
WW/WC
ROI
Point


RadSimCT
CT
DECT
Settings
About
Help
kV:
80
mAs:
203
Kernel:
Br36d-3
Mean: 109.35
StdDev: 22.61
Area: 323.19 mm²
C: 50, W: 500
Dose:4.16 mGy
kV:
150
mAs:
111
Kernel:
Br36d-3
C: 50, W: 500
Dose:3.47 mGy
Image 280 / 844
Patient: 20160219
Image 263 / 844
Patient: 20160219
Sync scroll
Load new series
WW/WC
ROI
Point
Load new series

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, Pantelis Gialias, Anna Rzepecka

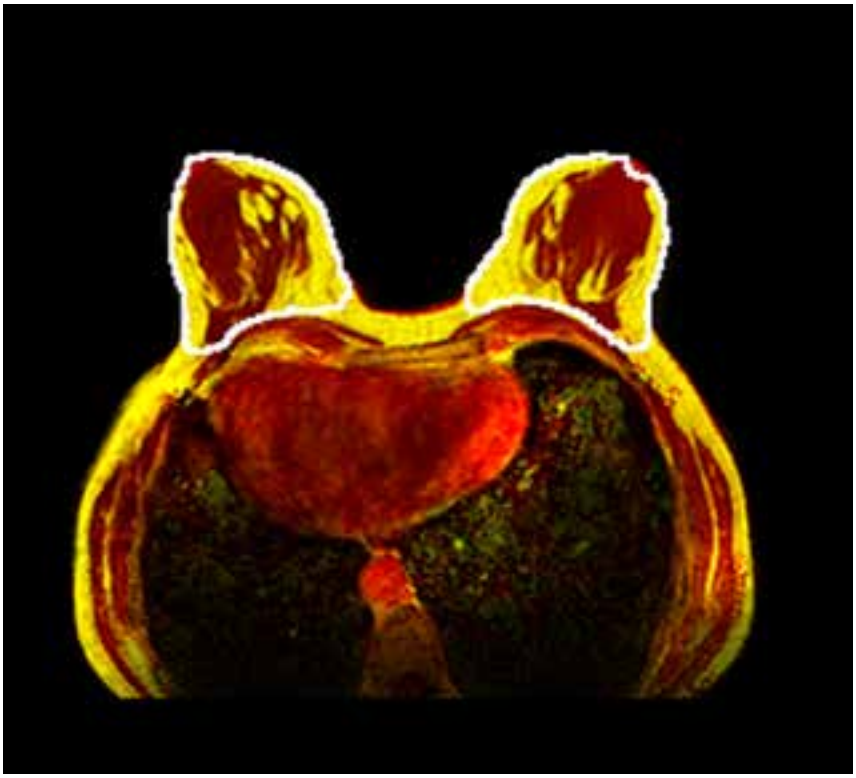
Grants
LiU-Cancer
The Swedish Cancer Society

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.

MRI
Oncology
Metabolism
Acquisition
Modeling
Imaging Biomarkers

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 regu-

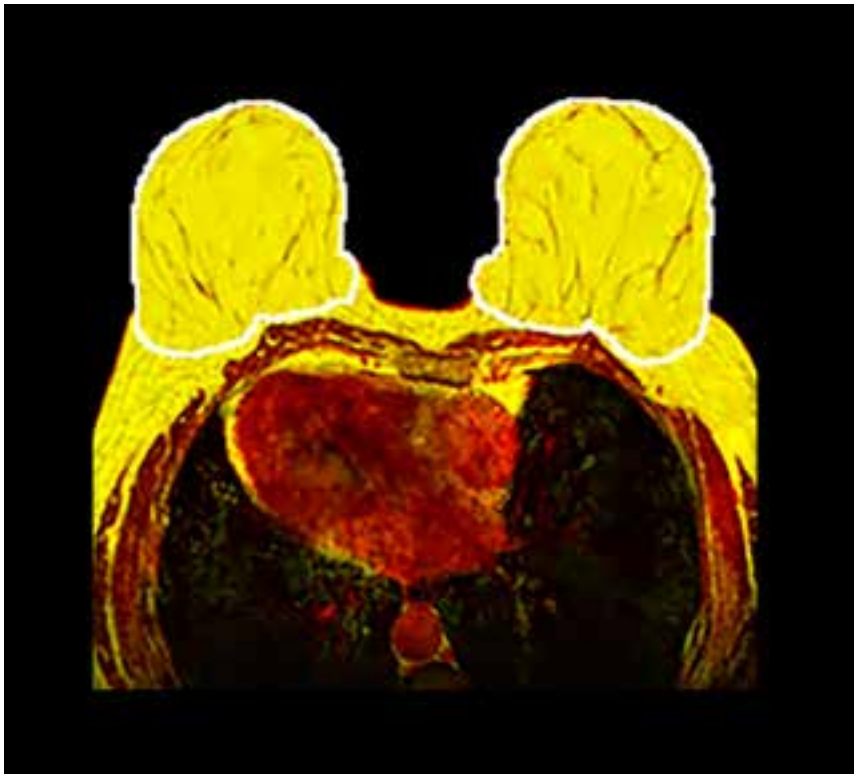


FIGURE. MR-quantification of lean tissue fraction in postmenopausal women attending the regular mammography screening program. The images are representative for dense (left) and non-dens (right) breasts.

larly use anti-inflammatory drugs.

Despite the wide use of mammography 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. ■

PROJECT INFORMATION

Project Name
Liver Function Evaluation

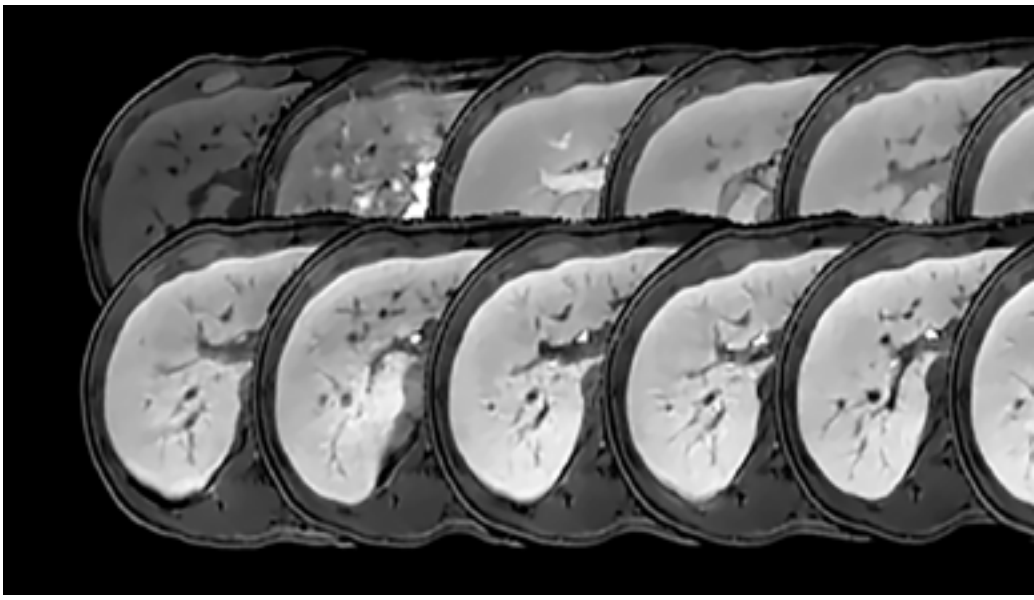
Project Leader
Peter Lundberg, Department of Medical and Health Sciences, Division of Radiological Sciences

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, Torkel Brismar, Martin Henriksson, Lars-Åke Levin, Wolf Bartholomä

Grants
VINNOVA 2013–2017
Swedish Research Council 2015–2018/2019

POPULAR SCIENTIFIC SUMMARY

PETER LUNDBERG

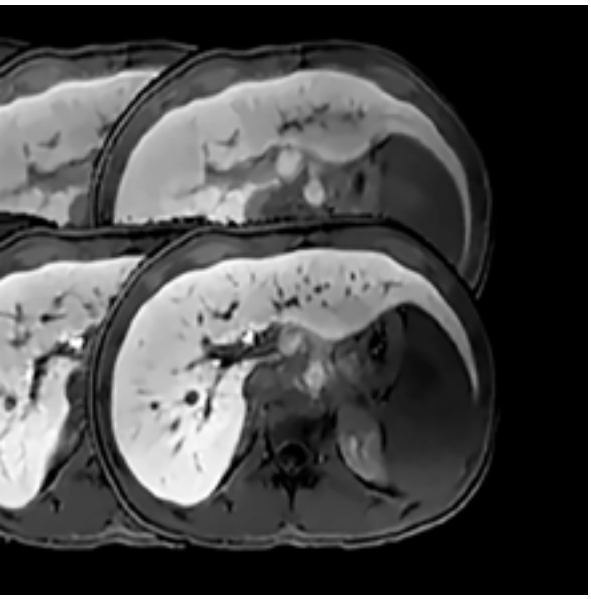


Liver Function Evaluation

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 better treatment of diffuse liver diseases and safer liver surgery.

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

Key Publications

Karlsson M, Ekstedt M, Dahlström N, Norén B, Forsgren MF, Ignatova S, Dahlqvist Leinhard O, Kechagias S, Lundberg P (2019).
Liver R2* is affected by both iron and fat: A dual biopsy-validated study of chronic liver disease. J Magn Reson Imaging. 2019 Jan 13. doi: 10.1002/jmri.26601.

Nasr P, Forsgren MF, Ignatova S, Dahlström N, Cedersund G, Leinhard OD, Norén B, Ekstedt M, Lundberg P, Kechagias S (2017).
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.

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).
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MRI
Digital Microscopy
Musculoskeletal
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POPULAR SCIENTIFIC SUMMARY

PETER LUNDBERG

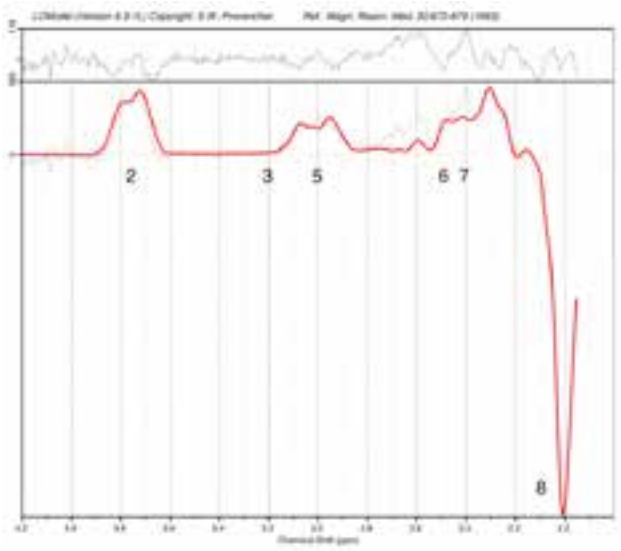
Detection and Neurological Effects of Manganese

Manganese (Mn) is a metal that occurs naturally in our environment. It is an essential substance that is part of several important enzyme systems for example it participates in body energy conversion and also protects against free radicals. Among the general population the food is the main source of exposure to manganese.

In working environment, exposure to manganese-containing dust and smoke occur mainly during welding, but also within the steel and smelting industry. Via inhalation of dust and smoke, manganese can be deposited in the respiratory tract where some is taken up and transported further into the body.

Manganese can pass the barriers that protect the brain and accumulate in specific areas of the brain, e.g. the basal ganglia. Welders examined with MRI have previously shown accumulation of manganese in the brain. When exposure is terminated, manganese is only gradually excreted and the concentration in the body is returned to natural equilibrium.

Workers that in their profession are exposed to high levels of manganese in the air (> 1 mg/m3) during a long period risk to be subject to manganism, a serious condition which is very similar to Parkinson's disease. Several studies have shown potentially harmful effects on the central nervous system such as influence on motor and cognitive functions, increased tremor and an in-



creased frequency of neuropsychiatric symptoms among groups of manganese exposed workers at significantly lower exposure levels than 1 mg/m3.

In many welding methods the air exposure is at levels where negative effects on the central nervous system have been demonstrated and there are indications that these effects may persist even when the exposure ceases. Compared to smelters, welders have much more manganese accumulated in the basal ganglia and thalamus and greater influence on neurological transmitter substances. This is despite the fact that traditional exposure measures such as the manganese concentration in air were 10 times lower for welders. The exposure form of manganese (particle size, and the chemical compound) therefore seems to have great significance for which areas of the brain are affected.

This project aims to investigate the effects of manganese accumulation primarily in the subcortical tissues and the cognitive effects thereof, in the brains of welders with certain types of occupational exposure. The protocol involves quantitative MR including spectral editing for detecting neurotransmitters, diffusion measurements and resting state fMRI. The complete project also involves a large range of occupational measurements including blood panels. ■

FIGURE. Spectral edited spectrum of brain which have been analyzed quantitatively using a linear combination of model compounds (LCModel).
Assignments: 2, Glx (-2CH-); 3, Choline (-N(CH3)3); 5, GABA+ (-4CH2-); 6, tNA (-3CH2-); 7, Glx (-4CH2-); 8, tNA (-2CH3).
Abbreviations: Glx, glutamate+glutamine; GABA+, γ-Aminobutyric acid (+macromolecule signal); tNA, total N-acetylaspartate (NAA + NAAG).

PROJECT INFORMATION

Project Name
Detection and Neurological Effects of Manganese (Mn) in the Brain of Welders and Other Subjects

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

Main Project Participants
Anders Tisell, Sofie Tapper, Ida Blystad, Per Thunberg, Karin Åberg, Göran Lidén, Karine Elihn, Gunilla Wastensson, Bernt Bergström, Louise Fornander, Göte Mölleby

Grants
FORTE

MRI
Neurology
Acquisition
Imaging Biomarkers

PROJECT INFORMATION

Project Name
Investigating Neurological Disease Using Amino Proton Transfer Chemical Exchange Saturation Transfer (IndCEST)

Project Leader
Anders Tisell, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Peter Lundberg, Ida Blystad, Maria Kristoffersen Wiberg, Annika Malmström, Munila Mudaisi, Pia Sundgren, Linda Knutsson, Marcel Warntjes

Grants
Strategic Cancer Research

Key publications
Blystad I, Larsson E-M, Smedby Ö, Lundberg P, Warntjes M, Tisell A, Cedersund G, Lundberg P (2018). qMRI using relaxometry detects non-visible peritumoural contrast enhancement in malignant gliomas, ECR (Vienna, Austria).

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Warntjes M, Dahlqvist O, West J, Lundberg P (2008). Rapid magnetic resonance quantification on the brain: Optimization for clinical usage, Magn Reson Med, 60: 320–329.

MRI
Neurology
Oncology
Acquisition
Imaging Biomarkers

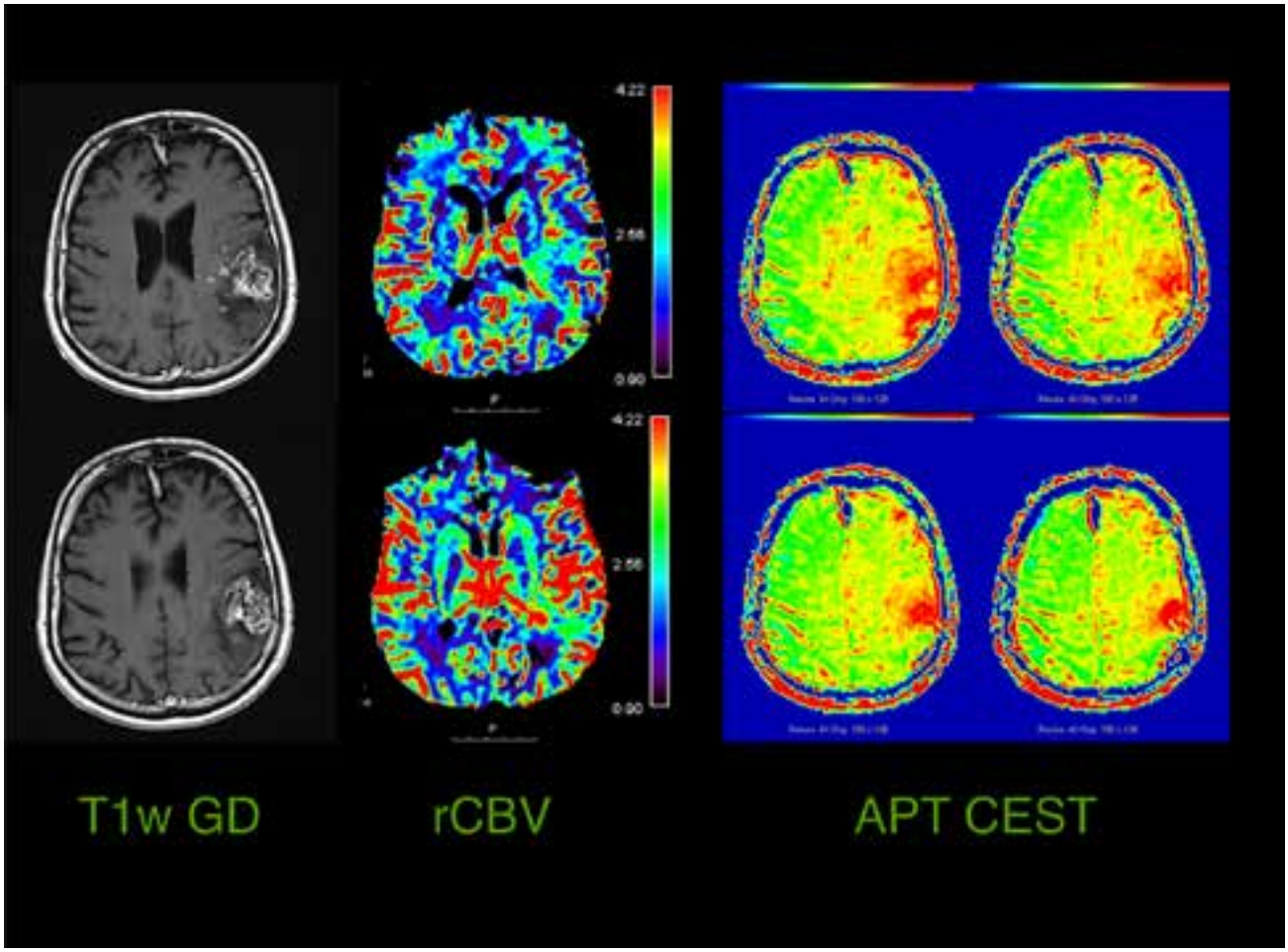
POPULAR SCIENTIFIC SUMMARY

ANDERS TISELL

Investigating Neurological Disease Using APT-CEST

Standard treatment for a high-grade brain tumor glioblastoma consists of radical surgical resection, by combined radiation- and chemotherapy, followed by adjuvant chemotherapy with temozolomide. Despite this, tumor recurrence is expected in these patients, and the median survival is therefore only 15 months. Moreover, up to 30 % of the patients develop 'pseudoprogression' due to a treatment-related effect from chemo- and radiation therapy that mimics tumour recurrence on conventional MRI.

Pseudoprogression is often correlated with an effective treatment response, and confirms that the planned adjuvant chemotherapy should be continued. In contrast, true tumour progression requires a change in therapy. Histopathological analysis is the gold standard for correct diagnosis. However, this will require a biopsy of the suspected lesion, which increases both morbidity and mortality, apart from increased healthcare costs for the treatment. Thus, the need for a reliable non-invasive imaging method for distinguishing pseudoprogression



from tumor progression is essential.

One promising novel method is »Chemical Exchange Saturation Transfer« (CEST) imaging, a new MRI contrast approach in which natural compounds containing exchangeable protons are selectively saturated.

CEST is a merge of MR-Spectroscopy (MRS) and MRI (Imaging), whereas quantitative MRI (qMRI) is a pure imaging technique. Following frequency specific saturation, selective saturation of magnetization is transferred, and subsequently detected indirectly via the water signal with a greatly enhanced sensitivity. This indirect and amplified detection of a tumor associated molecular species can be used to increase spatial, or temporal resolution of the imaging experiment. Thus, »Amide Proton Transfer-CEST« (APT-CEST) can potentially be used as an imaging biomarker for distinguishing pseudo-progression from true progression in glioma patients. The aim of this project is therefore to determine if APT-CEST, separately, or in combination with qMRI, is able to distinguish tumour recurrence from pseudo-progression. ■

FIGURE. Glioma progression detected using APT-CEST.

POPULAR SCIENTIFIC SUMMARY

ANDERS TISELL

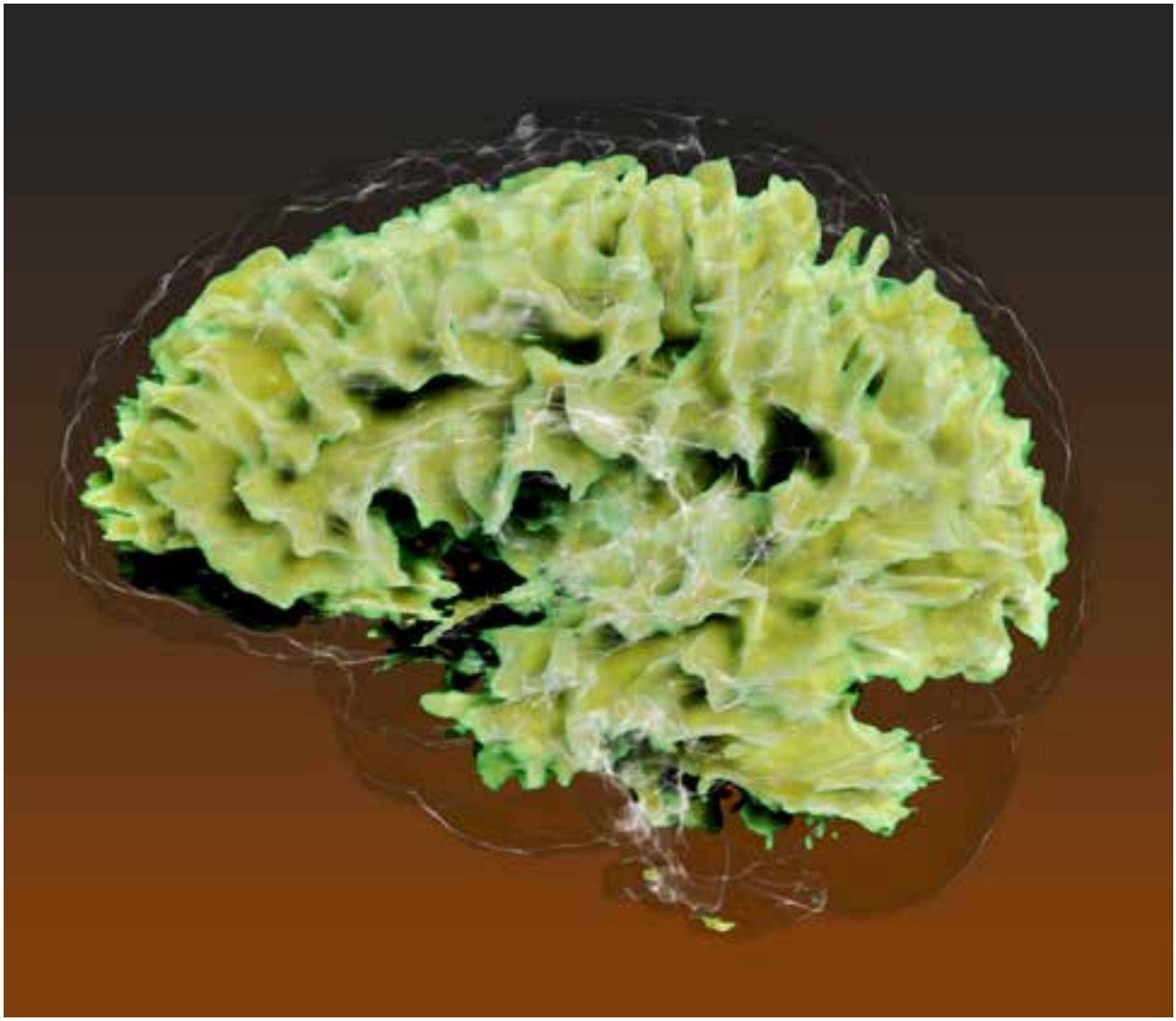


FIGURE. 3D MYELIN MAP (of human brain). Whole brain quantification of myelin using a 3D QALAS 3rd generation qMRI-brain technique in combination with 3D visualization.

SouthEast Sweden Neuro-inflammation Cohort (SESNIC)

Multiple Sclerosis (MS) is a chronic autoimmune disease in the central nervous system (CNS). MS often appears in young adulthood and lead to lifelong consequences for the individual, family and society.

This complex disease has both inflammatory and degenerative features even at early stages and the clinical picture may vary substantially between patients and over time. A well-known aspect of the disease is that it develops long before symptoms show and it is likely that the brain initially has a better capacity to compensate for pathological changes than in later disease stages. Accordingly, early treatment has shown to be crucial for long-term prognosis.

There are an increasing number of immunomodulatory treatments available for inflammatory active MS, but guidelines on how these potent therapies should be used are often lacking as are data on long-term outcome and side-effects of these drugs.

Taken together, there is consequently a need for reliable non-invasive methods to describe MS pathology in more detail and to develop and evaluate novel imaging biomarkers for prognosticating the disease course and monitoring treatment.

MS brain lesions cannot be detected by conventional non-quantitative MR. This advocate a shift from conventional MRI to the use of more advanced MR-methods including quantitative MRI methods (qMRI) like magnetic resonance spectroscopy (MRS). qMRI can be used for volume determination of grey and white matter, cerebrospinal fluid (CSF) and automatic lesion measurements in MS. Such accurate measures are critical when determining the overall atrophy of the brain. More specifically, qMRI can be used to create myelin concentrations maps that may be useful in determining the level of disease progression, at a regional or global level.

We have developed a suitable mathematical model for mapping myelin, based on our time-efficient qMRI-technique. In addition, qMRS has been developed further also for mapping the concentrations of neurotransmitters such as GABA (inhibitory) and glutamate (Glu) (excitatory), although further developments and validation are required.

The MR methods used in this project are combined with extended blood and CSF profiles for determining tissue degradation products and immunological parameters. A better definition of pathogenic mechanisms may characterize subtypes of MS and identify new targets for both prediction and treatment. ■

PROJECT INFORMATION

Project Name
SouthEast Sweden Neuroinflammation Cohort (SESNIC)

Project Leader
Anders Tisell, Department of Medical and Health Sciences, Division of Radiological Sciences

Main Project Participants
Johan Mellergård, Peter Lundberg, Jan Ernerudh, Ida Blystad, Kaj Blennow, Irene Håkansson, Bob Olsson, Charlotta Dahle, Magnus Vrethem, Daniel Jönsson, Marcel Warntjes, Maria Engström, Janne West

Grants
Swedish Research Council

Key publications
Mellergård J, Tisell A, Blystad I, Gronqvist A, Blennow K, Olsson B, Dahle C, Vrethem M, Lundberg P, Ernerudh J (2017). Cerebrospinal fluid levels of neurofilament and tau correlate with brain atrophy in natalizumab-treated multiple sclerosis. Eur J Neurol 24: 112–121.

Warntjes M, Engstrom M, Tisell A, Lundberg P (2016). Modeling the Presence of Myelin and Edema in the Brain Based on Multi-Parametric Quantitative MRI. Front Neurol 7: 16.

West J, Blystad I, Engstrom M, Warntjes JB, Lundberg P (2013). Application of quantitative MRI for brain tissue segmentation at 1.5 T and 3.0 T field strengths. PLoS One 8: e74795.

MRI
Neurology
Acquisition
Imaging Biomarkers

PROJECT INFORMATION

Project Name
The Neurocorrelates of Meditative Practice

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

Main Project Participants
Maria Engström

Grants
FORSS
Alzheimerfonden

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

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

MRI
Neurology
Acquisition
Modeling

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 does not 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-

FIGURE. 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.

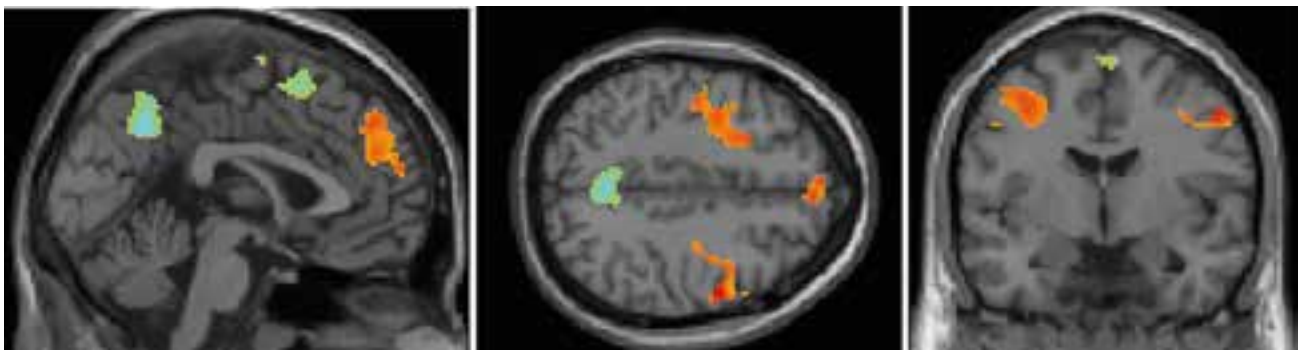

FIGURE. Activations in the default mode network for meditators during rest alone.

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
Natasha Morales Drissi, Thobias Romu, Anne-Marie Landtblom, Attila Szakács, Tove Hallböök, Niklas Darin, Magnus Borga, Olof Dahlqvist Leinhard, Maria Engström.
Unexpected fat distribution in adolescents with narcolepsy. Frontiers Endocrinology, 2018;9:728. doi: 10.3389/fendo.2018.00728.

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.

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POPULAR SCIENTIFIC SUMMARY

MARIA ENGSTRÖM

Sleep Abnormality Network Description

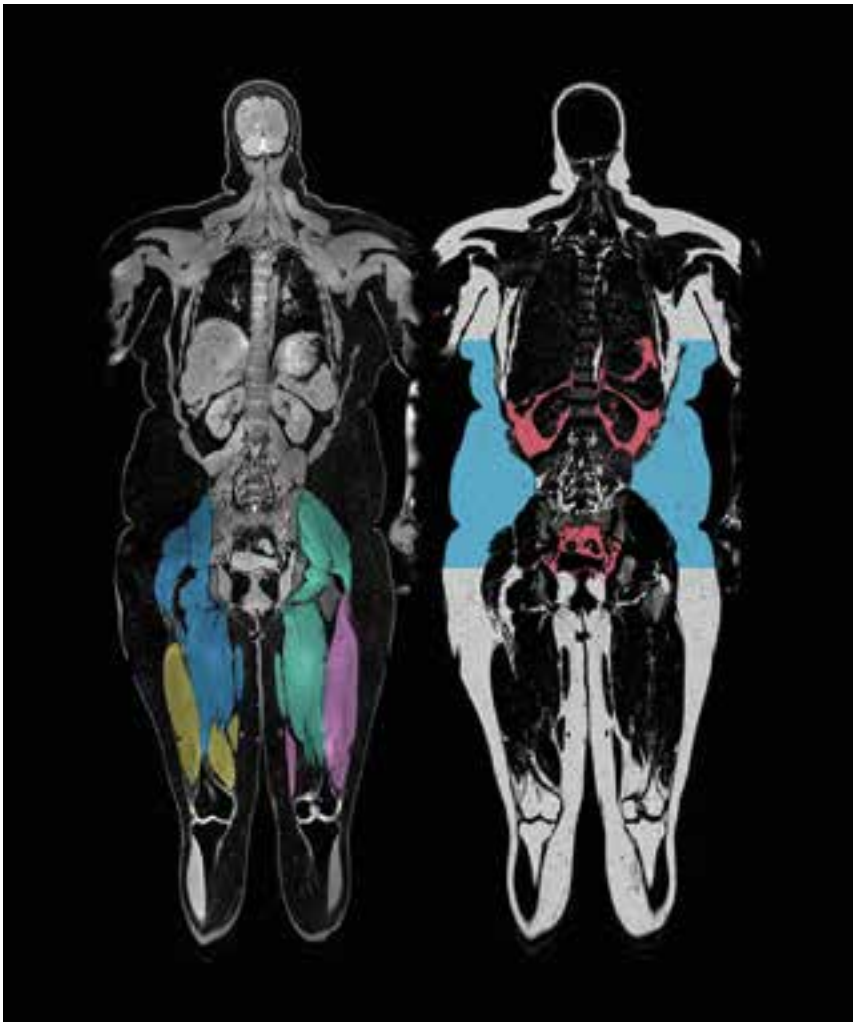

FIGURE 1. Body muscle and fat visualisation. The left image shows segmented tight muscles and the right image shows belly fat where inner fat is red and subcutaneous fat is blue.

In this project, we investigate brain function in patients with sleep disorders. The present study is about brain function and structure 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 a specific neurotransmitter called orexin, that takes part in the regulation of sleep and wakefulness, and also body metabolism. Orexin deficiency is therefore 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 wakeful 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 in cognitive resources manifested by decreased activation of the default mode network. This is pointing to a dysregulation within the sustained attention system, which could be the origin behind self-reported cognitive difficulties in narcolepsy.

In line with previous reports we recently showed that narcolepsy patients had more belly fat compared to their healthy controls (Figure 1). However, we also found that they had lower ratio between inner fat and total belly fat indicating a relative increase of subcutaneous fat. This relationship between inner and subcutaneous fat has been associated with a lower risk for metabolic disease.

Preliminary data (submitted manuscript) from quantitative MRI show structural changes in the brain stem's reticular formation in patients with narcolepsy. Figures 2A-D show areas with lower R2 relaxation rate, a finding that could be related to lower levels of neuromelanin in the locus coeruleus of narcolepsy patients. We also observed that the R2 deviant region was functionally connected to the cerebellum and the thalamus together with other subcortical areas involved in the orexin network (Figure 2E). ■

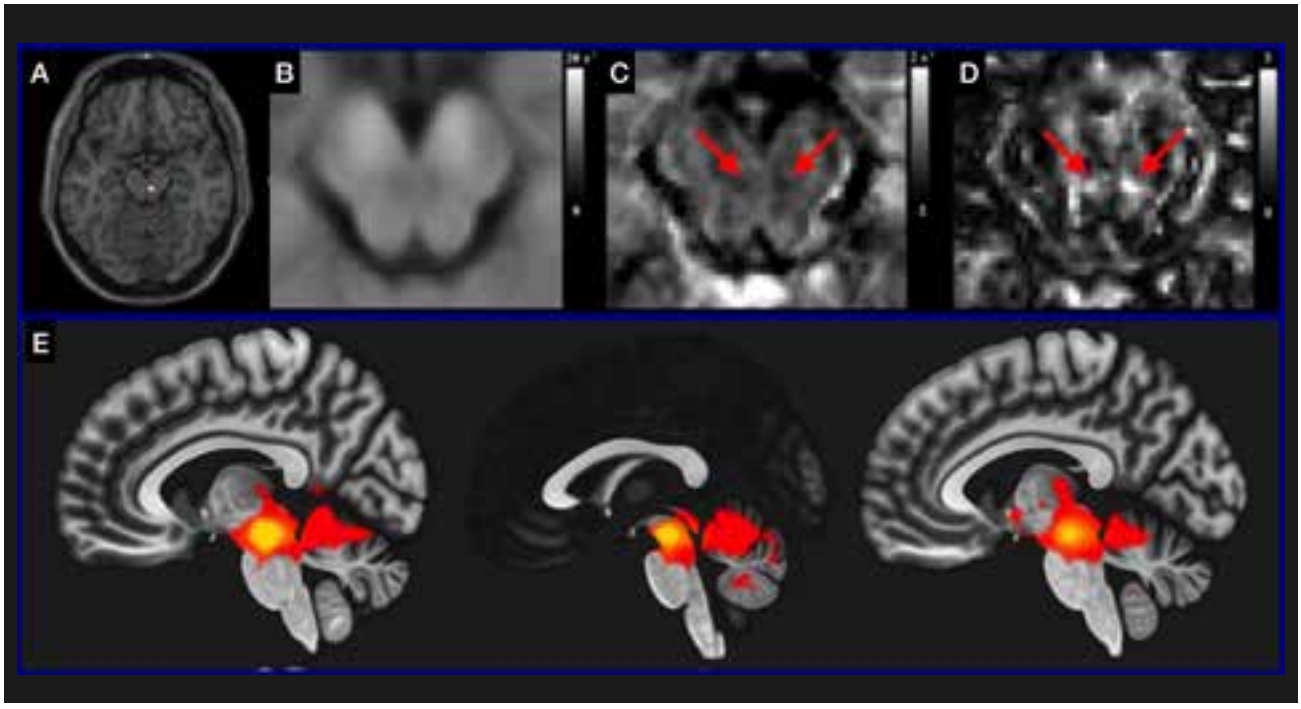

FIGURE 2. Structural anomaly in the brain stem's reticular formation in narcolepsy.
A) Lower R2 in the brain stem in narcolepsy. B) Mean R2 in all participants. C) Average difference in R2 between narcolepsy patients and healthy peers. D) The significance of the R2 difference. E) Functional connectivity related to the orexin network.

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.

MRI
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POPULAR SCIENTIFIC SUMMARY

MARIA ENGSTRÖM

Mathematical Modeling of Mechanisms in the Human Brain

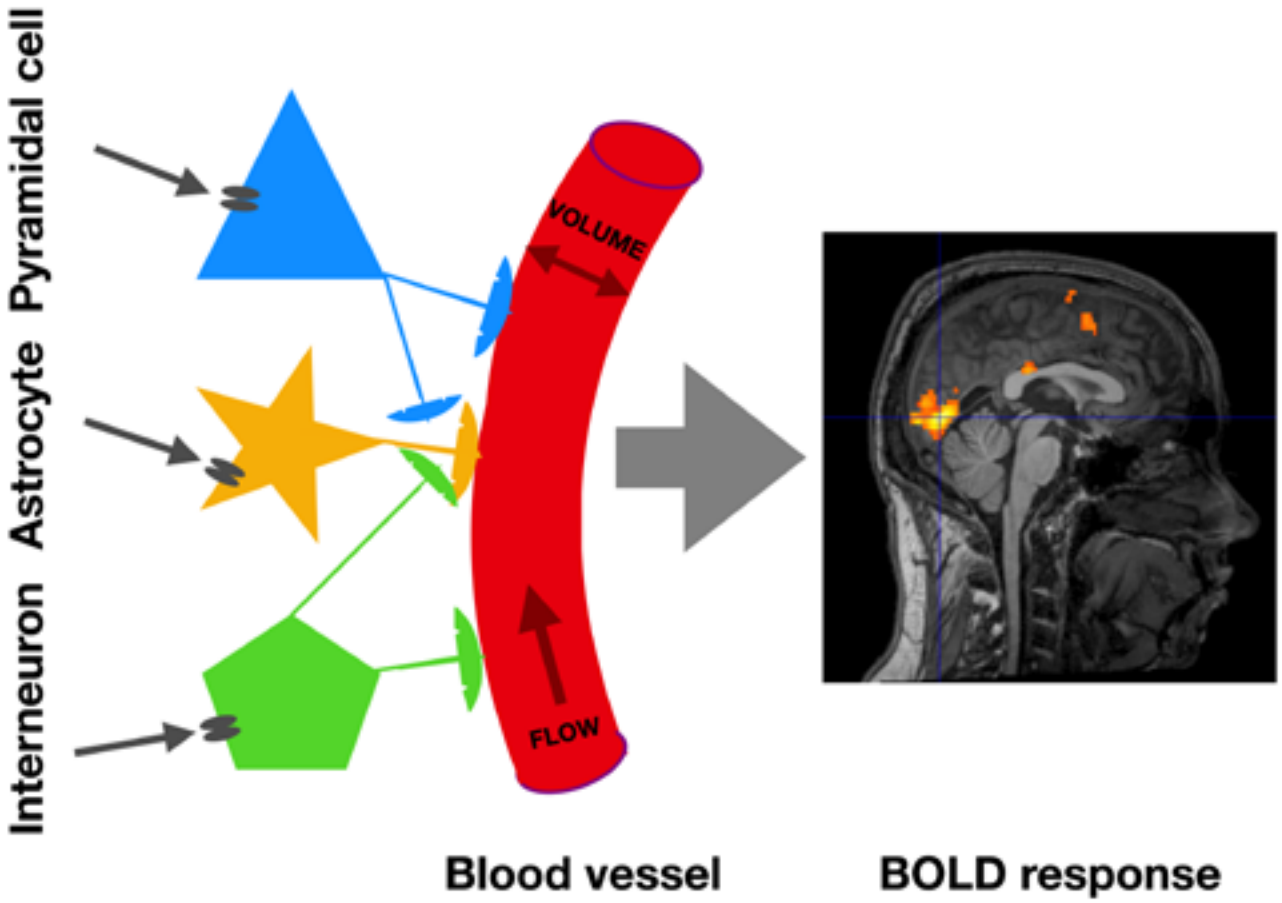
By functional magnetic resonance imaging (fMRI) we can visualize brain areas that are activated by certain tasks or sensory stimuli. Despite fMRI is widely used in both research and in the clinic, the biological mechanisms behind visualised brain activation are largely unknown. This means that we only have little information about the neurovascular coupling that underlie the blood oxygen level dependent (BOLD) response in fMRI.

This lack of information can be overcome by mathematical modeling 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 the neurovascular coupling underlying the BOLD response and we can also predict and thus simulate new fMRI data.

We have shown that a mechanistic model based on neurotransmitter influence on the brain's blood flow can explain and predict fMRI. Importantly, we have rejected the common hypothesis of brain metabolism being the driving force behind fMRI.

The fMRI signal can be both positive and negative with respect to baseline. 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. The modeled hypothesis is based on previous knowledge that brain activation involves 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.

Our modeling approach can advantageously be used to study pharma-



cological effects. We have shown that working memory activation in certain brain areas are influenced by the GABA modulator diazepam. 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.

Research during 2018 has been focused on explaining intra- and inter-cellular mechanisms that influence cerebral hemodynamics and thereby the BOLD response. This means that we are incorporating effects in excitatory pyramidal cells and inhibitory interneurons as well as astrocytes in our neurovascular model (figure).

In summary, by our modeling approach we can firmly reject hypotheses that cannot explain data, we can get information about hidden variables e.g., neurotransmitter action in excitatory pyramidal cells and inhibitory interneurons, and we can explain pharmacologically induced brain responses. The next step is to advance the model by including improved descriptions of blood flow and blood volume interactions. 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. Schematic description of the neurovascular coupling in fMRI. Several neural cells e.g., pyramidal cells and interneurons, and glial cells e.g., astrocytes are involved in the neurovascular coupling behind the blood oxygen level dependent (BOLD) response in fMRI. We are constructing mathematical models that can explain the influence of these cells on cerebral blood flow, volume, and oxygen metabolism and thereby provide mechanistic explanations of the BOLD response in fMRI.

POPULAR SCIENTIFIC SUMMARY

ANNELI PEOLSSON

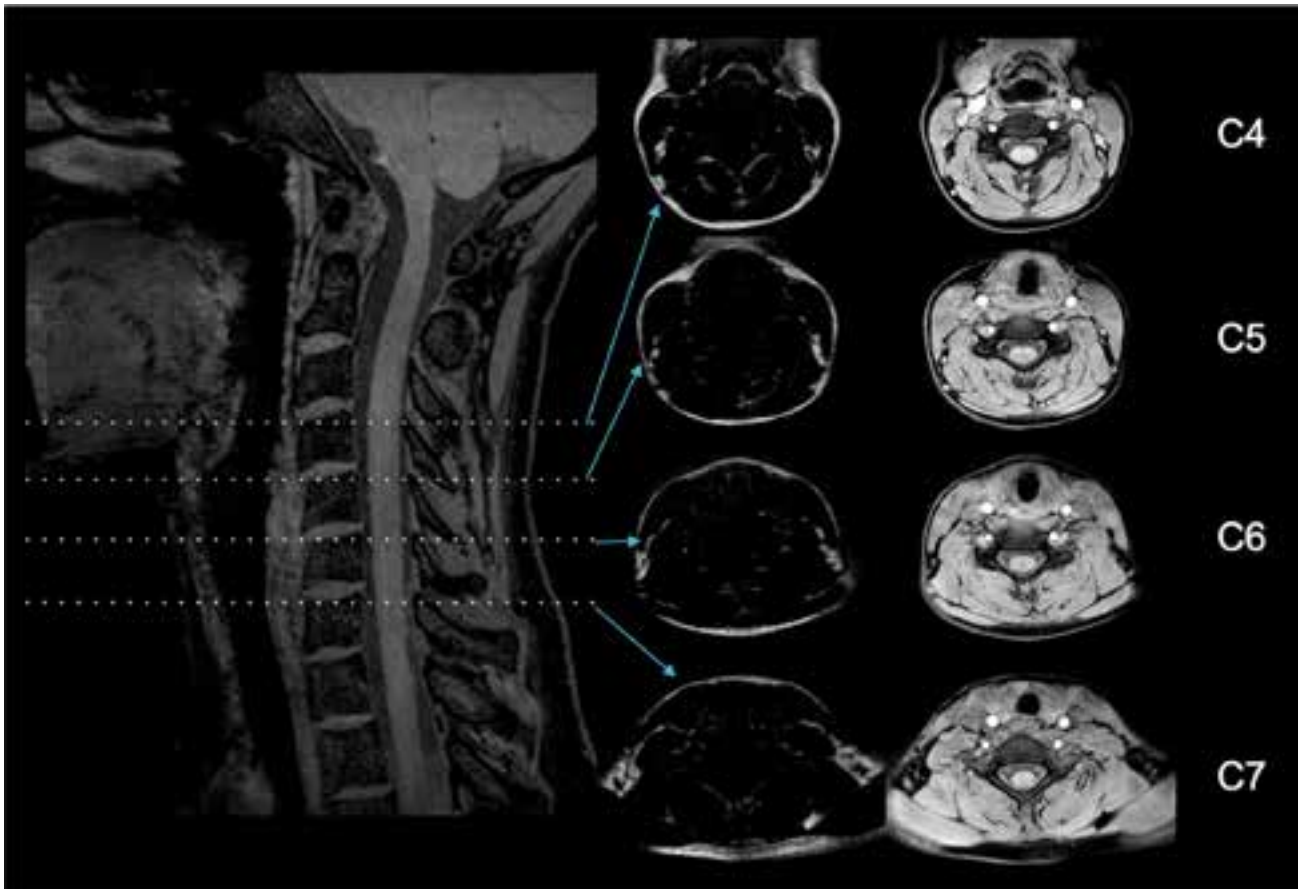


FIGURE. A sagittal section and four axial section (at cervical levels C4, C5, C6 and C7) of a fat and water separated volume over the neck. The volumetric resolution is 0.75×0.75×0.75 in order to see all the small muscles in the neck.

Pathophysiology Behind Whiplash Associated Disorders

There is insufficient knowledge about the pathophysiological parameters that regulate the mechanism behind prolonged Whiplash Associated Disorders (WAD). Therefore, whether changes can be restored by rehabilitation or not is unknown.

The aim of the project is to investigate imaging and molecular biomarkers, cervical kinaesthesia, postural sway and the association with pain, disability and other outcomes in individuals with longstanding WAD before and after a neck-specific intervention. The study will compare individuals with WAD with healthy controls.

The participants is a sub-group (n=30) of individuals recruited from an ongoing randomized controlled study (RCT). Measurements in this experimental prospective study will be made at baseline (before intervention) and at 3 months follow-up (end of physiotherapy intervention) and will include muscle structure and inflammation using magnetic resonance imaging (MRI), brain structure and function related to pain using functional MRI (fMRI), muscle function using ultrasonography, biomarkers using samples of blood and saliva, cervical kinaesthesia using the »Butterfly-test« and static balance test using an iPhone app. Association for other measures (self-reported and clinical measures) obtained in the RCT (e.g. background data, pain, disability, satisfaction with care, work ability, quality of life) may be investigated. Healthy volunteers matched for age and gender will be recruited as controls (n=30). The study results may contribute to the development of improved diagnostics and in improved rehabilitation methods for WAD. ■

PROJECT INFORMATION

Project Name
Pathophysiology Behind Prolonged Whiplash Associated Disorders: Study Protocol of an Experimental Study

Project Leader
Anneli Peolsson, Department of Medical and Health Sciences, Division of Physiotherapy

Main Project Participants
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Grants
Swedish Research Council
VINNOVA

MRI
Neurology
Imaging Biomarkers

PROJECT INFORMATION

Project Name
Visualizing the Clinical Model of Chronic Pain: Towards a Better Understanding of Pain Behavior and Treatment

Project Leader
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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
Helene Van Ettinger-Veenstra, Peter Lundberg, Peter Alföldi, Martin Södermark, Thomas Graven-Nielsen, Anna Sjörs, Maria Engström, Björn Gerdle.
Chronic Widespread Pain patients show disrupted cortical connectivity in Default Mode and Salience Networks, modulated by pain sensitivity. Journal of Pain Research under revision.

MRI
Neurology
Musculoskeletal
Acquisition
Modeling

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 using task-based functional magnetic resonance imaging (fMRI), as well during resting state (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.

How are the altered neural patterns of DMN and SN 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 that CWP patients had stronger connectivity in the posterior cingulate part of the DMN and weaker connectivity in the left anterior insula/superior temporal gyrus part of the SN compared to healthy controls. CWP effects were also observed in relation to increased pain sensitivity (pressure pain tolerance threshold), as increased SN and DMN-SN connectivity.

The results of this study demonstrate functional connectivity changes in the DMN and SN for CWP patients. In contrast to our CWP group, previous studies on FM patients more often report an increase than a decrease of posterior cingulate connectivity. An increase of connectivity in the anterior insula has been observed as an effect of acute pain, while this effect is observed without applying experimental pain in our study. Our study contributes to increase the sparse knowledge on CWP and fibromyalgia, and implicates that increased connectivity between DMN and SN is modulated by pain sensitivity. ■

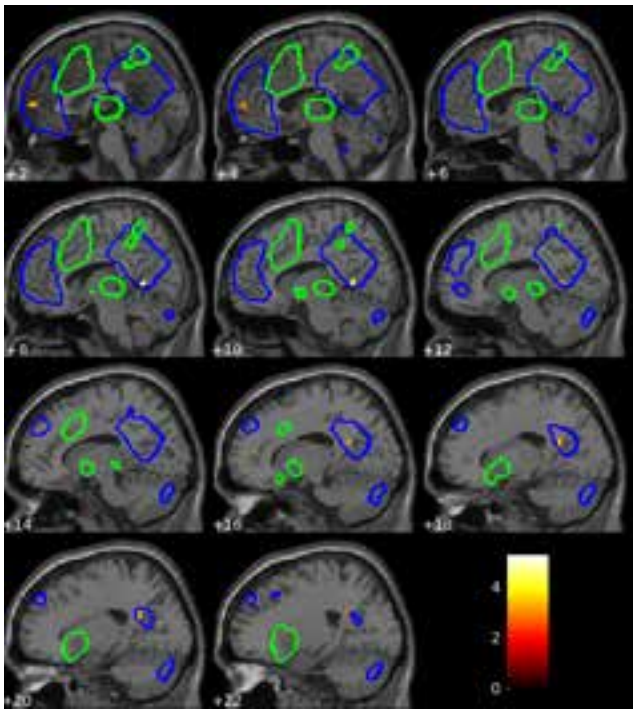

FIGURE 1. The figure shows the decreased connectivity related to the DMN for CWP compared to healthy controls. The decreased connectivity at x-coordinate 10 in the posterior cingulate region of the DMN template was significant at p<0.05 FWE-corrected. Blue overlay shows DMN template, green overlay shows SN template, the legend indicates the t-value), the image is thresholded at p<0.01 for illustrative purposes.

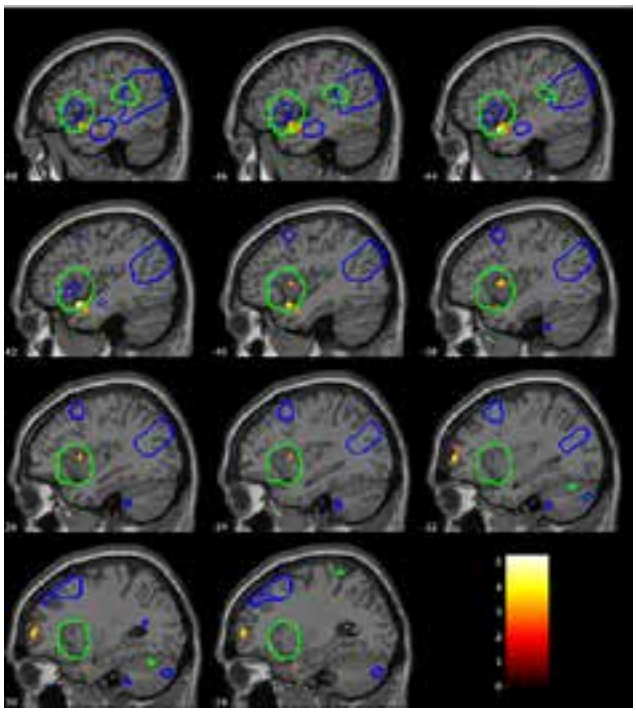

FIGURE 2. The figure shows the increased connectivity related to the SN for CWP compared to healthy controls. The increased connectivity at x-coordinate −44 in the left anterior insula region of the SN template was significant at p<0.05 FWE-corrected. Blue overlay shows DMN template, green overlay shows SN template, the legend indicates the t-value), the image is thresholded at p<0.01 for illustrative purposes.

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
Bednarska O, Walter SA, Casado-Bedmar M, Ström M, Salvo-Romero E, Vicario M, Mayer EA, Keita ÅV.
Vasoactive Intestinal Polypeptide and Mast Cells Regulate Increased Passage of Colonic Bacteria in Patients With Irritable Bowel Syndrome.
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Icenhour A, Bednarska O, Tapper S, Tisell A, Lundberg P, Witt S T, Elsenbruch S, Walter S.
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Neurogastroenterology & Motility; nr. 38, Volume 29, 2017 Issue Supplement S2.

Witt S T, Bednarska O, Keita Å V, Icenhour A, Jones M P, Elsenbruch S, Söderholm JD, Engström M, Mayer EA, Walter S.
Interactions between gut permeability and brain structure and function in health and irritable bowel syndrome.
Neuroimage Clin. 2018 Nov 17. pii: S2213-1582(18)30350-4.

MRI
Neurology
Gastrointestinal

POPULAR SCIENTIFIC SUMMARY

SUSANNA WALTER

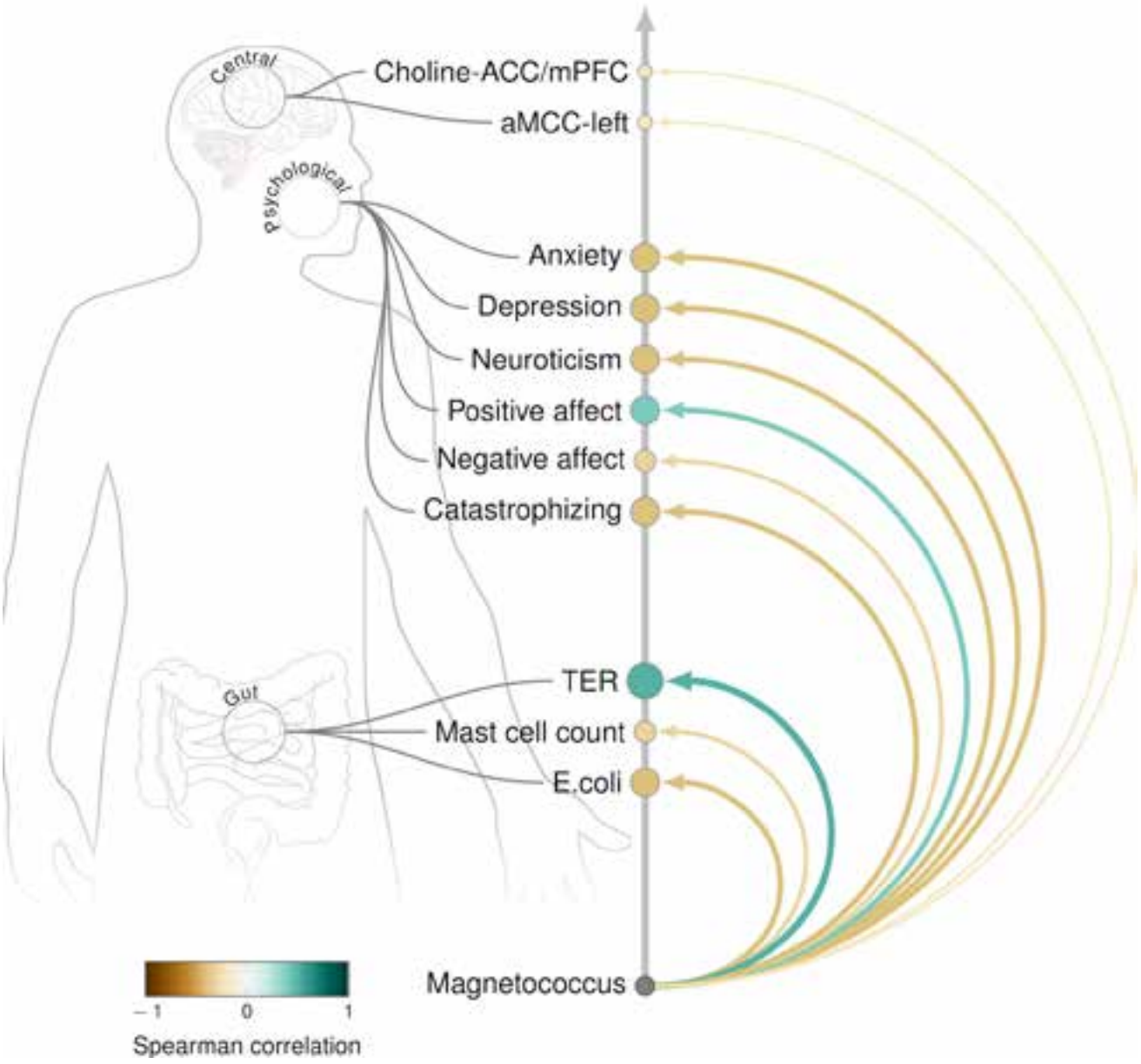
Brain-Gut Interactions in IBS

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

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.
Thalamo-striato-cortical determinants to fatigue in Multiple Sclerosis. Brain & Behaviour, 2013 November; 3(6): 715–728.

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MRI
Neurology

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.

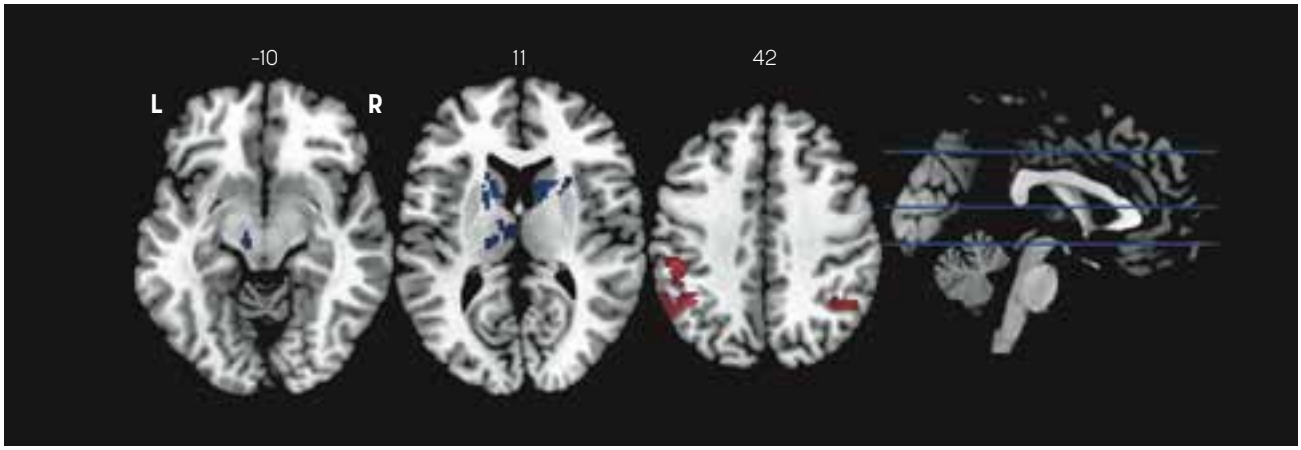

FIGURE 1. Differences in brain activation between MS participants and healthy participants in regions of interest in the brain. The red colour represents areas that were more activated in MS participants compared to controls, and the blue colour represents areas that were less activated in MS participants compared to controls.

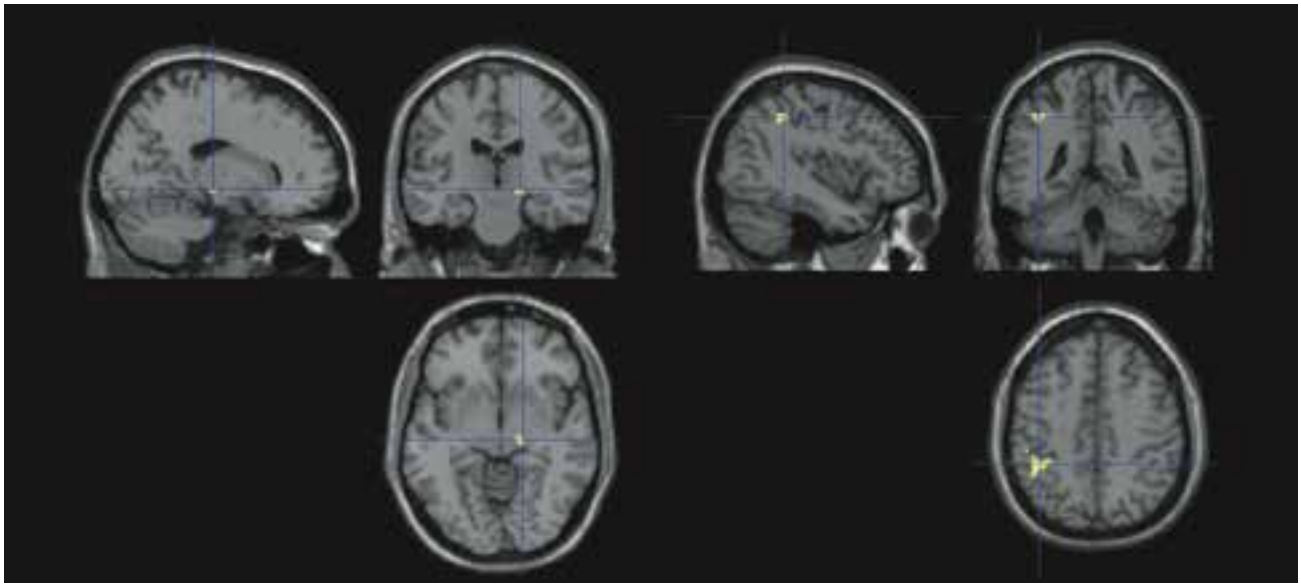

FIGURE 2. Brain activation with positive correlation to perceived fatigue during the working memory task. The images show activation in regions of interest: the right substantia nigra and the left posterior parietal cortex.

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). ■

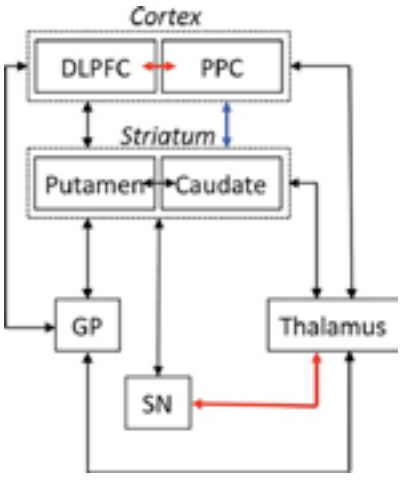

FIGURE 3. Schematic diagram of the thalamo-striato-cortical circuits, which describes the results of the present study. The red arrows describe couplings between areas that were more strongly connected in MS participants than controls during the working memory task. The blue arrow describes the coupling 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
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
Maria Engström, Peter Lundberg, Thomas Karlsson, Olof Dahlqvist Leinhard, Anders Tisell, Patrick Vigren, Christian Benedict

Grants
Kleine Levin Foundation

Key Publications
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.

Vigren P.
On the Kleine Levin Syndrome, Linköping University Medical Dissertations, 2017.

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MRI
Neurology
Acquisition
Modeling
Imaging Biomarkers

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=60), 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.

A late contribution in this project

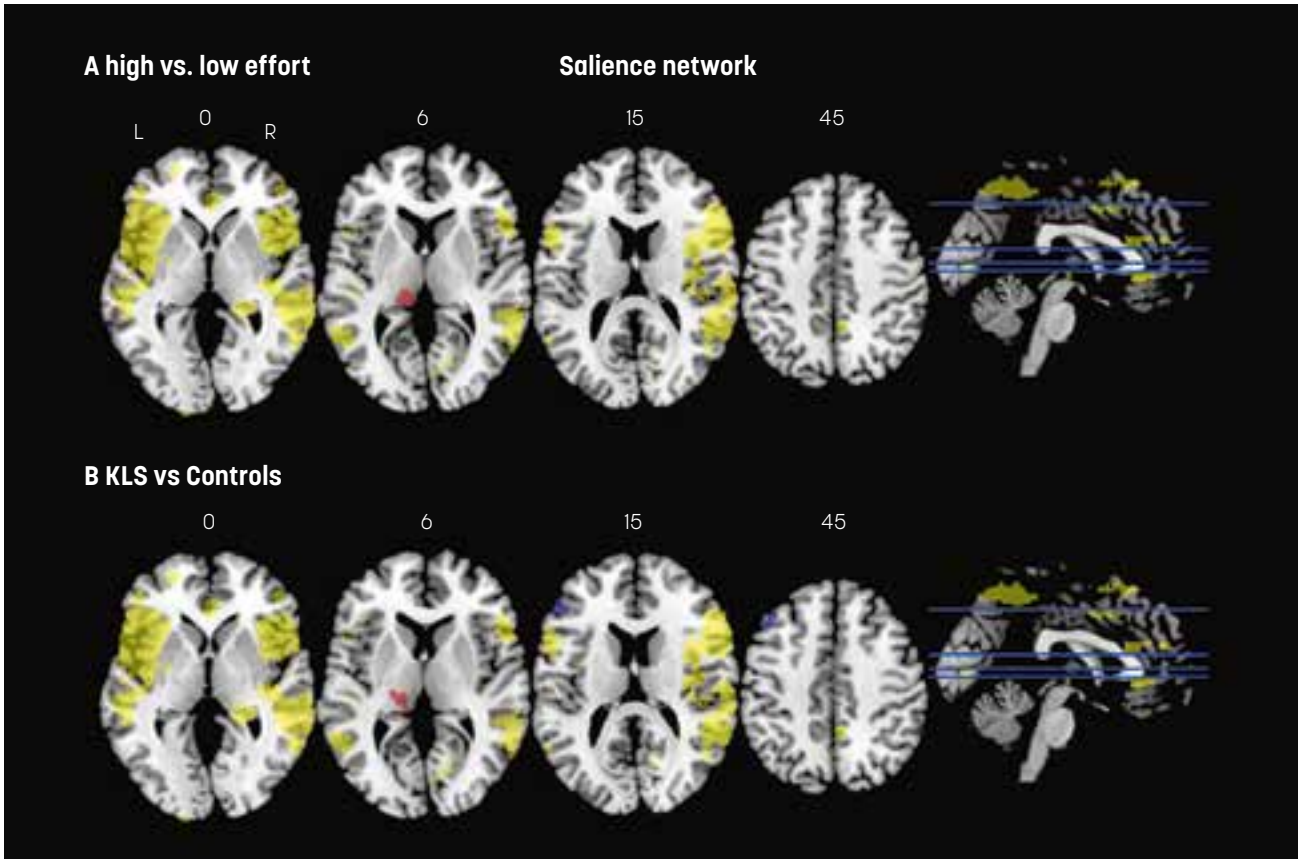


FIGURE. Functional connectivity in the salience network
Neural processing is often performed by an integrated network of several regions in the brain. Functional connectivity studies investigate the interaction of regions within these networks. Yellow areas show the network in selected slices. Red and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

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.

Two genetic studies have been performed with the aim to explore the full picture with genetics, imaging, physiologic and clinical findings in KLS. 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. Also, an analysis of the cognitive tests will be performed, in order to describe the working memory deficits in greater detail. ■

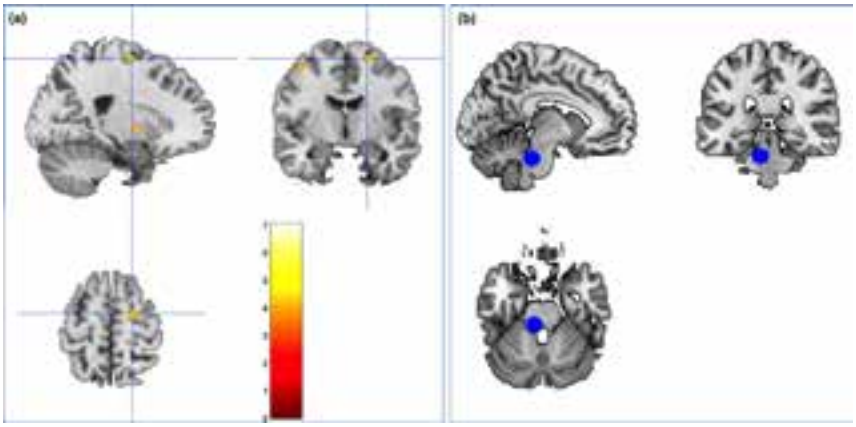


FIGURE. Pontine-frontal eye field connectivity in patients with Kleine-Levin syndrome (KLS).
(a) Patients with KLS had significantly lower connectivity between the left dorsal pons and the right frontal eye field. The cross-hair is located at the most significant voxel for the difference in connectivity 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.

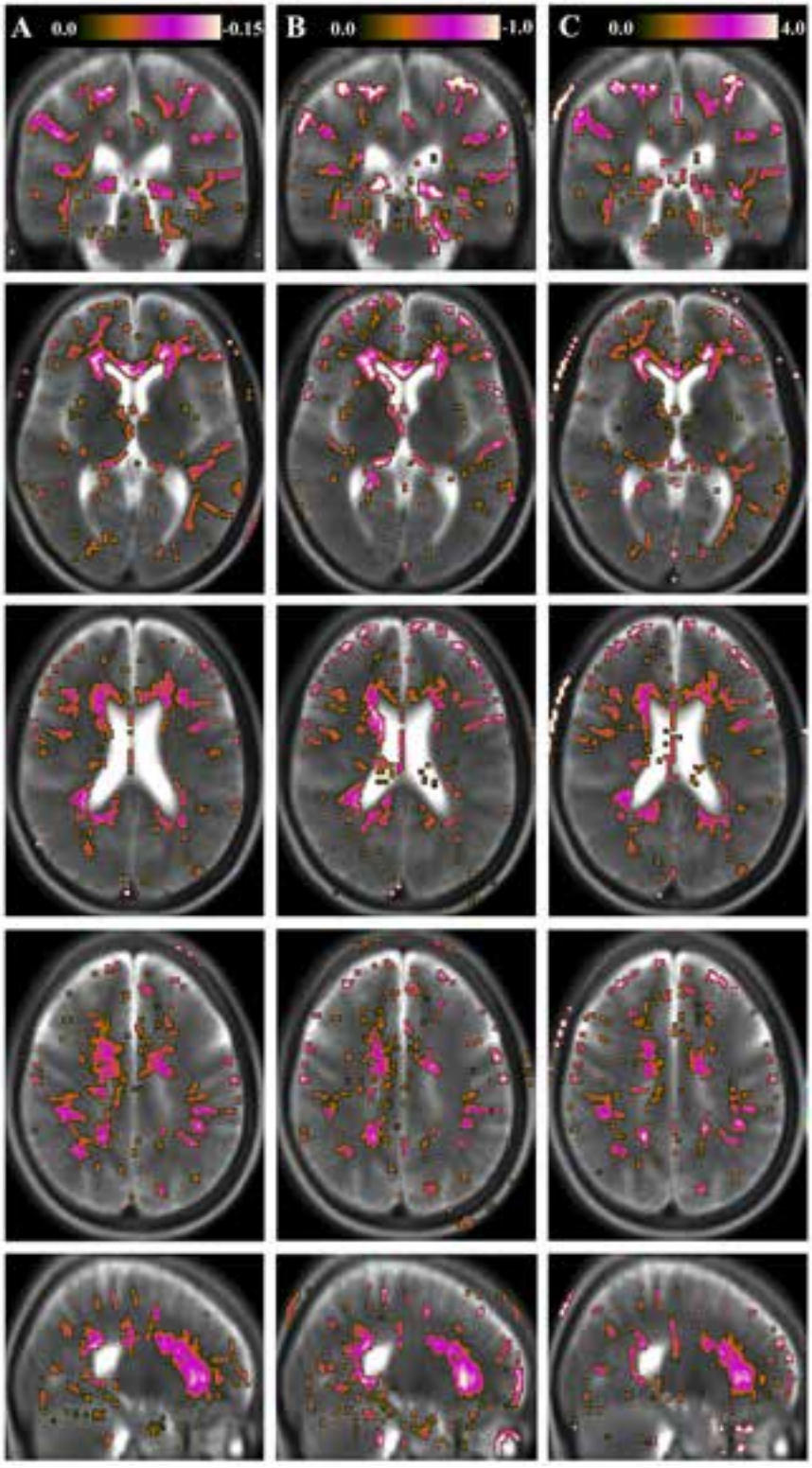
A new field that attracts interest in MS imaging, are the so called Diffuse Appearing White Matter lesions or DAWN. In our studies of MR negative patients, we also encountered such lesions and reported a correlation to atrophy.

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. 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 three different patient subgroups will be examined: 25 patients with established MS diagnosis, 25 patients with known ischemic brain disease and 10 healthy controls. Analysis will be performed with R1 och R2 determination in MS lesions, ischemic lesions and normal appearing white matter. Data collection is ongoing. ■

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

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.
Multiparametric representation of voxel based quantitative magnetic resonance imaging. PLoS One 2014 Nov 13;9:e111688.

MRI
Neurology
Metabolism
Acquisition
Modeling
Imaging Biomarkers

POPULAR SCIENTIFIC SUMMARY

MARY RUDNER

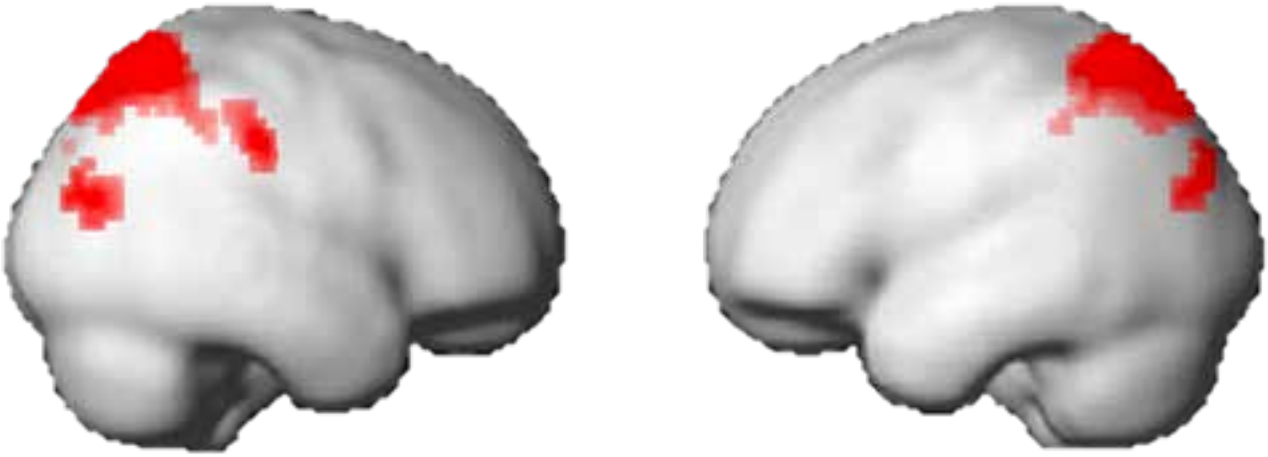


FIGURE. Effect of resolution on working memory for sign language (Reproduced from Andin et al., 2018).

Working Memory in Visual Noise

Sign language users strive to optimize communication by ensuring a good line of sight, good lighting and good contrast between clothes and the signing hands. This suggests that signal clarity is just as important for sign language communication as it is important for speech. Indeed, early research showed that gaussian noise added to videos of lexical signs made them harder to identify and more recent work has shown that data compression may influence the quality of visual digital communication. Thus, the effect of noise on working memory for sign language is an important phenomenon to study.

In the present study we are investigating the effect of poor visual resolution on working memory for sign language. To date we have collected data from 15 deaf early signers (DES) and 22 hearing non-signers (HNS) who performed a working memory task based on high and low resolution signs during functional Magnetic Resonance Imaging (fMRI).

Preliminary analyses targeting a region of interest in the parietal lobes showed greater neural activation for low resolution signs compared to high resolution signs in the superior and inferior parietal lobules. It also showed greater neural activation in the superior parietal lobule for higher working memory load.

Further, we found greater neural activation for DES than HNS in the angular gyrus and greater neural acti-

vation for HNS than DES in the superior parietal lobule. As the superior parietal lobule is part of the load-sensitive fronto-parietal working memory network, this preliminary pattern of results suggests, in line with expectations, that reducing stimulus resolution increases load during a sign-based working memory task. As the angular gyrus is part of the classical language-processing network, our preliminary results also suggest, in line with expectations, that DES solve the sign-based 2-back task linguistically, while HNS use a visuospatial strategy.

These preliminary results indicate generalization to sign language of previous results from the speech domain showing that reducing the resolution of the language signal increases pressure on working memory networks. This provides empirical evidence for the importance of signal clarity in sign language communication and has implications for visual digital interfaces and interaction in the signing classroom. ■

PROJECT INFORMATION

Project Name
Working Memory in Visual Noise

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

Main Project Participants
Josefine Andin, Emil Holmer

Grants
Swedish Research Council 2016–2020

Key publications
Rudner M.
Linguistic and cognitive representation – lessons from sign language. Invited symposium presentation. 13th Nordic meeting in neuropsychology, Stockholm, August 22–24, 2018.

Andin J, Holmer E, Stenbäck V, Rudner M
Neural correlates of working memory for signs with poor visual resolution in the parietal lobe. Poster. 13th Nordic meeting in neuropsychology, Stockholm, August 22–24, 2018.

Stenbäck V, Andin J, Holmer E. Rudner M
Effect of load and visual resolution on working memory for signs Poster. 13th Nordic meeting in neuropsychology, Stockholm, August 22–24, 2018.

MRI
Neurology

PROJECT INFORMATION

Project Name
Brain Correlates to Affective Processing in Typical Individuals and Clinical Groups

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

Main Project Participants
Per Gustafsson, Paul Hamilton, Robin Kämpe, Håkan Olausson, Irene Perini, Maria Zetterqvist

Grants
The Swedish Medical Research Council

Key publications
Perini I, Gustafsson PA, Hamilton JP, Kampe R, Zetterqvist M, Heilig M. The salience of self, not social pain, is encoded by dorsal anterior cingulate and insula. Sci Rep. 2018;8(1):6165.

Perini I, Gustafsson PA, Hamilton JP, Kämpe R, Mayo L, Heilig M, Zetterqvist M. Brain-Based Classification and Negative Social Bias in Female Adolescents with Nonsuicidal Self-Injury (02/14/2019 15:57:39).

MRI
Neurology
Acquisition

POPULAR SCIENTIFIC SUMMARY

MARKUS HEILIG

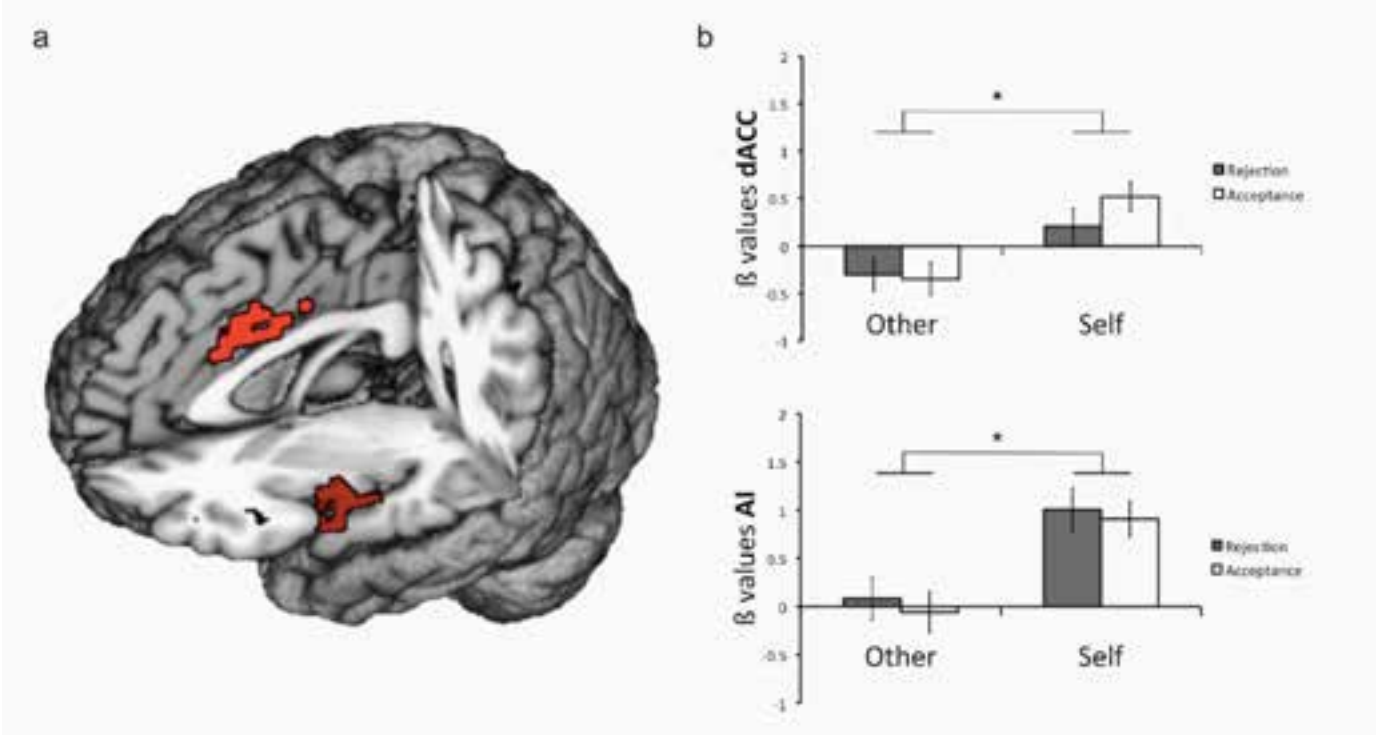
Brain Correlates to Affective Processing

With this project we want 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.

We use magnetic resonance imaging 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.

One of the aims of this project is to contribute to the understanding of the behavioral and brain mechanisms behind social processing in healthy subjects and in clinical groups. After characterizing typical responses in a group of healthy teenagers, we expanded our investigation to individuals with nonsuicidal self-injuri (NSSI) and autism spectrum disorder (ASD).

Healthy participants activate the salience network when they feel judged by others, during online social interaction, independently on the quality of the judgment (Figure). 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.

Findings in individuals with NSSI show some degree of overlap but important differences. First of all, relevant behavioral differences emerged between the groups. Individuals with NSSI showed a negative bias in reading the social interaction: they felt on average more disliked than controls and when their picture received a negative feedback they felt worse than controls.

Regarding brain activity, we did not identify significant differences between individuals with NSSI and age-matched controls in the salience network. However, using multi voxel pattern analysis, brain activity during the simulated online interaction could significantly classify the groups depending on their clinical profile.

In addition, classification scores correlated significantly to sensitiveness to negative feedback from others in the patients but not in the controls. These findings suggest that individuals with NSSI interpret social interactions more negatively than controls and that regions outside the salience network might influence such interpretation. The analysis in the ASD groups is still ongoing. ■

FIGURE. From Perini et al. 2018.
(a) Right anterior insula (rAI) and cingulate cortex (dACC) activated when the participants were judged by others.
(b) Bar graph show activation values for each region across condition. Both regions show increased activity to self-versus-other judgment conditions, independently on whether the judgment was positive (acceptance) or negative (rejection)

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

MRI
Neurology

POPULAR SCIENTIFIC SUMMARY

MARKUS HEILIG

Affective Processing when 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.

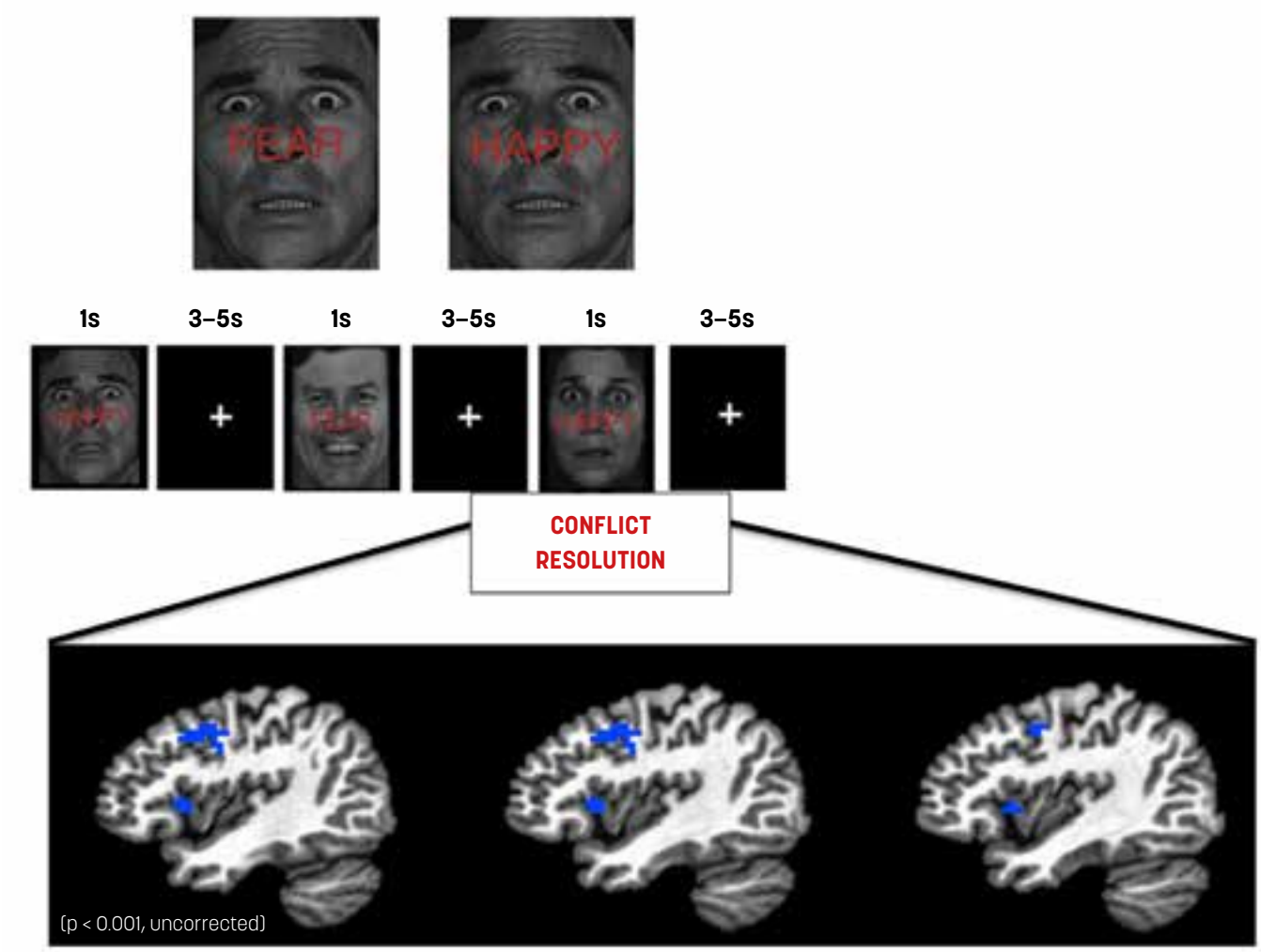
The specific aim regarding the MRIdata collection of this project is to investigate experimentally whether the regulation of affect and stress responses differs in individuals who have experienced early trauma, compared to controls.

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. ■


FEAR
HAPPY
1s
3–5s
1s
3–5s
1s
3–5s
CONFLICT
RESOLUTION
(p < 0.001, uncorrected)

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

MRI
Neurology

POPULAR SCIENTIFIC SUMMARY

MARKUS HEILIG

Effects of rTMS on Alcohol Use and Neuronal Response

The objectives of this study was to investigate the effects of repetitive transcranial magnetic stimulation (rTMS) targeting the insula on alcohol use and neural responses in alcohol-dependent patients. Craving and an impaired ability to stop alcohol use despite adverse consequences are key features of alcohol addiction. Functional brain imaging studies have shown that insula activity in response to drug cues is positively correlated with cravings. Modulation of insula activity may therefore represent a novel therapeutic approach in addiction, but non-invasive methods to modulate the activity of this structure have until recently not been available.

The ability of rTMS, a non-invasive tool for neuromodulation, to reduce craving and cue reactivity in addiction has been suggested by small pilot studies in alcohol, cocaine and opiate users. In these studies, rTMS has typically been applied to the dorsolateral prefrontal cortex (DLPFC), a superficial structure. The present study uses a different coil, designed to allow »deep TMS«, to examine whether stimulation of the insula offers a novel alcoholism treatment.

The study population consisted of treatment seeking alcohol dependent

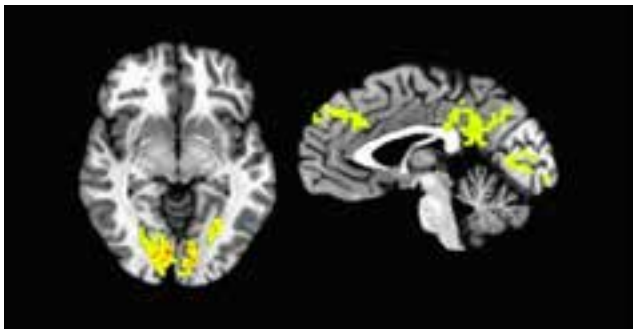


FIGURE 1. Alcoholics looking at images of alcoholic beverages vs alcoholics looking at images of non-alcoholic beverages. We see higher activity in visual cortex/dorsal attention network when they look at the alcoholic beverages. Meaning that they are investing more attentional resources on drug related stimuli. We expect less of a contrast in non-alcoholic people.

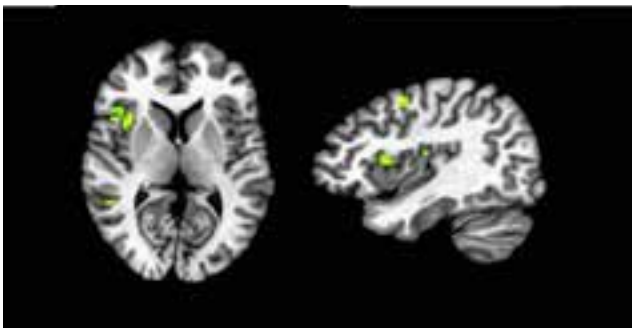


FIGURE 2. Alcoholics treated with TMS compared to alcoholics treated with SHAM TMS show an enhanced anterior insula activity when looking at alcoholic beverages compared to non-alcoholic beverages. This possible suggests that the TMS treatment (controlled for placebo) reorganizes insular activity in alcoholics.

subjects, who have first completed standard alcohol withdrawal treatment if needed. Participants underwent an MRI scan to collect resting state and structural data, and then received one of two treatments: active (10Hz) rTMS or sham stimulation, both targeting the insula bilaterally. The treatment procedure was double-blinded, meaning that both participants and study personnel were unaware of the randomization of the treatment. Rtms sessions were delivered five times per week, for 3 weeks, for a total of 15 sessions. A second MRI scan was obtained at the end of the treatment phase to assess changes in resting state connectivity, and to evaluate insula activity in well-established tasks known to activate this structure. Outcome measures included alcohol craving and consumption during treatment and follow-up phases. In addition, brain responses to alcohol related cues and reward were analyzed and compared between stimulation types.

We observed a significant effect of time in craving and drinking measures which was independent of stimulation. These results reflect decreases in craving and drinking during the 3 weeks of treatment in all the patients, disregarding of whether they received sham or real rTMS stimulation. Decreased craving and consumption did not last during the post-treatment period, which was measured up to 3 months. Although we did not observe long term effects in terms of alcohol craving and drinking, we found a significant attenuation of reported depressed mood up to 3 months after treatment, independent of stimulation. This finding highlights the overall positive experience associated with the study. In conclusion, compared to sham, real rTMS stimulation did not decrease craving or drinking measures in alcohol-dependent patients. ■

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

MRI
Neurology

POPULAR SCIENTIFIC SUMMARY

PAUL HAMILTON

Modulating Inflammation in the CNS in Major Depression

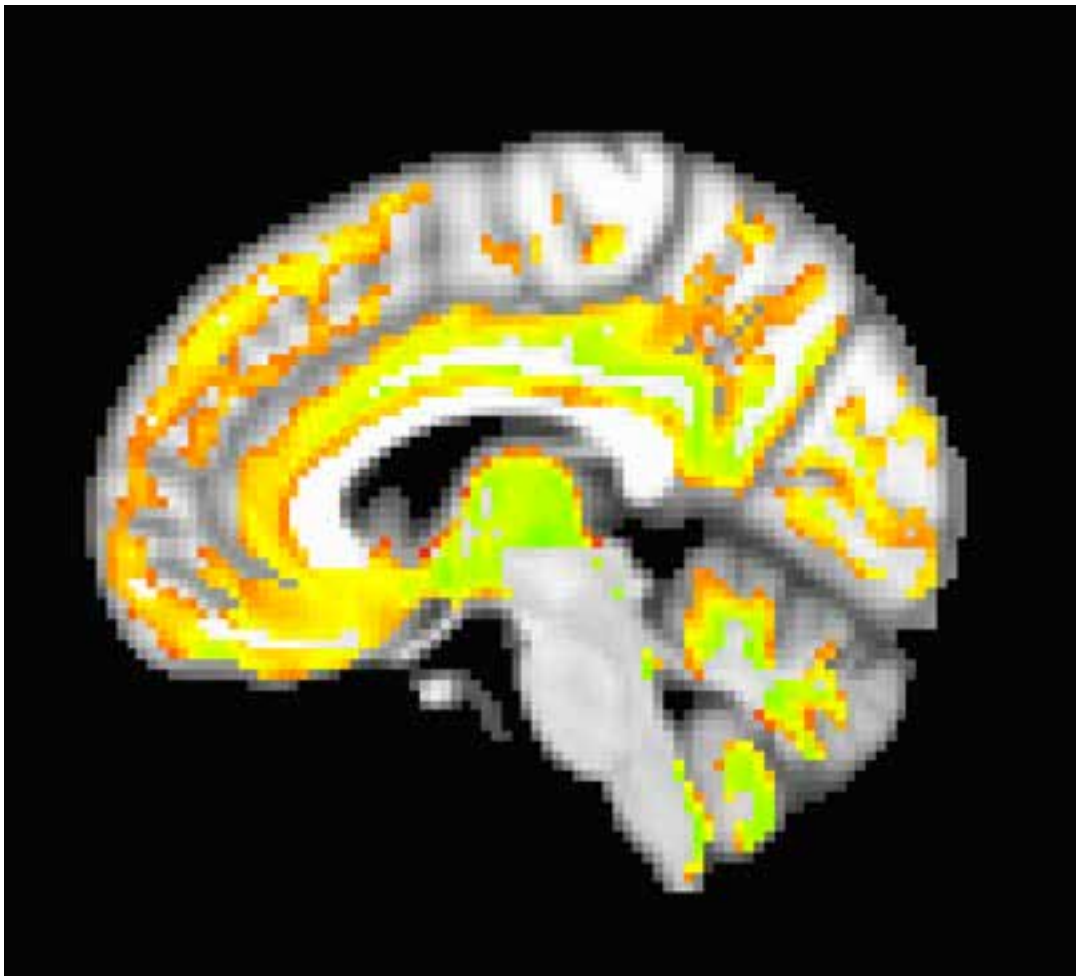
Major depressive disorder (MDD) is a leading contributor to the global burden of disease and is projected to be the second leading cause of global disability burden by the year 2020.

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.

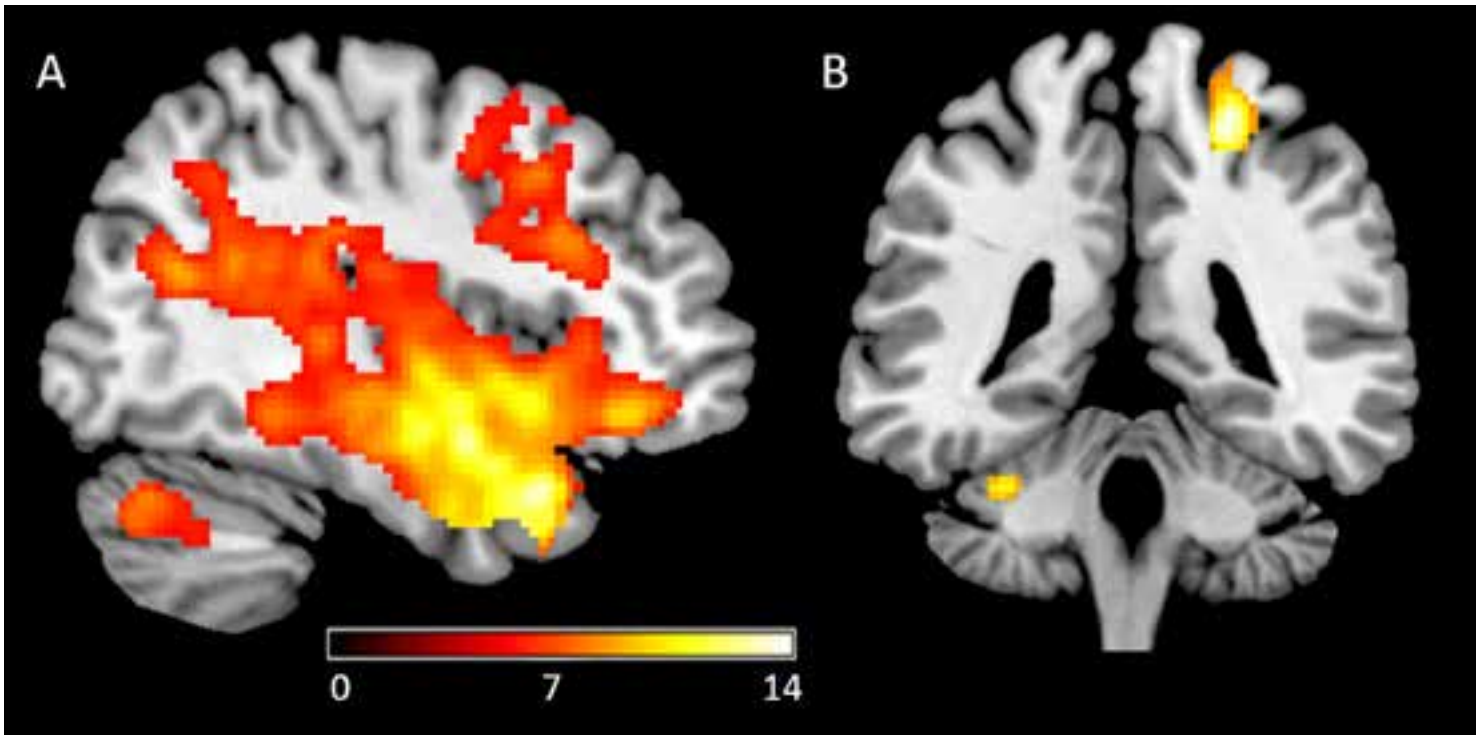
One week before and one week after four weeks of treatment or placebo, participants will be asked to provide cerebrospinal fluid (CSF), and magnetic resonance imaging (MRI) data. From the CSF, we will determine whether anti-inflammatory treatment reduces levels of chemical signaling of inflammation in 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.

POPULAR SCIENTIFIC SUMMARY

HÅKAN OLAUSSON



The Difference Between Social and Self-Touch

The distinction of »self« and »other« is necessary for social interactions and for a coherent concept of »self«. How to define the self is an ongoing philosophical discussion. Popular accounts of this question differentiate between hierarchical levels or layers of the self: The bodily self (also referred to as the minimal self or the phenomenological self) and the conceptual self (the autobiographical, narrative, social self). To establish a coherent minimal self-experience, a person needs to perceive signals from within their own body, i.e. proprioception and interoception – and identify these as their own. Proprioception refers to the position of own body parts. Interoception describes perceptions like heat and cold, hunger and thirst, the desire to breath, as well as affective social touch.

Affective interpersonal touch is conveyed by a specific receptor located in the hairy skin of mammals, the C-tactile fiber. These receptors react specifically to slow, light touch at skin-temperatures – exactly the kind of touch humans use to stroke their loved-ones. Touch is the first sensory perception an embryo perceives and the first way in which a newborn interacts with its environment, most importantly with its parents. Any dysfunction in the perception of affective social touch might invariably lead to an altered body perception and in consequence a changed, possibly dysfunctional self-concept.

In this project, we used a simple paradigm comparing self-touch to being touched by someone else. In healthy

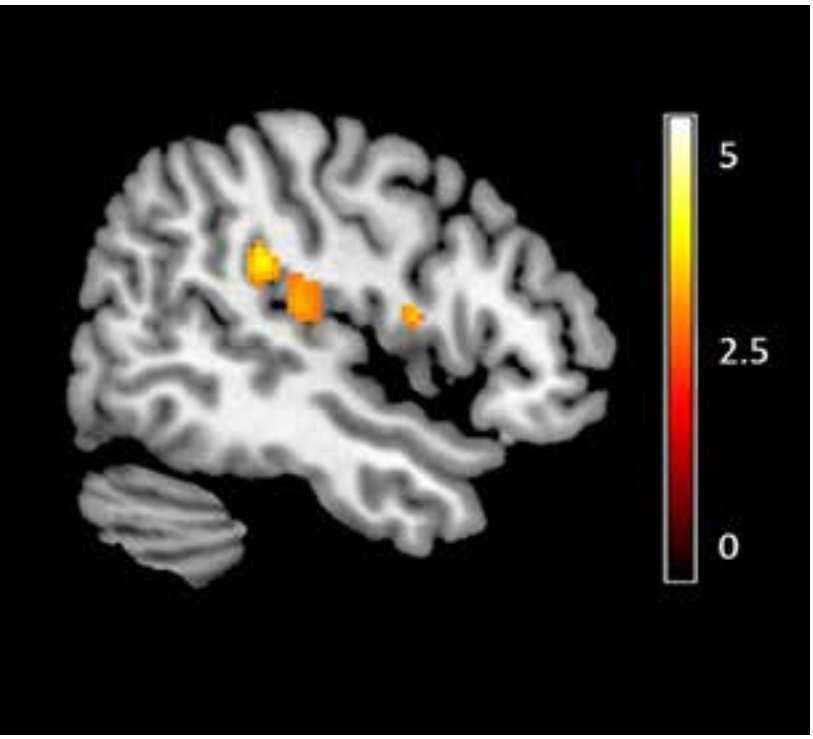


FIGURE. A) The difference between other-touch and self-touch, p<0.05, FEW-corrected at the whole brain level. B) ADHD-patients activate somatosensory cortex and temporo-parietal junction more than healthy controls during other-touch (p<0.001, uncorrected for display purpose).

participants, we find a clear distinction between self-touch and other-touch in a wide network of brain areas, including the primary somatosensory cortex, the insula – known to be involved in interoception and multisensory integration – and the anterior cingulate cortex – known to be involved when thinking about self and others. This difference was driven by activation when being touched by someone else, and by widespread deactivation during self-touch. Even areas hierarchically low as the thalamus and the brainstem expressed this pattern.

We are currently collecting data from different psychiatric populations (ADHD, Autism, major depression) in order to answer the question, whether disturbances of self-other-distinction can be found already at the basic level of tactile processing. This might provide the basis for a better understanding of the development of disorders of the self and perhaps help develop novel treatment approaches. ■

PROJECT INFORMATION

Project Name
The Difference between Social and Self-Touch in Healthy Participants and Psychiatric Disorders

Project Leader
Håkan Olausson, Department of Clinical and Experimental Research, Center for Social and Affective Neuroscience

Main Project Participants
Rebecca Böhme

Key publications
Rebecca Boehme, Steven Hauser, Gregory Gerling, Markus Heilig, Håkan Olausson.
Distinction of self-produced touch and social touch at cortical and spinal cord levels. Proceedings of the National Academy of Sciences, in press.

MRI
Neurology

PROJECT INFORMATION

Project Name
CABSOE – Cognition after Bilateral Salpingo-Oophorectomy

Project Leader
Gillian Einstein, Department of Thematic Studies, Gender Studies

Main Project Participants
Maria Engström, Preben Kjölhede, Nina Lykke, Elisabet Classon, Elisabeth Åvall Lundqvist, Jan Ernerudh, India Morrison, Giovanni Novembre, Lea Skewes, Cecilia Åsberg, Åsa Rydmark Kersley

Grants
The Swedish Cancer Society 2016–2019
FORSS

MRI
Neurology
Gynecological

POPULAR SCIENTIFIC SUMMARY

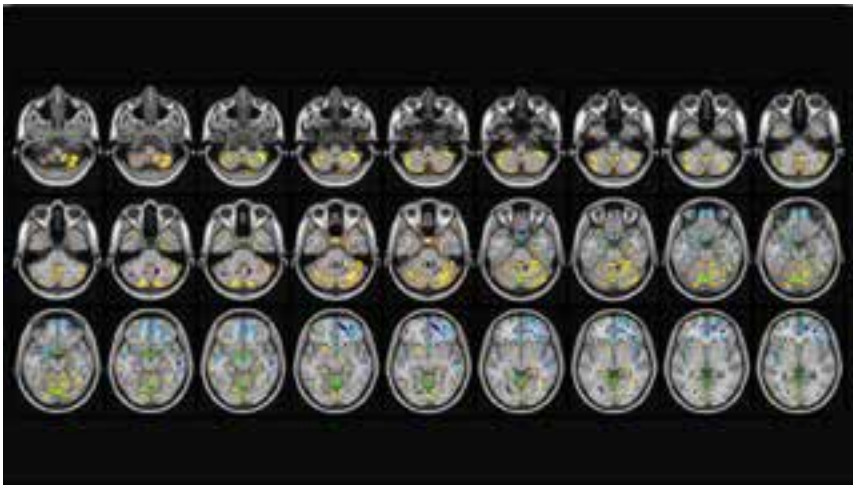
GILLIAN EINSTEIN

Cognition after Bilateral Salpingo-Oophorectomy

Women with bilateral salpingo-oophorectomy (removal of the ovaries; BSO) prior to the age of 50 have increased incidence of all causes of death including, Alzheimer's dementia (AD). One concequence of BSO is deprivation of the body's major source of 17-B-estradiol (E2, one of three naturally occurring estrogens). This suggest that early life withdrawal of E2 may be detrimental for cognition.

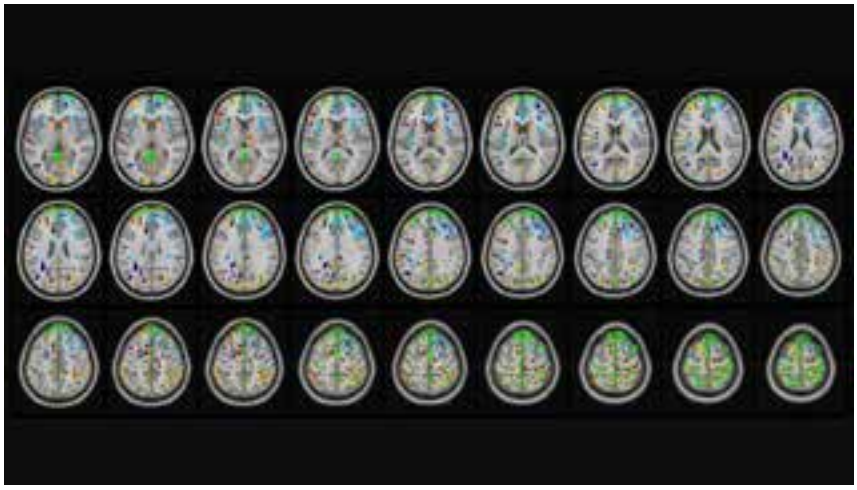
Women with the breast cancer gene mutations, BRCA1 and 2 are routinely counseled to have a BSO prior to the age of 50 to reduce the risk of ovarian cancer. This study aims to elucidate brain and cognitive alterations up to 10 years post-BSO.

This project explores the long term effects of BSO on cognition and brain. More broadly, it explores how breast cancer survivorship affects the brain. The objectives of the study are to determine domains in which cognition and memory change using neuropsychological testing and the effects of E2 withdrawal on brain regions involved



in memory using imaging. The project will also study the interaction between, E2 withdrawal, inflammation markers, and Apolipoprotein E (APOE) and their impact on brain changes and cognition. Methods used for this will be hormone assays, immunological testing, and genotyping. Finally, the women will be interviewed to determine their qualitative sense of surgery, quality of life, and memory.

This study may contribute to our understanding about how BSO, the increasingly common elective surgery for women with BRCA mutations effect cognition and the brain, as well as estrogen's role in young women's cognition and memory. It will also provide knowledge about survivorship of women with BSO. Knowledge particularly important for those who carry the AD risk factor variant of the APOE gene. Only with this knowledge will women be able to make fully informed decisions about BSO. This research may also lead to clinical trials of non-hormonal treatments and encourage invention of better ovarian imaging methods. ■



PROJECT INFORMATION

Key publications

Almey A, Gervais N, Duchesne A, Reuben R, Gravelsins L, Baker-Sullivan E, Witt ST, Rydmark Kersley Å, Classon E, Lykke N, Shildrick M, Åsberg C, Theodorsson E, Ernerudh J, Åvall Lundqvist E, Kjølhede P, Grady C &Einstein G (2018). The effect of bilateral salpingo-oophorectomy prior to spontaneous menopause on cortical thickness and measures of attention and working memory: preliminary findings. Poster at Society for Neuroscience, San Diego, CA. Nov 3–7.

Almey A, Gervais N, Duchesne A, Reuben R, Gravelsins L, Baker-Sullivan E, Witt ST, Rydmark Kersley Å, Classon E, Lykke N, Shildrick M, Åsberg C, Theodorsson E, Ernerudh J, Åvall Lundqvist E, Kjølhede P, Grady C, Rajah N & Einstein G (2018). The effect of bilateral salpingo-oophorectomy prior to spontaneous menopause on cortical thickness and measures of attention and working memory: preliminary findings. Poster presented at the International Neuroinformatics Coordinating Facility (ICNF) conference, Montreal, QC. Aug 9–10.

Witt ST, Rydmark Kersley Å, Classon E, Lykke N, Shildrick M, Åsberg C, Grady C, Theordorsson E, Ernerudh J, Åvall Lundqvist E, Kjølhede P & Einstein G (2018). Bilateral salpingo-oophorectomy prior to natural menopause is associated with Alzheimer's disease-like reductions in gray and white matter. Poster at Joint Annual Meeting International Society for Magnetic Resonance Imaging in Medicine & European Society for Magnetic Resonance Imaging in Medicine 3762.90., Paris, France. June 16–21.

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
The Swedish Cancer Society 2019–2021
Swedish Research Council 2017–2020

Key publications
Malusek A, Karlsson M, Magnusson M, 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.

Malusek M, Magnusson M, Sandborg M, Alm Carlsson G.
A model-based iterative reconstruction algorithm DIRA using patient-specific tissue classification via DECT for improved quantitative CT in dose planning. Med Phys 44 (6), pp. 2345–2356, 2017.

Magnusson M, Björnfot M, Carlsson Tedgren Å, Malusek A.
DIRA-3D – a Model-based Dual-Energy Iterative Algorithm for Quantitative 3D Helical CT, The Fifth International Conference on Image Formation in X-Ray Computed Tomography, Salt Lake City, Utah, USA, May 20–23, 2018.

CT
Oncology
Acquisition
Modeling
AI/Data analytics

POPULAR SCIENTIFIC SUMMARY

ÅSA CARLSSON TEDGREN

Classification Using DECT and Iterative Reconstruction

Today's computed tomography (CT) images are affected by inaccuracies and artifacts caused by the use of polyenergetic photon beams. Despite an active research in this field, even the most advanced image reconstruction algorithms still do not provide quantitatively accurate CT numbers. We have developed a dual-energy iterative image reconstruction algorithm (DIRA) which improves the accuracy of CT numbers by modeling the material composition of the imaged object. For instance image pixels of a patient are 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. The estimated material composition can be used for improved medical diagnosis and treatment. As an example, DIRA can be used for the determination of calcium content in the prostate gland. Such information is useful for radiation treatment planning in brachytherapy with low-energy photons; a high calcium content in the prostate changes the spatial distribution of absorbed dose since the dose strongly depends on the tissue's atomic number, Z. DIRA is also useful in proton radiation therapy since the position of the dose maximum is sensitive to the material composition of the patient tissues.

To verify the method, we applied DIRA on simulated projections of a mathematical pelvic phantom. The projections were calculated for tube voltages of 80 and 140kV, photon noise was included and the geometry was the same as for the CT-Scanner at CMIV. Figure 1 (left) shows the 80 kV image reconstructed via conventional filtered back-projection with water beam hardening correction. Figure 1 (right) shows the corresponding image obtained via DIRA in iteration 8. DIRA notably suppressed the beam-hardening artifact. Figure 2 shows the same phantom decomposed to the lipid, protein and water base material triplet. Knowledge of these mass fractions allows the estimation of the elemental composition of the phantom.

Our recent publications describe an implementation of DIRA that works with 3D helical geometries and an implementation of a segmentation algorithm based on deep-learning, see figure 3. Suitability of DIRA for radiation therapy was tested by evaluating the effect of zinc on the accuracy of the CT numbers. Ongoing research includes applications on new modalities of radiation therapy. ■

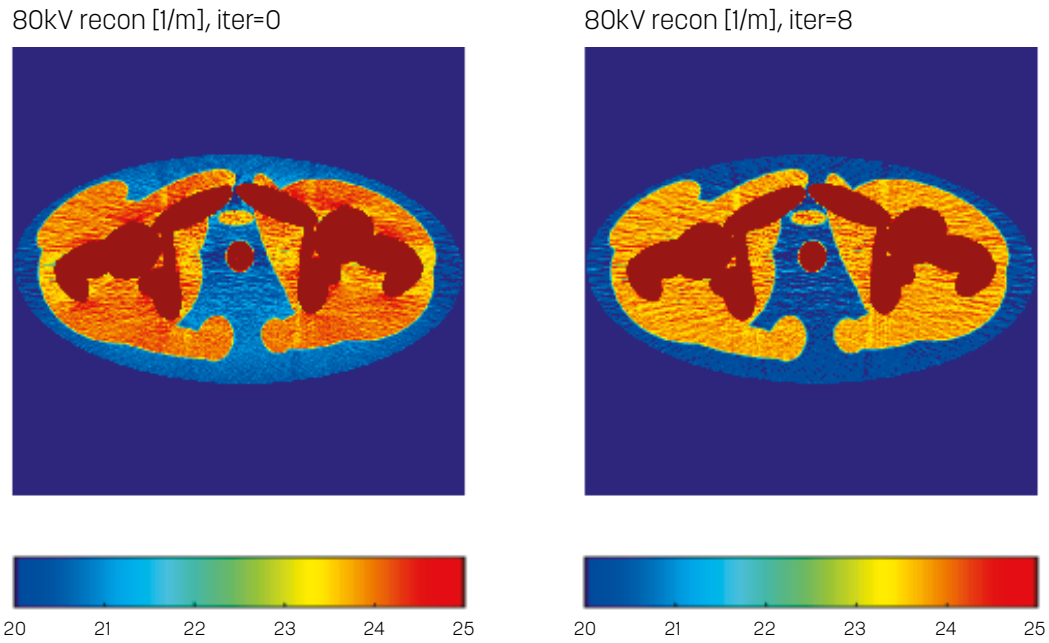


FIGURE 1. Suppression beam hardening artifacts in the human pelvic region from iteration 0 to iteration 8 in DIRA.

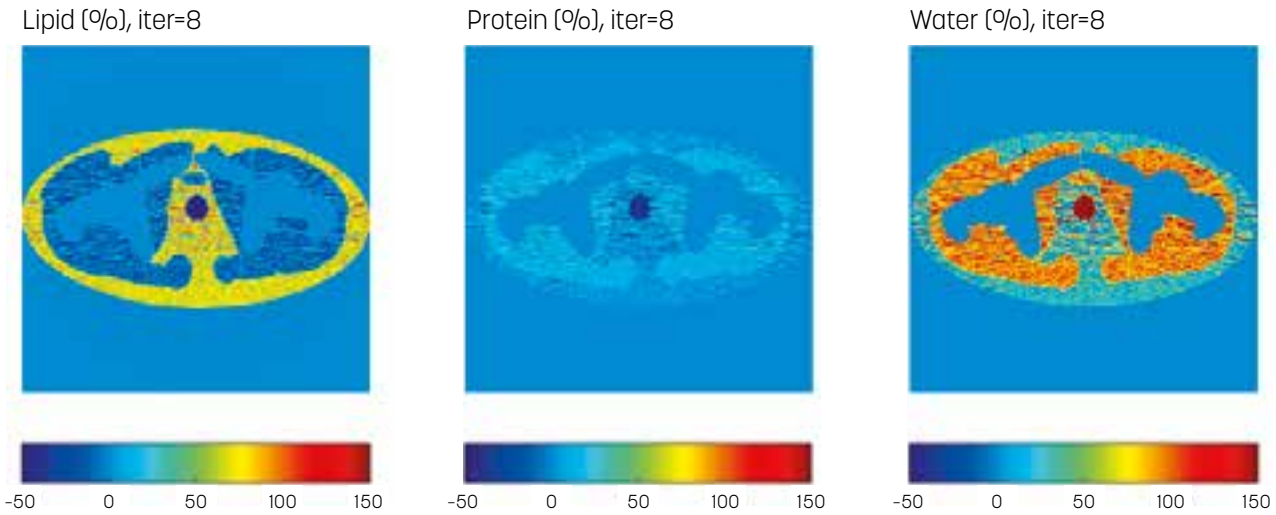


FIGURE 2. Soft tissue classification into lipid, protein and water (LPW) after 8 iterations of DIRA.

FIGURE 3. Segmentation of pelvic bones via the 3D U-Net architecture.
(A) Ground truth. (B) Prediction of our algorithm. (C) 3D view of the prediction.

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
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, 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, 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.

Daniel Jönsson, 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.

CT
MRI
Cardiovascular
Neurology
Modeling
Visualization
Simulation

POPULAR SCIENTIFIC SUMMARY

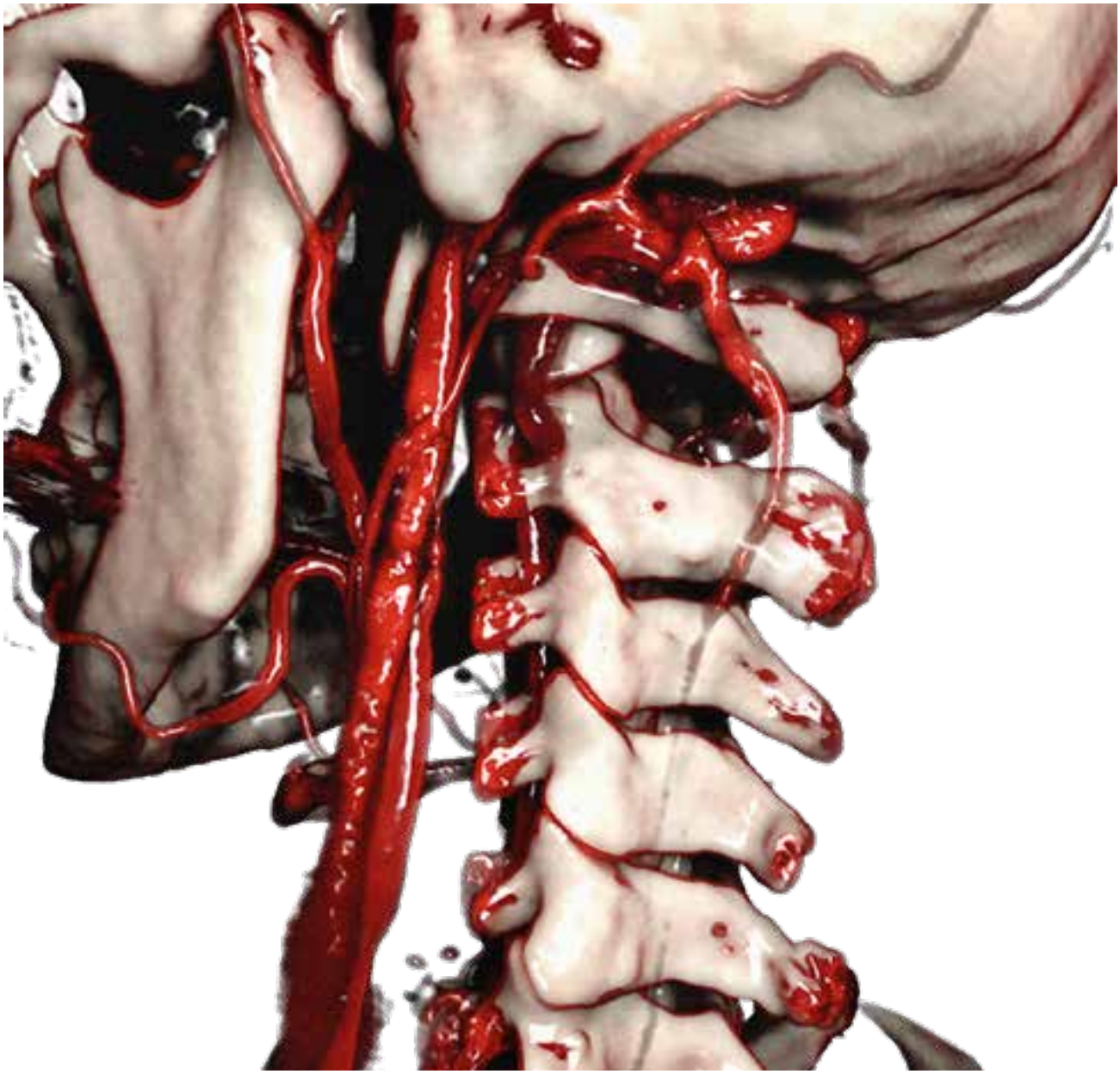
ANDERS YNNERMAN

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

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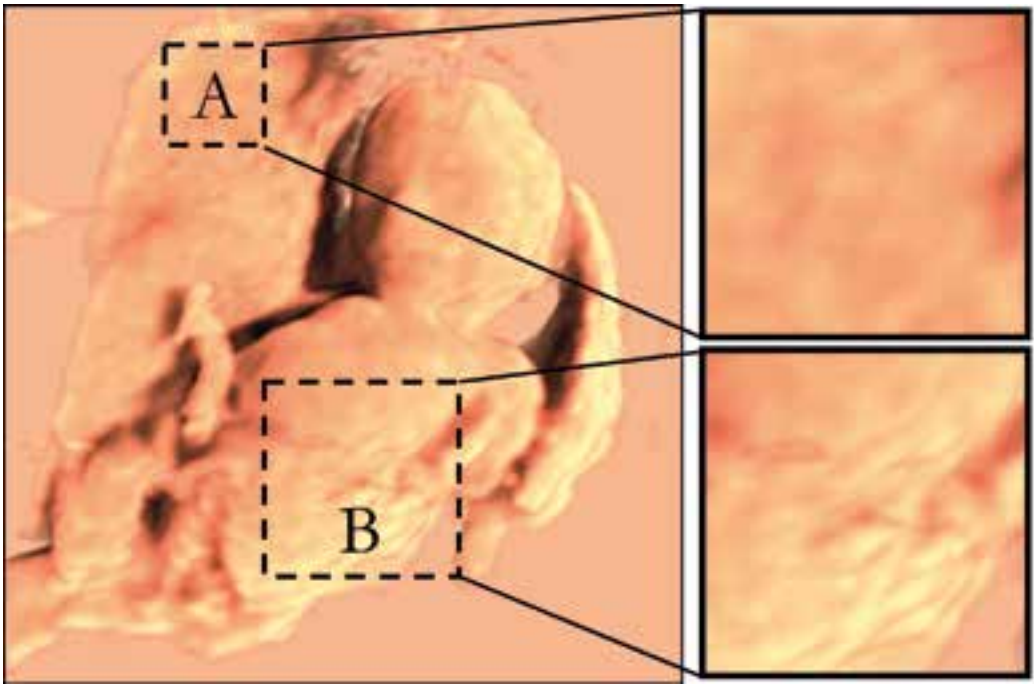
Joel Kronander, Daniel Jönsson, Joakim Löw, Patric Ljung, Anders Ynnerman, Jonas Unger. Efficient Visibility Encoding for Dynamic Illumination in Direct Volume Rendering. IEEE TVCG, Volume 18, Number 3, pages 447–462, 2012.

Ultrasound
Visualization
Simulation

POPULAR SCIENTIFIC SUMMARY

ANDERS YNNERMAN



High-Quality Illumination in Interactive Volume Graphics

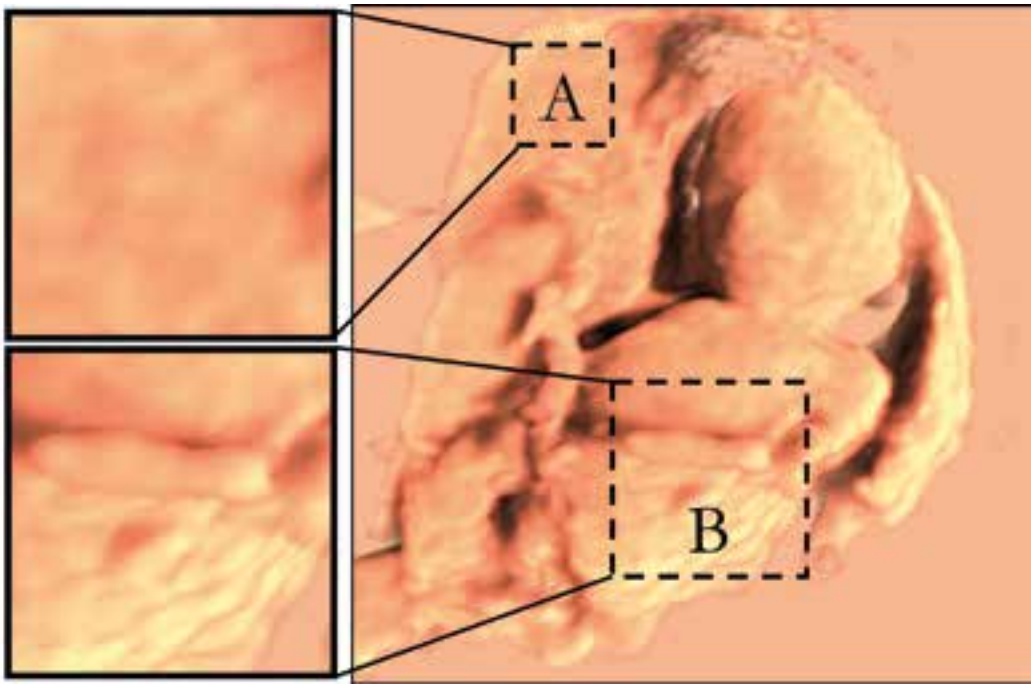


FIGURE. Highlights of two areas at different time-steps in a time-varying 3D ultrasound scan of a fetus. Region A changes little over time while a new feature appears in region B. By focusing the light transport computation on regions with highly changing areas, such as region B, we can reach interactive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

POPULAR SCIENTIFIC SUMMARY

CAROLINE BIVIK STADLER

DROID – Diagnostic Reference Oncology Imaging Database

Radiology and pathology, two important disciplines in diagnostic medicine 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 parts removed by surgery in high-resolution microscopes. Their diagnostic work relates to classification, detection and quantification of image features. This specialty is based on subjective assessments and therefore difficult and time-consuming to learn to master.

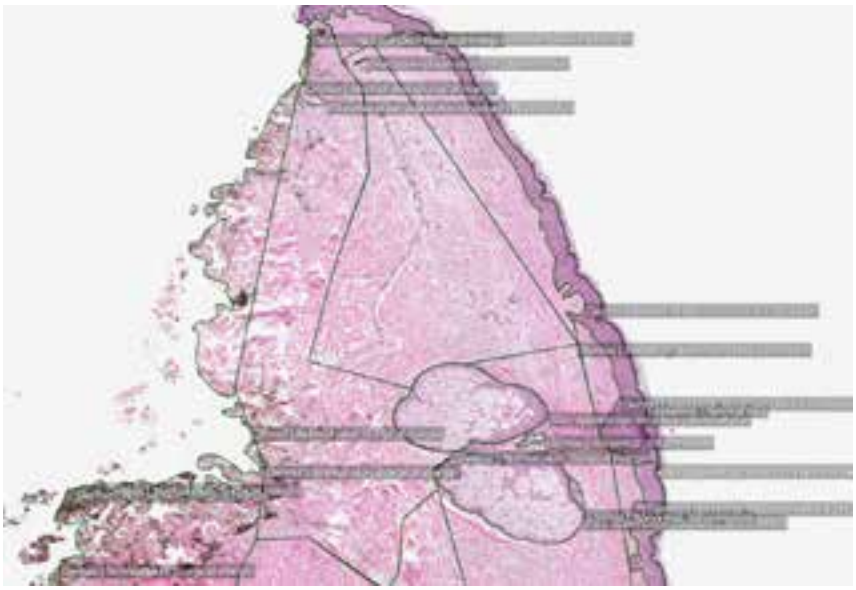


FIGURE 1. A digital image of a skin tissue section stained with hematoxylin-eosin (H&E). Manual annotations have been made to contour the histologic entities.

Today, many physicians place their hope in different artificial intelligence (AI) based decision support systems that are expected 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. For example, 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 analysis 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

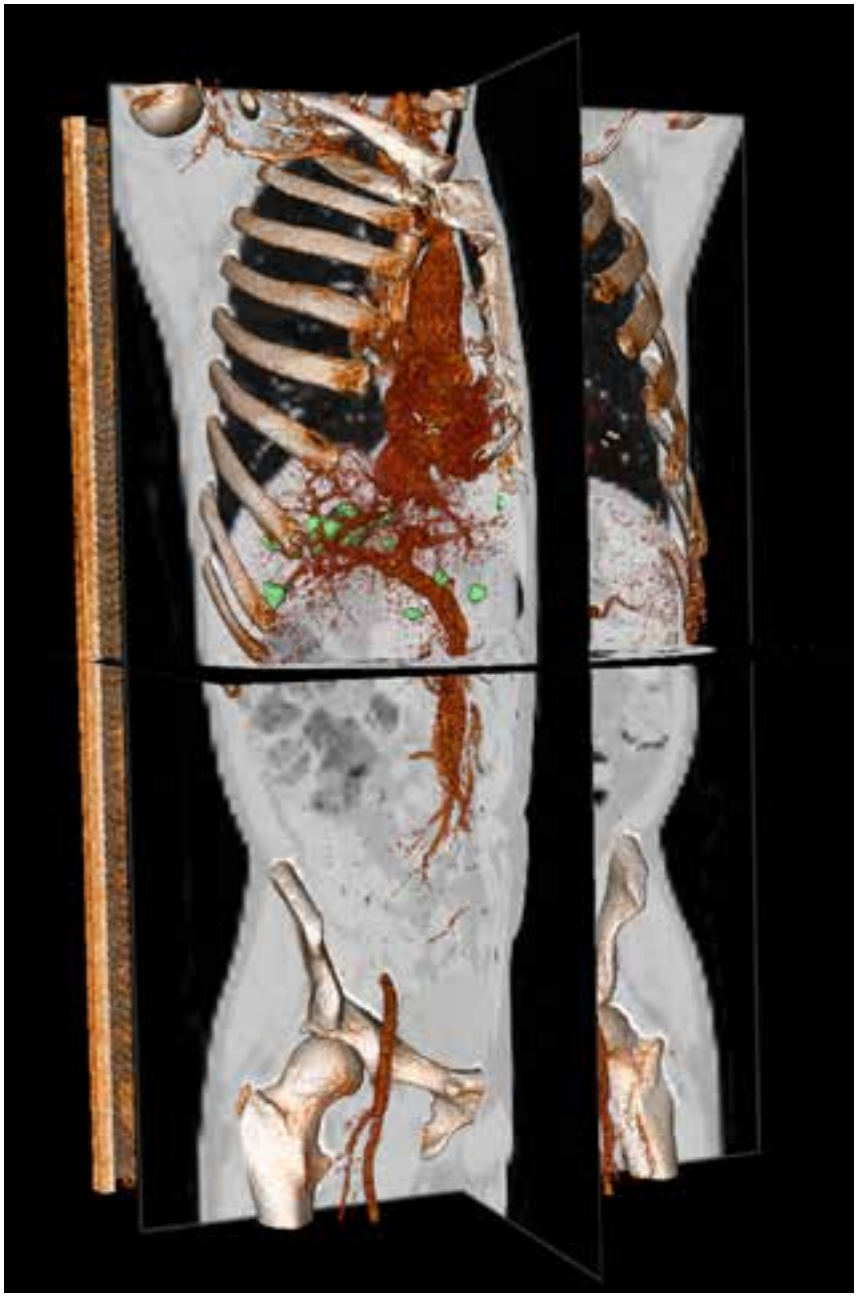


FIGURE 2. Liver lesion segmentations (green) in a CT abdomen examination.

for training is crucial and has a big impact on the performance of the system generated. The DROID project has compiled an open image database, containing detailed annotations of oncological images of several different types. The content of the image database is well diversified and contains images and annotations relevant to cancers linked to liver, skeleton, skin, colon, breast and ovary. Clinical experts have collected images, marked contours of specific morphological patterns and labeled them according to standardized anthologies. Based upon these annotated images, a number of AI-prototypes has been generated and trained, to validate the usefulness of the database.

The database includes 711 pathology whole-slide images and 113 computed tomography (CT) examinations. The image database has been published within the national arena AIDA hosted at CMIV. The database will be used for training of AI systems to support image diagnostic tasks in connection with diagnosis and follow-up of oncology patients, and in the long term to contribute to the large-scale use of AI in healthcare. Apart from CMIV the project involved Region Östergötland, Sectra and ContextVision. ■

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 Lindvall, Karin Stacke, Mischa Woisetschläger, Nils Dahlström, Johan Blomma, Anna Bodén, Karin Lindman, Jerónimo Rose, Nicolas Pinchaud, Ludwig Jacobsson, Darren Treanor, Claes Lundström, Martin Hedlund, Anders Persson

Grants
Visual Sweden 2017–2018

Publications
Karin Lindman, Jerónimo F. Rose, Martin Lindvall, Claes Lundström, Darren Treanor.
Annotations, ontologies and whole slide images – Development of an annotated ontology-driven whole slide image library of normal and abnormal human tissue. Accepted for publication in Journal of Pathology Informatics (2019).

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Breast data from the Visual Sweden project DROID. doi.org/10.23698/aida/drbr

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Skeletal data from the Visual Sweden project DROID. doi.org/10.23698/aida/drske

CT
Digital Microscopy
Oncology
Musculoskeletal
Gynecological
Modeling
AI/Data analytics

PROJECT INFORMATION

Project Name
Digital Pathology

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

Main Project Participants
Darren Treanor, Jeroen van der Laak, Anna Bodén, Karin Lindman, Sofia Jarkman, Jesper Molin, Martin Lindvall, Caroline Bivik Stadler, Martin Falk, Marie Waltersson, Martin Hallbeck, Peter Lundberg, Stergios Kechagias, Jeronimo Rose, Arrigo Capitanio, Helén Richard

Grants
VINNOVA 2017–2018

Key publications
Falk M, Ynnerman A, Treanor D, Lundström C.
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Homeyer A, Nasr P, Engel C, Kechagias S, Lundberg P, Ekstedt M, Kost H, Weiss N, Palmer T, Hahn H K, Treanor D, Lundström C.
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Lundström CF, Gilmore HL, Ros PR.
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Digital Microscopy
Cardiovascular
Neurology
Oncology
Musculoskeletal
Gastrointestinal
AI/Data analytics
Visualization

POPULAR SCIENTIFIC SUMMARY
CLAES LUNDSTRÖM

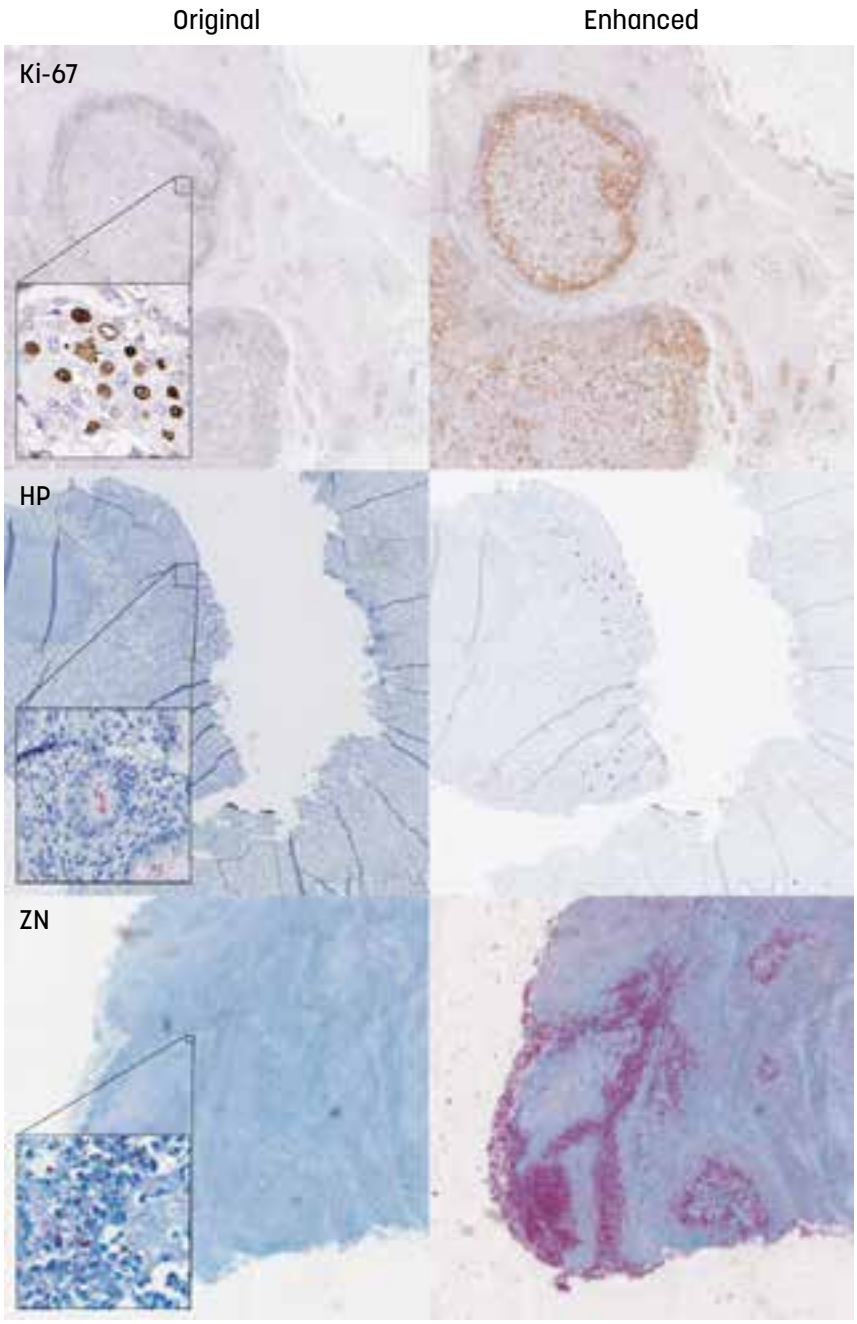
Digital Pathology

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.

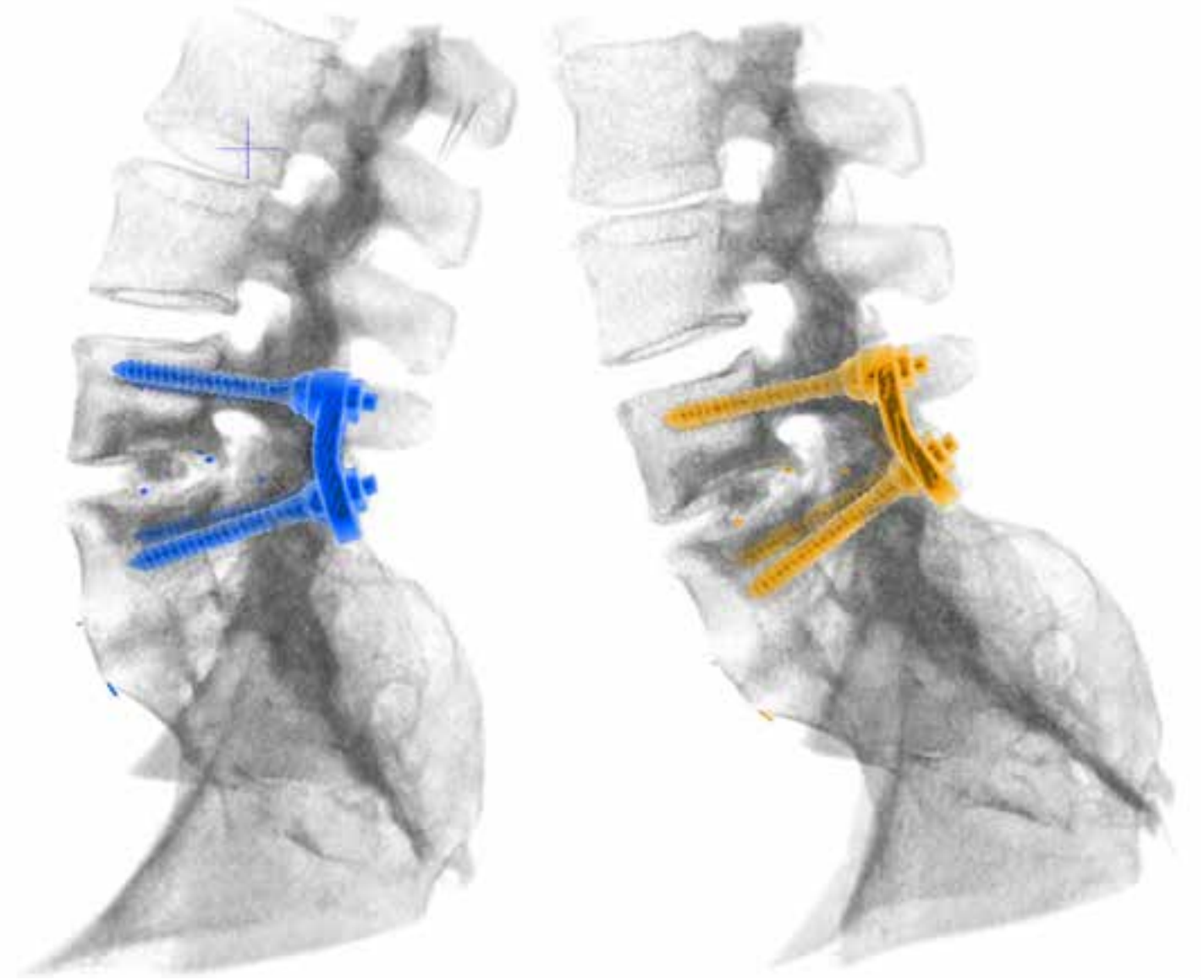
Analyzes of the pathology department show that digitization of the workflow from referral, finished preparation and scanning of samples to the pathologist´s workstation may result in a better overview of the workload, less administration and shorter turnaround times. Digital pathology also entails unique 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. ■

POPULAR SCIENTIFIC SUMMARY

CLAES LUNDSTRÖM

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 are being 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.

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.

Solutions are developed in five tracks, implant movement, patient movement, implant logistics, 3D print and pre-per-post integration, where CMIV primarily is 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.

A major milestone was reached in 2018 within the patient movement effort, led by Hans Tropp. The ground-breaking idea pursued is to combine a CT scan with marker-based motion capture, to create a dynamic model of the individual patient. There is now a working high-precision solution, that was demonstrated at the Swedish orthopedic congress. It is being used in a patient study of femoroacetabular impingement and studies of other applications are being planned. ■

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
Hans Tropp, Håkan Gauffin, Erik Sundén, Daniel Jönsson, 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 2017–2018

Key publications
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 (Phila Pa 1976). 2017 Jun 1;42(11):818–822.

CT
Musculoskeletal
Acquisition
Modeling
AI/Data analytics
Visualization
Simulation

POPULAR SCIENTIFIC SUMMARY

CLAES LUNDSTRÖM

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. CMIV is the host and physical meeting place of AIDA but aims to assist all Swedish actors in this domain.

The technical development within AI has been extremely strong in recent years. Modern AI is a toolbox that fits perfectly into the healthcare vision of »precision medicine«, the fully tailored treatment for each patient. Very few modern AI solutions have yet, however, reached actual use in imaging diagnostics. The reason is that the step from experiments to clinical routine entails many challenges. Even the most powerful algorithms need to be carefully placed in a context of workflow and interaction innovations to be useful.

AIDA's objective is to develop AI-based decision support solutions for imaging diagnostics that reach all the way to clinical use. An underpinning fundamental insight is that this complex challenge requires both interdisciplinary and cross-sectoral collaboration.

AIDA is built on three cornerstones. Most resources are used for projects developing AI-based decision support solutions. These are run by research groups in industry and academia across Sweden, in collaboration with healthcare providers. The second cornerstone is the AIDA core environment at CMIV, designed to support the development projects. All AIDA partners have access to a tailor-made technology platform, developed in collaboration with Sectra, and large amounts of training data will gradually be made available. Perhaps even more important is the meeting place aspect of the core environment,

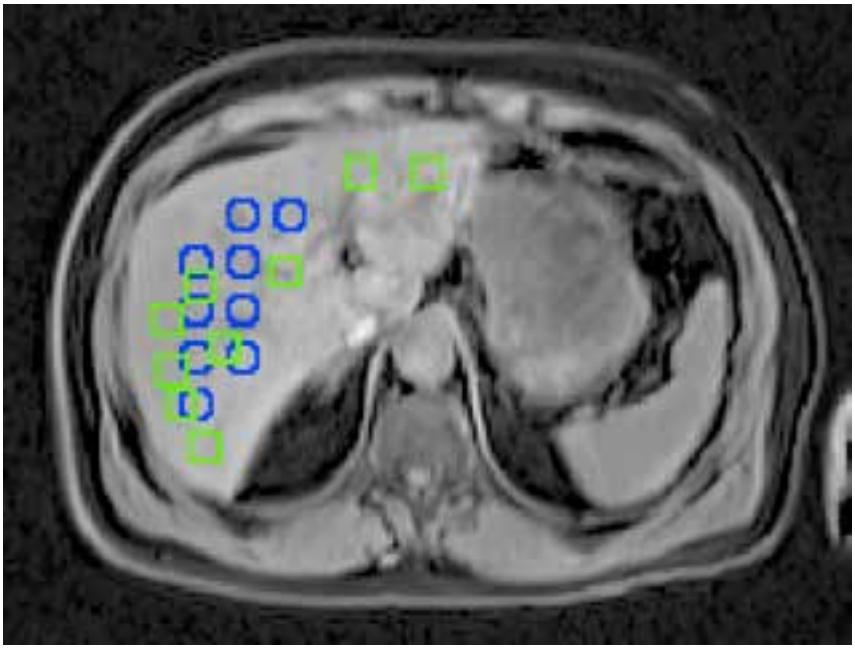


FIGURE. Development of an automated method, based on machine learning, for placement of regions of interest (ROI) in which the liver fat can be quantified. Diagnosis and grading of hepatocellular fat in patients with Non-alcoholic fatty liver disease (NAFLD) usually requires a liver biopsy and histology. However, as liver biopsy is an expensive, invasive, and painful procedure that is sensitive to sampling variability, the use of MRI as a non-invasive biomarker of liver fat has shown tremendous progress in recent years. Automation of this technology would further reduce costs for clinical use.

where workshops and meet-ups are frequently organized, providing valuable knowledge and exchanges.

The third cornerstone is clinical competence development, to give healthcare the right knowledge base to drive the AI development in the most effective direction. AIDA offers clinical fellowships where care provider employees carry out an individual project as continued education. AIDA also regularly organizes AI courses for physicians.

AIDA is an initiative within the Strategic innovation program Medtech4Health, jointly supported by VINNOVA, Formas and the Swedish Energy Agency. ■

PROJECT INFORMATION

Project Name
Analytic Imaging Diagnostic Arena

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

Main Project Participants
Caroline Bivik Stadler, Daniel Forsberg, Joel Hedlund, Jonas Unger, Maria Bolin, Marie Waltersson, Catrin Nejdeby, Gabriel Eilertsen, Darren Treanor, Magnus Borga

Grants
VINNOVA, Medtech4health

Key publications
Karin Lindman, Jerónimo F. Rose, Martin Lindvall, Claes Lundström, Darren Treanor.
Annotations, ontologies and whole slide images – Development of an annotated ontology-driven whole slide image library of normal and abnormal human tissue. Accepted for publication in Journal of Pathology Informatics (2019).

Mischa Woisetschläger, Johan Blomma, Nils Dahlström, Caroline Bivik Stadler, Daniel Forsberg (2019).
Liver data from the Visual Sweden project DROID doi:10.23698/aida/drli.

Karin Lindman, Jerónimo F. Rose, Martin Lindvall, Caroline Bivik Stadler, Claes Lundström, Darren Treanor (2019).
Skin data from the Visual Sweden project DROID doi:10.23698/aida/drsk.

- CT
- MRI
- Digital Microscopy
- Ultrasound
- Other
- Cardiovascular
- Neurology
- Oncology
- Musculoskeletal
- Gastrointestinal
- Gynecological
- Pulmonary
- Metabolism
- AI/Data analytics
- Visualization

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

Main Project Participants
Wolf-Dieter Zech, John Bäckman, Malgorzata Pietrzak

Key Publications
Schwendener N, Jackowski C, Persson A, Warntjes MJ, Schuster F, Riva F, Zech WD.
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.

Zech WD, Schwendener N, Persson A, Schuster F, Riva F, Jackowski C.
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.

Zech WD, Schwendener N, Persson A, Warntjes MJ, Riva F, Schuster F, Jackowski C.
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.

MRI
Acquisition

POPULAR SCIENTIFIC SUMMARY

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

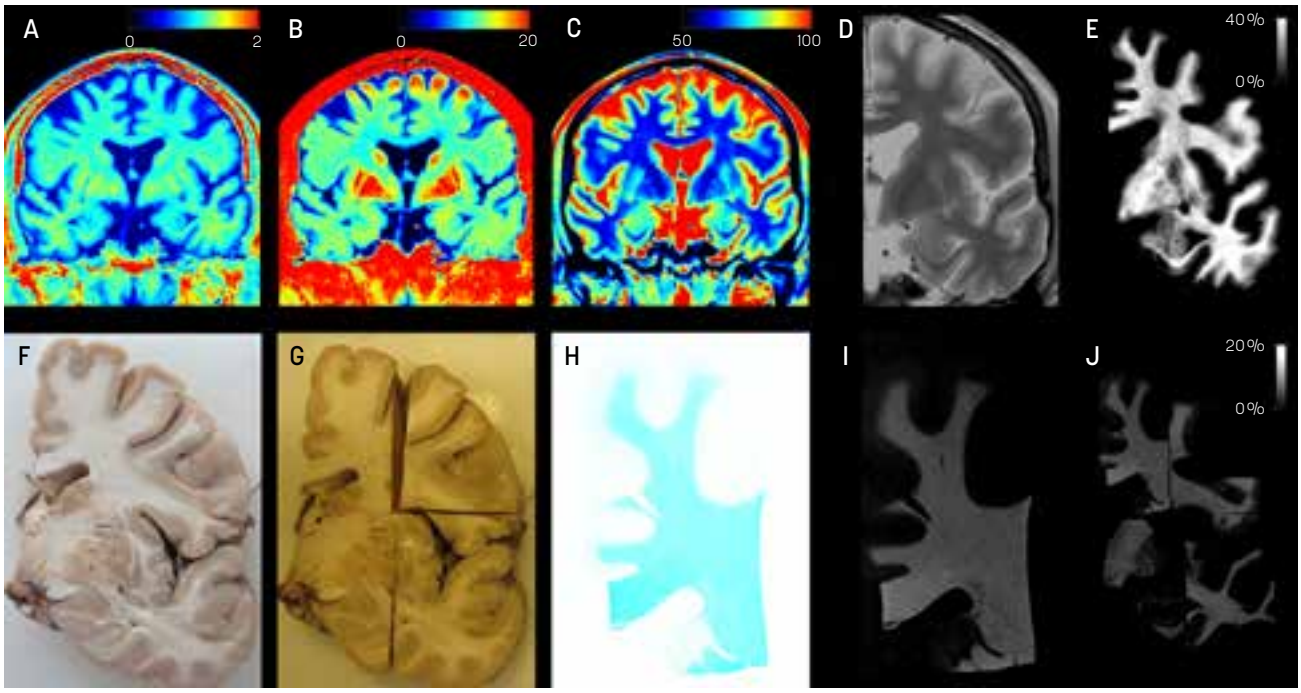


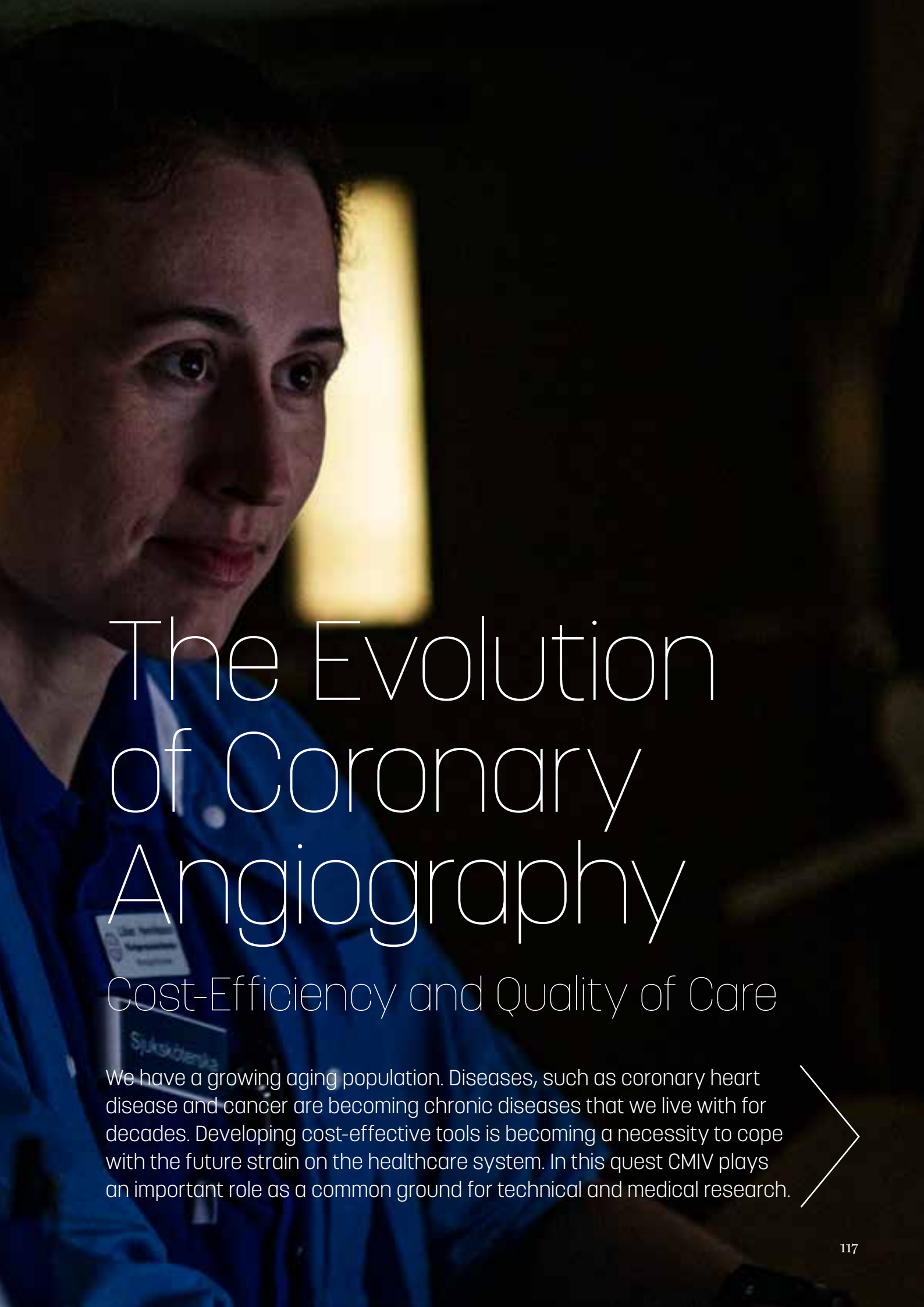
FIGURE. The process for myelin evaluation on a male subject, 69 years old, acquired at a temperature of 10 degrees.

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. ■



The Evolution of Coronary Angiography

Cost-Efficiency and Quality of Care

We have a growing aging population. Diseases, such as coronary heart disease and cancer are becoming chronic diseases that we live with for decades. Developing cost-effective tools is becoming a necessity to cope with the future strain on the healthcare system. In this quest CMIV plays an important role as a common ground for technical and medical research.

Cardiovascular disease is the most common cause of death, globally as well as in Sweden. The majority of these deaths are related to heart attack or stroke. Although it is still common cause of death in Sweden, heart attack incidence and mortality has shown a steady decrease during the last decade. As we generally live longer and longer we are moving towards an older and older population. Diseases as coronary heart disease and cancer are becoming chronic diseases that we live with for decades. This puts a new strain on the healthcare system and demands for cost-effective tools.

The innovation process in healthcare is not always straight forward. Often technical advances fail to transform into clinical tools. Letting the medical demands direct the technical research will ensure a clinically useful result.

A Cost-Efficient Healthcare

Magnus Janzon is a cardiologist, associate professor, and head of Cardiology Department at Linköping University Hospital. He has many years of research experience and started out with cost-effectiveness analyses in cardiovascular disease. The focus on cost-effectiveness has continued to be central in his research ever since.

– I think it is very important that we use the limited resources we have for healthcare in the most optimal way. There is always more to do than we have money for. We cannot use a method that is extremely expensive for every heart attack patient because it is not efficient, Magnus says.

Chest Pain Patients

Today, when a patient comes into the ER with chest pains a clinical examination is initiated with blood samples and ECG. High risk patients are hospitalized and an acute coronary angiography is performed.

A coronary angiography is an invasive

"I think it is very important that we use the limited resources we have for healthcare in the most optimal way. There is always more to do than we have money for."

Magnus Janzon

method where you access the coronary arteries with a catheter through the aorta. The catheter is inserted in an artery at the wrist and when it reaches the heart contrast agent is injected to visualize the coronary arteries on an X-ray image. A visible narrowing of the vessel lumen can be a sign of impaired heart function. If the obstruction is more than 50 % the vessel is adjusted through a balloon dilatation or with a stent.

Many patients with chest pains are of intermediate risk and they often enter the healthcare system through the primary care. Traditionally many of these patients end up with a coronary angiography to assess the status of the coronary arteries. However, around half of them does not need any further intervention since their arteries are found normal. Hence, the invasive procedure was done unnecessarily.

Imaging Pioneers

– In 2004 we started up a research project with CMIV where we used computed tomography (CT) to assess the coronary arteries. Since 2006 we have used CT in our clinical routine. At that time, we were one of very few hospitals in Sweden doing this procedure, Magnus explains.

CT angiography has a negative predictive value. This means that if the arteries look normal on the CT image you can be 99 % sure that they are normal but if the results show a narrowing you need to proceed with your investigation. For the patients with normal arteries the invasive procedure can be avoided in this way.

– An invasive procedure is always a risk for the patient. With the CT angiography you can do the examination at a much lower risk and at the same time, a much lower cost.

The research study is a collaboration between the Department of Cardiology and CMIV.

– This is a very fruitful collaboration. We have the patients and the clinical knowledge and CMIV have the imaging modalities and the technical expertise, Magnus says.

In the study 1200 patients with chest pains have been examined with CT angiography and the follow-up period is up to 7.5 years. Few other studies have a follow-up period of this size. The results show that the patients who are cleared by the CT image also will have a good long-term prognosis.

– When we start up a new method it is very important to follow up how the patients are doing and evaluate the results. With this method we were almost ten years ahead of the national guidelines on CT angiography and I think that this should be possible to do at a university clinic. But you always have to evaluate to ensure quality. We will continue to follow these patients to learn more about what will happen over time, Magnus continues.

Money to Save

The cost for a coronary angiography is very high. The cost for the procedure itself is twice as high as the cost for a CT angiography. Adding costs for hospitalization for the invasive method the hospital is saving around 10 million SEK every year on the patients that do not proceed to coronary angiography.

– This project which is both beneficial for the patient and cuts costs is an amazing example of how we need to work with research and development in healthcare, Robert Ring says, the Production Unit Manager at the Diagnostic Center at Region Östergötland.

– On the initiative of the regional heart clinics the CT angiography protocol will now be implemented at the regional hospitals, to ensure equal care throughout the region, Robert continues.

What the Eye Sees is not Always Correct
Both the coronary angiography and the CT angiography produce images of the coronary arteries for the radiologist to visually assess. In borderline cases this assessment is not conclusive enough. However, during the coronary angiography it is possible to do a pressure measurement on both sides of the obstruction. The quote of the values determines if the obstruction is significant or not. A value less than 0.8 means that the blood flow is lowered to a point where the heart muscle is affected. The method is called FFR, the functional flow reserve.

Inconclusive cases therefore still have to proceed from CT to invasive angiography to get properly diagnosed with FFR even though many of them end up not needing any intervention. This is of course not optimal since the patient then has gone through two radiology examinations unnecessarily.

Simulated Functional Flow
In a research setting it is now possible to use the CT data to simulate the flow in the arteries. Although it technically is a completely different method, it is called CT-FFR. A computer uses the data from the image and calculate the pressure drop below the obstruction. The value from the analysis is adjusted to match the values obtained from the traditional FFR.

Studies from, among others, the research group at CMIV show that the CT-FFR produce comparable results to the invasive measurement.

– Studies show that it is the pressure drop that is crucial in determining if a surgical correction is necessary or not. If we could manage that without an invasive procedure it would be fantastic, Magnus Janzon says.

What is holding the method back from clinical practice is the availability. The data is sent to the software company where the calculations are made. This causes a delay in the system.

– To be able to use this it needs to be fast and safe. We need the results immediately to be able to decide how to proceed with the patient, Magnus explains.

Innovation on Demand
The research group is part of a consortium with researchers from the universities of Krakow, Erasmus, Bejing and South Carolina. They are working on a new diagnostic tool for pressure drop determination. It is based on a deep learning algorithm that has been trained on 12 000 coronary arteries from actual patients. With the algorithm the computer can determine if the vessel is healthy or sick by looking at the image.

Just as CT-FFR the new method is calibrated to give values that are comparable to the original FFR method. The algorithm has been tested on patient materials where both CT-FFR and FFR data are available and the results show comparable results.

– I believe in this method and I think that the results are very promising, Magnus says.

As the only center in the world CMIV can now use the data collected in the CT angiography to visualize the blood flow in the whole heart and show how the heart moves. This method presents additional functional information of the heart that is not normally available from a traditional coronary artery examination. This research is described in more detail in the flagship 4D Flow CT.

Translational Research Efforts
Working integrated is one of the strengths in Östergötland. The university and the region have a well-established research collaboration. In many cases also the industry is involved. When the University Hospital constructs a new building for lab work the university will be involved from the start.

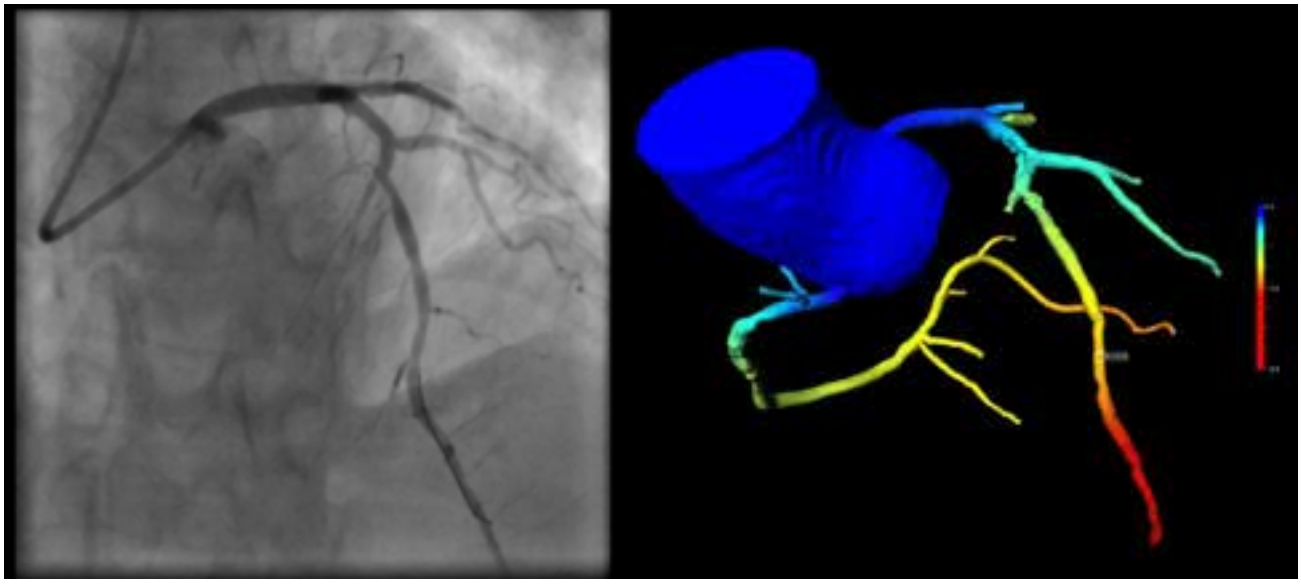
– Region Östergötland is involved in many research efforts but we should always strive to do more. Research and innovation are absolutely crucial for the development of healthcare, Robert Ring says. I think that it is a work environment issue as well. To provide good health care is hard work and research and development gives something extra to the job. The progress we experience gives us energy to continue.

Magnus Janzon agrees with Robert:
– To evaluate what we do in a scientific manner is absolutely crucial to maintain quality. Randomized studies are common for new treatments but new modalities are often just implemented. This is what we do with the new FFR methods. We evaluate thoroughly and when it is ready we will implement.

Magnus Janzon Goes Visionary
– If I should look visionary on the future I would say that the CT angiography with computer calculated FFR values will be the established protocol in a not too distant future. Then the invasive procedure can be reserved for patients that need a balloon dilatation or a stent. With the results from the CT you can be prepared and know exactly what should be done you can be very focused and use both less contrast agent and radiation dose.

– I think that we are moving towards more and more non-invasive methods and the CT angiography will have a central role there. Perhaps we could be completely non-invasive in the future, using shockwave therapy as with kidney stones.

– I see a fantastic development. You often believe that you have reached the ceiling but then you realize that you can always do more, Magnus concludes his vision. ■



Left: Coronary angiography with pressure guide wire in the left anterior descending coronary artery (LAD). FFR = 0.81.
Right: Corresponding CT-FFR color map with cFFR = 0.82.

Below: Magnus Janzon at one of the Seldinger labs where coronary angiographies are performed.

The CMIV Research School

The CMIV Research School offers a doctoral program with both medical and technological entries and a coherent research education. A basic principle for our doctoral program is the translational approach where we encourage projects to have a close connection to the clinic. Currently there are around 20 PhD students admitted to the research school. Here a selection of them presents their research.

ANETTE KARLSSON

Assessing Muscle Volume Using Magnetic Resonance Imaging

The entire muscle volume of humans can automatically be calculated after a ten minute examination in a magnetic resonance scanner. It is also possible to distinguish different muscles from each other and look at the amount of fat inside the muscles. This technique is today used as a part of a six minute neck-to-knee examination scan to calculate the muscle volume and the fat infiltration of the thigh muscles. The muscle volume and fat infiltration can then be analyzed together with the amount subcutaneous fat (fat between skin and muscles), visceral fat (the fat around abdominal organs), and liver fat fraction.

The greatest health challenges of today are either obesity related or ageing related. While getting older, you start losing muscle volume, 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.

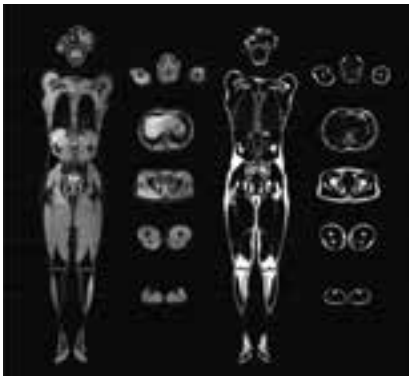


FIGURE 1. A paired magnetic resonance image where the left shows all the water within a whole body and the right shows all the fat.

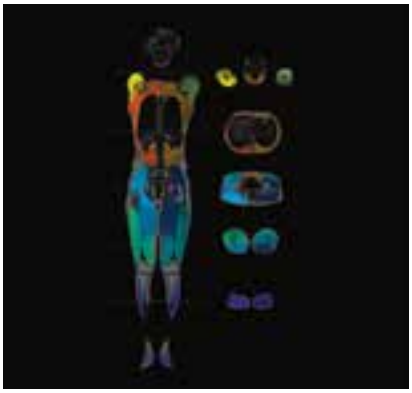


FIGURE 2. A typical result from the automatic method. The different muscle groups are shown in different colors. Grey color indicated that the automatic method has not considered that tissue as muscle tissue.

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. ■

PROJECT INFORMATION

Supervisors
Magnus Borga, Ola Friman, Janne West, Anneli Peolsson

Project
WADIT
MR-based Body Composition

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

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).

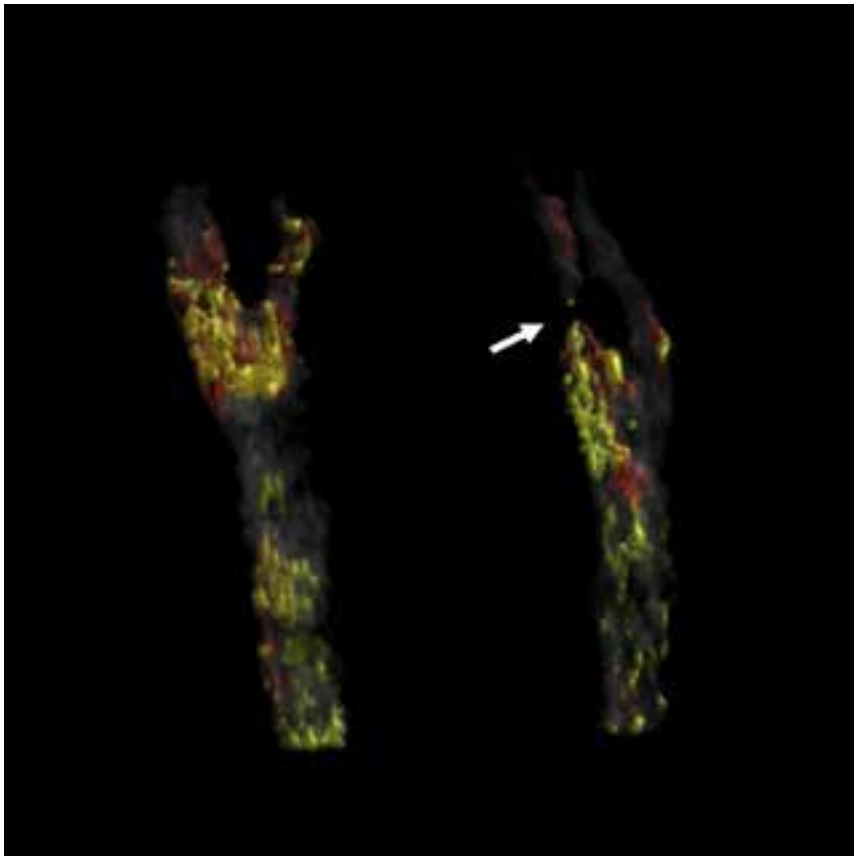
The CARMA-study is a prospective study of 53 patients with carotid atherosclerosis. The study uses a repeated-measures design where assessments were made at baseline, and after one year. Data collection started in 2017 and is finished.

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 have had a four-point Dixon and cardiac-triggered T1-weighted qMRI-assessment at two points in time, detecting LRNC and IPH by registering the Dixon images against the T1W images. We use a 3T Philips Ingenia scanner located at CMIV.

Now we are facing the part of the study where we will work with the data to look for changes in plaque morphology and plaque contents over the study year and compare any changes to alterations in the patients' cardiovascular risk, blood tests and even inflammatory markers in the blood.

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.

In 2018, a subgroup of the CARMA patients had a complementary assessment of their carotid plaques, using a hybrid PET/MRI in Uppsala. This resulted in collected image material from 12 patients with carotid atherosclerosis, and we look forward to work with the data in 2019, comparing PET and MRI measurements. Hybrid PET/MRI assessment of carotid plaques and the measurements we will perform are unique due to the new technical methodology, and will result in material that has not been published before by other research groups. ■



PROJECT INFORMATION

Supervisors
Ebo de Muinck, 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

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 brain activity and blood flow changes exists and is commonly referred to as the neurovascular coupling.

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 left, 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). However, the precise mechanisms which translate neural activity to these archetypal hemodynamic responses remain elusive. Furthermore, the neurovascular coupling is shown to dysfunction in different neurological disorders.

Here, the use of mathematical modeling, where biologically based hypotheses are translated into mathematical equations and evaluated in a systematic way has been successful. We have previously developed a mathematical model, illustrated in figure 2, which is based on state-of-the-art experimental insights of the neurovascular coupling. This model can describe and predict both positive and negative BOLD-responses from a variety of fMRI-data as well as arteriolar dilation dynamics in rodents. Furthermore, the model can accurately reproduce the effect of common anesthetics used both in rodent and human studies. These results pave the way for a better quantitative understanding of how neural activity and hemodynamic responses are connected and provides a new environment that allows for testing of potential therapeutics and their effect on brain hemodynamics. ■

FIGURE 1

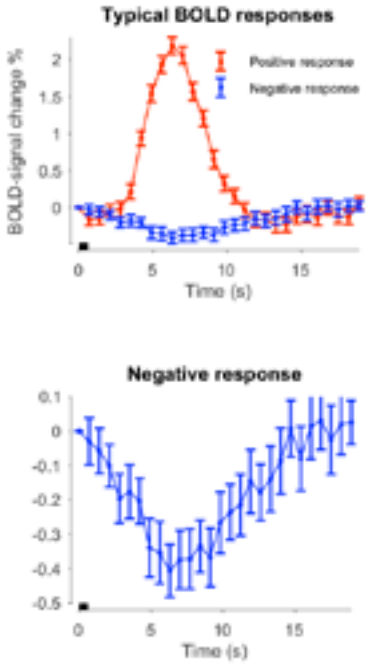
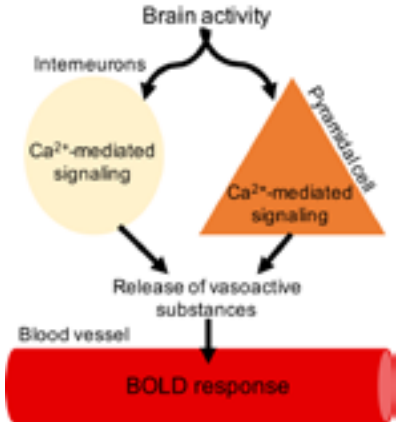


FIGURE 2



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's degree in engineering biology, Linköping University, 2011–2014

Research preparatory course I–II 2014–2015

BHARTI KATARIA

Evaluation of Optimization Methods for Abdominal Computed Tomography

In all diagnostic radiology examinations using ionization radiation it is imminent to produce images of good diagnostic quality, but at the same time to endeavor to keep the radiation dose as low as reasonably achievable (ALARA principle). Optimisation is not only about patient dose and image quality but also about the diagnostic task at hand i.e. the correct examination technique for a specific diagnostic enquiry.

Approximately one third of all CT examinations are abdominal CT's. These examinations deliver a high radiation dose to the patient as multiphase examinations are quite common in this region. 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.

The first two studies evaluated the dose reduction potential of two iterative reconstruction algorithms SAFIRE and ADMIRE. These studies concluded that SAFIRE at strength 1 allows for a 5–9 % dose reduction on a low-dose abdominal CT and ADMIRE strengths 3 & 5 showed a positive correlation between ADMIRE strength 3 and increasing potential dose reduction for all image criteria assessed but strength 5 showed image quality improvement for some aspects of image criteria assessed.

In the third study we aimed to compare visual image quality as well as detection of positive pathological findings between the three phases of our CT Urography protocol. The hypothesis was that the native phase is good enough in image quality when assessing the delineation of anatomical criteria as well as in detection of pathological findings compared to the nephrographic and excretory phases. The CT Urography protocol is defined to visualise renal anatomy. As expected, the individual criteria assessed were best visualised in the contrast enhanced phases depending on anatomical structure evaluated. There were marginal differences in pathology assessment between the three phases but these were not statistically significant. We failed to isolate the individual effects of dose and contrast enhancement on image quality. A prospective study with comparison of all three phases at different dose levels would have been more ideal to study the individual effects of dose and contrast enhancement. However, such a design would increase the radiation burden and therefore not ethically possible. ■

PROJECT INFORMATION

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

Background
Diploma in Diagnostic Radiography, Bristol School of Diagnostic & Therapeutic Radiography, 1981

Bachelor of Medical Science in Nursing; Linköpings University 2008

Master of Medical Science in Nursing; Linköpings University 2013

Work experience: 36 years' experience as a Diagnostic Radiographer performing CT; MRI; Emergency radiography and general radiography examinations:

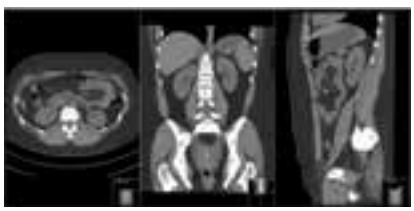
Diagnostic Radiographer in Kenya 1981–1985

Diagnostic Radiographer at Vrinnevi Hospital, Norrköping 1986–2014

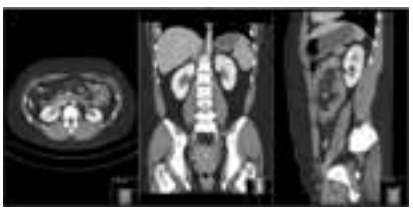
Diagnostic Radiographer at University Hospital in Linköping 2014–present

PhD student since January, 2014 at Linköpings University and CMIV

Native Phase



Nephrographic Phase



Excretory Phase

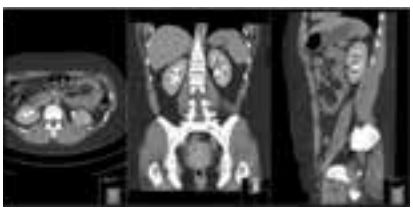


FIGURE. Comparison of the three phases of the CT Urography protocol in a study patient diesplayes in MPR reconstruction in three planes.

XUAN GU

Diffusion MRI Data Analysis

Diffusion MRI is a non-invasive technique used for studying brain tissue microstructures. Diffusion-derived scalar maps provide rich information about microstructural characterization. There are two major bottlenecks in obtaining the diffusion-derived scalar maps. First, it is expensive and time consuming to acquire high quality diffusion data. Second, accuracy of the diffusion-derived scalar maps relies on elaborate diffusion data processing pipelines, including preprocessing (head motion, eddy current distortion and susceptibility induced distortion corrections), diffusion model fitting and diffusion scalar calculation. Small errors occurring at any of these steps can contribute to bias of the diffusion-derived scalars. For some advanced diffusion models e.g. mean apparent propagator (MAP) MRI, processing of a single slice of the brain can take hours to finish.

Generative Adversarial Networks (GANs), a class off artificial intelligence algorithms, is one of the most important ideas in machine learning in the last 20 years. GANs can be trained to generate realistic images from a noise vector, or to translate between different domains (e.g. summer images to winter images). GANs have already been widely used for several applications in medical imaging, such as denoising, reconstruction, segmentation, detection, classification and image synthesis. However, GANs for medical image translation are still rather unexplored, especially for cross-modality translation of MR images.

In this project, we proposed a new application of CycleGAN to translate T1 images to diffusion-derived scalar maps (FA, fractional anisotropy, and MD, mean diffusivity). Data from 1,000 subjects were used to train the CycleGAN. Both qualitative and quantitative evaluations of generated images were carried out in order to assess the effectiveness of the method. The synthetic FA and MD images are remarkably similar to their ground truth.

Future research may focus on investigating whether training using more than one slice per subject can further improve performance. A comparison study of image translation using 2D and 3D GANs is thus worth looking into. ■

PROJECT INFORMATION

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

Background
B.Eng. in Communication Engineering, Beijing University of Posts and Telecommunications, China

M.Sc. in Wireless Communications, University of Southampton, UK

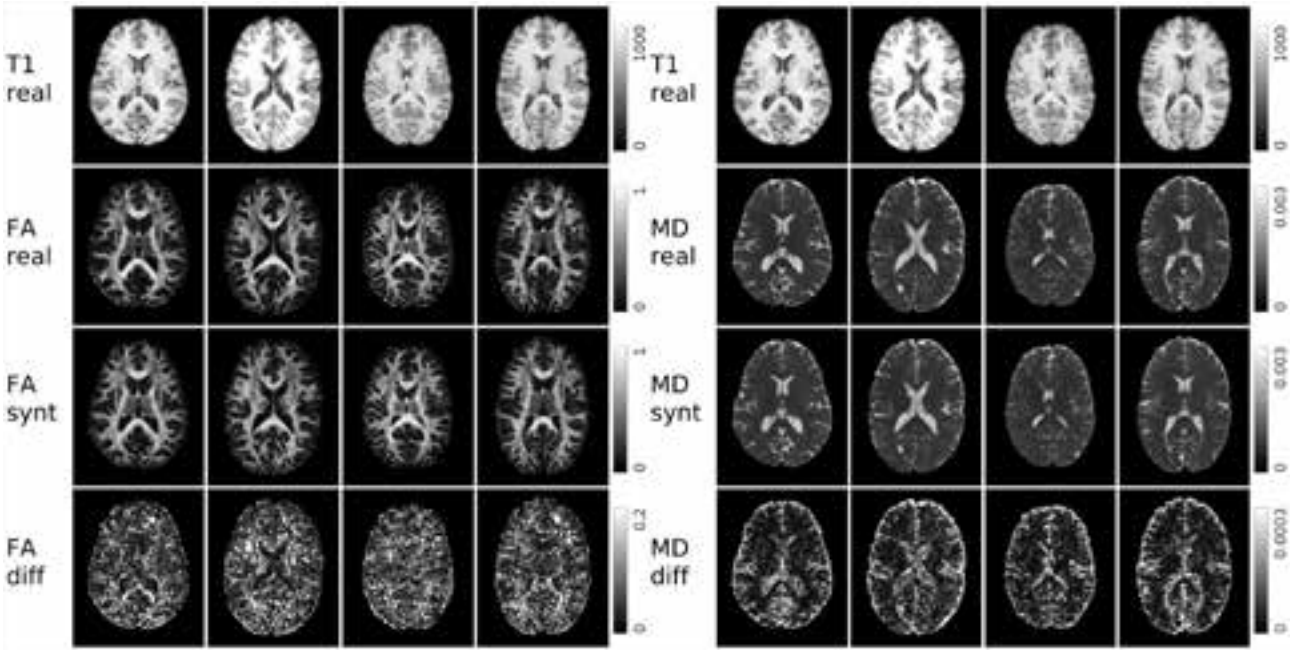


FIGURE. T1-to-FA and T1-to-MD image translation results for 4 test subjects. First row: True T1 images, second row: true FA and MD images, third row: synthetic FA and MD images, fourth row: error of true and synthetic FA/MD images.

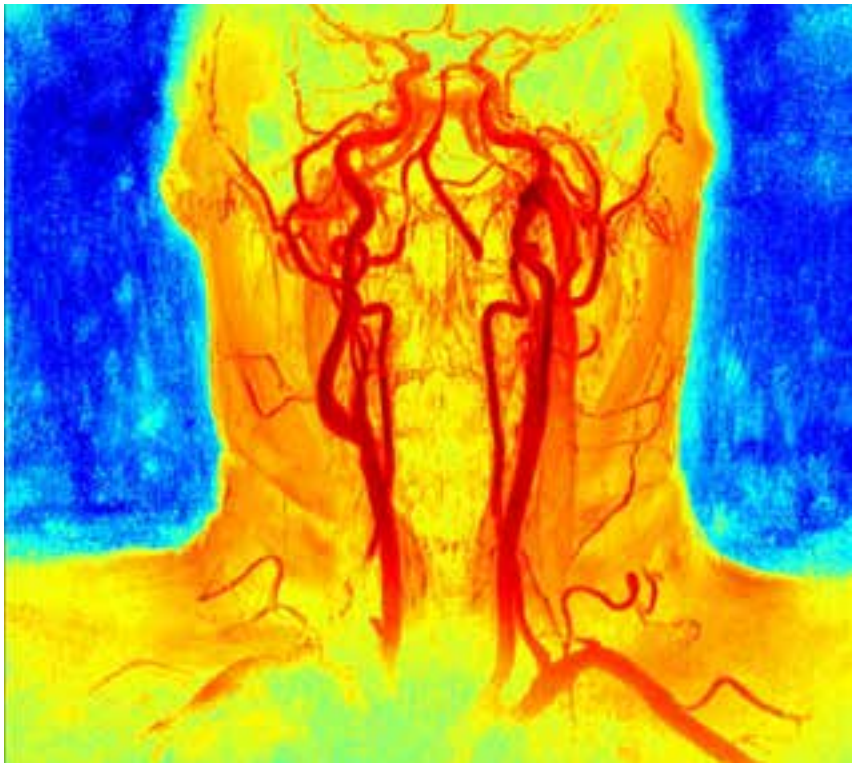


FIGURE. Stylized image of neck vasculature created using 4D Flow MRI imagery.

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 stenoses in the carotid bifurcation often have large levels of turbulent flow. Using 4D Flow MRI the stresses acting on the wall caused by turbulence and high velocity flow can be quantified, and with this new information, we can study how this abnormal flow characteristic impacts the vessel. To do this, we incorporate information about the composition of the wall, generated using the Dixon MRI technique. This lets us quantify and compare, for example, the amount of fat in the vessel wall against the stresses acting on the wall. This information could be useful in understanding the development of atherosclerotic plaques that often form in the carotid bifurcation. ■

PROJECT INFORMATION

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

Project
Non-Invasive Imaging 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

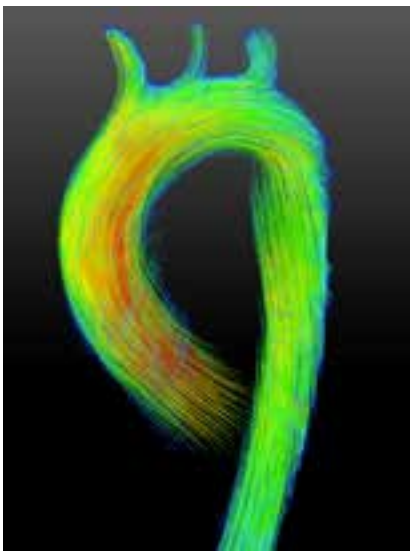
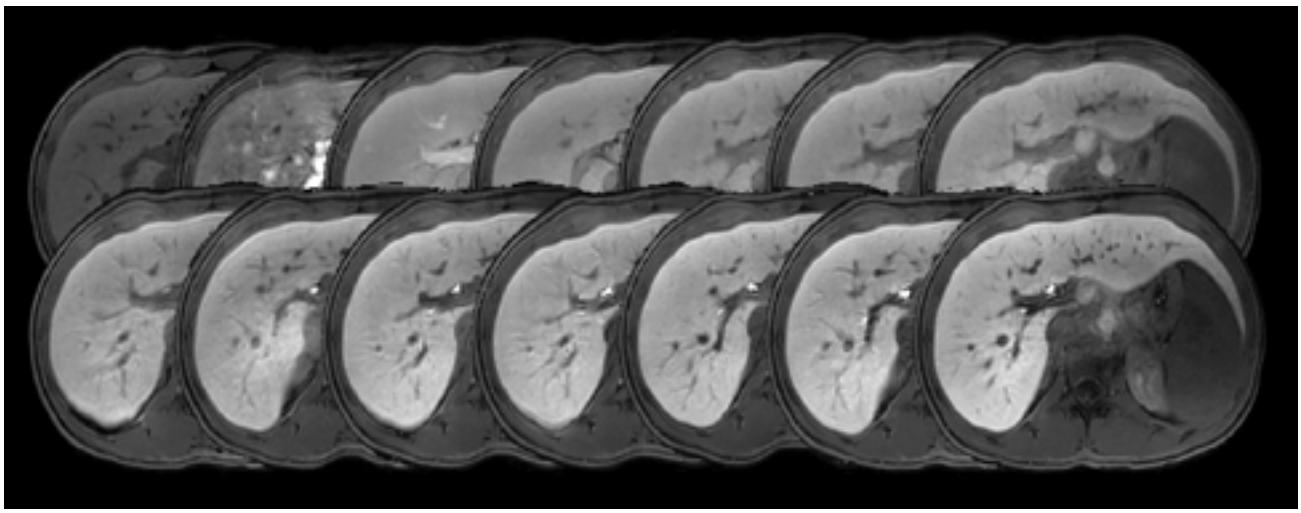


FIGURE. Streamline visualization of blood flow through the Aortic Arch in a healthy young volunteer created using 4D Flow MRI.

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, (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 the 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. ■

FIGURE. Examples of MR-images of the liver before and at several time points after injection of contrast agent. As can be seen, the liver becomes brighter as more contrast agent is accumulated in the liver.

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)

SOFIE TAPPER

Neurotransmitter Imaging of the Human Brain

The main inhibitory and excitatory neurotransmitters in the human brain are γ-aminobutyric acid (GABA) and glutamate respectively. The ratio between them has been shown to demonstrate the manifestation of certain neurological disorders. Therefore, it is important to develop a non-invasive clinical tool for reliable quantification of these neurotransmitters.

Single-voxel 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 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 method that reliably quantifies GABA and other metabolites. An MRS Imaging (multi-voxel) pulse sequence has been developed in collaboration 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.

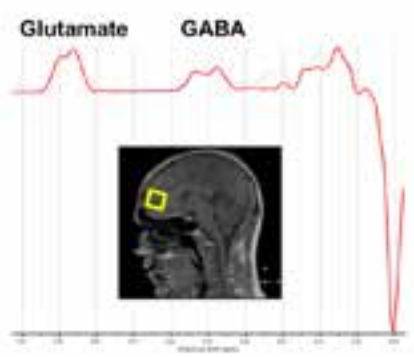


FIGURE 1. The GABA and Glutamate signals obtained from a GABA edited single-voxel MRS measurement.

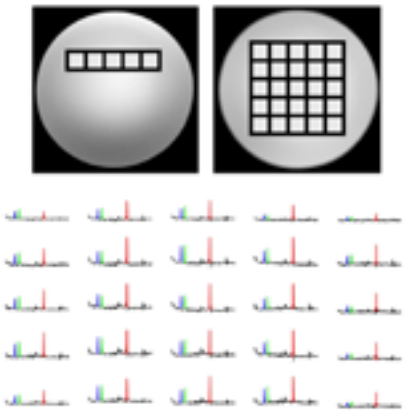


FIGURE 2. The resulting GABA concentration map from an MRSI GABA-edited measurement performed on a phantom. The inner cube is filled with a solution with 30 mM GABA, and the outer sphere does not contain any GABA.

In this project, the main clinical applications for single-voxel GABA quantification are as follows; 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

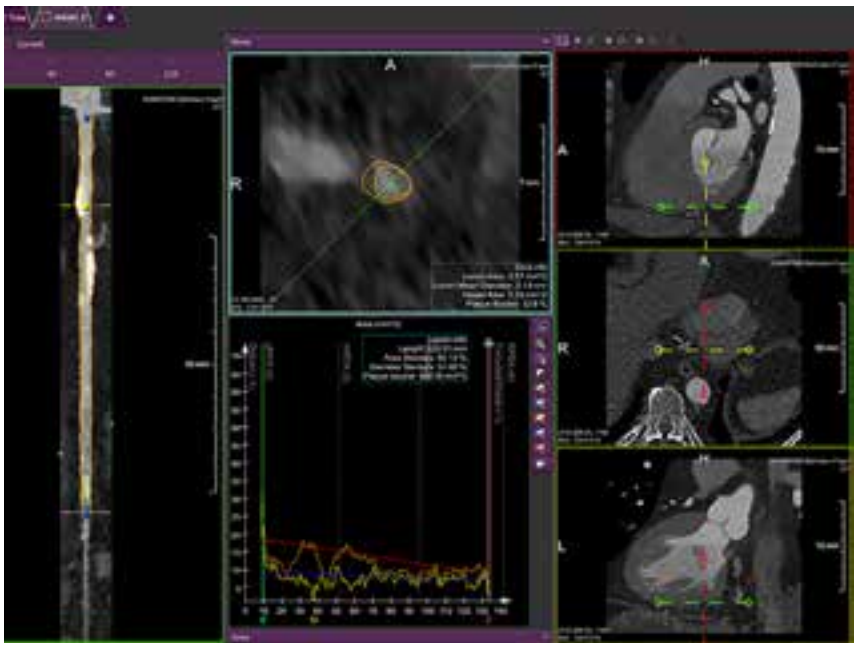
LILIAN HENRIKSSON

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

DAVID ABRAMIAN

fMRI Methods for Brain Tumour Treatment

Functional magnetic resonance imaging (fMRI) is an MRI modality used to reveal the location of brain activity when a subject performs a certain task. Its use has revealed a lot about functional localization in the brain, but its application is generally limited to the outer layers of the brain, the so-called gray matter. Gray matter is composed of neuronal bodies, and is where brain processing takes place. On the other hand, white matter constitutes approximately 50 % of the brain mass, and serves to connect distant brain regions. Whether it is possible to detect fMRI signal in white matter is a debated question, with the general consensus being that it is not. However, recent studies have suggested that while there are many reasons why this signal would be harder to detect in white matter, the possibility itself cannot be ruled out. Furthermore, it has been argued that one of the reasons why white matter activations are rarely reported is because the differences between gray and white matter are rarely acknowledged in the design of fMRI studies, which results in studies optimized solely for detection of activity in gray matter.

In our work we attempt to explore this line of reasoning, and consider the shape of any possible activations to be one of the principal differences between white and gray matter. Because white matter is made of long axonal strands, it has a very directed structure, and we believe it is reasonable to assume that activations in white matter would have an elongated shape that follows this structure. To incorporate this assumption into a standard fMRI processing pipeline, we devised a novel filtering approach informed by diffusion data, which encodes the direction of the neuronal axons at every point in the brain. We evaluated our filtering approach on 100 subjects from the Human Connectome Project dataset, and managed to find significant white matter activations on individual subjects that standard pipelines were not able to detect.

The possibility of detecting activity in white matter can bring about a new way to characterize, diagnose and prevent diseases. We believe that our work can be helpful in reaching this goal. Future avenues for research include investigating group-level activity and developing a functional atlas of white matter activity. ■

PROJECT INFORMATION

Supervisors
Anders Eklund, Evren Özarslan, Ida Blystad

Background
Master of Science in Electrical Engineering (double degree studies), Lund University, Lund, Sweden 2017

Master of Science in Telecommunications Engineering, Technical University of Madrid, Madrid, Spain 2017

Bachelor's Degree in Telecommunications Engineering, Technical University of Madrid, Madrid, Spain 2015

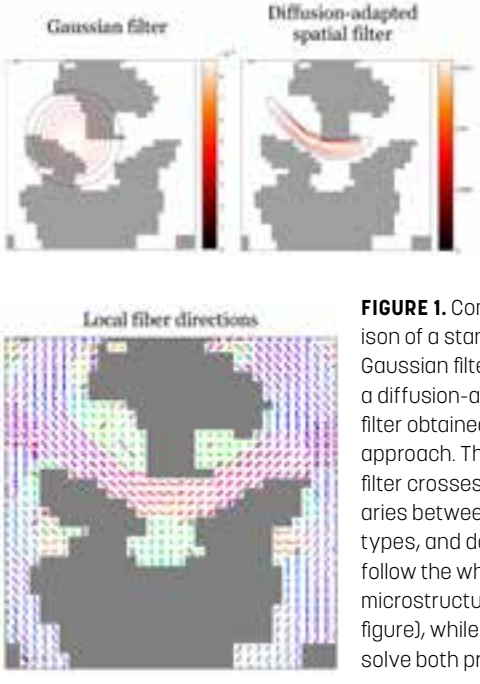


FIGURE 1. Comparison of a standard Gaussian filter with a diffusion-adapted filter obtained with our approach. The Gaussian filter crosses boundaries between tissue types, and does not follow the white matter microstructure (bottom figure), while our filters solve both problems.

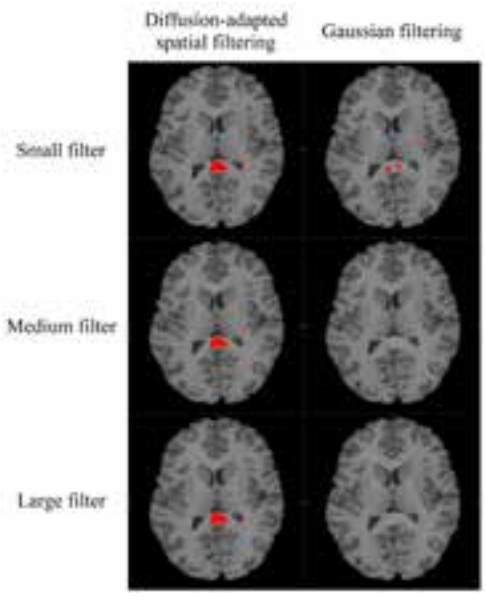


FIGURE 2. Comparison of fMRI activations detected using a standard Gaussian filter with those of a diffusion-adapted filter obtained with our approach. The Gaussian filter is only capable of finding faint activations when using small filter sizes, while our approach shows strong and consistent activations across filter sizes.

MARTIN LINDVALL

Human-AI Interaction for Medical Imaging

The last decade's advancements in machine learning (ML) has led to a dramatic increase in AI capabilities and the viability of learning by example. However, despite impressive technical advances and many successful research projects, machine algorithms for medical diagnostics are to a very small extent used in healthcare today. One challenge is that for ML algorithms with less than 100 % sensitivity and specificity the clinical user needs effective means to assess the validity of results and incorporate this knowledge within the broader context of their diagnostic process.

This project explores the technical and human factors that lead to successful human-machine cooperation when humans interact with narrow artificial intelligence. The research subjects in this project are primarily human computer interaction and technological design. Secondarily the research involves medical visualization, machine learning and artificial intelligence.

With roots in constructive design, this research is done in tight coherence with demonstrators and proof-of-concepts for medical decision support within imaging disciplines such as pathology and radiology.

Preliminary approaches involve viewing this interaction as a process that unfolds over time enabling reciprocal and continuous learning as well as framing machine learning as material in the design process and investigating the limits, extent and characteristic of the design space that this new material affords. ■

FIGURE 1. Tool for training a machine learning system to classify tissues. The design emphasizes rapid refinement by near-realtime feedback and enables human-machine synergies by improving by continuously improving with use.

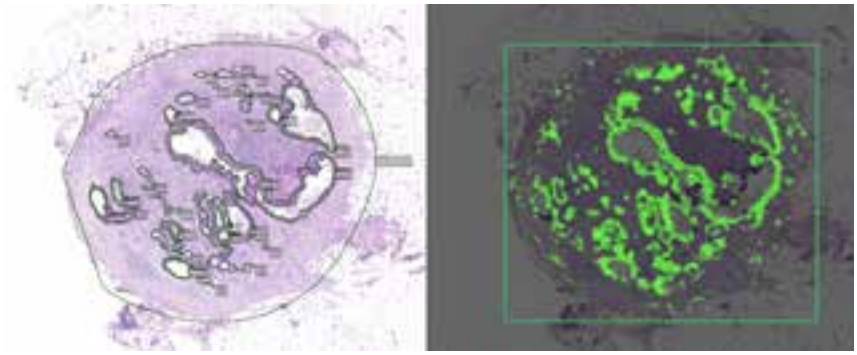


FIGURE 2. Iterative refinement of annotation strategy while developing an interactive tool in assisting lymphnode adenocarcinomas. The medical domain expert uses the output of the preliminary model to assess whether their annotation is wrong or the prediction is wrong. Unintuitively, this pixel-level reflection upon the nature of carcinomas is not part of their everyday experience.

PROJECT INFORMATION

Supervisors
Jonas Löwgren, Claes Lundström, Darren Treanor

Project
AIDA
DROID

Background
M.Sc, Cognitive Science, Linköping University, Sweden 2012

Senior Software Engineer at Sectra

MÅRTEN SANDSTEDT

Long-Term Prognostic Value of CCTA in Chest Pain Patients

Ischemic heart disease is caused by atherosclerotic narrowing of the coronary arteries, impairing blood flow to the heart muscle. It is the leading cause of morbidity and mortality in the world, not seldom associated with diagnostic challenges. Hence, it is essential with continuous developments in patient work-up, diagnosis and follow-up.

Coronary computed tomography angiography (CCTA) is a rapidly evolving, non-invasive cardiac imaging method used for diagnostic visualization of the coronary arteries. The method has an excellent sensitivity, with a reliable and robust ability to rule out coronary artery disease.

The aim of this study was to investigate the long-term prognostic value of CCTA in chest pain patients, examined due to suspected coronary artery disease.

We recruited 1205 patients who had CCTA examinations performed at CMIV between 2007 and 2014, all previously registered in a local part of the SWEDEHEART registry. All examinations were classified according to coronary artery findings, and data in the SWEDEHEART register was subsequently merged with the National Board of Health and Welfare Patient Registry and the Cause-of-death Registry. The creation of a common database enabled access to prognostic data, and a primary endpoint was defined as major adverse cardiac events, being a composite of cardiac death, myocardial infarction, unstable angina pectoris and late revascularization (>90 days after the CCTA examination).

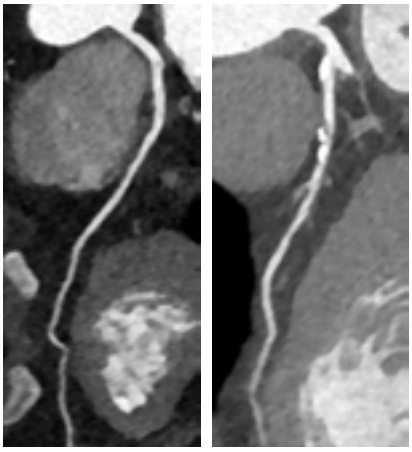


FIGURE. Multiplanar reconstructions of the left anterior descending coronary artery in two different patients.
Left: Normal artery. **Right:** Atherosclerotic narrowing of the proximal part of the artery.

Analyses demonstrated an excellent long-term prognosis in patients with normal coronary arteries, and the risk of suffering from a major adverse cardiac event became progressively worse in patients with increasing degree of coronary artery disease. A multivariate analysis with adjustment for clinical characteristics and classical risk factors identified pathological CCTA-findings as the only independent predictors of major adverse cardiac event. In addition, chest pain patients undergoing CCTA were, regardless of findings, frequently readmitted for chest pain or angina pectoris.

The study confirms CCTA as a clinically useful tool in risk stratification for chest pain patients. However, a wider, future role of CCTA in the follow-up in chest pain is yet to be defined. ■

PROJECT INFORMATION

Supervisors
Anders Persson, Joakim Alfredsson, Jan Engwall, Magnus Janzon

Background
Specialist in medical radiology, 2008

Dissertations

During 2018 six of the CMIV PhD students have finished their studies and defended their dissertations. The PhD students and the research school are an important part of CMIV and we are proud to present their dissertations here.


↑CMIV

THOBIAS ROMU

Fat-Referenced MRI: Quanitaive MRI for Tissue Characterizaion and Volume Measurement

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

The amount and distribution of adipose and lean tissues has been shown to be predictive of mortality and morbidity in metabolic disease. Traditionally these risks are assessed by anthropometric measurements based on weight, length, girths or the body mass index (BMI). These measurements are predictive of risks on a population level, where a too low or a too high BMI indicates an increased risk of both mortality and morbidity. However, today a large part of the world's population belongs to a group with an elevated risk according to BMI, many of which will live long and healthy lives. Thus, better instruments are needed to properly direct health-care resources to those who need it the most.

Magnetic resonance imaging can both accurately and safely measure internal adipose tissue compartments, and the fat infiltration of organs. Which is why MRI is often considered the reference method for non-invasive body-composition analysis. The two major challenges of MRI based body-composition analysis are, the between-scanner reproducibility and a cost-effective analysis of the images. This thesis presents a complete implementation of fat-referenced MRI, a technique that produces quantitative images that can increase both inter-scanner and automation of the image analysis. ■

BELÉN CASAS GARCIA

Towards Personalized Models of the Cardiovascular System Using 4D Flow MRI

Linköping University, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

One of the main goals of cardiovascular modelling is the development of personalized models based on clinical measurements. Recent years have seen remarkable advances in medical imaging and the use of personalized models is slowly becoming a reality. Modern imaging techniques can provide an unprecedented amount of anatomical and functional information about the heart and vessels. In this context, three-dimensional, three-directional, cine phase-contrast (PC) magnetic resonance imaging (MRI), commonly referred to as 4D Flow MRI, arises as a powerful tool for creating personalized models. 4D Flow MRI enables the measurement of time-resolved velocity information with volumetric coverage. Besides providing a rich dataset within a single acquisition, the technique permits retrospective analysis of the data at any location within the acquired volume.

This thesis focuses on improving subject-specific assessment of cardiovascular function through model-based analysis of 4D Flow MRI data. By using computational models, we aimed to provide mechanistic explanations of the underlying physiological processes, derive novel or improved hemodynamic markers, and estimate quantities that typically require invasive measurements. ■

MARIANA BUSTAMANTE

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

Linköping University, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

Magnetic resonance imaging (MRI) is frequently performed in the clinical setting to assess the morphology and function of the heart and vessels. When focusing on the cardiovascular system, blood flow visualization and quantification is essential in order to fully understand and identify related pathologies. Among the variety of MR techniques available for cardiac imaging, 4D Flow MRI allows for full three-dimensional spatial coverage over time, also including three-directional velocity information. In the clinical routine, flow analysis is typically done using two-dimensional imaging methods. This can be explained by their shorter acquisition times, higher in-plane spatial resolution and signal-to-noise ratio, and their relatively simpler post-processing requirements when compared to 4D Flow MRI.

This thesis aims to develop and evaluate techniques that facilitate the post-processing of thoracic 4D Flow MRI by automating the steps necessary to obtain hemodynamic parameters of interest from the data. The proposed methods require little to no user interaction, are fairly quick, make effective use of the information available in the four-dimensional images, and can easily be applied to sizable groups of data. The addition of the proposed techniques to the current pipeline of 4D Flow MRI analysis simplifies and expedites the assessment of these images, thus bringing them closer to the clinical routine. ■

SOFIA KVERNBY

Myocardial Tissue Characterization Using Magnetic Resonance Imaging

Linköping University, Department of Medical and Health Sciences, Division of Cardiovascular Medicine

In cardiovascular disease, which is the most common cause of death in the world, early diagnosis is crucial for disease outcome. However, diagnosis of cardiovascular disease can be challenging. Quantification of myocardial T1 and T2 relaxation times with MRI has demonstrated to be a promising method for characterizing myocardial tissue, but long measurement times have hampered clinical use.

The overall aim of this doctoral thesis was to develop, validate and, in patient studies, evaluate 3D-QALAS, a fast three-dimensional method for simultaneous quantification of myocardial T1 and T2 relaxation times in a three-dimensional volume of the heart. The method requires 15 heartbeats, to produce 13 short-axis slices of the left ventricle with voxel-wise information of both T1 and T2 relaxation times. The 3D-QALAS method was validated in phantoms and in 10 healthy volunteers by comparing the method with reference methods and demonstrated good accuracy and robustness both in-vitro and in-vivo.

The 3D-QALAS method was also applied and evaluated in patient cohorts where the heart muscle alters over time. Patients with severe aortic stenosis underwent MRI examinations with 3D-QALAS before, 3 months after and 12 months after aortic valve surgery. Changes in T1 and T2 were observed, which might be used as markers of myocardial changes with respect to edema and fibrosis, which may develop due to increased workload over a long period of time. ■

JENS SJÖLUND

Algorithms for Magnetic Resonance Imaging in Radiotherapy

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

Radiotherapy planning requires simulation of radiation transport. The necessary physical properties are typically derived from CT images, but in some cases only MR images are available. In such a case, a crude but common approach is to approximate all tissue properties as equivalent to those of water. In this thesis we propose two methods to improve this approximation. The first uses a machine learning approach to automatically identify bone tissue in MR. The second, Atlas-based regression, uses deformable registration to estimate a pseudo-CT of a new patient based on a database of aligned MR and CT pairs.

Cancerous tissue has a different structure from normal tissue. This affects molecular diffusion, which can be measured using MRI. The prototypical diffusion encoding sequence has recently been challenged with the introduction of more general gradient waveforms. We demonstrate that, by using the optimized gradient waveforms, it is technically feasible to perform whole-brain diffusional variance decomposition at clinical MRI systems with varying performance. The last part of the thesis is devoted to estimation of diffusion MRI models from measurements. We show that, by using a machine learning framework called Gaussian processes, it is possible to perform diffusion spectrum imaging using far fewer measurements than ordinarily required. ■

LUDVIG VAVRUCH

Adolescent Idiopathic Scoliosis: A Deformity in Three Dimensions

Linköping University, Department of Clinical and Experimental Medicine, Division of Surgery, Orthopedics and Oncology

Scoliosis is a complex three-dimensional deformity of the spine. Even though it has been known for centuries, treatment of the deformity has focused on correcting only in the frontal plane. In the last decades, the need for three-dimensional assessment regarding scoliosis has been highlighted to better understand the cause and the principles of treating scoliosis. The overall aim of this dissertation is to provide knowledge to assess scoliosis as a three-dimensional problem.

The severity of scoliosis is measured with the Cobb angle from standing radiographs. Computed tomography (CT) examinations are used throughout this thesis. Therefore, the first paper investigated the difference in Cobb angle measured from standing radiographs and supine CT examinations. The standing radiographs had larger Cobb angles with a mean difference of 11° and a linear correlation between the two examinations from 128 consecutive patients with adolescent idiopathic scoliosis (AIS) planned for surgery. The following papers examined different characteristics of the scoliotic spine as the axial shape of vertebrae and the pelvic incidence (PI).

Severe AIS is treated with corrective surgery. Two approaches are available: the predominant posterior approach and the anterior approach. In the fourth paper, these two approaches are evaluated with regard to three-dimensional correction, how well the correction is maintained over a 2-year follow-up and patient-reported outcome measures. ■

Equipment

Through a unique collaboration with the industry it is possible for CMIV to continue to be in the forefront of research. Having access to the latest equipment takes you a long way towards successful innovation.

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. 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.

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.

The 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.

In 2018 Compressed SENSE was installed on both Philips systems, enabeling up to 50 % faster scans.

The Siemens 3T Prisma has a 60 cm bore and gradients with 80mT/m@200 T/m/s simultaneously, which facilitate fMRI and DTI studies. 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 S2 000 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

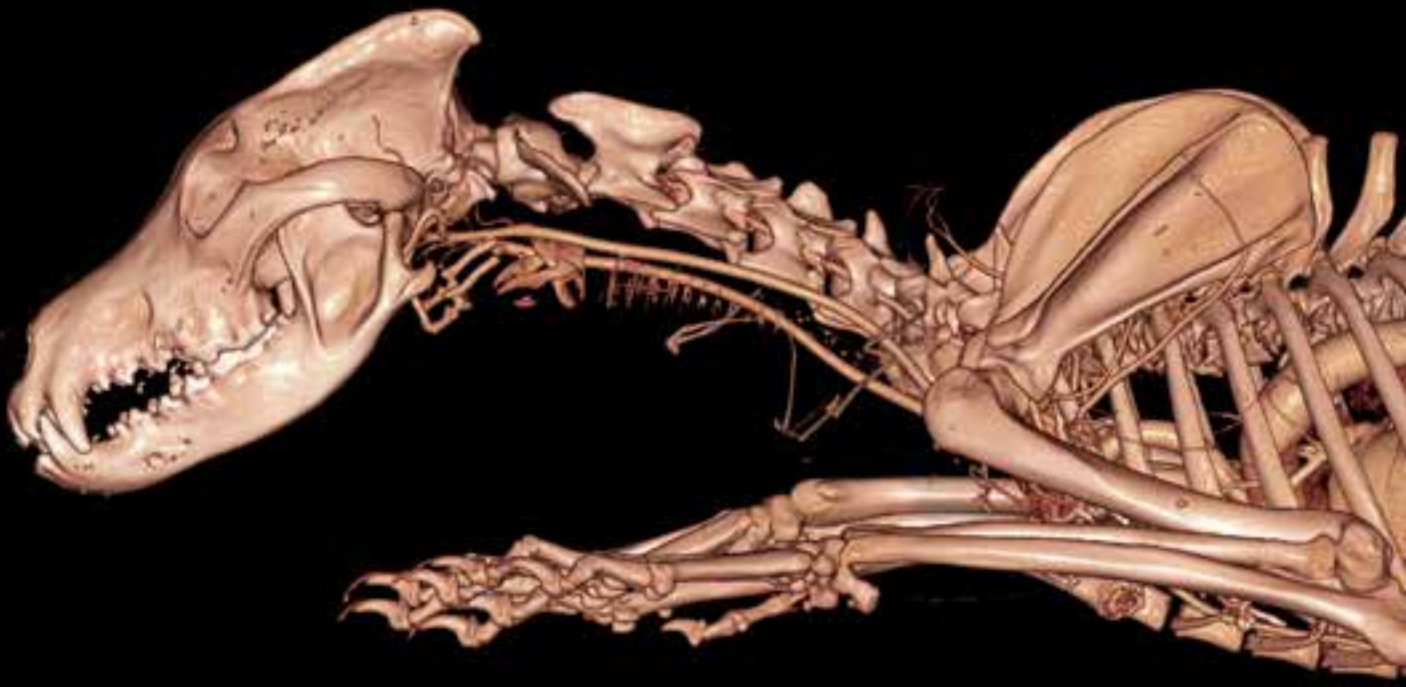
CMIV has its own Virtual Reality theatre with a capacity of 90 persons. The theatre is built around Barco DP4K-30L 6P Laser projector (21 000 lumens light output), with 4K resolution (4 096 × 2 160). The Barco Laser3D has a native 6-primary color-3D system. The system uses a Barco E2 Image processor, 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. During 2018 Wranne was upgraded to an advanced Zoom room enabling remote meetings and education.

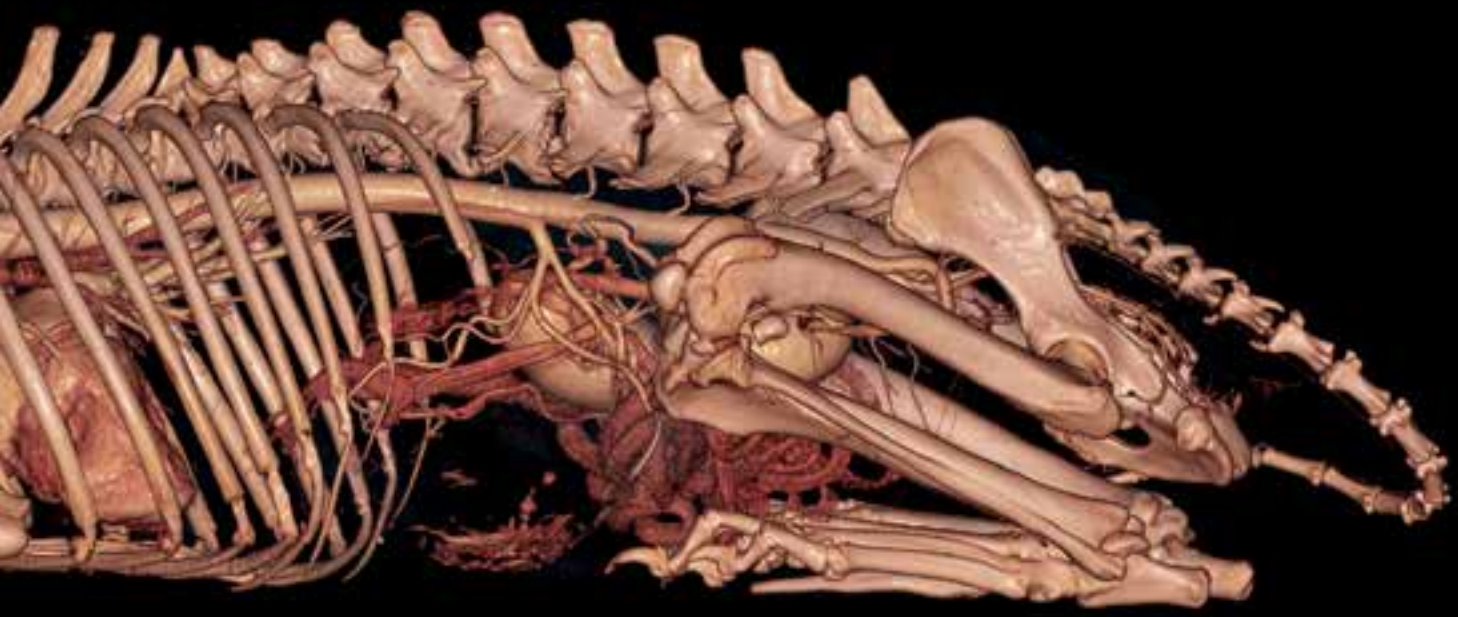
All computers at CMIV's network can be used for video conference system, allowing for 1080p HD conference meetings or video broadcasting. Several Advantage Workstations from GE Medical Systems are available at the hospital.

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 AND ANNOTATION

For histo-pathology CMIV has a glass scanner from Hamamatsu. The Nanozoomer 2.0HT converts glass slides into high-resolution digital data by high-speed scanning and has a capacity of scanning up to 210 glasses automatically. In addition, three workstations with touch screens are installed for annotation work. ■





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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Charalampos Georgiopoulos	IMH, Radiological Sciences
Marcus Gjerde	IMH, Cardiovascular Medicine
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Anette Karlsson	IMT, Biomedical Engineering
Markus Karlsson	IMH, Radiological Sciences
Bharti Kataria	IMH, Radiological Sciences
Sofia Kvernby	IMH, Cardiovascular Medicine
Robin Kämpe	IKE, Center for Social and Affective Neuroscience
Martin Lindvall	ITN, Media and Information Technology
Natasha Morales Drissi	IMH, Radiological Sciences
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Thobias Romu	IMT, Biomedical Engineering
Mårten Sandstedt	Department of Radiology, Region Östergötland
Jens Sjölund	IMT, Biomedical Engineering
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Sofie Tapper	IMH, Radiological Sciences
Ludvig Vavruch	IKE, Orthopedics
Magnus Ziegler	IMH, Cardiovascular Medicine

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Publications

The CMIV research efforts lead to a steady stream of scientific publications. An overview of the 2018 production is given in the following pages. As papers from CMIV researchers may be primarily registered under other affiliations the listing is not complete, but still shows a good representation of CMIV. The CMIV researchers have presented their work at conferences all over the world during the year, however conference abstracts are not included in this list unless published as a conference paper.

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, 2014–2018**

	Number of Publications	Number of Fractions
Journal articles – refereed	313	138.6
Conference publications	62	35.0
Chapters – other academic	1	0.3

Results	
% author shares level 2	12

Percentage of fractionalized publications published in journals / publishers of the highest scientific quality (level 2). Maximum shares of level 2 is 20 %.

TABLE 2. **Open Access, 2014–2018**

Articles	%
Articles	59
Conference publications	50
Chapters	0

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, 2014–2018**

Publications in Web of Science	Number of Publications	Number of Fractions
Articles, reviews, letters, proceedings papers	344	154.0

Coverage	%
Articles	92
Conference Proceedings	72

FIGURE 1. **Number of Fractionalized Publications**

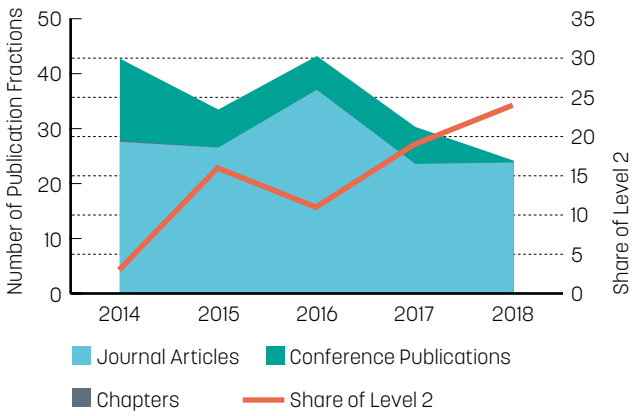

FIGURE 2. **Open Access Articles**

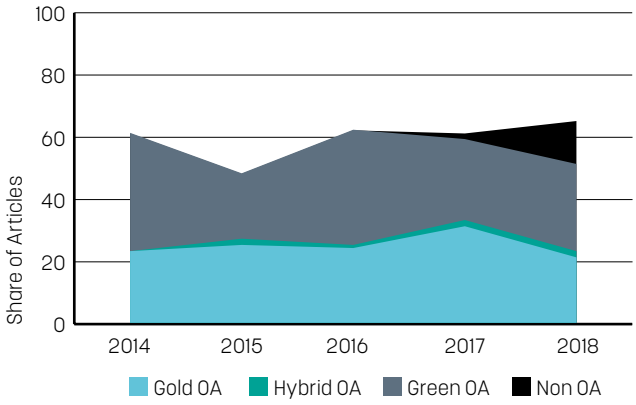

FIGURE 3. **Number of Fractionalized Journal Articles: Coverage in WoS, 92 %**

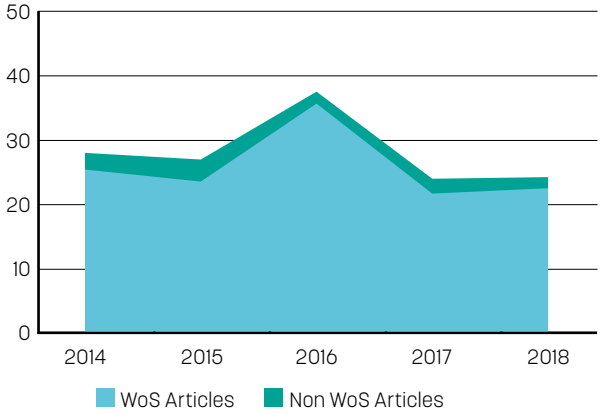

FIGURE 4. **Impact**

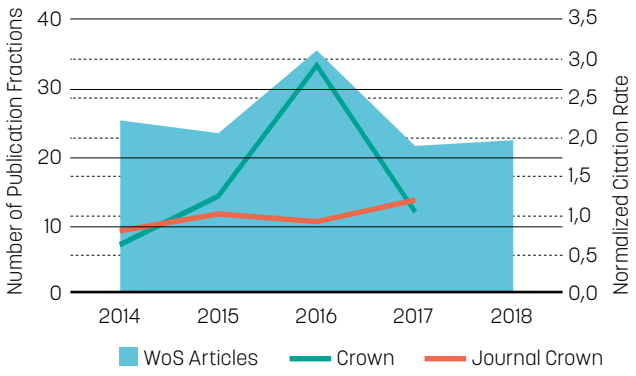

FIGURE 5. **Fractionalized Journal Articles in WoS: Co-Authorships**

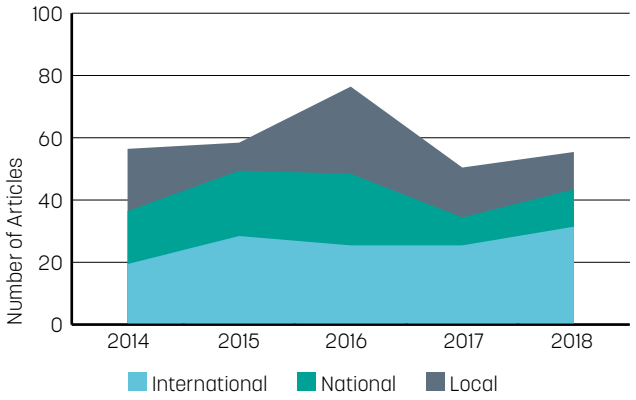

FIGURE 6. **Interdisciplinary Publications**

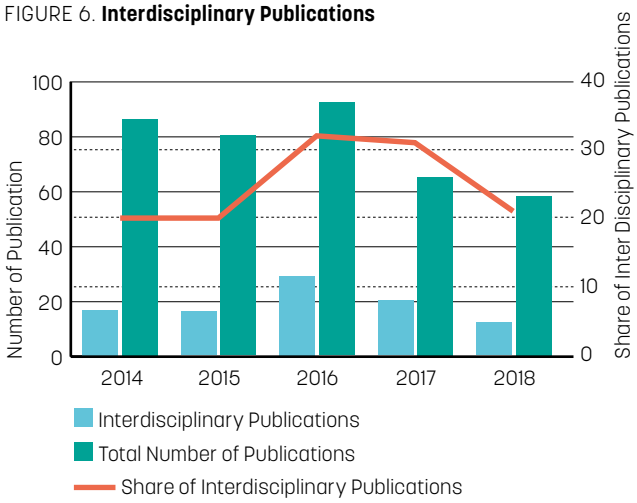

TABLE 4. **Citation Analysis, 2014–2017**

Publications in Web of Science	Number of Publications	Number of Fractions
Articles, reviews, letters	240	106.8

Results, 2014–2017	
Field-normalized citation rate (crown)	1.59
Share of top 10 %	10 %
Share of uncited publications	25 %
Field-normalized journal citation rate (journal crown)	0.94
Journal Impact Factor (JIF) ranking, mean	0.66

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, 2014–2018**

	%
Share of articles with international co-authors	43
Share of articles with national co-authors	28
Share of articles with local co-authors	29

TABLE 6. **Interdisciplinary Authorship (LiU faculties), 2014–2018**

Number	94
Share	25 %

Publications 2018

CMIV affiliated researcher are written in bold.

PEER-REVIEWED ORIGINAL ARTICLE

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DISSERTATIONS, COMPREHENSIVE SUMMARY

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Casas Garcia, B. (2018). Towards Personalized Models of the Cardiovascular System Using 4D Flow MRI (PhD dissertation). Linköping.

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Kvernby, S. (2018). Myocardial Tissue Characterization Using Magnetic Resonance Imaging (PhD dissertation). Linköping.

Romu, T. (2018). Fat-Referenced MRI: Quanitaive MRI for Tissue Characterizaion and Volume Measurement (PhD dissertation). Linköping.

Sjölund, J. (2018). Algorithms for magnetic resonance imaging in radiotherapy (PhD dissertation). Linköping.

REPORT

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Annual Accounts

During 2018 CMIV had a turnover of more than 52 million.
The financial result for CMIV in 2018 was 2 million SEK.

This fiscal year we have continued to develop our infrastructure by upgrading the conference system in Wrannesalen with new equipment including Zoom. Our Philips Ingenia 3.0T and Philips Achieva 1.5T were upgraded with Compressed Sense, which could enable faster MR-examinations, enhance image quality and evaluate diagnostic efficacy. We also installed 7 poster screens in the admin corridor at CMIV.

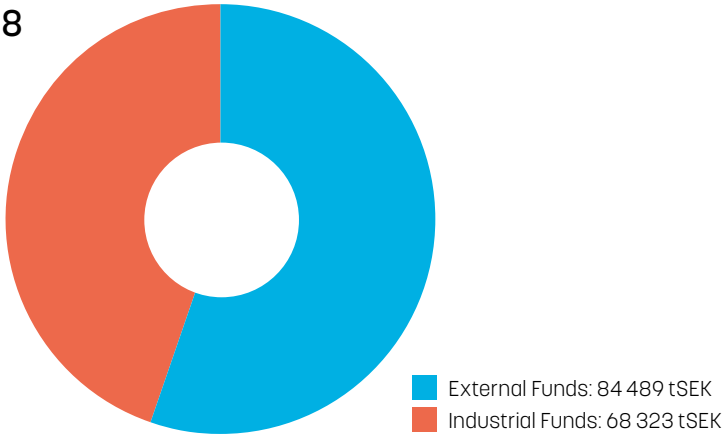
During 2018 CMIV had several ongoing research grant projects. In June VINNOVA announced increased funding of AIDA – Analytic Imaging Diagnostics Arena. This means the project will broaden and continue until 2020. The VINNOVA-financed project »Bringing orthopedic implant surgery to the era of precision medicine« continued. The project »Radsim: Simulation Based Training Program for CT Protocol, Iterative Reconstruction and Dual Energy Applications« continued. Radsim is funded by RSNA Research & Education Foundation. DROID (Open image database for AI-training) was started during 2017 and continued during 2018. DROID is funded by Visual Sweden. Both the Faculty of Medicine and Health Sciences and the Faculty of Science and Engineering continued to support CMIV:s work within the Digital pathology area. ■

ECONOMIC SUMMARY	2013	2014	2015	2016	2017	2018
Total revenue	35 576	48 762	39 298	40 655	48 165	52 059
EXPENSES						
Staff expenses	–16 756	–19 507	–18 593	–16 978	–15 772	–16 711
Cost of premises	–2 034	–2 058	–2 869	–9 135	–6 472	–6 657
Misc. operating expenses	–8 876	–17 334	–11 483	–12 158	–16 765	–18 704
Depreciation expenses	–5 336	–5 629	–4 980	–6 781	–7 819	–8 129
Financial expenses	–185	–102	–123	– 132	– 36	– 151
Total expenses	–33 187	–44 630	–38 048	–45 184	–46 864	–50 051
Result of operations	2 389	4 133	1 250	–4 519	1 300	2 008

NUMBERS IN THOUSANDS OF SEK

Research Funding at CMIV 2010–2018

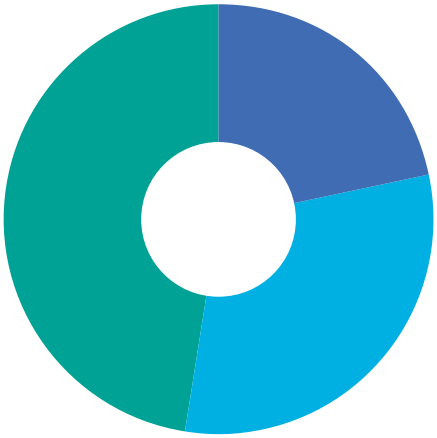
CMIV receives funding from research funds and the industry both directly to the R&D platform and to specific research projects. In addition, the affiliated researchers have their own funding; these grants will, however, not be presented here.



CT Research and Clinic, %

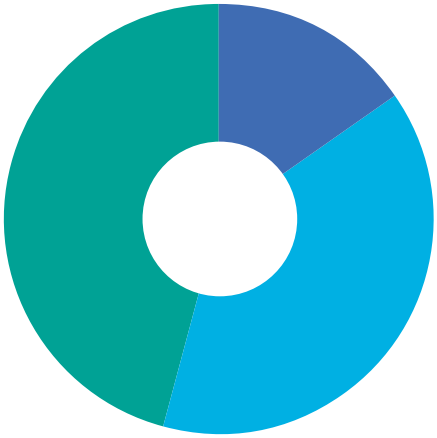
2018

- Combined Research and Clinic, 21.9
- SCAPIS, 30.8
- Clinic, 47.3



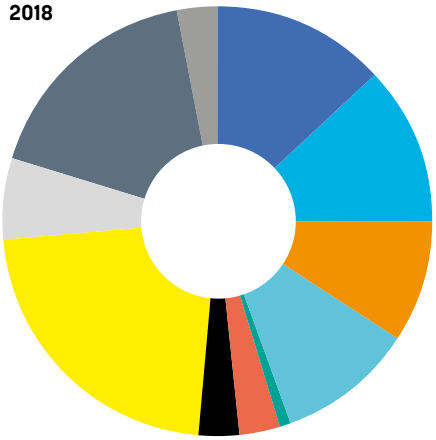
2017

- Combined Research and Clinic, 15.5
- SCAPIS, 38.8
- Clinic, 45.6



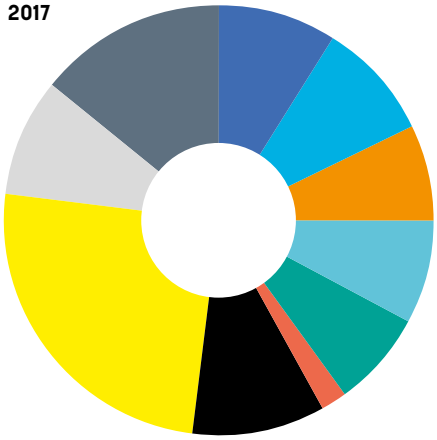
Distribution of Research on the MRI Cameras, %

2018



- Full Body Scan, 13.0
- Logistics, 12.0
- fMRI Neuro, 9.0
- Cardiovascular, 10.0
- Combined Clinic/Research, 1.0
- Spectro Neuro, 3.0
- Development Time, 3.0
- CSAN Neuro, 22.0
- SCAPIS, 6.0
- MSK, 17.0
- Neuro, 3.0

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

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